Impact of corpus callosum integrity on functional interhemispheric connectivity and cognition in healthy subjects

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Abstract

Background and purpose: To examine the corpus callosum's (CC) integrity in terms of fractional anisotropy (FA) and how it affects resting-state hemispheric connectivity (rs-IHC) and cognitive function in healthy individuals.

Methods: Sixty-eight healthy individuals were recruited for the study. The global FA (gFA) and FA values of each CC tract (forceps minor, body, tapetum, and forceps major) were evaluated using diffusion-weighted imaging (DWI) sequences. The homotopic functional connectivity technique was used to quantify the effects of FA in the CC tracts on bilateral functional connectivity, including the confounding effect of gFA. Brain regions with higher or lower rs-IHC were identified using the threshold-free cluster enhancement family-wise error-corrected p-value of 0.05. The null hypothesis was rejected if the p-value was ≤ 0.05 for the nonparametric partial correlation technique.

Results: Several clusters of increased rs-IHC were identified in relation to the FA of individual CC tracts, each with a unique topographic distribution and extension. Only forceps minor FA values correlated with cognitive scores.

Conclusions: The integrity of CC influences rs-IHC differently in healthy subjects. Specifically, forceps minor anisotropy impacts rs-IHC and cognition more than other CC tracts do.

List of abbreviations

- 3DT1-MP2RAGE = 3D T1-weighted Magnetization Prepared 2 Rapid Acquisition Gradient Echoes

- BOLD = Blood Oxygen Level Dependent

- CC = Corpus Callosum

- DTI = Diffusion Tensor Imaging

- DWI = Diffusion Weighted Imaging

- FA = Fractional Anisotropy

- FLAIR = FLuid-Attenuated Inversion Recovery

- fMRI = functional MRI

- GE-SWI = Gradient Echo Susceptibility-Weighted Imaging

- gFA = global Fractional Anisotropy

- GQI = Generalized Q-sampling Imaging

- IHC = Interhemispheric Connectivity

- ICBM152 = International Consortium for Brain Mapping 152

- HoFC = Homotopic Functional Connectivity

- LEMON = Leipzig Study for Mind-Body-Emotion Interactions

- LPS-2 = Leistungsprüfsystem 2

- LPS-2-S = Leistungsprüfsystem 2 score

- MP2RAGE = Magnetization Prepared 2 Rapid Acquisition

- MRI = Magnetic Resonance Imaging

- p = p-value

- p-FWE = Family Wise corrected p-value

- PFC = Pre-Frontal cortex

- ROI = Region Of Interest

- rs-IHC = resting-state Interhemispheric Connectivity

- rs-fMRI = resting state functional Magnetic Resonance Imaging

- T2*-EPI = T2*-weighted gradient-echo Echo Planar Imaging

- TAP = Test of Attentional Performance

- TAP-A = Test of Attentional Performance - alertness

- TAP-A-NS-S = Test of Attentional Performance - alertness (without signal) score

- TAP-A-S-S = Test of Attentional Performance - alertness (with signal) score

- TAP-I = Test of Attentional Performance - Incompatibility

- TAP-I-CS-E = Test of Attentional Performance - Incompatibility (compatible signals) errors

- TAP-I-CS-S = Test of Attentional Performance - Incompatibility (compatible signals) score

- TAP-I-IS-E = Test of Attentional Performance - Incompatibility (incompatible stimuli) errors

- TAP-I-IS-S = Test of Attentional Performance - Incompatibility (incompatible stimuli) score

- TAP-I-WS-E = Test of Attentional Performance - Incompatibility (whole stimuli) errors

- TAP-I-WS-S = Test of Attentional Performance - Incompatibility (whole stimuli) score

- TAP-WM = Test of Attentional Performance - Working Memory

- TAP-WM-E = Test of Attentional Performance - Working Memory errors

- TAP-WM-MM = Test of Attentional Performance - Working Memory missed matches

- TAP-WM-S = Test of Attentional Performance - Working Memory score

- TFCE= Threshold Free Cluster Enhancement

- TMT = Trail Making Test

- TMT-A = Trail Making Test A

- TMT-A-E = Trail Making Test A errors

- TMT-A-S = Trail Making Test A score

- TMT-B = Trail Making Test B

- TMT-B-E = Trail Making Test B errors

- TMT-B-S = Trail Making Test B score

- W = W-value

- WM = White Matter

1. **Introduction**

Although the integrative level of the corpus callosum (CC) has been extensively studied for its role as a crucial interhemispheric relay in experimental animals [De León Reyes et al., 2020] and humans [Gazzaniga, 2005], the dynamic aspects of these connections are still unknown. As the CC connects numerous distinct frontal and parietal regions [Swanson et al., 2017], it has been deemed worthwhile to investigate the effect of its microstructural integrity on specific interconnected brain regions. Interhemispheric connectivity (IHC), measured by resting-state functional magnetic resonance imaging (rs-fMRI), is associated with cognitive processing, creative thinking, and speech perception [Gotts et al., 2013; Chen et al., 2019; Jin et al., 2020].

