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Super-resolution track-density imaging studies of mouse brain: Comparison to histology

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ABSTRACT

The recently proposed track-density imaging (TDI) technique was introduced as a means to achieve super-resolution using diffusion MRI. This technique is able to increase the spatial resolution of the reconstructed images beyond the acquired MRI resolution by incorporating information from whole-brain fibre-tracking results. It not only achieves super-resolution, but also provides very high anatomical contrast with a new MRI contrast mechanism. However, the anatomical information-content of this novel contrast mechanism has not yet been assessed. In this work, we perform such a study using diffusion MRI of ex vivo mouse brains acquired at 16.4T, to compare the results of the super-resolution TDI technique with histological staining (myelin and Nissl stains) in the same brains. Furthermore, a modified version of the directionally-encoded colour TDI map using short-tracks is introduced, which reduces the TDI intensity dynamic range, and therefore enhances the directionality colour-contrast. Good agreement was observed between structures visualised in the super-resolution TDI maps and in the histological sections, supporting the anatomical information-content of the images generated using the TDI technique. The results therefore show that the TDI methodology does provide meaningful and rich anatomical contrast, in addition to achieving super-resolution. Furthermore, this study is the first to show the application of TDI to mouse brain imaging: the high-resolution, high-quality images demonstrate the useful complementary information that can be achieved using super-resolution TDI.
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Introduction

A new method to achieve super-resolution using diffusion MRI has been recently introduced (Calamante et al., 2010). This technique, referred to as super-resolution track-density imaging (TDI), is able to increase the spatial resolution of the reconstructed images beyond the acquired MRI resolution by incorporating information contained in whole-brain fibre-tracking results. For example, from 2.5 million tracks obtained using probabilistic fibre-tracking, human brain TDI maps with 125 μm isotropic resolution were created from diffusion MRI data acquired with 2.3 mm resolution on a 3 Tesla standard clinical scanner (Calamante et al., 2010), i.e. an approximately 6000-fold reduction in the voxel size. More recently, the super-resolution property of the TDI method was validated (Calamante et al., 2011), using both in vivo high-resolution human diffusion MRI data acquired at 7 T, and in silico diffusion MRI data from a well-characterised numerical phantom (Close et al., 2009). In that study, it was shown that the structures that could be identified in the TDI maps only after using super-resolution were consistent with the corresponding structures identified in the reference high-resolution maps without super-resolution (Calamante et al., 2011).

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; aca, anterior commissure, anterior part; acp, anterior commissure, posterior part; Br, Bregma; cc, corpus callosum; cg, cingulum; cp, cerebral peduncle; CPu, caudate putamen (striatum); CSD, constrained spherical deconvolution; DEC, directionally-encoded colour; δ, duration of the diffusion-weighted gradient pulse; Δ, time-interval between the onset of the two gradient pulses; dhc, dorsal hippocampal commissure; ec, external capsule; eml, external medullary lamina; f, fornix; FA, fractional anisotropy; fi, fimbria of the hippocampus; fmi, forceps minor of the corpus callosum; FOD, fibre orientation distributions; fr, fasciculus retroflexus; gcc, genu of the corpus callosum; Hb, habenula; ic, internal capsule; iFOD2, 2nd order integration over fibre orientation distributions; IMD, intermediodorsal thalamic nucleus; *lmax*, maximum harmonic order; LMol, stratum lacunosum-moleculare; lo, lateral olfactory tract; mfb, medial forebrain bundle; ml, medial lemniscus; MS, medial septal nucleus; mt, mammillothalamic tract; ns, nigrostriatal tract; opt, optic tract; PB, phosphate buffer; pf, precommissural fornix; RGB, red–green–blue; sm, stria medullaris; st, stria terminalis; str, superior thalamic radiation; *st*TDI, short-tracks track density imaging; tc, thalamic commissure; TDI, track density imaging; TE, echo-time; TR, repetition-time.

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The TDI technique not only provides a means to achieve super-resolution, but it also provides very high anatomical contrast, with a new MRI contrast mechanism not available from other MRI modalities (Calamante et al., 2010). However, the *anatomical information-content* of this novel contrast mechanism has not yet been thoroughly assessed. It remains to be shown whether the features identified on TDI maps correspond to real brain structures, which requires comparison of the TDI maps with an *anatomical* "gold-standard"; while no perfect version of the latter is available, it is widely accepted that histological staining of brain sections provides a very good representation of many structures.

This study attempts to fill this gap by investigating the anatomical information-content of the TDI technique. Diffusion MRI of ex vivo mouse brains was acquired at ultra-high magnetic field strength (16.4 T), and the results of the super-resolution TDI technique were compared to histological staining of the same brains, using Gallyas silver stain for myelin and Nissl stain for cell bodies. Anatomical features were identified in the super-resolution TDI maps, and their appearance and location were visually compared to features in the histological images.

