NeuroImage 46 (2009) 967–980

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Development of a human brain diffusion tensor template

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ARTICLE INFO

Article history:
Received 4 November 2008
Revised 4 March 2009
Accepted 18 March 2009
Available online 31 March 2009

Keywords:
Template
DTI
Brain
Human
Normalization
Registration
Turboprop
PROPELLER

ABSTRACT

The development of a brain template for diffusion tensor imaging (DTI) is crucial for comparisons of neuronal structural integrity and brain connectivity across populations, as well as for the development of a white matter atlas. Previous efforts to produce a DTI brain template have been compromised by factors related to image quality, the effectiveness of the image registration approach, the appropriateness of subject inclusion criteria, and the completeness and accuracy of the information summarized in the final template. The purpose of this work was to develop a DTI human brain template using techniques that address the shortcomings of previous efforts. Therefore, data containing minimal artifacts were first obtained on 67 healthy human subjects selected from an age-group with relatively similar diffusion characteristics (20–40 years of age), using an appropriate DTI acquisition protocol. Non-linear image registration based on mean diffusion-weighted and fractional anisotropy images was employed. DTI brain templates containing median and mean tensors were produced in ICBM-152 space and made publicly available. The resulting set of DTI templates is characterized by higher image sharpness, provides the ability to distinguish smaller white matter fiber structures, contains fewer image artifacts, than previously developed templates, and to our knowledge, is one of only two templates produced based on a relatively large number of subjects. Furthermore, median tensors were shown to better preserve the diffusion characteristics at the group level than mean tensors. Finally, white matter fiber tractography was applied on the template and several fiber-bundles were traced.

Introduction

The development of a brain template for diffusion tensor imaging (DTI) (Basser and Pierpaoli, 1996) is crucial for comparisons of neuronal structural integrity (Le Bihan et al., 2001) and brain connectivity (Basser et al., 2000) across populations, as well as for the development of a white matter atlas (Mori et al., 2008). The potential of DTI for detecting differences in brain tissue micro-architecture between healthy subjects and patients has been recognized in several studies on various brain-related diseases, such as schizophrenia (Lim et al., 1999), bipolar disorder (Bruno et al., 2008), alcoholism (Pfefferbaum and Sullivan, 2005), stroke (van Gelderen et al., 1994), multiple sclerosis (Bammer et al., 2000), Alzheimer's (Arfanakis et al., 2007), dyslexia (Klingberg et al., 2000), amyotrophic lateral sclerosis (Ellis et al., 1999), epilepsy (Arfanakis et al., 2002b), traumatic brain injury (Arfanakis et al., 2002a), and others. These studies have adopted one of two approaches for investigating intergroup differences: regions of interest (ROI) and voxel-based analyses. The first approach involves manual or semi-automated selection of ROIs, followed by comparison of the results from the selected ROIs between groups (Ellis et al., 1999; Arfanakis et al., 2002b). The main disadvantage of ROI analysis in DTI is that quantities such as the primary diffusion direction cannot be compared, since brain positioning varies between subjects. The second approach involves spatial normalization of the data in each group to a template and subsequent comparison between groups, either within selected ROIs, or on a voxel-by-voxel basis (Bruno et al., 2008; Klingberg et al., 2000). Tensor reorientation techniques that take into account the transformation applied during spatial normalization of DTI datasets have been developed (Alexander et al., 2001; Xu et al., 2003), and as a result, comparisons between quantities dependent on the tensor's orientation are feasible (Jones et al., 2002; Schwartzman et al., 2005). However, spatial normalization of the DTI data is typically achieved by first normalizing coregistered T_1 or T_2-weighted images from each subject to a template, such as the Montreal Neurological Institute (MNI) template, and then applying the same transformations to the corresponding DTI data; or by selecting one subject's DTI data as the reference, and registering the DTI data from all other subjects to the reference. When no tensor information is used for the normalization, it is not ensured that diffusion characteristics match between subjects. In addition, transformations that are estimated based on undistorted

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doi:10.1016/j.neuroimage.2009.03.046

images (e.g. T_1-weighted) are not appropriate for use with distorted conventional spin-echo echo-planar DTI (SE-EPI-DTI) maps, even when using parallel imaging, since the two datasets do not match spatially. Also, the artifacts present in SE-EPI-DTI data vary between subjects, as well as for the same subject in different head positions (Gui et al., 2008). These artifacts have a negative effect on the normalization process in brain regions such as the brainstem, the temporal and frontal lobes (Peng et al., 2008). Finally, when using a single subject's DTI data as reference, one needs to take into account the fact that a single subject's brain may not be representative of other subjects of the same cohort, and that a single subject's data contain more noise than a template produced by averaging multiple datasets. Noise reduces the accuracy of the normalization and the validity of group averaging, and limits the clinical potential of DTI. Therefore, careful development of a representative DTI human brain template is crucial for accurate comparisons of neuronal structural integrity and brain connectivity across populations.

Development of a DTI template that is representative of the healthy human brain is also important for the generation of a detailed white matter atlas. The existing brain atlases are either based on a small number of brains analyzed postmortem, and are not in digital format, or contain only limited information on white matter (Toga et al., 2006). Since the introduction of DTI, several white matter structures have been mapped in individual subjects (Wakana et al., 2004). DTI data from a large number of healthy human subjects can be combined and used to segment various white matter structures, in order to produce a digital atlas of human brain white matter (Mori et al., 2008).

