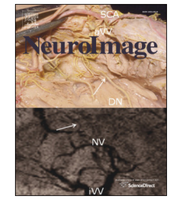
YNIMG-12292; No. of pages: 15; 4C: 9, 4, 5, 6, 7, 8, 11

NeuroImage xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg



Anatomically-adapted graph wavelets for improved group-level fMRI activation mapping

Hamid Behjat [a,*], Nora Leonardi [b], Leif Sörnmo [a], Dimitri Van De Ville [b,c]

[a] Biomedical Signal Processing Group, Department of Biomedical Engineering, Lund University, Lund, Sweden
[b] Institute of Bioengineering, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland
[c] Department of Radiology and Medical Informatics, University of Geneva, Geneva, Switzerland

ARTICLE INFO

Article history:
Received 30 January 2015
Accepted 2 June 2015
Available online xxxx

Keywords:
Statistical parametric mapping (SPM)
Functional MRI
Spectral graph theory
Graph wavelets
Wavelet thresholding

ABSTRACT

A graph based framework for fMRI brain activation mapping is presented. The approach exploits the spectral graph wavelet transform (SGWT) for the purpose of defining an advanced multi-resolutional spatial transformation for fMRI data. The framework extends wavelet based SPM (WSPM), which is an alternative to the conventional approach of statistical parametric mapping (SPM), and is developed specifically for group-level analysis. We present a novel procedure for constructing brain graphs, with subgraphs that separately encode the structural connectivity of the cerebral and cerebellar gray matter (GM), and address the inter-subject GM variability by the use of template GM representations. Graph wavelets tailored to the convoluted boundaries of GM are then constructed as a means to implement a GM-based spatial transformation on fMRI data. The proposed approach is evaluated using real as well as semi-synthetic multi-subject data. Compared to SPM and WSPM using classical wavelets, the proposed approach shows superior type-I error control. The results on real data suggest a higher detection sensitivity as well as the capability to capture subtle, connected patterns of brain activity.

Introduction

Functional magnetic resonance imaging (fMRI) is a key modality to localize brain activity based on the blood-oxygen-level-dependent (BOLD) signal (Ogawa et al., 1993). The most widely used approach in fMRI activation mapping is a mass univariate hypothesis-driven method that is implemented in many software packages such as statistical parametric mapping (SPM) (Frackowiak et al., 1997; Friston et al., 1994). Using regressors defined by the experimental paradigm, a general linear model (GLM) is fitted to the time course of every voxel of the brain, followed by a statistical test of a linear combination of the fitted parameters, leading to a statistical map indicating evidence for stimulus-related brain activity. Since using a Bonferroni correction is too conservative, SPM deals with the multiple comparison problem based on Gaussian random field theory (GRFT) (Poline et al., 1997). A key characteristic of GRFT is that it requires initial smoothing of the functional data by a fixed Gaussian filter. This pre-filtering not only is required to control the spatial smoothness of the data to comply with GRFT, but it also serves as a means to improve the signal-to-noise ratio (SNR) by virtue of the matched filter argument. However, such linear isotropic filtering comes at the expense of a loss in fine spatial details of the underlying activity.

As an alternative to GRFT, spatial wavelet transforms have been proposed as a means to non-linearly denoise functional data within frameworks of both classical inference (e.g., Aston et al., 2005; Ruttimann et al., 1998; Soleymani et al., 2009; Van De Ville et al., 2004, 2007; Wink and Roerdink, 2004) and Bayesian inference (e.g., Flandin and Penny, 2007; Sanyal and Ferreira, 2012). Since brain activity is highly localized in space (Bullmore et al., 2004), the property of sparse signal representation in the wavelet domain makes it possible to encode a cluster of active voxels with only a few coefficients. Such representation enhances the SNR as the background noise remains equally distributed among the wavelet coefficients, and thus, coefficient-wise statistical testing provides a higher sensitivity than voxel-wise testing. Wavelet-based SPM (WSPM) (Van De Ville et al., 2007) has the unique feature of treating thresholding within the wavelet domain as a denoising step only, and the statistical testing is deferred to a second thresholding on the reconstructed map within the spatial domain.