There is accumulating evidence that the CC plays a key role in IHC [Bloom & Hind, 2005; Hofer & Frahm, 2006; Yuan et al., 2020] via axonal fibers that connect homologous cortical areas, transferring and integrating signals from both cerebral hemispheres encompassing sensory, motor, and high-level cognitive functions [Goldstein et al., 2022]. *Roland et al.* [Roland et al., 2017] examined the role of CC in IHC by analyzing the changes in resting-state IHC (rs-IHC) in patients with refractory epilepsy following a partial (preserved posterior third of CC) or complete callosotomy. They found that the callosotomy significantly reduced IHC, with a greater effect in the multimodal associative regions of the frontal and parietal lobes; these effects varied depending on the surgical technique used [Roland et al., 2017]. In particular, a partial callosotomy had minimal effects on the visual networks of patients [Roland et al., 2017].

Several studies have demonstrated a positive correlation between white matter (WM) integrity and cognitive performance [Madden et al., 2009; Roberts et al., 2013; Wei et al., 2021]. Global fractional anisotropy (gFA), a quantitative structural marker of WM myelination and integrity using diffusion tensor imaging (DTI), has been shown to influence neural activity and networking in the limbic system [Porcu et al., 2021a]. In a recent study [Yuan et al., 2020], patients with migraines without auras had lower FA values of the genu and splenium of the CC and decreased IHC in the anterior cingulate cortex of the ACC compared to healthy subjects.

Therefore, it is plausible to hypothesize that variations in the microstructural properties of the CC may influence the IHC in healthy subjects and that the effects on the IHC and cognitive functions may vary depending on the segment of the CC involved. To test this hypothesis, an exploratory study was designed to examine the influence of the FA of the WM fiber tracts that constitute CC (forceps minor, body, tapetum, and forceps major [deMeloMussi et al., 2019]) corrected for gFA (used as a marker of WM integrity [Porcu et al., 2021a]) on i) the rs-IHC analyzed with the homotopic functional connectivity (HoFC) technique [Jin et al., 2020], and ii) the cognitive performance scores for logical deductive thinking, attentional processing, and cognitive flexibility. A graphical scheme of the research design is shown in Figure 1.

The study population and data were extracted from the "Leipzig Study for Mind-Body-Emotion Interactions" (LEMON) dataset [Babayan et al., 2019]. This publicly available dataset consists of a large collection of physiological, psychological, and neuroimaging measures from a population of deidentified 227 healthy adults, and it has been released to encourage the study of the relationships between brain and body [Babayan et al., 2019]. The reader is referred to the LEMON paper [Babayan et al., 2019] for additional information regarding the dataset.

2. **Materials and methods**

2.1. Study population

The study population was derived from the free and public LEMON dataset [Babayan et al., 2019], so no ethical approval was required.

The sample included 227 participants. Nonetheless, in analogy to *Porcu et al.* [Porcu et al., 2021a], the following exclusion criteria were applied to increase the homogeneity of the sample and to limit biases due to the presence of constitutional and pathological factors, as well as addictions, that have been demonstrated to alter the structure and functioning of the brain : a) left-handed individuals [Nielsen et al., 2013]; b) subjects with positive urine drug tests for buprenorphine, amphetamine, benzodiazepine, cocaine, methamphetamine, morphine/heroin, methadone and

tetrahydrocannabinol (urine test: Multi 8/2 Drogen-Tauchtest - Diagnostik Nord, Schwerin, Germany) [Niciu & Mason, 2014; Babayan et al., 2019]; c) diagnosis of previous or current psychiatric disease identified during the psychological and clinical examination, alcohol and drug addiction included [Niciu & Mason, 2014; Ji & Anticevic, 2019]; and d) smokers [Hudkins et al., 2012].

2.2. Imaging assessment

The subjects in the LEMON dataset [Babayan et al., 2019] underwent 3-Tesla MRI scans (MAGNETOM Verio, Siemens Healthcare GmbH, Erlangen, Germany), and all the MRI data were acquired on the same scanner at the same institution.

Similar to a previous study [Porcu et al., 2021a], the following sequences were extracted from the dataset: a) 3D T1-weighted magnetization with two gradient echoes (3DT1-MP2RAGE); b) T2*-weighted gradient-echo echo planar imaging (T2*-EPI) Blood Oxygen Level Dependent (BOLD) sequence (repetition time = 1,400 ms); and c) diffusion-weighted imaging (DWI) with 60 directions (b-value = 1,000 s/mm^2) and seven b0 images (details about these sequences are summarized in Supplemental table 1). The 3DT1-MP2RAGE and T2*-EPI sequences were utilized for rs-IHC analysis with the HoFC technique [Jin et al., 2020], whereas the DWI sequence was reconstructed into the diffusion tensor imaging (DTI) scheme for the analysis of gFA and in the generalized q-sampling imaging (GQI) method for the automated analysis of FA of the various tracts of CC (see below).

All of these sequences, as well as the other morphological sequences included in the MRI protocol (i.e., the T2-weighted sequence, the T2-weighted fluid-attenuated inversion recovery [FLAIR] sequence, and the gradient echo susceptibility-weighted imaging (GE-SWI) sequence, were blind reviewed by an expert neuroradiologist (L.S., 15 years of radiological experience) for identifying pathological findings and congenital anomalies. Those subjects with at least one of these conditions were excluded from the final study population.

