Quantitative Imaging of Magnetization Transfer in the Myelin Mutant *Shaking* Pup

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Introduction: Magnetization transfer (MT) imaging is widely used to characterize white matter (WM) diseases such as multiple sclerosis (MS). However, the traditional MT ratio (MTR) used for MT effect quantification is pulse sequence dependent, and represents the net contributions of several physically meaningful parameters. This limits the pathological specificity of MTR such that, for example, demyelination cannot reliably be discriminated from axonal degeneration. Quantitative MT imaging (qMTI) allows estimation of the underlying parameters governing MT effects in tissues [2-4], and may potentially improve the specificity of MT imaging. Traditionally, a simplified, two-pool cross-relaxation model of tissue is considered in qMTI [2]. In this model, macromolecular protons (bound pool) are considered in magnetization exchange with free water protons (free pool). Typically, several parameters of the model are estimated from a series of MT measurements with different offset frequencies and MT pulse flip angles. These include the bound pool fraction (*f*, the ratio of protons bound to macromolecules to the total number of protons), cross-relaxation rate constant (*k*, the rate of magnetization exchange between the free and bound pools), and T2 of the bound pool fraction (T2b). Typical values for these parameters are well-studied for the human brain [2-6]. In this abstract, we report initial results on the qMTI parameters in the *shaking* (*sh*) pup, one of the "myelin mutant" animal models of dysmyelinating disease in humans. qMTI parameters were measured in anticipation of a trial of remyelination therapy by transplantation of neural stem cells; qMTI parameters may be useful to track the progress of remyelination noninvasively.

Materials and Methods: The data were acquired in one *sh* pup and one normal dog on a 3T GE SIGNA scanner (Waukesha, Wisconsin, USA). The protocol included collection of MT-weighted data, data for relaxation rate (R1) and proton density (PD) mapping, and data for B1 mapping. MT images were acquired for four offset frequencies Δ=3, 6, 9, 12 kHz at two power levels of saturation pulse corresponding to flip angles 600° and 850°. The MT data were collected using a 3D TOF SPGR-based sequence (TR/TE=34/1.7 ms, flip=10, 8 ms Fermi saturation pulse, image matrix 160x128, FOV=14 cm, slice thickness 1.6 mm, 64 slices, total 35 min). The data for R1/PD mapping were collected using the same sequence but without the saturation pulse (TR/TE=20/1.7 ms, total 11 min) at flip angles 4°, 10°, 20°, and 30°. The data for B1 mapping were collected using multishot SE EPI sequence (TR/TE=4000/8.9 ms, image matrix 96x96, FOV=14 cm, slice thickness 3.2 mm, 31 slices) with two sets of flip and refocusing angles (60°/120° and 120°/240°).

R1 and PD maps were estimated by fitting data to the SPGR signal equation. B1 maps were estimated as described in Ref. 7. MT data were fitted to the first-order analytical approximation to the expression for steady-state magnetization in pulsed MT experiments based on SPGR sequences [4]. The direct saturation effect was considered negligible due to the sufficiently high offset frequency and low power of a saturation pulse. Several parameters were fixed or approximated using other parameters as explained in Ref. 4; these included the relaxation rate of bound pool (R1b=1 s^{-1}) and relaxation rate of free pool (Rf). B1 maps were used to account for regional variations in both MT pulse and excitation flip angles, which should increase the accuracy of parameter estimation. Signal drift was monitored during the scan in a water phantom and used to correct MT data before fitting. The brain was segmented from surrounding tissues using intensity thresholding and morphological erosion applied to the thresholded images. Post-processing was implemented in MATLAB and required approximately 40 minutes per slice. Parameter means were calculated from ROIs drawn manually on a single slice. WM ROI was placed in centrum semiovale, GM ROI in caudate nucleus.

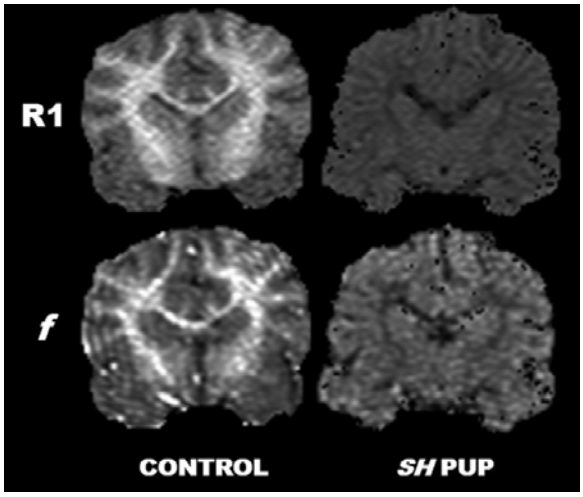

Figure 1. Example of qMTI in a *sh* pup (right) and a normal dog (left). R1 (top) and bound pool fraction (*f*, bottom) are markedly decreased in the hypomyelinated WM of the *sh* pup.

Results and Discussion: The results are shown in Table 1 and Fig. 1. The putative myelin-related parameters *f* and *k* appear markedly decreased in the WM of the *sh* pup relative to the control, as expected from the mutant's profound paucity of myelin. The T2b in the *sh* pup is also slightly decreased compared to control, similar to the decrease of T2b previously seen in MS lesions [2,4]. R1 is markedly decreased in the *sh* pup; since axons are known to be relatively well preserved in the mutant, this observation contradicts any implications of axonal specificity attributed to T1 relaxation based on the "T1 black holes" of chronic MS lesions. We also scanned a 1 month *sh* pup, with slightly different parameters (MT flip angles); the MT measures and T1 values were consistent with those in the 8 month old pup. Further study is needed to assess the myelin-specificity achievable through these qMTI parameters and to determine their ability to track remyelination *in vivo*. We recently transplanted a *sh* pup with human oligodendrocyte progenitor cells; post-transplant qMTI data and histopathological correlations are pending.

	White Matter		Gray Matter	
	Sh pup	Control	*Sh* pup	Control
f (%)	2.3	15.6	3.4	5.5
k (sec^{-1})	1.6	3.0	2.6	1.9
T2b (μsec)	10.3	11.6	10.7	11.3
T1 (ms)	2740	1010	2080	1600

Table 1. qMTI parameters in WM and GM (ROI means) of one *sh* pup and one control dog. Parameters: *f*=bound pool fraction, *k*=cross-relaxation rate constant, T2b = T2 of bound pool, T1=1/R1.

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