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BRAIN RESEARCH

Research Report

Spatiotemporal dynamics of diffusional kurtosis, mean diffusivity and perfusion changes in experimental stroke

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ABSTRACT

Diffusional kurtosis imaging (DKI), which measures the non-Gaussianity of water diffusion, has been demonstrated to be a sensitive biomarker in many neuropathologies. The goal of this study was to longitudinally examine the spatiotemporal dynamics of DKI in cerebral ischemia in an animal model of permanent and transient (45 min) middle cerebral artery occlusion (MCAO) during the hyperacute, acute and chronic phases. Diffusional kurtosis showed different spatiotemporal dynamics. In particular, mean kurtosis (MK) was sensitive to hyperacute and acute stroke changes, and exhibited different contrast than mean diffusivity (MD) and higher contrast than fractional anisotropy (FA) and T2. MK contrast persisted 1 to 7 days post-occlusion, whereas MD showed renormalization at day 1–2 and reversed contrast at day 7. The current study showed that DKI has the potential to complement existing stroke imaging techniques, particularly in the assessment of subacute to early chronic stroke evolution.

1. Introduction

The anatomical mismatch between diffusion-weighted (DWI) and perfusion-weighted imaging (PWI) abnormality offers remarkable sensitivity to ischemic brain injury (Schlaug et al., 1999). However, some mismatch tissue are oligemic, some are salvageable and some are not, depending on the duration and nature of ischemic injury, and proximity of patent vessels, among other factors. Thus, the perfusion–diffusion mismatch only approximates the ischemic penumbra. Despite its shortcomings (Kidwell et al., 2003), the mismatch is commonly used to guide clinical decision making in acute stroke management. By contrast, conventional T2-weighted (T2W) images and computed tomography could not detect ischemic injury until at least 6 hours after stroke onset, coinciding with vasogenic edema at which point the tissue has already become infarct (Baird and Warach, 1998). Other methods are being explored to improve characterization of ischemic brain injury.

Diffusional kurtosis is a measure of the non-Gaussianity of water diffusion (Jensen et al., 2005). Free, unrestricted water diffusion has a Gaussian distribution, and thus a zero diffusional kurtosis. Restricted water diffusion has a distribution that is sharper than Gaussian, hence positive diffusional kurtosis. Tissue microstructures that restrict water diffusion include cell membranes, organelles and tissue compartments, among other factors. In other words, diffusional kurtosis characterizes the complexity or heterogeneity of the tissue microenvironment (Jensen et al., 2005). In diseases, such as ischemic brain injury, diffusional kurtosis could change due to: i) cytotoxic edema, ii) progressive alteration in cell packing geometry, iii) cell membrane permeability changes, and/or iv)

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change in cell size distribution as a result of cell necrosis (Baird and Warach, 1998; Fung et al., 2011). Diffusional kurtosis imaging (DKI) has some advantages over conventional DTI because of its sensitivity to tissue heterogeneity, especially isotropic grey matter (GM) (Jensen and Helpern, 2010; Jensen et al., 2005). DKI thus has the potential to provide additional insights of tissue microstructure (Jensen and Helpern, 2010).

DKI has recently been used to study human ischemic stroke. Diffusional kurtosis increased at 1 to 5 days after stroke onset (Helpern et al., 2009; Jensen et al., 2010; Latt et al., 2009b; Peeters et al., 2010; van Westen et al., 2010) and exhibited distinct abnormalities that were not apparent on conventional DWI/DTI or apparent diffusion coefficient (ADC) map (Helpern et al., 2009). Latt et al. investigated the presence of water exchange in ischemic lesion by varying the diffusion time in DKI acquisition in humans (Latt et al., 2009b). Diffusional kurtosis of both white matter (WM) and, to a lesser extent, GM lesions varied with diffusion time at 1 to 5 days after stroke onset, while mean diffusivity (MD) and normal tissue did not. DKI has also been used to study normal WM and GM microstructures (Cheung et al., 2009; Falangola et al., 2008; Fieremans et al., 2010; Hui et al., 2008), brain glioma (Raab et al., 2010), attention-deficit hyperactivity disorder (Helpern et al., 2011), and traumatic brain injury (Grossman et al., in press). DKI studies in animal stroke models, however, have not been reported, and the temporal evolution of DKI-derived metrics with respect to DWI and PWI changes in animal models has yet to be systematically investigated. Animal models where focal ischemia can be reproducibly studied under controlled conditions would be important for characterizing DKI contrast, which could ultimately lead to better characterization and staging of human stroke.