Accounting for intra-subject gray matter structure

Gaussian filters as well as standard wavelets such as those deployed by WSPM share several basic properties: they are (i) isotropic in structure, (ii) defined within regular Euclidean spaces (either a square in 2-D space or a cube in 3-D space) and (iii) stationary and quasi shift-invariant, meaning that their structure does not vary as applied to different regions within a volume. To various extents, these properties are opposed to the expected geometrical properties of the activation

* Corresponding author at: Department of Biomedical Engineering, Lund University, Box 118, 221 00 Lund, Sweden.
E-mail address: hamid.behjat@bme.lth.se (H. Behjat).

http://dx.doi.org/10.1016/j.neuroimage.2015.06.010
1053-8119/

pattern. Since the gray matter (GM), within which the BOLD response is expected, has a convoluted structure, isotropically shaped activation patterns that cross boundaries of GM are unlikely. Moreover, due to the differences in the structure of the sulci and gyri across the brain, *intra-subject* variability of GM geometry is widely observed (Fischl et al., 2002; Riviere et al., 2002). Thus, it is essential to construct filters that adapt to the intricately convoluted GM domain rather than assuming the spatial characteristics of the underlying signal independent of its location. As a step in this direction, surface-based approaches have been proposed that restrict the analysis to the cortex by using reconstructions of the cortical surface. One such approach is the anatomically-informed basis function (AIBF) method proposed in Kiebel et al. (2000) and Kiebel and Friston (2002), where a forward model is determined for solving the inverse problem of explaining the distribution of the functional data using circular Gaussian basis functions defined on the cortical surface. In other approaches, here collectively referred to as cortical surface mapping (CSM), an interpolation scheme is used to map the functional data to the extracted cortical surface, followed by iteratively smoothing the data on the surface using different procedures such as diffusion smoothing (Andrade et al., 2001), heat kernel smoothing (Chung et al., 2005; Hagler et al., 2006) and spline smoothing (Qiu et al., 2006). Nevertheless, the problem of loss in spatial accuracy remains in CSM due to the irreversible smoothing. Aside from that, the mapping of volumetric data to a surface is challenging due to the variability in cortical thickness.

In the present paper, we introduce an alternative approach where we define a *volumetric* GM domain with the help of graph theory, where the graph vertices correspond to irregularly sampled points of the 3-D Euclidean space. Numerous neuroimaging applications have benefited from brain data being modeled as graphs and graph signals (Bullmore and Sporns, 2009; Richiardi et al., 2013). Here, we propose constructing brain graphs that encode local structural connectivity of GM *geometry* (irregular domain in 3-D), as opposed to the surface-based approaches which mainly incorporate cortical *topology* (2-D surface that is folded). Functional data can then be modeled as a scalar function (signal) defined on the vertices, and graph filters that diffuse only within the GM volume can be constructed. As such, the performance in fMRI brain activation mapping can be improved by attenuating the effect of non-signal components that originate from outside the GM.

With the increased interest in graph approaches to data analysis, a great amount of research has been devoted to generalizing signal processing operations to the graph setting (Shuman et al., 2013). This includes wavelet transforms, with the spectral graph wavelet transform (SGWT) proposed in Hammond et al. (2011) being an example. To prevent linear irreversible smoothing and to perform analysis at multiple scales, we propose the tight-frame SGWT (Leonardi and Van De Ville, 2013) to construct GM-adapted wavelets that are utilized to implement an advanced spatial transformation on fMRI data, integrated within the statistical analysis of the WSPM framework.

Accounting for inter-subject GM variability

Group-level fMRI activation mapping is further complicated by the *inter-subject* GM variability that is important to address. This variability renders the need for normalization of functional data to a template space, which, in turn, leads to better domain matching across subjects and improved statistical power as activations better overlap. Due to the observed difference in the extent of geometrical GM variety in the cerebrum and the cerebellum across subjects, it is advantageous to define cerebral and cerebellar template spaces separately.

