

## research papers

# No Association Between Structural Properties of Corpus Callosum and Handedness: Evidence from the Constrained Spherical Deconvolution Approach

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**Abstract.** Handedness is the most prominent trait of functional asymmetry in humans, associated with lateralized cognitive functions and considered in relation to mental disorders. However, the neuroanatomical correlates of handedness are still unclear. It has been hypothesized that the structural properties of sub-regions of the corpus callosum (CC) are linked to handedness. Nevertheless, tractography studies of the relation between directly measured structural properties of CC sub-regions and handedness are lacking. The Constrained Spherical Deconvolution (CSD) approach enables full reconstruction of the sub-regions of the CC. The current study aimed to investigate the relation between the structural properties of the CC, such as volume and the CSD metric, referred to as hindrance modulated orientational anisotropy (HMOA), and handedness. Handedness was considered in two dimensions: direction (right-handed, ambidextrous, left-handed) and degree (the absolute values of Handedness quotient). We found no association between 1) volume or HMOA as a proxy of microstructural properties, namely the axonal diameter and fiber dispersion, of each sub-region and 2) either the direction or the degree of handedness. These findings suggest the absence of a direct relation between sub-regions of the CC and handedness, demonstrating the necessity of future tractography studies.

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**Keywords:** functional asymmetry, handedness, corpus callosum, tractography, constrained spherical deconvolution

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## Introduction

Handedness is the most studied example of functional asymmetry in human beings (Marcori & Okazaki, 2019; McManus, 2019). The lateralized cognitive functions, such as language (Somers et al., 2015) and spatial attention (O'Regan & Serrien, 2018), are related to handedness. Moreover, bipolar depression and schizophrenia are more represented in non-right-handers (Ravichandran et al., 2017). It has been shown that about 90% of humans are right-handed, the remaining 10% being left-handed or ambidextrous (Papadatou-Pastou et al., 2020). Genetic and epigenetic regulations were proposed to affect the development of handedness (de Kovel & Francks, 2019; Ocklenburg et al., 2017). Nevertheless, the manifestation of these factors at the level of brain anatomy is still unclear (Ocklenburg et al., 2020).

Besides grey matter asymmetries, the interhemispheric interaction, which is mainly conveyed through the corpus callosum (CC), has been suggested to have an association with handedness (Budisavljevic, Castiello, & Begliomini, 2020; Ocklenburg et al., 2016). At the functional level, this interaction is explained by two models. The excitatory model is represented by the activation of the hemispheres by each other through fibers of the CC, which mostly rely on the excitatory neurotransmitter, glutamate (Bloom & Hynd, 2005). According to the inhibitory model, the dominant hemisphere for handedness suppresses the other through the inhibitory interneurons of the CC (van der Knaap & van der Ham, 2011). In various studies, evidence is presented for the excitatory model (Luders et al., 2010) and the inhibitory model (Josse, Seghier, Kherif, & Proce, 2008). Given the distinct sub-regions of the CC, which contain the fibers with different properties (Aboitiz, Scheibel, Fisher, & Zaidel, 1992), both models might appear (Ocklenburg et al., 2016).

The majority of handedness studies have focused on the midsagittal surface in structural images to estimate the properties of the CC sub-regions (Ocklenburg et al., 2016). Nevertheless, using structural images does not reflect the properties of the CC fibers, in contrast to tractography (Basser & Jones, 2002). Currently, there are four tractography studies based on diffusion-tensor imaging (DTI) that investigated the relation between microstructural properties, but not the volume of the sub-regions, and handedness (Budisavljevic et al., 2020). The tractography studies have shown the fractional anisotropy (FA) metric of DTI, as a microstructural property of the sub-regions, to be larger in left-handers (McKay, Iwabuchi, Häberling, Corballis, & Kirk, 2017; Westerhausen et al., 2003; Westerhausen et al., 2004, 2006). However, even DTI has limitations linked to the reconstruction of sub-regions of the CC in areas with multiple fiber crossings (Caeyenberghs & Leemans, 2014). Imperfect reconstruction of fiber crossings causes the DTI metrics to indirectly represent the microstructural properties for most sub-regions (Friedrich et al., 2020; Vos, Jones, Jeurissen, Viergever, & Leemans, 2012; Wheeler-Kingshott & Cercignani, 2009). Constrained Spherical Deconvolution (CSD) overcomes this limitation of DTI by enabling full reconstruction of the fibers of the sub-regions, as shown in several studies (Dell'Acqua et al., 2010).

