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Statistical analysis of brain tissue images in the wavelet domain: Wavelet-based morphometry

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ABSTRACT

Wavelet-based methods have been developed for statistical analysis of functional MRI and PET data, where the wavelet transformation is employed as a tool for efficient signal representation. A number of studies using these approaches have reported better estimation capabilities, in terms of increased sensitivity and specificity, than the standard statistical analyses in the spatial domain. In line with these previous studies, the present report proposes a statistical analysis in the wavelet domain for the estimation of inter-group differences from structural MRI data. The procedure, called wavelet-based morphometry (WBM), was implemented under a voxel-based morphometry (VBM) style analysis. It was evaluated by comparing the gray-matter images of a group of 32 healthy subjects whose images were artificially altered to induce thinning of the cortex, with a different group of 32 healthy subjects whose images were unaltered. In order to quantify the performance of the reconstruction from a practical perspective, the same comparison was also conducted with standard VBM using SPM's Gaussian random fields and FSL's cluster-based statistics, family-wise error corrected, for datasets spatially-normalized via two different registration methods (i.e., SyN and FNIRT). The effect of using different amounts of smoothing, Battle–Lemarié filters and resolution levels in the wavelet transform was also investigated. Results support the proposed approach as a different and promising methodology to assess the structural morphometric differences between different populations of subjects.

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Introduction

Voxel-based morphometry (VBM) is a whole-brain technique for characterizing regional cerebral volume differences from magnetic resonance imaging (MRI) data (Ashburner and Friston, 2000). In recent years, VBM has been useful in characterizing subtle changes in brain structure in a variety of diseases associated with neurological and psychiatry dysfunction (Mechelli et al., 2005) such as schizophrenia (Bora et al., 2011; Pomarol-Clotet et al., 2010; Radua et al., 2012), bipolar disorders (Selvaraj et al., 2012), autism (Radua et al., 2011), anxiety disorders (Radua et al., 2010), attention deficit hyperactivity disorder (Nakao et al., 2011), obsessive–compulsive disorder (Radua and Mataix-Cols, 2009), temporal lobe epilepsy (Keller and Roberts, 2008), Parkinson's disease (Beyer et al., 2007), Huntington's disease (Hobbs et al., 2010), developmental and congenital disorders (Garrido et al., 2009), Klinefelter's syndrome (Bryant et al., 2011), progressive supranuclear palsy (Price et al., 2004), Down's syndrome (Teipel et al., 2004), herpes simplex encephalitis (Gitelman et al., 2001), progressive aphasia and Alzheimer's disease (Zahn et al., 2005), to cite a few. The technique has been also used with healthy subjects to investigate the impact of learning and practice on brain structures (Maguire et al., 2003; Sluming et al., 2002), as well as the impact of aging (Hutton et al., 2009). The number of publications using VBM has increased considerably. In the last ten years, more than 1900 publications were entered into a major database of medical literature, PubMed, under the keyword "Voxel-based morphometry".

At its simplest, VBM involves a voxel-wise comparison (i.e., statistical test) of the local probability of gray-matter tissue images between two groups of subjects. The statistical test is computed by means of a General

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Linear Model (GLM) that is able to correct for the effects of no interest. The spatial location of the inter-group differences is identified by applying an appropriate threshold to the resulting statistical map. The selection of this threshold is challenging because of the large number of brain voxels under investigation (e.g., typically $N \approx 450{,}000$ for a voxel resolution of $1.5 \times 1.5 \times 1.5$ mm^3, $N \approx 200{,}000$ for a voxel resolution of $2 \times 2 \times 2$ mm^3), and the inevitable spatial correlation among voxels caused by the acquisition process and the spatial pre-processing of data. Use of uncorrected p-values would lead to high false positive rates, while Bonferroni correction (Bonferroni, 1936) for multiple comparisons would require such low p-values that only very strong effects could be detected.

A widely adopted strategy to maximize sensitivity while controlling for false positive rate, is to identify cluster patterns of significant inter-group differences rather than identify isolated significant voxels (Bullmore et al., 1999; Hayasaka and Nichols, 2003). These cluster-based thresholding techniques make use of spatial neighborhood information to boost belief in extended areas of statistical difference. However, they are limited by the need to define ad-hoc initial parameters in the algorithm such as the initial cluster-forming threshold, which has been reported to have a large impact on the results (Smith and Nichols, 2009). More importantly, the theory behind this type of analysis is based on the assumption that the smoothness of the residuals is spatially invariant throughout the brain. However, this is unlikely to be the case in real studies due to the highly non-stationary nature of the underlying brain anatomy (Mechelli et al., 2005). This non-stationary in smoothness may lead to the inexact identification of clusters of significant differences. For instance, by chance alone, clusters of large size will occur in regions where images are very smooth and small size clusters will occur in regions where the images are very rough. In consequence, cluster-based thresholding is biased towards detecting findings in some regions while not detecting findings in others (Good et al., 2001; Mechelli et al., 2005).

