The relative contributions of the transition metals iron and manganese to T_1 and T_2 in white and gray matter

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***Introduction**:* In the brain, a major contributing factor to MRI contrast between gray matter (GM) and white matter (WM) is the myelin sheath[1]. However, the paramagnetic transition metals iron (Fe) and manganese (Mn) also contribute to overall contrast. This study thus aimed to disentangle the effects of myelin, Fe, and Mn on the MR parameters T1 and T2 using control rats and mutant Shaker rats, whose brains are completely devoid of myelin (**Fig. 1**). We made quantitative T_1 and T_2 MRI measurements *in vivo*, and metal measurements using synchrotron radiation X-Ray fluorescence (XRF) in fresh, freeze dried sections. These measurement conditions were essential because tissue fixatives flush metals from the tissue and alter MRI relaxation [3].

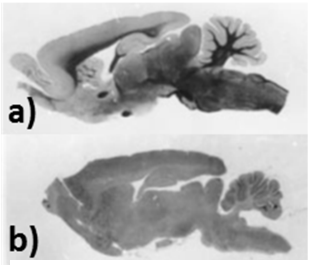

***Figure 1**: Myelin staining in normal (a) and Shaker (b) rat brain [2].*

***Theory**:* To express the contributions of myelin, Fe, and Mn to relaxation, the relaxation constants T_1 and T_2 were decomposed into linear functions of the same form: $1/T_{1,2\ obs} = R_{1,2\ 0} + r_{1,2\ myelin}[myelin] + r_{1,2\ Fe}[Fe] + r_{1,2\ Mn}[Mn]$ [4] where the "r" terms represent the relaxivities. The remaining unspecified contributors to contrast were collected into the R_0 term. This equation can be rewritten as $1/T_{1,2\ obs} = A + B$ where $A = R_{1,2\ 0} + r_{1,2\ myelin}[myelin]$ and $B = r_{1,2\ Fe}[Fe] + r_{1,2\ Mn}[Mn]$, to separate the contributions of R_0 and myelin from Fe and Mn to the $1/T_{1,2}$ of a given tissue.

***Methods**:* Quantitative *in vivo* 7T MRI data from the cerebellum of 12 mature (16 wks) Shaker rats on a Long Evans (LE) background and 7 age-and-diet-matched LE controls were combined with XRF (from I18, Diamond Light Source, UK) maps (from 1 Shaker and 1 control) of the transition metal concentration in excised brain tissue (**Fig. 2**). For each of Shaker and control rats, estimates of average T_1 and T_2, Fe and Mn concentration were obtained in WM and GM regions of interest (**Table 1**). Relaxivities of transition metals were obtained from the literature, in units of g/(μg*s) tissue dry weight and are as follows: Fe relaxivity r_1 = 2.9x10^{-5} [5], r_2 = 2.99x10^{-3} [5]. Mn relaxivity r_1 = 0.155 [6], r_2 = 0.958 (derived from a combination of [4] and [6]).

Results: Combining the observed relaxation values and transition metal concentrations (Table 1) with their relaxivity values from the literature, the proportional contribution of the transition metals can be obtained from (B/(A+B)). In control WM and GM, the transition metals account for 35 % and 43 % of observed $1/T_1$ respectively. These values increase, as expected given the absence of a myelin contribution, in the Shaker animals to 55 % and 46 %. $1/T_2$ contrast appears to be dominated by the R_0 and myelin terms, with the transition metals accounting for 7.5 % and 7.7 % of observed T1 in control WM and GM, increasing to 11.3 % and 9.2 % in the Shaker animals.

Table 1

		T1 (ms)	T2 (ms)	[Fe] (μg/g)	[Mn] (μg/g)
Control rat	WM	1340 ± 70	44 ± 4	13 ± 3	1.7 ± 0.2
	GM	1550 ± 60	44 ± 1	23 ± 5	1.8 ± 0.2
Shaker rat	WM	1880 ± 90	60 ± 3	20 ± 3	1.9 ± 0.2
	GM	1650 ± 130	51 ± 2	25 ± 11	1.8 ± 0.5

Discussion and Conclusion: Endogenous transition metals are responsible for a substantial percentage of T_1 in white matter and gray matter. T_2, on the other hand, is more resilient to changes in transition metals. This suggests that it is more appropriate to use T_2 to investigate demyelinating disease when there is suspected transition metal involvement. It is interesting to note, despite the lack of myelin, there is overall good T_1 and T_2 contrast in the Shaker rats which is driven by changes in transition metals between gray and white matter.

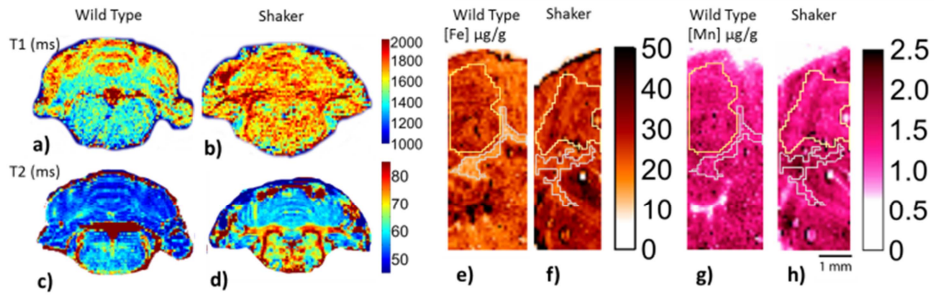

Figure 2: *T_1, T_2, Fe and Mn maps in the cerebellum of control and Shaker rats.*

References: *1. Koenig, S.H. et al., MRM, 1991.* ***20****(2). 2. Kwiecien, J. et al., J. Neurocyt., 1998.* ***27****(8) 3. Schrag, M. et al., Biometals, 2010.* ***23****(6). 4. Zhang, N. et al., NMR Biomed., 2009.* ***22****(4). 5. Ghugre, N.R. et al. MRM, 2005.* ***54****(5). 6. Bock, N.A. et al. Brain Res., 2008.* ***1198****.*