TECHNICAL REPORT

Super-Resolution Track-Density Imaging of Thalamic Substructures: Comparison With High-Resolution Anatomical Magnetic Resonance Imaging at 7.0T

Fernando Calamante,^{1,2} Se-Hong Oh,^{3,4} Jacques-Donald Tournier,^{1,2}
Sung-Yeon Park,³ Young-Don Son,³ Jun-Young Chung,^{3,5} Je-Geun Chi,³
Graeme D. Jackson,^{1,2} Chan-Woong Park,³ Young-Bo Kim,³
Alan Connelly,^{1,2} and Zang-Hee Cho^{3*}

¹Brain Research Institute, Florey Neuroscience Institutes, Melbourne, Victoria, Australia

²Department of Medicine, Austin Hospital, University of Melbourne, Melbourne, Victoria, Australia

³Neuroscience Research Institute, Gachon University of Medicine and Science, Incheon, Korea

⁴Department of Radiology, University of Pennsylvania, Pennsylvania

⁵Department of Biomedical Engineering, College of Health Sciences, Eulji University, Korea

Abstract: The thalamus is one of the most important brain structures, with strong connections between subcortical and cortical areas of the brain. Most of the incoming information to the cortex passes through the thalamus. Accurate identification of substructures of the thalamus is therefore of great importance for the understanding of human brain connectivity. Direct visualization of thalamic substructures, however, is not easily achieved with currently available magnetic resonance imaging (MRI), including ultra-high field MRI such as 7.0T, mainly due to the limited contrast between the relevant structures. Recently, improvements in ultra-high field 7.0T MRI have opened the possibility of observing thalamic substructures by well-adjusted high-resolution T₁-weighted imaging. Moreover, the recently developed super-resolution track-density imaging (TDI) technique, based on results from whole-brain fiber-tracking, produces images with sub-millimeter resolution. These two methods enable us to show markedly improved anatomical detail of the substructures of the thalamus, including their detailed locations and directionality. In this study, we demonstrate the role of TDI for the visualization of the substructures of the thalamic nuclei, and relate these images to T₁-weighted imaging at 7.0T MRI. *Hum Brain Mapp* 34:2538–2548, 2013. © 2012 Wiley Periodicals, Inc.

FC, J-DT, GDJ, and AC have a patent application on the TDI method.

Fernando Calamante and Se-Hong Oh contributed equally to this work.

Contract grant sponsor: Basic Science Research Program Through the National Research Foundation (NRF), the Ministry of Education, Science and Technology; Contract grant number: 2008-2004159 and 2010-0029262; Contract grant sponsor: Korea Science and Engineering Foundation (KOSEF), Korea government (MOST); Contract grant number: 20100002134.

*Correspondence to: Zang-Hee Cho, Ph.D., Neuroscience Research Institute, Gachon University of Medicine and Science, 1198 Kuwol-dong, Namdong-gu, Incheon 405-760, Korea.
E-mail: zcho@gachon.ac.kr

Received for publication 19 August 2011; Revised 21 February 2012; Accepted 23 February 2012

DOI: 10.1002/hbm.22083

Published online 14 November 2012 in Wiley Online Library (wileyonlinelibrary.com).

Key words: thalamus; thalamus substructures; track-density imaging; TDI; 7.0T MRI; diffusion weighted imaging

INTRODUCTION

The thalamus functions as a relay hub for the various cortical and subcortical areas in the cerebral cortex, and is one of the most important structures of the brain. Most incoming neural signals directed toward the cortex are routed via the thalamus. The inner structures of the thalamus are, however, so small and delicately subdivided cytoarchitectonically (Guillery and Sherman, 2002; Jones, 1981, 1991) that it has been difficult to identify them with existing imaging devices, especially in the in vivo human brain. Until recently, direct visualization of thalamic substructures has only been possible histologically (Morel et al., 1997) and more recently a high-resolution 3D model of the thalamus from histological section was reported (Krauth et al., 2010). However, accurate identification of substructures of the thalamus is of great importance not only for localization of specific nuclei but also to understand their functional connectivities. For example, this is especially the case in psychotic disorders such as schizophrenia, which are thought to reflect deficiencies in neuronal connectivity (Karlsgodt et al., 2008). Decreased fractional anisotropy (FA) in the anterior thalamic radiation has been reported recently in individuals at high risk for psychosis (Karlsgodt et al., 2009) or in the initial psy-

chotic episode (Perez-Iglesias et al., 2010). However, the diagnosis is dependent on a constellation of symptoms. Thus, in vivo direct observation of the thalamic nuclei or connectivity in the human brain has been one of the most sought after goals in psychotic disorders. In fact, research on the parcellation of the thalamus has been a major area of research in neurosciences (Behrens et al., 2003; Johansen-Berg et al., 2005; Krauth et al., 2010).

The role of in vivo structural imaging for the identification of substructures of the thalamus has been limited by the difficulty of obtaining high-resolution and high-contrast images that can distinguish the fine substructures of the thalamus (Deoni et al., 2005; Gringel et al., 2009). Part of this may be because the thalamus is intermediate in signal characteristics between grey and white matter, and histologically it is a mixture of these elements at a voxel level. Despite these limitations, several studies have been conducted to define human thalamic sub-regions using magnetic resonance imaging (MRI). For example, previous studies have proposed that the thalamic sub-regions can be distinguished based on the local orientation of the structures as measured by diffusion tensor imaging (Wiegell et al., 2003), by the connectivity patterns based on diffusion tensor probabilistic tractography (Behrens et al., 2003; Devlin et al., 2006; Johansen-Berg et al., 2005), or by the functional activation of the thalamus using ultra-high field (UHF) MRI (Metzger et al., 2010).

