ROI-based analysis of diffusional kurtosis estimates for identification of MCI-patients at high risk for conversion to Alzheimers disease in a heterogeneous MCI cohort

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Introduction: Diffusion tensor imaging (DTI) is sensitive to neurodegeneration with diffusivity changes in mild cognitive impairment (MCI) and Alzheimer´s disease (AD) reported in the corpus callosum (CC), cingulate gyrus (CG), superior longitudinal fasciculus (SLF) and the hippocampus [1]. Diffusional kurtosis imaging (DKI) is an extension of DTI that characterizes the non-Gaussian random motion of water molecules, with its dimensionless parameters mean kurtosis (MK) and radial kurtosis (RK) being sensitive to tissue complexity [2]. In MCI patients, conversion to AD is predicted by CSF-biomarkers [4]. Here, we investigate if the diffusion parameters MK, RK as well as mean diffusivity (MD) and fractional anisotropy (FA) differentiate MCI-patients with pathological CSF ($MCI_{p\text{-}CSF}$) from MCI-patients without pathological CSF ($MCI_{np\text{-}CSF}$) and from controls using ROI-based analysis.

Method: Sixty-two MCI-patients and thirty-one controls (mean age 70.3±4.0; 51.6 % females) participated in the study. MCI-patients were defined as $MCI_{p\text{-}CSF}$ (n = 32; mean age 71.6±5.1; 53.1 % females) if Aβ42:P-tau ratio < 6.5 and T-tau > 350 ng/L and Aβ42 < 530 ng/l in CSF, and as $MCI_{np\text{-}CSF}$ if tau < 400 ng/L and Aβ42:P-tau ratio > 6.5 and Aβ42 > 530 (n = 30; mean age 69.1±6.2; 60.0 % females). DKI data (33 slices, slice thickness = 3 mm, pixel size = 2x2 mm^2) were acquired on a Siemens Trio 3T MRI using a 2D SE pulse sequence (TE/TR = 112 ms/5000 ms) and diffusion weighting along 20 encoding directions with b values, 0, 500, 1000, 2500 and 2750 s/mm^2. Motion correction and eddy current correction was performed using Elastix [5]. Parameter maps were calculated using in-house developed software in Matlab. ROIs of 2x2 pixels were defined in eight areas: the genu and splenium of the corpus callosum (CC), the left and right posterior cingulum, the left and right superior longitudinal fasciculus (SLF) and the left and right hippocampus (Figure 1). Mean parameters values were determined in each ROI (average of four values, one in each pixel); in addition, the mean value for all WM ROIs was calculated.

Fig 1. ROI placement (white squares) (a) in the CC genu, (b) in the CC splenium, (c, d) in the right and left posterior CG, (e, f) in the right and left SLF and (g, h) in the right and left hippocampus.

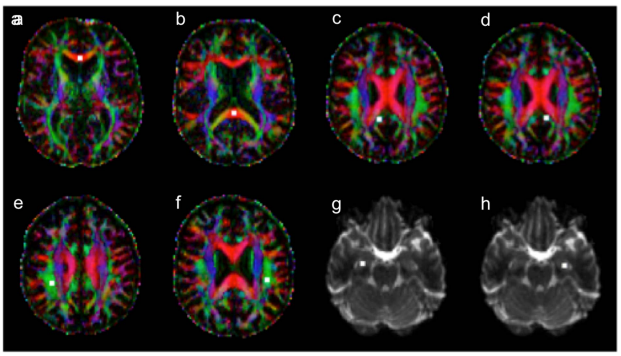

Table 1. Diffusion parameters (mean and standard deviation) in patients with $MCI_{p\text{-}CSF}$, $MCI_{np\text{-}CSF}$, all MCI patients and controls, respectively. The four rows at the bottom show the average value from the six WM areas.

