WHOLE-BRAIN HISTOGRAMS OF THE BOUND POOL FRACTION REVEAL DELAYED WHITE AND GRAY MATTER DAMAGE AFTER BLAST-INDUCED MILD TRAUMATIC BRAIN INJURY (MTBI)

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Introduction

Blast-induced brain trauma producing mild traumatic brain injury (mTBI) is characterized by widespread axonal damage caused by linear and rotational forces generated during rapid acceleration/deceleration of the brain (1). Cross-relaxation imaging (CRI) is a new method for quantitative mapping of parameters describing magnetization transfer (MT) between mobile water protons (free pool) and macromolecular protons (bound pool) in tissues (2). One of these parameters, bound pool fraction (f) was shown to be highly sensitive to regional white matter (WM) organization, particularly allowing visualization of major fiber tracts based on distinctions in fiber density and myelination (2). It was also recently demonstrated (3) that bound pool fraction is highly variable in gray matter (GM) structures with a general trend of an increase in regions with a higher axonal density. The purpose of this study was to test the capability of CRI to quantitatively identify post-traumatic changes in brain tissues caused by blast-induced mTBI.

Methods

Subjects: Two groups of subjects participated in this cross-sectional case-control study. The mTBI group consisted of 15 Iraq war veterans with at least one blast exposure causing mTBI by American College of Rehabilitation Medicine criteria (4) occurred within 2-5 years before this study (all male, age range 24-46 years). The control group contained 7 healthy volunteers (5 male, 2 female, age range 25-53 years) with no history of any neurological or psychiatric disorder or head trauma.

MRI protocol: Subjects were imaged on a 3T whole-body scanner (Philips Achieva) with a transmit/receive head coil. Whole-brain CRI data were acquired using an MT-prepared 3D spoiled gradient echo (GRE) sequence (TR/TE = 43/2.3 ms, $\alpha = 10°$) with two data points at variable offset frequencies (Δ=4 and 8 kHz) of the off-resonance saturation pulse (effective flip angle 950°, duration 19 ms). Reference images for data normalization were acquired using the same sequence with $\Delta = 96$ kHz. Complementary R_1 maps necessary for parameter fitting were obtained using the variable flip angle (VFA) method with a 3D spoiled GRE sequence (TR/TE = 20/2.3 ms, α = 3, 10, and 20°). All images were acquired with spatial resolution 1.5x1.5x3.0 mm (zero-interpolated to 1.0x1.0x1.5 mm) and one signal average. Scan time was 3.5 minutes and 2 minutes per point for variable-offset and VFA images, respectively. To account for effects of B_0 and B_1 heterogeneity, whole-brain B_0 and B_1 maps were acquired using previously described techniques (5,6) to establish actual offset frequencies of the saturation pulse and determine actual flip angles for parameter fitting.

Image processing: A modified CRI (2) processing algorithm was used. In brief, the method involves a single-parameter (f) fit of the matrix model of pulsed MT (2) to normalized high offset frequency data with just two data points. This approach offers several advantages, such as a minimal impact of direct saturation, a dramatic reduction of necessary data with corresponding shortening of the scan time, and robustness of the fitting procedure (in contrast to multi-parameter fit techniques). While information about the cross-relaxation rate constant k appears unavailable within the above technique, literature data (2,3) suggest that this parameter is subjected to a large variability caused by distinctions in measurement protocols and processing algorithms. In addition, previous studies (2,3) indicate that the inverse rate constant R is fairly constant across brain anatomic structures, and therefore, k and f are strongly correlated. As such, we assume that the above f-mapping technique allows extracting common for both parameters information primarily related to tissue macromolecular composition. Accordingly, the following constraints were used for other two-pool model parameters: $R=k(1-f)/f$=28 s^{-1}, T_2^F=24 ms (3), T_2^B=11 μs (2,3), and $R_1^F=R_1^B=R_1$ (longitudinal relaxation rates of pools are assumed equal). An example f map reconstructed from 2-point data is presented in Fig. 1.