In low-field structural MR images, due to the limited resolution and contrast of the images, it is not easy to clearly show the thalamic substructures (Cho et al., 2008, 2010). More recently, however, UHF MRI at 7.0T has been used to visualize in vivo the glucose metabolism in the substructures of the thalamus in humans (Cho et al., 2011). By using 7.0T MRI, we were able to acquire high-contrast and high-resolution images of the in vivo human brain, including for example hippocampal substructures, as well as metabolic functions and, more recently, the substructures of the thalamus (Cho et al., 2011). Also, a new technique known as super-resolution track-density imaging (TDI) has been developed as a means to create very high-resolution images of track-density using the results obtained from whole-brain tractography (Calamante et al., 2010). The super-resolution property of this technique was recently validated using in vivo and in silico data (Calamante et al., 2011), and its anatomical contrast compared with histological sections (myelin and Nissl staining) from ex vivo mouse data (Calamante et al., 2012a). The high TDI contrast previously shown in the thalamus at 3.0T MRI, combined with the enhanced resolution that can be achieved with this methodology and subsequent targeted

Abbreviations

ATh	anterior
CSD	constrained spherical deconvolution
DEC	directionally encoded color
DWI	diffusion-weighted images
EPI	echo planar imaging
FA	fractional anisotropy
iFOD2	second order integration over fiber orientation distributions
IML	internal medullary lamina
MB	the mammillary body
MD	mediodorsal nuclei
MRI	magnetic resonance imaging
PSF	point spread function
Pul	pulvinar
R	red nucleus
sm	stria medullaris
SN	substantia nigra
ST	stria terminalis
stTDI	short-tracks TDI
TDI	track-density imaging
UHF	ultra-high field
VLA	the ventrolateral anterior nuclei
VLP	the ventrolateral posterior nuclei

fiber-tracking (Calamante et al., 2010), suggest a possible role for TDI in thalamic mapping and thalamo-cortical connectivity measurements in the in vivo human brain. In this study, we demonstrate the role of TDI for direct visualization of the substructures of the thalamus in conjunction with optimized high-resolution T_1 -weighted anatomical images of the thalamus (Cho et al., 2011) obtained by 7.0T MRI.

MATERIALS AND METHODS

MRI Data Acquisition

Data from four healthy volunteers (referred to as subjects S1–S4; two male and two female, aged between 27 and 31 years) were obtained from a 7.0T research prototype MRI scanner (Magnetom 7.0T, Siemens) with 40 mT/m gradient field strength. For each subject, a set of diffusion-weighted images (DWI) (the base data for TDI) and 3D T_1 -weighted images (MPRAGE) were acquired on separate sessions. The specific imaging parameters used for the single-shot DW echo planar imaging (EPI) were as follows: TR/TE = 6,000/83 ms; matrix = 128×128 ; 1.8-mm isotropic resolution; 64 DW-directions; $b = 0$ and 2000 s/mm², three repeats; GRAPPA with factor 3 and 45 slices.

T_1 -weighted MPRAGE images were obtained using the following imaging parameters: TR/TE/TI = 400/5.26/900 ms; matrix = 276×384 ; $0.375 \times 0.375 \times 1.5$ mm³ resolution; flip angle = 45°; bandwidth = 30 Hz/pixel. The latter are thalamus-specific 7.0T MRI parameters we have recently optimized, in conjunction with a custom-built 7.0T optimized 8-channel Tx/Rx head-only RF coil; this coil was designed to provide good B_1 homogeneity in the center of the brain, as well to minimize power deposition.

To minimize head motion, we fixed the subject's head using soft pad. To minimize registration error, T_1 and DWI images were acquired aligned with AC-PC reference line (axial imaging plane is parallel with the AC-PC line and coronal imaging plane is perpendicular with the AC-PC line). With this acquisition scheme, T_1 and DWI images have the same orientation. The T_1 images were then registered to the DWI data using affine registration.

MRI Data Processing at 7.0T

Geometric distortion correction

DWI images acquired using EPI suffer from distortion artifacts caused by magnetic susceptibility and B_0 field inhomogeneities, especially at high field strengths. Accurate geometric distortion correction is, therefore, essential for high-resolution DWI imaging at UHF MRI such as 7.0T. The DWI data were therefore corrected for geometric distortions using a combined dimensional point spread function (PSF) mapping method developed by the authors (Oh et al., 2010, in press). The newly improved PSF technique improved image quality substantially. This approach takes into account both the distortion and non-distortion

dimensional PSF corrections schemes, in contrast to previous methods where only either non-distortion (Zaitsev et al., 2004) or distortion dimensional (Chung et al., 2011) correction were used. The processing time for the PSF distortion correction step, including offline image reconstruction and Nyquist ghost phase correction, was ~ 4 h for each dataset included in this study.

After distortion correction using the PSF technique, we performed affine registration to non-diffusion weighted ($b = 0$ s/mm²) images to correct for any minor head motion present in the data. In all subjects, the rotations were $< 5^\circ$ and the translations were < 1 mm.

