Correlation of cognitive reappraisal and the microstructural properties of the forceps minor: an exploratory diffusion tensor imaging study.

Michele Porcu[1*], Luigi Cocco[1*], Riccardo Cau[1], Jasjit S Suri[2], Lorenzo Mannelli[3], Mirko Manchia[4,5,6], Josep Puig[5], Yang Qi[6], Luca Saba[1]

[1]Department of Radiology, AOU Cagliari, University of Cagliari, Italy

[2]Stroke Monitoring and Diagnostic Division, AtheroPoint™, Roseville, California, USA

[3]Department of Radiology, IRCCS SDN, Italy

[4]Unit of Psychiatry, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy.

[5]Unit of Clinical Psychiatry, University Hospital Agency of Cagliari, Cagliari, Italy.

[6]Department of Pharmacology, Dalhousie University, Halifax, Nova Scotia, Canada.

[7]Department of Radiology (IDI) and Girona Biomedical Research Institute (IDIBGI), Hospital Universitari de Girona Dr Josep Trueta, Girona, Spain.

[8]Xuanwu Hospital, Capital Medical University, No.45 Changchun Street, Xicheng District, Beijing, China

*Contributed equally: co-first authors

Corresponding author: Michele Porcu (e-mail: micheleporcu87@gmail.com / institutional mail: m.porcu@aoucagliari.it); Department of Medical Imaging, Azienda Ospedaliera Universitaria di Cagliari – S.S: 554, km 4,500 – CAP: 09042 – Monserrato (Cagliari, Italy)

Abstract

Cognitive reappraisal (CR) is a mechanism for emotion regulation, and the prefrontal cortex (PFC) plays a central role in the regulation of emotions. We tested the hypothesis of an association between CR function and microstructural properties of forceps minor (a commissural bundle within the PFC) in healthy subjects (HS).

We analyzed a population of 65 young HS of a public dataset. The diffusion tensor imaging (DTI) sequence of every subject was analyzed to extract the derived shape (diameter and volume) and DTI metrics in terms of fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) of the forceps minor. The CR subscale of the german version of the emotion regulation questionnaire (ERQ) was used for CR assessment. The Shapiro-Wilk test was applied to test the assumption of normality in all these parameters, adopting a statistical threshold at $p < 0.05$. Whenever appropriate a non-parametric two-tailed partial correlation analysis was applied to test for correlations between the CR ERQ score and the derived shape and DTI metrics, including age and sex as confounders, adopting a statistical threshold at $p < 0.05$.

The non-parametric two-tailed partial correlation analysis revealed a mildly significant correlation with FA ($\rho = 0.303$; $p = 0.016$), a weakly significant negative correlation with MD ($\rho = -0.269$; $p = 0.033$), and a mildly significant negative correlation with RD ($\rho = -0.305$; $p = 0.015$).

These findings suggest a correlation between DTI microstructural properties of forceps minor and CR.

Keywords: DTI; Cognitive reappraisal; Forceps minor.

.

List of abbreviations

- ACC = Anterior cingulate cortex
- AD = Axial diffusivity
- ADHD = attention-deficit-hyperactivity disorder
- CR = Cognitive reappraisal
- CR ERQ score = Score of the cognitive reappraisal subscale of the german version of the emotion regulation questionnaire
- DAN = Dorsal attention network
- DMN = Default mode network
- DTI = Diffusion tensor imaging
- DWI = Diffusion weighted imaging
- ERQ = Emotion regulation questionnaire
- FLAIR = Fluid attenuated inversion recovery
- FA = Fractional Anisotropy
- fMRI = functional Magnetic Resonance Imaging
- GE = Gradient echo
- HS = Healthy subjects
- LEMON = Leipzig study for mind-body-emotion interactions
- MD = Mean diffusivity
- MP2RAGE = Magnetization prepared 2 rapid acquisition
- MRI = Magnetic resonance imaging
- PFC = Prefrrontal cortex
- ROA = Region of avoidance
- RD = Radial diffusivity
- rs-FC = resting-state functional connectivity
- SWI = Susceptibility-weighted imaging

