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Averaging of diffusion tensor imaging direction-encoded color maps for localizing substantia nigra

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ABSTRACT

Diffusion tensor imaging (DTI) is a form of MRI that has been used extensively to map in vivo the white matter architecture of the human brain. It is also used for mapping subcortical nuclei because of its general sensitivity to tissue orientation differences and effects of iron accumulation on the diffusion signal. While DTI provides excellent spatial resolution in individual subjects, a challenge is visualizing consistent patterns of diffusion orientation across subjects. Here we present a simple method for averaging direction-encoded color anisotropy maps in standard space, explore this technique for visualizing the substantia nigra (SN) in relation to other midbrain structures, and show with signal-to-noise analysis that averaging improves the direction-encoded color signature. SN is distinguished on averaged maps from neighboring structures, including red nucleus (RN) and cerebral crus, and is proximal to SN location from existing brain atlases and volume of interest (VOI) delineation on individual scans using two blinded raters.

1. Introduction

Diffusion tensor imaging (DTI) is a form of magnetic resonance imaging (MRI) that is sensitive to the diffusion of water molecules [1]. Since brain tissue is coherently organized and therefore presents barriers to random diffusion, DTI has proven extremely helpful for systematically mapping in vivo the white matter architecture of the human brain [2,3]. DTI has also been used for mapping the location and subdivisions of subcortical nuclei, most notably the thalamus [4], which contains extensive connectivity with the cortical mantle. Other smaller nuclei, such as the subthalamic nucleus (STN) and substantia nigra (SN), can be visualized albeit with varying degrees of difficulty on individual subject DTI datasets [5,6], but are nonetheless critical to locate. This is especially true for targeted electrical stimulation that can alleviate some symptoms of devastating neurological disorders like Parkinson's disease [7,8]. Yet, deep brain stimulation implants are complicated by failure rates during the targeting of small subcortical structures [9,10]. Averaging of multiple direction-encoded color maps (DECM) is one simple method for potentially improving signal-to-noise and visualization of these structures within individual subjects for targeted surgical procedures.

Another challenge is visualizing consistent patterns of the orientation of the diffusion signal across groups of subjects. While the most widely referenced DTI brain atlases present color-coded diffusion orientation maps constructed from individual subject data [11], emerging techniques seek to combine data from multiple subjects in standard space to map consistent patterns of diffusion orientation [12]. These types of DTI population studies are important for building confidence about the average location and variability of brain structures that are difficult to localize. They are also important for tracking changes over time, as degeneration occurs slowly during aging and the accumulation of iron can affect the MRI signal [13–15].

The SN, a nucleus containing dopaminergic projection neurons, is vulnerable to degeneration even before the initial symptoms of

Abbreviations: AFNI, analysis of functional neuroimages; ANOVA, analysis of variance; DECM, direction-encoded color map; DTI, diffusion tensor imaging; FA, fractional anisotropy; fMRI, functional magnetic resonance imaging; MNI, Montreal Neurological Institute; MRI, magnetic resonance imaging; RGB, red, green, and blue; RN, red nucleus; SN, substantia nigra; SNc, pars compacta; SNr, pars reticulata; SNR, signal-to-noise ratio; STN, subthalamic nucleus; VOI, volume of interest

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Parkinson's disease manifest [16]. The SN is difficult to resolve on a conventional T1-weighted MRI. However, several specialized MRI sequences and analysis techniques have been used to improve the ability to resolve the SN, including proton density-weighted MRI with short inversion-time recovery images [17], neuromelanin-sensitive MRI [18], quantitative T2 mapping [19], segmented inversion recovery ratio imaging [20–22], a combination of T2* and diffusion-weighted imaging [23,24], connectivity-based parcellation using probabilistic diffusion tractography [25], and multi-spectral MRI sequences [26].

Several of these specialized techniques have been deployed with the goal of distinguishing the *pars compacta* (SNc) from the *pars reticulata* (SNr) subdivisions of the SN. However, these studies [17,25] have provided ambiguous results regarding decreases in the volume of the SNc, the subdivision containing excitatory dopaminergic projections to the dorsal striatum, in Parkinson's patients. While it has been demonstrated that the SN can be resolved on individual subject DTI DECM [6,11], questions remain about the consistency with which the SN can be identified from these color maps *across* subjects. Additional questions remain about the location of SN on these color maps with respect to stereotactic coordinates of the SN referenced from available brain atlases.

To address these questions, we developed a simple method for averaging direction-encoded anisotropy-modulated color maps in standard space. Then we explored the improvement that signal averaging affords for localizing the SN in relation to other structures of the human midbrain. We chose the SN because its small size presents a continual challenge for localization, its critical landmark status for deep brain stimulation, and its importance as a candidate biomarker of early degeneration in patients at risk of developing Parkinson's disease [27]. Our primary objective is to demonstrate, using a large sample of healthy controls, the utility of a simple and fast directional anisotropy averaging approach for visualizing the SN in relation to nearby structures, including the red nucleus (RN) and cerebral peduncle. Using two blinded raters, we then explore the location of the SN on average DECM with respect to the delineation of this structure on individual subject DTI datasets, and in relation to reported SN coordinates from the most frequently cited brain atlases.

