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Optimally-Discriminative Voxel-Based Morphometry significantly increases the ability to detect group differences in schizophrenia, mild cognitive impairment, and Alzheimer's disease

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ABSTRACT

Optimally-Discriminative Voxel-Based Analysis (ODVBA) (Zhang and Davatzikos, 2011) is a recently-developed and validated framework of voxel-based group analysis, which transcends limitations of traditional Gaussian smoothing in the forms of analysis such as the General Linear Model (GLM). ODVBA estimates the optimal non-stationary and anisotropic filtering of the data prior to statistical analyses to maximize the ability to detect group differences. In this paper, we extensively evaluate ODVBA to three sets of previously published data from studies in schizophrenia, mild cognitive impairment, and Alzheimer's disease, and evaluate the regions of structural difference identified by ODVBA versus standard Gaussian smoothing and other related methods. The experimental results suggest that ODVBA is considerably more sensitive in detecting group differences, presumably because of its ability to adapt the regional filtering to the underlying extent and shape of a group difference, thereby maximizing the ability to detect such difference. Although there is no gold standard in these clinical studies, ODVBA demonstrated highest significance in group differences within the identified voxels. In terms of spatial extent of detected area, agreement of anatomical boundary, and classification, it performed better than other tested voxel-based methods and competitively with the cluster enhancing methods.

Introduction

Voxel-Based Morphometry (VBM) (Ashburner and Friston, 2000; Davatzikos et al., 2001a; Good et al., 2001), which analyzes the whole brain in an automated manner, has been developed to characterize brain changes on structural Magnetic Resonance Imaging (MRI), without defining labor-intensive and potentially-biased regions of interest (ROIs). To date, VBM has been widely applied in investigating different types of brain disorders, including schizophrenia, mild cognitive impairment (MCI), and Alzheimer's disease (AD). However, in conventional VBM methods which implement the General Linear Model (GLM) (Friston et al., 1994), integrating imaging signals from a region using Gaussian pre-smoothing proves challenging due to the difficulty in selecting the appropriate kernel size (Jones et al., 2005; Zhang et al., 2008). If the kernel is too small for the task, statistical power is lost and large numbers of false negatives are bound to confound the analysis; if the kernel is too large, the extensive smoothing will reduce both sensitivity and spatial resolution, typically blurring unrelated structural regions and leading to false positive conclusions about the origin of the structural abnormalities.

Most importantly, Gaussian smoothing will always lack the spatial adaptivity necessary to optimally match image filtering with an underlying (unknown a priori) region of interest. Some spatially adaptive methods have been developed to address this drawback. Davatzikos et al. (2001b) developed a spatially adaptive filter whose shape changes with the assistance of a pre-defined atlas (also known as ROIs). This method would be effective if true group abnormalities coincide with these pre-defined anatomical boundaries, but this is not always the case. More generally in image processing, full data-driven spatially adaptive methods which do not require ROIs have been pursued in various contexts. Perona and Malik (1990) developed the Anisotropic Diffusion scheme which removes noise using gradient information while preserving object boundaries. This method was subsequently extended (Gerig et al., 1992) into MRI applications. Polzehl and Spokoiny (2000, 2006) proposed a local density estimation-based method for adaptive weights smoothing, named Propagation–Separation (PS), which preserves spatial extent and shapes of the activated regions in images having large homogeneous areas and sharp discontinuities. This method has subsequently been applied to fMRI activation detection (Tabelow et al., 2006). A wavelet-based denoising method was proposed by Pizurica et al.

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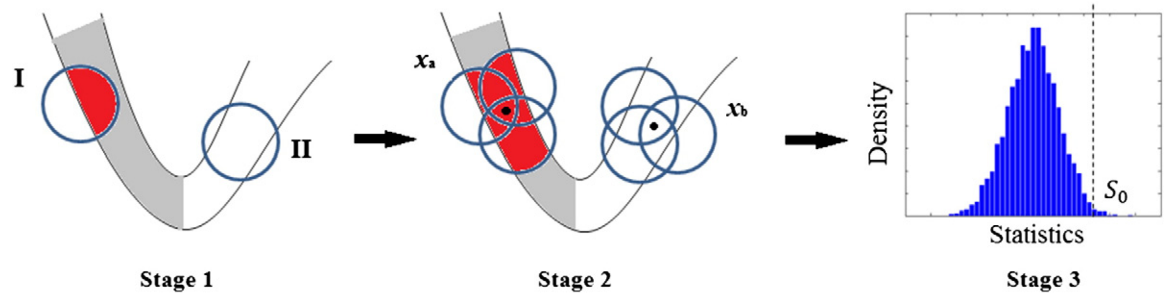

Fig. 1. Illustration of the flowchart of ODVBA. ODVBA works in three stages including 1) regional nonnegative discriminative projection, 2) determining each voxel's statistic, and 3) permutation tests. The gray color in Stage 1 and Stage 2 indicates the area with underlying structural changes and the red color indicates the highlighted area via regional discriminative analysis in ODVBA.

