Analysis of Individual Brain Activation Maps Using Hierarchical Description and Multiscale Detection

J. B. Poline and B. M. Mazoyer

Abstract—We propose a new method for the analysis of brain activation images that aims at detecting activated volumes rather than pixels. The method is based on Poisson process modeling, hierarchical description, and multiscale detection (MSD). Its performances have been assessed using both Monte Carlo simulated images and experimental PET brain activation data. As compared to other methods, the MSD approach shows enhanced sensitivity with a controlled overall type I error, and has the ability to provide an estimate of the spatial limits of the detected signals. It is applicable to any kind of difference image for which the spatial autocorrelation function can be approximated by a stationary Gaussian function.

I. INTRODUCTION

OVER THE past ten years, a number of medical imaging techniques have been successfully applied to the study of human brain cognitive functions. This mainly concerns positron emission tomography (PET) [1], and more recently functional magnetic resonance imaging (fMRI) [2]. In all cases, repeated brain scans are obtained in subjects while performing different cognitive tasks, and so-called brain activation maps (BAM) are generated by computing the difference between brain scans acquired during the execution of two different tasks [3].

Analysis of these brain activation maps is made up of two different steps: 1) the detection of activated foci, and 2) the definition of their anatomical localization. Because of the intrinsically low signal-to-noise ratio of individual difference images, the detection step usually requires both some sort of low pass filtering [4]–[7] and a procedure for averaging brain maps across subjects. The most widely accepted way of doing this [4], [5], [8] is to apply spatial transformations to the individual brain maps that will bring them in the so-called standard Talairach space where these individual maps can then be averaged. Another possibility is to define regions of interest in each individual brain [9], which is a sort of morphological low pass filter, and to average the regional variation of the signal over the subject population.

Although they have proven their potentials and provided some very new insights in brain functional organization [10]–[13], the intersubject detection methods suffer from some limitations and may, in some cases, lead to spurious results [14]. First of all, because of the known interindividual brain anatomy and function variability [15], these methods are limited in sensitivity since they may lose small signals through the averaging process. Secondly, the low pass filtering and intersubject averaging processes make the second step of the analysis, e.g., the activation localization, problematic and, in practice, prevent any detailed study of the correlation between brain anatomy and function. Finally, and by essence, these methods do not allow the investigation of the interindividual variability of functional neuroanatomy which is known to exist in the human brain.

Despite the limited SNR of individual BAM, which could be partially overcome in the new generation of 3-D PET scanners and/or by functional MRI instrumental progress, there is still a clear need for methods that would aim at detecting activated volumes in individual BAM. In fact, some of the detection methods used in the analysis of stereotactically averaged PET data are applicable to single subject images. In 1988, Fox et al. proposed an outlier detection test over the distribution of the local extrema. More recently, Friston et al. [5] and Worsley et al. [6] proposed the modelization of the PET data by a Gaussian process and a test of the number of process upcrosses above a threshold that is chosen to control the false positive rate. All these methods are based on the extremal values of the image (or volume). A new approach that tests the number of connected pixels above a given threshold has been recently proposed by Poline and Mazoyer [7] and showed an increased sensitivity compared to Fox’s earlier detection. However, since this method only tests a number of pixels, its use is limited to large signals. In addition, all of the above methods increase the image SNR by some kind of arbitrary low pass filtering, but large filters do have important weaknesses: not only do they degrade the image resolution, but they also may decrease the SNR of small signals (and therefore their detectability). Indeed, the signal corresponds to an optimal filter that will maximize the SNR or another detection criteria. Note, for instance, that in the ideal case, the signal is entirely known (in shape, size, and intensity), and some maximum likelihood procedure can be applied. We will present, in this paper, a detection algorithm that partially gets rid of the arbitrary low pass filter choice, has a larger range of application, and increases the detection sensitivity over previous methods.