The reader is referred to the LEMON paper [Babayan et al., 2019] for additional information regarding the MRI protocol sequences of the LEMON dataset.

2.3. DWI analysis

Using the DSI studio software (2021.12.03 "Chen" Release – http://dsi-studio.labsolver.org), a DWI analysis was conducted. An automatic quality control tool verified the accuracy of the b-table for every DWI sequence [Schilling et al., 2019; Yeh et al., 2019]. As previously described [Porcu et al., 2021a], we excluded subjects who met at least one of the following criteria: a) incomplete or poor quality/defective scans (DWI count 67; image dimension 128 × 128 × 88; image resolution 1.7 × 1.7 × 1.7 mm; maximum b-value 1,000); b) presence of at least one poor quality slice due to signal dropout; c) sequences with a neighboring DWI correlation value < 0.80.

DWI sequences were reconstructed using the DTI model-based method to obtain the gFA value within the individual space for each subject [Porcu et al., 2021a]. The diffusion tensor was computed using a deterministic fiber-tracking algorithm [Yeh et al., 2013] with augmented tracking strategies [Yeh et al., 2020] to improve reproducibility. The entire brain was contained within the seeding region. In analogy to Yeh [Yeh, 2020], the anisotropy threshold was chosen at random between 0.5 and 0.7 of the Otsu's threshold [Otsu, 1979], the change threshold was 20% [Wade et al., 2021], and the angular threshold was chosen at random, between 15° and 90°. The step size was chosen at random between 0.5 and 1.5 voxels. A total of 100,000 seeds were placed, and tracks shorter than 25.7812 mm or longer than 257.812 mm were discarded [Bergamino et al., 2020].

For the analysis of the FA of the CC tracts, the DWI sequences were reconstructed using the GQI model [Yeh et al., 2010] with a shell diffusion sampling scheme and a diffusion sampling length ratio of 1.25. The AutoTrack tool of DSI Studio was used for the automated analysis of the FA of the forceps minor (forceps minor FA), the body (body FA), the tapetum (tapetum FA), and the forceps major (forceps major FA). This automatic deterministic fiber tracking algorithm [Yeh et

al., 2013] aimed to map the target pathways by performing a non-linear registration of subject data to Montreal Neurological Institute (MNI) space [Collins et al., 1994] and utilizing pathway recognition based on a tractography atlas [Yeh et al., 2018] to filter out false tracks and unrelated tracks, along with augmented tracking strategies [Yeh, 2020] to improve reproducibility. Every subject's forceps minor, body, tapetum, and forceps major were mapped according to International Consortium for Brain Mapping 152 (ICBM152) atlas [Mazziotta et al., 2001] with an 18-mm distance tolerance by automatically placing a seeding region in the tractography atlas's track region [Yeh et al., 2018]. The track-to-voxel ratio was set to 2. Even in this case, in analogy to Yeh [Yeh, 2020], for each individual's streamline, the anisotropy threshold was randomly selected between 0.5 and 0.7 of the Otsu's threshold [Otsu, 1979], the angular threshold was randomly selected from 15° to 90°, and the step size was randomly selected from 0.5 to 1.5 voxels. Tracks with lengths less than 30 mm or greater than 300 mm were discarded, and topology-informed pruning [Yeh et al., 2019] was used with 32 iterations to remove false connections from the tractography.

Each subject's segmental CC fiber tracking and morphological sequences were evaluated blindly by the same expert neuroradiologist. Subjects whose fiber tracking in at least one tract of the CC was deemed insufficient or inaccurate were excluded from the study. Figure 2 depicts a graphical representation of the CC track.

2.4. rs-fMRI data analysis

The rs-IHC analysis was done on the Matlab platform vR2020b (Mathworks, Inc., California, USA) with the CONN-fMRI toolbox v21.a [Whitfield-Gabrieli and Nieto-Castanon, 2012], which is based on the SPM 12 software package (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm).

The preprocessing of 3DT1-MP2RAGE and T2*-EPI and the denoising procedure (with band-pass filtering between 0.008–0.09 Hz) adopted in our study were the same as those used in previous studies [Porcu et al., 2020; Porcu et al., 2021a; Porcu et al., 2021b]. For further

information about these steps, the reader is referred to Supplemental text 1 and/or the relative papers.

In analogy to previous studies [Porcu et al., 2021a; Porcu et al., 2021b], those subjects with at least one of the following characteristics identified in the quality control after the preprocessing step were excluded from the study population: a) number of inadequate scans > 10% of the total amount; b) maximum global-signal z-value change > 9 standard deviations; c) maximum subject motion > 2 mm.

Once the data were processed, we conducted the rs-IHC analysis with the HoFC technique [Jin et al., 2020], which was done by computing the interhemispheric correlation maps characterizing IHC at each voxel (i.e., the Fisher-transformed correlations between voxels placed at the same anatomical location in both hemispheres). The CONN's default atlas was used for identifying the cerebral regions of interest: the Harvard-Oxford Atlas [Desikan et al., 2006] was used for cortical and subcortical regions, whereas the Automated Anatomical Labeling Atlas [Tzourio-Mazoyer et al., 2002] was used for cerebellar regions. The atlas regions and their relative abbreviations are reported in Supplemental table 2.