The aim of the present study was to estimate the association between structural properties of the CC and handedness. CSD allows us to investigate this association reliably, because the lateral motor fibers of the sub-regions mostly projecting into the primary motor cortices can be reconstructed (Steventon, Trueman, Rosser, & Jones, 2016; Wahl et al., 2007). It is the first tractography study to be focused on the volume of the sub-regions in relation to handedness and to be carried out with CSD. In addition, the CSD metric, referred to as hindrance modulated orientational anisotropy (HMOA), was used as a microstructural property instead of the DTI metrics. HMOA represents the axonal diameter and fiber dispersion based on CSD, an approach which is sensitive to the number of distinct fibers (Dell'Acqua et al., 2013). To obtain more diverse values of handedness, participants included an equal number of right-handed and left-handed individuals, and a group of ambidextrous people. We examined the relation of the CC to the direction of handedness (Luders, 2003), comparing the structural properties of the sub-regions among groups of right-handed, ambidextrous, and left-handed participants. Besides the direction of handedness, we also considered the relation of the sub-regions to the degree of handedness (Corballis, 2009).

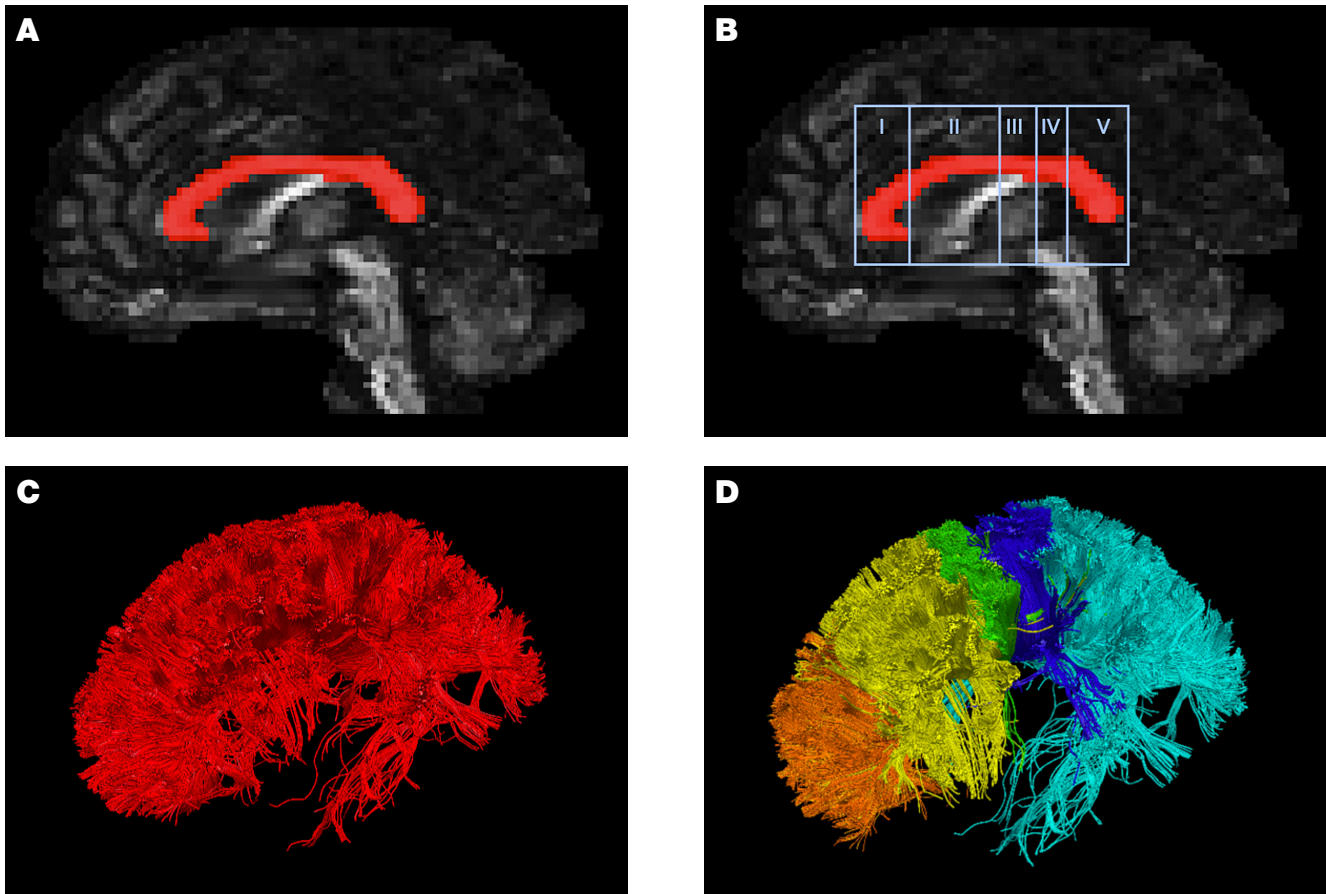
## Method

### Participants

Fifty neurologically healthy individuals with no history of psychiatric or neurological diseases participated in the study (15 males, 25 females; mean age = 24.7,  $SD=5.1$ , range = 18 to 37 years). The handedness quotient (HQ) of each participant was estimated using the Edinburgh inventory (Oldfield, 1971). Twenty participants with scores from +45 to +100 were classified as right-handed (7 males, 13 females; mean age = 24.9,  $SD=5.7$ , range = 18 to 37 years), 10 participants with scores from -45 to +45 were classified as ambidextrous (3 males, 7 females; mean age = 23.2,  $SD=3.1$ , range = 19 to 27 years), and 20 participants with scores from -100 to -45 were classified as left-handed (6 males, 14 females; mean age = 23.8,  $SD=4.0$ , range = 19 to 30 years). The study was conducted in accordance with the Declaration of Helsinki and all participants gave written informed consent to take part in the study.

### Magnetic Resonance Imaging

MRI data acquisition was performed using a Siemens 3T Magnetom Verio MRI scanner. Anatomical T1 images were obtained using a 3D MP-RAGE sequence with  $TR=1900$  ms;  $TE=2.2$  ms; flip angle =  $9^\circ$ . Each T1-image contained 176 axial slices (no gap) with the  $FOV=320 \times 320$  mm<sup>2</sup> and spatial resolution =  $1 \times 1 \times 1$  mm<sup>3</sup>. Diffusion-weighted images (DWIs) were performed using a single-shot spin echo EPI sequence with  $TR=13700$  ms;  $TE=101$  ms; 65 axial slices;  $FOV=240 \times 240$  mm<sup>2</sup>; spatial resolution =  $2 \times 2 \times 2$  mm<sup>3</sup>;  $b$ -value = 1500 s/mm<sup>2</sup>. Sixty four diffusion directions and one image with  $b=0$  s/mm<sup>2</sup> were collected in the AP phase encoding direction, twice for 47 participants and once for 3 participants. An additional field map for the DWIs was acquired using a dual-echo GRE sequence with  $TR=698$  ms;  $TE_1=4.92$  ms;  $TE_2=7.38$  ms; 65 axial slices;



**Figure 1.** CSD reconstruction of the CC and the division into sub-regions. (A) An inclusion ROI on the midsagittal surface on the FA map. (B) The schematic division of the CC into five sub-regions according to Hofer's DTI scheme. (C) Sagittal view of the CSD reconstruction of the CC as a unitary body. (D) Sagittal view of the reconstructed CC-I, projecting into the prefrontal area (orange); CC-II — premotor supplementary motor areas (yellow); CC-III — primary motor area (green); CC-IV — primary sensory area (dark blue); CC-V — parietal, temporal, and occipital lobes (light blue).

FOV =  $240 \times 240$  mm<sup>2</sup>; spatial resolution =  $2 \times 2 \times 2$  mm<sup>3</sup>. For 47 participants, two DWI sequences with AP phase encoding direction were merged to increase signal-to-noise ratio. DWIs were corrected for the eddy current and subject motion distortions by aligning to the image with  $b=0$  s/mm<sup>2</sup> as well as for the EPI distortion by applying the field map for each participant in the FMRIB Software Library (<http://www.fmrib.ox.ac.uk/fsl/>). The diffusion tensor was fitted at each voxel in the ExploreDTI software package (<http://www.exploredti.com/>). CSD reconstruction based on the damped Richardson-Lucy algorithm was performed with the fiber response =  $1.5 \times 10^{-3}$  mm<sup>2</sup>/s<sup>-1</sup>, 400 iterations, a maximum deflection angle =  $45^\circ$  with uniform seed point resolution = 1 mm<sup>3</sup> and step size = 1 mm in the StarTrack software package (<https://www.mr-startrack.com/>). The CC was manually reconstructed for each participant in native space using the TrackVis software package (<http://trackvis.org/>). An inclusion region of interest (ROI) was placed in the midsagittal slice, while exclusion ROIs were used to remove artifactual trajectories of the CC, such as fiber loops. The CC was divided according to Hofer's DTI scheme, which is obtained by applying tractography, in contrast to the other schemes using structural images (Hofer & Frahm, 2006). The sub-regions were identified as CC-I whose fibers project into the prefrontal area; CC-II — premotor and supplementary motor areas; CC-III — primary motor area; CC-IV — primary sensory area; CC-V — parietal, temporal, and occipital lobes (Hofer

& Frahm, 2006; Josse et al., 2008). Figure 1 presents the CSD reconstruction of the CC and the sub-regions.

