



## Review Article

Received: December 31, 2018

Revised: January 23, 2019

Accepted: February 1, 2019

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# Mini-Review of Studies Reporting the Repeatability and Reproducibility of Diffusion Tensor Imaging

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**Purpose:** Diffusion tensor imaging (DTI) data must be analyzed by an analyzer after data processing. Hence, the analyzed data of DTI might depend on the analyzer, making it a major limitation. This paper reviewed previous DTI studies reporting the repeatability and reproducibility of data from the corticospinal tract (CST), one of the most actively researched neural tracts on this topic.

**Materials and Methods:** Relevant studies published between January 1990 and December 2018 were identified by searching PubMed, Google Scholar, and MEDLINE electronic databases using the following keywords: DTI, diffusion tensor tractography, reliability, repeatability, reproducibility, and CST. As a result, 15 studies were selected.

**Results:** Measurements of the CSTs using region of interest methods on 2-dimensional DTI images generally showed excellent repeatability and reproducibility of more than 0.8 but high variability (0.29 to 1.00) between studies. In contrast, measurements of the CST using the 3-dimensional DTT method not only revealed excellent repeatability and reproducibility of more than 0.9 but also low variability (repeatability, 0.88 to 1.00; reproducibility, 0.82 to 0.99) between studies.

**Conclusion:** Both 2-dimensional DTI and 3-dimensional DTT methods appeared to be reliable for measuring the CST but the 3-dimensional DTT method appeared to be more reliable.

**Keywords:** Diffusion tensor imaging; Diffusion tensor tractography; Corticospinal tract; Repeatability; Reproducibility

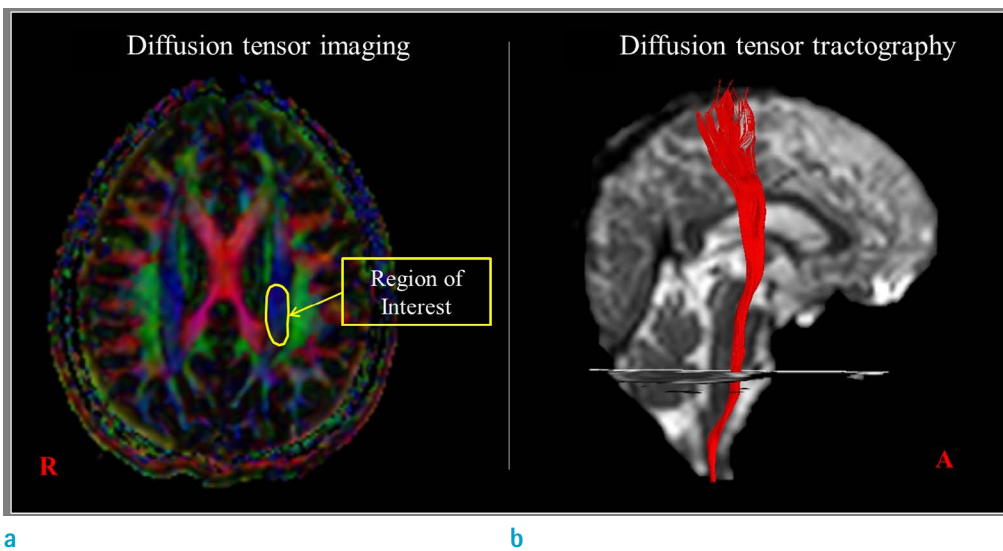
## INTRODUCTION

Diffusion tensor imaging (DTI) provides valuable information on the subcortical white matter that is unavailable with conventional CT and MRI. Therefore, the development of DTI in the 1990s led to a new era for examination of the subcortical white matter in live human brains (1). In addition, diffusion tensor tractography (DTT), which is reconstructed from DTI data, is used to visualize and estimate the neural tracts in the subcortical white matter of the brain (2, 3). As a result, DTI has contributed to the revolutionary development of neuroscience. For example, it allows the detection of brain lesions, which are undetectable by conventional MRI in various brain pathologies, including axonal injury in a concussion, stroke, hypoxic-ischemic brain injury, and cerebral palsy (4-7).