2.5. Neurocognitive assessment

The neurocognitive assessment centered on the evaluation of five cognitive abilities: logical deductive thinking, attentional processing, and cognitive flexibility.

Through Subtest 3 of the Performance Testing System (Leistungsprüfsystem 2, LPS-2) [Kreuzpointner et al., 2013; Babayan et al., 2019], logical deductive thinking was analyzed. The test scores are based on how many symbol-rows the subject correctly processed (LPS-2-S) [Kreuzpointner et al., 2013; Bain et al., 2004].

The Test of Attentional Performance (TAP) version 2.3.1 was used to measure several aspects of attentional processing [Zimmermann & Fimm, 2012; Babayan et al., 2019]. This examination consisted of three subtests: the TAP-alertness (TAP-A) for the analysis of reaction

speed, the TAP-incompatibility (TAP-I) for the analysis of the interference tendency by stimulus-reaction incompatibility (i.e., the Simon effect [Simon, 1969]), and TAP-working memory (TAP-WM) for the analysis of working memory [Zimmermann & Fimm, 2012; Babayan et al., 2019]. Regarding the TAP-A subtest, we calculated the mean reaction time (in milliseconds) for the sessions with (TAP-A-S-S) and without (TAP-A-NS-S) signals (ms). For the TAP-I subtest, scores were reported in terms of mean time for compatible (TAP-I-CS-S), incompatible (TAP-I-IS-S), and whole stimuli (TAP-I-WS-S), all expressed in milliseconds (ms); additionally, for each subject, the number of errors the subjects made during the presentation of the stimuli (TAP-I-CS-E for compatible stimuli, TAP-I-IS-E for incompatible stimuli) were registered. The TAP-WM subtest, which measures working memory capacity, yielded the mean reaction time for correct pressed buttons (TAP-WM-S), as well as the number of incorrect matches (TAP-WM-E) and missed matches (TAP-WM-MM) for each subject.

The Trail Making Test (TMT) was used to evaluate cognitive flexibility [Reitan, 1992; Babayan et al., 2019]. TMT-A and TMT-B are the two subtests that make up TMT. The scores of both tests (TMT-A-S and TMT-B-S, respectively) were reported as the time to complete the task in seconds and milliseconds (s.ms.).

The reader is encouraged to refer to Supplemental text 2, the LEMON dataset paper [Babayan et al., 2019], and the relevant literature for complete information regarding these tests.

2.6. Statistical analysis

2.6.1. *rs-fMRI: HoFC analysis*

Using the CONN toolbox and the HoFC method, a second-level fMRI data analysis was performed. Four separate analyses were performed to examine the effects of forceps minor FA (Analysis 1), body FA (Analysis 2), tapetum FA (Analysis 3), and forceps major FA (Analysis 4), adopting multiple regression statistics in the model and including gFA as a confounding variable

and a measure of global WM integrity. A nonparametric statistics model based on threshold-free cluster enhancement (TFCE) with 1,000 permutation iterations of the original data, and a peak family-wise corrected p-value (p-FWE) of 0.05 for voxel threshold was used to identify clusters of decreased or increased IHC [Smith & Nichols, 2009; Nieto-Castanon, 2020].

2.6.2. *Relationships between neurocognitive tests and FA of the CC fiber tracts*

The Shapiro-Wilk test was used to examine the normality assumption of the forceps minor FA, body FA, tapetum FA, forceps major FA, gFA, LPS-S, TAP-A-NS-S, TAP-A-S-S, TAP-I-CS, TAP-I-IS, TAP-I-WS, TAP-WM, TMT-A, and TMT-B. Whenever appropriate, a non-parametric partial correlation analysis was used to test for correlations (ρ) between forceps minor FA, body FA, tapetum FA, forceps major FA, LPS-S, TAP-A-NS-S, TAP-A-S-S (including gFA as a control variable), TAP-I-CS-S (including gFA and TAP-I-CS-E as control variables), and TAP-I-WS. All statistical analyses were conducted using SPSS-24 statistical software (SPSS Inc., Chicago, IL, USA).

3. **Results**

3.1. Study population and DWI analysis

After applying all exclusion criteria to the entire LEMON dataset [Babayan et al., 2019], the final study population consisted of 68 individuals: 39 males and 29 females. The age of the entire study population was expressed in the dataset using five-year progressive categories (category 1 = 0–5 years old; category 2 = 5–10 years old, etc.), with a median overall age category of 6 (25–30). The DWI analysis revealed a mean gFA of 0.462 (standard deviation = 0.017). Additionally, the analysis of the tracts of the CC revealed the following mean values: forceps minor FA = 0.501 (0.032); body FA = 0.510 (standard deviation = 0.024); tapetum FA = 0.525 (standard deviation = 0.041); and forceps major FA = 0.553 (standard deviation = 0.032). The overall population's neurocognitive analysis revealed a mean LPS-2-S value of 20.264. Concerning the TAP, the overall