The volumes of the sub-regions were extracted and normalized by the division by the total volume of the grey and white matter obtained from the T1 image for each participant. HMOA was obtained for each CC sub-region for each participant in the StarTrack software package. Table 1 presents the participants' volumes and HMOA of each sub-region.

### Statistical Analysis

Handedness was considered in two dimensions: direction and degree. A one-way ANOVA was used to examine differences in the normalized volumes of the sub-regions as well as HMOA among groups that differed in handedness. In addition, Bayes factors (a Bayesian one-way ANOVA) were calculated using the *bayesFactor* MATLAB Toolbox (<https://github.com/klabhub/bayesFactor/>) to compare differences in the normalized volume and HMOA among right-handers, ambidextrous individuals, and left-handers for each sub-region. The degree of handedness of each participant was represented as the absolute value of the HQ. We built general linear models using the Bonferroni correction ( $\alpha = .017$ ) to evaluate the relation between the absolute values of the HQ and the normalized volume and HMOA as predictors. All statistical analyses were performed using MATLAB R2014b (MathWorks; Natick, MA, USA).

**Table 1.** Means and Standard Deviations (SD) of the Volumes (cm<sup>3</sup>) and HMOA for Each Sub-Region

Sub-Region	Right-Handers		Ambidexters		Left-Handers	
	Volume, Mean (SD)	HMOA, Mean (SD)	Volume, Mean (SD)	HMOA, Mean (SD)	Volume, Mean (SD)	HMOA, Mean (SD)
CC-I	51.73 (17.33)	$2.10 \times 10^{-2}$ ( $0.58 \times 10^{-2}$ )	58.21 (13.03)	$2.27 \times 10^{-2}$ ( $0.45 \times 10^{-2}$ )	54.79 (16.34)	$2.17 \times 10^{-2}$ ( $0.39 \times 10^{-2}$ )
CC-II	67.69 (20.70)	$2.96 \times 10^{-2}$ ( $0.35 \times 10^{-2}$ )	83.28 (21.23)	$2.95 \times 10^{-2}$ ( $0.26 \times 10^{-2}$ )	69.75 (23.06)	$2.98 \times 10^{-2}$ ( $0.33 \times 10^{-2}$ )
CC-III	28.63 (8.60)	$2.57 \times 10^{-2}$ ( $0.40 \times 10^{-2}$ )	31.16 (9.79)	$2.75 \times 10^{-2}$ ( $0.46 \times 10^{-2}$ )	28.24 (11.78)	$2.73 \times 10^{-2}$ ( $0.30 \times 10^{-2}$ )
CC-IV	23.10 (9.98)	$2.63 \times 10^{-2}$ ( $0.37 \times 10^{-2}$ )	22.73 (6.51)	$2.80 \times 10^{-2}$ ( $0.47 \times 10^{-2}$ )	24.92 (14.76)	$2.84 \times 10^{-2}$ ( $0.37 \times 10^{-2}$ )
CC-V	108.59 (35.89)	$3.56 \times 10^{-2}$ ( $0.28 \times 10^{-2}$ )	131.67 (20.26)	$3.53 \times 10^{-2}$ ( $0.34 \times 10^{-2}$ )	97.6 (29.37)	$3.48 \times 10^{-2}$ ( $0.35 \times 10^{-2}$ )

Note. HMOA = hindrance modulated orientational anisotropy.

## Results

Table 2 shows the results of a one-way ANOVA and Bayes factors for each sub-region. The one-way ANOVA revealed no significant difference among the right-handed, ambidextrous, and left-handed participants in the normalized volume and HMOA for each sub-region. In addition, the Bayes factors (a Bayesian one-way ANOVA) showed strong evidence in favor of  $H_0$  ( $BF_{01} > 3$ ), thus indicating no significant difference in the normalized volumes among the right-handed, ambidextrous, and left-handed participants for each sub-region. The Bayes factors also suggested strong evidence in favor of  $H_0$  ( $BF_{01} > 3$ ), thus indicating no significant difference for the CC-I, CC-II, CC-III, CC-V; there was no clear evidence of differences ( $BF_{01} = 2.2$ ) for CC-IV in HMOA.