Calculation of fiber orientation distributions

Following geometric distortion correction of the DWI data, whole-brain probabilistic fiber-tracking was performed as an initial step to generate the track-density maps. This analysis was carried out using in-house software based on the MRtrix software package (Brain Research Institute, Melbourne, Australia, <http://www.brain.org.au/software/>). To estimate the fiber orientation distributions (FOD), constrained spherical deconvolution (CSD) (Tournier et al., 2007) was used with a maximum spherical harmonic order $l_{\max} = 8$. [Note: $l_{\max}$ determines the FOD “sharpness” (Tournier et al., 2004, 2007, 2008)]. The CSD technique is able to model multiple fiber populations within an imaging voxel, thus overcoming the well-known limitation of the diffusion tensor model in “crossing fiber” regions.

Due to the DWI signal inhomogeneities observed at 7T, the FODs in peripheral white matter (particularly subcortical areas) were artifactually scaled down, with their amplitude much smaller than those in the corpus callosum (see Fig. 1b). If left uncorrected, this effect leads to reduced tracking in these peripheral areas, and therefore reduced TDI intensity. Therefore, to correct for this effect, we applied an empirical correction to scale the calculated FODs. The correction method consisted of two steps:

- i. First, we used a scaling factor K_1 equal to the inverse of the zeroth order spherical harmonic term of the FOD (i.e., the $l = 0$ term, or DC term; this term corresponds to the average FOD amplitude and therefore its inverse can be used to scale up FODs with low amplitude). However, this scaling also boosted the amplitude of the FODs in isotropic areas, such as gray matter and cerebrospinal fluid (see Fig. 1c), since they also had low FOD amplitude (Fig. 1b).
- ii. To limit the scaling in these isotropic areas, we therefore also applied a second scaling factor K_2 based on the FA map:

$$K_2 = \min\{5 \times FA, 1\} \quad (1)$$

where “min{ }” indicates the minimum function [NB. To minimize the effect of noise in low FA regions, a $3 \times 3 \times 3$ median filtered FA map was in practice used in Eq. (1)]; this

Figure 1.

Scaling of the fiber orientation distributions (FOD). (a) Axial FA map. The white box indicates the zoomed-area shown in the other images; (b) Zoomed-area with FODs overlaid. Note the attenuation of the FOD amplitude in subcortical white matter areas; (c) FODs after scaling using DC image (i.e., the K_1 factor).

Note the increase in FOD amplitude in subcortical white matter areas, as well as in isotropic areas; (d) FODs after scaling also using FA information (i.e., the K_2 factor). Note the selective attenuation of FOD amplitude in isotropic areas.

second scaling selectively attenuates the FOD amplitudes for all voxels with $FA < 0.2$, whose value was chosen empirically such that it effectively only influenced isotropic areas such as cortical gray matter and cerebrospinal fluid (see Fig. 1d). Note that for our diffusion MRI protocol, the FA in crossing fiber regions (including the thalamus) was above this 0.2 threshold, as can be appreciated by the lack of attenuation in the voxels with low FA and multiple FOD lobes seen in regions with crossing fibers in Figure 1c (cf. corresponding FOD amplitudes in Fig. 1d). The resulting scaled FODs were then used for fiber-tracking.

Fiber-tracking

Tractography was carried out with probabilistic streamlines using the second order integration over fiber orientation distributions (iFOD2) algorithm (Tournier et al., 2010).

Tracking was performed by seeding randomly throughout the brain with the following relevant parameters: 1 mm step-size, maximum angle between steps = 45° , three FOD samples/step, and termination criteria: exit the brain or FOD amplitude < 0.4 . Four million tracks were generated for each dataset.

Track-density imaging

From the reconstructed fiber-tracks, super-resolution TDI maps were generated by calculating the number of tracks in each element of a grid. A salient point of the TDI mapping is that the grid element is made smaller than the acquired voxel size, so that the final map is generated at much higher resolution than the original DWI data (Calamante et al., 2010). For this study, a 200- μ m isotropic grid-size was used, which constitutes a factor of ~ 730 reduction in the volume of the voxel.

Figure 2.

Example of whole-brain fiber-tracking results from 7T data for subject S1. Axial section (left), coronal section (top-right), and sagittal section (bottom-right) of whole-brain fiber-tracking results. Each section displays the tracks within a 1.8-mm slab.

The colour-coding indicate the local fiber orientation (red: left-right, green: anterior-posterior, blue: inferior-superior). For ease of visualization, the results from only 75,000 tracks are displayed.

Directionally encoded color (DEC) TDI maps [the super-resolution equivalent of the DEC map in diffusion tensor imaging (Calamante et al., 2010)] were also generated for each dataset. In these maps, the color-coding indicates the local fiber orientation (as given by averaging the colors of all the streamline segments contained within each grid element). In particular, the *DEC short-tracks TDI (stTDI)* map method (Calamante et al., 2012a) was employed, in which the DEC-TDI map is created after constraining the maximum length of each track to 18 mm (corresponding to 10 acquired voxels); this modified DEC-TDI approach was shown to have increased directional information as compared with the standard DEC-TDI technique (Calamante et al., 2012a). To compensate for the reduced intensity associated with the length constraint, a much larger number of tracks need to be generated to maintain a reasonable contrast-to-noise ratio for the DEC-stTDI map (Calamante et al., 2012a). For this study, 52 million tracks were therefore generated for each subject with the short track constraint, and DEC stTDI maps constructed with 200- μ m isotropic resolution.

