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Oscillating Gradient Diffusion Kurtosis Imaging of Normal and Injured Mouse Brains

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Abstract

Recent advances in diffusion MRI employ multiple diffusion encoding schemes with varying diffusion direction, weighting, and diffusion time to investigate specific microstructural properties in biological tissues. In this study, we examined time-dependent diffusion kurtosis contrast in the adult mouse brains and in neonatal mouse brains after hypoxic-ischemic (HI) injury. *In vivo* diffusion kurtosis maps were acquired at a short diffusion time using an oscillating gradient spin-echo (OGSE) sequence at 100Hz and a relatively long diffusion time (20 ms) using a pulsed gradient spin-echo (PGSE) sequence. In the adult mouse brain, we found that the cortex and hippocampus showed larger differences between OGSE kurtosis and PGSE kurtosis than major white matter tracts. In neonatal mouse brains with unilateral HI injury, the OGSE kurtosis map overall provided stronger edema contrast than the PGSE kurtosis map, and the differences between OGSE and PGSE kurtosis measurements in the edema region reflected heterogeneity of injury. This is the first *in vivo* study that demonstrated multi-direction OGSE kurtosis contrasts in the mouse brain. Comparing PGSE and OGSE kurtosis measures may provide additional information on microstructural changes after ischemic stroke.

Graphical abstract

We examined time-dependent diffusion kurtosis contrast in the adult mouse brain and in neonatal mouse brains after hypoxic-ischemic (HI) injury. In the adult mouse brain, we found that the cortex and hippocampus showed greater decreases of kurtosis with decreasing diffusion times than major white matter tracts. In neonatal mouse brains with unilateral HI injury, the edema contrast in

oscillating gradient diffusion kurtosis map at 100 Hz was different from the edema contrast in pulsed gradient diffusion kurtosis map with a diffusion time of 20 ms.

Keywords

diffusion MRI; diffusion time; kurtosis; oscillating gradient; mouse brain; ischemia; cortex; hippocampus

Introduction

Diffusion MRI¹ is a powerful tool for studying the anatomy and pathology of the brain. Its sensitivity to microstructural organization² in the brain enables detection of acute ischemic brain injuries³ and assessments of the integrity of white matter tracts⁴. With the aim to reconstruct white matter tracts and tissue microstructural composition, many groups have made tremendous progress by exploring the dependency of diffusion MRI signals on diffusion encoding direction (e.g., diffusion tensor imaging⁵, Q-ball imaging⁶, and high angular resolution diffusion imaging⁷) and diffusion weighting (b) or q (e.q. q -space diffusion-weighted MRI⁸). The latest fast acquisition techniques have allowed simultaneous exploration in both directions, with diffusion spectrum imaging⁹ as a leading example.

Recently, diffusion time dependency of diffusion MRI signals has shown potential in revealing unique properties of tissue microstructure. The introduction of oscillating-gradient spin echo (OGSE) diffusion MRI^{10,11} has made it feasible to perform experiments at diffusion times much shorter than previously attainable with conventional pulsed-gradient spin echo (PGSE) diffusion MRI using commercially available gradient systems. At such short diffusion times, it is assumed that diffusion MRI signals are more sensitive to microstructural barriers at subcellular spatial scales (e.g., the nucleus) than those obtained at long diffusion times, as suggested by simulation¹² and *in vitro*^{12–14} studies. Diffusion time dependency has been reported in the brain at both short diffusion times (~ 1 ms) using OGSE diffusion MRI¹⁰ as well as at long diffusion time (up to 600 ms)¹⁵. Several studies reported that the measured diffusion time dependency may be used to examine microstructural properties including cell and organelle size, membrane permeability, surface-to-volume ratio, and axonal diameter^{12,16–21}. The feasibility of measuring diffusion time dependency of diffusion MRI signals from brain tissues has been demonstrated in animals under normal^{22–24} or pathological^{10,25–28} states, as well as in human brains^{29,30}.

