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Fully-integrated framework for the segmentation and registration of the spinal cord white and gray matter

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ABSTRACT

The spinal cord white and gray matter can be affected by various pathologies such as multiple sclerosis, amyotrophic lateral sclerosis or trauma. Being able to precisely segment the white and gray matter could help with MR image analysis and hence be useful in further understanding these pathologies, and helping with diagnosis/prognosis and drug development. Up to date, white/gray matter segmentation has mostly been done manually, which is time consuming, induces a bias related to the rater and prevents large-scale multi-center studies. Recently, few methods have been proposed to automatically segment the spinal cord white and gray matter. However, no single method exists that combines the following criteria: (i) fully automatic, (ii) works on various MRI contrasts, (iii) robust towards pathology and (iv) freely available and open source. In this study we propose a multi-atlas based method for the segmentation of the spinal cord white and gray matter that addresses the previous limitations. Moreover, to study the spinal cord morphology, atlas-based approaches are increasingly used. These approaches rely on the registration of a spinal cord template to an MR image, however the registration usually doesn't take into account the spinal cord internal structure and thus lacks accuracy. In this study, we propose a new template registration framework that integrates the white and gray matter segmentation to account for the specific gray matter shape of each individual subject. Validation of segmentation was performed in 24 healthy subjects using T_2^*-weighted images, in 8 healthy subjects using diffusion weighted images (exhibiting inverted white-to-gray matter contrast compared to T_2^*-weighted), and in 5 patients with spinal cord injury. The template registration was validated in 24 subjects using T_2^*-weighted data. Results of automatic segmentation on T_2^*-weighted images was in close correspondence with the manual segmentation (Dice coefficient in the white/gray matter of 0.91/0.71 respectively). Similarly, good results were obtained in data with inverted contrast (diffusion-weighted image) and in patients. When compared to the classical template registration framework, the proposed framework that accounts for gray matter shape significantly improved the quality of the registration (comparing Dice coefficient in gray matter: $p=9.5\times10^{-6}$). While further validation is needed to show the benefits of the new registration framework in large cohorts and in a variety of patients, this study provides a fully-integrated tool for quantitative assessment of white/gray matter morphometry and template-based analysis. All the proposed methods are implemented in the Spinal Cord Toolbox (SCT), an open-source software for processing spinal cord multi-parametric MRI data.

Abbreviations: ALS, amyotrophic lateral sclerosis; CSF, cerebrospinal fluid; CSM, cervical spondylotic myelopathy; DC, dice coefficient; DTI, diffusion tensor images; DWI, diffusion weighted images; fMRI, functional MRI; FSE, fast spin echo; GM, gray matter; HD, Hausdorff distance on skeletonized segmentations; MD, median distance on skeletonized segmentations; MEDIC, multi-echo data image combination; mpMRI, multi-parametric MRI; MR, magnetic resonance; MRI, magnetic resonance imaging; MS, multiple sclerosis; MT, magnetization transfer; MTR, magnetization transfer ratio; PCA, principal component analysis; ROI, region of interest; SC, spinal cord; SCI, spinal cord injury; WM, white matter

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Introduction

The spinal cord (SC) is the main relay between the brain and the peripheral system and contains neurons notably responsible for complex functions such as locomotion (Rossignol, 2006). The SC white matter (WM) and gray matter (GM) can selectively be affected by a large number of pathologies such as multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS) or trauma. Being able to precisely segment the WM and GM would be useful for obtaining more specific knowledge about the origin and mechanics of these pathologies, e.g., quantification of GM atrophy for monitoring motor neuron degeneration in ALS or in MS (Kearney et al., 2013; Schlaeger et al., 2015). However, it is often difficult to properly segment the WM and GM due to the small size of these structures, the motion of the spinal cord, the limited resolution and the relatively poor contrast in conventional MR sequences (e.g., T_1- or T_2-weighted) (Mikulis et al., 1994; Dietrich et al., 2008).

Recent progress in MRI methods for the SC (in hardware as well as in pulse sequences) has enabled the acquisition of images with higher resolution and better contrasts (Stroman et al., 2014), allowing to further investigate SC anatomy, function, and pathologies (Wheeler-Kingshott et al., 2014). In parallel, there are ongoing developments for processing MRI data, and in particular for segmenting the WM/GM (De Leener et al., 2016b). Some methods are based on fuzzy logic and require manual steps for initialization (Yiannakas et al., 2012; Ellingson et al., 2007b) and some were developed for specific applications (diffusion tensor imaging, DTI) and are therefore not applicable to a variety of contrasts (Ellingson et al., 2007b; Tang et al., 2013). Another approach consists in registering an MR-based template and WM/GM atlas to the data using non-linear transformations (Taso et al., 2015; De Leener et al., 2015). While this approach can be fully automatic, it is also more prone to inaccuracies related to poor contrast, artifacts or pathology. Recently, multiple new approaches have been presented at conferences, that are based on probabilistic templates (Blaiotta et al., 2016), active contours (Datta et al., 2016) or patch matching associated with local template selection (based on similarity estimation) (Prados et al., 2016), revealing the growing interest of the community to develop such tools.

