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A template-based procedure for determining white matter integrity in the internal capsule early after stroke

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ABSTRACT

The integrity of descending white matter pathways, measured by fractional anisotropy from DW-MRI, is a key prognostic indicator of motor recovery after stroke. Barriers to translation of fractional anisotropy measures into routine clinical practice include the time required for manually delineating volumes of interest (VOIs), and inter-examiner variability in this process. This study investigated whether registering and then editing template volumes of interest 'as required' would improve inter-examiner reliability compared with manual delineation, without compromising validity. MRI was performed with 30 sub-acute stroke patients with motor deficits (mean NIHSS = 11, range 0–17). Four independent examiners manually delineated VOIs for the posterior limbs of the internal capsules on T1 images, or edited template VOIs that had been registered to the T1 images if they encroached on ventricles or basal ganglia. Fractional anisotropy within each VOI and interhemispheric asymmetry were then calculated. We found that 13/30 registered template VOIs required editing. Edited template VOIs were more spatially similar between examiners than the manually delineated VOIs ($p = 0.005$). Both methods produced similar asymmetry values that correlated with clinical scores with near perfect levels of agreement between examiners. Contralesional fractional anisotropy correlated with age when edited template VOIs were used but not when VOIs were manually delineated. Editing template VOIs as required is reliable, increases the validity of fractional anisotropy measurements in the posterior limb of the internal capsule, and is less time-consuming compared to manual delineation. This approach could support the use of FA asymmetry measures in routine clinical practice.

1. Introduction

Diffusion tensor imaging provides information about tissue composition that reflects the microstructural integrity of white matter tracts in the brain (Basser, 1995; Basser and Pierpaoli, 1996). Fractional anisotropy (FA) quantifies the extent to which water diffusion is directionally restricted and is the most common DTI parameter used to assess white matter integrity (Jang, 2010). Disruption of white matter tracts results in less restriction on water diffusion and a lowering of the FA value (Basser and Pierpaoli, 1996; Werring et al., 2000). After stroke, reduced white matter integrity can occur acutely within the primary lesion location, and can be a delayed and distant consequence of anterograde and/or retrograde axonal degeneration (Thomalla et al., 2004; Werring et al., 2000). FA derived from DTI correlates with upper limb function in chronic stroke patients (Stinear et al., 2007), and can be used to predict recovery of upper limb motor function at both early (Jang et al., 2005, 2008; Maeda et al., 2005; Stinear et al., 2012) and chronic stages of stroke (Stinear et al., 2007).

Two approaches to DTI-based analysis can be used to evaluate FA values in white matter tracts. The first is white matter tractography, in which three-dimensional reconstructions of tract trajectories are calculated from the DTI vector field (Mori and van Zijl, 2002). Regions of interest are defined, typically on a single axial slice, as seeds, waypoints and endpoints for subsequent tractography. Mean FA values along the tracts can then be compared between contralesional and ipsilesional hemispheres (Borich et al., 2012; Puig et al., 2012; Wakana et al., 2007). This approach can be confounded by anatomical variations or stroke lesions, and requires at least a part of the tract of interest to be intact from start to finish (Borich et al., 2012; Puig et al., 2011; Tang et al.,

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2010; Wakana et al., 2007). Moreover, tractography is a complex and time-consuming process, and results vary depending upon the particular algorithm employed (Chung et al., 2011; Ciccarelli et al., 2008).

A second approach involves defining a three-dimensional VOI and then calculating the mean FA within the volume. A typical choice of VOI is the posterior limb of the internal capsule (PLIC). Mean FA is calculated bilaterally within the PLIC VOIs to determine FA asymmetry (Borich et al., 2012; Stinear et al., 2007). FA asymmetry correlates with current upper limb motor function (Lindenberg et al., 2010; Zhu et al., 2010), and can be used as a predictor of motor recovery in both chronic (Stinear et al., 2007) and acute patients (Jang et al., 2005; Stinear et al., 2012).

The most commonly used method to define VOIs is manual tracing, in which experienced examiners delineate anatomical structures (Karnath and Perenin, 2005; Moro et al., 2008; Mort et al., 2003). Manual drawing methods remain the gold standard for the exact delineation of anatomical structures as they require fewer computing resources than tractography-based approaches and are more intuitive for clinical use. However, shortcomings of manual tracing include: being limited to regions identifiable by anatomic landmarks (Eckert et al., 2008); being labor intensive (Ashton et al., 2003; Seghier et al., 2008); and erroneous inclusion of structures such as gray matter and other tracts (Holodny et al., 2005; Park et al., 2008). For these reasons, an automated method of VOI delineation may be preferable. Automated methods are much faster, and they may also minimize inter-examiner disagreements (Wilke et al., 2011). However, automated methods may have shortcomings for studies of stroke patients, such as inadequate compensation for the structural distortions introduced by lesions that may result in gray matter or CSF being included in the VOI. Additionally, there may be inadequate correction for anatomical variability between subjects (Fiez et al., 2000). A compromise between manual and automated approaches exists in which VOIs produced by an automated technique are manually edited as required to correct any inappropriate inclusion of gray matter or CSF. It is not clear whether manual or edited VOI delineation methods produce measures that are the more reliable and accurate.