The geometry of the cerebral cortex is not consistent across subjects. Although there are similarities in terms of the main fissures, the GM foldings are very inconsistent across individuals even in standard populations (Mangin et al., 2004; Riviere et al., 2002), see Fig. 1. The most commonly used cortical templates are based on either the anatomy of a single subject (Tzourio-Mazoyer et al., 2002) or the ensemble average over many subjects, such as the ICBM-152 (Evans et al., 1993) that defines the Montreal Neurological Institute (MNI) space. Such templates can be viewed as two extremes in GM representation: single subject templates take no account for inter-subject variability, and the group averaged templates, such as the ICBM-152, lack fine anatomical detail of the cerebral GM, which makes both categories unsuitable for our purpose. To address this problem, study specific template construction methods such as DARTEL (Ashburner, 2007) are of great benefit. The fast diffeomorphic image registration scheme proposed by Ashburner is among the best performing (Klein et al., 2009) and can produce a detailed group-averaged template GM through iterative, nonlinear warping of the segmented GM of a set of subjects.

The structural variability within the cerebellum is lower than in the cerebral cortex, since the cerebellar structure is relatively consistent across individuals in terms of the number and shape of its fissures (see Fig. 1). This observation has made it possible to create atlas templates of the cerebellum that prevent a loss in spatial accuracy of the anatomical detail. The spatially unbiased infra-tentorial (SUIT) cerebellum template (Diedrichsen, 2006) is the most accurate cerebellar template available to date. Compared to the ICBM 152 template (Evans et al., 1993) that is designed through averaging of T1 scans from 152 different subjects, SUIT is constructed from scans of 20 subjects, and at the same time, has the unique feature of being spatially unbiased; that is, the location of each of the structures is equal to its expected location in the MNI space across subjects (Diedrichsen, 2006).

Therefore, we propose the use of the SUIT atlas as the basis for defining a canonical cerebellar subgraph and the DARTEL for constructing study-dependent template cerebral subgraphs. A full GM-adapted brain graph is then defined by merging the two subgraphs.

Overview

The paper is organized as follows. In the Transform-based SPM (tSPM) section, WSPM is reviewed by generalizing the framework such that it 1) incorporates any linear spatial transform and 2) is set out for group-level analysis. In the Spectral graph wavelet transform (SGWT) section, we review the necessary concepts from graph theory and wavelet design. In the Spectral graph wavelet based SPM ($tSPM^{sgwt}$) section, we introduce the construction of GM-adapted graphs and wavelets, the required preprocessing steps and contrast mappings. In the Datasets section, we introduce a real dataset as well as the design

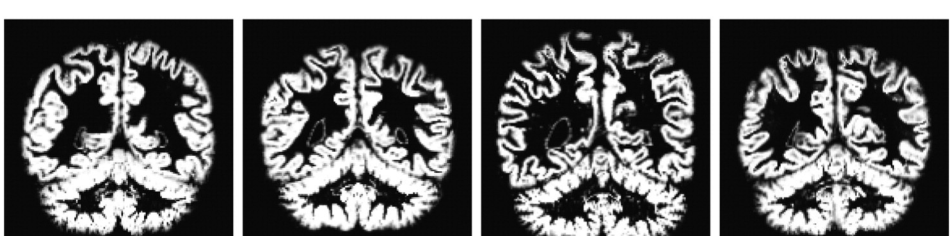


Fig. 1. Segmented gray matter of four individuals from an experimental dataset (see Experimental dataset section) illustrating the inter-subject variability. The variability is less significant in the cerebellum, as opposed to the cerebrum where the pattern of folding varies greatly from one individual to the other.

Please cite this article as: Behjat, H., et al., Anatomically-adapted graph wavelets for improved group-level fMRI activation mapping, NeuroImage (2015), http://dx.doi.org/10.1016/j.neuroimage.2015.06.010