2. Methods

2.1. Image acquisition

A diffusion-weighted imaging sequence was obtained from 58 normal control subjects (mean age 34.1, 28 females, 5 left handed) using a 3 T Philips MRI scanner (32 diffusion directions; repetition [TR]/echo time [TE] 8500/67 ms; flip angle = 90 degrees; 128 × 128 matrix, FOV = 224 mm; 2 mm thick axial slices; *b*-value = 800 s/mm^2). A high-resolution 3D T1-weighted magnetization-prepared rapid acquisition turbo field echo sequence (TR/TE = 8.4/3.9 ms; flip angle = 8 degrees; matrix size = 256 × 256; field of view = 240 mm; 1.0 mm thick sagittal slices) was acquired in each subject, as well as a T2-weighted turbo-spin echo 3D volume acquisition (TR/TE = 2500/367 ms; echo-train length = 120; pixel bandwidth = 380; flip angle = 90 degrees; matrix size = 256 × 256; field of view = 240 mm; 1.0 mm thick sagittal slices) in a subset of 16 subjects.

2.2. Image processing

Analysis was performed in Analysis of Functional Neuroimages (AFNI) [28]. For each subject, the T1-weighted MRI volume was stripped of scalp and skull. To correct for subject motion over time, individual diffusion-weighted volumes were then aligned to the skull-stripped T1 volume in native space. Separately, the T2-weighted volume was aligned to the T1 volume.

At each voxel of the 32 aligned native-space diffusion volumes, a diffusion tensor was estimated by a linear least squares fitting method to obtain the three shape (eigenvalues) and three orientation parameters (eigenvectors) of the diffusion ellipsoid:

$$\overline{D} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix} \rightarrow \lambda_1, \lambda_2, \lambda_3, \nu_1, \nu_2, \nu_3 \tag{1.1}$$

Using the eigenvalues, the extent of anisotropy, ranging from 0 to 1, was expressed at each voxel by computing fractional anisotropy (FA):

$$\mathrm{FA} = \sqrt{\frac{3}{2}} \sqrt{\frac{(\lambda_1 - \hat{\lambda})^2 + (\lambda_2 - \hat{\lambda})^2 + (\lambda_3 - \hat{\lambda})^2}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}} \tag{1.2}$$

With the trace:

$$\hat{\lambda} = (\lambda_1 + \lambda_2 + \lambda_3)/3 \tag{1.3}$$

With respect to the orientation parameters, we discard ν_2 and ν_3 and use ν_1 at each voxel, which is the orientation of the major eigenvector and represents local tissue orientation as defined by the principal diffusion direction. The major eigenvector ν_1 is a unit vector consisting of *x*, *y*, and *z* components ($\nu_1 = [x,y,z]$ where $x_1 + y_1 + z_1 = 1$). The *x*, *y*, and *z* components are mapped to a combination of red, green, and blue (RGB) colors representing left–right, anterior–posterior, and superior–inferior principal diffusion directions. For example, when ν_1 is [1,0,0] the RGB channels receive [255,0,0] representing a primarily left–right diffusion orientation, and when ν_1 is $[1/\sqrt{2}, 1/\sqrt{2}, 0]$ the RGB channel is [181,181,0] which maps to the color yellow.

In native space, the computed 24-bit ν_1 orientation vector map was then split into three separate 8-bit volume maps, ν_{1x}, ν_{1y}, ν_{1z}, which are the three color channels making up a combination RGB at each voxel.

Separately, the native space skull-stripped T1 MRI volume was spatially normalized to the Montreal Neurological Institute (MNI) Colin N27 average brain, and a 12-parameter affine transformation matrix was saved. The T2 volumes were also spatially normalized using the same transform.

Then, each separate 8-bit component color channel map, ν_{1x}, ν_{1y}, ν_{1z}, was spatially transformed to MNI space by applying the transform derived by affine normalization of the skull-stripped T1 to MNI space. The three spatially normalized color channel maps were concatenated to form a new 24-bit RGB major eigenvector map, $\nu_{1\mathrm{norm}} = [\nu_{1x\mathrm{norm}} + \nu_{1y\mathrm{norm}} + \nu_{1z\mathrm{norm}}]$, and multiplied by FA to produce an intensity modulated DECM in MNI space. Finally, the DECM in MNI space were averaged across subjects and used to construct a single average color map. Averages of the T1 and T2 volumes were also created for comparison.

To explore how efficiently the SN could be localized using DECM information from single-subject DTI data, two raters blinded to each other's measurements and to the final average DECM outlined the SN bilaterally as a volume of interest (VOI) mask in a subset of 11 subjects. Their native space VOI masks were then spatially summed, and each pixel value was expressed as a percentage of agreement from 0 to 100. A value of 100 means that both raters agreed, in all subjects, that a given pixel belonged to the SN.

To provide statistical quantification of the improvement in discerning the SN as increasing numbers of DECM are averaged, a signal-to-noise analysis was performed. Within the combined 827 pixel left and right SN volume of interest mask (Fig. 3), a