Histogram analysis: Bound pool fraction histograms were calculated with the bin size of 0.125% for the brain parenchyma segmented using BET software (7). Individual histograms were normalized to the total number of voxels and fitted with a three-peak Gaussian model heuristically chosen to describe voxels containing GM, WM, and mixed contribution of WM and GM:

$$H = \sum_{i=1}^{N=3} A_i /(w_i \sqrt{\pi/2}) \exp[-2(f - f_i)^2 / w_i^2]$$

where f_i are the positions, w_i are the widths (defined as 2SD), and A_i are the areas of the peaks. Typical fitted and experimental histograms are shown in Fig 2. Histogram parameters were compared between groups by independent two-tailed t-test (0.05 significance level).

Results

In all subjects, high-quality f maps were obtained (Fig. 1), and the three-component model resulted in adequate histogram shape representation (Fig. 2). No visible brain abnormalities were found on routine diagnostic MRI scans in all subjects. Mean group histograms are shown in Fig. 3, and group histogram parameters are listed in Table 1. Significant differences were identified in peak positions of all three histogram components (WM, GM, and mixed WM-GM) with a general trend of a decrease of f in mTBI patients. Also, a significant decrease of the width of the GM peak was found, which, in conjunction with a decrease of mean f, may reflect a loss of GM heterogeneity due to predominant axonal damage in structures with a higher axonal density (e.g. thalamus, brainstem, and cerebellum).

Conclusions

This report provides the first evidence of the sensitivity of CRI to diffuse brain damage in blast-induced mTBI. An observed reduction of the bound pool fraction in all three histogram components is consistent with the mechanism of diffuse axonal injury, which mainly affects the GM/WM junctions of the frontal and temporal lobes, the internal capsule, the corpus callosum, deep gray matter, and the brainstem (1,8). Histogram parameters of the macromolecular proton fraction have a high potential as prospective quantitative biomarkers of brain injury for various treatment and rehabilitation studies.
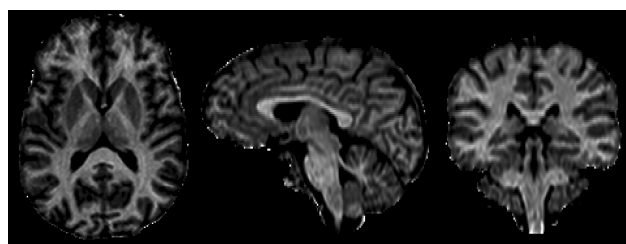

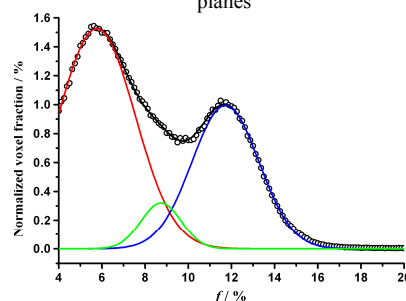**Fig. 1.** Example 3D f map reformatted in axial, sagittal, and coronal planes

Fig. 2. Experimental and fitted whole-brain f histogram of a single subject with superimposed plots of GM (red), WM (blue), and mixed WM-GM (green) components.
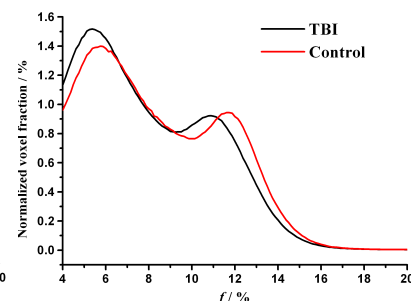

Fig. 3. Group mean whole-brain f histograms of mTBI (black) and control (red) subjects.

Table 1. Bound pool fraction histogram parameters (mean±SD) and comparisons between groups

Parameter		mTBI	Control	P
GM	f_1 / %	**5.38±0.31**	**5.73±0.28**	**0.019**
	w_1 / %	**3.61±0.26**	**4.04±0.59**	**0.026**
	A_1	6.80±0.23	7.11±0.64	0.105
WM	f_2 / %	**11.15± 0.61**	**11.79± 0.22**	**0.016**
	w_2 / %	2.98±0.32	3.08±0.28	0.460
	A_2	3.49±0.43	3.51±0.45	0.946
Mixed	f_3 / %	**8.27±0.44**	**8.76±0.16**	**0.011**
	w_3 / %	2.48±1.69	1.83±0.34	0.330
	A_3	0.99±0.50	0.64±0.47	0.135

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