Related to segmentation and restoration procedures, signal detection is a very general problem, often addressed in terms of defect detection or signal recognition. While the latter requires
a model of the signal (see, for instance, the tumor detection problem [16]), the former is usually based on high frequency or edge detection [17]. In PET difference activation images, because of instrumental and/or biological reasons, signals may very well not be characterized by sharp edges. Other methods that fall more within the restoration framework [18], [19] do not deal with the hypothesis testing aspect of the activation detection problem. In our work, because of the absence of information about the signal shape, size, and intensity, we propose the use of a multiscale approach (i.e., multiresolution), which has proved to be useful in other image processing areas, such as segmentation [20], and increases the SNR of various magnitudes. Since we aim at detecting brain regions with higher magnitude and/or larger extent than what is expected in noise, our detection algorithm tests these two parameters on objects defined by a hierarchical decomposition of the PET difference images. The testing is performed with reference to a bidimensional distribution assessed in pure noise images by Monte Carlo simulations. In addition, a signal removal step is applied to enhance the segmentation aspect of this algorithm so that the shape of the detected signal will be close to the real one.

Section II of this paper describes the multiscale detection (MSD) and the hierarchical decomposition (HD) algorithms in detail. Its characteristics are presented both in simulations and in experimental PET individual difference images in Sections III and IV, where the method sensitivity, specificity, and robustness are assessed and compared to other detection procedures used for PET data analysis. In Section V, we discuss the method limitations and propose some possible improvements.

Fig. 2. Unidimensional example of a hierarchical decomposition procedure. At a given scale, a 1-D curve (a) is decomposed into six objects (A–F). The corresponding object tree is shown in (b).

II. OBJECT DETECTION AND MULTISCALE APPROACH

A. The MSD Algorithm: General Description

A multiscale approach decomposes an original image into a series of images that contain less and less details as the scale increases. Here, the scale refers to the bandwidth of a low pass filter applied to the original image [20], [21]. The idea underlying the multiscale approach is to increase the SNR of signals of different sizes, and therefore to improve the overall detection sensitivity. Some theoretical considerations and a priori constraints, such as causality and isotropy, establish the Gaussian filter as the unique scale-space filter [22], although Gaussian filters can create spurious details when going from higher to lower resolution [21]. Therefore, a series of Moving Average Gaussian (MAG) filters is applied to the original image. In this study, we chose to successively apply Gaussian filters of width $w = 1.5, 2, 2.5$, and 3, where $w$ is expressed in pixel units and is related to the Gaussian function full width at half maximum (FWHM) by $w = \text{FWHM} / \sqrt{8 \ln(2)}$ [6]. The choice of the width series is based on some practical considerations made under our experimental images, but it may be optimized in future works. At each scale level (i.e., at each $w$ value), the image is first standardized in pixel standard deviation units (so that pixels in the resulting image have a unit standard deviation), and then decomposed, in a hierarchical way [23], in a list of embedded objects (see Section II-B). Object sizes and magnitudes are then tested, with respect to a reference distribution assessed in noise only images (see Section II-C). Once something has been labeled as “anomalous,” and therefore considered as containing some signal, it is removed from the currently processed image. This signal removal step (called the interscale signal removal step) prevents a small signal, detected at a high resolution scale, from being detected at a coarser level, and thus would lead to a poor signal delimitation. The general description of the algorithm is shown in Fig. 1.

B. Object Definition by Hierarchical Image Decomposition

At each scale level, the image is hierarchically decomposed into a list of objects enclosed in each other, as initially proposed by Kirsch [23] for a segmentation purpose. This decomposition is illustrated in the unidimensional (1-D) case in Fig. 2. In a more formal way, a level 0 object (null level) is a four-connected subset of the space that contains one and only one local maximum and has a maximal pixel number. An object of level 1 is composed with two level 0 objects, and level $n$ objects are formed with level $m$ objects where $m < n$ (Fig. 2).
C. Hierarchically Decomposed Object (HDO) Detection at a Given Scale

1) An Overview of the Detection at a Given Scale: Once an image has been hierarchically decomposed, we compute for each object a probability of occurrence in noise only images. We characterize an object by its size (number of pixels), denoted \( s \), and its mean intensity, denoted \( m \) (mean pixel value), and will refer to such an object as \( O(s,m) \). Recall that the pixel mean value is expressed in image pixel standard deviation (SD) units. Signal detection starts with the level 0 objects and proceeds by ascending level. Once an object is considered as significantly different from noise either by its mean and/or its size, it is removed from the image and a new hierarchical description is computed. This will be referred to as the intrascale removal procedure, where “removal” means that all pixels belonging to a detected object are set to the lowest object pixel value. Its aim is the same as the interscale removal procedure. Fig. 3 shows the detection algorithm overview at a given scale level.

