Age-related changes of the bound pool fraction in white matter

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Target Audience: Researchers and clinicians interested in quantitative magnetization transfer, bound pool mapping and white matter demyelination.

Purpose/Introduction: While conventional MRI allows to assess several macroscopic features of the ageing brain including the accumulation of white matter hyperintensities (WMH) and brain atrophy,[1] microstructural changes remain largely undetected. The magnetization transfer ratio (MTR) has been proposed as a sensitive measure for assessing microstructural tissue changes,[2,3] but it is only a relative measure of the MT phenomenon. In this work, we therefore have hypothesized that the bound pool fraction (BPF) is more sensitive than the MTR for age related tissue changes such as extravascular widening, demyelination and tissue rarefication. The bound pool fraction is a fundamental parameter of the two-pool model[4] for brain tissue and reflects the macromolecular proton density, i.e. the relative amount of bound protons that are involved in magnetization transfer. It is commonly believed that the BPF directly reflects myelin density and macromolecular content.

Subjects and Methods: The study cohort consisted of 99 healthy volunteers (39-80 years) with no history or signs of neuropsychiatric disorder. MRI was performed on a 3T Tim Trio System (Siemens Healthcare, Erlangen, Germany). The BPF was mapped with a recently proposed sequence[5] that consists of a stimulated echo preparation, which ensures that exclusively the free proton pool is labeled, followed by a single shot EPI readout at multiple mixing times (FOV of 25x25x10 cm, matrix = 100x100x11, avg = 5, acquisition time = 4.8 minutes). An MPRAGE sequence with 1mm isotropic resolution was acquired as a basis for automated segmentation of various white matter regions. For comparison, a conventional MTR was obtained from a gradient echo sequence that was performed with and without an off-resonance saturation pulse. The BPF was calculated as described by Soellinger[5], using a two parameter monoexponential fit implemented in MATLAB. To assess MT in the WM regions we used the human brain WM atlas[6], which was registered nonlinearly to the MPRAGE scan from each volunteer using FSL FNIRT (FSL; FMRIB, Oxford, UK). WMH that were identified on FLAIR images were excluded from the masks. In each of the obtained masks the median of the BPF values was taken to avoid noise effects. A total of 29 regions were analyzed, where the left and right hemispheres were merged. The same procedure was applied on the MTR maps.

Results: BPF as well as MTR values showed a linear decrease with age in all WM regions (table 1). Although BPF maps had considerably more noise, they yielded a higher sensitivity for age related changes. This was evident from the relative change and from a steeper slope of the regression line (figure 1). The highest changes were found in the anterior corona radiata, followed by the posterior thalamic radiation (described in table 1 and visualized in figure 2).

Conclusion: While the MTR benefits from the high SNR of the underlying gradient echo sequence, this work proves that the BPF is more sensitive and therefore more specific for age related white matter changes. This is further supported by the observation that the age dependent decrease of the BPF is strongest in normal appearing areas where the highest density of age related WMH is usually expected. Further work will have to assess the relationship between local BPF changes, cognition and the prognostic values for the development of WMH.

REGION	BPF		MTR		BPF (%)	BPF (%)
	R^2	p	R^2	p	39-50	70-80
Ant. corona radiata	**0,227**	0,0001	0,154	0,0001	14,92	12,15
Post. Thal. radiation	**0,194**	0,0001	0,148	0,0001	14,04	11,86
Body of CC	**0,169**	0,0005	0,139	0,0002	12,99	10,44
Genu of CC	0,135	0,0004	**0,175**	0,0001	13,54	11,93
Splenium of CC	**0,129**	0,0005	0,095	0,0032	13,21	12,19
External capsule	**0,103**	0,0050	0,082	0,0056	11,32	10,49
Ant. limb of int. capsule	**0,103**	0,0018	0,092	0,0028	13,85	11,86
Ret. part of int. capsule	**0,054**	0,0357	0,0197	0,1812	13,80	12,53
Total white matter	**0,206**	0,0001	0,1540	0,0001	13,12	11,51

Table 1: Changes of BPF and MTR values with age, showing the R^2 and p-values of the regression analysis and median BPF values of middle-aged and old volunteers

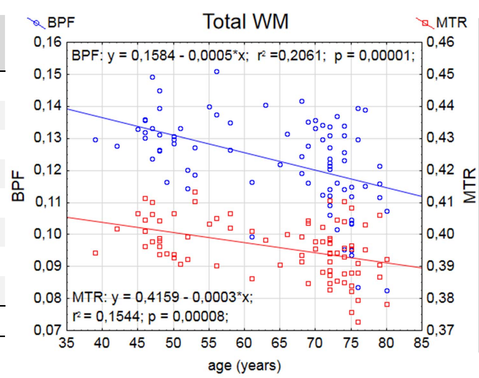

Figure 1: Regression of the BPF (blue) and the MTR (red) in all white matter regions assessed over age;

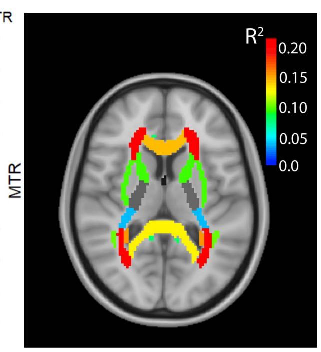

Figure 2: Age-related changes of the BPF for each WM region; WM atlas weighted with $\mathbf{R^2}$ values of each region, overlaid on the MNI152.

References:

1. Enzinger C et al. Neurology 2005;64(10):1704-11;
2. Ropele S et al. AJNR 2010;31(7):1297-301;
3. Rovaris M et al. Radiology 2003;227(3):731-8;
4. Morrison C, Henkelman R M. MRM 1995;33(4):475-82;
5. Soellinger M et al. MRM 2011;66(3):717-24;
6. Oishi K et al. NeuroImage 2008;33(7):447-57;