Table 3 shows the results of the general linear model for each sub-region. A general liner model with the Bonferroni correction ( $\alpha = .017$ ) revealed that the HQ was not related to the normalized volume and HMOA for each sub-region. Thus, there is no significant association between the degree of handedness and the normalized volume and HMOA for each sub-region.

## Discussion

The aim of the current study was to investigate the relation between the structural properties of five sub-regions of the CC and the direction and degree of handedness. We considered the sub-regions according to Hofer's DTI

scheme, instead of referring to the CC as a unitary body. This approach was motivated by the fact that the sub-regions have differential microstructural properties, which can be associated with either their excitatory or inhibitory role in relation to handedness (Bloom & Hynd, 2005; Aboitiz et al., 1992). Additionally, ours was the first tractography study that explored the link between volume and HMOA as a microstructural property, and handedness.

We found no significant association between the volume of each reconstructed CC sub-region and the direction of handedness. These findings are in line with Luders (2003), but differ from the results of Cowell and Gurd (2018) and Denenberg, Kertesz, and Cowell (1991) who detected a larger CC size in the isthmus region in left-handers and non-consistent right-handers. The distinctions might be explained by different classification schemes used to divide the CC. Previous studies divided the mid-sagittal surface of the CC using Denenberg's scheme obtained on the structural image, while in the current tractography study Hofer's DTI scheme was applied. However, we did not replicate the result of Josse et al. (2008), the study with the same classification scheme but with structural images that showed a larger CC-II for right-handers, CC-II being the sub-region that connects the premotor and supplementary motor areas. Nevertheless, that study did not detect a difference in CC-III, the sub-region that connects the primary motor areas.

Besides direction we considered the degree of handedness, based on research by Corballis (2009). However, we found no associations between the volume of each sub-region and that metric. This result contrasts with the large

**Table 2. Results of a One-Way ANOVA and Bayes Factors for Each Sub-Region**

Sub-Region	Volume			HMOA		
	$F(2, 47)$	$p$	$BF_{01}$	$F(2, 47)$	$p$	$BF_{01}$
CC-I	0.46	.63	6.6	0.35	.71	7.0
CC-II	1.49	.23	8.1	0.02	.98	9.0
CC-III	0.19	.83	9.0	1.12	.33	3.8
CC-IV	0.23	.79	7.9	1.57	.22	2.2
CC-V	3.09	.06	6.2	0.33	.72	6.5

Note. HMOA = hindrance modulated orientational anisotropy;  
 $BF_{01}$  = Bayes factor, indicates the ratio of the likelihood of  $H_0$  compared to  $H_1$ .

**Table 3. Results of Linear General Model for Each Sub-Region**

Predictor	(Intercept)	Volume	HMOA	Predictor	(Intercept)	Volume	HMOA		
<b>CC-I</b>				<b>CC-IV</b>					
$p$	<.001	.21	.41	$p$	.06	.89	.91		
95% CI	UL	159.50	327.60	1041.60	95% CI	UL	123.72	1275.60	2263.90
	LL	45.54	-1534.60	-2556.30		LL	-1.32	-1109.10	-2018.70
SE	29.07	475.06	917.85	SE	31.90	608.34	1092.50		
Estimate	102.52	-603.52	-757.34	Estimate	61.20	83.29	122.63		
<b>CC-II</b>				<b>CC-V</b>					
$p$	.10	.11	.62	$p$	.07	.15	.89		
95% CI	UL	152.25	110.86	3198.40	95% CI	UL	192.55	103.19	2438.60
	LL	-13.14	1154.30	-1887.10		LL	-5.88	-726.33	-2802.10
SE	42.19	322.75	1297.30	SE	50.62	211.61	1336.90		
Estimate	69.56	-521.73	655.65	Estimate	93.33	-311.57	-181.76		
<b>CC-III</b>									
$p$	.04	.83	.86						
95% CI	UL	144.65	1298.20	2058.00					
	LL	3.63	-1624.90	-2462.50					
SE	35.97	745.69	1153.20						
Estimate	74.14	-163.31	-202.26						

Note. HMOA = hindrance modulated orientational anisotropy;  
 $SE$  = standard error;  $CI$  = confidence interval;  $LL$  = lower limit;  $UL$  = upper limit.

study that revealed a negative correlation between CC size of the midsagittal surface in midbody and the degree of handedness (Luders et al., 2010). The number of right-handers in that study was much higher than the number of left-handers, however, which led to bias in the degree of handedness. For this reason, we balanced our groups of right- and left-handed participants, and included ambidextrous participants to increase diversity of the degree of handedness.

