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Diffusion MRI connectometry automatically reveals affected fiber pathways in individuals with chronic stroke

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ABSTRACT

Building a human connectome database has recently attracted the attention of many researchers, although its application to individual subjects has yet to be explored. In this study, we acquired diffusion spectrum imaging of 90 subjects and showed that this dataset can be used as a norm to examine pathways with deviant connectivity in individuals. This analytical approach, termed diffusion MRI connectometry, was realized by reconstructing patient data to a common stereotaxic space and calculating the percentile rank of the diffusion quantities with respect to those of the norm. The affected tracks were constructed with deterministic tractography using the local tract orientations with substantially low percentile ranks as seeds. To demonstrate the performance of the connectometry, we applied it to 7 patients with chronic stroke and compared the results with lesions shown on T_2-weighted images, apparent diffusion coefficient (ADC) maps, and fractional anisotropy (FA) maps, as well as clinical manifestations. The results showed that the affected tracks revealed by the connectometry corresponded well with the stroke lesions shown on T_2-weighted images. Moreover, while the T_2-weighted images, as well as the ADC and FA maps, showed only the stroke lesions, connectometry revealed entire affected tracks, a feature that is potentially useful for diagnostic or prognostic evaluation. This unique capability may provide personalized information regarding the structural connectivity underlying brain development, plasticity, or disease in each individual subject.

1. Introduction

Cerebral connectivity is believed to play an important role in the function of the human brain and could aid in the discovery of disease biomarkers (Akil et al., 2011). Measuring the structural connectivity of the human brain in vivo is a major challenge in the field of neuroscience. By modeling diffusion MRI data with a diffusion ellipsoid, diffusion tensor imaging (DTI) (Basser et al., 1994) can characterize the structural integrity of axonal fibers via fractional anisotropy (FA) and apparent diffusion coefficient (ADC) analyses (Basser and Pierpaoli, 1996; Pierpaoli and Basser, 1996; Pierpaoli et al., 1996). The principle orientation of the diffusion tensor can also facilitate fiber tracking to reveal structural connectivity (Basser et al., 2000; Conturo et al., 1999; Mori et al., 1999). Although DTI has been widely used in group studies, its application to individual patients remains hampered, partly due to the limitation that the tensor model can only describe fibers with a single orientation and that it is subjected to various sources of partial volume effects (Alexander et al., 2001; Metzler-Baddeley et al., 2012; Oouchi et al., 2007).

More advanced diffusion MRI methods have been proposed to provide superior angular resolution and to overcome the limitations of DTI (Jones et al., 2012). Studies have used high angular resolution diffusion imaging (HARDI) (Tuch et al., 2002) and diffusion spectrum imaging (DSI) (Wedeen et al., 2005) to model the diffusion characteristics of axonal fibers. These methods provide orientation distribution functions of the diffusion to resolve multiple fiber orientations, which can be used in deterministic fiber tracking to delineate fiber trajectories (Hagmann et al., 2008; Honey et al., 2009; Wedeen et al., 2008). This progress further led to the study of the connectivity matrix (Hagmann et al., 2007; Hagmann et al., 2010a) and its application to real world research problems (Hagmann et al., 2010b; Robinson et al., 2010). Although connectivity analysis has been applied to group wise studies, its application to individual subject is yet to be explored.

In this paper, we acquired diffusion spectrum imaging of 90 subjects and used it as a norm to examine deviant connectivity in individuals with chronic stroke. Two novel strategies were adopted to carry out this analysis. First, the diffusion data was reconstructed in a common space using the q-space diffeomorphic reconstruction (QSDR) algorithm

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(Yeh and Tseng, 2011), which is a model-less reconstruction approach that applies spatial normalization to diffusion data. QSDR transforms the distribution of diffusion spins to a template space based on a given deformation field, and the transformed distribution can be used to calculate the spin distribution function (SDF), which quantifies the amount of spins that diffuses at any orientation. SDF is similar to diffusion orientation distribution function estimated using DSI, but the difference is that SDF scales with spin density, thus making it comparable across voxels and less susceptible to corrupted signals due to partial volume effect (Yeh et al., 2011). Moreover, SDF has an analytical solution, and it is less susceptible to error in numerical estimation (Yeh et al., 2010). The SDFs of the normal population can be used as a norm to obtain the percentile ranks of the diffusion quantities in an individual, and local tract orientations with a substantially low percentile rank indicated a potential connectivity change.

The second strategy is that instead of measuring cortical–cortical connectivity and comparing their differences, we first obtained the local differences in SDFs and then track *only* those with substantial differences to reveal the affected portion of the fiber pathways. This strategy bypassed the complexity of defining cortical–cortical connectivity and thus less affected by the limitation of fiber tracking algorithm in differentiating branching or crossing patterns. This analytical method, termed diffusion MRI connectometry, provides personalized information of the studied subject and constitutes a new diagnostic tool of brain disease.

To demonstrate the performance of diffusion MRI connectometry, we applied the connectometry to 7 patients with chronic stroke to examine their affected tracks. As the affected tracks should correspond to the chronic stroke lesions shown on T_2-wieghted images, we used the findings on the T_2-wieghted images to assess the accuracy of the connectometry.

