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Assessing a standardised approach to measuring corticospinal integrity after stroke with DTI

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ABSTRACT

The structural integrity of the corticospinal tract (CST) after stroke is closely linked to the degree of motor impairment. Simple and reliable methods of assessing white matter integrity within the CST would facilitate the use of this measure in routine clinical practice. Commonly, diffusion tensor imaging is used to measure voxel-wise fractional anisotropy (FA) in a variety of regions of interest (ROIs) representing the CST. Several methods are currently in use with no consensus about which approach is best. ROIs are usually either the whole CST or the posterior limb of the internal capsule (PLIC). These are created manually on brain images or with reference to an individual's CST determined by tractography. Once the ROI has been defined, the FA can be reported as an absolute measure from the ipsilesional side or as a ratio in comparison to the contralesional side. Both corticospinal tracking and manual ROI definition in individual stroke patients are time consuming and subject to bias. Here, we investigated whether using a CST template derived from healthy volunteers was a feasible method for defining the appropriate ROI within which to measure changes in FA. We reconstructed the CST connecting the primary motor cortex to the ipsilateral pons in 23 age-matched control subjects and 21 stroke patients. An average healthy CST template was created from the 23 control subjects. For each patient, FA values were then calculated for both the template CST and for their own CST. We compared patients' FA metrics between the two tracts by considering four measures (FA in the ipsilesional side, FA in the contralesional side, FA ratio of the ipsilesional side to the contralesional side and FA asymmetry between the two sides) and in two tract-based ROIs (whole tract and tract section traversing the PLIC). There were no significant differences in FA metrics for either method, except for contralesional FA. Furthermore, we found that FA metrics relating to CST damage all correlated with motor ability post-stroke equally well. These results suggest that the healthy CST template could be a surrogate structure for defining tract-based ROIs with which to measure stroke patients' FA metrics, avoiding the necessity for CST tracking in individual patients. CST template-based automated quantification of structural integrity would greatly facilitate implementation of practical clinical applications of diffusion tensor imaging.

1. Introduction

Diffusion tensor imaging (DTI) is commonly used to investigate tissue microstructure in the central nervous system, particularly through the measurement of fractional anisotropy (FA). FA reflects the degree of anisotropic diffusion (Basser and Pierpaoli, 1996) and is a potentially powerful tool for assessing residual structural architecture in a number of central nervous system disorders. After stroke for example, FA might be used to assess the integrity of the corticospinal tract (CST) to help predict motor outcomes or direct clinicians to the most appropriate therapy (Stinear et al., 2012). However, there are a variety of approaches used in assessing CST integrity with FA values; the lack of consensus over which is the most appropriate is a potential barrier to widespread clinical use of this tool.

FA values are often averaged across specific regions of interest (ROIs), for example the posterior limb of the internal capsule (PLIC). These ROIs can be defined with or without reference to the individual's CST reconstructed using tractography (Jayaram et al., 2012; Madhavan et al., 2011; Qiu et al., 2011; Stinear et al., 2007). In other words, tract-based ROIs are determined within the reconstructed CST of an individual subject and may refer to the whole tract (Lindenberg et al., 2012; Rüber et al., 2012) or a subsection of the tract (Globas et al., 2011; Lindenberg et al., 2010; Lotze et al., 2012; Puig et al., 2010,

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2011). Alternatively, anatomical landmark-based ROIs refer to regions manually delineated on the brain, relying on anatomical landmarks, without reconstruction of the CST by tractography (Jayaram et al., 2012; Lindberg et al., 2007; Liu et al., 2012; Madhavan et al., 2011; Qiu et al., 2011; Stinear et al., 2007; Yeo et al., 2011).

Once the ROI has been defined, the FA can be reported as an absolute measure from the ipsilesional side (FA_{ipsi}) (Jang et al., 2006; Lindenberg et al., 2012; Møller et al., 2007; Nelles et al., 2008; Pierpaoli et al., 2001; Puig et al., 2010) or contralesional side (FA_{contra}) (Jang et al., 2006; Lindenberg et al., 2012; Pierpaoli et al., 2001; Puig et al., 2010). Alternatively, the ratio of the ipsilesional to contralesional side (FA_{ratio}) (Globas et al., 2011; Jang et al., 2005; Lindberg et al., 2007; Lotze et al., 2012; Puig et al., 2010) or FA asymmetry ($FA_{asymmetry}$), defined as $(FA_{contra} - FA_{ipsi})/(FA_{contra} + FA_{ipsi})$ (Globas et al., 2011; Jayaram et al., 2012; Lindenberg et al., 2010; Madhavan et al., 2011; Qiu et al., 2011; Stinear et al., 2007) may be reported.

Many of these approaches have been used to demonstrate a relationship between tract integrity and motor ability in stroke patients, but the factors that will influence uptake of these approaches on a large scale include feasibility and reliability. Tract-based ROIs appear to be at least as reliable as approaches using anatomical landmark-based ROIs (Borich et al., 2012; Hong et al., 2008; Partridge et al., 2005; Tang et al., 2010). However, CST tracking in individual stroke patients is often difficult because of interruption of fibres by the infarct which can result in the unreliable morphology of the tracts. On the other hand, manual placement of ROIs in individual patients is also problematic being open to operator bias. In both cases the procedures are time consuming, limiting feasibility and therefore generalisability.

