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Research Report

Long-term evolution of diffusion tensor indices after temporary experimental ischemic stroke in rats

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ABSTRACT

Diffusion tensor (DT) imaging measures the random molecular diffusion of water in vivo and provides information on the microstructure of tissue. Ischemic brain damage leads to tissue disorganization and structural lost. We aimed to evaluate these changes in a rat model of focal stroke from the hyperacute to chronic phase by utilizing several DT indices. Adult male Wistar rats, subjected to temporary focal cerebral ischemia by suture occlusion of the middle cerebral artery for 90 min, and sham controls were serially imaged at 4.7 Tesla. DT scans were collected repeatedly during the hyperacute (2 and 3.5 h), acute (1, 2, and 3 days), subacute (4, 7, and 14 days), and chronic (4, 6, and 8 weeks) phases. We measured the evolution of DT indices (mean diffusivity (MD), axial diffusivity ($\lambda_\parallel$), radial diffusivity ($\lambda_\perp$), and fractional anisotropy (FA)) in the cortex, subcortex, and corpus callosum of the ischemic hemisphere. In the hyperacute phase, MD, $\lambda_\parallel$, and $\lambda_\perp$ reduced with no change in FA. From the acute to subacute phase, MD, $\lambda_\parallel$, and $\lambda_\perp$ normalized and thereafter increased, whereas FA decreased in all the tissues. In the chronic phase, MD, $\lambda_\parallel$, and $\lambda_\perp$ continued to rise, whereas FA normalized in the corpus callosum and subcortex, but remained low in the cortex. We described structural tissue changes in ischemic rat brain longitudinally utilizing DT analysis. DT indices reveal different individual patterns reflecting different facades and phases of tissue injury. The use of several DT indices may improve accuracy in estimating the age of the brain injury and in detecting ongoing pathological events.

1. Introduction

Quantitative diffusion tensor (DT) indices, such as mean diffusivity (MD), axial and radial diffusivity ($\lambda_\parallel$ and $\lambda_\perp$), and fractional anisotropy (FA), may offer useful information about the underlying pathology of ischemic brain tissue. Experimental (Bihel et al., 2010; Carano et al., 2000; Ding et al., 2008; Jiang et al., 2006; Liu et al., 2007; Shereen et al., 2011; Sun et al., 2005;

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Abbreviations: $\lambda_\parallel$, axial diffusivity; $\lambda_\perp$, radial diffusivity; BBB, blood-brain barrier; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; EPI, echo-planar imaging; FA, fractional anisotropy; GM, gray matter; MCAO, middle cerebral artery occlusion; MD, mean diffusivity; MRI, magnetic resonance imaging; ROI, region of interest; WM, white matter

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van der Zijden et al., 2008) and clinical studies (Sakai et al., 2009; Sorensen et al., 1999; Tamura et al., 2009; Zelaya et al., 1999) show that DT indices may serve as a non-invasive tool for exploring tissue structure. To understand the whole range of tissue characteristics in healthy and ischemic brain tissue, one must understand the reciprocity between the DT indices (Hasan and Narayana, 2006).

Numerous pathological changes, such as axonal injury, edema formation, loss of myelin, and breakdown of the microstructure, occur after ischemic stroke. That conventional imaging parameters change after ischemic brain injury is well-known (Carano et al., 1998; Matsumoto et al., 1995), however not being sensitive to differentiate between axonal injury and loss of myelin whereas the results of DT work remain to be validated.

Although several studies have reported on DT after cerebral ischemia in experimental models, most reports employed only a single DT index (usually FA) (Bihel et al., 2010; Carano et al., 2000; Ding et al., 2008; Jiang et al., 2006; Liu et al., 2007; van der Zijden et al., 2008), described only a short period after inducing ischemia (Carano et al., 2000), or had only a few imaging points covering over a longer post-ischemia period (Bihel et al., 2010; Ding et al., 2008; Granziera et al., 2007; Jiang et al., 2006; van der Zijden et al., 2008). Because FA is a ratio measure, it is not recommended for use as a biophysical measure alone, but should be interpreted with other DT indices (Hasan and Narayana, 2006).

To our knowledge, no studies have yet attempted to extensively monitor temporal changes in FA, MD, $\lambda_{\parallel}$, and $\lambda_{\perp}$ over a long follow-up period after experimental focal brain ischemia. Consequently, the present investigation aimed to run a comprehensive DT investigation to evaluate changes in the cortex, subcortex, and corpus callosum in a rat model of temporary middle cerebral artery occlusion (MCAO) starting at 2 h (hyperacute) and ending at 8 weeks (chronic) post-MCAO.

