Determinants of iron accumulation in the normal ageing brain

Lukas Pirpamer[1], Edith Hofer[1], Paul Freudenberger[2], Stephan Seiler[1], Christian Langkammer[3], Franz Fazekas[1], Stefan Ropele[1], and Reinhold Schmidt[1]
[1]*Department of Neurology, Medical University of Graz, Graz, Styria, Austria,* [2]*Molecular Biology and Biochemistry, Medical University of Graz, Styria, Austria,*
[3]*MGH/HST Martinos Center for Biomedical Imaging, Harvard Medical School, Boston, MA, United States*

Target audience: Researchers and clinicians interested in brain-iron and the influence of risk-factors and iron related clinical parameters.

Purpose/Introduction: In a recent postmortem study, R2* relaxometry in gray matter (GM) of the brain has been validated as a non-invasive measure for iron,[1] which is an important trace element for normal brain development and function. Iron accumulation in the normal ageing brain is a repeatedly recognized finding[2] and seems to be related to brain maturation and degeneration. However, it remains unclear how brain iron relates to serum levels of iron, iron-associated genetics and cerebrovascular risk factors. Therefore, the goal of this study was to investigate which of those factors could affect iron accumulation in the ageing brain.

Subjects and Methods: The study cohort consisted of 314 healthy volunteers (38-82 years, 120 male, 194 female) from a prospective single-center community-based study with the goal of examining the frequency of vascular risk factors and their effects on cerebral morphology and function in the healthy elderly. MRI was performed on a 3T Tim Trio System (Siemens Healthcare, Erlangen, Germany), including a sequence for R2* relaxometry in addition to a clinical MRI protocol. R2* mapping was based on a 3D multi-echo gradient echo sequence with following parameters: FOV = 187x230x128mm^3, matrix = 208x256, TE = 4.92ms, echo-spacing = 4.92ms, TR = 35ms, slice-thickness = 2mm, number of slices = 64, number of echoes = 6. A MPRAGE sequence with 1mm isotropic resolution was used for automated segmentation of GM regions with FREESURFER.[3]
Overall, 18 factors related to lifestyle (body mass index (BMI), smoking, alcohol), cerebrovascular risk factors (hypertension, hypercholesterolemia, cholesterol, HDL, LDL, mean-diastolic and mean-systolic blood pressure, cardiac-disease, diabetes, HbA1c), serum levels of iron (transferrin, ferritin) and iron-associated single nuclear polymorphisms (SNPs) (rs3811647, rs1799945, rs1049296) were investigated with respect to regional iron accumulation. Further parameters were age, sex and normalized GM-volume. The median of R2* values was assessed in all GM regions from the FREESURFER segmentation with a minimum volume of 30 voxels. The statistical analysis was performed in R-statistics and was comprised of two-steps. First, univariate linear regressions were performed to assess correlations between R2* and each factor followed by a multiple regression analysis with the potentially significant factors (p-value < 0.1) as predictors, tested for multicollinearity with the variance inflation factor (<3). To check for mediating effects, we used the SPSS extension by A.F. Hayes (www.afhayes.com). All analyses were corrected for age, sex and GM volume.

Results: Among all factors, the lifestyle and vascular risk factors showed the strongest effect on iron in GM, while iron-associated genetics and serum levels did not show any significant relationship. The result of the multivariate model is presented in table 1. The most striking finding of the study was that BMI is the strongest determinant for iron accumulation in cortical and deep GM. Additionally, in line with previous studies,[1,2,4] deep GM showed also a significant association with age and with smoking (number of recent smoking years with no break longer than three years). The result of this multivariate model applied on each GM region, obtained by the FREESURFER segmentation, is shown graphically in figure 1, where the significant beta-value of BMI is color encoded. Regions with a p-value less than 0.05 are not visualized. The most remarkable region was the hippocampus (beta: 0.139 p-val. <0.0001). Figure 2 shows the direct association of R2* values in total GM and in the hippocampus, plotted for each quartile of BMI. Between the lowest and the highest BMI quartile, a R2* increase of 2Hz could be observed.

Discussion: BMI seemed to be the most relevant determinant of increased R2* values in the brain, especially in the hippocampus. This observation is independent from age and GM volume and is in line with a recent report which has demonstrated that the cortical thickness is reduced with increased visceral fat and BMI.[5] R2* values in the hippocampus might play an interesting role in dementia, as increased iron concentration has also been observed in Alzheimer and Parkinson's diseases.[6]

Conclusion: This study showed that BMI is the most relevant risk-factors for elevated R2* values as marker for increased iron accumulation. The highest correlation was found in the hippocampus, which stands in line with the hypothesis that BMI is an independent risk factor for dementia.[7] Further studies are needed to explore the mechanisms of these finding.

	Total GM	Cortical GM	Deep GM
	beta	beta	beta
BMI	**0.077**	**0.076**	**0.051**
hypertension	0.097	0.094	0.117
smoking (Recent-PackYears)	0.004	0.004	**0.018**
HDL	0.001	0.001	-0.003
embolic disease	0.069	0.070	0.142
age	0.005	0.006	**0.029**
HBA1C	0.012	0.023	-0.121
mean systolic bp	-0.001	-0.001	-0.001

Table 1: The result of the multiple regression analysis shows the determinant for total GM, cortical GM and deep GM iron; significant values are highlighted

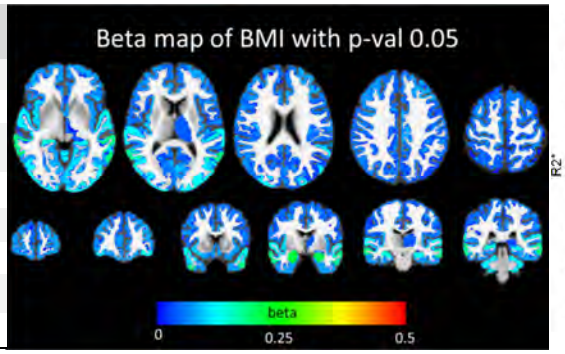

Figure 1: Statistical parameter mapping reveals the regional effect of BMI on iron content in gray matter

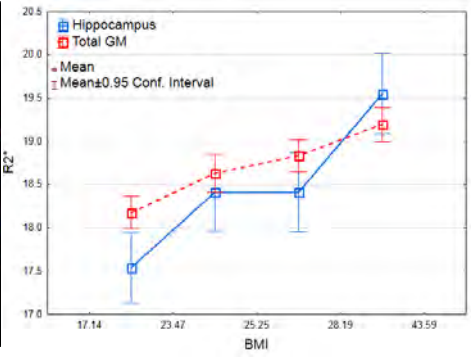

Figure 2: R2* in total GM and Hippocampus, shown for each quartile of BMI

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