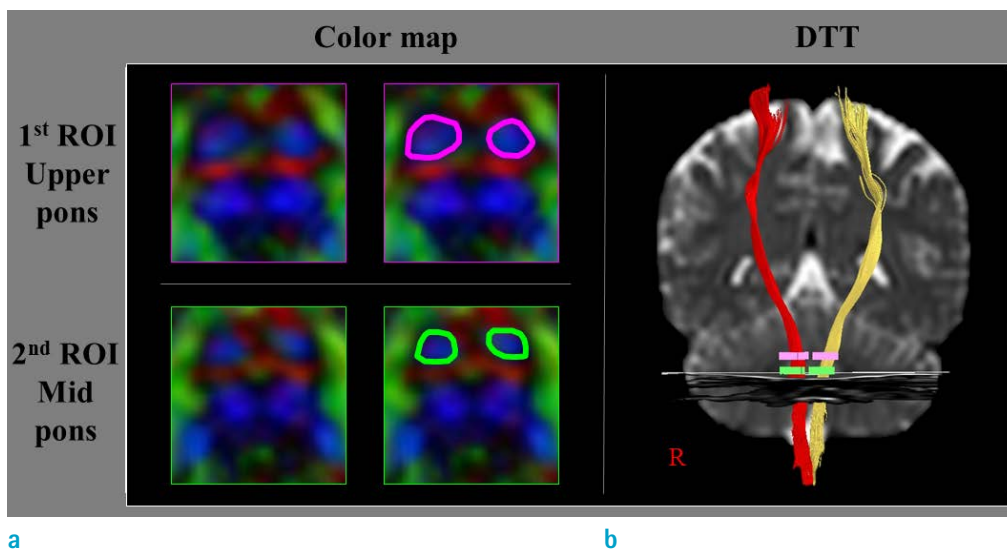
Because DTI data must be analyzed by an analyzer (operator) after data processing, the results may depend on the analyzer, making it a major limitation (8, 9). To address this possible limitation, many studies have reported the repeatability and reproducibility of analyzed DTI data (10-24). The analyses methods for DTI data can be grossly classified into two methods: 1) a 2-dimensional DTI method using the region of interest (ROI), which involves measurements of the DTI parameters in a certain ROI on a 2-dimensional DTI image of the brain (Fig. 1a); and 2) a 3-dimensional DTT method for neural tracts (10-24) (Fig. 1b). Because the placement of an ROI in a certain brain area by an analyzer might be inaccurate and subjective,

the results may vary (Fig. 2a). This might result in low repeatability, low reproducibility, and high variation of the analyzed DTI data (11, 14, 15, 22). In contrast, DTT can show excellent repeatability, excellent reproducibility, and low variation of analyzed DTI data because the application methods involving ROIs and the analytical conditions are well-defined in many neural tracts of the brain (10, 12, 13, 16-21, 23-25) (Fig. 2b).

This paper reviewed DTI studies reporting the repeatability and reproducibility of measurements of the corticospinal tract (CST), which is one of the most actively researched neural tracts on this topic (10-24).



**Fig. 1.** Measurement of parameters using the region of interest on diffusion tensor imaging (a) and using the reconstructed corticospinal tract on diffusion tensor tractography (b).



**Fig. 2.** (a) First and second regions of interest (ROIs: roundly drawn area) are applied to the corticospinal areas in the upper pons and mid-pons, respectively. (b) The reconstructed corticospinal tracts that are commonly passed through the first and second ROIs.

**MATERIALS AND METHODS**

Relevant studies from January 1990 to December 2018 were identified by searching PubMed, Google Scholar, and MEDLINE electronic databases using the following keywords/abbreviations: DTI, DTT, reliability, repeatability, reproducibility, and CST. This review was limited to studies of humans and relevant studies were selected according to the flow diagram presented in Figure 3 (first selection keyword, DTI or DTT; second selection keyword, reliability or repeatability or reproducibility; and exclusion criteria, not related the CST). As a result, 15 studies were reviewed (10-24) (Table 1).

