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An automatic framework for quantitative validation of voxel based morphometry measures of anatomical brain asymmetry

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ABSTRACT

The study of anatomical brain asymmetries has been a topic of great interest in the neuroimaging community in the past decades. However, the accuracy of brain asymmetry measurements has been rarely investigated. In this study, we propose a fully automatic methodology for the quantitative validation of brain tissue asymmetries as measured by Voxel Based Morphometry (VBM) from structural magnetic resonance (MR) images. Starting from a real MR image, the methodology generates simulated 3D MR images with a known and realistic pattern of inter-hemispheric asymmetry that models the left-occipital right-frontal *petalia* of a normal brain and the related rightward bending of the inter-hemispheric fissure. As an example, we generated a dataset of 64 simulated MR images and applied this dataset for the quantitative validation of optimized VBM measures of asymmetries in brain tissue composition. Our results suggested that VBM analysis strongly depended on the spatial normalization of the individual brain images, the selected template space, and the amount of spatial smoothing applied. The most accurate asymmetry detections were achieved by 9-degrees of freedom registration to the symmetrical template space with 4 to 8 mm spatial smoothing.

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Introduction

The human brain is anatomically asymmetrical (Toga and Thompson, 2003). During the last decades, thanks to the increased availability of high resolution structural three dimensional (3D) MR images, there has been a considerable number of in vivo studies investigating the anatomical inter-hemispheric brain asymmetry and its links to age (Kovalev et al., 2003), gender (Kovalev et al., 2003), mental diseases (Pepe et al., 2013; Shenton et al., 2001), and asymmetrical behavioral traits, such as hand and foot preference (Amunts et al., 2000; Beaton, 1997; LeMay, 1977; Moffat et al., 1998), auditory perception (Keenan et al., 2001), and language production (Amunts et al., 1999; Binder, 2000; Dapretto and Bookheimer, 1999; Foundas et al., 1996; Geschwind and Galaburda, 1985).

The earliest in vivo studies of anatomical brain asymmetries from 3D MR images mainly focused on the manual delineation of a specific region-of-interest (ROI) and the analysis of differences in its size across hemispheres. These studies were limited by the burden and the subjectivity of manual ROI delineation and by the use of local and poorly sensitive traditional measures such as ROI's length. More recently, automatic morphometric techniques have been applied to study structural brain asymmetries (Good et al., 2001b; Hopkins et al., 2008; Luders et al., 2004; Pepe et al., 2013). Of particular relevance among them here are the voxel-based morphometry (VBM) (Ashburner and Friston, 2000; Wright et al., 1995) and other VBM techniques (Good et al., 2001a, 2001b; Luders et al., 2004; Mechelli et al., 2005; Sowell et al., 1999; Watkins et al., 2001).

In a VBM based study of neuroanatomical asymmetries, subjects' brain MR images are spatially normalized into a common reference space. Spatially normalized brain images are then partitioned into gray matter (GM), white matter (WM), and cerebro-spinal fluid (CSF) tissue classes, and the resulting brain tissue images are reflected with respect to their planes of symmetry. Next, measures of voxel-level asymmetry are derived from the differences between the original and left–right flipped brain tissue images. Voxel-wise hypothesis tests followed by multiple comparison correction are finally performed on smoothed (tissue-specific) difference images (maps) to establish the statistical significance of asymmetry measures and presented in the form of statistical parametric maps.

VBM analyses of brain asymmetries of normal controls have replicated previously well established postmortem and in vivo brain asymmetries (such as the left-occipital right-frontal brain *petalia* and the *planum temporale* asymmetry (Good et al., 2001b; Watkins et al., 2001)) as well as previously unreported asymmetry findings (such as a pattern of inter-hemispheric asymmetry in the insular cortex found

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in Watkins et al. (2001)). Even though there are encouraging VBM findings in partial agreement with the neuroanatomical literature (Good et al., 2002; Luders et al., 2004; Sowell et al., 1999) and VBM findings on brain asymmetry confirming existent knowledge on certain disease states and normal conditions (Luders et al., 2004), inconsistent findings have also been reported. For example, Heschl's gyrus asymmetry was observed in the VBM study of Good et al. (2001b) but not in Watkins et al. (2001). Interestingly, Heschl's gyrus and *planum temporale* asymmetries appeared not to be correlated with the hemispheric language dominance in Dorsaint-Pierre et al. (2006) and Keller et al. (2011). See Toga and Thompson (2003) or Jancke and Steinmetz (2003) for a review on brain asymmetry findings.

A crucial intrinsic assumption of VBM methods is that spatial normalization establishes the anatomical correspondence of brain structures at voxel-level while maintaining individual anatomical differences, and that voxel-level statistics can be used to verify specific hypotheses on the data (Good et al., 2001a,b; Salmond et al., 2002). The validity of VBM-based inferences is affected by spatial normalization inaccuracies (Bookstein, 2001; Davatzikos, 2004; Mechelli et al., 2005; Senjem et al., 2005), the choice of the spatial normalization template and spatial normalization method (Good et al., 2001b; Mechelli et al., 2005; Shen et al., 2007), and by the amount of spatial smoothing applied (Good et al., 2001b; Mechelli et al., 2005). Related to this, the use of customized (tissue type and population specific) templates for spatial normalization, known as optimized VBM, is expected to produce more accurate VBM results (Good et al., 2001b; Mechelli et al., 2005; Shen et al., 2007). Although less obvious and less investigated in the literature, we hypothesize that normal patterns of brain asymmetry in controls might also cause mis-matches in asymmetrical brain regions that can thus propagate to other parts of the brain.