Since techniques to acquire diffusion MRI data with varying diffusion encoding directions, b or q values, and diffusion times are available, it is ready to explore the sensitivity of diffusion MRI signals to tissue microstructure in all three dimensions. One interesting area is diffusion-time dependency of diffusion kurtosis in biological tissues. Diffusion kurtosis imaging (DKI) ³¹ quantifies the non-Gaussian behaviors of water diffusion by measuring diffusion along different directions at multiple b -values ³², and it has been used to characterize pathological changes in brain tissues ³³, including multiple sclerosis ³⁴ and traumatic brain injury ^{35,36}. In particular, several groups reported that the estimated mean kurtosis is more sensitive to ischemic brain injury than commonly used mean diffusivity ^{37–41}. Using Monte Carlo simulations, Fieremans et al. showed that, while the estimated diffusivity decreased monotonously with increasing diffusion times, the estimated kurtosis initially increases with increasing diffusion times, reaches a peak, and then gradually decreases with increasing diffusion times ⁴². The initial increase is due to increased exposure of water molecules to microstructural barriers, and the later decrease is caused by exchange between intracellular and extracellular compartments, which becomes significant at long diffusion times. While diffusion time dependent changes in kurtosis were previously reported in the postmortem rat hippocampal sections ⁴³ and adult rat brains ³³, the non-monotonic relationship between diffusion kurtosis and diffusion time has only recently been demonstrated in the normal adult rat cortex ²⁴ and a postmortem pig spinal cord ⁴⁴. Yet, multi-directional OGSE kurtosis imaging of the brain has not been reported.

In this study, we compared *in vivo* multi-directional kurtosis data acquired using OGSE and PGSE sequences from normal adult mouse brains and neonatal mouse brains that received unilateral hypoxic ischemic (HI) insult. We mapped the differences between PGSE and OGSE diffusion kurtosis measurements, which may reflect microstructural features of different brain regions and microstructural changes due to pathological perturbations.

Experimental Details

Animals

All animal procedures were approved by the Animal Use and Care Committee at the Johns Hopkins University School of Medicine. The study involved two groups of animals, six normal adult C57BL/6 mice (6 month-old, female), and five HI injured neonatal C57BL/6 mice (Jackson Laboratory, Bar Harbor, ME, USA). At postnatal day 10 (P10), the neonatal mice were subjected to unilateral ligation of the right carotid artery, followed by 45 minutes of hypoxia ($\text{FiO}_2=0.08$), as described previously in ^{45,46}. The mice were recovered and imaged at 24 hours after the insult on P11.

Data acquisition

In vivo MRI of the adult and neonatal mouse brains was performed on a horizontal 11.7 Tesla Bruker scanner (Bruker Biospin, Billerica, MA, USA) with a B-GA 9S gradient system (maximum gradient strength = 740 mT/m, maximum slew rate = 6,600 T/m/s), and a 72-mm volume transmit coil. Signals were acquired using a 15-mm single channel planar surface receive coil that was placed on top of the mouse brains. During imaging, mice were

anesthetized with 1% isoflurane together with air and oxygen mixed at 3:1 ratio via a vaporizer.

OGSE dMRI¹⁰ was implemented using a cosine-trapezoid oscillating gradient waveform at an oscillating frequency (f) of 100 Hz (equivalent diffusion time = 2.5 ms¹⁰), two oscillating cycles, 30 diffusion directions, $b = 1000$ and 2000 s/mm², and a maximum gradient strength of 585 mT/m. The sequence has been calibrated previously as described in²⁷. PGSE dMRI was performed with diffusion duration (δ)/diffusion separation (Δ) = 4/20 ms and the same diffusion directions and b-values as the OGSE experiments. For the adult mouse brains, both PGSE and OGSE data were acquired using four-segment multi-slice EPI readout with a partial Fourier factor of 1.32, echo time (TE)/repetition time (TR) = 55/3000 ms, four signal averages, field of view (FOV) = 16 mm $\times$ 16 mm, matrix size = 96 $\times$ 96, in-plane resolution of 0.17 mm $\times$ 0.17 mm, eight coronal slices at a slice-thickness of 0.8 mm, and scan time of 50 minutes. For the HI-injured mice at 24 hours after HI injury, PGSE and OGSE data were acquired using a two-segment EPI readout, in-plane resolution of 0.2 mm $\times$ 0.2 mm, slice-thickness of 1 mm, TE/TR = 55/3000 ms, four signal averages, and a scan time of 26 minutes. T₂-weighted images were acquired using a fast spin-echo sequence with eight echo trains at TE/TR = 50/3000 ms, the same FOV and slice thickness as the diffusion MRI images, two signal averages, and in-plane resolution of 0.1 mm $\times$ 0.1 mm.