Asman et al. introduced a multi-atlas based method, which uses a pre-established model constructed from a dictionary of T_2^*-w images and manual segmentations (Asman et al., 2014). The dictionary images are used to construct a low-dimensional space (model space) describing the intensity variability within the dictionary. The image to segment is then projected into the model space and WM and GM segmentations are estimated using a selection of dictionary labels (manual segmentations) based on image similarity and a label-fusion method. While providing good results, this method is intrinsically limited to the contrast of the data used to generate the model (i.e., T_2*-w images). Moreover, this method is blind to the vertebral level, which can somewhat limit the robustness of the method given that the SC GM shape changes substantially along the superior-inferior direction (Fradet et al., 2014). In the present study, we built on the method of Asman et al. and included additional features to improve the quality of the WM and GM segmentation and allow the segmentation of images having different contrasts.

In addition to being useful for morphometric analysis, segmenting the WM/GM could also be used for improving the quality of registration for template-based analysis (Lévy et al., 2015; Taso et al., 2014). Typically, anatomical T_1- or T_2-w data are registered to an existing template and the warping field is then used to register multi-parametric MRI (mpMRI) data, such as functional MRI (fMRI) (Kong et al. 2014; Stroman et al., 2005), diffusion-weighted images (DWI) (Duval et al. 2015; Taso et al., 2016) or magnetization transfer data (MT) (Lévy et al., 2015; Taso et al., 2016). One current issue with this approach is that typical anatomical data don't exhibit sufficient WM/GM contrast, rendering difficult the use of SC internal structure information for properly registering a template to the mpMRI data. Building from the proposed automatic WM/GM segmentation, we propose a novel multi-label registration framework that accounts for the SC internal structure for improving the accuracy of atlas-based analysis.

The goals of the study were to: (i) improve the existing multi-atlas-based method for automatic WM/GM segmentation by including prior shape information based on vertebral labeling, and by making segmentation independent from image contrast (e.g., DWI) using an intensity normalization approach based on a model pre-registration; and (ii) integrate WM/GM segmentation into a framework for registering mpMRI data to a SC template while accounting for internal structure using a multi-label registration approach. This paper is organized as follows: in the methods, we present the improved multi-atlas-based segmentation method, we introduce the multi-label registration framework that accounts for GM shape and we present the validation framework from healthy and pathological subjects. Results show qualitative and quantitative evaluation of the segmentation and registration methods, with proof-of-concept applications in DWI data and in patients. The discussion addresses the pros/cons of the methods, raises the limitations of validation metrics and opens on potential improvements and applications.

Material and methods

Gray matter segmentation

The dictionary was built from T_2*-w data from 37 subjects. T_2-weighted data were used for obtaining information about vertebral labeling, as detailed below.

Model data acquisition

The dictionary is composed of T_2*-w MR images of the cervical SC from 37 subjects (representing 367 2D axial slices from C1 to T2 vertebral levels). Subjects were recruited and scanned at two different sites.

At the first site (Montreal), 22 healthy subjects (eleven females and eleven males, mean age 23.6 ± 3.1 years old, 271 slices in total) were scanned on a 3T MRI scanner (TIM Trio, Siemens Healthcare, Erlangen, Germany) using the standard 12-channel head and 4-channel neck coils. Anatomic T_2-w images were acquired using a 3D slab-selective fast spin echo (FSE) (TR=1500 ms, TE=119 ms, flip angle=140°, bandwidth=723 Hz/voxel, resolution=1×1×1 mm^3). T_2*-w images were acquired using a 2D spoiled gradient echo sequence with multiple echoes (MEDIC) averaged (axial orientation, TR=540 ms, TE=[5.41, 12.56, 19.16] ms, flip angle=35°, bandwidth=200 Hz/voxel, resolution=0.5×0.5×5 mm^3).

At the second site (Marseille) 15 healthy subjects (six females and nine males, mean age 27.5 ± 4.7 years old, 96 slices in total) were scanned on a 3T MRI scanner (MAGNETOM Verio, Siemens Healthcare, Erlangen, Germany) using a 12-channel head coil and a 4-channel neck coil array. T_2*-w images were acquired using a multi-echo gradient-echo (one slab (C1–C7) of seven non-contiguous transverse slices (one slice per vertebral level), approximated TR=800 ms based on ECG synchronisation (trigger delay 300 ms), five echoes with an effective TE=27 ms, flip angle=28°, bandwidth=150 Hz/pixel, resolution=0.47×0.47×5 mm^3).

Data preprocessing

Spinal cord segmentation and vertebral labeling. The anatomical T_2-w and T_2*-w data were automatically segmented using PropSeg (De Leener et al., 2014). The vertebral levels associated with the volume images were obtained by registering and warping the MNI-Poly-AMU template (Fonov et al., 2014) to each T_2*-w image. Note that this step could have been done with any SC template that includes vertebral level information, such as the more recent PAM50 template (De Leener et al., 2016a).

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