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# Using double pulsed-field gradient MRI to study tissue microstructure in traumatic brain injury (TBI)

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ABSTRACT

Double pulsed-field gradient (dPFG) MRI is proposed as a new sensitive tool to detect and characterize tissue microstructure following diffuse axonal injury. In this study dPFG MRI was used to estimate apparent mean axon diameter in a diffuse axonal injury animal model and in healthy fixed mouse brain. Histological analysis was used to verify the presence of the injury detected by MRI.



## 1. Introduction

Traumatic brain injury (TBI) is a major cause of disability and death worldwide, accounting for about 30% of all injuries related deaths in the USA [1]. One of the most common pathologies which is present in about 40%–50% of cases of traumatic brain injury (TBI) cases is diffuse axonal injury (DAI) [2], resulting in preferential damage to white matter [3]. DAI ranges from mild to severe, and is accompanied by tissue microstructural alterations including axonal abnormalities such as varicosities and axonal loss, as well as gliosis and microglia cell infiltration [4,5]. While clinical MRI is routinely used to detect gross anatomical and vascular abnormalities, the subtle white matter changes associated with DAI are challenging to diagnose and characterize using conventional MRI methods. Often DAI can only be detected at autopsy [2]. Diffusion MRI methods such as diffusion tensor imaging (DTI) [6] show promise for probing subtle changes in brain microstructure [7–9], however, the resulting metrics such as fractional anisotropy (FA), and mean diffusivity (MD) lack sufficient specificity to suggest the biophysical origin of these changes. Diffusion correlation methods such as double pulsed-field gradient (dPFG) [10,11], illustrated in Fig. 1, in which the MRI signal is sensitized to displacement correlations rather than the mean-squared net displacements, may improve both sensitivity and specificity in detecting brain abnormalities following injury. In the central nervous system (CNS), dPFG data may be used to characterize features of a cylindrical pack of axons that constitute white matter fascicles. By using a dPFG variant with vanishing mixing time between the two diffusion encoding blocks

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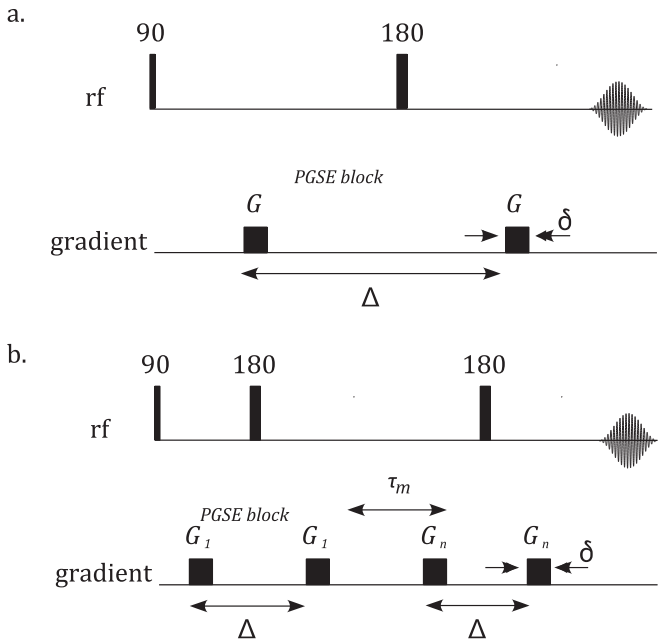


**Fig. 1.** Pulse sequences of a. Pulsed-field gradient [18], encoding net displacements; b. Double pulsed-field gradient, encoding diffusion correlation.

(i.e., $\tau_m = 0$) average axon diameter (AAD) [12–15] or axon mean diameter (AMD) and axon diameter distribution [16,17] can be estimated.

The objective of this study was to apply a 3D implementation of the dPFG acquisition and modeling of axon diameters to a recently developed closed-head impact model of engineered rotation acceleration (CHIMERA) that induces DAI in the mouse brain in select white matter tracts, including the optic tract [5]. We present pilot results in using the dPFG method to detect cellular alterations in the CHIMERA injury model by comparison of the more conventional FA metric computed from DTI with the AMD metric in the optic tract.