2. Results

During the study period, our sample size decreased from 9 to 8 at 2 weeks, and then to 7 at 4 weeks. The animals showed no differences in body weight and body temperature at baseline or during surgical and imaging procedures (data not shown). All the animals that underwent 90 min of right MCAO showed substantial DWI hyperintensity at the first time point (2 h after MCAO), encompassing both cortical and subcortical regions in the right MCA territory. The sham animals showed no DWI hyperintensity (their DT indices appear in Table 1).

2.1. *Evolvement of diffusion tensor indices over time*

Evolution of the DT indices in the right MCA territory over time from the hyperacute to chronic phase appears in Fig. 2. The direction of change of the DT indices for each region of interest (ROI) studied appears in Table 2.

In the hyperacute phase, MD, $\lambda_{\parallel}$, and $\lambda_{\perp}$ decreased significantly (Figs. 2A–C, Fig. 3, and Table 2), whereas FA remained unchanged in all regions measured (Fig. 2D and Table 2). MD normalization was characteristic of all the tissues in the acute phase and later rose in the subacute phase (Fig. 2A and Table 2). In the white matter (WM), MD became significantly elevated already by day 2 and remained elevated throughout the rest of the study. During the acute to subacute phase, $\lambda_{\parallel}$ normalized in all the tissues (Fig. 2B and Table 2). Meanwhile, $\lambda_{\perp}$ normalized in the acute phase and rose in the subacute phase (Fig. 2C and Table 2). Significant reductions in FA occurred in the acute and subacute phases in all regions measured (Fig. 2D, Fig. 3, and Table 2). In the chronic phase, all the tissues showed significantly elevated MD, $\lambda_{\parallel}$, and $\lambda_{\perp}$ (Figs. 2A–C, Fig. 3, and Table 2). The FA of the gray matter (GM) remained significantly low until 8 weeks, whereas the FA of the WM normalized at 4 weeks (Fig. 2D and Table 2).

Table 1 – DT indices of the sham animals.

	FA	MD	$\lambda_{\parallel}$	$\lambda_{\perp}$
Cortex	0.18±0.03	0.66±0.003	0.78±0.02	0.60±0.02
Subcortex	0.25±0.07	0.64±0.03	0.80±0.02	0.53±0.03
Corpus callosum	0.45±0.08	0.65±0.06	1.06±0.14	0.49±0.06
	*,**,***	—	**,***	*,**,***

The normal values (mean±SD) of FA, MD ($\times 10^{-3}$ (mm^2/s)), $\lambda_{\perp}$ ($\times 10^{-3}$ (mm^2/s)), and $\lambda_{\parallel}$ ($\times 10^{-3}$ (mm^2/s)) of the sham animals in the brain cortex, subcortex, and corpus callosum. Significant difference ($p<0.05$) between the cortex and subcortex is marked with a star (*), between the cortex and corpus callosum with a double star (**), between the subcortex and corpus callosum with a triple star (***). A line (—) means that we found no significant difference between the values from different brain regions.

2.2. *Evolution of DWI lesion*

DWI lesion was already present at 2 h, peaked on day 2, and decreased thereafter (Fig. 4). In the beginning of the chronic phase (4 weeks), DWI lesion volume approached zero and remained unchanged thereafter.

To examine the effect of vasogenic edema on the DT indices from the acute to subacute phase of ischemia, we measured correlations between DWI lesion volume and DT indices: the cortex and subcortex showed a significant linear correlation between MD and DWI lesion volume evolvement (cortex: $r=0.90$, $p=0.01$; subcortex: $r=0.85$, $p=0.03$), $\lambda_{\parallel}$ and DWI lesion volume

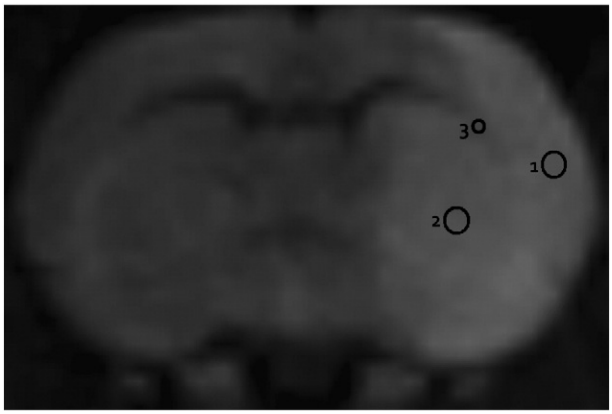

Fig. 1 – The placement of the region of interests is presented in diffusion-weighted image ($b_1=1000$ s/mm^2) 2 h after ischemia; cortex (1), subcortex (2), and corpus callosum (3).