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NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 24 (2005) 763–770

ROC evaluation of statistical wavelet-based analysis of brain activation in $[^{15}O]$-H_2O PET scans

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Received 29 April 2004; revised 12 August 2004; accepted 25 August 2004

This paper presents and evaluates a wavelet-based statistical analysis of PET images for the detection of brain activation areas. Brain regions showing significant activations were obtained by performing Student's *t* tests in the wavelet domain, reconstructing the final image from only those wavelet coefficients that passed the statistical test at a given significance level, and discarding artifacts introduced during the reconstruction process. Using Receiver Operating Characteristic (ROC) curves, we have compared this statistical analysis in the wavelet domain to the conventional image-domain Statistical Parametric Mapping (SPM) method. For obtaining an accurate assessment of sensitivity and specificity, we have simulated realistic single subject $[^{15}O]$-H_2O PET studies with different hyperactivation levels of the thalamic region. The results obtained from an ROC analysis show that the wavelet approach outperforms conventional SPM in identifying brain activation patterns. Using the wavelet method, activation areas detected were closer in size and shape to the region actually activated in the reference image.

Keywords: ROC; Wavelet-based analysis; $[^{15}O]$-H_2O PET

Introduction

Statistical parametric mapping (SPM) methods are commonly used for the analysis of functional neuroimaging studies. These methods consist in performing a statistical test independently at every voxel of the brain image, yielding a *t*- or *F*-map where each voxel expresses the evidence against a null hypothesis of no effect at that voxel (Frackowiak, 1997). In the broadly used software package SPM2 (from the Welcome Department of Cognitive Neurology, London, UK) (Frackowiak, 1997), the methodological procedure for studying functional neuroimaging data requires a pre-smoothing step that improves signal to noise ratio and, to some extent, introduces neighboring information in the analysis. This prior manipulation of the images leads to a certain loss of resolution depending on the size of the filter kernel used, theoretically chosen to match the signal to be detected. Normally, the neighboring information is exploited in a post-processing step to enhance the shape of the activation areas detected (McColl et al., 1994) or to correct the significance levels according to the spatial extent of the activated region (Poline et al., 1997).

Several multiresolution approaches have been proposed to detect statistically significant brain activation regions taking advantage from spatial neighborhood information (Poline and Mazoyer, 1994a,b; Shafie et al., 2003; Siegmund and Worsley, 1995, 2001; Worsley et al., 1996a). These methods are based on applying a sequence of smoothing kernels of different width, and performing the statistical analysis in the set of low-pass-filtered images obtained. As the decomposition used in these methods is redundant and non-orthogonal, the number of statistical tests unnecessarily increase, incurring in a reduction of the specificity of the detection method due to multiple testing unless the significance level is corrected (Ruttimann et al., 1998).

Another alternative for studying functional brain images with multiresolution methods is to use wavelet transform, which decomposes a signal into different spatial-scale sub-bands. It is possible to analyze functional studies taking advantage of this spatial correlation if the statistical tests are applied in the wavelet domain. Moreover, the wavelet transform clusters the relevant information into a few coefficients while maintains the distribution of the Gaussian noise, thus permitting the use of parametric statistical tests and improving the signal-to-noise ratio (SNR) (Ruttimann et al., 1998; Unser et al., 1995).

Several approaches for the statistical analysis of functional brain studies in the wavelet domain have been reported with

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Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2004.08.052

promising results. A wavelet methodology for detecting differences in activity of [^{18}F]-FDG PET images was first proposed by Unser et al. (1995). In their approach using bidimensional orthogonal spline wavelets, χ^2 tests with Bonferroni correction permitted to discard those wavelet sub-bands not significantly different from noise. Then, the method applied z-tests to the coefficients in the remaining sub-bands and reconstructed a final image showing activation regions from only those statistically significant wavelet coefficients. A similar procedure has also been applied to functional magnetic resonance images (fMRI) using cubic spline wavelets (Ruttimann et al., 1998). Brammer (1998) proposed a slightly different wavelet-based methodology for fMRI studies using a three-dimensional discrete wavelet transform (DWT) with the orthogonal 12-tap Daubechies' base. In this method, a Kolmogorov–Smirnov test determined which wavelet coefficients showed statistically significant differences.

All these initial multiresolution studies using wavelet transform claimed better results than the standard statistical analysis in the image domain on the sole basis of an increase in sensitivity. However, sensitivity rate alone provides incomplete information: an accurate assessment should be based on both sensitivity and specificity values.