## 2. Materials and methods

All animals were housed and treated according the national animal care guidelines and institutional oversight by the NIH/NIAAA IACUC. Brain specimens were obtained from two mice (C57BL/6N, males), one following CHIMERA injury and one with a sham injury (i.e., placed in device, but without impact). The CHIMERA [5] involves delivering an impact of a defined energy to a mouse head. During impact head motion is not constrained. The injury is caused by shear force developing within the brain following impact. Note, this injury model affects predominantly white matter while the skull remains intact. The injury was induced with 0.5 J impact energy and repeated three times with 24 h interval between injuries. One week after the third injury, mice underwent transcardial perfusion with cold 4% formaldehyde in PBS and the fixed brains were removed from the skull. Following a 24 h post-fixation period in 4 °C, brains were rehydrated and stored in PBS with 0.03% sodium azide prior to MRI scanning.

All experiments were performed on a 7 T Bruker vertical wide-bore magnet with an AVANCE III MRI spectrometer equipped with a Micro2.5 microimaging probe and three GREAT60 gradient amplifiers, which have a nominal peak current of 60 A per channel. This configuration can produce a maximum nominal gradient strength of 24.65 mT $m^{-1}$ $A^{-1}$ along each of the three orthogonal directions. The ambient temperature of the magnet bore was 16.8 °C.

Diffusion tensor imaging (DTI) MRI data were acquired using a 3D EPI MRI sequence with the following MRI parameters: echo time (TE)/repetition time (TR) = 23/700 ms, 8 segments, and voxel resolution of $100 \times 100 \times 100\ \mu m^3$; DTI parameters were: gradient pulse duration, δ, of 3 ms, diffusion time, Δ, of 20 ms, and the b-value ($b = \gamma^2\delta^2G^2[\Delta - \delta/3]$, where $\gamma$ is the gyromagnetic ratio and $G$ is the diffusion gradient amplitude) of 400 and 2000 s $mm^{-1}$. DPFG imaging parameters were acquired with the same imaging

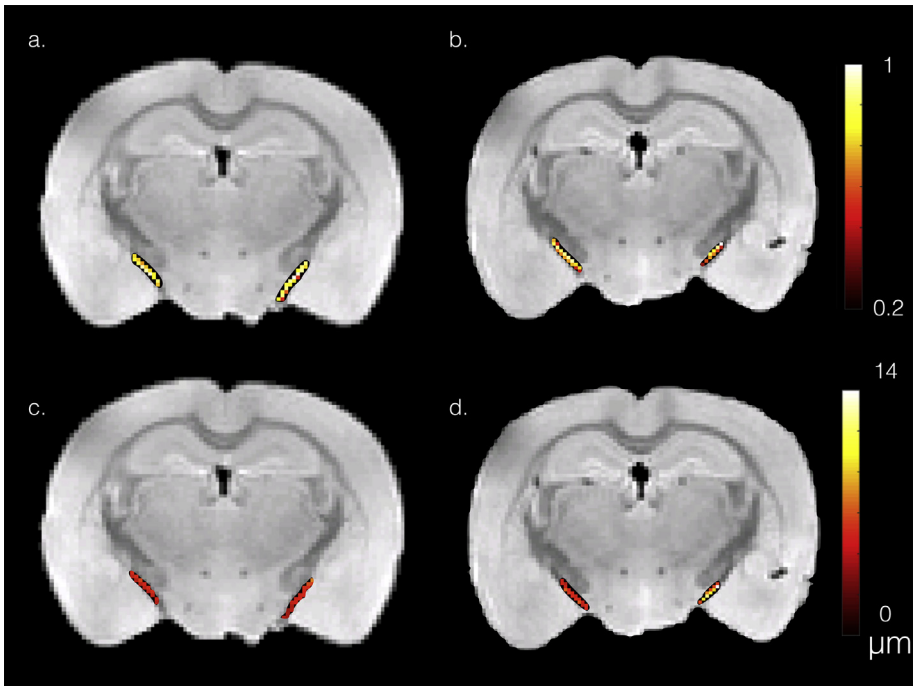


**Fig. 2.** DTI FA (a–b) and dPFG AMD (c–d) maps of the optic tract overlay a structural image of the sham (a, c) and CHIMERA (b, d) mouse brains.

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