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Feasibility of prefronto-caudate pathway tractography using high resolution diffusion tensor tractography data at 3 T

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Abstract

Mapping the human brain frontostriatal pathways using non-invasive diffusion tensor imaging (DTI) has been hampered by the inadequate imaging sensitivity, poor spatial resolution, lower tensor anisotropy within gray matter, increased partial volume averaging effects and poor signal-to-noise ratio. We investigated *for the first time* the utility of high spatial resolution DTI-based fiber-tractography using the fiber assignment by continuous tracking (FACT) to reconstruct and quantify bilaterally the prefronto-caudo-thalamic connections within the human brain at 3 T. Five healthy right-handed men (age range 24–37 years) were studied. We traced the anterior thalamic radiation and prefronto-caudo-thalamic pathways bilaterally and measured the volume of each tract and the corresponding diffusion tensor metrics in all subjects. The anterior thalamic radiation tract volume and corresponding fractional anisotropy (FA) were significantly larger bilaterally than prefronto-caudate pathway, whereas the mean diffusivity (D_{av}) values were similar ($p > 0.7$). For both anterior thalamic radiation and prefronto-caudate pathway the tract volume and corresponding DTI metrics (FA, D_{av}) were not significantly different between the two hemispheres ($p > 0.2$). Our DTI acquisition protocol and analysis permitted the reconstruction of the connectivity of the caudate with the thalamus as well as with the prefrontal cortex and allowed tracking of the whole trajectory of the prefronto-caudo-thalamic pathway.

Keywords

diffusion tensor imaging; high spatial resolution; frontostriatal; caudate; tractography

1. Introduction

The caudate and putamen nuclei are the principal input of the basal ganglia circuit in the human brain (Afifi, 1998). The neural circuit linking prefrontal cortex and striatum (caudate and putamen) has a role in cognitive control (Casey, 2002). The Caudate nucleus curves

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around the ventricular system and receives projections from association areas of the cortex (Afifi, 1998). The projections are particularly dense from the prefrontal cortex and frontal pole which project to the head of the caudate (Afifi, 1998).

Several diffusion tensor imaging (DTI) studies have investigated the frontostriatal tract involvement in pathologies such as bipolar mood disorders (Haznedar et al., 2005), schizophrenia (Rose et al., 2006), attention-deficit/hyperactivity disorder (Casey et al., 2007), and obsessive-compulsive disease (Valente et al., 2005), in which cognitive control deficits have been shown to be associated with abnormalities in frontostriatal structures (Casey et al., 2007; Valente et al., 2005). These studies investigated the diffusion tensor metrics of caudate and prefrontal cortex using two-dimensional (2D) regions-of-interest (ROIs) or voxel-based morphometric (VBM) analyses. The location and size of ROIs were not clearly defined in some of the previous studies (Casey et al., 2007; Valente et al., 2005).

Diffusion tensor tractography (DTT) is a technique based on DTI that has been successfully used for 3D reconstruction of the cortical and subcortical connections of the human brain (Behrens et al., 2003; Leh et al., 2007). In the current study, we used DTT and the fiber assignment by continuous tracking (FACT) algorithm to reconstruct and quantify the 3D model of the anatomical distribution of prefronto-caudate pathway of this minute but important pathway in normal human brain.

The noninvasive mapping and quantification of the frontal lobe connections to the thalamus and basal ganglia would help advance our knowledge of brain-behavior relations (Liston et al., 2006; Lehericy et al., 2004) as a result of natural aging (Hasan et al., 2008), or pathologies such as Huntington's disease (Kloppel et al., 2008), bipolar mood disorders (Haznedar et al., 2005), and attention-deficit/hyperactivity disorder (Casey et al., 2007). This technical report explored the feasibility of *in vivo* mapping, visualization and quantification of white matter sub-structure connections within the human caudate nuclei such as frontostriatal pathway using data acquired with a recently described high resolution DTI protocol and analyzed using deterministic tractography methods.

2. Materials and Methods

2.1 Study Subjects

This work was approved by our institutional review board (IRB) and was health insurance portability and accountability act (HIPAA) compliant. Five right-handed healthy men (age range 24–37 years) were included in this study and written informed consent was obtained from all the subjects.