(2003) to adaptively preserve useful image features against the degree of noise reduction by using a wavelet domain indicator of local spatial activity. However, all the above methods work on each single subject separately; that is, they do not take into account the population information, i.e., discriminative information, in a two-group comparison analysis. Hence, the selected filter is adaptive to each subject's morphological or functional characteristics, but may not be optimal for the purpose of performing group comparisons.

Optimally-Discriminative Voxel-Based Analysis (ODVBA) (Zhang and Davatzikos, 2011) is a recently-developed framework of group analysis utilizing a new spatially adaptive scheme in order to determine group differences with maximal sensitivity. A regional discriminative analysis, with non-negativity constraints on the respective weight coefficients, is conducted in a spatial neighborhood around each voxel to determine the optimal coefficients that best highlight the difference between two groups in that neighborhood. The components of the resultant discriminatory direction can be viewed as weights of a local spatial filter, which is optimally designed to highlight group differences. The weights determined for a given voxel from all the regional analyses it belongs to are combined into a map representing statistically significant voxel-wise group differences, using permutation tests. Adaptive smoothing is inherent in ODVBA, and is similar in concept to the nonstationarity adjustment in smoothness (Hayasaka and Nichols, 2003; Hayasaka et al, 2004; Salimi-Khorshidi et al, 2009) utilized in cluster-level statistical inference studies. ODVBA has been evaluated (Zhang and Davatzikos, 2011) by using both simulated and real data and has been found to precisely identify the shape and location of group differences with high sensitivity and specificity.

In this paper, we apply ODVBA to three previously published studies in which the traditional Gaussian smoothing plus GLM was used. In addition, we compare ODVBA to not only GLM but also two other spatially adaptive smoothing methods: PS (Polzehl and Spokoiny, 2000, 2006) and wavelet denoising (WL) (Pizurica et al., 2003), and two versions of the newly-proposed cluster enhancing method, Threshold-Free Cluster Enhancement (TFCE): the original GLM-based TFCE (G-TFCE) (Smith and Nichols, 2009), and an ODVBA-based TFCE (O-TFCE). The three published studies used for this group comparison include 1) a sample of well-characterized patients with schizophrenia and matched controls (Davatzikos et al., 2005), 2) early-stage MCI patients and the normal controls (Davatzikos et al., 2008), and 3) MCI patients who convert to AD and MCI patients who remain stable (Misra et al., 2009).

Methods

Participants and imaging protocol

The details on participants' information and MRI acquisition can be found in Davatzikos et al. (2005, 2008) and Misra et al. (2009). Here, we only provide the basic information of the subjects.

Dataset1: Sixty-nine patients (46 men and 23 women) (Davatzikos et al., 2005) with schizophrenia and seventy-nine controls (41 men 38 women) were involved in the study.

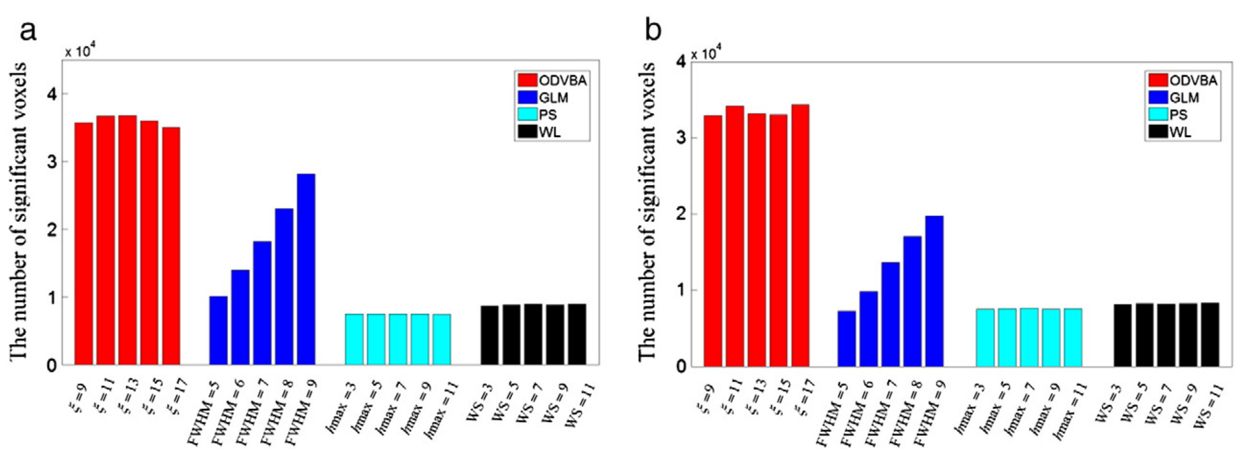

Fig. 2. The number of significant voxels versus smoothing kernel sizes. (a) The results are obtained from group comparison between the schizophrenia patients and the normal controls in *Dataset1* where the voxels are counted if the unadjusted p value < 0.001; (b) The results are obtained from group comparison between the MCI-to-AD converters and the non-converters in *Dataset3* where the voxels are counted if the unadjusted p value < 0.005. The results from *Dataset2* are not included since GLM, PS, and WL did not have detections for most of kernel sizes, with a reasonable low p value threshold.