NeuroImage xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Can diffusion kurtosis imaging improve the sensitivity and specificity of detecting microstructural alterations in brain tissue chronically after experimental stroke? Comparisons with diffusion tensor imaging and histology

S. Umesh Rudrapatna [a], Tadeusz Wieloch [b], Kerstin Beirup [b], Karsten Ruscher [b], Wouter Mol [a], Pavel Yanev [a], Alexander Leemans [c], Annette van der Toorn [a], Rick M. Dijkhuizen [a]

[a] Biomedical MR Imaging and Spectroscopy Group, Image Sciences Institute, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
[b] Laboratory for Experimental Brain Research, Department of Clinical Sciences, Division of Neurosurgery, Lund University, BMC A13, S-22184 Lund, Sweden
[c] PROVIDI Lab, Image Sciences Institute, University Medical Center Utrecht, Utrecht, The Netherlands

ARTICLE INFO

Article history:
Accepted 4 April 2014
Available online xxxx

Keywords:
Diffusion kurtosis imaging
DKI
DTI
Diffusion
Microstructure
Chronic stroke

ABSTRACT

Imaging techniques that provide detailed insights into structural tissue changes after stroke can vitalize development of treatment strategies and diagnosis of disease. Diffusion-weighted MRI has been playing an important role in this regard. Diffusion kurtosis imaging (DKI), a recent addition to this repertoire, has opened up further possibilities in extending our knowledge about structural tissue changes related to injury as well as plasticity.
In this study we sought to discern the microstructural alterations characterized by changes in diffusion tensor imaging (DTI) and DKI parameters at a chronic time point after experimental stroke. Of particular interest was the question of whether DKI parameters provide additional information in comparison to DTI parameters in understanding structural tissue changes, and if so, what their histological origins could be. Region-of-interest analysis and a data-driven approach to identify tissue abnormality were adopted to compare DTI- and DKI-based parameters in post mortem rat brain tissue, which were compared against immunohistochemistry of various cellular characteristics.
The unilateral infarcted area encompassed the ventrolateral cortex and the lateral striatum. Results from region-of-interest analysis in the lesion borderzone and contralateral tissue revealed significant differences in DTI and DKI parameters between ipsi- and contralateral sensorimotor cortex, corpus callosum, internal capsule and striatum. This was reflected by a significant reduction in ipsilateral mean diffusivity (MD) and fractional anisotropy (FA) values, accompanied by significant increases in kurtosis parameters in these regions. Data-driven analysis to identify tissue abnormality revealed that the use of kurtosis-based parameters improved the detection of tissue changes in comparison with FA and MD, both in terms of dynamic range and in being able to detect changes to which DTI parameters were insensitive. This was observed in gray as well as white matter. Comparison against immunohistochemical stainings divulged no straightforward correlation between diffusion-based parameters and individual neuronal, glial or inflammatory tissue features.
Our study demonstrates that DKI allows sensitive detection of structural tissue changes that reflect post-stroke tissue remodeling. However, our data also highlights the generic difficulty in unambiguously asserting specific causal relationships between tissue status and MR diffusion parameters.

Introduction

Discovery of curative treatments for chronic-phase stroke patients may benefit immensely from improved understanding of post-stroke structural tissue (re)organization. For the past few years, diffusion tensor imaging (DTI) has been a popular method to assess changes in tissue structure after stroke (Dijkhuizen et al., 2012; Sotak, 2002; Sundgren et al., 2004), e.g., in an experimental stroke model, it has been shown that fractional anisotropy (FA) in the corpus callosum and ipsilesional corticospinal tracts has a significant correlation with functional recovery (van Meer et al., 2012).

