NeuroImage 86 (2014) 60–66

Contents lists available at ScienceDirect

NeuroImage

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

Distance informed Track-Weighted Imaging (diTWI): A framework for sensitising streamline information to neuropathology

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ARTICLE INFO

Article history:
Accepted 29 July 2013
Available online 3 August 2013

Keywords:
HARDI
Diffusion imaging
Tractography
Glioma
Infiltration
PET imaging

ABSTRACT

Track-Weighted Imaging (TWI), where voxel intensity is based on image metrics encoded along streamline trajectories, provides a mechanism to study white matter disease. However, with generalised streamline weighting, it is difficult to localise the precise anatomical source and spread of injury or neuropathology. This limitation can be overcome by modulating the voxel weight based on the distance of the voxel from a given anatomical location along the tract, which we term diTWI: distance informed Track-Weighted Imaging. The location of known neuropathology can be delineated on any given imaging modality (e.g. MRI or PET). To demonstrate the clinical utility of this approach, we measured tumour cell infiltration along WM fibre tracts in 13 patients with newly diagnosed glioblastoma and 1 patient with Anaplastic Astrocytoma. TWI and diTWI maps were generated using information obtained from dynamic contrast enhanced MRI (area under the curve, AUC) and diffusivity maps (ADC and FA) with tumour boundaries automatically extracted using a logistic regression classifier. The accuracy of the derived tumour volumes was compared to those generated using 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA) PET imaging. The accuracy of the tumour volumes generated from the diTWI maps was superior to volumes derived from the TWI, geometric distance or baseline AUC, FA and ADC maps. The relative overlap and relative dissimilarity rates for the diTWI generated tumour volumes after classification were found to be 82.3 ± 15.3% (range 69.1–91.9) and 16.9 ± 8.8% (range 7.9–37.5), respectively. These findings show that diTWI maps provide a useful framework for localising neuropathological processes occurring along WM pathways.

Introduction

Diffusion-weighted MRI (dMRI), together with fibre tracking, shows significant potential for assessing the microstructure of white matter (WM) pathways in the human brain in vivo (Mukherjee et al., 2008; Nucifora et al., 2007). This is normally achieved by measuring quantitative diffusivity indices derived from the diffusion tensor (Basser and Pierpaoli, 1996) such as fractional anisotropy (FA) or apparent diffusion coefficient (ADC). The introduction of whole-brain fibre tracking has enabled not only the investigation of complex neural networks based on structural connectivity analyses (Hagmann, 2005; Sporns et al., 2005), but also the generation of whole brain Track Density Images (TDI), where the image contrast is determined by the number of streamlines traversing each voxel (Calamante et al., 2010). With this approach, super-resolution TDI maps can be generated with higher spatial resolution compared to the acquired diffusion data. However, unresolved issues relating to reproducibility and normalisation confound the clinical use of track density measures (Besseling et al., 2012; Jones et al., 2013).

To overcome these limitations, we have previously introduced the concept of the average pathlength map (APM), where the image contrast is encoded by the mean length of all streamlines traversing each

Abbreviations: ADC, apparent diffusion coefficient; APM, average pathlength map; AUC, area under the concentration curve; CE, contrast enhanced; DCE, dynamic contrast enhanced; DIST, diffusion indices sampled along streamline trajectories; dMRI, diffusion-weighted MRI; FDOPA, 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine; FLAIR, fluid attenuated inversion recovery; FA, fractional anisotropy; PET, positron emission tomography; ROI, region-of-interest; TDI, track density imaging; TWI, Track-Weighted Imaging; WHO, World Health Organisation.

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http://dx.doi.org/10.1016/j.neuroimage.2013.07.077

voxel (Pannek et al., 2011a). This approach can be extended by weighting the streamlines with quantitative diffusivity metrics, such as FA and ADC, providing a range of tractography maps with novel contrast. This can be achieved using a number of recently reported techniques, namely diffusion indices sampled along streamline trajectories (DIST, Pannek et al., 2011b) and Track-Weighted Imaging (TWI). Furthermore, multimodal image information derived from functional MRI data can also be used to weight streamlines to provide novel (TW) FC maps with super-resolution (Calamante et al., 2013).

Although DIST and TWI maps provide novel mechanisms to study disease through generalised streamline weighting, it is difficult to localise the precise anatomical source and possible spread of the injury or neuropathology. To overcome this limitation, we introduce a new technique, named diTWI: distance informed Track-Weighted Imaging. In contrast to DIST and TWI, the image contrast in diTWI is derived by modulating the streamline weighting based on the distance of each voxel from a given anatomical location along the tract. A brain lesion or a region of known neuropathology delineated on any given imaging modality (e.g. MRI or PET) can be used as the target region to derive diTWI maps. To demonstrate the clinical utility of diTWI, we show that this technique can be used to assess the infiltration of tumour cells along WM fibre tracts in patients with newly diagnosed high-grade gliomas. The propensity for gliomas to infiltrate along white matter structures is well established from pathology studies (Daumas-Duport et al., 1983; Scherer, 1940).

