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NeuroImage

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NeuroImage 40 (2008) 68–76

Parallel transport in diffeomorphisms distinguishes the time-dependent pattern of hippocampal surface deformation due to healthy aging and the dementia of the Alzheimer's type

Anqi Qiu,[a,*] Laurent Younes,[b,e,f] Michael I. Miller,[b,f,g] and John G. Csernansky[c,d]

[a] *Division of Bioengineering, National University of Singapore, 7 Engineering Drive 1, Block E3A #04-15, Singapore 117574, Singapore*
[b] *Center for Imaging Science, Johns Hopkins University, Baltimore, MD 21218, USA*
[c] *Department of Psychiatry, Washington University School of Medicine, St. Louis, MO 63110, USA*
[d] *Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis MO 63110, USA*
[e] *Department of Applied Mathematics and Statistics, Johns Hopkins University, Baltimore, MD 21218, USA*
[f] *Institute for Computational Medicine, Johns Hopkins University, Baltimore, MD 21218, USA*
[g] *Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD 21218, USA*

Received 9 August 2007; revised 1 November 2007; accepted 29 November 2007
Avaialble online 8 December 2007

Hippocampal surface structure was assessed at twice 2 years apart in 26 nondemented subjects (CDR 0), in 18 subjects with early dementia of Alzheimer type (DAT, CDR 0.5), and in 9 subjects who converted from the nondemented (CDR 0) to the demented (CDR 0.5) state using magnetic resonance (MR) imaging. We used parallel transport in diffeomorphisms under the large deformation diffeomorphic metric mapping framework to translate within-subject deformation of the hippocampal surface as represented in the MR images between the two time points in a global template coordinate system. We then performed hypothesis testing on the longitudinal variation of hippocampal shape in the global template. Both subjects with early DAT and converters showed greater rates of hippocampal deformation across time than nondemented controls within every subfield of the hippocampus. In a random field analysis, inward surface deformation across time occurred in a non-uniform manner across the hippocampal surface in subjects with early DAT relative to the nondemented controls. Also, compared to the controls, the lateral aspect of the left hippocampal tail showed inward surface deformation in the converters. Using surface deformation patterns as features in a linear discriminant analysis, we were able to respectively distinguish converters and patients with early DAT from healthy nondemented controls at classification rates of 0.77 and 0.87, which were obtained in the same training set using the leave-one-out cross validation approach.

Keywords: LDDMM; Alzheimer's disease; Hippocampus; Shape analysis; Parallel transport

Introduction

MR-based volumetric assessment of the hippocampus has been widely employed in normal aging and various neuropsychiatric disorders, including DAT, mild cognitive impairment, schizophrenia, temporal lobe epilepsy, and major depression (Convit et al., 1997; Shenton et al., 2001; Cardenas et al., 2003; Wang et al., 2003; Csernansky et al., 2005; Frisoni et al., 2005; Apostolova et al., 2006a,b; Frisoni et al., 2006; Wang et al., 2006; Frisoni et al., 2007; Whitwell et al., 2007). In particular, progressive hippocampal volume loss has been identified to be one of the hallmarks of DAT. Using brain warping techniques, neuroimaging studies previously found that increased rates of hippocampal volume loss as well as different patterns of hippocampal shape change distinguished early DAT from healthy aging (Fox et al., 1996; Cardenas et al., 2003; Wang et al., 2003; Apostolova et al., 2006b; Ridha et al., 2006). However, among the group of nondemented subjects, there was considerable variation in the rate of hippocampal volume loss and shape change, possibly because of the presence of subjects within this group with preclinical forms of Alzheimer's disease (AD) (i.e., subjects are cognitively normal but have histopathological AD). More sensitive methods for assess the degree and pattern of structural change in the hippocampus are still needed to optimally distinguish subjects with early forms of AD (including preclinical AD) from subjects who are aging in the absence of the AD process.

To precisely assess the location of volume loss within the complex structure of the hippocampus requires studying within-subject time-dependent deformation of the hippocampal surface, as illustrated in the first level analysis of Fig. 1. However, the absence of a common coordinate system across subjects can undermine hypothesis testing related to time-dependent within-

* Corresponding author. Fax: +65 6872 3069.
E-mail address: bieqa@nus.edu.sg (A. Qiu).
Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2007.11.041