**RESULTS**

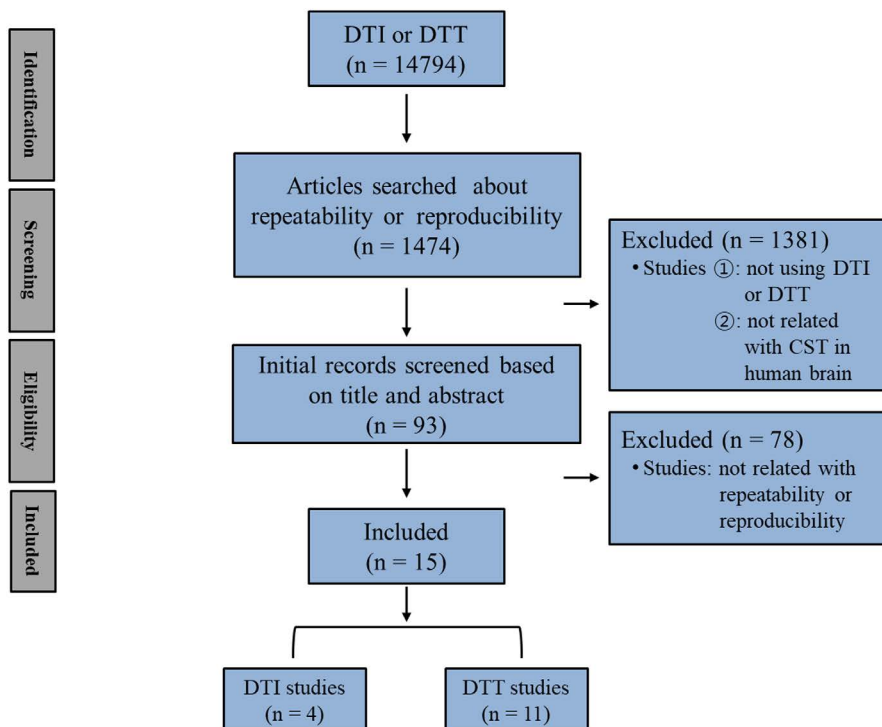
**Repeatability and Reproducibility of Diffusion Tensor Imaging**

Since the introduction of DTI, many studies have reported the repeatability and/or reproducibility of DTI for the CST (10-24). Among these studies, four studies examined the CST using the intra-class correlation coefficient (ICC) (11, 14, 15, 22). In 2007, Bonekamp et al. (11) measured the fractional anisotropy (FA) and apparent diffusion coefficient (ADC) at several ROIs that the CST passes through, the

cerebral peduncle, the posterior limb of the internal capsule, and the superior corona radiata in 40 normal children. They reported substantial to excellent repeatability and reproducibility in the FA and ADC values at each ROI (ICC, 0.66 to 0.99) (11). In 2012, Borich et al. (14) reported substantial to excellent repeatability and reproducibility of DTI by measuring the FA of the posterior limb of the internal capsule in ten chronic stroke patients (ICC, 0.76 to 0.94). During the same year, Hakulinen et al. (15) reported the repeatability of DTI using two other methods of setting the ROI (circular and freehand) in 30 normal subjects and found substantial to excellent repeatability in the FA and ADC (ICC, 0.63 to 0.90). In 2017, Acheson et al. (22) examined the reproducibility of DTI using the ICC between inter-scans of DTI in 12 normal adult subjects and 89 children and adolescents and demonstrated substantial to excellent reproducibility in the FA of the posterior limb of the internal capsule and corona radiata (ICC, 0.72 to 0.87).

**Repeatability and Reproducibility of Diffusion Tensor Tractography**

Eleven studies have reported the repeatability and/or reproducibility of 3-dimensionally reconstructed CST using the DTT method. Seven studies used the ICC, two studies employed the Kappa value, and two studies used the chi-squared test and coefficients of variation (10, 12, 13, 16-



**Fig. 3.** Flow diagram of the approach used to select the studies to be reviewed.

**Table 1. Repeatability and Reproducibility of Diffusion Tensor Imaging and Diffusion Tensor Tractography of the Corticospinal Tract**

DTI	Authors	Publication year	Subjects no.	Statistical analysis	Repeatability	Reproducibility	Region of interest
	Bonekamp et al. (11)	2007	40 healthy children	ICC	Intra-raters	Inter-raters	1. Cerebral peduncle
					1. CP	1. CP	2. Posterior limb of internal capsule
					FA - ICC: 0.96	FA - ICC: 0.90	
					ADC - ICC: 0.98	ADC - ICC: 0.92	3. Superior corona radiata
					2. PLIC	2. PLIC	
					FA - ICC: 0.97	FA - ICC: 0.91	
					ADC - ICC: 0.99	ADC - ICC: 0.98	
					3. SCR	3. SCR	
					FA - ICC: 0.99	FA - ICC: 0.97	
					ADC - ICC: 1.00	ADC - ICC: 0.99	
						Inter-scans	
						1. CP	
						FA - ICC: 0.81	
						ADC - ICC: 0.86	
						2. PLIC	
	FA - ICC: 0.66						
	ADC - ICC: 0.82						
	3. SCR						
	FA - ICC: 0.79						
	ADC - ICC: 0.93						
	Borich et al. (14)	2012	10 chronic stroke patients 10 healthy adults	ICC	Intra-raters FA - ICC: 0.94	Inter-raters FA - ICC: 0.71	Posterior limb of internal capsule
	Hakulinen et al. (15)	2012	30 healthy adults	ICC	Circular ROI		1. Pons
					1. Pons		1. Pons
					FA - ICC: 0.74		2. Cerebral peduncle
					ADC - ICC: 0.83		3. Posterior limb of internal capsule
					2. CP		
					FA - ICC: 0.74		4. Corona radiate
					ADC - ICC: 0.19		5. Centrum semiovale
					3. PLIC		
					FA - ICC: 0.90		
					ADC - ICC: 0.76		
					4. CR		
					FA - ICC: 0.84		
					ADC - ICC: 0.76		
					Freehand ROI		
					1. Pons		
FA - ICC: 0.63							
ADC - ICC: 0.70							