Although tumour boundaries can be accurately delineated with PET imaging employing labelled amino acid radiotracers, availability of advanced PET imaging in neuro-oncology is limited. For other, more widely available imaging modalities such as MRI, measuring glioma infiltration presents a significant challenge (Heiss et al., 2011). Conventional T1, T2 and FLAIR sequences do not reliably identify tumour margins. Infiltrating glioma cells extend well into the peritumoural territory beyond the regions delineated on contrast enhanced (CE) T1-weighted MRI. Previous studies have shown that diffusivity indices such as FA and ADC, sampled within the peritumoural territory, show promise for the delineation of tumour infiltration along WM fibre tracts (Deng et al., 2010; Kinoshita et al., 2010; Pavlisa et al., 2009; Price et al., 2006; Server et al., 2009; Stecco et al., 2011; Wang et al., 2009). Furthermore, measures of fibre density generated from whole brain tractography analysis have been shown to correlate with tumour cell number and the percentage of tumour infiltration (Stadlbauer et al., 2010). However, as outlined above, there is still some debate regarding whether tractography generated fibre density measures represent true quantitative measures (Jones et al., 2013).

To improve the delineation of glioma boundaries, we generated diTWI maps from a number of target ROIs of tumour defined using several methods. The signal intensity of points along the streamlines entering the ROIs was modulated based on the distance from these ROIs. ROIs, which are believed to reflect tumour infiltration, were automatically delineated on co-registered MRI maps, including the area under the concentration curve (AUC) derived from dynamic contrast enhanced (DCE) MRI and diffusivity measures (FA and ADC) generated from dMRI. The AUC is a simple but robust measure of the tumour vascular microenvironment (Evelhoch, 1999; Mills et al., 2010) calculated as the integral of the pharmacokinetic model fit to the DCE-MRI voxels across the volumes using the Levenberg–Marquardt fitting algorithm. Likewise, reduced ADC and FA indices have been reported to be associated with enhanced tumour cellularity (Cha, 2006). With this strategy, the contrast of the individual diTWI maps depended on the location and volume of the ROIs (AUC, ADC and FA) used to generate the maps, each of which highlights different pathological features or microenvironments within the tumour. For comparison, TWI (i.e. without distance information) and geometric distance maps (i.e. linear distance information instead of streamline distance) were also generated from the same AUC, ADC and FA maps.

To enable comprehensive assessment of this new strategy, tumour volumes derived from the baseline AUC, FA and ADC maps along with their geometric distance, TWI and diTWI counterparts were automatically generated using a logistic regression classifier (Gal et al., 2012; Jain et al., 2000) (Fig. 1). The accuracy of delineating tumour infiltration using these approaches was assessed by comparing the extracted tumour volumes with the tumour margins delineated on 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA) PET images. A number of studies have highlighted the use of FDOPA PET imaging for delineating glioma infiltration and proliferation (Chen, 2007; Chen et al., 2006; Fueger et al., 2010; Jora et al., 2011; Ledezma et al., 2009; Pafundi et al., 2013; Tripathi et al., 2009; Walter et al., 2012).

Methods

Patients

Data from 14 patients (9 males, age range 47 to 85 years) with histopathologically confirmed high-grade glioma (WHO grade III or IV) were used in this study. These patients were enrolled in a larger study aimed at developing FDOPA PET–MRI fusion guided therapy for patients with newly diagnosed primary brain tumours. The Institutional Review Board approved the study and written informed consent was obtained from each participant. Demographic information for the patients is provided in Table 1.

Imaging protocols

Both the MRI and FDOPA PET studies were acquired less than 48 h before tumour resection. MRI scans were acquired using a 3 T Siemens TimTrio (Siemens, Erlangen, Germany). Routine diagnostic scans were supplemented with high resolution T1-weighted MRI scans (FOV 24 × 25.6 × 17.6 cm, TR/TE/TI 2300/2.26/900 ms, flip angle of 9°, 1 mm isotropic resolution) acquired before and after administration of contrast agent (0.1 mmol/kg of body weight, Gd-DTPA-BMA; Omniscan™, Amersham Health AS, Oslo, Norway). Diffusion images were acquired using High Angular Resolution Diffusion Imaging (HARDI) with the following parameters: 60 axial slices, FOV 30 × 30 cm, TR/TE 9200/112 ms, 2.5 mm slice thickness, acquisition matrix 128 × 128 with a 2.3 mm in plane image resolution, an acceleration factor of 2 and a maximum diffusion encoding gradient strength of $b = 3000\ s\ mm^{-2}$. Sixty-four diffusion-weighted images were acquired at $b = 3000\ s\ mm^2$, in which the encoding gradients were uniformly distributed in space (Jones et al., 1999), along with 1 minimally diffusion weighted image ($b = 0$). A field map was acquired using two 3D gradient recalled echo images (TE1/TE2 4.76/7.22 ms) to assist in the correction for distortion of diffusion images due to susceptibility inhomogeneities at tissue boundaries. Dynamic contrast-enhanced image series were acquired using a 3D fast gradient echo sequence with the following parameters; field of view of 220 mm, slice thickness 4 mm, acquisition matrix 256 × 256, 56 slices, repetition time 8.1 ms, 4 averages and flip angle of 20°. The dynamic series were acquired after bolus injection of the contrast agent. A total of 12 volumes were used in the analysis: 1 pre-contrast and 11 post-contrast scans.

FDOPA preparation took place in a radiochemistry laboratory using a previously reported synthesis (Namavari et al., 1992). PET imaging was performed using a Philips Gemini GXL PET/CT scanner (Eindhoven, Netherlands). An 18F-DOPA activity of 151 MBq on average was administered intravenously (range 138 to 164 MBq). A low dose transmission CT scan was performed followed by a 75-minute list mode acquisition. The images were reconstructed using ordered subset expectation maximisation (Nuyts et al., 2001) with corrections for attenuation and scatter (Kinahan et al., 1998). The final volume had a matrix size of 128 × 128, consisting of 90 planes of $2 \times 2 \times 2mm^3$ voxels.