The processing time for the various steps using the MRtrix software on a standard desktop workstation (Intel Core2 Quad 2.8 GHz, 4Gb RAM, 64-bit Linux) were 2 min for the CSD analysis, $\sim$ 3 h for generating 4 million standard (long) tracks using iFOD2, $<$ 10 min to generate the

corresponding TDI map at 0.2-mm isotropic resolution, $\sim$ 16 h for generating 52 million short tracks using iFOD2 and $\sim$ 25 min to generate the super-resolution DEC-stTDI at 0.2-mm resolution.

To align TDI and DEC-stTDI maps with MPAGE images, we used FLIRT (Jenkinson et al., 2002) from the FMRIB Software Library (FSL, Oxford, United Kingdom, <http://fsl.fmrib.ox.ac.uk/fsl>) to co-register the MPAGE images with the DWI $b = 0$ source images, as the latter are inherently spatially aligned with the TDI and DEC-stTDI maps.

RESULTS

Figure 2 shows an example of the whole-brain fiber-tracking results (from subject S1). As can be appreciated in the figure, very good quality fiber-tracking results can be generated from 7T EPI data with the acquisition and analysis methods used in this study.

Figure 3 shows the comparison results of our native resolution FA images and their corresponding DEC FA images with the equivalent TDI maps and their corresponding DEC-stTDI image, all focused on to the thalamic region for a typical subject (subject S2). As shown in Figure 3a,b, only minimal details of the substructures or

Figure 3.

Conventional FA and the new track-density imaging (TDI) maps at three different axial slices (labeled i-iii) for subject S2; all maps were generated from the same data obtained by diffusion-weighted imaging at 7.0T. (a) FA maps and (b) corresponding DEC FA maps; (c) super-resolution TDI maps, and (d) corresponding super-resolution DEC-stTDI maps. Both FA (a) and DEC-FA (b) maps were calculated based on the diffusion tensor model, with original 1.8-mm isotropic resolution. Super-resolution TDI (c) and DEC-stTDI (d) maps were generated on a 200-

μm isotropic grid by using 4 million and 52 million tracks, respectively; (e) axial TDI maps. The red box indicates the zoomed-area shown in the other images. The color-coding indicates the main local orientation (red: left-right, green: anterior-posterior, blue: inferior-superior), defined based on the streamline segments contained within the grid element (for the TDI maps) or on the principal direction of the diffusion tensor (for the tensor-based maps). "ic": internal capsule; "cc": corpus callosum.

inner-structures of the thalamus are visible in the tensor-based FA maps, while the TDI and DEC-stTDI images (shown in Fig. 3c,d) provide much improved definition of the thalamic inner-regions as well as the surrounding internal capsules and corpus callosum.

In Figures 4–6, we have displayed a set of coronal and axial TDI images of the thalamus together with anatomically equivalent T_1 -MPRAGE and histological-derived diagrams as a reference, for a typical subject (subject S1). Several brain structures in the thalamic and surrounding areas (Figs. 4b,d, 5b,d, and 6b,d) are clearly identifiable in the high-resolution anatomical images. Numerous structures can also be seen in the corresponding TDI maps (Figs. 4e, 5e, and 6e), with markedly higher resolution and contrast. Furthermore, by incorporating directionality information, the super-resolution DEC-stTDI maps (Figs. 4f, 5f, and 6f) enhance the differentiation between the various substructures. TDI maps show excellent correlation with the anatomical images obtained by T_1 -weighted MPRAGE imaging and histological-derived diagrams as shown in the Figures 4–6. Besides the obvious landmark structures such as the corpus callosum and internal capsule, we can

also clearly identify inner structures, such as the anterior (ATH) and mediodorsal (MD) nuclei, the ventrolateral anterior (VLA) and posterior (VLP) nuclei, pulvinar (Pul), internal medullary lamina (IML), stria medullaris (sm), the mammillary body (MB), and stria terminalis (ST), substantia nigra (SN), and red nucleus (R), amongst others. The results shown in Figures 4–6 are typical of the subjects included in this study.

Figure 7 shows DEC-stTDI maps from a similar axial location for each of the four subjects. For a more detailed anatomical reference of the inner structures of the thalamus, an histological-derived diagram (Morel et al., 1997) is also included. As can be appreciated in this figure, there is a very good correlation between the structures in the DEC-stTDI maps and those in the diagram.

DISCUSSION

The results from our study suggest that the TDI and DEC-stTDI maps allow many hitherto unseen thalamic substructures and fiber distributions to be visualized. As

Figure 4.

Examples of the results obtained from subject S1. We display coronal view images. (a) Axial MPRAGE images to show the location of the coronal imaging plane; the red line indicates the acquired imaging plane; (b) MPRAGE images of high-resolution 7.0T MRI. The red box indicates the zoomed-area shown in the other images; (c) histological-derived reference diagrams (Anterior view 9) reproduced from Mai, J., and Paxinos, G., Atlas of the Human Brain, 2008, Elsevier/Academic Press; (d) zoomed-MPRAGE images; (e) super-resolution TDI maps; and (f) super-resolution DEC-stTDI maps. The colors represent the main local orientation (red: left–right, green: anterior–posterior, blue: inferior–superior).

rior view 9) reproduced from Mai, J., and Paxinos, G., Atlas of the Human Brain, 2008, Elsevier/Academic Press; (d) zoomed-MPRAGE images; (e) super-resolution TDI maps; and (f) super-resolution DEC-stTDI maps. The colors represent the main local orientation (red: left–right, green: anterior–posterior, blue: inferior–superior).