Recently, diffusion kurtosis imaging (DKI), an extension to DTI that can capture the non-Gaussian nature of water diffusion in tissues, has been shown to exhibit enhanced sensitivity to microstructural changes in comparison with the conventional DTI parameters, FA and mean diffusivity (MD) (Gooijers et al., 2013; Hui et al., 2008; Jensen et al., 2005; Lu et al., 2006; van Cauter et al., 2012; Wu and Cheung, 2010). While DTI

E-mail addresses: umesh@invivonmr.uu.nl (S.U. Rudrapatna), r.m.dijkhuizen@umcutrecht.nl (R.M. Dijkhuizen).

http://dx.doi.org/10.1016/j.neuroimage.2014.04.013
1053-8119/

has played a significant role in understanding (changes in) tissue architecture, especially in cerebral white matter studies, DKI parameters can potentially be more effective in elucidating cerebral gray matter changes (Jensen et al., 2005).

The advantages offered by DKI over DTI have been reported in several recent studies. In an experimental traumatic brain injury model in rats, Zhuo et al. (2012) observed the continued sensitivity of mean kurtosis (MK) to structural tissue changes even into sub-acute stages, when DTI parameters had re-normalized. Raab et al. (2010) reported that gliomas of two different grades could be separated only by using MK values. In an experimental stroke study on the spatio-temporal evolution of kurtosis parameters (Hui et al., 2012a), the differences in MK between healthy and injured tissue areas were found to persist up to seven days post stroke, when MD values had normalized. Hui et al. (2012b) also reported the distinct patterns on kurtosis and MD maps and the greater dynamic range of kurtosis parameters in comparison with MD. Recently, Vanhoutte et al. (2013) reported the suitability of DKI metrics to detect amyloid deposition in a mouse model of Alzheimer's disease, when plain DTI metrics failed to do so. These studies indicate that kurtosis parameters bring in original information, which DTI parameters may not be able to provide. Furthermore, studies on brain maturation (Cheung et al., 2009), temporal lobe epilepsy (Gao et al., 2012) and stroke lesion visualization (Grinberg et al., 2012) have reported the enhanced sensitivity of DKI parameters over DTI parameters in discerning differences in tissue status. In other studies (Blockx et al., 2012; Cheung et al., 2012; Grossman et al., 2012), a combined use of kurtosis and DTI parameters proved to be advantageous in detecting tissue changes. These observations indicate that kurtosis parameters can discriminate healthy from abnormal tissue under various pathophysiological conditions. Thus, given that perilesional white and gray matter undergo significant changes following stroke (Floyd, 2012; Schaechter et al., 2006), DKI holds promise in furthering our understanding of restructuring in both cerebral tissue types.

Although kurtosis parameters may provide additional information over DTI parameters in assessing microstructural changes after stroke (Grinberg et al., 2012; Hui et al., 2012a, 2012b), there are few DKI studies (Blockx et al., 2012; Zhuo et al., 2012) which empirically link the changes in diffusion kurtosis-based contrasts to possible biological underpinnings, or ascertain their specificity to particular tissue alterations. These issues are central to the application of any contrast in imaging, and especially so in the case of diffusion-based contrasts, since it is known that many different but concurrent biological processes can affect diffusion parameters in a similar manner (Beaulieu, 2002; Wang et al., 2011). In addition, there are several other factors that may further modulate diffusion metrics in a nontrivial way, such as the tensor estimation approach (Veraart et al., 2013), partial volume effects (Szczepankiewicz et al., 2013; Vos et al., 2011), and violations of model assumptions (Tournier et al., 2011; Vos et al., 2012). A better understanding of the biological processes at play and how they can affect diffusion contrasts is therefore crucial for evaluating the benefit of one contrast over the other and more importantly, in correctly interpreting what is being observed.

In this work, we chose to apply a high-resolution post-mortem MRI approach, to elucidate the possible advantages of DKI parameters over DTI parameters in characterizing altered tissue structure chronically after stroke, when injury and plasticity mechanisms are known to have induced tissue remodeling around a stroke lesion (Schaechter et al., 2006). We used discrepancies in the relative status of DTI and DKI parameters (in homologous ipsi- and contralateral regions) to deduce if DKI parameters provide enhanced sensitivity in comparison with DTI parameters under these circumstances. A data-driven approach was used to further identify regions with abnormal DKI and DTI contrasts (in comparison to the values in the contralateral hemisphere), with the aim of detecting whether DKI provides information unavailable from DTI parameters. To understand the histological underpinnings of the observed changes in diffusion parameters and thus discern what the specific information conveyed by DKI contrasts could be, we performed immunohistochemistry and compared histological stainings with various MR diffusion parameters in the same tissue samples.