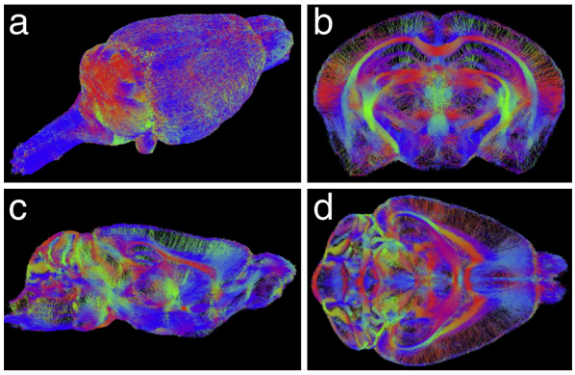

Fig. 1. Example of whole-brain fibre-tracking results from mouse *m3*. (a) Surface view from a dorso-posterior direction. (b) Coronal section, (c) sagittal section, and (d) horizontal section of whole-brain fibre-tracking results; each section displays the tracks within a 0.2 mm slab. The colour-coding indicates the local fibre orientation (red: left–right, green: dorsal–ventral, blue: cranial–caudal). The results correspond to 100,000 tracks.

Materials and methods

Three 12-week old adult C57 BL6 mice (*m1*, *m2* and *m3*) were included in this study. Mice were anaesthetised and perfused with 4% paraformaldehyde containing 0.5% Magnevist. The brains were removed from the skull and placed in Fomblin for MRI. All mice were housed and handled in accordance with Queensland Animal Care and Protection Act 2001 and the current NHMRC Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (UQ ethics approval CMR/907/08/NHMRC).

MRI data acquisition

Diffusion MRI data were acquired using previously published protocols (Moldrich et al., 2010). In brief, MRI data were acquired on a 16.4 Tesla vertical bore animal system (Bruker Biospin, Germany) using Micro2.5 gradient system and a 15 mm linear surface coil (M2M, Australia). The diffusion acquisition consisted of a 3D diffusion-weighted spin-echo sequence, with TE/TR = 22.8/400 ms, 0.1 mm isotropic resolution, field-of-view: $11.2\times19\times8$ mm (for mouse *m1* and *m2*) or $11.5\times22\times8.5$ mm (for mouse *m3*), two $b=0$ s/mm^2 images and 30 uniformly distributed diffusion gradient-encoding directions (Jones et al., 1999) with $b=5000$ s/mm^2 ($\delta/\Delta=2.5/14$ ms). Data acquisition was performed at 22°, with a total acquisition time of ~32 h.

Fibre-tracking

Mouse whole-brain fibre-tracking was carried out using in-house software based on *MRtrix* (Brain Research Institute, Melbourne, Australia, http://www.brain.org.au/software/). The analysis included constrained spherical deconvolution (CSD) (Tournier et al., 2007) to model multiple fibre orientations in each voxel, with a maximum harmonic order $l_{max}=6$; this parameter determines the 'sharpness' of the fibre orientation distributions (Tournier et al., 2004, 2008). Probabilistic fibre-tracking (Behrens et al., 2003) was performed using the 2nd order integration over fibre orientation distributions (iFOD2) algorithm (Tournier et al., 2010); this included the following relevant parameters: 0.1 mm step-size, maximum angle between steps = 45°, three FOD samples/step, any track with length <0.4 mm was discarded, termination criteria: exit the brain or when the CSD fibre-orientation distribution amplitude was <0.01 (Note: this FOD cut-off value was reduced compared with that used for in vivo human brain studies (Calamante et al., 2011; Tournier et al., 2010), and was empirically chosen based on a preliminary visual assessment of the fibre-tracking results from one of the ex vivo mouse brains; the histological data were not used during this empirical tuning). To achieve whole-brain tracking, random seeds were placed throughout the mouse brain, and tracking was performed bi-directionally. A total of 4,000,000 tracks were generated for each mouse data-set.

Track-density imaging (TDI)

TDI maps were generated using *MRtrix* by calculating the total number of tracks present in each element of a grid. By selecting a grid-element smaller than the voxel size of the source data, the spatial resolution of the final map can be increased, thus achieving super-resolution (see Calamante et al. (2010) for further details). For each mouse dataset, a 20 μm isotropic grid was used to generate the super-

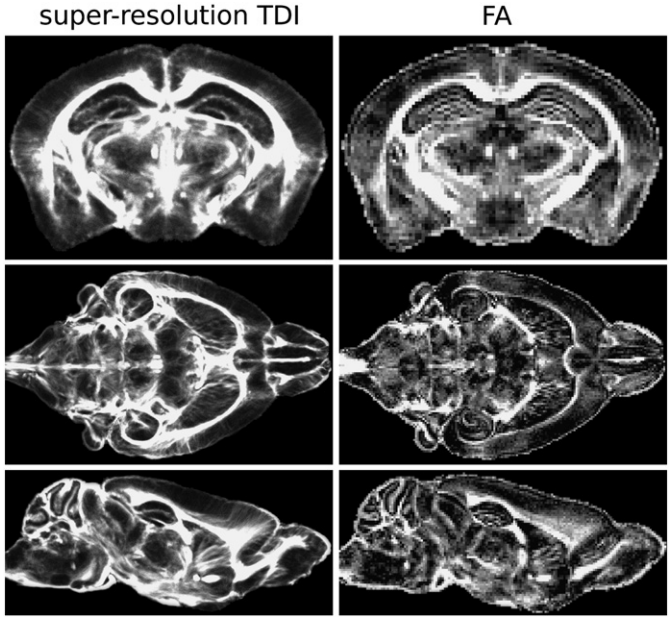

Fig. 2. Super-resolution TDI maps (left column) and FA maps (right column), for coronal (top), horizontal (middle) and sagittal (bottom) orientations. The TDI maps have 20 μm isotropic resolution; the FA maps have 100 μm resolution (i.e. the resolution of the acquired diffusion-weighted imaging data). The data correspond to mouse *m3*.

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