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A comparison of seven different DTI-derived estimates of corticospinal tract structural characteristics in chronic stroke survivors

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HIGHLIGHTS

- The most accurate estimate of CST microstructure for this stroke cohort is individual tractography-derived CST FA asymmetry.
- Template-derived CST estimates do not account for shifted location of ipsilesional CST.
- FA asymmetry at PLIC or CP does not represent the entire CST microstructure.
- Only the individual tractography-derived CST FA estimate was significantly correlated with motor performance in this cohort.

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ABSTRACT

Background: Different diffusion tensor imaging (DTI) has been used to estimate corticospinal tract (CST) structure in the context of stroke rehabilitation research. However, there is no gold standard for the estimate of CST structure in chronic stroke survivors. This study aims to determine the most accurate DTI-derived CST estimate that is associated with a clinical motor outcome measure.
Methods: We obtained imaging and behavioral data from a phase-I stroke rehabilitation clinical trial. We included thirty-seven chronic stroke survivors with mild-to-moderate motor impairment. Imaging data were processed using BrainSuite16a software. We calculated mean FA for each of 7 different ROIs/VOIs that include manually drawn 2-D ROIs and 3-D VOIs of CST from individual tractography or standard atlas. We compared ipsi- and contralesional CST FA for each method. Partial correlation was conducted between each CST FA asymmetry index and a time-based motor outcome measure, controlling for age and chronicity.
Results: Ipsilesional CST FA was significantly lower than contralesional CST FA for each of the 7 methods Only CST FA asymmetry from the 3-D individual CST tractography showed a significant correlation with the primary motor outcome ($r = 0.46$, $p = .005$), while CST FA from the other six methods did not.
Comparison with existing methods: Compared to the six other methods, CST FA asymmetry from 3-D individual tractography is the most accurate estimate of CST structure in this cohort of stroke survivors.
Conclusion: We recommend this method for future research seeking to understand brain-behavior mechanisms of motor recovery in chronic stroke survivors.

1. Introduction

The corticospinal tract (CST) delivers motor commands from primary motor and sensory cortices to the spinal cord through direct (lateral and medial corticospinal tract) and indirect pathways. As such, the amount of post-stroke damage affecting this descending motor pathway is a crucial factor that determines the level of motor impairment following stroke (Corbetta et al., 2015;

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Jang, 2011). Diffusion tensor imaging (DTI)-derived estimate of CST structural damage to the CST has been used to predict motor recovery in stroke survivors. DTI-derived metrics of CST (Koyama et al., 2013; Lindenberg et al., 2012, 2010, Puig et al., 2013, 2011), specifically fractional anisotropy (FA) asymmetry and the ratio between ipsi- and contra-lesional CST, are the most frequently used predictor variables in prognostic studies (Lindenberg et al., 2010; Puig et al., 2013; Stinear et al., 2012). In general, FA of ipsilesional CST is decreased after stroke, leading to an increase in FA asymmetry (Stinear et al., 2012).

Although DTI-derived estimates of ipsilesional CST are widely used, the specific estimation method varies considerably (Lindenberg et al., 2010); as such, comparison across studies is challenging. The four most common regions/volumes of interest that investigators have used to estimate CST structure are: 1) a 2-dimensional region of interest (2-D ROI) at the posterior limb of the internal capsule (PLIC); 2) a 2-D ROI at the cerebral peduncle (CP); 3) a 3-dimensional (3-D) volume of interest (3-D VOI) of CST from individual stroke patient's CST tractography; and 4) a 3-D VOI of CST from non-disabled adults' CST template (Kim and Winstein, 2017).

For 2-D ROI-based methods, a PLIC or CP ROI is manually drawn on structural images (Koyama et al., 2012). To perform CST structural estimation using 3-D CST VOI, one can reconstruct the individual CST of each individual using diffusion tensor-based tractography (Lindenberg et al., 2012, 2010; Yu et al., 2009). Template CST tractography is reconstructed from age-matched non-disabled participants' DTI data, or an established template standard CST atlas can be used (Park et al., 2013).