2) Assessing the Object Occurrence Probability in Noise: Since we are looking for objects with anomalous size and/or mean intensity, the testing procedure of an object takes these two parameters into account. However, deriving the theoretical 2-D distribution of these parameters in pure noise images (null hypothesis) seems intractable. Therefore, we assessed this 2-D distribution by Monte Carlo simulations for each of the four chosen Gaussian filters. The assumptions needed for these simulations to fit with our experimental images are discussed in Section III-C, and the computer simulations are fully described in Section II-E. Note first that this object occurrence probability depends on the observed image size in the experimental case, the image size is the number of pixels belonging to the brain, since the larger the size is, the more likely an object of high mean and/or large pixel number may occur by chance. This remark corresponds to the phenomenon that leads to Bonferroni correction for multiple testing and to the fact that the Friston and Worsley formula depends on the image size [5], [6].

Let \( B(s,m,S) \) be the number of objects \( O(s,m) \) observed in an image size \( S \) (in number of pixels). Let \( C(s,m,S) \), the object number cumulative distribution, be

\[
C(s,m,S) = \sum_{x>\alpha,y>m} B(x,y,S).
\]

We then denote by \( P \) the 2-D parameter space and define \( P_{inf} \) a subset of \( P \) by

\[
P_{inf}(s,m,S) = \{(x,y) \in P | C(x,y,S) \leq C(s,m,S)\}.
\]

Since \( C(s,m,S) \) is a monotonically decreasing function in \( s \) and \( m \) (see definition above), \( P_{inf} \) is a connected subset of \( P \). The border of the subset \( P_{inf} \) is a line such that \( C(s,m,S) \) is constant (isocumulative line). Let us now define \( I(s,m,S) \) as

\[
I(s,m,S) = \sum_{(x,y) \in P_{inf}(s,m,S)} B(x,y,S)
\]

where \( I(s,m,S) \) is the (scalar) result of a random variable denoted by \( I^*(s,m,S) \). It represents the number of objects that fall in \( P_{inf} \) in an image of size \( S \), i.e., the number of events “behind” the isocumulative line “\( C(s,m,S) \) constant.” One can observe that when two parts of the image (with respective size \( S_1 \) and \( S_2 \)) are disjoint, \( I^*(s,m,S_1) \) and \( I^*(s,m,S_2) \) are independent. In addition, we focus our interest on rare events where probability law tends to be Poisson law [25]. These two remarks led us to modelize the \( I^* \) variables by Poisson variables. This assumption is not rejected by a Chi-2 test for events that appear, on average, five times over 100 simulations in a 64 × 64 image at the 0.05 confidence level. At this stage, we can define a Poisson process intensity as

\[
i(s,m) = \frac{I(s,m,S)}{S}
\]

so that \( i(s,m) \) does not depend any longer on the size \( S \) [26]. The unit of \( i(s,m) \) is in number of objects per pixel. \( S \) represents the simulated image size in which the process intensity \( i(s,m) \) is assessed. Its value was set to reach a good precision on this assessment (see Section II-E). Under our assumptions (Poisson process) and in a particular image with size \( S' \), we expect on average

\[
\lambda = i(s,m) \cdot S'
\]

objects to appear by chance only in the \( P_{inf}(s,m,S') \) space with the variable \( I^*(s,m,S') \) following a Poisson law of parameter \( \lambda \). This eventually yields the assessment of
the occurrence probability \( p \) of one or more events in the \( P_{\text{int}}(s, m, S') \) space by

\[
p = \text{Prob}_\lambda(P(s, m, S') \geq 1)
\]

where \( \text{Prob}_\lambda(X = n) = \lambda^ne^{-\lambda}/n! \) is the probability of a Poisson variable of parameter \( \lambda \). If \( p \) is less than a chosen risk of error \( \alpha_0 \), the object \( O(s, m) \) will be said to be anomalous (or detected) in the volume \( S' \).