Figure 5.

Examples of the results obtained from subject S1. We display coronal view images (obtained from same subject as in Fig. 4 but different slice). (a) Axial MPRAGE images to show the location of the coronal imaging plane; the red line indicates the acquired imaging plane; (b) MPRAGE images of high-resolution 7.0T MRI. The red box indicates the zoomed-area shown in the other images; (c) histological-derived reference diagrams (Anterior

view 10) reproduced from Mai, J., and Paxinos, G., Atlas of the Human Brain, 2008, Elsevier/Academic Press; (d) zoomed-MPRAGE images; (e) super-resolution TDI maps; (f) super-resolution DEC-stTDI maps. The colors represent the main local orientation (red: left–right, green: anterior–posterior, blue: inferior–superior).

Figure 6.

Examples of the results obtained from subject S1. We display axial view images (obtained from same subject as in Fig. 4). (a) Coronal MPRAGE images to show the location of the axial imaging plane; the red line indicates the acquired imaging plane; (b) MPRAGE images of high-resolution 7.0T MRI. The red box indicates the zoomed-area shown in the other images; (c) histo-

logical-derived reference diagrams (Dorsal view 7) reproduced from Mai, J., and Paxinos, G., *Atlas of the Human Brain*, 2008, Elsevier/Academic Press; (d) zoomed-MPRAGE images; (e) super-resolution TDI maps; and (f) super-resolution DEC-stTDI maps. The colors represent the main local orientation (red: left-right, green: anterior-posterior, blue: inferior-superior).

previously shown, thalamo-cortical connectivity can be inferred from these using targeted fiber-tracking (Calamante et al., 2010). Our results show that the DEC-stTDI maps are particularly useful in helping to visualize structures in the thalamic area: the combination of the local directional-information and the super-resolution property of the TDI technique (200 μm isotropic in our examples) provide high contrast and high resolution to delineate many thalamic substructures that correlate well with known anatomy. This does not imply that the TDI technique provides superior contrast to T_1 -weighted imaging at 7.0T in every structure. In fact, these new high-resolution TDI images provide important complementary information to the anatomical T_1 images, as shown in Figures 4–6.

It should be noted that, since the contrast in TDI originates from the results of fiber-tracking, not all the relevant thalamic substructures have high intensity in the TDI maps. Some of these structures appear hypointense (e.g., the anterior nucleus in Fig. 4), with the edges of these nuclei clearly delineated by their surrounding structures with high track-density (e.g., the internal medullary lamina in Fig. 4). Therefore, this contrast in the TDI intensity clearly assists us in separating the thalamic structure from that of the surrounding fiber tracts, thus serving as a new contrast source for high-resolution imaging.

This study therefore serves to confirm the suggested role that the TDI methodology can have in the study of

the thalamus and its disorders (Calamante et al., 2010). While the thalamic results described in the original TDI publication were very compelling, the key missing factor was the lack of an alternative image modality to corroborate those thalamic TDI findings. The use of UHF MRI, on the other hand, allows the visualization of structures within the thalamus using optimized T_1 -weighted imaging. Given that the contrast in these images does not rely on any model (cf. the contrast in the TDI maps, which rely on whole-brain fiber tracking), they provide a very good imaging modality to corroborate, on a subject-by-subject basis, the structures visualized by the TDI technique in the thalamus. The similarity between many of the structures identified in this study in the TDI maps to those in the MPRAGE images suggests that the super-resolution TDI method provides a useful imaging modality for mapping of thalamic and surrounding structures. Importantly, since the diffusion contrast mechanism is B_0 -independent, the TDI technique has been shown to also produce high-quality thalamic images at more commonly used magnetic field strengths such as 3T (Calamante et al., 2010). Therefore, the super-resolution TDI technique should play a very important role in the direct visualization of sub-thalamic structures for studies on non-UHF scanners, where the role of conventional MRI is more limited.

Delineation of the various sub-regions of the thalamus has been the subject of active research. This study provides further evidence of the role of MRI for in vivo

Figure 7.

Axial examples of super-resolution DEC-stTDI maps of the Thalamus area from four subjects (a)–(d). Note: (a) and (b) images are same as in Fig. 6f and Fig. 3d-i, respectively. (e) Histological-derived reference diagram (Dorsal view 5.4) reproduced from Morel A, Magnin M, Jeanmonod D., *J Comp Neurol*, 1997, 387, 588–630. To match the notations between aforementioned reference diagrams (reproduced from Mai, J., and Paxinos, G., *Atlas of the Human Brain*, 2008, Elsevier/Academic Press) with this, we changed several notations (AM to ATH, CeM to CM, IC to ic, PuM and PuL to Pul, VLA to VLA, and VLP to VLP). The colors represent the main local orientation (red: left–right, green: anterior–posterior, blue: inferior–superior). Legends: 3n: oculomotor nerve, 3V: third ventricle, ac: anterior commissure, aic: anterior limb of the internal capsule, Amg: amygdale, AN: anterior nuclei, ATH: anterior thalamic nucleus, bfx: body of fornix, cc: corpus callosum, CCB: body of corpus callosum, CG: cingulate gyrus, Cgc: cingulum, supracallosal, chpx: choroid plexus of the lat. Ventricle, CL: central lateral nucleus, Cl: claustrum, CLV: central part of lateral ventricle, CM: centromedian thalamic nucleus, CN: caudate nucleus, cp: cerebral peduncle, DMmc: dorsomedial nucleus, magnocellular part, DSF: dorsal superficial

