

A reliable spatially normalized template of the human spinal cord – Applications to automated white matter/gray matter segmentation and tensor-based morphometry (TBM) mapping of gray matter alterations occurring with age

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ARTICLE INFO

Article history:

Received 5 February 2015

Accepted 13 May 2015

Available online 21 May 2015

Keywords:

MRI

Spinal cord

Tensor-based morphometry

Segmentation

Template

Gray matter

Atrophy

ABSTRACT

Recently, a T_2^* -weighted template and probabilistic atlas of the white and gray matter (WM, GM) of the spinal cord (SC) have been reported. Such template can be used as tissue-priors for automated WM/GM segmentation but can also provide a common reference and normalized space for group studies. Here, a new template has been created (AMU₄₀), and accuracy of automatic template-based WM/GM segmentation was quantified. The feasibility of tensor-based morphometry (TBM) for studying voxel-wise morphological differences of SC between young and elderly healthy volunteers was also investigated.

Sixty-five healthy subjects were divided into young ($n = 40$, age < 40 years old, mean age 28 ± 5 years old) and elderly ($n = 25$, age > 50 years old, mean age 57 ± 5 years old) groups and scanned at 3 T using an axial high-resolution T_2^* -weighted sequence. Inhomogeneity correction and affine intensity normalization of the SC and cerebrospinal fluid (CSF) signal intensities across slices were performed prior to both construction of the AMU₄₀ template and WM/GM template-based segmentation. The segmentation was achieved using non-linear spatial normalization of T_2^* -w MR images to the AMU₄₀ template. Validation of WM/GM segmentations was performed with a leave-one-out procedure by calculating DICE similarity coefficients between manual and automated WM/GM masks. SC morphological differences between young and elderly healthy volunteers were assessed using the same non-linear spatial normalization of the subjects' MRI to a common template, derivation of the Jacobian determinant maps from the warping fields, and a TBM analysis.

Results demonstrated robust WM/GM automated segmentation, with mean DICE values greater than 0.8. Concerning the TBM analysis, an anterior GM atrophy was highlighted in elderly volunteers, demonstrating thereby, for the first time, the feasibility of studying local structural alterations in the SC using tensor-based morphometry. This holds great promise for studies of morphological impairment occurring in several central nervous system pathologies.

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Introduction

MRI plays a key role in the evaluation of spinal cord (SC) pathologies (Wheeler-Kingshott et al., 2014). The hardware and methodological

developments that occurred in the past decade now allow not only to acquire high resolution SC anatomical images with high contrast between the white (WM) and gray matter (GM) in an acceptable acquisition time (Held et al., 2003), but also to use other challenging MR techniques (diffusion, magnetization transfer, spectroscopy) (Stroman et al., 2014) for an accurate assessment of SC morphological, structural and functional integrity.

To facilitate multimodal and tissue-specific image analysis and perform group studies, there is a need for processing tools such as automated

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SC segmentation and SC templates that could allow regional spinal cord WM/GM analysis as existing for the brain (Collins et al., 1994; Mazziotta et al., 2001).

So far, most of the studies have reported automated segmentation of the cord contour, based on T_1 and T_2 -weighted imaging (Chen et al., 2013; De Leener et al., 2014; Giulietti et al., 2011; Horsfield et al., 2010; Valsasina et al., 2012). A few studies also reported SC WM/GM segmentation, based on 3D gradient-echo sequence (Yiannakas et al., 2012), diffusion imaging (Ellingson et al., 2007), or even multiple deformable atlases using the STAPLE framework (Asman et al., 2014), but all these studies were performed as proof of concept at a single-subject basis, not evidencing the ability to perform group or longitudinal studies. Similarly, the SC templates developed so far (average templates based on T_1/T_2 weighted imaging) lack tissue-specific information (Horsfield et al., 2010; Stroman et al., 2008; Valsasina et al., 2012) and did not allow GM/WM regional analyses. Very recently, the MNI-Poly-AMU template (Fonov et al., 2014) that associates a T_2 -w unbiased average template of the spinal cord with our previous probabilistic WM/GM atlas (Taso et al., 2014), has been developed, allowing researchers to perform group and/or longitudinal studies with SC imaging. Using a pre-registration to the MNI-Poly-AMU T_2 -weighted template, subsequent WM/GM segmentation is possible using the probabilistic WM/GM atlases that come with the template. One issue however is that these atlases have different contrast dynamics than that found in T_2^* -weighted scans, and therefore are sub-optimal for registration purposes.