A number of studies have produced average human brain DTI data using different approaches. Jones et al. (2002) used affine transformations to register fractional anisotropy (FA) maps from ten human subjects to the FA map of another subject, and then applied the transformation parameters to reorient the diffusion tensors. All FA maps were produced with EPI-based DTI. Muller et al. (2007) used affine spatial normalization to coregister the image volumes with no diffusion weighting ($b=0$ s/mm^2) from thirteen subjects, in MNI space. The transformation parameters were then applied on the diffusion tensors, and the tensors were reoriented. All datasets were acquired with EPI-based DTI. Goodlett et al. (2006) normalized five EPI-based DTI datasets in two steps. In the first step, the $b=0$ s/mm^2 images were registered to a T_2-weighted image-template using affine alignment, and the transformation parameters were applied to the diffusion tensors. In the second step, deformable registration improved correspondence between the 5 DTI datasets and the template. Six diffusion directions were used for data acquisition. Zhang et al. (2006) normalized nine EPI-based DTI datasets in two steps. In the first step, the diffusion anisotropy maps from eight subjects were matched to the maps of the ninth subject (assumed to be the template) using affine transformation. In the second step, the aligned images were registered to the template using deformable registration. Mori et al. (2008) normalized 81 EPI-based DTI datasets acquired on two 1.5 Tesla (T) MRI scanners with parallel imaging and acceleration of 2, from a group of subjects with ages ranging from 18 to 59 years. The mean diffusion-weighted (DW) images were first coregistered using affine alignment, and the transformation parameters were then applied to the diffusion tensors. Park et al. (2003) used Line-Scan DTI, which provides distortion free DTI data, and non-linear registration to normalize DTI data from 16 subjects. Due to the low signal to noise ratio (SNR) per unit time achieved with Line-Scan DTI, the slice thickness was increased to 4 mm, and only 6 diffusion directions were used. The main characteristics of these and other efforts to develop a human brain DTI template are summarized in Table 1. However, in each study mentioned above, a combination of several sources of error prohibited the development of an accurate DTI template: a) EPI-related image artifacts, b) suboptimal diffusion encoding schemes or imaging protocol, c) the use of affine instead of non-linear registration, d) the use of a single scalar quantity for normalization, which often did not include any DTI information, e) limited number of subjects, and f) averaging data across age-groups with different diffusion properties (Table 1).

The purpose of this work was to develop a DTI human brain template using an approach that addresses the shortcomings of previous studies. Therefore, Turboprop-DTI data, which contain minimal distortions and other artifacts (e.g. artifacts caused by magnetic susceptibility variations and eddy-currents) (Pipe and Zwart, 2006; Arfanakis et al., 2005; Gui et al., 2008), were first obtained on a large number of healthy human subjects selected from an age-group with relatively similar diffusion characteristics. Non-linear image registration techniques were employed, and information from multiple quantities derived from the diffusion tensor was taken into account during registration. The use of different combinations of quantities in the registration process was quantitatively evaluated. Furthermore, the accuracy of the final registration was estimated based on the ability to match selected brain landmarks between subjects. Tensor reorientation was performed in order to produce a template that contains complete tensors. The use of median vs. mean tensors to summarize the group's diffusion properties was evaluated. The DTI brain template was produced in the spatial coordinates of the ICBM-152 brain template (International Consortium for Brain Mapping) that is often used in the neuroimaging community, and was made publicly available. The resulting template was compared to those produced in previous studies, and primarily to that of Mori et al., 2008, which is currently the only other publicly available DTI template also based on a large number of subjects. Finally, white matter fiber tractography was applied on the resulting template and several fiber-bundles were traced.

Table 1
A list of critical methods and parameters used in this and other studies on the development of a human brain DTI template.

Study	# of Subj.	Age-range (years)	B_0 (T)	Pulse sequence	TE (ms)	# of diff. dirs	Voxel size (mm^3)	Gap	Normalization approach
This study	67 M:27 F:40	20–40	3	Turboprop	94	12	10.5	No	Non-linear, (FA and mean DW)
Jones et al., 2002	11 M:11 F:0	25–39	1.5	EPI	107	64	15.6	No	Affine, (FA)
Mori et al., 2008	81 M:42 F:39	18–59	1.5	EPI, parallel imaging	N/A	30	15.6	No	Affine, (mean DW)
Muller et al., 2007	13 M:10 F:3	53.1 ± 15.3	1.5	EPI	93	12	4.95	No	Affine, ($b=0$ s/mm^2)
Goodlett et al., 2006	5	1	3	EPI	73	6	8	No	Non-linear, (FA)
Zhang et al., 2006	9	19–30	3	EPI	99	12	8.88	Yes	Non-linear, (Diffusion anisotropy)
Park et al., 2003	16	30–51	1.5	Line-Scan	64	6	8.77	Yes	Non-linear, (multi-channel)
Chiang et al., 2008	34 M:20 F:14	73.6 ± 9	1.5	EPI	106	44	7.92	Yes	Non-linear, (Tensors)
Xu et al., 2003	9	N/A	1.5	EPI, segmented	N/A	6	11.4	No	Non-linear, (T_1-weighted)
Ardekani and Sinha, 2006	10 M:8 F:2	31 ± 3	3	EPI, parallel imaging	91	6	3.4	No	Non-linear, (Trace and FA)
Van Hecke et al., 2008	20 M:8 F:12	25 ± 3	1.5	EPI	100	60	8	N/A	Non-linear, (Tensors)

The total number of subjects, number of subjects per gender, age-range, magnetic field strength (B_0), pulse sequence, echo-time (TE), number of diffusion directions, voxel size, gap between slices, normalization approach, and information used for the normalization are listed.