2.2 Conventional MRI Data Acquisition

All MRI studies were performed on a 3T Philips Intera scanner with a dual quasar gradient system with a maximum gradient amplitude of 80 mT/m, maximum slew rate 200 mT/ms/m, and an eight channel SENSE-compatible head coil (Philips Medical Systems, Best, Netherlands). The conventional MRI (cMRI) protocol included axially prescribed 3D spoiled gradient (repetition time /echo time/ flip angle = $TR/TE/\alpha = 8 \text{ ms} / 4 \text{ ms} / 6^\circ$), 3-D proton density-weighted ($TR/TE/\alpha = 10,000 \text{ ms} / 10 \text{ ms} / 90^\circ$) and 3-D T_2 -weighted ($TR/TE/\alpha = 10,000 \text{ ms} / 60 \text{ ms} / 90^\circ$), with a square field-of-view (FOV) = 256 mm $\times$ 256 mm and a matrix of 256 $\times$ 256 pixels. The slice thickness for the cMRI sequences was 1.0 mm with 120 contiguous axial slices (3-D slab) covering the entire brain (foramen magnum to vertex).

2.3 DTI Data Acquisition

Diffusion-weighted image (DWI) data were acquired axially from the same graphically prescribed cMRI volumes using a single-shot multi-slice 2D spin-echo diffusion sensitized and fat-suppressed echo planar imaging (EPI) sequence, with the balanced *Icosa21* tensor encoding scheme which uses twenty one uniformly distributed encoding directions (Hasan et al. 2001; Hasan et al., 2009). The b-factor = 500 sec mm⁻², TR/TE = 14460/60 msec. The spatial coverage for DTI data matched the 3D cMRI spatial coverage (FOV = 256 mm × 256 mm and slice thickness / gap/ #slices = 1 mm / 0 mm / 120). The EPI phase encoding used a SENSE k-space undersampling factor of two, with an effective k-space matrix of 112×112 and an image matrix after zero-filling in k-space of 256×256. The acquisition spatial resolution for DTI data was ~ 2.29 mm × 2.29 mm × 1 mm, and the nominal resolution after image construction was 1 mm × 1 mm × 1mm. The number of b-factor ~ 0 (b₀) magnitude image averages was four. The total DTI acquisition time was ~ seven minutes for the diffusion-weighted acquisition. The DTI acquisition was repeated three times to enhance signal-to-noise ratio (SNR). The selection of the b-factor, parallel imaging, repetition and echo times enabled entire brain coverage using single-shot and interleaved EPI. The thin slice acquisition in space and replication of data in time combined with the DTI encoding provided several quality control options to study signal-to-noise ratio (Hasan, 2007) and partial volume effects on the DTI tracking results (Hasan et al., 2009).

2.4 White Matter Fiber Tracking

After data preparation that included registration and residual image distortion correction, and quality assessment (Hasan et al., 2009), compact WM fiber tracking was performed using DTI Studio software (Johns Hopkins University, Baltimore, Maryland; <http://cmrm.med.jhmi.edu/>). Fiber tracking was based on the fiber assignment by continuous tracking (FACT) algorithm with a fractional anisotropy (FA) threshold of 0.22 and angle threshold of 60 degrees (Mori et al., 2002; Wakana et al., 2007). Reproducibility of the fiber construction in both hemispheres was tested by two experienced raters on all subjects. Two ROIs (two coronal slices) were applied to obtain anterior thalamic radiations and prefronto-caudate pathways and an “AND” operation was performed to include the fibers passing through both of the ROIs. Once a fiber tract was reconstructed, the entire trajectory was verified on a slice by slice basis to ensure consistency with established anatomical landmarks based on atlas of anatomy (Afifi, 1998). The exact locations of the ROIs selected for each pathway are shown in Fig. 1. The corresponding coronal levels are illustrated on a midsagittal T1-weighted image in Fig. 2.

2.5 White Matter Fiber Tracts

2.5.1 Anterior thalamic radiation—The anterior thalamic radiation (ATR) pathway originates from the thalamus and passes through the anterior limb of internal capsule (ALIC) to the frontal cortex (Cowan et al., 2005; Wakana et al., 2007). Two coronal ROIs were selected to delineate this pathway. The first ROI was placed on the whole anterior limb of internal capsule at the coronal level which anterior commissure is visible (on the green fibers in the DTI color-coded map) (Fig. 1a corresponding to the coronal level A in Fig. 2). This followed by an “AND” operation on The second ROI which was placed at the coronal level passing through the middle of the fornix in the midsagittal cut on the fibers passing through the thalamus (Fig. 1b corresponding to the coronal Level B in Fig. 2).