- W = W-value
- WM = White matter

1. Introduction

Emotion regulation is a fundamental function for human adaptation [Ochser & Gross, 2005; McRae & Gross, 2020], and its dysregulation typically characterizes both mood and anxiety disorders [Amstadter, 2008; Cutulli, 2014]. This regulatory system is based on various emotion-regulation strategies, included acceptance, avoidance, reappraisal, problem-solving, rumination, and suppression [Aldao et al., 2010]. Much of the existing research has primarily focused on cognitive reappraisal (CR), that can be defined as the attempt to reframe an emotion-eliciting situation in order to moderate one's emotional response [Cutulli, 2014; McRae & Gross, 2020].

The understanding of the neural mechanisms underlying CR regulation can be critically important for individuals affected by a broad range of psychological and psychiatric disorders characterized by impairments in emotional response [Wang & Yin, 2023]. Several pharmacological and non-pharmacological therapies, including cognitive-behavioral therapies [Kazantis et al., 2018] and transcranial direct current stimulation [Feeser et al., 2014], have been developed and are currently employed to enhance cognitive control during emotion regulation. A comprehensive understanding of the neural mechanisms underlying cognitive reappraisal (CR) can aid researchers and clinicians in identifying potential biological marker to refine existing therapeutic techniques and identify potential new targets for therapy [Wang & Yin, 2023].

Several functional magnetic resonance imaging (fMRI) studies have demonstrated that the prefrontal cortex (PFC) plays a central role in the generation and regulation of emotions [Dixon et al., 2017] Specifically regarding CR, meta-analytical findings have indicated an association between CR and increased activation in both PFC and the anterior cingulate cortex (ACC) [Ochsner et al., 2014]. Notably, CR appears to engage a network of cerebral regions involved in several important cognitive functions, in particular the dorsolateral PFC (attention allocation and working memory), the medial PFC (interpretation of internal and external emotional states), the ventrolateral PFC (response inhibition and selection information from memory), and the dorsal ACC (performance monitoring) [Nelson et al., 2015]. Additionally, it is known that CR tends to reduce activation in limbic regions, particularly the amygdala [Buhle et al., 2014; Nelson et al., 2015].

Despite these findings, several aspects of the mechanisms underlying CR still require further clarification, such as for example the influence of white matter (WM) status. WM is crucial for human behavior by mediating the proper functioning of neural networks [Filley & Douglas Fields, 2016]. mong the non-invasive imaging techniques used for in vivo analysis of WM fibers, Diffusion Tensor Imaging (DTI) tractography is widely employed [Assaf & Pasternak, 2008; Boucher et al., 2020]. This technique enables the virtual dissection of WM fibers and the assessment of WM microstructural integrity through the quantification of several DTI metrics [Catani & Thiebaut de Schotten, 2008; Boucher et al., 2020]. Recent DTI studies have demonstrated a positive correlation between the ability to regulate emotions through CR and the microstructural integrity of several association fiber bundles within the CR network. These bundles include the uncinate fasciculus, which connects the amygdala with the PFC [Wycoco et al., 2013]) [d'Arbeloff et al., 2018], as well as of the superior longitudinal fasciculus which connects the PFC with the parietal, temporal, and occipital lobes [Wycoco et al., 2013]) [Vitolo et al., 2022].

Regarding commissural fiber bundles, a recent meta-analysis of voxel-based DTI studies by *Jenkins et al.* [Jenkins et al., 2016] revealed microstructural alterations in the forceps minor, an associative fiber bundle situated in the anterior part of the corpus callosum, in individuals with various emotional disorders. The forceps minor connects the bilateral medial and lateral prefrontal cortex (PFC) [Goldstein et al., 2022], and it plays a pivotal role in the control of attention skills [Mamiya et al., 2018]. In this context, we postulated that a similar association between CR and the WM status of the forceps minor could also be found in physiological conditions. To investigate this, we conducted a study aiming to examine the relationships between the microstructural and shape properties of WM, assessed through the DTI technique, and CR measured using the emotional regulation questionnaire (ERQ) [Gross & John, 2003]. We obtained data from a population of young healthy subjects (HS) extracted from the publicly available "Leipzig Study for Mind-Body-Emotion Interactions" (LEMON) dataset [Babayan et al., 2019].