It is important to note that the two parameters \( m \) and \( s \) (object mean and size) play similar roles here; an “anomalous” object can be detected either because of its large size or its high intensity. This corresponds to the fact that the \( P \) variables are identical on the isocumulative lines \( (C(s, m) \text{ constant}) \) that define the partition of \( P \). Any other partition could have been chosen: for instance, an iso-size line (parameter \( s \) constant) would lead to selecting rare events only on the basis of the object size (and, in that case, the dimension of \( P \) could be reduced to 1). In fact, selecting a partition of the parameter space \( P \) is the way to introduce some \textit{a priori} information on what should be considered a signal.

D. MSD and Global Type I Error Control

At a given scale, our approach is designed to control the type I error denoted \( \alpha_0 \), where \( \alpha_0 \) is set by the experimenter (previous section). However, because of the multiscale procedure, we increase the risk of false positive events. Clearly, if images observed at different scales were independent, a simple Bonferroni correction applied to \( \alpha_0 \) would ensure the control of the global type I error denoted \( \alpha_g \) by setting the type I error of each scale \( \alpha_0 \) to \( \alpha_g/n \), where \( n \) is the number of scales used. Instead, we set the \( \alpha_0 \) value using a trial and error method on several simulation sets of 3000 noise only 64 x 64 images. Eventually, we found that with \( \alpha_0 = 0.035 \), the upper bound of \( \alpha_g \) confidence interval was less than 0.05 (i.e., \( P(\alpha_g < 0.05) < 0.05 \)). This was checked on another simulation set (Section III-B2).

E. Monte Carlo Simulations and Computer Implementation

1) Poisson Process Intensity Estimation: The 2-D parameter distribution, and therefore the Poisson process intensity of object occurrence, was assessed with Monte Carlo simulations of pseudo-random Gaussian noise. Images of 64 x 64 pixels were chosen to minimize edge effects since that approximatively corresponds to the size of a human brain PET slice in our institution (in an experimental PET image, only the pixels within the brain are taken into account). The number of simulations was taken so that an event that occurs five times over 100 simulations in an image size approximately equal to the size of seven PET brain slices (see below) would be less than 5% in error. This yields a simulation of 49,000 64 x 64 images for each scale. Fast Fourier Transform (FFT) provided a time efficient way to compute Gaussian convolution. An example of the process intensity for a filter of width \( w = 2.0 \) pixels is shown in Fig. 4. The 2-D distributions only have to be assessed once and may be used for all kinds of experimental images that can be modeled by Gaussian noise distribution and a Gaussian autocovariance function.

Fig. 4. Object occurrence iso-intensity curves detected in noise only images filtered with a 2.0 pixel width Gaussian filter as a function of object size and magnitude. Isointensity curves were assessed in 49000 64 x 64 pseudo-Gaussian noise images. For instance, the iso-intensity curve \( 10^{-5} \) approximately corresponds to the 5% confidence limit at which an object that has its size and mean beyond this limit would be detected in a 64 x 64 image.

2) Computer Implementation: Because of the large number of images to be simulated, we implemented a fast hierarchical decomposition based on a regular thresholding algorithm (applied on the filtered images in which pixel standard deviation equals one). We present here a short description of this algorithm. Thresholds of decreasing values are successively applied with a constant step of 0.01 SD (highest value: \( \tau_h = 4 \), lowest value \( \tau_l = 1.5 \)). Two other \( \tau_l \) were investigated (1.0 and 2.0) without any major changes on the experimental results. At each threshold level \( i \), images are binarized and current connected components (CC) are sought. For each of them, we record \( "n_{i-1}" \), the number of CC computed at the previous threshold level that are located in the current CC. If \( n_{i-1} = 0 \), this corresponds to the birth of a new object, and its location is stored. If \( n_{i-1} = 1 \), an already existing object is growing. If \( n_{i-1} \geq 2 \), this corresponds to the definition of objects contained in the current CC, and a new object of superior level begins to grow. This algorithm was found much faster than the local minima and saddle points research which is, in addition, hampered by some possible plateau in the image. Also, it seems easily extendable to the 3-D case. Using FFT convolution, intensity assessment lasted about 48 h per scale level on a Sparc 2 Sun workstation (4.2 Mflops).