Data analysis

Diffusion tensors were estimated based on the data acquired with $b = 1000$ s/mm² in Matlab (mathworks.com), from which, the mean, axial, and radial diffusivity (MD, D_{//}, and D_⊥) and fractional anisotropy (FA) were calculated. Mean, axial, and radial kurtosis (MK, K_{//}, and K_⊥) of the OGSE and PGSE data were estimated based on the 30-direction and dual b -value measurements using the Diffusion Kurtosis Estimator (DKE) software (<http://academicdepartments.musc.edu/cbi/dki/dke.html>) with constrained linear weighted tensor fitting⁴⁷. The images were smoothed using Gaussian kernel with a full width at half maximum (FWHM) of 1.25 voxel size before kurtosis tensor reconstruction.

Several regions of interest (ROIs) in major white matter and gray matter regions of the normal adult mouse brains were manually defined using ROEditor (www.mristudio.org), based on fractional anisotropy (FA) contrast. In the HI-injured neonatal mouse brains, ROIs were placed in the ipsilateral edema regions, including cerebral cortex, the dorsomedial and ventrolateral hippocampus, and thalamus based on the MD maps. Matching ROIs on the contralateral side were defined based on FA map, which served as comparators for the injured side. The non-uniform sensitivity profile of the surface coil used in this study resulted in higher signal-to-noise ratio (SNR) in the dorsal cortex and hippocampus (134 $\pm$ 56 and 149 $\pm$ 55, respectively) than the thalamus (86 $\pm$ 32), but should be sufficient to ensure reliable diffusivity and kurtosis measurements⁴⁸.

Statistical tests were performed using GraphPad Prism (<http://www.graphpad.com/scientific-software/prism/>). The differences between the PGSE and OGSE measurements in the normal adult mice were evaluated by paired two-tailed Student's t -tests. The effects of HI injury between the ipsilateral and contralateral regions in the neonatal HI mouse brains and the differences between PGSE and OGSE were evaluated using two-way ANOVA, followed by

post-hoc Wilcoxon's rank sum test. For each HI injured animal, correlation analysis between MD ($MD_{OGSE} - MD_{PGSE}$) and MK ($MK_{OGSE} - MK_{PGSE}$) was performed for pixels in ipsilateral dorsal hippocampus, ipsilateral ventral hippocampus, and contralateral hippocampus regions.

Tissue processing and histopathology

After MRI, mice were transcardially perfused with phosphate buffered saline (PBS) followed by 4% paraformaldehyde in PBS. Perfusion fixed mouse brains were removed from skulls and cryo-protected in 30% sucrose. The brains were cut serially on a sliding microtome of 60 microns. Every 12th section was stained with cresyl-violet. The histological slides were imaged with a Nikon microscope (Nikon Instruments Inc., Melville, NY, USA).

Results

OGSE and PGSE kurtosis contrasts of the adult mouse brain

In the PGSE ($\tau = 20$ ms) mean kurtosis (MK) map of the adult mouse brain (Fig. 1A), white matter tracts had higher MK values than gray matter structures, e.g., the cortex and hippocampus. The contrast was further enhanced in the PGSE $K_{\perp}$ map. The OGSE ($f = 100$ Hz) kurtosis maps shared similar contrast patterns but had lower kurtosis values. In the MK map ($MK_{PGSE} - MK_{OGSE}$), the cortex and the CA1 subfield of the hippocampus showed the highest differences between PGSE and OGSE (Fig. 1B). Kurtosis measurements from the ROIs defined in Fig. 1C) showed that the OGSE-MK values in the cortex, hippocampus, and thalamus were $43.6 \pm 1.1\%$, $28.5 \pm 3.3\%$, and $26.8 \pm 3.1\%$ lower than the corresponding PGSE-MK values (Fig. 1D and Table 1). Both the corpus callosum (cc) and the cerebral peduncle (cp) — two major white matter tracts in the mouse cerebrum, showed significant but smaller degrees of decreases in MK (Fig. 1D), with larger PGSE/OGSE differences in $K_{\perp}$ than those in $K_{\parallel}$ (Fig. 1E–F).