In this study, we have investigated how using a CST template acquired from healthy subjects performs in comparison to the approaches described above. Recently, tract templates acquired from healthy subjects have been used to quantify damage to thalamocortical connections in patients with traumatic brain injury (Squarcina et al., 2012) as well as CST integrity in stroke patients (Schulz et al., 2012). Here we systematically examine the effects of varying both the type of FA measurement (FA_{ipsi}, FA_{contra}, FA_{ratio} or $FA_{asymmetry}$) and spatial extent of an ROI (whole tract or tract section comprising the PLIC) when using CST acquired from either healthy subjects or from individual stroke patients. Since there is no gold standard in the assessment of CST integrity, our approach was to compare the relationship between CST integrity and motor ability in a group of chronic stroke patients. Based on our previous experience (Schulz et al., 2012), we hypothesised that CST integrity assessed using 'normal' and individual patient tracts would perform equally as well.

2. Methods

2.1. Subjects

Twenty-one stroke patients (53.90 ± 14.07 years) participated in this study. All had unilateral hemispheric infarcts occurring between 4 and 165 months previously. The clinical characteristics of the patients are described in Table 1. Twenty-three age-matched (p value = 0.4524) healthy subjects (50.61 ± 14.69 years) who reported no history of neurological illness, psychiatric history, vascular disease or hypertension served as controls.

Full written consent was obtained from each subject in accordance with the Declaration of Helsinki. The study was approved by the Joint Ethics Committee of the Institute of Neurology, UCL and National Hospital for Neurology and Neurosurgery, UCL Hospitals NHS Foundation Trust, London.

2.2. Motor tests

The patients showed motor deficits of the contralesional upper extremity which was assessed using the Action Research Arm Test (Lyle, 1981), grip strength (Sunderland et al., 1989) Motricity Index (Bohannon, 1999) and Nine-Hole Peg Test (Kellor et al., 1971). In order to alleviate floor and ceiling effects in individual scores, the first principle component (PC1) of the scores of the four motor tests was calculated as a representative measure of motor ability. PC1 accounted for 65.16% of the total variance of the four scores. Motor scores including the PC1 are listed in Table 1.

Table 1
Demographic and clinical characteristics of patients included in the study.

No	Age (years)	Time since stroke (months)	Gender	Affected hand	Lesion location	Lesion volume (mm^3)	Lesion load of CST (%)	Motor performance				
								ARAT (0-57)	GRIP (%)	MI -UL (0-100)	NHPT (%)	PC1 (a.u.)
1	77	26	F	R	NCM	1339.875	10.172	38	57.2	77.0	9.0	−0.1463
2	60	41	M	L	CM	44,931.375	0.087	39	20.1	65.0	0.0	−0.3016
3	59	79	M	L	CM	59,025.375	29.896	21	50.3	73.0	0.0	−0.2963
4	53	31	F	L	NCM	290.250	0.520	50	40.0	91.0	50.0	0.0414
5	51	60	M	R	NCM	1282.500	7.069	45	104.0	92.0	31.0	0.1194
6	66	26	M	R	CM	32,285.250	23.017	35	81.0	65.0	39.0	−0.0972
7	69	9	M	R	NCM	5943.375	0.000	57	80.5	100.0	69.7	0.2595
8	55	5	F	L	NCM	594.000	3.986	55	64.0	93.0	97.0	0.2405
9	61	13	M	L	NCM	3084.750	1.386	45	51.1	65.0	19.7	−0.1530
10	75	6	M	L	NCM	1852.875	0.780	57	96.6	100.0	73.7	0.3050
11	66	5	M	L	NCM	290.250	0.000	57	63.4	92.5	98.2	0.2507
12	44	8	M	L	NCM	11,994.750	13.605	36	78.6	81.0	5.1	−0.0993
13	36	20	M	R	NCM	492.750	3.707	54	81.9	93.0	31.0	0.1244
14	59	165	F	L	NCM	14,846.625	16.118	29	18.2	68.0	0.0	−0.3477
15	43	20	F	R	NCM	20,476.125	1.121	41	71.0	91.0	31.0	0.0178
16	33	63	M	R	NCM	529.875	2.931	57	71.7	100.0	68.9	0.2378
17	48	7	M	L	NCM	93,528.000	6.724	31	35.3	42.0	0.0	−0.4201
18	53	12	M	R	NCM	8120.250	11.872	48	52.0	91.0	53.0	0.0642
19	18	5	F	L	CM	17,4997.125	0.690	44	27.7	93.0	5.9	−0.1113
20	51	4	M	R	NCM	276.750	2.253	57	64.2	100.0	89.6	0.2681
21	55	9	M	L	NCM	3.375	8.190	19	97.7	100.0	51.3	0.0439

CST, template corticospinal tract acquired from healthy controls; ARAT, Action Research Arm Test; GRIP, grip strength of affected hand given as a % of less affected hand; MI-UL, Motricity Index (upper limb component); NHPT, Nine-Hole Peg Test score of affected side given as a % of less affected side; PC1, first principle component of the four motor test scores (given as normalised values, arbitrary units); F, female; M, male; L, left; R, right; CM, infarcts affecting primary and secondary motor cortices; NCM, infarcts sparing primary and secondary motor cortices.