

## R2\* in the normal ageing brain and its relation to serum iron

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**INTRODUCTION:** Iron is critically important for brain development and brain function. Iron accumulation in the ageing brain is a repeatedly recognized finding<sup>1</sup> and seems to be related to brain maturation and degeneration. Supply with iron is mostly provided by transferrin which facilitates iron to transverse the blood-brain barrier through receptors in the vascular endothelial cells. However, it remains unclear how brain iron scales with serum levels of iron and how this relates to the presence of age related white matter hyperintensities (WMH) and cerebrovascular risk factors.

To goal of this study therefore was to investigate this relationship in a large cohort of normal ageing subjects. Assessment of brain iron was achieved with R2\* relaxometry, which has been recently validated in a postmortem study<sup>2</sup>.

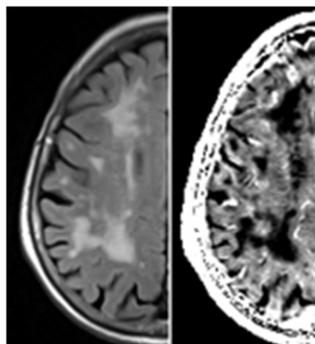
**METHODS:** In this study, 275 healthy subjects (112 male, 163 female, mean age 64.9,  $\pm 10.1$ ) from a prospective single-center community-based study with the goal of examining the frequency of vascular risk factors and their effects on cerebral morphology and function in the healthy elderly. MRI was done on a 3T scanner (TimTrio, Siemens Medical Systems, Germany) and included a sequence for R2\* relaxometry in addition to a clinical MRI protocol. R2\* mapping was based on a 3D multi-echo gradient echo sequence (FOV of 187 x 230 x 128 mm<sup>3</sup>, matrix = 208 x 256, BW= 190Hz/px, TE of first echo = 4.92ms, echo spacing = 4.92ms, TR=35ms, slice thickness = 2mm, number of slices = 64, number of echoes = 6). A FLAIR sequence was used to identify and score WMH according to the Fazekas scale and to generate corresponding lesion masks. The FLAIR and 3D gradient echo sequence were registered with FSL-FLIRT using a high resolution MPRAGE scan as reference. R2\* maps were generated by a mono-exponential fit to the multi echo data which took the noise level for each echo into account. R2\* was assessed in WMH, normal appearing white matter (NAWM), and in deep gray matter structures.

In addition to the MRI, blood was collected to determine total transferrin iron and ferritin in the serum. Additionally, cerebrovascular risk factors including hypertension were assessed. Statistical analyses were performed using linear and multiple regression models.

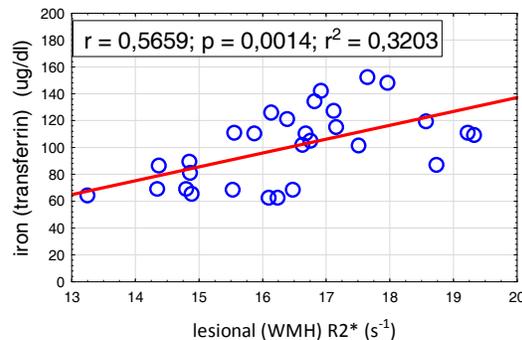
**RESULTS:** R2\* in deep gray matter was not related to serum iron and did not scale with WMH volume. R2\* in WMH was significantly lower than in NAWM ( $17.99 \text{ s}^{-1} \pm 1.93 \text{ s}^{-1}$  vs.  $21.81 \text{ s}^{-1} \pm 1.29 \text{ s}^{-1}$ ) whereas R2\* was decreasing with larger WMH volume (Figure 1). As can be seen in Figure 2 and Table 1, R2\* in WMH was negatively associated with age and positively associated with serum iron. The effect of iron was only seen in subjects suffering from hypertension and with WMH score 2 or 3 (confluent and early confluent lesions). In these subjects (n=29), a similar relationship was also found in NAWM but with a weaker effect of serum iron.

**DISCUSSIONS AND CONCLUSIONS:** Our results are consistent with previous reports of lower R2\* in WMH<sup>3</sup>. While R2\* changes in white matter may also reflect changes in the diamagnetic myelin content, the positive association with serum iron suggests increased iron levels in more severe WMH. Whether iron crosses the disrupted blood brain barrier or accumulates in the vascular endothelial cells remains unclear, but vascular risk factors and microangiopathy seem to play a major role for iron accumulation.

**REFERENCES:** 1. Hallgreen B, Sourander P. Journal of neurochemistry. 1958; 3(1):41–51.  
 2. Langkammer C, Krebs N. Radiology. 2010; 257(2):455–462.  
 3. Paling D, et al. Journal of neurology. 2012; 83(8):785–92.



**Figure 1.** Subject with WMH score 3 (left: FLAIR, Right: R2\* map).



**Figure 2.** Correlation between R2\* in lesional WMH and total transferrin in the serum of hypertensive patients with a high WMH-score

WMH-score	HT	variable	$\beta$	p-value
0 & 1	yes	age	-0.250	0.012
		iron	0.172	0.081
	no	age	-0.270	0.001
		iron	0.116	0.259
2 & 3	yes	age	-0.217	0.172
		iron	0.561	0.001
	no	age	-0.318	0.246
		iron	0.220	0.417

**Table 1:** Results of the multiple regression analysis. R2\* in WMH was independently predicted by age and serum iron (total transferrin).