In comparison, less apparent regional difference was shown in the subtraction image between the OGSE and PGSE diffusivity maps (Fig. 2A–B). In the MD map ($MD_{OGSE} - MD_{PGSE}$), the dentate gyrus (DG) in the hippocampus (solid arrows) was highlighted. A layered structure (approximately pyramidal neuron layer) in the hippocampus CA1 region showed high $D_{\perp}$ values (dashed arrows in Fig. 2B). The cortical and hippocampal OGSE-MD values showed mostly less than 10% increase from the PGSE MD values (Fig. 2C and Table 1), which was less than the relative changes in kurtosis (18–44% decrease in MK). In the corpus callsoom, OGSE diffusivity measurements were slightly higher than PGSE measurements but the increases were not statistically significant (Fig. 2D). In the cerebral peduncle, MD, $D_{\parallel}$, and $D_{\perp}$ showed significant increases from PGSE to OGSE (Figure 2E).

OGSE and PGSE kurtosis contrast in HI-injured neonatal mouse brains

At 24 hours after HI injury, severe edema developed in the ipsilateral cerebral cortex and hippocampus, manifested with hyper-intense signals in T_2 -weighted images (Fig. 3A). Cresyl-violet stained section (Fig. 3B) showed wide-spread necrosis in the cortex and ventrolateral hippocampus, with dorsomedial part of the hippocampus relatively spared. The loss of tissue in the CV-stained section occurred during sectioning process as tissues in the

edema regions were fragile. The PGSE MD decreased by 50%, 31%, and 16% in the ipsilateral cerebral cortex, hippocampus, and thalamus, respectively, compared to the contralateral side (Fig. 4A and Table 2). The OGSE-MD showed less edema contrast with 37%, 21%, and 9% decreases in the cortical, hippocampal, and thalamic edema regions with respect to the contralateral side. As a result, the edema region was highlighted in the MD ($MD_{OGSE} - MD_{PGSE}$) map compared to its contralateral counterpart (Fig. 3C). Kurtosis values were drastically elevated in the edema regions (Fig. 3D), with approximately 50–200% increase in PGSE-MK and 60–300% increase in OGSE-MK (Fig. 4B and Table 2).

MK was significantly higher in the edema regions compared to the contralateral side (Fig. 3D). Scatter plots of pixel-wise MD and MK values showed correlations between them in the contralateral hippocampus in all 5 mice and in the ipsilateral dorsal hippocampus in three of the five mice ($p < 0.05$). However, no significant correlations between MD and

MK values were found in the ipsilateral ventral hippocampus (Fig. 5), which often present more severe tissue damages.

Heterogeneous MK signals within the edema region were observed. For example, the ipsilateral dorsomedial hippocampus (defined in Fig. 3A) showed less increase in MK than the ventrolateral hippocampus and the cortex (Table 2). Similar heterogeneity was also visible in the MD maps as well as in the MD and MK maps, which agreed with the degree of tissue damage from histology (Fig. 3B). Within the ipsilateral dorsomedial hippocampal edema region, the MK map showed that the DG area (yellow arrows in Fig. 3D) had higher MK than the CA1 area (red arrows in Fig. 3D). Cresyl-violet stained histology sections indicated that the two areas had different cellular pathology (Fig. 6). The CA1 pyramidal neurons exhibited necrotic pathology with dissolved cytoplasm and swollen nuclei; whereas DG granule neurons showed apoptotic pathology with collapsed and condensed nuclei.