Following this idea, Feilner et al. (2000) presented an improvement of the procedure proposed in Ruttimann et al. (1998) for fMRI data using t tests instead of z tests. Based on the false detection rate (Type I + Type II errors), they comparatively assessed different bidimensional fractional spline basis and decompositions, Daubechies basis, and SPM. In their experiments, they defined ellipses as activation patterns. They found that spline basis outperformed Daubechies wavelets, reporting that their approach was quite competitive with SPM. In another study, Desco et al. (2001) used a computer-simulated phantom and Receiver Operating Characteristic (ROC) curves for comparing the performance of bidimensional multiresolution analysis versus SPM in the detection of brain activation in fMRI. The Gabor transform and several families of wavelets were included in the study (*Daubechies*, *Lemarie*, *Symmlets*, *Spline*), testing different orders and decomposition levels. The study showed that multiresolution analysis provided better results than SPM, the Gabor decomposition offered the best results, and the other wavelet basis did not show major differences among them.

The present study proposes a three-dimensional wavelet-based method for the detection of brain activations in PET images, and compares this approach against the conventional SPM using ROC analysis. To enable a comprehensive ROC evaluation of the two methods, a set of realistic [^{15}O]-H_2O PET studies was simulated to create a reference gold standard.

Materials and methods

Simulated PET studies

We generated a simulated series of [^{15}O]-H_2O PET studies, each one consisting of three baseline [$\boldsymbol{I}_{Bi}(x,y,z)$; i = 1,2,3] and three activation [$\boldsymbol{I}_{Ai}(x,y,z)$; i = 1,2,3] scans (matrix size of 128 × 128 × 55 and voxel size of 1.8 × 1.8 × 3.0 mm), following a procedure similar to the one proposed by Davatzikos et al. (2001). Hyperactivation in the thalamic region was simulated increasing the intensity level of the region by 2%, 5%, 10%, 15%, and 20%.

For the simulation of baseline [^{15}O]-H_2O PET scans, we started from a single 3-D magnetic resonance image (MRI) of a healthy subject (T1-weighted 3D gradient echo sequence, flip angle = 30°, TR = 15.4 ms, TE = 4.6 ms; matrix size of 256 × 256 × 110 and voxel size of 0.9 × 0.9 × 1.5 mm). An experienced radiologist manually set to zero extra-cranial voxels (Fig. 1a). Using a thoroughly validated automatic method (Ashburner and Friston, 2000), we segmented this edited image into grey matter (GM), white matter (WM), and cerebral spinal fluid (CSF). The radiologist checked and corrected, if necessary, any inconsistency of the automatic segmentation. On the basis of the segmentation mask obtained, relative gray level intensities of 100:25:2 were assigned to GM, WM, and CSF, respectively (Fig. 1b) (Davatzikos et al., 2001). Then, we filtered the image volume with a smoothing Gaussian kernel (FWHM = 8 × 8 × 6 mm) to simulate the point spread function of the PET camera. Each slice of this smoothed image was projected at 128 angles and decimated at 2:1. The global count level of the entire volume was set to 5×10^6. Poisson noise was added to each voxel, with a standard deviation equal to the voxel intensity value. Finally, we applied the inverse Radon transform to the volume image using a back-projection algorithm with a ramp filter multiplied by a Hann window (Fig. 1c). As a result of this process, we obtained a realistic phantom image of a [^{15}O]-H_2O PET scan in baseline condition.

For generating the activation [^{15}O]-H_2O PET scans, we used the same MRI image. An expert radiologist segmented the thalamus manually (Fig. 1d) and its intensity value was increased by factors of 2%, 5%, 10%, 15%, and 20% before applying the PET simulation procedure (Fig. 1e). All the baseline and activation scans were normalized in intensity with proportional scaling, thus forcing all of them to have the same mean intensity value.

Selection of the wavelet base

The choice of an appropriate wavelet base should be aimed towards an efficient representation of the signal in the wavelet domain for the subsequent statistical analysis, considering the following properties (Ruttimann et al., 1998): (1) any orthogonal transformation preserves white noise distribution in the wavelet domain; (2) symmetric wavelets do not introduce phase distortion in the decomposition and consequently permit a more reliable signal localization in the wavelet domain; (3) a wavelet with a higher number of vanishing moments obtains better signal decorrelation in the wavelet domain; and (4) a wavelet with small support size (number of filter wavelet coefficients) obtains a better localization of the signal in the spatial domain.

However, the support size of the wavelet increases with its number of vanishing moments, which makes it necessary to establish a trade-off between data decorrelation and spatial localization (Mallat, 1999). In the light of the theoretical properties mentioned above, and also considering the results reported in a previous study (Desco et al., 2001), we selected the *symmlets* filters with four vanishing moments. *Symmlets* are separable orthogonal wavelets bases, almost symmetrical and with the minimum support size associated to a given number of vanishing moments (Mallat, 1999).