nucleus, EGP: external globus pallidus, Ent: entorhinal cortex, fx: fornix, gic: internal capsule, genu, GP: globus pallidus, Hb: habenula, HCd: head of caudate nucleus, ic: internal capsule, IGP: internal globus pallidus, IML: Internal medullary lamina, ipf: interpeduncular fossa, LD: lateral dorsal thalamic nuclei, LF: lenticular fasciculus, LP: lateral posterior nuclei, LV: lateral ventricle, MB: mammillary body, MD: mediodorsal thalamic nucleus, MDmc: mediodorsal nucleus, magnocellular division, MDpc: mediodorsal nucleus, parvocellular division MDpl: mediodorsal nucleus, paralamellar division, MTT: mamillothalamic tract, opt: optic tract, PHG: parahippocampal gyrus, Pi: pineal gland, pic: Internal capsule, posterior limb, Pu: putamen, Pul: pulvinar thalami, Pv: paraventricular nuclei, R: red nucleus, RNc: red nucleus, capsule, Rt: reticular nucleus of thalamus, SB: striatal cell bridge, SFO: subfornical organ, sm: stria medullaris of thalamus, SN: substantia nigra, ST: stria terminalis, STh: subthalamic nucleus, TCd: Tail of caudate nucleus, Th: thalamus, VA: ventral nucleus, anterior, VAmc: ventral anterior nucleus, magnocellular division, VL: ventral lateral thalamic nucleus, VLA: ventrolateral nucleus, anterior, VLP: ventrolateral nucleus, posterior, VP: ventral nucleus, posterior, VPL: ventral posterior lateral nucleus.

mapping of thalamic structures. Compared with previous studies (Behrens et al., 2003; Devlin et al., 2006; Johansen-Berg et al., 2005; Metzger et al., 2010; Wiegell et al., 2003), our methodology allows direct visualization of many of these substructures at very high spatial resolution (200- μ m isotropic resolution, in this particular study), which was not possible by these previous diffusion MRI based approaches.

The issue of whether the structures identified by TDI (or indeed other diffusion MRI based images) can be used to define thalamic nuclei, which are traditionally defined by their cytoarchitecture, could be a point of debate. Strong

evidence in favor of this can be found from the work by Behrens et al. In their 2003 seminal study (Behrens et al., 2003), diffusion tensor tracking was used to parcellate the thalamus using “connectivity-defined regions,” in what they hypothesized corresponded to thalamic nuclei or nuclear groups. Their parcellation corresponded well with those defined by direct anatomical studies of non-human primates (see Fig. 2 in Behrens et al., 2003). More importantly, in a subsequent study (Johansen-Berg et al., 2005), the same group provided functional corroboration (based on previously published locations of the centers of functional activation within the thalamus during motor or

executive tasks) and anatomical corroboration (based on volumetric predictions based on a histological atlas) of their thalamic parcellation hypothesis. Therefore, their findings provide strong support to the agreement between diffusion MRI connectivity-based regions and thalamic nuclear groups. This in turn suggests the TDI structures (which are based on whole-brain fiber tracking count) can also provide relevant information for thalamic parcellation, consistent with the results shown in Figures 4–6.

Other studies have also exploited the increased SNR at 7.0T to obtain human high-resolution diffusion MRI data (e.g., (Heidemann et al., 2010)); however, to the best of our knowledge, there is no published whole-brain diffusion MRI work with sub-millimeter isotropic resolution of the in vivo human brain. While our acquired diffusion MRI resolution is also not sub-millimeter, the super-resolution TDI methodology opens up the possibility of generating diffusion-related images with a spatial resolution beyond what is practically achievable by standard imaging acquisition methods (e.g., whole-brain 200- μ m isotropic resolution, as shown in this study), as well as a different image contrast with very high anatomical information (Calamante et al., 2010). These features were instrumental in the characterization of the substructures of the thalamus in this study.

This study has shown that the super-resolution TDI maps provide a useful contrast to delineate the thalamic substructures. While the TDI technique was introduced primarily as a new imaging modality with high anatomical contrast, the maps could, in principle, be used also in a quantitative manner (Calamante et al., 2010). In fact, a recent study by Bozzali et al. (2011) using an approach with similarities to the TDI method (although without super-resolution) suggested its potential role in quantitative voxel-based analysis. However, very limited work has been carried out to characterize the quantitative properties of the TDI technique (Pannek et al., 2011). More recently, we have extended the TDI principles and presented a generalized framework for track-weighted imaging (TWI) (Calamante et al., 2012b), which might be more suited for quantitative analysis. However, further work is needed to determine its quantitative properties and utility in neuroscience applications.