Discussions

In this study, we demonstrated unique diffusion kurtosis contrasts in the mouse brain obtained using the OGSE sequence in comparison with PGSE results. The observed differences between OGSE and PGSE kurtosis measurements may reflect the difference in diffusion times and several inherent differences in sensitivity to restrictive environments between OGSE and PGSE. Diffusion time dependency of kurtosis has been demonstrated previously using both OGSE and PGSE measurements^{24,33,43,44}. Due to the non-monotonic relationship between kurtosis measurements and diffusion times⁴², the observed differences in kurtosis measurements will depend on the choice of diffusion times. Experimentally, the diffusion-time with peak kurtosis was reported to be less than 10 ms in the cerebral cortex of live rats based on both OGSE and PGSE measurements²⁴, and approximately 40 ms in the fixed pig spinal cord using only PGSE measurements⁴⁴. Due to the relatively long acquisition time and high gradient strength associated with multi-directional DKI, we investigated two diffusion times using PGSE at $\Delta = 20$ ms and OGSE at $f = 100$ Hz in this *in vivo* study. While post-mortem studies allow acquisition of kurtosis measurements at additional diffusion times, death and chemical fixation alter tissue microstructural properties⁴⁹ and the edema contrasts²⁷, which may also affect the diffusion-time dependency. While previous studies have shown that diffusion time dependent changes in diffusivity is related to

the surface-to-volume ratio at short diffusion time regime and large scale microstructural organization patterns at long diffusion time regime⁵⁰, the diffusion times of PGSE and OGSE experiments in this study are most likely in the intermediate regime, and little is known on the relationships between diffusion time dependent behaviors of kurtosis and microstructural organizations. Future studies with measurements at more diffusion times and quantitative modeling^{18,42} will likely provide comprehensive information on the diffusion time dependency of kurtosis in brain tissues, and is feasible with recently developed fast kurtosis imaging techniques⁴⁸.

Even at comparable diffusion times, there are inherent differences between OGSE and PGSE in their sensitivity to restrictive environments that should also be considered. Portnoy et al⁴³ reported that OGSE kurtosis values were lower than PGSE kurtosis values at comparable diffusion times in postmortem rat hippocampal sections. Numerical simulations in the same study further demonstrated that the observed difference between PGSE and OGSE kurtosis depends on the spatial scales of structural barriers to water molecule diffusion⁴³. The evidence suggests that the differences between PGSE and OGSE gradient spectra allow PGSE to be more sensitive to the restrictive effects of tissue compartments than OGSE, even at comparable diffusion times. In this study, comparing OGSE and PGSE kurtosis measurements at comparable diffusion times was hindered by the requirement of specialized high performance gradient hardware, and is beyond the scope of the current study.

In the normal adult mouse brain, regional differences in MK values were apparent between gray matter structures (e.g., the cerebral cortex and hippocampus) and white matter structures (e.g. the corpus callosum). This potentially reflects differences in spatial scales of tissue microstructural barriers to water diffusion in these regions. For example, the radius of pyramidal neurons in the mouse hippocampus is approximately 10 μm ⁵¹, which is comparable to the root-mean-square displacement of freely diffusing water molecules at body temperature within the diffusion time (diffusion length scale) of the OGSE acquisition and shorter than the diffusion length scale of the PGSE acquisition. In comparison, the axonal diameters in the corpus callosum (1–2 μm)⁵² is well below the diffusion length scales of both OGSE and PGSE acquisitions.

The observation that the relative changes in MK were larger than that in MD in the normal brain (Table 1) suggested that kurtosis might be more sensitive to the spatial scale of restrictive barriers than diffusivity, and we further tested this in a mouse model of neonatal HI brain injury. Upon acute HI-injury, the neonatal mouse brains demonstrated extensive changes in diffusivity and kurtosis in the edema region. Similar to earlier stroke studies^{37–39,53,54}, the kurtosis measurements provided enhanced sensitivity in detecting ischemic edema. We observed 50–200% increase of MK as opposed to 10–50% decrease of MD, based on the PGSE measurements. In comparison, the OGSE-MK data at 100 Hz showed an even higher edema contrast than PGSE-MK ($\Delta = 20\text{ms}$), e.g., PGSE-MK in the injured cortex was elevated to 3 times of the contralateral side, whereas OGSE-MK was elevated to 3.75 times (Table 2). The enhanced edema contrast in OGSE-MK suggested that, even at a relatively short diffusion time ($\sim 2.5\text{ ms}$), the kurtosis measurements remain highly sensitive to HI-induced microstructural changes; whereas OGSE-MD gave a reduced edema contrast.