2. Materials and methods

2.1. Study population

The study population was extrapolated from the LEMON dataset [Babayan et al., 2019]. Since we utilized this freely available public dataset, ethical approval was not required.

The original dataset consisted of 227 participants. To enhance the homogeneity of the study population and minimize confounding factors we implemented the following exclusion criteria for selection of individuals for the analysis: (a) patients > 55 years old (i.e. subjects from the elderly group of the LEMON dataset [Babayan et al., 2019]); given that age was reported as a categorical variable with 5-year intervals, we grouped the patients' age into 16 progressive categories, from category 1 (0-5 years) to category 16 (75-80 years), so we excluded all the patients with age category > 12 (55-60 years); (b) non right-handed participants [McKay et al., 2017]; (c) diagnosis of previous or current psychiatric disease, including alcohol and drug addiction, and participants with positive urine test for drug presence; (d) individuals who reported smoking status [Hudkins et al., 2012].

2.2. Cognitive reappraisal and imaging assessment

The CR assessment was codnucted using the CR subscale of the german version of the ERQ (CR ERQ score) [Gross & John, 2003; Abler & Kessler, 2009]. Briefly, the ERQ is a 10-items scale questionnaire designed for the evaluation of two emotion regulation strategies: CR and expressive suppression. Of the 10 items, 6 are dedicated to CR evaluation, while 4 assess expressive suppression. Each item is rated on a seven-point Likert-type scale ranging from 1 (strongly disagree) to 7 (strongly agree) [Gross & John, 2003; Li et al., 2017]. Only participants who completed the CR ERQ subscale were included in this study.

Regarding the MRI analysis, the diffusion-weighted imaging (DWI) sequence was extrapolated from the MRI protocol used in the LEMON dataset [Babayan et al., 2019]. This sequence was acquired with the following parameters: acquisition plane: axial; number of slices: 88; imaging matrix: 128 x 128; voxel size: 1.7 mm, isotropic; diffusion-encoding gradient directions: 60 with maximum b-value = 1000 s/mm^2, and 7 non-diffusion-weighted with b-value = 0, distributed in the sequence; TR: 7000 ms; TE = 80 ms; FA = 90°. The other morphological sequences included in the MRI protocol were the T2-weightted sequence, the T1-weighted magnetization prepared 2 rapid acquisition (MP2RAGE) gradient echoes (GE) sequence, the T2-

weighted fluid-attenuated inversion recovery (FLAIR) sequence, and the GE susceptibility-weighted imaging (SWI) sequence. These morphological sequences were analyzed by an expert neuroradiologist (M.P., 9 years of radiological experience) to identify intracranial pathological findings such as brain tumors and/or congenital anomalies such as like partial or complete corpus callosum agenesia; subjects with at least one of these conditions were excluded from the final study population.

For detailed information about the imaging protocol of the LEMON dataset, the reader is referred to check the LEMON paper [Babayan et al., 2019].

2.3. DTI reconstruction and metrics analysis

The DTI analysis was made using the DSI studio software (2021.12.03 "Chen" Release - http://dsi-studio.labsolver.org). An automatic quality control routine was employed to check the b-table of each DWI sequence for accuracy [Schilling et al., 2019]. Similarly to previous researches [Porcu et al., 2021; Porcu et al., 2022], subjects were excluded from the analysis if they met any of the following criteria: a) incomplete or low quality/defective scans (DWI count < 67; image dimension ≠ 128 x 128 x 88; image resolution ≠ 1.7 x 1.7x 1.7 mm; max b-value < 1000); b) presence of ⩾ 1 bad slices due to signal dropout; c) sequences with neighboring DWI correlation value <0.80.