The goal of this study was to longitudinally examine the spatiotemporal dynamics of diffusional kurtosis in cerebral ischemia in an animal model of permanent and transient (45 min) middle cerebral artery occlusion (MCAO) during the hyperacute, acute and chronic phases (up to 7 days post-occlusion). Comparisons were longitudinally made with MD, fractional anisotropy (FA), T2W MRI, and perfusion changes in the same animals.

2. Results

2.1. *Permanent MCAO*

Fig. 1 shows the spatiotemporal dynamics of the absolute CBF, MD, MK, FA maps and T2W images of an animal subjected to permanent MCAO. CBF of the ischemic lesion was markedly reduced and did not change over time. MD reduction and MK increase were apparent in hyperacute (0–2 hrs) and acute (24 hrs post-occlusion) phases. FA and T2W images did not change until 24 hrs post-occlusion.

The group-averaged temporal evolution of CBF, MD, MK and FA were analyzed for the cortex and striatum ROIs (Fig. 2). CBF of the ischemic tissue dropped by ~79% immediately after MCAO and did not change with time. MD reduced by ~24% at 30 min post-occlusion and further decreased with time, while MK elevated by ~59% but did not further increase until after 2 hrs post-occlusion. ICortex FA increased by ~11% up to 1 hr post-occlusion and gradually decreased with time, whereas IStriatum FA did not decrease until 2 hrs post-occlusion. Notice that the CBF and FA of the contralateral ROIs also changed at 24 hrs post-occlusion.

The analysis of CNR showed that MD was more sensitive to ischemic changes than MK and CBF during the hyperacute phase (Fig. 3). FA showed no significant contrast till 24 hrs after MCAO.

Fig. 4 shows the evolution of LV determined from MD and MK abnormalities that were 3 SDs away from the mean of normal tissue. Note that only LV from CBF immediately and T2W 24 hrs after occlusion are shown and extrapolated to other time points. LV determined from MD and MK increased slightly during the first 2 hrs post-occlusion, and increased further at 24 hrs post-occlusion. LVs of MD and MK were largely similar across all time points, and were comparable to that of T2W at 24 hrs after MCAO.

2.2. *Transient MCAO*

Fig. 5a shows the spatiotemporal dynamics of the absolute CBF, MD, MK, FA maps and T2W images of an animal

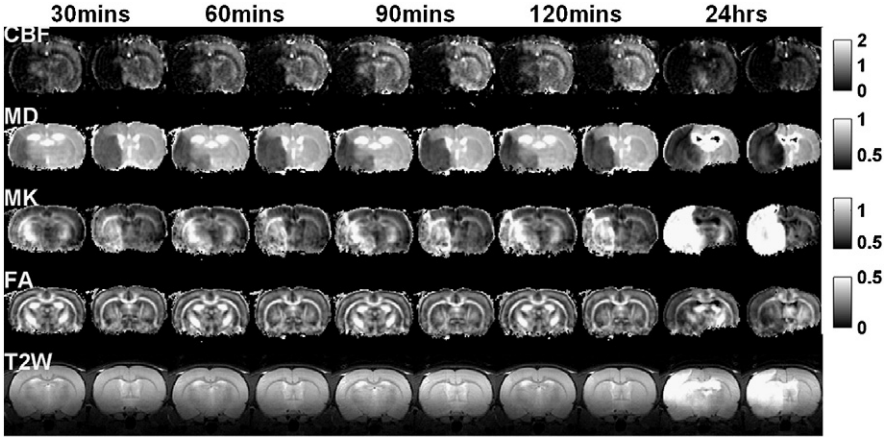

Fig. 1 – CBF, MD, MK, FA maps and T2W images (two brain slices) of a rat subjected to permanent MCAO obtained at 30, 60, 90, 120 min and 1 day after occlusion. Maps across all time points were displayed with the same scale. Units for CBF and MD are ml/g/min and $\mu m^2/ms$, respectively. FA and T2W are unitless.