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White matter structural connectivity is associated with sensorimotor function in stroke survivors

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ABSTRACT

Purpose: Diffusion tensor imaging (DTI) provides functionally relevant information about white matter structure. Local anatomical connectivity information combined with fractional anisotropy (FA) and mean diffusivity (MD) may predict functional outcomes in stroke survivors. Imaging methods for predicting functional outcomes in stroke survivors are not well established. This work uses DTI to objectively assess the effects of a stroke lesion on white matter structure and sensorimotor function.

Methods: A voxel-based approach is introduced to assess a stroke lesion's global impact on motor function. Anatomical T1-weighted and diffusion tensor images of the brain were acquired for nineteen subjects (10 post-stroke and 9 age-matched controls). A manually selected volume of interest was used to alleviate the effects of stroke lesions on image registration. Images from all subjects were registered to the images of the control subject that was anatomically closest to Talairach space. Each subject's transformed image was uniformly seeded for DTI tractography. Each seed was inversely transformed into the individual subject space, where DTI tractography was conducted and then the results were transformed back to the reference space. A voxel-wise connectivity matrix was constructed from the fibers, which was then used to calculate the number of directly and indirectly connected neighbors of each voxel. A novel voxel-wise indirect structural connectivity (VISC) index was computed as the average number of direct connections to a voxel's indirect neighbors. Voxel-based analyses (VBA) were performed to compare VISC, FA, and MD for the detection of lesion-induced changes in sensorimotor function. For each voxel, a t-value was computed from the differences between each stroke brain and the 9 controls. A series of linear regressions was performed between Fugl-Meyer (FM) assessment scores of sensorimotor impairment and each DTI metric's log number of voxels that differed from the control group.

Results: Correlation between the logarithm of the number of significant voxels in the ipsilesional hemisphere and total Fugl-Meyer score was moderate for MD ($R2 = 0.512$), and greater for VISC ($R2 = 0.796$) and FA ($R2 = 0.674$). The slopes of FA ($p = 0.0036$), VISC ($p = 0.0005$), and MD ($p = 0.0199$) versus the total FM score were significant. However, these correlations were driven by the upper extremity motor component of the FM score (VISC: $R2 = 0.879$) with little influence of the lower extremity motor component (FA: $R2 = 0.177$).

Conclusion: The results suggest that a voxel-wise metric based on DTI tractography can predict upper extremity sensorimotor function of stroke survivors, and that supraspinal intraconnectivity may have a less dominant role in lower extremity function.

1. Introduction

Diffusion tensor imaging (DTI) of brain white matter structural connectivity may have prognostic value for acute stroke patients at risk of motor impairment. In particular, DTI of the corticospinal tract has been a primary focus for predicting stroke severity and clinical outcome (Puig et al., 2010; Thomalla et al., 2004). In the corticospinal tract of stroke survivors, DTI measures that indicate structural integrity in white matter correlate with muscle strength (Chen et al., 2008; Puig et al., 2010; Schulz et al., 2012), walking ability (Jayaram et al., 2012), hand function and motor recovery (Lindenberg et al.,

Abbreviations: DTI, diffusion tensor imaging; FA, fractional anisotropy; FOV, field of view; FM, Fugl-Meyer; LDV, log difference volume; LE, lower extremity; MD, mean diffusivity; TE, echo time; TFIRE, Tactful Functional Imaging Research Environment; TR, repetition time; UE, upper extremity; VISC, voxel-wise indirect structural connectivity.

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2010; Schaechter and Fricker, 2009; Thomalla et al., 2004; Vargas et al., 2012). Corticospinal tract size and damage to the corticospinal tract, estimated using DTI in the acute setting, also correlate with long-term recovery (Pannek et al., 2009; Parmar et al., 2006; Zhu et al., 2010). In addition to the natural recovery from stroke, information about corticospinal tract loss predicts the extent of motor recovery obtained from therapeutic interventions (Riley et al., 2011; Stinear et al., 2007). Thus, the predominant approach in developing imaging biomarkers in stroke survivors has been corticospinal tract-specific measures based on manually-identified or atlas-based regions of interest (Borich et al., 2012). These previous approaches highlight the potential value in utilizing DTI data to predict functional outcomes; however, analyses based on specific regions of interest require subjective region selection, and might not account for impairments associated with damage to or connections to other regions of the brain. The purpose of the current study was to develop and test a new imaging parameter as a biomarker for sensorimotor function in stroke survivors based on a whole brain, voxel-wise analysis of anatomical connectivity.

Although DTI measures of the corticospinal tract provide valuable information about stroke, a whole brain voxel-based analysis of brain structure might have advantages over corticospinal tract region of interest approaches. Namely, voxel-based analyses are simple to apply, objective, and test the structural changes across the entire brain. A voxel-based analysis involves the normalization of images (through registration and spatial filtering) followed by statistical comparisons of DTI parameters of the resulting maps (Ashburner and Friston, 2000; Wright et al., 1995). These analyses have been applied to DTI parameters of the brain in normal development and aging (Della Nave et al., 2007; Snook et al., 2007), following traumatic injury (Bendlin et al., 2008; Chu et al., 2010) and during progressive disease (Agosta et al., 2007; Sage et al., 2009; Thivard et al., 2007). Conversely, there are limitations to voxel-based analyses including dependence on the quality of image registration across subjects and effects of smoothing applied to the images (Abe et al., 2010; Ashburner and Friston, 2001; Bookstein, 2001; Van Hecke et al., 2011). Consequently, an alternative voxel-based approach for assessing brain white matter, Tract-Based Spatial Statistics (TBSS) (implemented within the FMRIB Software Library (FSL)) has been developed (Smith et al., 2006). This technique accounts for the registration and smoothing issues by using a tract 'skeleton' obtained from fractional anisotropy (FA) values. In addition to a number of other applications, TBSS has been applied to the brain of stroke survivors and detects FA changes in white matter tracts that correlate to upper extremity function (Schaechter and Fricker, 2009).