population analysis revealed the following mean scores: TAP-A-NS-S = 236.674 ms; TAP-A-S-S = 233.676 ms; TAP-I-CS-S = 433.205 ms; TAP-I-CS-E = 0.941; TAP-I-IS-S = 471.029 ms; TAP-I-IS-E = 1.426; TAP-I-WS-S = 452.117 ms; TAP-I-WS-E = 2.367; TAP-WM-S = 563.64 ms; TAP-WM-E = 1.500; TAP-WM-MM = 1.632. The analysis of the TMT revealed the following mean values: TMT-A-S = 27.420 s.m.; TMT-A-E = 0.283; TMT-B-S = 62.477 s.m.; TMT-B-E = 0.441. A resume of the demographic statistics of the study population is reported in Table 1.

The details of the study population selection process are reported in Supplemental table 3. Supplemental table 4 provides full information on each subject of the whole study population. Regarding the evaluation of the quality of the DWI sequence, the reader is referred to Supplemental table 5.

3.2. HoFC analysis

The full details of the quality check of the preprocessing step of the fMRI data are reported in Supplemental table 6.

Regarding the HoFC analyses, Analysis 1 (focused on the effects of forceps minor FA) revealed 16 clusters of increased rs-IHC (TFCE ranged from 662.22 to 1287.94) that cover several supratentorial and infratentorial regions, including the cingulate gyrus, the precuneus, the putamen, the limbic system, and the cerebellum (results are reported in Table 2, and the full data are reported in Supplemental table 7). Analysis 2 (focused on the effects of body FA) revealed only two very small clusters of increased rs-IHC for a total of 38 voxels (TFCE = 668.78; degree of freedom = 66), adjacent to and within the insular cortex and putamen of both sides (TFCE = 668.78; degree of freedom = 66) (Table 3). Analysis 3 (concerning the effects of tapetum FA) revealed four clusters of increased rs-IHC (TFCE between 644.23 and 947.61) in the brainstem and cerebellum only (Table 4). Analysis 4 (which focused on the effects of forceps major FA) uncovered 14 clusters of increased rs-IHC (TFCE between 611.38 and 853.16), which spanned several regions of the occipital and temporal cortex as well as the brainstem and cerebellum (results shown in Table 5, full

data shown in Supplemental table 8). In none of the above-mentioned analyses, clusters of decreased rs-IHC were found to be statistically significant. The results are graphically reported in Figure 3 and Figure 4.

3.3. Relationships between the FA of the CC fiber tracts and neurocognitive tests

The Shapiro-Wilk test revealed that only forceps major FA (W = 0.981; p = 0.414) and LPS-2-S (W = 0.987; p = 0.731) had normal distributions, while the other variables had non-normal distributions (Supplemental table 9).

There were statistically significant correlations between the forceps minor FA and LPS-S (ρ = 0.424; p = 0.001), TAP-A-NS-S (ρ = -0.261; p = 0.034), and TAP-I-IS-S (ρ = -0.317; p = 0.010), TMT-A-S (ρ = - 0.321; p = 0.009), and with TMT-B- S (ρ = -0.353; p = 0.004); no statistically significant correlations were found between the FA of the other CC fiber tracts and the neurocognitive tests. Table 6 shows the findings of the non-parametric partial correlations.

4. Discussion

The status of WM fibers influences connectivity patterns and cognition [Bennett et al., 2014; Mollink et al., 2019; Porcu et al., 2021a]. It has been emphasized that the key role of CC in IHC is to link homologous cortical areas of the brain, transferring and integrating information in the frontal and parietal lobes and their correlated associative areas [Bloom & Hind, 2005; Hofer & Frahm, 2006; Yuan et al., 2020; Goldstein et al., 2022]. Regarding the cognitive sphere, while the physiological mechanisms underlying their functioning are still under investigation [Verma & Kumar, 2022], scientific literature has established that logical deductive thinking is based on neural networks [Wang et al., 2020], and attentional processing [Miller & Buschman, 2013] and cognitive flexibility [Kim et al., 2011] involve multiple cortical areas in both hemispheres linked through polysynaptic connections.

In this research, we evaluated the effects of the microstructural properties of CC on IHC and their associations with cognitive function. FA measures the degree of anisotropic diffusion of water molecules, and it is sensitive to multiple WM integrity features, including myelination and axonal degeneration [Aung et al., 2013; Friedich et al, 2020; Porcu et al., 2021a]. Further, it is also known that axonal diameter and inter-axonal space affect the mean FA value [Hofer et al., 2006; Stikov et al., 2011]. For instance, a recent study by Friedich et al. [Friederich et al., 2020] found that the spatial distribution of the FA value varies throughout the CC, with higher values observed in the splenium and genu and lower values in the body. These findings are consistent with the anatomical assessment of the CC, which primarily consists of fibers with a diameter < 1 μm in the splenium and genu, and thicker fibers with a diameter > 3 μm in the midbody [Aboitiz et al., 1992].