continued

Authors	Publication year	Subjects no.	Statistical analysis	Repeatability	Reproducibility	Region of interest
				2. CP		
				FA - ICC: 0.74		
				ADC - ICC: 0.29		
				3. PLIC		
				FA - ICC: 0.66		
				ADC - ICC: 0.78		
				4. CR		
				FA - ICC: 0.86		
				ADC - ICC: 0.86		
Acheson et al. (22)	2017	12 healthy adults 89 children and adolescents	ICC		Inter-raters 1. IC FA - ICC: 0.72 2. CR FA - ICC: 0.87	1. Posterior limb of internal capsule 2. Corona radiate
DTT Stieltjes et al. (10)	2001	6 healthy adults	Kappa	FA threshold 0.25 - k: 1.00 0.35 - k: 1.00	FA threshold 0.25 - k: 0.92 0.35 - k: 0.97	
Wakana et al. (12)	2007	10 healthy adults	Kappa	AND - k : 0.94 CUT - k : 0.95	AND - k : 0.80 CUT - k : 0.80	
Danielian et al. (13)	2010	10 healthy adults	ICC	Intra-raters FA - ICC: 0.99 MD - ICC: 0.99 TV - ICC: 0.93	Inter-raters FA - ICC: 0.99 MD - ICC: 0.99 TV - ICC: 0.86	
					Inter-scans FA - ICC: 0.95 MD - ICC: 0.83 TV - ICC: 0.82	
Lee et al. (16)	2012	12 patients with HI-BI 12 healthy adults	ICC	Intra-raters FA, ADC, and TV - ICC: 0.92 - 0.99	Inter-scans FA, ADC, and TV - ICC: 0.85 - 0.99	
Kristo et al. (18)	2013	17 healthy subjects	Coefficients of variation (CV)		Inter-scans FA - CV: 2.08% MD - CV: 2.32% TV - CV: 12.62%	
Jang et al. (17)	2013	54 stroke patient	ICC	Intra-raters FA, ADC, and TV - ICC: 0.88 - 0.99	Inter-raters FA, ADC, and TV - ICC: 0.87 - 0.99	
Kwon et al. (19)	2014	76 healthy subjects	chi- squared test		Turning angles 45°: 98.7% 60°: 98.7% 75°: 98.0%	

continued

Authors	Publication year	Subjects no.	Statistical analysis	Repeatability	Reproducibility	Region of interest
Paldino et al. (20)	2014	30 pediatric patients	ICC		Inter-raters FA - ICC: 0.99 MD - ICC: 0.97	
Rijken et al. (21)	2015	7 healthy subjects 58 patients with craniosynostosis syndromes	ICC	Intra-raters FA, ADC, and TV - ICC: 0.93	Inter-raters FA, ADC, and TV - ICC: 0.94	
Ius et al. (23)	2017	37 patients with low-grade glioma	ICC		Inter-raters TV - ICC: 0.99	
Rosenstock et al. (24)	2017	30 patients with high grade glioma	ICC		Distance between tumor and CST - ICC: 0.99 FA - ICC: 0.94 ADC - ICC: 0.96 TV - ICC: 0.90	

ADC = apparent diffusion coefficient; DTI = diffusion tensor imaging; DTT = diffusion tensor tractography; FA = fractional anisotropy; ICC = intra-class correlation coefficient; MD = mean diffusivity; TV = tract volume