Incorporating measurements of white matter structural connectivity of the brain within DTI voxel-based approaches may offer additional opportunities for the characterization of structural changes after stroke. The loss of white matter tracts after stroke has implications throughout the brain, including functional processes that require the integration of information from multiple brain areas. The primary tool for characterizing the structural connectivity between brain regions is DTI tractography (Conturo and Lori, 1999; Jones and Simmons, 1999; Mori et al., 1999). Tractography models have been used to identify anatomical tracts and features of the tractography analysis, such as the number of fibers passing through a voxel (Calamante et al., 2010; Roberts et al., 2005). A structural connectivity matrix can then be obtained by combining white matter fiber trajectories with gray matter anatomical regions of interest segmented from a high resolution anatomical MR image (Hagmann et al., 2007; Sporns, 2011). This matrix represents the anatomical connectivity of the specific regions of the brain, but depends on the segmentation of specific regions of gray matter as nodes in the connectivity matrix. In contrast, voxel-based connectivity models make no assumptions about the parcellation of brain volume into ROIs, nor do they require a priori knowledge about the physiology of the tissue within a voxel (Scheinost et al., 2012). The absence of assumptions in a voxel-based approach is appealing for generalizing connectivity models for clinical application.

In this study, we developed a unique metric of structural connectivity as a biomarker for loss of sensorimotor function in subjects with chronic stroke. Our metric characterized the anatomical connectivity of each voxel of the brain based on diffusion tractography (i.e. a voxel-wise indirect structural connectivity (VISC)). This VISC metric was designed to have high sensitivity to lesions of prominent white matter tracts, which normally connect large numbers of voxels. A voxel-based analysis of stroke and control brains was conducted on the VISC metric and compared to a voxel-based analysis of FA and mean diffusivity in the same samples. Sensitivity to sensorimotor function was tested by correlating the volume of differences in VISC, between stroke subjects and controls, with sensorimotor impairment measured by the Fugl-Meyer Assessment (Fugl-Meyer, 1975).

2. Methods

2.1. Data collection

2.1.1. Subject recruitment and Fugl-Meyer testing

Ten subjects with chronic post-stroke hemiparesis (5 female, age 55.20 ± 7.06 years, at least 1.1 years since stroke) and nine age-matched control subjects (6 female, age 53.40 ± 13.10 years) participated in this study. Each subject provided written consent to the experimental protocol, which was approved by the Institutional Review Boards at Marquette University and the Medical College of Wisconsin. In recruiting subjects, a sample of convenience was used. General inclusion criteria were ability to provide informed consent and the ability to move the legs with no contraindications to light exercise. Additional inclusion criteria for stroke survivors were a single cortical or subcortical stroke at least 6 months earlier, clinically detectable movement impairment on one side of the body, communication adequate to follow instructions for the experiment, and no neurological impairments other than stroke. Control subjects had to be free of stroke or other neurological impairments.

Each stroke subject completed a slightly modified system of upper extremity (UE) and lower extremity (LE) portions of the Fugl-Meyer (FM) Assessment (Fugl-Meyer, 1975) for global impairment (maximum possible score is 130 for UE and 96 for LE). The scoring system for the FM Assessment is shown in Table 1, and the FM scores for each subject are shown in Table 2. Note that lower scores indicate greater impairment. FM assessments were completed by a physical therapist with 9 years of clinical experience. Reliability and validity assessments were not done for this study; however, the FM has been shown to have excellent construct validity, good concurrent validity with other stroke motor scores, satisfactory predictive validity for functional level at discharge from hospital ($r = 0.72$), and excellent intra- and inter-tester reliability (ICC = 0.98) (Gladstone et al., 2002; Hsueh et al., 2008). The maximum score for the UE portion of FM is 130 because it includes UE reflexes (max = 6), UE movements in and out of synergy (max = 30), voluntary movements of the wrist and hand (max = 24), and UE coordination (max = 6), parachute responses (max = 4), UE light touch (max = 4), UE proprioception (max = 8), UE range of motion (max = 24), and UE pain (max = 24). Nevertheless, the scale required adjustment to better reflect the possible range of scores. Since the control subjects did not have any lesions and the Fugl-Meyer assessment is a measure of impairment, sensorimotor function in control subjects was not tested.

2.1.2. MRI scans

After completing MRI safety screening, the nineteen subjects were imaged with a 3 T clinical MR system (GE Signa Excite, GE Healthcare, Milwaukee). For each subject, an axial DTI sequence was acquired with one b0 image, 25 noncollinear, equally spaced diffusion directions, b-value = 1000 s/mm^2, matrix = 128 × 128, FOV = 24 cm, slice thickness = 4 mm, TE = 86.5 ms, TR = 10 s, NEX = 2. As an