For the fMRI analysis, we selected the HoFC technique due to its ability to investigate functional integration between the two brain hemispheres [Jin et al., 2020]. Furthermore, we included the gFA, a marker of WM status that has been previously analyzed and used in the literature [Porcu et al., 2021a; Porcu et al., 2022; van der Plas et al., 2022] as a confounding factor in both the fMRI models and in the correlation analyses with the neurocognitive tests.

We found that the FA of individual CC fiber tracts affects the rs-IHC of multiple brain regions in distinct ways, with varying implications for cognitive performance. In particular, we observed significant correlations between the minor FA values of the forceps and several scores (LPS-2-S, TAP-A-NS-S, TAP-I-IS-S, TMT-A-S, and TMT-B-S). Higher FA values resulted to be mildly directed correlated with the scores of the LPS-2 test (indicating better performances in logical deductive thinking). Further, forceps minor FA values were weakly inversely correlated with the time of execution of the TAP-A-NS and TAP-I-IS tests (indicating better attentional performances); lastly, they resulted to be weakly inversely correlated with the time of execution of the TMT-A test and mildly inversely correlated with the time of execution of the TMT-B test (indicating better peformances in cognitive flexibility). Higher FA values in the forceps minor were also associated with an increase in rs-IHC in both the supratentorial and infratentorial regions,

including the cingulate gyrus, precuneus, limbic system, and cerebellum. By considering these results in their complex context, we could hypothesize that for the same global WM status (in terms of gFA), better WM myelination and integrity of the forceps minor can guarantee a greater rs-IHC of different areas of the brain and that, ultimately, these mechanisms could at least partially explain the superior cognitive performance of subjects with higher FA values.

The forceps minor, the most anterior CC tract, connects homologous areas of the anterior portion of the frontal lobes in the two hemispheres [Fame et al., 2011; Fabri et al., 2014; Mamiya et al., 2018]. Among these regions, the frontopolar cortex is important for cognitive behaviors in both humans and nonhuman primates [Semendeferi et al., 2001; Boschin et al., 2015; Mamiya et al., 2018]. It has also been demonstrated that the neural activity recorded at this level corresponds to animals' decision-making during feedback learning. The structure of the forceps minor influences critical cognitive function in humans [Lillo et al., 2012]; patients with frontotemporal dementia have lower FA values in the forceps minor compared to healthy subjects. In pathological conditions, such as in some hypertensive patients, the WM integrity of the forceps minor has also been found to be compromised [Carnevale et al., 2018]. In terms of processing speed and executive function performance, a recent study [Ferris et al., 2022] found that FA in forceps minor FA has a positive correlation with TMT-A-S and TMT-B-S in patients with chronic stroke. Although these results were obtained in a population with a specific chronic condition and using a different method of analysis, they are consistent with our findings. The association between forceps minor FA and control skills has also been demonstrated in the field of psychology, with higher forceps minor FA values assessed in healthy subjects compared to those whose families have a high risk of major depressive disorders [Winter et al., 2022].

Together, the evidences of the aforementioned studies are consistent with our findings, as they suggest that neural activity in the anterior frontal region is crucially involved in the control of attention and that subjects with higher diffusion properties of the brain fiber pathway connecting

bilateral anterior frontal regions, in particular the forceps minor, had superior control of attention skills compared to those with lower diffusion properties [Mamiya et al., 2018].

The results of HoFC analyses indicate that the WM integrity of the forceps minor significantly affects brain activity, suggesting that the integrity of the intercommunication between the frontal areas acts more broadly than at the local level, particularly in areas where the default mode network function plays a central role in the neurocognitive sphere, such as the anterior and posterior division of the cingulate gyrus [Bush et al., 2000; Leech & Sharp, 2014] and the precuneus.

These results are consistent with a previous publication [Slater et al., 2019], which demonstrated that the forceps minor has the highest myelination investments for a given axonal caliber, while the corticospinal fibers have the lowest myelination investments. In addition, a theoretical aspect of the present study is suggested by the fact that the forceps minor can be regarded as a true hub in neural networking, which, given its pivotal position in associative structures, may play a crucial role in optimizing higher functions. Interestingly, the frontal and retrosplenial agranular cortexes, which belong to the aforementioned areas, are among the most targeted neurons by the callosal fibers due to their composition of GABAergic parvalbumin-positive interneurons, a specific neural population structured on the sixth layer, which, by impinging distant areas, induces extensive empowerment of interconnected multifunctional brain networks [Karayannis et al., 2007].

However, other brain regions whose involvement in the cognitive process may appear less straightforward, such as the temporo-occipital regions, the brainstem, and the cerebellum, exhibited increased rs-IHC concerning increased forceps minor FA values. This finding allows us to hypothesize that the influence of the WM status of the forceps minor is not restricted to the cognitive domain but also influences other noncognitive higher cerebral functions, consistent with the demonstrated "control center" role of the frontal cortex for the brain's activities [Godefroy et al., 1999; Rae et al., 2015; Badre & Nee, 2018]. Overall, the findings of our study do not contradict

those of *Roland et al.* [Roland et al., 2017], who found that callosotomy, whether complete or partial, significantly reduces the rs-IHC in the multimodal associative areas of the frontal and parietal lobes, even though this study was conducted on patients with medically refractory epilepsy.