III. EXPERIMENTAL RESULTS AND COMPARISON WITH TWO EXISTING DETECTION METHODS: SIMULATED DATA

A. Other PET Images Detection Methods

We briefly recall two classical methods described in the literature for PET activation data analysis. Up to now, these methods have been mainly applied to averaged PET data but, in principle, they could also be applied to individual difference images.
1) The Gamma-2 Outlier Detection (G2D): The test of the one-sided Gamma-2 (G2) statistic for PET data was originally proposed by Fox et al. [4]. This method computes the kurtosis of the image local maxima distribution. This kurtosis was found to be lower than that of a normal law in the absence of signal, but gets larger when some signal produces the occurrence of outliers in the local maxima distribution (LMD). This is a global test on the LMD and the question of which local maxima are considered as centers of signals remains unsolved, although it is usually done with a Z-score criterion. While the G2 outlier detection (G2D) was, up to now, applied to stereotactically averaged 3-D data, we implemented it in 2-D (see characteristics of our tomograph, subsection C) for individual images. Previous to the G2 test, images were filtered with a low pass moving average disk shaped filter (radius four pixels), as suggested by Mintum et al. [27].

2) A Threshold Assessment Detection (TAD) Method: More recently, Friston et al. (2-D case [5]) and Worsley et al. (3-D case [6]) suggested the following detection algorithm. First, PET difference images are modeled by a stationary Gaussian white noise process convolved with a Gaussian kernel. Secondly, a theoretical formula is used to assess the number of times that a given threshold will be passed by the image pixel value, depending on the Gaussian kernel width $w$ (also called the process smoothness), the image size, and the threshold. Then, the smoothness is assessed on PET experimental images using a property of Gaussian processes for which a formula relates the process smoothness with the process partial derivative variance (PDV)

$$w = \frac{1}{\sqrt{2\text{var}(X')}}$$

where $X'$ is the process partial derivative and $w$ the Gaussian kernel width. The threshold is then set so that the probability of an upcross is less than 0.05. We also applied the Gaussian filter used by the authors (width 4.25 pixels) before TAD. Worsley showed that the correct formula and Friston formula were related by a 0.79 multiplication factor [6]. In this paper, we have compared our MSD algorithm to the Friston formula, which provides some slightly better detection results than the correct formula at the expense of false positive risk slightly greater than 5%.

B. Sensitivity, Specificity and Robustness
Assessed Using Simulated Images

1) Sensitivity

a) Method: We assessed the MSD sensitivity by adding disk signals of various size and magnitude to 64 x 64 noise images. Magnitude ranged from 0.25 to 2 image pixel SD and disk radius from 2 to 6 pixels. The signal was said to be detected whenever its center of mass was located within the original disk. The same criterion was applied to the TAD method. G2 detection is more difficult to compare since it is a global test. However, we considered that a significant result for the G2 test meant that the signal was found, i.e., at least one local maximum was localized within the original disk contour.

<table>
<thead>
<tr>
<th>SNR</th>
<th>0.25</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1/1/4</td>
<td>1/15</td>
<td>11/25</td>
<td>18/34</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>7/43/35</td>
<td>22/38/45</td>
<td>90/25/36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>24/1/5</td>
<td>24/1/5</td>
<td>25/50/6</td>
<td>85/60/93</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>96/22/1</td>
<td>82/32/40</td>
<td>70/49/20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>124/84/3</td>
<td>81/60/64</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE I
DETECTION SENSITIVITY (IN %) AS A FUNCTION OF DISK SIGNAL SIZE (RADIUS $r$ IN PIXEL) AND SIGNAL-TO-NOISE RATIO (SNR) IN A 64 X 64 IMAGE FOR THREE DETECTION METHODS: MSD, MULTISCALE DETECTION, TAD: THRESHOLD ASSESSMENT DETECTION, AND G2D: GAMMA-2 DETECTION, SIGNIFICANTLY HIGHER PERCENTAGES ARE UNDERLINED FOR EACH SNR LEVEL. THE FIRST NUMBER IS FOR MSD, THE SECOND NUMBER IS FOR TAD, AND THE THIRD NUMBER IS FOR G2D