The TDI methodology is based on the results of whole-brain fiber-tracking. However, in practice, partial brain coverage is sometimes used to reduce scan time. Partial brain coverage could have an effect on the actual intensity values on the TDI map in the thalamus (since some streamlines that would have originated in the missing brain regions do not contribute to the calculated track-density). This could be a relevant factor for quantitative studies, where the actual intensity values are of interest. On the other hand, it should have minimal effect on the visualization of the thalamic substructures, as was the subject of this study. Using our diffusion MRI protocol, only a small proportion of the superior part of the brain and the inferior part of the cerebellum were missing from the

acquired volume (see Fig. 2), and the effect should therefore be minimal. The effect of partial coverage is even less important when the short-track version of the TDI maps is used (i.e., DEC-*st*TDI), since only the tracks from a local neighborhood contribute to the map.

If severe motion artifacts are present in the diffusion MRI data, and these are not properly corrected for, they will have a direct effect on the quality of the TDI results: uncorrected motion artifacts lead to errors in the estimated fiber orientations at the voxel level, which would translate into fiber-tracking errors; since TDI relies on the results from whole-brain fiber tracking, tractography errors will lead to errors in the TDI maps. As is the case with other diffusion MRI applications, it is therefore important to correct for motion artifacts when these are present in the data to generate high-quality TDI maps.

Functional imaging data have made it clear that the brain operates as a network that includes cortical and sub-cortical structures, and altered connections or timing between cortical inputs may be critical in disease pathophysiology (for example schizophrenia, epilepsy, autism, mood disorder, and dyslexia among others). The thalamus plays a critical role in the modulation of inputs to the cortex, and in the regulation of output functions and inter-cortical connections. This work provides for the first time in the in vivo human brain a direct visualization not only of the thalamic substructures at very high spatial resolution but also of their directionality. This is demonstrated by ultra-high resolution anatomical images using UHF 7.0T MRI (Cho et al., 2011) and the new super-resolution TDI mapping technique (Calamante et al., 2010) performed on the same scanner. This is a basic technology that is likely to be of wide application in the understanding of many disorders of brain function and human disease.

ACKNOWLEDGMENTS

FC, J-DT, GDJ, and AC are grateful to the National Health and Medical Research Council (NHMRC) of Australia, Austin Health, and the Victorian Government's Operational Infrastructure Support Program for their support. The authors thank Mr. Suk-Min Hong, Mr. Joshua H. Park, Mr. Hong-Bae Jeong, and Mr. Myung-Kyun Woo for making coil.

REFERENCES

- Behrens TE, Johansen-Berg H, Woolrich MW, Smith SM, Wheeler-Kingshott CA, Boulby PA, Barker GJ, Sillery EL, Sheehan K, Ciccarelli O and others. (2003): Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nat Neurosci* 6:750–757.
- Bozzali M, Parker GJ, Serra L, Embleton K, Gili T, Perri R, Caltagirone C, Cercignani M. (2011): Anatomical connectivity mapping: A new tool to assess brain disconnection in Alzheimer's disease. *NeuroImage* 54:2045–2051.