Other HoFC analyses indicated that there were no statistically significant correlations between the FA of the body, the FA of the tapetum, the FA of the forceps minor, and the neurocognitive test results. This appears to suggest that the status of white matter and the integrity of the posterior CC tract may have the greatest impact on higher non-cognitive cerebral functions.

The results of HoFC Analysis 2 (which evaluated the impact of body FA on rs-IHC) revealed only two small clusters of increased rs-IHC in the insular cortex and putamen [Fabri et al., 2014]. The CC connects homologous regions, primarily the frontal and parietal lobes. These structures are involved in the somatosensory circuit [Innocenti et al., 2022], as are the putamen and the insular cortex [Starr et al., 2011; Uddin et al., 2017]. The fact that only a small cluster of voxels with increased rs-IHC was found in relation to the increase in body FA value may appear surprising at first when compared to the vast number of cerebral regions linked by CC body fibers and the extension of these regions. However, we believe that the mode of MRI acquisition influences these results. In actuality, the functional T2*-EPI sequences were acquired during a state of relative inactivity in the precentral and postcentral regions. As suggested by previous research [Khorrami et al., 2011; Zhang et al., 2021], a fascinating future research topic could be analyzing the effects of body FA on rs-IHC during tasks that stimulate sensory-motor circuitry, such as the mental planning of a movement, execution of a specific motor task, or external tactile or painful stimulation.

The results of HoFC Analysis 3 (that evaluated the influence of Tapetum on rs-IHC that) evidenced that increasing values of FA of the Forceps Major are accompanied by increased rs-IHC in the brainstem and cerebellum, whereas the HoFC Analysis 4 (evaluated the influence of Forceps Major FA on rs-IHC) evidenced increased rs-IHC in the posterior regions of the brain, included temporal and occipital areas, besides the brainstem and the cerebellum. Considered in the context of their complexity, these results suggest that the influence of the posterior tracts of the CC is less

widespread than that observed with forceps minor FA analysis and is more concentrated in the cerebral regions adjacent to these commissural fibers. Specifically, the results of our study indicate that the WM status of both the tapetum and forceps major is essential to ensure the correct interhemispheric transmission and integration of neural information at a local level with the nearby brain regions, including the brainstem and the cerebellum, regions typically involved in the processing and integration of visual and auditory functions [Chaplin et al., 2018]. In fact, the forceps major connects homologous occipital regions [Goldstein et al., 2022], whereas the tapetum connects the middle and posterior temporal lobes [Sindou & Guenot, 2003]. Functionally, the forceps major is an essential component of the visual association pathways [Thomas et al., 2011], and the degree of myelination of these fibers influences the speed of visual information transmission and contributes to the dynamic distribution of this information to the processing resources for visual object recognition and discrimination [Lin et al., 2020].

Furthermore, the connectometry study by *Sihvonen et al.* [Sihvonen et al., 2021] has shown that the tapetum, forceps major, and cerebellum are important structures involved in the reading process, particularly for reading skills and phonological processing, and that dysconnectivity at the level of the forceps major and tapetum appears linked with decreased connectivity between the ventral occipital areas essential for reading and may contribute to occipitotemporal lateralization deficits observed in dyslexia. The results of our study do not contradict previous findings [Roland et al., 2017], which observed that the rs-IHC in the visual networks was largely unaffected in medically refractory epilepsy patients who underwent partial callosotomy (in which the posterior third of the CC was spared). Nonetheless, similar to what was reported for the results of Analysis 2, future resting-state and tasking fMRI studies may help to confirm these findings.

Even though the obtained results are extensively displayed in the data presented in the preceding section, it seems worthwhile to add several critical issues that collectively serve as the basis for our conclusions. The decision to study a relatively small population, despite its homogeneity, was based on the application of strict exclusion criteria to maximize the

representativeness of the sample. A potential weakness of the study could be related to the automatic identification and analysis of CC tracts on DWI data using an automatic deterministic fiber tracking algorithm on the GQI reconstruction model, instead of manual identification and analysis on the DTI model. However, considering that the reproducibility of tractography results has long been a persistent issue in the scientific community [Rheault et al., 2020], this choice was made to ensure a standardized model of analysis of the CC tracts with good reproducibility and moderate test-to-test reliability [Yeh et al., 2020]. Additionally, an expert neuroradiologist blind-checked the results to avoid potential biases in subsequent analyses.. Lastly, we focused on the effects of a subset of neurocognitive functions that may have hindered an exhaustive analysis of other relevant neurological and neuropsychological functions, but with this study, we hope to provide implicit talking points for extending and implementing our findings.

5. <u>Conclusion</u>

Depending on the topology of the CC tract, the integrity of the CC influences the rs-IHC in a variety of ways. In particular, the forceps minor tends to have a more extensive effect on the rs-IHC of the brain than was observed for the other CC tracts, with repercussions on the neurocognitive sphere. The relationships between CC tracts, FA, and other cognitive and noncognitive functions are worthy of further investigation. Despite the limitations outlined above, these findings represent a first attempt to investigate these relationships.