The difference between the ipsilateral CA1 and DG regions after HI in the MK map may be explained by the distinct pathology in these two regions. The dissolved cytoplasm and swollen nuclei in the CA1 region potentially increase the sizes of several microstructural barriers with respect to the diffusion length scale defined by the diffusion time, whereas the condensed nuclei in the DG region potentially have the opposite effect. Further investigation, especially at earlier time points than 24 hours, is needed to see whether MK is sensitive to specific type of ischemic stroke injuries.

Conclusions

In this study, PGSE and OGSE kurtosis contrasts in the normal and HI-injured mouse brains were investigated using oscillating and pulsed gradient waveforms. Regional differences in the decrease of kurtosis measurements from long to short diffusion times were observed, reflecting the microstructural features in normal brain and pathological changes under after HI injury. Our results demonstrate the possibility of simultaneous manipulation of the diffusion encoding directions, q , and diffusion time to optimize the sensitivity of diffusion MRI to characterize ischemic brain injury.

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Abbreviations

cc	corpus callosum
cp	cerebral peduncle
CX	cortex
DG	dentate gyrus
DH	dorsomedial hippocampus
EPI	echo planar imaging
FA	fractional anisotropy
FOV	field of view
HARDI	high angular resolution diffusion imaging
HI	hypoxic ischemic
HP	hippocampus
PGSE	pulsed gradient spin echo
OGSE	oscillating gradient spin echo
ROI	region of interest

SNR	signal-to-noise ratio
TE	echo time
TH	thalamus
TR	repetition time
VP	ventrolateral hippocampus

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Fig. 1. *in vivo* PGSE and OGSE kurtosis maps of the normal adult mouse brain. (A) Mean, axial, and radial kurtosis (MK , $K_{//}$, and $K_{\perp}$) maps measured using PGSE and OGSE diffusion MRI sequences, and the differences between the PGSE and OGSE maps (ΔMK , $\Delta K_{//}$, and $\Delta K_{\perp}$) (B). (C) The corresponding fractional anisotropy image with ROIs defined for the cortex (CX), hippocampus (HP), thalamus (TH), corpus callosum (cc), and cerebral peduncle (cp). (D) Mean MK values in the ROIs as defined in (C). (E–F) PGSE and OGSE $K_{//}$ and $K_{\perp}$ measured in the corpus callosum and cerebral peduncle. **: $p<0.01$ and ***: $p<0.001$.

Fig. 2. *in vivo* PGSE and OGSE diffusivity maps of the normal adult mouse brain. **(A)** Mean, axial, and radial diffusivity (MD, $D_{//}$, and $D_{\perp}$) maps measured using PGSE and OGSE diffusion MRI sequences, and the differences between the PGSE and OGSE maps (ΔMD , $\Delta D_{//}$, and $\Delta D_{\perp}$) **(B)**. The solid and dashed arrows indicate the locations of the dentate gyrus, and the CA1 pyramidal layer of the hippocampus, respectively. **(C)** Mean MD values in the ROIs as defined in Fig. 1C. **(D–E)** PGSE and OGSE $D_{//}$ and $D_{\perp}$ measured in the corpus callosum and cerebral peduncle. *: $p < 0.05$, **: $p < 0.01$ and ***: $p < 0.001$.

Fig. 3. PGSE and OGSE MD and MK maps of a hypoxia-ischemia (HI) injured neonatal mouse brain. (A) T₂-weighted image of a representative HI-injury mouse with ROIs defined for the cerebral cortex (CX), dorsomedial and ventrolateral hippocampus (DH and VH), and thalamus (TH). (B) The matching Cresyl-violet stained section of the same mouse brain. (C–D) PGSE and OGSE MD and MK maps and MD and MK maps of the same mouse.

Fig. 4.

PGSE and OGSE based MD (**A**) and MK (**B**) values in HI-injured neonatal mouse brains (n=5) in the ROIs defined in Fig. 3A and their contralateral counterparts. *: p<0.05, **: p<0.01 and ***: p<0.001 by two-way ANOVA tests of the ipsilateral and contralateral differences, as well as the PGSE and OGSE differences.

Fig. 5.