This problem has been addressed via the Random Field Theory (RFT) (Worsley and Friston, 1995). In RFT the final threshold can be obtained without penalizing by the extent statistic related to the size of the clusters (Mechelli et al., 2005). However, the random field approximation commonly used in Statistical Parametric Mapping (SPM) analysis (Ashburner, 2009) hinges on strict assumptions about the distribution of the data that may not always be applicable to VBM (Silver et al., 2011). It assumes that the error fields are a reasonable lattice approximation to an underlying continuous random process with a multivariate Gaussian distribution, which may not be the case in small and moderate samples where the error fields will not be very smooth. In practice, to promote the validity of this assumption, the data is pre-smoothed with a Gaussian filter with fixed size. This operation improves the signal-to-noise ratio and the compliance with the referred Gaussian distributional assumption, but at the cost of a loss of resolution and an increase in the spatial correlation among voxels. By smoothing the images with a filter of fixed size, the probability of detecting "signals" of that particular size is maximized (Mutihac, 2008). The explanation for this comes from the matched filter theorem in signal processing, which states that a signal added to white noise is best detected by smoothing with a filter with the same size and shape as the signal. Therefore, the strategy of using a Gaussian kernel with fixed size may not be optimal for situations where the spatial extent of the local differences in brain morphometry is different in different parts of the brain. Furthermore, it is not easy to a priori choose the optimal smoothing level because the size and shape of the signal of interest are not known in advance. Several methodologies have become available to detect signals at different smoothing levels (Poline and Mazoyer, 1994a,b; Shafie et al., 2003; Worsley, 2001; Worsley et al., 1996). These approaches fall within the class of multi-resolution methods, in which the images are first smoothed with kernels with different sizes, and the statistical analysis is carried out in the resulting set of filtered images. The main shortcoming of this style of analysis, however, is the potential reduction of specificity caused by the increase in the number of statistical tests, which is a consequence of the non-orthogonality and redundancy of the decompositions (Desco et al., 2005).

Another multi-resolution technique is based on the wavelet transform. Concisely, the discrete orthogonal wavelet transform (DOWT) projects an image onto a set of basis functions without alterations. It transforms estimators in one domain into estimators in the other domain, with isometry of risks (Donoho and Johnstone, 1995). DOWT has a property of data compaction; the energy of a signal tends to be concentrated in a few large wavelet coefficients while the energy of the noise is more evenly distributed across a large number of much smaller coefficients (Gençay et al., 2002). Some interesting links between the Gaussian smoothing in SPM and the wavelet decomposition have been demonstrated (Fadili and Bullmore, 2004; Van De Ville et al., 2003).

The DOWT has the ability to decompose the images at different spatial-scale sub-bands and to concentrate the information from high spatial correlated neighboring voxels into a few number of (approximately decorrelated) wavelet coefficients in an adaptive manner (i.e., without a priori assumptions about the size and shape of the lesions and the underlying unknown smoothness). This style of analysis allows one to take advantage of the spatial correlations in the data (Desco et al., 2001). The application of univariate tests over a small number of large wavelet coefficients has been advocated as a way of reducing the search space or the number of tests required for whole brain mapping (Desco et al., 2001; Fadili and Bullmore, 2004). Some functional imaging studies (e.g., fMRI and PET) in the wavelet domain have reported better estimation capabilities, in terms of increased sensitivity (Brammer, 1998; Ruttimann et al., 1998; Unser et al., 1995) and specificity (Desco et al., 2005) than the standard statistical analyses in the spatial domain. However, it should be pointed out that the statistical inference based on DOWT has its own limitations. Importantly, it is not yet clear how to fully transfer the estimated significant differences from the wavelet to the spatial domain (Van De Ville et al., 2007).

The first report in fMRI analysis working in the wavelet domain was presented in Ruttimann et al. (1998), in which an omnibus χ^2 test on all coefficients in each level of the DOWT was used to identify which levels represented signals. In a second step, only the coefficients in those selected levels were individually tested using a Bonferroni-corrected threshold (Bonferroni, 1936). Subsequently, different strategies have been reported to select the optimal subset of wavelets coefficients, including a procedure based on the generalized degrees of freedom measure (Shen et al., 2002) and a Bayesian bivariate shrinkage algorithm (Sendur and Selesnick, 2002). Similarly, the significance threshold has been computed using different techniques such as the false discovery rate (FDR) procedure (Fadili and Bullmore, 2004; Shen et al., 2002), re-sampling techniques (Sendur et al., 2007) and Bayesian regression (Turkheimer et al., 2006). As was indicated in Bullmore et al. (2004), the working philosophy behind some of these approaches can be summarized as follows:

(1) Calculate the wavelet coefficients of the image.
(2) Use a wavelet shrinkage algorithm to eliminate the majority of noisy coefficients, retaining a reduced number of coefficients.
(3) Apply a standard multiple hypothesis testing algorithm, to test the reduced subset of coefficients.
(4) Estimate the signal by the inverse wavelet transform using only those coefficients which survived step (3).

In line with these previous studies, the present report proposes the implementation of a methodology in the wavelet domain for the statistical estimation of inter-group differences from brain gray-matter magnetic resonance images. The procedure is called wavelet-based morphometry (WBM), in analogy with the well-known VBM method (Ashburner and Friston, 2000).

The methodology is evaluated by comparing the gray-matter images obtained from two different groups of 32 healthy subjects. Images corresponding to one group have been artificially altered in order to induce

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