Figure legends

Figure 1: A graphical scheme of the research design is shown, where the FA value of each CC fiber tract (forceps minor, body, tapetum, and forceps major) and the gFA value were calculated from the DWI sequences for each subject in the study population. Four different HoFC analyses were then conducted to investigate the influence of forceps minor FA, body FA, tapetum FA, and forceps major FA on rs-IHC, using gFA as a confounding variable. Finally, a correlation analysis was performed between the FA of the CC fiber tracts and cognitive test scores (LPS-2 for logical deductive thinking, TAP for attentional processing, and TMT for cognitive flexibility), with the gFA value used as a confounding variable.

Figure 2: Example of CC fiber track. The color of the fibers follows the FA value according to the color bar on the left. The single CC tracts are shown on the left.

Figure 3: Results of HoFC analyses according to the CC tract analyzed (TFCE statistics). Areas of increased rs-IHC are shown according to the TFCE colorimetric scale. No areas of reduced rs-IHC were identified.

Figure 4: Three-dimensional representation of the results of HoFC analyses according to the CC tract analyzed (TFCE statistics); reddish areas represent areas of increased rs-IHC; no areas of reduced rs-IHC were identified. It is possible to observe that the FA of individual CC fiber tracts affects the rs-IHC of multiple brain regions in distinct ways. In particular, the forceps minor FA affects the rs-IHC of the whole brain more than at the local level. The influence of body FA was limited to very small areas of the insular cortex and putamen, whereas the influence of tapetum and forceps major FA is localized in the posterior regions of the brain, including temporal and occipital areas, as well as the brainstem and cerebellum.

Table legends

- **Table 1**: Statistics of the study population; for the full details please refer to the Supplemental table 4.

- **Table 2**: Results of Analysis 1 (Forceps minor FA). Only clusters of increased rs-IHC were found, diffusely localized in the whole brain; their localization according to the coordinates of the MNI space and their composition according to the CONN's default atlas is reported. TFCE = threshold free cluster enhancement; p-FWE = family wise error corrected p; p-FDR = p corrected for false discovery rate; p-unc = uncorrected p. The full details of all the voxels identified and relative brain areas is reported in supplementary table 6.

- **Table 3**: Results of Analysis 2 (Body FA). Only very small clusters of increased rs-IHC were found, located respectively in the insular cortex and putamen; their localization according to the coordinates of the MNI space and their composition according to the CONN's default atlas is reported. TFCE = threshold free cluster enhancement; p-FWE = family wise error corrected p; p-FDR = p corrected for false discovery rate; p-unc = uncorrected p.

- **Table 4**: Results of Analysis 3 (Tapetum FA). Only clusters of increased rs-IHC were found, especially in the cerebellum and brainstem; their localization according to the coordinates of the MNI space and their composition according to the CONN's default atlas is reported. TFCE = threshold free cluster enhancement; p-FWE = family wise error corrected p; p-FDR = p corrected for false discovery rate; p-unc = uncorrected p.

- **Table 5**: Results of Analysis 4 (Forceps major FA). Only clusters of increased rs-IHC were found in analysis, especially in the posterior regions of the brain, cerebellum and brainstem; their localization according to the coordinates of the MNI space and their composition according to the CONN's default atlas is reported. TFCE = threshold free cluster

enhancement; p-FWE = family wise error corrected   p; p-FDR = p corrected for false discovery rate; p-unc = uncorrected p. The the full details of all the voxels identified and relative brain areas is reported in supplementary table 7

- **Table 6**: Results of the partial non-parametric correlations. Statistically significant correlations were found between the forceps minor FA and the following cognitive test scores: mildly positive with LPS-2-S (indicating better performances in logical deductive thinking); weakly negative for TAP-A-NS-S and mildly negative for TAP-I-IS-S (indicating better attentional performances); mildly negative for TMT-A-S and TMT-B- S (indicating better peformances in cognitive flexibility). No other statistically significant correlations were found.

Supplemental table legends

- **Supplemental table 1**: MR sequences used for DWI and HoFC [Babayan et al., 2019].

- **Supplemental table 2**: Atlas – ROIs legends [Desikan et al., 2006; Tzourio-Mazoyer et al., 2002].

- **Supplemental table 3**: Details of the population study selection process.

- **Supplemental table 4**: Full details of the study population and DWI analysis.

- **Supplemental table 5**: Full details of the quality assessment of the DWI sequence.

- **Supplemental table 6**: Full details of the preprocessing of fMRI data. BOLD = Blood oxygen level dependent; std = standard deviation.

- **Supplemental table 7**: Full results of Analysis 1 (Forceps minor FA). TFCE = threshold free cluster enhancement; p-FWE = family wise error corrected p; p-FDR = p corrected for false discovery rate; p-unc = ncorrected p.

- **Supplemental table 8**: Full results of Analysis 4 (Forceps major FA). TFCE = threshold free cluster enhancement; p-FWE = family wise error corrected p; p-FDR = p corrected for false discovery rate; p-unc = uncorrected p.

- **Supplemental table 9**: Statistics of the Shapiro-Wilk test.

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