2.5.2 Prefronto-caudate tract—The prefronto-caudate tract originates from prefrontal cortex (frontal pole) and traverses through the caudate head and terminates in the thalamus and is located parallel and medially to the anterior thalamic radiation. Two coronal ROIs were applied to obtain prefronto-caudate pathway. The first ROI was placed at the coronal

level which passes through the intersection of genu and rostrum of the corpus callosum on the head of caudate nucleus (Fig. 1c corresponding to the coronal level C in Fig. 2). Then an “AND” operation was performed on the second ROI at the prefrontal cortex at the most anterior coronal level of cingulate sulcus in the midsagittal plane (Fig. 1d corresponding to the coronal Level D in Fig. 2).

3. Results

The tractograms of anterior thalamic radiation and prefronto-caudate tracts in the five subjects studied had comparable architectures. A representative tractogram of anterior thalamic radiation and prefronto-caudate pathways in one of the subjects on the 1 mm slice thickness acquisition is shown in Fig 3. As can be seen on the 2D images, the ATR fibers originate from the thalamus, pass through the anterior limb of internal capsule, and terminate in the prefrontal cortex. The prefronto-caudate pathways (pink fibers) originate from the prefrontal cortex, pass through the head of caudate nucleus (medially to the ATR fibers but not through the ALIC) and terminate in the thalamus.

Table 1 provides a summary of the mean and standard deviation values of the fiber tract volume and corresponding fractional anisotropy and average diffusivity (D_{av}) values of the bilateral frontostriatal and ATR fiber tracts on the five subjects. Note that the anterior thalamic radiation tract volume and corresponding fractional anisotropy were significantly larger ($p < 0.02$; t-test) bilaterally than prefronto-caudate pathway, whereas the mean diffusivity values were similar ($p > 0.7$; Table 1). For both anterior thalamic radiation and prefronto-caudate pathway the tract volume and corresponding DTI metrics (FA, D_{av}) were not significantly different between the two hemispheres ($p > 0.2$; paired t-test; Table 1).

4. Discussion

Human DTI studies of the frontostriatal pathways have been limited by inadequate spatial resolution (in-plane and slice thickness), and lower anisotropy within the gray matter, partial volume effect and poor SNR (Hasan, 2007). Improving the DTI acquisition methodology by sequence optimization with respect to shorter echo time and decreased partial volume averaging effects (Oouchi et al., 2007), will be advantageous to study these thin fibers (Hasan et al., 2009).

Diffusion tensor tractography of white matter connections between the cortex and deep gray matter structures is affected by the overestimation of anisotropy at low SNR (Hasan et al., 2008) and partial volume averaging due to using large voxel volumes (Alexander et al., 2001). The advantage of high resolution 3D fiber tract reconstruction over 2D ROI placement in DTI studies is the ability to show better the integrity of the fiber tract trajectory or interruption by lesions (Mori et al., 2002; Wakana et al., 2007). Challenges of 2D DTI studies also include partial volume contamination with adjacent pathways due to the selection of size and location of ROIs. The availability of high spatial resolution 3D tractography combined with clear anatomical landmarks would help resolve these problems (Hasan et al., 2009).

Areas of most tissue partial volume averaging artifacts (e.g. white matter /gray matter or white matter / CSF) or of white matter partial volume averaging effects (where two fiber systems cross the same voxel in different orientations) are examples of where the DTI model will fail. Indeed, areas of white matter where two or more fiber systems pass within the same voxel each having different orientations will appear hypointense on diffusion anisotropy maps. Consequently, the single tensor DTI model cannot account for the two

fiber systems which will appear to have low anisotropy (Papadakis et al., 2002; Tuch et al., 2002).

Partial volume averaging effects caused by low spatial resolution negatively affects the DT-MRI results (Hasan et al., 2009; Alexander et al., 2001). Since the prefronto caudate fiber connections are much smaller in volume than other projection fibers of the central nervous system (for example ATR, see Table 1), higher spatial resolution is needed to achieve optimal results (Oochi et al., 2007). In this work, we mapped and quantified the cortico-striatal pathway using high resolution DTI data to minimize partial volume averaging effects resolving the crossing fibers and reducing the incoherency within the voxel enabling the FACT algorithm to trace the prefronto-caudate pathways. The choice of thinner slice thickness reduces the signal (Hasan 2007; Kim et al. 2006), but also provided higher and more detectable tensor anisotropy within gray matter structures such as the caudate and thalamus nuclei (Hasan et al., 2009; Jaerman et al., 2008).

