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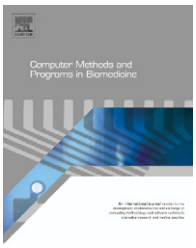

Automated approaches for analysis of multimodal MRI acquisitions in a study of cognitive aging

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ABSTRACT

In this work we describe an integrated and automated workflow for a comprehensive and robust analysis of multimodal MR images from a cohort of more than hundred subjects. Image examinations are done three years apart and consist of 3D high-resolution anatomical images, low resolution tensor-valued DTI recordings and 4D resting state fMRI time series. The integrated analysis of the data requires robust tools for segmentation, registration and fiber tracking, which we combine in an automated manner. Our automated workflow is strongly desired due to the large number of subjects. Especially, we introduce the use of histogram segmentation to processed fMRI data to obtain functionally important seed and target regions for fiber tracking between them. This enables analysis of individually important resting state networks. We also discuss various approaches for the assessment of white matter integrity parameters along tracts, and in particular we introduce the use of functional data analysis (FDA) for this task.

1. Introduction

The present work is related to a longitudinal study of cognitive aging following a cohort of more than 100 healthy elderly people in the Bergen area, Norway. Two waves, about three years apart, have been completed in the ongoing study, each consisting of extensive neuropsychological assessment and multimodal MRI examinations. Genetic profiling was performed in the first wave. A major aim of the longitudinal study is to investigate how variations in neuropsychological test scores (cognitive aging) correlate with changes in MRI parameters (e.g. brain volumes, cortical thicknesses, and white matter integrity) over time. In the second wave we also added a "resting state" and a "finger-tapping" fMRI protocol (4D data) to the 3D anatomical scans and diffusion tensor imaging

(DTI) scan. The fMRI protocol was added in order to assess resting state networks (RSNs) in the brain, including the "default mode network" (DMN) [1] and functional connectivity between segmented brain regions [2]. In this paper we address challenges and solutions related to multimodal MRI analysis, in particular multimodal registration, segmentation of fMRI signals and the analysis of white matter fiber tracts. Also, we focus on automated workflow requirements, which are required in the presence of a large dataset.

Image registration is crucial for analysis of multimodal MRI data, and we present image registration challenges related to (i) intra-subject, multimodal MR image registration between

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3D high-resolution-anatomical images, low resolution tensor-valued DTI recordings, and 4D resting state fMRI and (ii) intra-subject registration between image recordings obtained at wave-1 and wave-2, respectively. Traditionally, registration of MRI images is either subject- [3] and/or template [4–6] driven. In general, template-driven approaches have access to a segmentation atlas, thus enabling inter-subject comparison. For multimodal image registration, mutual information is normally the cost functional of choice [3,7–9], but there are also powerful edge-matching approaches [9]. However, multimodal nonlinear registration is a challenging task due to the lack of simultaneous and local information between the image and the template. Moreover, the evaluation of multimodal registration performance is non-trivial because a gold-standard is usually missing. Still, an evaluation can partly be accomplished by checkerboard images [10], landmarks [6], visual inspection [3], estimation of ROI based characteristics before and after registration [4,11], artificial perturbations [9,12] and by estimation of variance of MRI parameters across subjects [5,6].

Segmentation of anatomical brain regions can provide regions of interest (ROIs) for the analysis of white matter integrity and for fiber tracking. However, the structurally defined regions are not necessarily optimal for defining functionally ROIs since they comprise neuronal tissue that may not be involved in specific and coherent brain activity. Alternatively, ROI selection can be obtained from segmentation of processed fMRI signals. This is usually performed by *global thresholding* on the following quantities: fMRI signals [13], z-scores [14–16], *t*-maps [17], *p*-values of general linear models (GLM) [18–20], *t*-tests [21,22], nonparametric multiple comparisons [23], or on ICA components [24–27]. In our work, we propose to combine global thresholding with a data-driven fMRI approach, addressing the individual variability within the group by utilizing segmented ICA components as seeding points for tracking and also for region based analysis.