Methods

Stroke model

Transient middle cerebral artery occlusion (MCAO) was induced in adult male Wistar rats (320–400 g), housed under diurnal light conditions as described in Memezawa et al. (1992). They were anesthetized (initially with 4% Isoflurane, Intervet, Schering Plough in N_2O/O_2 (70:30), and during surgery with 2% Isoflurane in N_2O/O_2). The right common carotid artery (CCA) and external carotid artery were occluded permanently and the internal carotid artery (ICA) was exposed. A nylon filament (top diameter 0.3–0.4 mm) was introduced into the ICA via a small incision into the distal end of the CCA and advanced to occlude the origin of the MCA. The subsequent decrease in cortical blood flow during MCA occlusion was monitored with a laser-Doppler device and arterial pO_2, pCO_2, pH and rectal temperatures were measured. After occlusion of the MCA, the wounds were sutured and the rats were allowed to wake up. At 90 min after occlusion, the neurological score was assessed and only rats showing rotational asymmetry and dysfunctional limb placement were included in the study. At 120 min after MCA occlusion, the animals were reperfused under anesthesia by removing the nylon filament. All wounds were sutured and the rats were allowed to wake up. After a recovery period of eight weeks, the animals were perfusion-fixed with paraformaldehyde, and decapitated. After overnight post-fixation at 4 °C, brains inside intact skulls were cold-stored in phosphate-buffered saline with sodium azide (0.5 g/l). Twenty-two brain samples were collected in this manner and used for scanning with MRI.

MRI data acquisition

Within 15 days after perfusion-fixation, DKI acquisitions of the brains inside the intact skull were performed on a 9.4 T pre-clinical MRI scanner (Varian Inc., Palo Alto, CA, USA), equipped with a gradient insert capable of operating at 100 G/cm, with the following DKI scan parameters: 2d-multislice echo-planar imaging (EPI) sequence; repetition time (TR): 3.4 s; echo time (TE): 26 ms; interleaves: 10; field-of-view (FOV): 20 × 30 × 11 mm; matrix size: 100 × 150 × 55 (read-out × phase encoding × slices) (isotropic resolution of 200 μm). Diffusion-weighting was performed in 30 optimized directions (Cook et al., 2007) with parameters δ: 3.63 ms and Δ: 13.67 ms.

Choosing the set of appropriate b-values for a DKI study needs several considerations to be taken into account, like the applicability of DKI fitting under the range of b-values in use, the achievable signal-to-noise ratio (SNR) etc. To date, most in-vivo DKI studies have used maximum b-values of around 2000–3000 s/mm^2 (Jensen and Helpern, 2010). In animals, the mean diffusivity in perfusion-fixed brains has been observed to be nearly half of that compared to in-vivo brain tissue (D'Arceuil et al., 2007). Thus, the b-value range for ex-vivo DKI studies in rodent brains needs to be nearly double of those used for in-vivo studies, in order to achieve levels of signal attenuation where the DKI model is relevant. Thus, we used four b-values (1125, 2250, 3375 and 4500 s/mm^2) along with eight b = 0 scans for this study. Test scans were performed on one sample to ensure the suitability of this range of b-values for DKI. For each brain-sample, seven averages of such 128 (30 × 4 + 8) EPI datasets were acquired over a period of 8.5 h.

Estimation of DTI and DKI parameters

Mean kurtosis (MK), parallel kurtosis (ParK) and perpendicular kurtosis (PerK) were estimated (Tabesh et al., 2011) from the reconstructed