We applied parallel imaging with reduced echo time to acquire high resolution in vivo DTI at 3 T. Parallel imaging led to a significantly enhanced image quality due to reduced geometric image distortions and decreased echo time and enabled the whole-brain coverage (Jaerman et al., 2008). Our whole-brain data acquisition protocol covered both cerebellum and cerebrum to investigate the feasibility of fiber tracking of other pathways such as the somatosensory system (Kamali et al., 2009).

The diffusion b-factor selected in the current work (e.g. 500 s mm^{-2}) helped reduce the echo time and enabled acquiring as many as 120 slices using single-shot echo planar imaging. The b-factor selected was in a range that has been shown previously not to affect the estimated anisotropy (Poonawalla et al., 2004).

Using higher spatial resolution combined with higher magnetic field strength improved the detectable diffusion anisotropy in gray matter (caudate and thalamus) along with reducing partial volume effects (Alexander et al., 2001; Jaerman et al., 2008). This allowed tracking of the whole trajectory of prefronto-caudate pathway as well as the caudo-thalamic connection to reveal more anatomical details within the gray matter and to map the whole prefronto-caudo-thalamic fiber trajectory (Hasan et al., 2009; Jaerman et al., 2008). In our experience, anterior thalamic radiation is traceable using whole brain axial acquisition with a slice thickness of 3 mm, while the prefronto-caudate pathway are not traceable using the deterministic FACT approach using 3 mm sections. This is attributable to mixing of fibers in different orientations within the voxel leading to aberrant reduction in needed anisotropy in gray matter using larger voxel volume which was solved in our present work by using thinner slices and smaller voxel volume (Hasan et al., 2009, Jaerman et al., 2008).

The current study is the first deterministic DTI tractography study of the frontostriatal pathway. We used a deterministic tracking approach as implemented in a widely used software package (e.g. DTIstudio). Alternative approaches not attempted in this work include probabilistic tracking. Both deterministic and probabilistic tracking methods have limitations and may produce false positive results due to crossing and kissing fibers in a voxel (Jones et al., 2005; Hagler et al. 2009; Lawes et al. 2008; Yamada et al., 2008). The major drawback of the deterministic approach is that it mostly reproduces the major trajectory of the fiber pathway and some branching of fasciculi may not be represented (Jones et al., 2005). The probabilistic approach however can reproduce all the branching but the uncertainty of these generated trajectories remains the major concern as the probabilistic approach will also include gray matter (Hagler et al. 2009; Lawes et al. 2008; Yamada et al., 2008).

Applying higher spatial resolution and multiple ROI approach using deterministic tracking led to the reduction of partial volume effects in the voxel and the inclusion of more branching fibers. Future advancements in high magnetic field and hardware technology may improve the time efficiency of the current high spatial resolution method. The methods used in this work can be enhanced further by using more b-factors and high angular diffusion sampling (e.g. diffusion spectrum imaging) to overcome the intra-voxel heterogeneity and crossing fibers (Wedeen et al. 2008; Landman et al. 2010). The results of the current work obtained on a large population may be used to extend current human brain atlases to automatically delineate and quantify the frontostriatal fibers (Mori et al., 2008; Lawes et al., 2008; Hagler et al., 2009; Hasan and Frye, 2010).

5. Conclusions

In the current preliminary study we demonstrated *for the first time* using a high-resolution DTI technique and deterministic fiber tractography the feasibility to quantify the volume and diffusion tensor metrics of the prefronto-caudo-thalamic pathway and visualize selectively the white matter sub-structure within the human caudate and thalamic nuclei *in vivo*.

Potential clinical applications of our preliminary results include studies on natural aging (Hasan et al., 2008), Parkinson's disease (Taylor et al., 1990), Huntington disease (Kloppel et al., 2008), multiple sclerosis (Henry et al., 2009; Santiago et al., 2007), brain trauma (Kumar et al., 2009; Yuan et al., 2007), schizophrenia (Suzuki et al., 2004), and other cognitive disorders (Casey et al., 2007; Haznedar et al., 2005; Rose et al., 2006; Valente et al., 2005). The ability to trace the prefronto-caudate connections *in vivo* can be very helpful in assessment of these pathologies noninvasively.