In quantitative analysis of white matter fiber tracts, fractional anisotropy (FA) values are normally averaged across fiber bundles of interest. However, this approach is not sensitive to local changes of FA along specific fiber tracts. Therefore, methods have been introduced that can provide estimated FA variation *along* white matter fiber tracts [28–33], giving additional information to global estimates. Gong et al. [30] used a scale-invariant polar parametrization of the arc to study the circular-like shaped cingulum. However, this approach is limited to approximately circular-shaped fiber tracts. In other studies, the tracts were parameterized into a larger set of small segments [28,29,31,32]. In Gerig et al. [34], the parametrization was performed within a spline representation of the fiber. This approach has the advantage of reducing the problematic differences of tract length between subjects, thus enabling a proper comparison.

In our work a central aim was to achieve an automated and time-efficient workflow. Fully automated approaches to image registration and segmentation have several advantages compared to methods that require manual interaction, e.g. (i) automation enables repeated evaluations for different parameter settings; (ii) results are reproducible and less subjective; (iii) misalignment (or misclassification errors) are often systematic and more easy to detect at early stages, whereas, in manual approaches, errors are normally less predictable and coalesce with the data in a non-suspicious way, hence harder to detect. On the other hand, one should ensure that the accuracy of the automated method is adequate for the particular application, and robust to typical variations in data quality. In some cases a semi-automated approach is necessary to achieve these goals. In our complete application for analysis of multimodal MRI acquisitions we obtained an automated workflow except from one stage where manual editing of *FreeSurfer* segmentations was needed in several subjects, since the automatically segmented regions were inaccurate according to anatomical knowledge. This was the only manual intervention needed in our processing chain. We consider the design and implementation of the automated processing chain to be an important contribution of this work.

2. Methods

2.1. *Multimodal MRI acquisitions and description of the various measurements*

In this study of cognitive aging, we used a 1.5T GE Sigma Echospeed scanner with an eight-channel head coil. Two consecutive T1-weighted 3D volumes were acquired using a fast spoiled gradient echo (FSGR) sequence (TR/TE/TI/FA = 9.11 ms/1.77 ms/450 ms/7°); 124 saggital slices and voxel size $0.94 \times 0.94 \times 1.4\,mm^3$. This protocol enabled a good signal-to-noise ratio (SNR) for a semi-automated brain segmentation procedure that was performed later. Diffusion tensor images (DTI) were acquired with a spin-echo echo planar sequence (TR/TE/FA = 7900 ms/104.9 ms/90°); 5 images with $b = 0$; 25 directional images with $b = 1000\,s/mm^2$ and 25 axial slices were obtained, yielding a voxel size of $1.88 \times 1.88 \times 4\,mm^3$. The fractional anisotropy (FA) image was computed from the DTI data using Diffusion Toolkit [35]. For BOLD fMRI, a total of 256 volumes were recorded with a temporal resolution of 2 s using a gradient echo echo planar imaging (GRE-EPI) sequence with 25 axial slices per volume (TR/TE/FA = 2000 ms/50 ms/90°, acquisition matrix 64×64, field of view 240 mm, slice thickness 5 mm, and slice gap 0.5 mm). The participants were instructed to lie still with their eyes closed during this examination. All recordings, i.e. 3D anatomy, DTI and BOLD fMRI were acquired during the same imaging session so that the positional information stored in the DICOM file headers could be used as initial spatial configuration in the subsequent multimodal image registration, cf. Section 2.7.

Spatial characteristics of our multimodal MRI protocol are given in Table 1. Note the variation in grid and voxel sizes between the different modalities (MR measurement techniques), and between original acquisitions and processed data e.g. *FreeSurfer*-segmented anatomy, FA values calculated from eigen decomposition of diffusion tensor images, and spatial ICs derived from independent component analysis (ICA).

Examples of recorded and calculated images are shown in Fig. 1 (note that all images are shown in their original voxel orientation). The T1-weighted anatomical image (Fig. 1B) is used for skull stripping, tissue segmentation and brain surface reconstruction by *FreeSurfer* [36,37]. In this process a