2. Materials and methods

2.1. Subjects

A total of 90 healthy subjects and 7 patients with chronic stroke were recruited in the study. The study was approved by the Research Ethics Committee of the National Taiwan University Hospital, and written informed consent was obtained from the participants. The healthy subjects (45 males and 45 females) had no previous history of neurological or mental disorders. The mean ages of the male and female volunteers were 32.58 (standard deviation = 12.96) and 33.58 years of age (standard deviation = 12.26), respectively, and the age difference was not statistically significant ($p = 0.7078$, two-tail). All 7 patients had a first-episode stroke approximately 6 months prior to the study. The NIHSS score ranged from 2 to 8, equivalent to mild to moderate stroke (see Table 1 for the demographics).

Table 1
Patient demographics.

Patient	Age/sex	Stroke location in MRI	NIHSS	FM UE Motor at day 30	FM UE Motor at day 180
1	55/M	Left PLIC	7	34	56
2	49/M	Left PLIC	8	46	55
3	69/F	Right PVWM	5	61	66
4	51/M	Right PVWM	2	61	64
5	51/M	Left posterior frontal WM	3	61	66
6	66/F	Right BG	5	64	66
7	53/M	1. Left thalamus	7		
		2. Left medial temporal region		63	66
		3. Left medial occipital region			

BG: basal ganglia, FM: Fugl-Meyer, PLIC: posterior limb of internal capsule, PVWM: periventricular white matter.

2.2. MRI acquisitions

All subjects were scanned in a 3 T MRI scanner (Trio, Siemens, Erlangen, Germany) using a 12-channel phased-array head coil. All of the images were prescribed in a trans-axial view parallel to the anterior commissure–posterior commissure line. T_2-weighted images were acquired with a fast spin echo sequence, TR/TE = 5920/102 ms, slice thickness = 3.0 mm, field of view = 25 × 25 cm, matrix size = 256 × 256, and slice number = 35. DSI was performed using a pulsed-gradient spin-echo diffusion EPI sequence with twice-refocused balanced echoes (Reese et al., 2003). The maximum diffusion sensitivity (b-max) was 6000 s/mm^2 and TR/TE was 9100/142 ms. The in-plane spatial resolution was 2.9 mm, and the slice thickness was 2.9 mm.

A total of 203 grid sampling points were sampled in the diffusion-encoding space (q space), as was proposed in an optimization study (Kuo et al., 2008). Forty-five slices were acquired to cover the entire brain. The total scan time was approximately 45 min.

2.3. Reconstructing spin distribution functions in a common space

The diffusion data of each subject were reconstructed in a common stereotaxic space using q-space diffeomorphic reconstruction (QSDR) (Yeh and Tseng, 2011), a method that satisfies the conservation of diffusible spins and can be applied to diffusion datasets acquired with different diffusion sampling schemes, including the single shell scheme (also known as high angular resolution diffusion images, HARDI), multiple shell scheme, and grid scheme (also known as the DSI scheme). QSDR uses diffusion signals to calculate the spin distribution function (SDF), $\psi(\mathbf{r},\hat{\mathbf{u}})$, which is defined as the number of spins at location $\mathbf{r}$ that diffuse along the orientation $\hat{\mathbf{u}}$. The formula for the calculation of SDF is as follows:

$$\psi(\mathbf{r},\hat{\mathbf{u}}) = \left|J_\varphi(\mathbf{r})\right| Z_0 \sum_i W_i(\varphi(\mathbf{r}))\mathrm{sinc}\left(\sigma\sqrt{6Db_i} < \hat{\mathbf{g}}_i, \frac{J_\varphi(\mathbf{r})\hat{\mathbf{u}}}{\left\|J_\varphi(\mathbf{r})\hat{\mathbf{u}}\right\|} >\right) \quad (1)$$

where $\mathbf{r}$ represents the coordinates in the template space, and the function φ is a mapping function that maps a template space coordinates $\mathbf{r}$ to its corresponding coordinates in the subject's native space. The mapping function φ was obtained by registering the FA maps of the subject to the FMRIB 1 mm FA template (FSL, Oxford, UK) using a nonlinear registration (Ashburner and Friston, 1999) implemented in DSI Studio (http://dsi-studio.labsolver.org). The goodness-of-fit was evaluated using the R^2 between the warped image and template image. All patients in this study had R^2 greater than 0.64. $J_\varphi(\mathbf{r})$ is the Jacobian matrix of the mapping function at $\mathbf{r}$, and $|J_\varphi(\mathbf{r})|$ is the Jacobian determinant. $W_i(\varphi(\mathbf{r}))$ is the diffusion MR signals at $\varphi(\mathbf{r})$ and can be estimated numerically using trilinear interpolation. b_i and $\hat{\mathbf{g}}_i$ are the b-value and the diffusion gradient direction of the diffusion signal, respectively. σ is the diffusion sampling ratio, for which a recommended value of 1.25 was used in this study. D is the diffusivity of water. Z_0 is the constant estimated by the diffusion signals of free water diffusion, as conducted in our original study (Yeh and Tseng, 2011). The free water calibration was automatically conducted using voxels located in the lateral ventricles at (6, 0, 18) and (−6, 0, 18) in the Montreal Neurological Institute (MNI) space. The QSDR reconstruction yields maps of SDFs at 2 mm isotropic resolution. To estimate the number of anisotropic spins, each reconstructed SDF is subtracted by its minimum value. After the QSDR reconstruction and minimum subtraction, the SDF value can then be used to estimate the number of spins that diffuse preferentially along the fiber orientation. Our previous study demonstrated that the SDF value was linearly related to the volume fraction of the fibers regardless of the partial volume effect from the isotropic component (Yeh et al., 2010), thereby making it an index for measuring local structural connectivity.