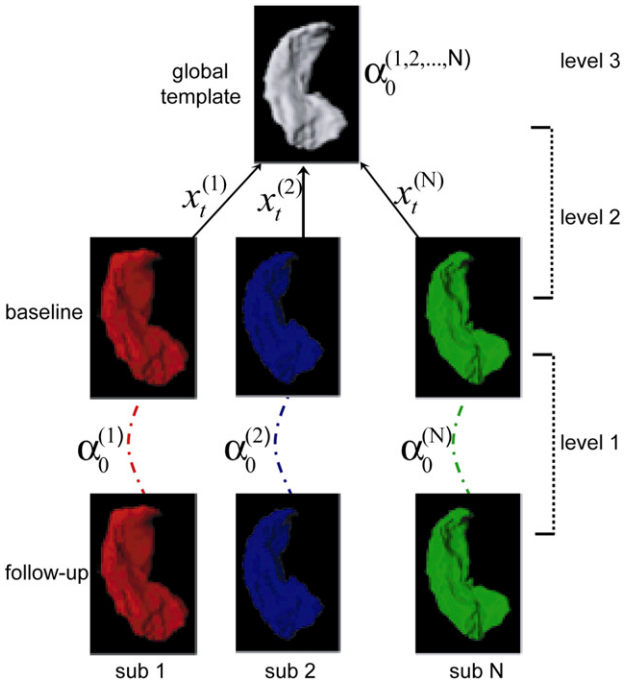

Fig. 1. Schematics of transport in diffeomorphisms for studying longitudinal shape variation. There are three levels of analysis. In the first level, the initial momentum $\alpha_0^{(j)}$ encoding the deformation of the hippocampus between the baseline and follow-up within subject j is computed via LDDMM surface mapping. The geodesic $x_t^{(j)}$ connecting subject j at the baseline to the global template is also computed via LDDMM surface mapping in the second level of the analysis. Finally, $\alpha_0^{(j)}$ is parallel transported to the global template along $x_t^{(j)}$ via the technique described in Methods.

subject deformation. Previously, subjects' hippocampi at different time points were mapped to a single hippocampal atlas via brain warping techniques (Wang et al., 2003; Apostolova et al., 2006b). The difficulty with this approach is that the transformations used to assess longitudinal changes in the hippocampal surface included both the variation of the transformation between different time points within and across subjects. The weakness of this approach for detecting within-subject changes is that the variation across subjects is generally larger than the variation within subjects.

In this paper, we demonstrate three-level analyses under the large deformation diffeomorphic metric mapping framework (LDDMM) for comparing longitudinal shape variation of the hippocampus across clinical populations. As illustrated in Fig. 1, the first two levels assess deformations within subjects and between a global template and subjects, respectively, via LDDMM. In the third-level analysis, we use a novel technique, parallel transport in diffeomorphisms, which allows us to translate within-subject deformation between time points in a global template without incorporating across-subject deformation. We applied this approach to a study of hippocampal shape change in 26 healthy nondemented subjects (CDR 0), 18 patients with DAT (CDR 0.5), and 9 subjects who converted from being nondemented to being demented. Our aim was to distinguish subjects with very mild AD and subjects with preclinical forms of AD from healthy comparison subjects using time-dependent patterns of hippocampal surface deformation.

Methods

General approach

Template-based morphometric methods have been successful for describing anatomical variations between a collection of shapes and a reference. Among these, the large deformation diffeomorphic metric matching (LDDMM) algorithms provide a range of diffeomorphic matching methods (landmarks, images, curves, surfaces), each of which can produce a metric evaluation of the size of the variation. Moreover, LDDMM provides a mechanism that allows for the reconstitution of the variations by encoding precise variations of anatomies relative to the template. The resultant template-based representation can be interpreted as a change of coordinates and can be used to represent anatomies in a local chart centered at the template.

In the present study, we were primarily interested in quantifying anatomical variation within each subject between two time points. This variation is naturally represented by the deformation needed to pass from the anatomy at the first time point to one at the second time point within a subject. When comparing two or more subjects, one then needs to decide how change in the anatomy of one subject can be translated into the similar deformation that occurs in another subject.

The metric structure on anatomies provided by LDDMM offers a consistent approach for the translation of this information. This operation, parallel translation taken from Riemannian geometry, displaces vectors along a curve without changing properties such as the norms of the vectors or their dot products. In Euclidean space, this operation is the standard translation of vectors; i.e., the infinitesimal displacement of subject 1 is applied to subject 2 without change. In curved spaces, however, parallel translation is nonlinear and can be computed by solving a differential equation. The special form of this equation on the LDDMM setting will be described in the parallel transport in diffeomophisms section, after having introduced the notation and formalism related to LDDMM in Large deformation diffeomorphic metric matching section.

We thus present three levels of analysis for studying time-dependent deformation of anatomies as schematized in Fig. 1. The first level of analysis was to characterize within-subject variations between the baseline and follow-up. The second level of analysis constructed a curve connecting the baseline anatomies and the global template and characterized cross-subjects variations between them. In the third level, the parallel transport operation moved within-subject time-dependent variations to the global template along this curve: from the baseline to the global template. The first two levels involve spatial normalization of anatomies implemented by the LDDMM algorithm in the Large deformation diffeomorphic metric matching section. The technique of parallel transport was applied in the third level of the analysis as described in the Parallel transport in diffeomorphisms section.

Large deformation diffeomorphic metric matching

LDDMM background

The first- and second-level analyses in Fig. 1 involve the registration between two anatomical structures. In our case, the surface of the hippocampus was represented by a triangulated mesh with a finite number of points. In the LDDMM setting, we developed mapping algorithms for registering two point sets that represent three types of different anatomical manifolds: landmarks,