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Comparison of probabilistic tractography and tract-based spatial statistics for assessing optic radiation damage in patients with autoimmune inflammatory disorders of the central nervous system

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ABSTRACT

Background: Diffusion Tensor Imaging (DTI) can evaluate microstructural tissue damage in the optic radiation (OR) of patients with clinically isolated syndrome (CIS), early relapsing-remitting multiple sclerosis and neuromyelitis optica spectrum disorders (NMOSD). Different post-processing techniques, e.g. tract-based spatial statistics (TBSS) and probabilistic tractography, exist to quantify this damage.
Objective: To evaluate the capacity of TBSS-based atlas region-of-interest (ROI) combination with 1) posterior thalamic radiation ROIs from the Johns Hopkins University atlas (JHU-TBSS), 2) Juelich Probabilistic ROIs (JUEL-TBSS) and tractography methods using 3) ConTrack (CON-PROB) and 4) constrained spherical deconvolution tractography (CSD-PROB) to detect OR damage in patients with a) NMOSD with prior ON (NMOSD-ON), b) CIS and early RRMS patients with ON (CIS/RRMS-ON) and c) CIS and early RRMS patients without prior ON (CIS/RRMS-NON) against healthy controls (HCs).
Methods: Twenty-three NMOSD-ON, 18 CIS/RRMS-ON, 21 CIS/RRMS-NON, and 26 HCs underwent 3 T MRI. DTI data analysis was carried out using JUEL-TBSS, JHU-TBSS, CON-PROB and CSD-PROB. Optical coherence tomography (OCT) and visual acuity testing was performed in the majority of patients and HCs.
Results: Absolute OR fractional anisotropy (FA) values differed between all methods but showed good correlation and agreement in Bland-Altman analysis. OR FA values between NMOSD and HC differed throughout the methodologies (p-values ranging from $p < 0.0001$ to 0.0043). ROC-analysis and effect size estimation revealed higher AUCs and R^2 for CSD-PROB (AUC = 0.812; $R^2 = 0.282$) and JHU-TBSS (AUC = 0.756; $R^2 = 0.262$), compared to CON-PROB (AUC = 0.742; $R^2 = 0.179$) and JUEL-TBSS (AUC = 0.719; $R^2 = 0.161$). Differences between CIS/RRMS-NON and HC were only observable in CSD-PROB (AUC = 0.796; $R^2 = 0.094$). No significant differences between CIS/RRMS-ON and HC were detected by any of the methods.
Conclusions: All DTI post-processing techniques facilitated the detection of OR damage in patient groups with

Abbreviations: AD, axial diffusivity; AUC, area under the curve; CIS, clinically isolated syndrome; CON, Contrack; CSD, constrained spherical deconvolution; DTI, diffusion tensor imaging; DWI, diffusion weighted imaging; DW-MRI, diffusion weighted magnetic resonance imaging; FA, fractional anisotropy; FOD, fiber orientation distribution; HC, Healthy Control; JHU, Johns Hopkins University DTI white matter atlas; JUEL, Juelich histological atlas; LGN, lateral geniculate nucleus; MD, mean diffusivity; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; OCT, optical coherence tomography; ON, optic neuritis; OR, optic radiation; PROB, probabilistic tractography; RD, radial diffusivity; RNFL, retinal nerve fiber layer thickness; ROC, receiver operating characteristic; ROI, region of interest; RRMS, relapsing-remitting multiple sclerosis; SD, standard deviation; SEM, standard error of the mean; TBSS, tract-based spatial statistics

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severe microstructural OR degradation. The comparison of distinct disease groups by use of different methods may lead to different - either false-positive or false-negative - results. Since different DTI post-processing approaches seem to provide complementary information on OR damage, application of distinct methods may depend on the relevant research question.

1. Introduction

The optic radiation (OR) is an integral part of the afferent visual system and belongs to the most frequently affected white matter pathways in autoimmune neuroinflammatory disorders of the central nervous system, i.e. multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) (Backner et al., 2018; Balcer et al., 2015; Bennett et al., 2015; Finke et al., 2018; Martínez-Lapiscina et al., 2014; Pache et al., 2016a, 2016b; Pache et al., 2016a, 2016b; Petzold et al., 2014; Pfueller and Paul, 2011; Scheel et al., 2014; Schmidt et al., 2017; Sinnecker et al., 2015b; Wingerchuk et al., 2015). Diffusion-weighted magnetic resonance imaging (DW-MRI) yields the potential to non-invasively investigate microstructural OR integrity (Assaf and Pasternak, 2008; Filippi et al., 2013).