<table>
<thead>
<tr>
<th>SNR=1</th>
</tr>
</thead>
<tbody>
<tr>
<td>p</td>
</tr>
<tr>
<td>MSD</td>
</tr>
<tr>
<td>TAD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SNR=0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>p</td>
</tr>
<tr>
<td>MSD</td>
</tr>
<tr>
<td>TAD</td>
</tr>
</tbody>
</table>

b) Results: An example of the multiscale approach, the hierarchical decomposition, and the detection algorithm result is shown in Fig. 5. Results for the three detection methods are presented in Table I for at least 500 64 x 64 image simulations. One can observe that MSD performed better in most cases as compared to TAD and G2D, and this is particularly visible for small radius disk signals. This was expected since the filter width used by Friston et al. before TAD is quite large ($w = 4.25$ pixels) and even larger for Worsley et al. in the 3-D case. Secondly, as expected, the TAD and MSD method sensitivities were also functions of the total volume to be analyzed, as shown in Table II, but the detection scores were affected earlier and more strongly for TAD. This result is important since a real subject sliced brain size corresponds approximatively to seven 64 x 64 images. Thirdly, sizes of detected regions pooled over all magnitudes were found correlated to the true signal sizes for the MSD method, while the number of suprathreshold pixels gave almost no information on the signal size for the TAD method (Table III). A further segmentation or restoration step may still be useful for both detection algorithms but, as they stand, MSD has a more accurate signal delimitation power than TAD.
Fig. 5. Illustration of the MSD detection method on a 64 × 64 simulated image. The top row shows a disk signal on the left (SNR 0.5, size 49 pixels) and the noisy image on the right after addition of Gaussian noise of unit standard deviation and zero mean. Successive Gaussian filtering (σ = 1.5, 2.0, 2.5, 3.0) of the simulated image is shown in row 2. The corresponding image hierarchical decomposition and object detection and removal procedure is presented in row 3, in which the interscale removal procedure is seen between the second (scale w = 2.0) and the third (scale w = 2.5) image. The fourth row shows the detected object found at scale w = 2.0 (size 48 pixels, SNR 3.3 pixel image standard deviation) and the corresponding filtered image masked by the detected object that is an approximation of the original signal.

| TABLE III |
| DETECTED SIGNAL SIZE IN PIXELS (POOLED OVER ALL SIGNAL MAGNITUDES) FOR MSD AND TAD AS COMPARED TO TRUE SIGNAL SIZE, MSD: MULTISCALE DETECTION, TAD: THRESHOLD ASSESSMENT DETECTION |
| Signal size | 29 | 49 | 81 | 113 |
| MSD | 48±13 | 62±21 | 70±35 | 91±36 |
| TAD | 31±20 | 35±20 | 26±18 | 35±20 |

2) Specificity and Robustness of MSD and TAD with Error on Smoothness Assessment

a) Method: Specificity (false positive rate) was assessed using sets of noise only 64 × 64 images. Since in both TAD and MSD methods the assessment of the image smoothness is essential, the false positive detection scores were assessed with a ±5% variation of the filter width value. A larger filter width corresponds to an underestimated smoothness value. With a +5% and −5% smoothness assessment error for MSD, the filter width series were 1.575, 2.1, 2.625, 3.15, and 1.425, 1.9, 2.375, 2.85, respectively. For TAD, the Gaussian kernel widths were taken to be 4.46 and 4.04, while the smoothness value was not assessed but set to 4.25. All these figures are in pixel units.

b) Results: It was observed that G2D has a very low false positive detection rate (less than 1%), while the TAD score was slightly (but significantly) greater than 5% (6.10%), as explained by Worsley et al. [6]. Both TAD and MSD were found to be sensitive to the smoothness parameter assessment. The type I error was increased by a 5% overestimated smoothness for TAD (7.18%) and by a 5% underestimated smoothness for MSD (7.62%).