The aims of this study were to compare the reliability and validity of manual and edited VOI methods for defining the PLIC on MR images from sub-acute stroke patients. We hypothesized that editing registered templates would produce valid and more reliable FA values, compared to the more time-consuming process of manual delineation.

2. Material and methods

2.1. Participants

Participants were recruited if they were at least 18 years old and had experienced a first-ever ischemic stroke resulting in persistent unilateral upper limb impairment. Exclusion criteria were any neurological or other conditions that would prevent informed consent or hinder the acquisition or interpretation of the data, such as cognitive or communication deficits, previous stroke, and contra-indications to MRI. Participants were screened using a MRI safety checklist. The study was approved by the regional ethics committee, and all participants provided written informed consent, in accordance with the Declaration of Helsinki.

There were 30 participants in this study (20 females; mean age 68 years, range 31 to 92 years; 19 with right hemisphere lesions and 11 with left hemisphere lesions; Table 1, Fig. 1) and all except one was right-hand dominant before their stroke. All participants completed MR imaging within a mean of 11 (range 4 to 22) days of stroke. At a mean of 13 (range 5 to 23) days after stroke, a clinical assessor evaluated stroke severity using the National Institutes of Health Stroke Scale (NIHSS), motor impairment of the affected upper limb using the Fugl-Meyer (FM) scale, maximum score 66 (Fugl-Meyer et al., 1975); and upper limb function using the Action Research Arm Test (ARAT), maximum score of 57 (Lyle, 1981). The clinical assessor was blinded to the MR images.

2.2. MR data acquisition

Scanning was performed using a Siemens Magnetom Avanto 1.5 T MRI system. To provide anatomical reference, T1-weighted images were obtained with a 3D MPRAGE sequence (TR = 11 ms, TE = 4.94 ms, field-of-view = 256 mm and voxel dimensions of 1.0 × 1.0 × 1.0 mm) aligned to an axial plane parallel to the anterior and posterior commissures (the AC–PC line).

Diffusion tensor imaging was conducted with a single shot spin echo EPI pulse sequence (factor = 128, TR = 6700 ms, TE = 101 ms, field-of-view = 230 mm and voxel dimensions of 1.8 × 1.8 × 3.0 mm) with 30 uniformly distributed (Stejskal and Tanner, 1965) motion-probing gradient orientations ($\beta = 2000\ s/mm^2$). Head movement was constrained with expandable foam cushions. MR images were visually inspected for motion artifact or instrumental noise. Scanning was repeated if major artifacts were present. Overall time in the scanner was approximately 20 min per participant.

2.3. Manual PLIC delineation

Each examiner pre-processed the images and manually delineated the PLIC VOIs using FSL (FMRIB Software Library, Oxford) (Smith et al., 2004; Woolrich et al., 2009). Four independent examiners (expert: V.K.; examiner 1: M.P.; examiner 2: C.Z.; examiner 3: E.V.) performed cross-sectional VOI delineation of each PLIC. V.K. is a neurologist with clinical experience in interpreting MR images, and hence was deemed to be an 'expert' examiner for the purposes of this study. The other 3 'novice' examiners were medical researchers who had previous experience in identifying the pertinent structures. None of the examiners had prior experience in VOI drawing and so were trained in the use of the software packages and the required workflow.

Examiners used the T1-weighted images to delineate the PLICs and no other images were consulted while drawing in order to prevent any bias that FA maps could introduce when determining the PLIC borders. Training for the VOI drawing task was accomplished using previously delineated examples in reference atlases of healthy brains.

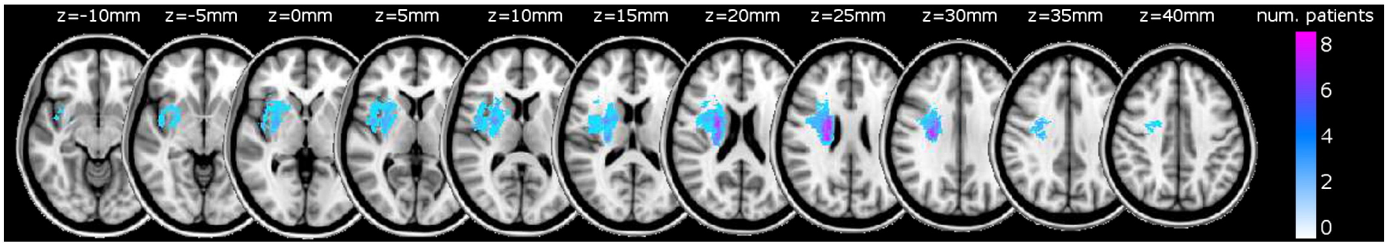

Fig. 1. Lesion overlap map. Images have been flipped so all lesions appear in the right hemisphere.