There are advantages and disadvantages of each estimate of CST structure. The benefits of using 2-D PLIC or CP ROIs are that both ROIs are easily identified on structural images, and the FA value of these regions has been shown to provide an accurate estimation of CST structural damage (Kuzu et al., 2012). A decreased FA at these regions is thought to reflect the Wallerian degeneration that occurs across the entire CST after stroke (Koyama et al., 2012; Kuzu et al., 2012; Lindenberg et al., 2012). Thus, determination of the DTI-derived metrics at a remote CST section, such as PLIC or CP, is assumed to represent the degree of degeneration of the entire CST without underestimation. However, the ROI-based methods may be biased, particularly when PLIC or CP ROIs are manually drawn (Lindenberg et al., 2010). To control for possible bias introduced by these manual methods, some researchers have instead used PLIC or CP sections of CST tractography or established subcortical white matter atlases (Park et al., 2013).

Compared with 2-D ROI-based methods, individual tractography-based CST estimation methods can represent the entire CST structure using the subject's own reconstructed fiber tracts. However, the individual CST method may not be appropriate for cases in which some if not most CST fibers cannot be traced using diffusion tensor-based tractography (Cho et al., 2007a,b).

In general, template-based CST estimates are considered a more objective method compared to ROI-based methods, as it relies on automated processes known to reduce operator-dependent bias (Park et al., 2013). However, the brain of chronic stroke survivors may present with an aberrant ipsilesional CST trajectory due in part to significant subcortical white matter atrophy; in this case, an estimate of CST structure that relies on template CST volume will likely be incorrect (Jang, 2011).

Although these different DTI-derived estimates for CST structure are widely used in stroke rehabilitation research, there is no gold standard which most accurately represents CST structural characteristics in chronic stroke survivors. Thus, this study aims 1) to determine which method most accurately estimates CST structural damage, and 2) to examine the degree to which the measure of CST structural damage correlates with a well-known clinical motor outcome in chronic stroke survivors with mild-to-moderate motor impairment.

To determine the most accurate estimate of CST structure, each method was evaluated based on three criteria: 1) the method can capture a significant decrease in ipsilesional CST fractional anisotropy (FA) compared to the FA of contralesional CST; 2) CST FA asymmetry range falls within the normative range between −0.03 and 0.25; and 3) significant relationship between CST FA asymmetry and clinical motor outcome.

Our expected findings are that the most accurate method for this cohort will be the 3-D individual tractography-based CST method, and the CST FA asymmetry derived from this method will result in the strongest correlation with our primary motor outcome. Our hypotheses are based on two primary assumptions: 2-D ROIs may not represent the entire CST structure, and 3-D template CST VOI may not represent the distorted ipsilesional CST trajectory commonly seen in the chronic stroke brain.

2. Methods

2.1. Participants

The clinical and neuroimaging data were from a single-site randomized trial of stroke rehabilitation conducted in the Motor Behavior and Neurorehabilitation Laboratory at Division of Biokinesiology and Physical Therapy, University of Southern California (ClinicalTrials.gov ID: NCT 01749358). The clinical trial was conducted in accordance with the Declaration of Helsinki and all procedures were carried out with the adequate understanding and written consent of the participants. The clinical trial was approved by the Institutional Review Board of the University of Southern California. The purpose of this clinical trial was to determine the effect of different doses of therapy on motor outcomes in chronic stroke. Predefined inclusion and exclusion criteria for the RCT are described in Supplementary Table 1. For this project, a total of 37 out of 42 trial participants' data met inclusion criteria that required a complete set of baseline clinical motor outcome scores and DTI neuroimaging. Five data sets were excluded because of missing neuroimaging or artifacts present on imaging.

2.2. Clinical motor outcome measure

We utilized an arm-specific clinical motor outcome measure. Specifically, we employed a subset of laboratory-based Wolf Motor Function Test (WMFT). WMFT time score is a reliable and valid method to evaluate UE motor performance after stroke, particularly in the research environment (Lin et al., 2009; Wolf et al., 2001). This measure includes fifteen timed motor tasks. The timed tasks can be distributed into two task categories: 1) tasks related to joint-segment movements, and 2) tasks related to integrative functional movements (Wolf et al., 2001). The joint-segment movement tasks are primarily those with proximal joint control (e.g., shoulder and elbow), while the integrative functional tasks require some level of hand dexterity for object manipulation. Given our sample of those with mild-to-moderate motor impairment, tasks related to proximal joint-segment movements had ceiling effects on assessing the upper extremity motor performance (Fig. A1 in Appendix A). Thus, we employed the WMFT-distal time score (WMFT-distal), the log-transformed average time score for the integrative functional task items (i.e., distal arm control task items), to minimize the ceiling effect from the tasks associated with joint-segment movements.