- Calamante F, Tournier JD, Jackson GD, Connelly A. (2010): Track-density imaging (TDI): Super-resolution white matter imaging using whole-brain track-density mapping. *NeuroImage* 53:1233–1243.
- Calamante F, Tournier JD, Heidemann RM, Anwender A, Jackson GD, Connelly A. (2011): Track density imaging (TDI): Validation of super-resolution property. *NeuroImage* 56:1259–1266.
- Calamante F, Tournier J-D, Kurniawan N, Yang Z, Gyengesi E, Galloway G, Reutens D, Connelly A. (2012a): Super-resolution track-density imaging studies of mouse brain: Comparison to histology. *NeuroImage* 59:286–296.
- Calamante F, Tournier JD, Smith RE, Connelly A. (2012b): A generalised framework for super-resolution track-weighted imaging. *NeuroImage* 59:2494–2503.
- Cho ZH, Kim YB, Han JY, Kim KN, Choi SH, Min HK, Veklerov E, Shepp LA. (2008): New Brain Atlas -Mapping the Human Brain In-vivo with 7.0T MRI and Comparison with Postmortem Histology. *IJIST* 18:2–8.
- Cho ZH, Han JY, Hwang SI, Kim DS, Kim KN, Kim NB, Kim SJ, Chi JG, Park CW, Kim YB. (2010): Quantitative analysis of the hippocampus using images obtained from 7.0 T MRI. *NeuroImage* 49:2134–2140.
- Cho ZH, Son YD, Kim HK, Kim NB, Choi EJ, Lee SY, Chi JG, Park CW, Kim YB, Ogawa S. (2011): Observation of Glucose Metabolism in the Thalamic Nuclei by Fusion PET/MRI. *J Nucl Med* 52:401–404.
- Chung J-Y, In M-H, Oh S-H, Zaitsev M, Speck O, Cho Z-H. (2011): An improved PSF mapping method for EPI distortion correction in human brain at ultra high field (7T). *Magn Reson Mater Phys* 24:179–190.
- Deoni SC, Josseau MJ, Rutt BK, Peters TM. (2005): Visualization of thalamic nuclei on high resolution, multi-averaged T1 and T2 maps acquired at 1.5 T. *Hum Brain Mapp* 25:353–359.
- Devlin JT, Sillery EL, Hall DA, Hobden P, Behrens TE, Nunes RG, Clare S, Matthews PM, Moore DR, Johansen-Berg H. (2006): Reliable identification of the auditory thalamus using multimodal structural analyses. *NeuroImage* 30:1112–1120.
- Gringel T, Schulz-Schaeffer W, Elolf E, Frolich A, Dechent P, Helms G. (2009): Optimized high-resolution mapping of magnetization transfer (MT) at 3 Tesla for direct visualization of substructures of the human thalamus in clinically feasible measurement time. *J Magn Reson Imaging* 29:1285–1292.
- Guillery RW, Sherman SM. (2002): Thalamic relay functions and their role in corticocortical communication: Generalizations from the visual system. *Neuron* 33:163–175.
- Heidemann RM, Porter DA, Anwender A, Feiweier T, Heberlein K, Knosche TR, Turner R. (2010): Diffusion imaging in humans at 7T using readout-segmented EPI and GRAPPA. *Magn Reson Med* 64:9–14.
- Jenkinson M, Bannister P, Brady M, Smith S. (2002): Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage* 17:825–841.
- Johansen-Berg H, Behrens TE, Sillery E, Ciccarelli O, Thompson AJ, Smith SM, Matthews PM. (2005): Functional-anatomical validation and individual variation of diffusion tractography-based segmentation of the human thalamus. *Cereb Cortex* 15:31–39.
- Jones EG. (1981): Functional subdivision and synaptic organization of the mammalian thalamus. *Int Rev Physiol* 25:173–245.
- Jones EG. (1991): The anatomy of sensory relay functions in the thalamus. *Prog Brain Res* 87:29–52.
- Karlsgodt KH, Sun D, Jimenez AM, Lutkenhoff ES, Willhite R, van Erp TG, Cannon TD. (2008): Developmental disruptions in neural connectivity in the pathophysiology of schizophrenia. *Dev Psychopathol* 20:1297–1327.
- Karlsgodt KH, Niendam TA, Bearden CE, Cannon TD. (2009): White matter integrity and prediction of social and role functioning in subjects at ultra-high risk for psychosis. *Biol Psychiatry* 66:562–569.
- Krauth A, Blanc R, Poveda A, Jeanmonod D, Morel A, Szekely G. (2010): A mean three-dimensional atlas of the human thalamus: Generation from multiple histological data. *NeuroImage* 49:2053–2062.
- Metzger CD, Eckert U, Steiner J, Sartorius A, Buchmann JE, Stadler J, Tempelmann C, Speck O, Bogerts B, Abler B and others. (2010): High field FMRI reveals thalamocortical integration of segregated cognitive and emotional processing in mediodorsal and intralaminar thalamic nuclei. *Front Neuroanat* 4:138.
- Morel A, Magnin M, Jeanmonod D. (1997): Multiarchitectonic and stereotactic atlas of the human thalamus. *J Comp Neurol* 387:588–630.
- Oh SH, Chung JY, Park SY, Kim DS, In MH, Zaitsev M, Kim YB, Speck O, Cho ZH. (2010): Distortion Correction Method for Single Echo DTI at 7T MRI using Non-distortion and Distortion Dimension Combined PSF Mapping Technique. *International Society for Magnetic Resonance in Medicine*, 2010, Stockholm #1626.
- Oh SH, Chung JY, In MH, Zaitsev M, Kim YB, Speck O, Cho ZH. (2012): Distortion correction in EPI at ultra-high-field MRI using PSF mapping with optimal combination of shift detection dimension. *Magn Reson Med*. 68:1239–1246.
- Pannek K, Mathias JL, Bigler ED, Brown G, Taylor JD, Rose SE. (2011): The average pathlength map: A diffusion MRI tractography-derived index for studying brain pathology. *NeuroImage* 55:133–141.
- Perez-Iglesias R, Tordesillas-Gutierrez D, Barker GJ, McGuire PK, Roiz-Santianez R, Mata I, de Lucas EM, Quintana F, Vazquez-Barquero JL, Crespo-Facorro B. (2010): White matter defects in first episode psychosis patients: A voxelwise analysis of diffusion tensor imaging. *NeuroImage* 49:199–204.
- Tournier JD, Calamante F, Gadian DG, Connelly A. (2004): Direct estimation of the fiber orientation density function from diffusion-weighted MRI data using spherical deconvolution. *NeuroImage* 23:1176–1185.
- Tournier JD, Calamante F, Connelly A. (2007): Robust determination of the fibre orientation distribution in diffusion MRI: Non-negativity constrained super-resolved spherical deconvolution. *NeuroImage* 35:1459–1472.
- Tournier JD, Yeh CH, Calamante F, Cho KH, Connelly A, Lin CP. (2008): Resolving crossing fibres using constrained spherical deconvolution: Validation using diffusion-weighted imaging phantom data. *NeuroImage* 42:617–625.
- Tournier JD, Calamante F, Connelly A. (2010): Improved probabilistic streamlines tractography by 2nd order integration over fibre orientation distributions. In: *Proc. 18th Annual Meeting of the International Society of Magnetic Resonance in Medicine (ISMRM)*, Stockholm, Sweden.:#1670.
- Wiegell MR, Tuch DS, Larsson HB, Wedeen VJ. (2003): Automatic segmentation of thalamic nuclei from diffusion tensor magnetic resonance imaging. *NeuroImage* 19(2 Pt 1):391–401.
- Zaitsev M, Hennig J, Speck O. (2004): Point spread function mapping with parallel imaging techniques and high acceleration factors: Fast, robust, and flexible method for echo-planar imaging distortion correction. *Magn Reson Med* 52:1156–1166.