Despite its wide use, the validation of VBM is still largely lacking and partially inconclusive due to the difficulties involved in the generation of large datasets of simulated images with a known and realistic inter-hemispheric asymmetry pattern, as well as of ground truth for the validation of automatic morphometric methods. This is true for the VBM in general and specifically for applications of VBM to brain asymmetry studies.

We present here an automatic framework for the quantitative validation of VBM-based measurements of brain asymmetries via construction and analysis of simulated 3D MR images. The main contributions of this study can be summarized as follows.

(i) We propose and implement a method to generate simulated 3D MR images with a known pattern of inter-hemispheric asymmetry based on real MR images via parametric modeling of brain asymmetry. The employed parametric model mimics two of the most consistently reported macroscopic patterns of brain asymmetry in normal human brains, namely the left-occipital right-frontal *petalia* and the related rightward bending of the inter-hemispheric fissure, also referred to as brain torque or Yakovlevian torque.

(ii) We generate a ground truth image of brain asymmetry values using the aforementioned parametric model. This ground truth image can be used, in conjunction with the simulated dataset in (i), for the quantitative validation of methods for the analysis of brain shape asymmetry.

(iii) The choices of spatial normalization, template space, and spatial smoothing might affect the results of VBM analysis (Bookstein, 2001; Davatzikos, 2004; Good et al., 2001a,b; Salmond et al., 2002; Senjem et al., 2005; Shen et al., 2007). We evaluate these effects by performing VBM analysis of asymmetry for a simulated dataset of 64 images and comparing the VBM results to the ground truth values. To the best of our knowledge, there exists no other quantitative validation study evaluating the accuracy of VBM measures of brain asymmetries. More generally, the literature regarding VBM validation studies is scarce and mainly focused on qualitative observations in clinical conditions (Keller et al., 2004; Senjem et al., 2005). As Senjem et al. (2005) recognize, the qualitative visual comparison of VBM results to the previously reported pathology of a certain disease is not the ideal method for comparing various VBM image processing algorithms.

(iv) The dataset in (i), the ground truth in (ii), and the whole automatic framework in (i)–(iii) are to be made freely available to promote further quantitative studies aiming at the validation of morphometric methods for the analysis of neuroanatomical asymmetries. This is important, e.g., to evaluate the accuracy and robustness of novel and existing morphometric methods of brain asymmetry, and possibly to clarify contradicting findings on anatomical brain asymmetries in normal and clinical conditions.

Materials and methods

Participants, MR image acquisition and pre-processing

64 healthy right-handed subjects (16 males, 48 females) in the adult lifespan (aged from 18 to 93; mean age = 39.4 years; SD =18.8 years) were selected from the OASIS dataset, a larger and freely available sample which has been described in detail elsewhere (Marcus et al., 2007; http://www.oasis-brains.org). All participants were non-demented as assessed by clinical evaluations (Marcus et al., 2007) and by the Clinical Dementia Rating scale (Morris, 1993; Morris et al., 2001), and had no major gross anatomical abnormalities or known history of head trauma, stroke, use of psychoactive drugs, and neurological or psychiatric illness.

Enrolled subjects were imaged either 3 or 4 times within a single imaging session. Imaging was performed using a 1.5-T Vision scanner (Siemens, Erlangen, Germany) with a T1-weighted magnetization prepared rapid gradient-echo sequence (MP-RAGE) and the following image acquisition parameters: TR = 9.7 ms, TE = 4.0 ms, flip angle = 10°, TI = 20 ms, TD = 200 ms, matrix size = $128 \times 256 \times 256$ voxels, voxel sizes = $1.25 \times 1 \times 1$ mm^3.

To correct for motion artifacts and thus enhance the signal to noise ratio, co-registered images of the individual scans in the native acquisition space were averaged, interpolated to isotropic voxel sizes (matrix size = $160 \times 256 \times 256$ voxels, voxel size = $1 \times 1 \times 1$ mm^3), and provided for download by the OASIS distribution. These co-registered and averaged images were screened for artifacts and then used as the sample of this study.

Methods overview

This work introduces a novel and fully automatic framework for the quantitative validation of VBM and its applications for the analysis of inter-hemispheric asymmetries. First, based on each of the 64 brain MR images included in this study, we generated a simulated MR image with perfect inter-hemispheric anatomical symmetry modeling the extreme case of a brain with low or no inter-hemispheric asymmetry. Then, based on this simulated and symmetrical image, we generated a simulated MR image with a parametrically known pattern of inter-hemispheric asymmetry that mimicked the brain *petalia* and the Yakovlevian torque as often found in normal conditions. The workflow of dataset generation is presented in Fig. 1 and described in detail in the Synthetic dataset generation section. Second, an optimized VBM analysis of voxel-level inter-hemispheric asymmetries in brain tissue composition was performed, in both sets consisting of symmetrical and asymmetrical images (see an example in Fig. 3), and applied for the quantification of detected asymmetries compared with ground truth values, and its relations to the spatial normalization scheme, template space, and amount of smoothing used. The applied VBM analysis is presented in detail in the VBM analysis section and overview of it can be seen in Fig. 3. For the sake of brevity, we consider only GM asymmetries.

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