The influence of the registration on voxel-based statistics of fractional anisotropy images: using detected white matter degenerations associated with juvenile myoclonic epilepsy as a gold standard

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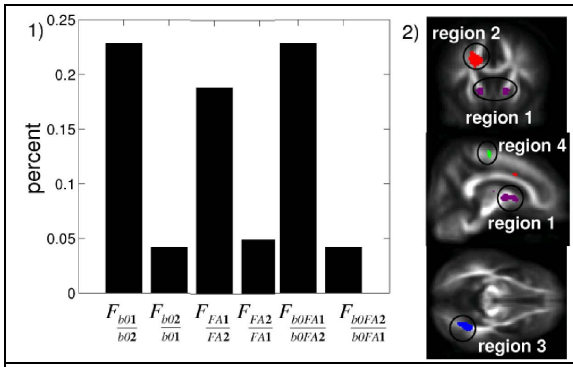
Introduction: Recent developments have enabled automated voxel-based statistical (VBS) analyses of DTI data, so that fractional anisotropy (FA) images, for example, may be quantitatively compared between groups of subjects without manual investigator dependency. In contrast to conventional VBM of T1w images, spatial normalization for VBS of FA images (FA-VBS) may be based on different image contrasts such as structural T1w images, T2w images measured without diffusion gradient (i.e. with b=0 s/m2, here denoted as the b0 image) or FA images. In another study, we developed a SPM normalization toolbox for FA-VBS that enables the construction of single- and multi-contrast registrations based on FA and b0 images [1]. In particular, each registration can be employed iteratively to improve the registration accuracy. Yet, the questions, which registration contrast is best for FA-VBS and if iterative registration is necessary, could not be sufficiently answered, due to the lack of a gold standard. In this study, we apply our toolbox to investigate the influence of the spatial registration on FA differences detected by voxel-based statistics. To assess the influence of the registration on the FA-VBS results, we analyze the white matter of juvenile myoclonic epilepsy (JME) patients with *a-priori* known damage that correlates with the frequency of generalized tonic-clonic seizures (GTCS) [2].

Objective: (i) To assess the registration accuracy when using iterative registration. (ii) To investigate the correlation between FA reduction and GTCS increases when the registration accuracy is improved.

Methods: Sixty-six healthy subjects and ten subjects with JME participated in this study. Diffusion tensor imaging (DTI) was performed by using echo planar imaging at 3T (20xb=1000 s/mm^2; 3xb=0 (b0 images)). DTI data were pre-processed and FA values were generated using in-house developed software. *Analysis I:* To assess the registration accuracy, we calculated in a first step the *F*-map by the quotient of the FA variance between single-step registration (e.g. b01) and iterative registration (b02): $F\frac{FA1}{FA2}$ =var(FA_{b01})/var(FA_{b02}), with FA_{b01} being the normalized FA images after b01 registration and FA_{b02} after b02 registration. In a second step, all significant voxels in the *F*-map were summed and dived by the number of voxel in the brain. *Analysis II*: For all subjects FA-VBS analyses were used to detect clusters that correlate with the number of GTCS. In particular, we compared two single-contrast registrations, based on the b0 and FA contrast respectively and a multi-contrast registration that employs the b0 and FA contrast registration one after the other. Each registration procedure was employed once (b01, FA1 and b0FA1) and iteratively (twice: b02, FA2 and b0FA2). Next, all FA images were smoothed using an isotropic Gaussian Kernel of 4 mm full-width-at-half-maximum. The resulting images were then entered into voxel-wise regression analysis (SPM8) using the GTCS as a covariate ($p<0.05$, uncorrected, cf. Fig. 1 and 2). For VBS a FA mask was used (threshold: FA>0.2).



	region 1	region 2	region 3	region 4
b01	-,2373	-,7894	-,3004	-,4047
	p=,509	p=,007	p=,399	p=,246
b02	-,2605	-,7499	-,4663	-,6236
	p=,467	p=,012	p=,174	p=,054
FA1	-,1637	-,7840	-,7605	-,7873
	p=,651	p=,007	p=,011	p=,007
FA2	-,2259	-,6404	-,7886	-,7282
	p=,530	p=,046	p=,007	p=,017
b0FA1	-,2361	-,7164	-,8488	-,7906
	p=,511	p=,020	p=,002	p=,006
b0FA2	-,7160	-,7281	-,7747	-,8684
	p=,020	p=,017	p=,009	p=,001

Figure: 1.) The improvement of registration accuracy due to iterative registration was assessed for each registration procedure by the integrated *F*-map. 2) The regression coefficient and the p-value are shown for different regions that correlate with the GTCS.

Results and Discussion: The iterative registration improves the registration accuracy for both, single- and multi-contrast registration (Fig. 1). For different brain regions we showed that (i) the correlation between FA and GTCS increases substantially if iterative registration is used and (ii) that the correlation improves when the multi-contrast registration is used relative to single-contrast registration.

Conclusion: We report that iterative registration is superior to single-step registration given the fewer systematic misregistrations detected by the *F*-map. By using white matter degenerations associated with juvenile myoclonic epilepsy as a gold standard this study provides quantitative evidence for future studies to advocate multi-contrast, iterative registration for VBS studies of FA images.

References: [1] Glauche et al., SPM normalization toolbox for diffusion weighted images, ISMRM 2010, Abstract: 5504, [2] Deppe et al. (2008), Nerve fiber impairment of anterior thalamocortical circuitry in juvenile myoclonic epilepsy, Neurology 71, S. 1981.