Subsequently, an automated analysis of shape and DTI metrics of forceps minor of every subject was then performed by using the AutoTrack tool of DSI Studio. The DTI metrics included fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), while the shape metrics encompassed the diameter and volume (in terms of number of voxels passed by all streamlines multiplied by the voxel size). This automatic deterministic fiber tracking algorithm [Yeh et al., 2013] aims to map a target pathway (the forceps minor in our case), by making a non-linear registration of subject data to Montreal Neurological Institute (MNI) space [Collins et al., 1994], and utilizing a tractography atlas-based pathway recognition algorithm [Yeh et al. 2018] to filter out false and unrelated tracks. Augmented tracking strategies [Yeh et al., 2020] were used to improve reproducibility. The forceps minor was mapped in each subject with a distance tolerance of 18 mm, by automatically placing a seeding region at the track region indicated by the tractography atlas [Yeh et al. 2018]. A region of avoidance (ROA) was positioned at track tolerance region (+38, +41, +33 mm) in the MNI space, with a volume size of 3.2 mm^3. The track-to-voxel ratio was set to 2. The anisotropy threshold was randomly selected. The angular threshold was randomly selected from 15° to 90°. The step size was randomly selected from 0.5 to 1.5 voxels. Tracks with length shorter than 30 mm or longer than 300 mm were discarded. Topology-informed pruning [Yeh et al., 2019] was applied to the tractography with 32 iterations to remove false connections. Finally, shape analysis [Yeh et al., 2020] was performed to derive shape and DTI metrics.

The accuracy of the results of the automated fiber tracking for the forceps minor of each subject included in the study population was checked by the same expert neuroradiologist who analyzed the morphological sequences. Subjects whose fiber tracking was deemed incomplete or incorrect were excluded from the study. A graphical example of the forceps minor track is reported in Figure 1.

2.4. Statistical analysis

The Shapiro-Wilk test was employed to test the normality assumption of the CR ERQ scores, DTI metrics (FA, MD, AD, and RD), and shape metrics (diameter and volume) of the forceps minor, adopting a statistical threshold of $p < 0.05$. When appropriate, a non-parametric two-tailed partial correlation analysis was conducted to examine correlations (ρ) between DTI and shape metrics of the forceps minor and CR ERQ scores. Age category and sex were included as confounders to account for the inhomogeneity of the study population. A statistical threshold of $p < 0.05$ as statistical threshold to reject the null hypothesis. All statistical analyses were made using SPSS 24 statistical package (SPSS Inc, Chicago, IL, USA).

3. **Results**

3.1. Study population, cognitive reappraisal assessment and DTI metrics analysis

After applying all the exclusion criteria, the final study population consisted of 65 subjects; the details of the population study selection process are reported in table 1.

Specifically, the final population study comprised 23 females and 42 males, with ages ranging from category 5 (20-25) to category 7 (30-35). The median overall age category was 5 (20-25). The details of the demographic statistics are presented in table 2.

Regarding CR assessment, the mean CR ERQ score was 4.635 (minimum value = 1.333; maximum value = 7). The statistics of the reappraisal scores of the ERQ are reported in table 3.

Analysis of the DTI metrics of the forceps minor revealed a mean FA value = 0.513, mean MD value = 0.835 × 10^{-3} mm^2/s, mean AD value = 1.366 × 10^{-3} mm^2/s, and mean RD value = 0,569 × 10^{-3} mm^2/s. For what concern shape metrics, the analysis revealed a mean diameter value = 20.591 mm, and a mean volume value = 34.086 cm^3. Complete results of the DTI analysis, including shape metrics, can be found in table 4.

The comprehensive demographic and DTI data of each subject included in the study are provided in the supplementary table.

3.2. Relationships between cognitive reappraisal and DTI metrics

The Shapiro-Wilk test revealed the non-normal distribution of MD (W = 0.988; p = 0.049), and the normal distribution of FA (p = 0.773), AD (p = 0.352), RD (p = 0.756), diameter (p = 0.157), volume (p = 0.265), and CR ERQ (p = 0.075). All the results are reported in Table 5.