IV. EXPERIMENTAL RESULTS: APPLICATION TO PET DIFFERENCE ACTIVATION IMAGES

A. PET Protocol

Scans were performed on the TTV03 time-of-flight PET scanner, which provides seven slices 12 mm apart [28]. Because of this large interplane distance, we limited our algorithm to the 2-D case. Experimental activation studies consisted of repeated H215O 80 mCi intravenous bolus injections [29]. After each injection, a single 80-s duration scan was reconstructed starting at the arrival of the radioactivity in the brain. The somewhat longer scan duration (longer than the usual 40 s) has been shown to improve the signal-to-noise ratio in difference images [30]. Prior to emission scans, a 10^6 events transmission scan was acquired to serve for correction of the head attenuation. Images were reconstructed in 128 ×
128 format, with a $2 \times 2$-mm pixel size, using a Hanning filter with a 0.25 mm$^{-1}$ cut-off frequency. This gives a 7-mm transaxial resolution at the center of the field-of-view.

Five right-handed, young, male, normal, French volunteers were scanned during three different states denoted $R, A$, and $B$; this sequence was repeated twice (denoted by subscripts 1 and 2) for a total of six scans ($R_1, R_2, A_1, A_2, B_1, B_2$). States $A$ and $B$ were cognitive tasks while state $R$ consisted of a control state. For each of the five subjects, outer head contours were drawn on MR images acquired at the same levels as the PET images and further visually aligned to them. Each scan was then normalized by the global activity in the brain [3], defined as the average radioactivity within the brain contours over the seven PET slices. For each subject, three scans of experimental noise ($N$ scan: $N = X_1 - X_2$, where $X$ stands for $A, B,$ or $R$) and a signal scan ($S$ scan: $S = A_1 + A_2 - R_1 - R_2$) were computed.

In this cognitive protocol, subjects were asked to listen attentively to stories in French (state $A$) or in an unknown language (state $B$). Stimuli were presented binaurally over earphones; texts were read by the same bilingual speaker. Different texts were used for scans $A_1$ and $A_2$ and for $B_1$ and $B_2$. Control state ($R$) consisted in resting silent in darkness. In addition to TAD, G2D, and MSD statistical methods, this data set was also analyzed using a region of interest analysis method [9].

B. Are the Assumptions Valid for the Analysis of PET Images with MSD?

The distribution of pixels in a PET noise difference image was found to be very close to a normal distribution [5], [7]. This is not surprising since the original desintegration event follows a Poisson law and the tomographic reconstruction process sums up thousands of such events which approach normal law by the central limit theorem.

The MSD and TAD methods are adequate approaches if noise only PET images are well approximated by random noise convolved with Gaussian kernel (GK). It is known that the resulting process of such a convolution has a Gaussian autocorrelation function (ACF). We first observed that, due to the reconstruction filter, noise only PET images have a sinus cardinal shaped ACF. The main lobe of this experimental ACF was well approximated by a Gaussian function. Using this approximation, simulated and experimental noise images showed very similar patterns [7]. This also provides a way to assess the process smoothness $w$, using the fact that the width $w_{ACF}$ of the process ACF is simply related to $w_{w} = w_{ACF}/\sqrt{2}$. The simplex optimization algorithm was implemented to compute the Gaussian 2-D function that best fitted the experimental ACF. Because the smoothness is due to the reconstruction process, it was taken to be constant over all subjects and its value assessed using the 15 noise difference scans ($N$ scans) and found to be $0.68 \pm 0.05$, leading to the filter series 1.34, 1.88, 2.4, 2.92.

Although PET scanners do not have stationary ACF, we made this approximation for the resulting process. The non-homogeneity of pixel variance (ACF value in $(0, 0)$) depends on several parameters, some of them having opposite effects. Finally, we found that the ACF width of our PET scanner can also be considered constant on the first approximation [31].

C. Results for PET Images

We first applied MSD on the 15 experimental noise only scans at the $\alpha_0 = 0.05$ level. Only one region was found to be detected (expected: 1 false positive per 20 analyses). This result confirms that the type I risk on real PET data should be close to 5%, and that the ACF modeling is precise enough for this application. However, it is impossible to say whether or not the detected region corresponds to a true rCBF increase. With TAD, two regions were detected, and none were detected with G2D.