ROI	$MCI_{p\text{-}CSF}$ (n = 37)	$MCI_{np\text{-}CSF}$ (n = 32)	All MCI (n = 69)	Controls (n = 35)
Genu CC MD	0.74 (0.11)	0.75 (0.10)	0.74 (0.10)	0.72 (0.08)
Genu CC FA	0.80 (0.09)	0.81 (0.07)	0.80 (0.08)	0.83 (0.05)
Genu CC MK	1.04 (0.17)	1.04 (0.15)	1.04 (0.16)	1.08 (0.11)
Genu CC RK	1.53 (0.56)	1.47 (0.54)	1.50 (0.55)	1.61 (0.39)
Splenium CC MD	0.62 (0.10)	0.62 (0.10)	0.62 (0.10)	0.59 (0.09)
Splenium CC FA	0.89 (0.06)	0.89 (0.07)	0.89 (0.07)	0.91 (0.05)
Splenium CC MK	1.19 (0.18)	1.17 (0.16)	1.18 (0.17)	1.16 (0.21)
Splenium CC RK	2.06 (0.68)	1.90 (0.62)	1.99 (0.66)	1.75 (0.87)
Cingulum right MD	**0.71 (0.07)** [1]	0.69 (0.08)	**0.70 (0.07)** [4]	0.67 (0.06)
Cingulum right FA	0.59 (0.06)	0.59 (0.06)	0.59 (0.06)	0.60 (0.07)
Cingulum right MK	**0.97 (0.09)** [1]	**0.96 (0.12)** [3]	**0.97 (0.10)** [4]	1.03 (0.11)
Cingulum right RK	1.19 (0.22)	1.18 (0.28)	1.18 (0.25)	1.25 (0.23)
Cingulum left MD	0.71 (0.08)	0.70 (0.08)	**0.70 (0.08)** [4]	0.68 (0.06)
Cingulum left FA	0.57 (0.07)	0.59 (0.06)	0.58 (0.07)	0.59 (0.07)
Cingulum left MK	0.95 (0.08)	0.96 (0.11)	0.95 (0.10)	0.99 (0.13)
Cingulum left RK	1.17 (0.24)	1.20 (0.28)	1.18 (0.26)	1.22 (0.26)
SLF right MD	**0.72 (0.08)** [1, 2]	0.68 (0.05)	0.70 (0.07)	0.68 (0.06)
SLF right FA	0.67 (0.08)	0.69 (0.07)	0.68 (0.08)	0.70 (0.05)
SLF right MK	1.03 (0.13)	1.01 (0.12)	1.02 (0.13)	1.03 (0.11)
SLF right RK	1.53 (0.42)	1.46 (0.37)	1.49 (0.40)	1.53 (0.35)
SLF left MD	0.68 (0.10)	0.67 (0.06)	0.68 (0.09)	0.65 (0.06)
SLF left FA	0.68 (0.09)	0.70 (0.07)	0.69 (0.08)	0.71 (0.06)
SLF left MK	1.00 (0.14)	1.00 (0.12)	1.00 (0.13)	1.03 (0.11)
SLF left RK	1.45 (0.43)	1.45 (0.36)	1.45 (0.40)	1.51 (0.30)
Hippocampus right MD	**0.95 (0.13)** [2]	0.88 (0.07)	0.92 (0.11)	0.90 (0.09)
Hippocampus right FA	0.15 (0.03)	0.15 (0.04)	0.15 (0.04)	0.15 (0.04)
Hippocampus right MK	0.72 (0.07)	0.71 (0.07)	0.72 (0.07)	0.74 (0.08)
Hippocampus right RK	0.68 (0.08)	0.67 (0.07)	0.67 (0.08)	0.71 (0.10)
Hippocampus left MD	0.91 (0.11)	0.91 (0.10)	0.91 (0.11)	0.92 (0.10)
Hippocampus left FA	0.15 (0.04)	0.16 (0.05)	0.16 (0.04)	0.17 (0.06)
Hippocampus left MK	**0.71 (0.07)** [1]	**0.69 (0.08)** [3]	**0.70 (0.07)** [4]	0.76 (0.07)
Hippocampus left RK	**0.66 (0.09)** [1]	**0.63 (0.09)** [3]	**0.65 (0.09)** [4]	0.73 (0.07)
WM average MD	**0.69 (0.06)** [1]	0.69 (0.05)	**0.69 (0.06)** [4]	0.67 (0.03)
WM average FA	**0.70 (0.05)** [1]	0.71 (0.03)	**0.70 (0.04)** [4]	0.72 (0.03)
WM average MK	1.03 (0.10)	1.02 (0.09)	1.03 (0.09)	1.05 (0.09)
WM average RK	1.49 (0.27)	1.44 (0.25)	1.47 (0.26)	1.48 (0.30)

[1]Statistically significant vs. controls ($p < 0.05$).
[2]Statistically significant vs. $MCI_{np\text{-}CSF}$ ($p < 0.05$).
[3]Statistically significant vs. controls ($p < 0.05$).
[4]Statistically significant vs. controls ($p < 0.05$).

Results

Results are presented in Table 1. In patients with $MCI_{p\text{-}CSF}$ compared to both patients with $MCI_{np\text{-}CSF}$ and controls, MD was increased in the right SLF and in the right hippocampus (significance threshold: 0.05). MCI patients (whole group) and controls differed in some areas and parameters only, implying that the magnitude of this difference was below the level of detection in this ROI-based analysis. For MK, RK, MD and FA in the averaged WM data, a relative effect size (calculated as the ratio of difference in means between all MCI and the control group, to the mean of control group) of 5.1 %, 11% 4.6 % and 3.1 % is needed in order to obtain a statistical power of 0.8 using t-test with a significance threshold of 0.05. Thus, the difference in means between MCI-patients and controls is most likely smaller than 5.1 % and 11% for MK and RK, respectively.

Discussion and conclusions:

The most sensitive parameter for detecting brain tissue alterations in MCI was MD. The new DKI parameters, MK and RK, did not outperform FA and MD for differentiation between patients with $MCI_{p\text{-}CSF}$, patients with $MCI_{np\text{-}CSF}$ and controls, likely due to the higher variability for these parameters and the associated loss in statistical power. Also, the group with $MCI_{np\text{-}CSF}$ may contain individuals with other diseases than incipient AD that may affect white matter, for example depression and vascular dementia.

References

[1] Sexton et al. Neurobiol Aging 2011;32:2322.e5
[2] Jensen J *et al*. MRM 2005:1432-40
[3] Lu H *et al*. NMR Biomed 2006;19:236–247.
[4] Hansson et al, Lancet Neurol 2006;5:228-34.
[5] *Kleinet a*. IEEE Trans Med Img 2010;29:196-205.