Abbreviations

ALIC	anterior limb of internal capsule
ATR	anterior thalamic radiation
DTI	diffusion tensor imaging
DTT	diffusion tensor tractography
FA	fractional anisotropy
FACT	fiber assignment by continuous tracking
ROI	region of interest
SNR	signal-to-noise ratio

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Figure 1.

ROI locations (ROI 1 and 2) used for reconstructions of the anterior thalamic radiation and prefronto-caudate pathways. (a, b) anterior thalamic radiation tract. (c, d) prefronto-caudate tract. The ROIs are depicted by shapes outlined in pink, which yielded a tract reconstruction in yellow color on a DTI principal vector coded map (red = right-left; green = anterior-posterior; blue = superior-inferior). In Fig. 1a, the ROI 1 was placed in on the whole anterior limb of internal capsule at the coronal level which anterior commissure is visible (level A in Fig 2). In Fig 1b, ROI 2 was seeded on the fibers generated which are passing through the thalamus at the coronal level cutting through the middle of the fornix in the midsagittal slice (level B in Fig 2). In Fig 1c, ROI 1 was seeded on the head of caudate nucleus at the coronal level which passes through the intersection of genu and rostrum of the corpus callosum (level C in Fig 2) and ROI 2 in Fig 1d was selected on the fibers generated in the prefrontal cortex at the most anterior coronal level of cingulate sulcus (CS) in the midsagittal plane (level D in Fig 2). Fig 1e and 1f are color-coded map equivalent of the Fig 1c and 1d. Well delineated anatomical landmarks are labeled as follows: AC = anterior commissure; ALIC = anterior limb of internal capsule; CH = caudate head; Th = thalamus.

Figure 2.

Structural (T1-weighted) MRI of the sagittal midline plane showing the different coronal sections which was used for ROI placement in Fig 1. Level A: the coronal slice passing through the anterior commissure. Level B: the coronal slice which passes through the middle of the fornix in the midsagittal plane. Level C: the coronal level which passes through the intersection of genu and rostrum of the corpus callosum. Level D: the most anterior coronal level of cingulate sulcus (CS) in the midsagittal plane.

Figure 3.

The reconstructed tracts overlaid on a 3D DTI color-coded map (a) and concordant T1-weighted MR images (b) in anterolateral views. Red fibers are anterior thalamic radiation fibers which are originating from the thalamus (Th) and pass through the anterior limb of internal capsule (ALIC) and project to the prefrontal cortex in comparison to prefronto-caudate pathways (pink fibers) which are originating from the prefrontal cortex and pass through the head of caudate and end in thalamic nuclei. (c, d) Transverse T1-weighted MR images for mapping the anterior thalamic radiation (red) and prefronto-caudate tract (pink). The red fibers are passing through the anterior limb of internal capsule (ALIC) but the pink fibers are passing through the head of caudate (CH).

Table 1

Summary and comparison of reconstructed diffusion tensor fractional anisotropy (FA) and average diffusivity (D_{av}) for the ATR (anterior thalamic radiation) and FS (frontostriatal or prefronto-caudo-thalamic tract) in both hemispheres.

	Tract Volume (mL = cm ³)	FA ($\mu \pm \sigma$)	D_{av} ($\times 10^{-3}$ mm ² sec ⁻¹)
ATR Right	5.93 $\pm$ 0.90	0.46 $\pm$ 0.02	0.85 $\pm$ 0.02
ATR Left	5.15 $\pm$ 1.25	0.46 $\pm$ 0.02	0.83 $\pm$ 0.02
p (R vs. L)	0.22	0.49	0.37
FS Right	2.20 $\pm$ 0.374	0.41 $\pm$ 0.035	0.85 $\pm$ 0.04
FS Left	2.25 $\pm$ 0.503	0.41 $\pm$ 0.031	0.84 $\pm$ 0.04
p (R vs. L)	0.64	0.79	0.37
Right p (ATR vs. FS)	2.8 $\times 10^{-5}$	0.02	1
Left p (ATR vs. FS)	0.001	0.03	0.77