It should be noted that all previous studies that investigated the volume of the sub-regions were based on the midsagittal surface of the CC (Budisavljevic et al., 2020). This makes our tractography results based on CSD more reliable compared to the previous studies. We revealed no relation between the volume of the sub-regions and either the direction or degree of handedness. The current tractography study is the first to consider the volume of the sub-regions in relation to handedness, while previous tractography studies examined the microstructural properties of the sub-regions in the relation to handedness. In addition to volume, we estimated the CSD metric HMOA, which reflects the axonal diameter and fiber dispersion (Dell'Acqua et al., 2013). We found no association between the HMOA of each sub-region and the degree of handedness. No difference in HMOA among right-handers, ambidexters, and left-handers was represented with strong evidence for CC-I, CC-II, CC-III, CC-V. We did not reveal clear evidence of a difference in HMOA for CC-IV, which projects into the primary sensory area and does not contain the lateral motor fibers. Thus, future studies should investigate the relation between the properties of CC-IV and the direction of handedness. Nevertheless, the results are inconsistent with the tractography studies that reported larger values of FA in left-handers (McKay et al., 2017; Westerhausen et al., 2003; Westerhausen et al., 2004, 2006). However, the DTI metrics are not interpreted as microstructural properties because of the DTI limitations which are overcome by CSD (Dell'Acqua & Tournier, 2019). For this reason, we estimated HMOA in this study.

The current study had a few limitations. HQ was estimated using questionnaires, without the direct measurement of hand preference. Also, despite the balanced groups, the sample size of the present study was not very large compared to other studies (Ocklenburg et al., 2020). These factors might influence the results. Finally, despite the advantage of CSD, there are no studies to assess the validity of HMOA on large clinical and normal populations. Thus, the usage of HMOA to explore the microstructural properties is not experimentally confirmed. To our knowledge, currently there is no direct tractography metric of the microstructural properties. Further studies should address the direct link between the microstructural properties of fibers, and handedness.

To conclude, ours was the first tractography study with CSD that investigated the association of the volume and HMOA of CC sub-regions to handedness. Our results in a representative set of participants with different handedness did not demonstrate an association between the volume of the CC sub-regions and either the direction or the degree of handedness. Also, we revealed no link between HMOA as a proxy of microstructural properties of the CC fibers and the degree of handedness. A difference

in HMOA among right-handers, ambidexters, and left-handers for all of the sub-regions was not found, except for CC-IV which projects into the primary sensory area. Further tractography studies are needed to replicate no relation between the microstructural properties of the CC and handedness.

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## ■ экспериментальные сообщения ■

# Отсутствие связи между структурными свойствами мозолистого тела и мануальной асимметрией: данные трактографии, основанной на ограниченной сферической деконволюции

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**Аннотация.** Мануальная асимметрия является самым изучаемым проявлением функциональной асимметрии человека, связанным с латерализацией когнитивных функций и рассматриваемым для понимания психических заболеваний. Однако анатомические корреляты мануальной асимметрии до сих пор неизвестны. Существует гипотеза о связи структурных свойств сегментов мозолистого тела (МТ) и мануальной асимметрии, однако трактографические исследования, демонстрирующие эту связь напрямую, не представлены. Метод ограниченной сферической деконволюции (ОСД) позволяет полностью реконструировать сегменты МТ. Настоящее исследование было направлено на изучение связи структурных свойств МТ, таких как объема и показателя ОСД — сбалансированной шумом ориентационной анизотропии (СШОА), с мануальной асимметрией. Рассматривались две метрики мануальной асимметрии: направление (группы правой, амбидекстров, левой) и степень (абсолютные значения коэффициента измеренной мануальной асимметрии). Мы не обнаружили связи между объемом или СШОА как показателем микроструктурных свойств, а именно диаметра аксонов и направления нервных волокон каждого сегмента МТ, и направлением или степенью мануальной асимметрии. Эти результаты свидетельствуют об отсутствии прямой связи между структурными свойствами сегментов МТ и мануальной асимметрией, демонстрируя необходимость будущих трактографических исследований.

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**Ключевые слова:** функциональная асимметрия, мануальная асимметрия, мозолистое тело, трактография, ограниченная сферическая деконволюция

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