21, 23, 24). In 2001, Stieltjes et al. (10) reported "almost perfect" repeatability and reproducibility of DTT for the CST in six normal subjects using the Kappa value, which were determined for spatially superimposed images (k-value, 0.92 to 1.00). In 2007, Wakana et al. (12) demonstrated "substantial" repeatability and reproducibility of the CST using pair-wise combinations via the Kappa value in ten normal subjects (k-value, 0.79 to 0.80). In 2010, Danielian et al. (13) measured the DTT parameters (the FA, mean diffusivity [MD], and tract volume [TV]) of the CST, and obtained excellent repeatability and reproducibility using the ICC (intra-rater ICC, 0.93 to 0.99; inter-raters ICC, 0.86 to 0.99; inter-scans ICC, 0.82 to 0.95). In 2012, Lee et al. (16) reported excellent repeatability and reproducibility of the DTT parameters (the FA, ADC, and TV) of the CST in 12 patients with hypoxic-ischemic brain injury (intra-rater ICC, 0.92 to 0.99; inter-raters ICC, 0.85 to 0.99). In 2013, Kristo et al. (18) investigated the reproducibility of measurements of the DTT parameters (the FA, MD, and TV) in the CST for twice-scanned data in 17 normal subjects and found low architectural and microstructural variability in the DTT parameters (the FA and MD) using the coefficients of variation (CV, 0.87 to 3.37). During the same year, Jang et al. (17) reported the excellent repeatability and reproducibility of DTT using DTT parameters (FA, ADC, and TV) of the reconstructed CST in 54 stroke patients using the ICC (intra-rater ICC, 0.88 to 0.99; inter-raters ICC, 0.87 to 0.99). In 2014, Kwon et al. (19) examined the reproducibility via the

incidence of transcallosal motor fibers using a chi-squared test in the reconstructed CST for 76 normal subjects and found no significant difference between the three tract-turning angles (45°, 60°, and 75°). They reported excellent reproducibility of the reconstruction rate, at 98.0 to 98.7 percent (19). In 2015, Rijken et al. (21) reported excellent repeatability and reproducibility using DTT parameters (the FA, ADC, and TV) of the CST in seven normal subjects and 58 patients with craniosynostosis syndromes using the ICC (intra-rater ICC, 0.93; inter-raters ICC, 0.94). Recently, Ius et al. (23) demonstrated excellent reproducibility in the TV value for the CST in 37 patients with low-grade glioma using the ICC (inter-rater ICC, 0.99). During the same year, Rosenstock et al. (24) measured the DTT parameters (the FA, ADC, and TV) and the closest distance between the tumor and the CST in 30 patients with high-grade gliomas, and demonstrated excellent reproducibility via the ICC (inter-raters ICC, 0.90 to 0.99).

## DISCUSSION and CONCLUSION

This paper reviewed 15 DTI studies reporting the repeatability and reproducibility of the CST. A summary of the results follows. Measurements of the CST using the ROI method on 2-dimensional DTI generally showed excellent repeatability and reproducibility of more than 0.8 with high variability (0.29 to 1.00) between studies (11, 14,

15, 22). In contrast, measurements of the CST using the 3-dimensional DTT method revealed excellent repeatability and reproducibility of more than 0.9 with low variability (repeatability, 0.88 to 1.00; reproducibility, 0.82 to 0.99) between studies (10, 12, 13, 16-21, 23, 24). As a result, both methods for measuring the CST appeared to be reliable but the 3-dimensional DTT method was more reliable than the 2-dimensional DTI method (10-24).

The above results can be attributed to several factors. Accurate placing of the ROIs on the 2-dimensional DTI image repeatedly is difficult, both in intra-analyzer and inter-analyzer tests. In addition, the anatomical location of the CST varies between individual subjects (26, 27) (Fig. 1a). In contrast, in 3-dimensional DTT for the CST, analysis of the CST using the combined conditions of multiple ROIs on the isolated CST areas with known analysis conditions (FA and angle change between pixels) can reconstruct the CST more objectively and accurately with less subjective error than the 2-dimensional DTI method (10, 12, 13, 16-21, 23-25) (Fig. 1b).

In conclusion, both the 2- and 3-dimensional DTI methods appeared to be reliable for measuring the CST. On the other hand, the 3-dimensional DTT method appeared to be more reliable than the 2-dimensional DTI method. However, repeatability and reproducibility were affected by scanning conditions, including gradient directions and the number of excitations (28). Further studies on the optimal conditions for the number and anatomical locations of ROIs are needed to achieve better repeatability and reproducibility of the CST measurements.

### Acknowledgments

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2016R1A6A3A11933121).

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