Scatter plots of ΔMK and ΔMD values in the ipsilateral dorsal hippocampus (yellow dots), ipsilateral ventral hippocampus (red dots), and contralateral hippocampus (blue dots) in three HI-injured neonatal mouse brains. The R^2 values from correlation analysis are shown for each subject. *: $p < 0.05$.

Fig. 6. Cellular level pathology in the hippocampal CA1 and dentate gyrus (DG) of a HI-injured mouse brain. In the low magnification Cresyl-violet stained section (A), the loss of staining can be observed in the ipsilateral CA1 region (within region B') but not in the ipsilateral DG region (region C'). High magnification images of the CA1 region (B-B') show dissolved cytoplasm and swollen nuclei, typical in HI induced necrosis. Images of the DG region (C-C') show collapsed and condensed nuclei, typical in HI induced apoptosis.

Table 1

Percentage of differences between PGSE and OGSE diffusivity and kurtosis measurements (normalized to PGSE) in the cortex (CX), hippocampus (HP), corpus callosum (CC), and cerebral peduncle (CP), obtained from normal adult mouse brains (n=6). Data are presented as mean $\pm$ standard deviation across the six mice.

ROI	MD	D//	D _T	MK	K//	K _T
CX	2.2 $\pm$ 1.7%	1.0 $\pm$ 1.2%	2.9 $\pm$ 2.8%	43.6 $\pm$ 1.1%	41.5 $\pm$ 2.2%	41.9 $\pm$ 2.8%
HP	6.6 $\pm$ 2.2%	5.9 $\pm$ 1.4%	7.2 $\pm$ 2.7%	30.3 $\pm$ 2.8%	30.3 $\pm$ 2.9%	30.1 $\pm$ 3.2%
TH	9.5 $\pm$ 1.5%	9.1 $\pm$ 1.0%	9.8 $\pm$ 1.8%	26.8 $\pm$ 3.1%	23.9 $\pm$ 2.9%	27.3 $\pm$ 3.2%
CC	0.8 $\pm$ 3.0%	0.1 $\pm$ 4.8%	2.3 $\pm$ 1.4%	25.0 $\pm$ 1.9%	24.1 $\pm$ 2.0%	33.5 $\pm$ 1.9%
CP	11.6 $\pm$ 1.8%	10.3 $\pm$ 1.7%	13.3 $\pm$ 4.3%	18.7 $\pm$ 3.0%	16.4 $\pm$ 1.6%	22.0 $\pm$ 3.3%

MD and MK values in the ipsilateral and contralateral ROIs in the cortex, dorsomedial and ventrolateral hippocampus of the HI-injured mice (n=5), measured from PGSE and OGSE diffusion MRI. Data are presented as mean $\pm$ standard deviation across the six mice.

Table 2

		MD (10^{-3} mm ² /s)		MK	
		Ipsilateral	Contralateral	Ipsilateral	Contralateral
Cortex	PGSE	0.37 $\pm$ 0.01	0.74 $\pm$ 0.01	1.74 $\pm$ 0.31	0.57 $\pm$ 0.10
	OGSE	0.49 $\pm$ 0.04	0.78 $\pm$ 0.03	1.24 $\pm$ 0.18	0.33 $\pm$ 0.09
Dorsomedial Hippocampus	PGSE	0.60 $\pm$ 0.04	0.79 $\pm$ 0.01	1.06 $\pm$ 0.16	0.68 $\pm$ 0.12
	OGSE	0.67 $\pm$ 0.04	0.81 $\pm$ 0.03	0.67 $\pm$ 0.10	0.36 $\pm$ 0.10
Ventrolateral Hippocampus	PGSE	0.49 $\pm$ 0.03	0.79 $\pm$ 0.02	1.41 $\pm$ 0.26	0.70 $\pm$ 0.10
	OGSE	0.59 $\pm$ 0.04	0.80 $\pm$ 0.03	0.87 $\pm$ 0.20	0.40 $\pm$ 0.10
Thalamus	PGSE	0.62 $\pm$ 0.03	0.74 $\pm$ 0.02	0.95 $\pm$ 0.26	0.62 $\pm$ 0.08
	OGSE	0.67 $\pm$ 0.03	0.74 $\pm$ 0.03	0.53 $\pm$ 0.14	0.35 $\pm$ 0.09