Secondly, we have applied the detection method for the French story versus Rest images for the five subjects. The same data were used for TAD and G2 tests. An example of original PET difference images and the detected regions using the MSD method is presented in Fig. 6 and shows the cortical localization of these regions. For the five subjects, TAD showed five suprathreshold regions, while MSD detected 20 regions in meaningful cortical localization (Temporal poles, Superior temporal gyri, left Middle temporal gyrus, and Inferior frontal gyri). G2 test reached the 0.05 significance level for subject 1, 2, and 5. These results and their locations were consistent with those obtained with the region of interest (ROI) analysis method [9]. We discuss in Section IV a possible strategy for selecting the local maxima that may be considered as signal centers.

V. DISCUSSION AND CONCLUSION

A. MSD and Other Methods Drawbacks and Possible Improvements

1) MSD Method: MSD sensitivity may be increased by a more specific characterization of objects found in noise. This could be done by adding a new parameter, such as the lowest object pixel value. A 3-D parameter space $P$ would be generated without any change in the detection methodology. However, adding a new dimension to the parameter space with a fine sampling scale for the third parameter would lead to a large memory space requested for the 3-D distribution (from $2^{16}$ in 2-D to $2^{34}$ floating point values in 3-D). Another way to increase the sensitivity is to incorporate more a priori information given by previous experiments or other techniques.

Once the MSD has been applied one time and some regions have been detected, these regions could be removed from the original $A_1 + A_2$ image and a new PET normalization computed (see PET protocol, Section IV-A). This may improve the sensitivity since small signals could be "hidden" by more important ones through the PET normalization process. The pixel variance, in particular, would be reassessed without previously detected signals and the volume mean reset to 0 (it becomes negative whenever a positive area is detected and removed). However, this again will be a heavy computer burden.

We observed that the intrascale signal removal procedure, as described in Section II, has the following drawback. Once the signal is removed, the noise pattern in this area is different
from the rest of the image. This sometimes induces the
detection of some objects because of an anomalous large size.
A way to avoid this is to modelize the detected area with
a constant signal to remove this constant signal (with value
equal to the mean object value) from the original image before
refiltering this image. However, this procedure would be very
computer-time consuming. Another possibility would be to
apply a further segmentation step (see subsection C).

2) G2D Method: Gamma-2 outlier detection may be im-
proved in two ways. First, the global test could be made more
sensitive, since the type I error is present less than 5% of the
time for noise only images. Second, one can think of a way of
choosing which local maxima (LM) may be considered signal
centers by removing iteratively the highest LM, so long as the
G2 statistics stays above a chosen threshold.

3) TAD Method: A multiscale approach to TAD may allow
this method to detect a larger range of signals. Simulation sets
would give the significance level to work with at a given scale
in order to keep the global type I error below 5%.

B. MSD Method for 3-D Data from PET Scanners or
Other Functional Mapping Techniques

A 2-D MSD method has been implemented, because our
PET tomograph has a low interplane correlation. This becomes
clearly untrue with recent PET scanners where data should be
considered as 3-D. The method can be extended for 3-D data
with: 1) the assessment of a 3-D ACF, and 2) the simulation
of noise only volumes. This is independent from the parameter
distribution dimension (2)) that can remain the same (object
pixel mean and volume size) or be increased.

C. A Further Segmentation Step

Once a region has been labeled as significant, a second step
may decide which pixels of the region should be considered
signals. Such a segmentation (or restoration) procedure should
operate in a conservative manner, with, for instance, no more
than 5% of the region pixels erroneously labeled as signals.
We think that the region delimitation should not depend on
the testing procedure, and therefore we are now working on
this second step. Since this may not be an easy task, the
MSD method provides at present a useful approximation of
the biological signal.

VI. CONCLUSION

We have designed a new detection method of high intensity
area in low SNR images that can be approximated by white
noise convolved with Gaussian kernel. We have shown that
with nearly no a priori information on a signal placed in a
very noisy background, a multiscale approach, together with
a hierarchical decomposition and Monte Carlo simulations, enabled us to increase detection sensitivity with a control over the global type I error. An application to PET individual activation images also demonstrated increased performances, as compared to other detection procedures.

ACKNOWLEDGMENT

The authors are deeply indebted to N. Tsourio (Groupe d’Imagerie Neurofonctionnelle) for providing PET and MRI data.

REFERENCES


