# Assessment of bound pool fractions in the aging brain with stimulated echoes

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## Introduction

Besides degeneration of axons, normal aging of human cerebral white matter (WM) is histologically associated with changes in myelin sheaths [1,2]. Exchange of magnetization between protons of tissue water and those bound to macromolecules is used in MRI to determine the bound pool fraction (BPF). BPF, the molar fraction of bound protons is associated with intact myelin and was previously suggested as a predictor of myelin content in postmortem white matter [3]. A recently presented single-shot EPI (sshEPI) imaging sequence, which is based on stimulated echo amplitude modulation (STEAM) allows for fast quantification of BPF [4]. The multislice method enables coverage of central brain areas in five minutes and is low in SAR, and therefore applicable at higher field strengths. Consequently, the STEAM approach seems promising for BPF mapping in clinical routine. To determine normative BPF ranges of the human brain, we conducted a pilot study in healthy volunteers of different age. BPF of five different WM brain structures and its difference were evaluated for two age groups of ten subjects each.

## Subjects and methods

Study population consisted of one group of 10 young subjects aged between 31 and 44 years (5 male / 5 female, mean age 31y) and a second group of 10 subjects in the range of 47 to 77 years (4 male / 6 female, age: mean age 60y). A total of 23 subjects underwent MRI, of which 3 were excluded from further analysis due to motion artifacts.

Measurements were performed on a 3T Tim Trio (Siemens Healthcare, Erlangen, Germany). As described in [4], the applied sequence consists of a tagging preparation followed by a multiple sshEPI scheme (Figure 1). Slice permutation enables imaging of multiple mixing times (TM) for a single tagging preparation. The basic experiment is repeated n times permuting the slice order such, that all TMs are acquired for each slice. Imaging parameters were: TM from 3.2ms to 603.2ms with 60ms TM-spacing, echo time of the EPI readout was 22ms, TR=2600ms, spatial resolution: 2.5x2.5x5 mm$^3$, slice gap: 20%, 11 slices, 11 experiments, NSA=10. Measurements TM2–TM10 were used for monoexponential fitting [4]. Signal acquired with minimal TM was assumed for net magnetization before any magnetization transfer occurred. Total acquisition time for covering a FOV of 25x25x6.6 cm$^3$ was 4.8 minutes. T1 maps, which are obtained automatically as a by-product of the BPF estimation procedure, were used to manually outline regions of interest including splenium and genu of the corpus callosum, and corona radiata, frontal and occipital white matter were separately assessed for each hemisphere. To evaluate the significance of differences between the two age groups a sampled t-test, in which p<0.01 was considered to be statistically significant, was applied.

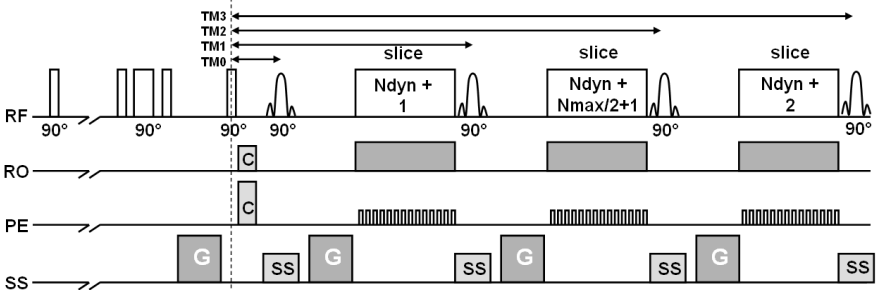


***Figure 1:*** *Schematic of the applied multislice STEAM sequence. Non-slice-selective water-only preparation is followed by slicewise sshEPI readout of different TMs. The slices are permuted with each experiment (Ndyn).*

## Results

Mean regional BPFs (n=10) for the two age groups (Table 1) were in good agreement with published data using other methods [5,6]. Standard deviations of both age groups were in the range of recently presented in-vivo BPF measurements at 3T in 5 subjects [5] but higher than reported for a balanced stead state free precession (bSSFP) approach at 1.5T in 12 subjects [6]. Except for frontal WM, all WM regions evaluated had significantly lower mean BPFs for the older age group (Table 1).

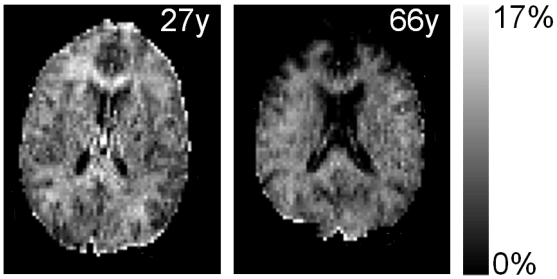


***Figure 2:*** *Exemplary bound pool fraction maps of a 27 and a 66 years old woman.*

***Table 1:*** *Mean bound pool fractions (BPF) for two age groups (n=10 per group) and standard deviations (SD). Significance of regional differences of the two groups was assumed for p<0.01.*

| Age group | | 26-44y | | 47-77y | | p |
|---|---|---|---|---|---|---|
| | L/R | Mean BPF | SD | Mean BPF | SD | |
| WM cc genu[1] | | 0.176 | 0.026 | 0.153 | 0.020 | 0.04 |
| WM cc splen[2] | | 0.152 | 0.020 | 0.134 | 0.016 | 0.03 |
| WM frontal | left | 0.149 | 0.017 | 0.136 | 0.018 | 0.11 |
| | right | 0.143 | 0.018 | 0.132 | 0.017 | 0.16 |
| WM occipital | left | 0.134 | 0.007 | 0.125 | 0.008 | 0.017 |
| | right | 0.131 | 0.010 | 0.121 | 0.012 | 0.07 |
| WM cor rad[3] | left | 0.129 | 0.012 | 0.114 | 0.008 | 0.005 |
| | right | 0.121 | 0.015 | 0.106 | 0.009 | 0.014 |

[1]*corpus callosum genu* [2]*corpus callosum splenium* [3]*corona radiate*

## Discussion

Main advantages of the applied method, its speediness and its applicability at 3T (SAR was well below limits for all measurements), come to the prize of limited resolution. Still, regional BPF quantification was feasible in the elderly with mild atrophy associated with normal aging. Thus, investigations of small effects associated with normal aging, which rely on the measurements of big cohorts and ROI analyses, are feasible. As mentioned above, three scans had to be repeated due to motion artifacts. High motion sensitivity mainly arises from the use of STEAM with long mixing times and EPI phase correction imperfections. In order to calculate BPF, signal intensities acquired with minimal mixing time are divided by intensities estimated by a monoexponetial fit of ten different mixing times. Therefore, proper EPI phase correction at minimal TM is crucial for accurate BPF reconstruction.

## Conclusion

The presented pilot study focusing on regional, age related variations in BPF, indicates a decrease of BPF in several WM regions as a consequence of aging. While the main limitation of the method applied was its motion sensitivity, its short acquisition time was especially appreciated by the elderly. This allows gathering larger cohorts to gain sufficient coverage of adulthood up to high age, which should give more insights into age related myelin changes of WM.

**References** [1] Morrison JH et al Science. 278(5337): 412-9 (1997) [2] Bowley MP et al J Comp Neuro 518: 3046-64 (2010) [3] Schmierer K et al JMRI 26(1):41–51 (2007) [4] Soellinger et al Proc. ISMRM18 (2010):5148 [5] Underhill HR et al NeuroImage 47: 1568-1578 (2009) [6] Garcia M et al Neuroimage 52: 532-537 (2010)