A multitude of DW-MRI post-processing techniques have been used in recent studies to investigate OR damage in neuroinflammatory disorders (Hasan et al., 2011). TBSS is a widely used fully automated method to perform whole brain tract diffusion tensor imaging (DTI) analyses. ConTrack (CON-PROB) (Sherbondy et al., 2008a, 2008b) and CSD-based probabilistic tractography (CSD-PROB) (Lim et al., 2015; Martínez-Heras et al., 2015; Tournier et al., 2007) provide high sensitivity to delineate tracts through crossing fiber regions (Auriat et al., 2015), facilitate the selection of pathways that connect two regions (Sherbondy et al., 2008b) and allow subsequent in-depth analysis, for example tract profiling, by calculating DTI values at different nodes along the OR. However, implementation of probabilistic tractography algorithms in the individual patient is frequently more time consuming due to manual predefinition of seed and target regions as well as manual or semi-automated cleaning of tractography results. Moreoever, accurate OR delineation in vivo is hampered by its complex structure with the sharp bending in the Meyer's loop (Martínez-Heras et al., 2015), the reduced fiber densitiy in this area compared to the body of the OR (Lim et al., 2015; Wu et al., 2012) and the presence of crossing fibers along the pathway (Sherbondy et al., 2008b).

Previous investigations using CON-PROB found OR DTI metrics to be altered in long-standing MS patients compared to healthy controls with correlations between OR FA and OR T2 lesion volume (Klistorner et al., 2014). A study investigating clinically isolated ON patients with CON-PROB found reduced fractional anisotropy (FA) and elevated radial diffusivity (RD) to be associated with OR lesions. No correlation between OR DTI and retinal nerve fiber layer thickness (RNFL) measured by optical coherence tomography (OCT) was found (Raz et al., 2015). By contrast, investigations using TBSS in MS patients with and without prior ON found strong correlations between RNFL and FA within the OR, suggesting trans-synaptic neurodegeneration after ON to explain the link between low RNFL thickness and low FA values in the OR (Scheel et al., 2014). These contradictory results fall in line with previous studies either favoring (Oertel et al., 2017; Pache et al., 2016a, 2016b; Reich et al., 2009; Rocca et al., 2013) or disfavoring (Dasenbrock et al., 2011) evidence on trans-neuronal changes in neuroinflammatory disorders. The conflicting diversity of published DTI studies might be partially owing to cohort inhomogeneities with regards to time from disease onset, severity of structural damage and clinical deficit as well as total and region-specific lesion load. Beyond this, the heterogeneous usage of different DTI post-processing techniques and their specific inherent limitations may account for inconsistent reports.

Validation studies of sensitivity, specificity and technical advantages and disadvantages of different DTI post-processing methods are thus highly required. Unfortunately, there is no “gold-standard” for non-invasive DTI-based OR tract-probing (Lim et al., 2015; Thomas et al., 2014), making comparability between methods and validation of techniques difficult. To overcome these limitations, different methods need to be compared against each other under one specific research question.

The purpose of our study was to compare distinct TBSS-based and probabilistic tractography-based approaches in the delineation of OR and the detection of OR damage. We therefore investigated OR damage with different severity levels and compared a) NMOSD patients with prior ON with suspected severe OR damage, b) clinically isolated syndrome (CIS) and early relapsing-remitting multiple sclerosis (RRMS) patients with ON and suspected moderate OR damage and c) CIS and early RRMS patients without prior ON and potential OR damage against healthy controls (HCs). We evaluated inter-method agreement of FA values and compared the capacity of all methods to detect OR FA differences in all patient cohorts compared to HCs.

2. Material and methods

2.1. Subjects

Sixty-two patients were retrospectively analyzed from our research database. This included CIS and early RRMS with ON (CIS/RRMS-ON), CIS and early RRMS without ON (CIS/RRMS-NON), NMOSD with ON (NMOSD-ON) as well as 26 HCs (see Table 1). All patients were examined under supervision of a board-certified neurologist at the NeuroCure Clinical Research Center, Charité-Universitätsmedizin Berlin between January 2011 and July 2015.

Table 1
Study cohort description.

	HC	CIS/RRMS-NON	CIS/RRMS-ON	NMOSD-ON
Subjects [n]	26	21	18	23
Sex [f(m)]	22(4)	11(10)	11(7)	20(3)
Age [years; mean ± SD]	43.7 ± 15.7	33.4 ± 8.6	31.2 ± 7.7	46.7 ± 14.5
Disease duration [months; mean ± SD]	*n.a.*	5.40 ± 6.67	4.63 ± 5.15	94.17 ± 95.72
EDSS [median; range]	*n.a.*	1.5 (0–4.0)	1.5 (0–3.5)	4.0 (0–6.5)
RRMS diagnosis [n]	*n.a.*	5 (23.8%)	3 (16.7%)	*n.a.*
AQP4-ab-positive [n]	*n.a.*	*n.a.*	*n.a.*	19
History of bilateral optic neuritis	*n.a.*	*n.a.*	0	4

HC = healthy control; CIS/RRMS-NON = clinically isolated syndrome without prior optic neuritis; CIS/RRMS-ON = clinically isolated syndrome with prior optic neuritis; NMOSD-ON = neuromyelitis optica spectrum disorder with prior optic neuritis; EDSS = expanded disability status scale; RRMS = relapsing-remitting multiple sclerosis; AQP4-ab-positive = Aquaporin-4-antibody positive.