Meanwhile, methodologies for group studies and morphometry using statistical mapping analyses have been developed for brain studies for more than a decade (Ashburner and Friston, 2000; Good et al., 2001). These statistical parametrical mapping (SPM) methods can either be based on spatial normalization of MR volumes and tissue classification into WM/GM followed by a statistical analysis of the different concentration in WM/GM between groups (defined as Voxel-Based Morphometry, VBM), or based on the derivation of structural differences (in shape, volume) materialized by the calculation of the Jacobian matrix of the deformation fields (method referred to as tensor-based morphometry, TBM).

Nonetheless, although both VBM and TBM are widely used in neuroimaging to study brain structural alterations, their application in spinal cord studies have been very sparse and limited to the cord itself, without tissue-specific information on the WM and GM (Rocca et al., 2013; Valsasina et al., 2012, 2013) mainly because of the lack of robust

automated GM segmentation method and proper non-linear normalization procedures. Having such tools at disposal would allow subtler morphometric studies of regional structural alterations in the SC and thereby give an increased understanding of some neurodegenerative processes occurring with age or central nervous system (CNS) pathologies such as amyotrophic lateral sclerosis (ALS), which specifically affects cortical and spinal motor neurons, as well as corticospinal tracts.

In line, GM atrophy due to increasing age, largely reported in the brain (Agosta et al., 2007; Good et al., 2001) with either GM volume assessment or VBM, has also been studied and established in vivo in the SC with however only absolute GM area measurement (Fradet et al., 2014), i.e. with no spatial information.

Therefore, the current study had three main objectives:

- First, to propose an optimized version of a WM/GM probabilistic atlas and T_2^* -w MRI template of SC (AMU₄₀), with an increase of subjects and intensity normalization.
- Second, to perform WM/GM automatic segmentation based on a non-linear normalization procedure of high-resolution T_2^* -w MR images to the AMU₄₀. Accuracy of the template-based segmentation was achieved by comparing it to manual delineation.
- Third, to apply voxel-wise tensor-based morphometry analysis to characterize differences between young and elderly healthy volunteers.

Material and methods

Volunteers

Fifty-nine healthy European volunteers were enrolled in this study and divided into 2 groups according to age: a young group ($n = 40$, 13 women, 27 men, mean age 28 ± 5 years old, ranging from 20 to 38 years) and an elderly group ($n = 25$, 12 women, 13 men, mean age 57 ± 5 years old, ranging from 52 to 68 years). Exclusion criteria included history of SC injury or CNS pathology. The MR protocol was approved by our institutional Committee on Ethics and written informed consents were obtained from all subjects prior to examination.

MRI acquisitions

Acquisitions were performed on a 3 T MR scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany). The body coil was used for RF

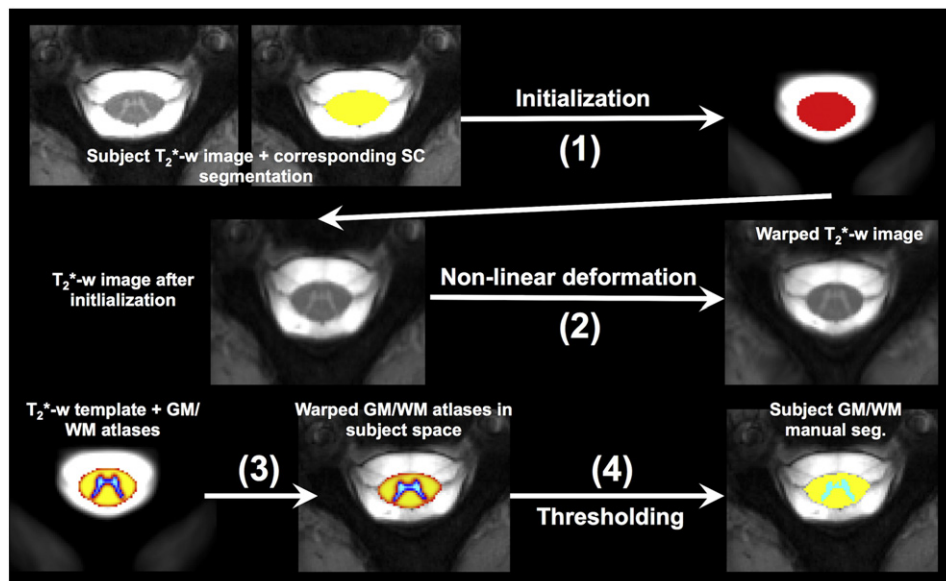


Fig. 1. Processing pipeline for automatic WM/GM segmentation of SC.

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