Although only MD was found to be not normally distributed, we chose to use the non-parametric two-tailed partial correlation statistic to analyze the correlations between CR ERQ score and all DTI metrics. This decision was made to ensure a uniform statistical analysis considering the exploratory nature of the study and the relatively small study population [Fagerland, 2012]. The non-parametric two-tailed partial correlation analysis revealed the following statistically significant correlations between CR ERQ score and DTI metrics: a) mildly positive correlation with FA (ρ = 0.303; p = 0.016); b) weakly negative correlation with MD (ρ = - 0.269; p = 0.033); c) mildly negative correlation with RD (ρ = - 0.305; p = 0.015). Taken as a whole, these results indicate that as the value of CR ERQ score increases, FA tends to increase, while MD and RD tend to decrease. The results are reported in table 6 and figure 2.

.

4. **Discussion**

Emotion regulation can be defined as the attempt to influence the processing and expression of emotions in ourselves and/or others, and it is considered a fundamental field of research in psychology and neuroscience [McRae & Gross, 2020]. CR is an important adaptive strategy for emotion regulation [Gross & John, 2003]. This mechanism operates by modifying emotional experiences at their early stages through cognitive processes that reinterpret emotional events [Gross et al., 1998; Cutuli, 2014]. Furthermore, the use of CR has been demonstrated to be associated with healthier patterns of affect, social functioning, and well-being [Cutuli, 2014]. For example, emotion regulation results to be impaired in severe mood disorders such as bipolar disorder type 1 [Corbalán et al., 2015] and social anxiety disorder [Goldin et al., 2009]. The ERQ is a widely used tool recently developed and validated for evaluating CR and expressive suppression [Gross & John, 2003]. Studies utilizing the ERQ have demonstrated that the habitual use of CR remains stable over time and is scarcely related to personality traits, social desirability, and intelligence [Gross & John, 2003; John & Gross, 2004; Abler et al., 2010]. Additionally, it has been shown to have no effects on mnesic performances [Cutuli, 2014].

In the last decades, several fMRI studies have aimed to uncover the neural mechanisms underlying CR. It is known that CR involves the activation of dorsolateral, ventrolateral, and medial PFC, as well as the dorsal ACC [Ochsner et al., 2014]. More recently, a tasking fMRI study by *Sokolowski et al.* [Sokolowski et al., 2022] demonstrated that the application of CR was associated with stronger activation of bilateral PFC during the regulation of positive emotions, particularly showing stronger activation of the left dorsolateral and ventrolateral PFC. Further, a study by *McRae et al.* [McRae et al., 2012], that examined CR in children, adolescents, and young adults, observed a linear age-related increase in neural activation of the ventrolateral PFC, as well as a quadratic linear age-related increase in neural activation in the medial PFC, posterior cingulate, and anterior temporal cortex in relation to CR. Collectively, these findings emphasize the central role of PFC in CR.

As we have seen in the introduction, DTI tractography is one of the most used non-invasive imaging techniques for analyzing WM microstructure thanks to its ability to virtually dissect the WM tracts and to quantify several DTI metrics [Assaf & Pasternak, 2008; Boucher et al., 2020; Catani & Thiebaut de Schotten, 2008; Boucher et al., 2020].The DTI metrics analyzed in our research (FA, MD, RD and AD) reflect different aspects of WM properties [Winston, 2012; Winklewski wt al., 2018; Martinez-Heras et al., 2021; Figley et al., 2022]. These metrics are among the most used in scientific literature for analyzing the WM microstructure both in normal [Krogsrud et al., 2016] and pathological conditions such as Parkinson's disease [Zhang et al., 2020] and Alzheimer's disease [Xiao et al., 2022]. Traditionally, FA and MD have been considered markers of local cellularity, RD as a marker of local demyelination, and AD as a marker of axonal injury [Winston, 2012]. In the last years it has been evidenced that the interpretation of the DTI metrics is actually more complex, since each WM voxel contains multiple fiber populations with different trajectories, geometries, and microstructural properties [Figley et al., 2022]. For these reasons, it has been suggested that the DTI studies should be conducted by analyzing at the same time multiple DTI metrics, rather than focusing solely on a single metric [Figley et al., 2022]. Among the fibers that contribute to the interconnection and the proper functioning of PFC, the forceps minor plays a pivotal role. This WM tract mainly consists of homotopic fibers that interconnect the lateral and medial surfaces of the frontal lobes, including the medial and ventral PFC, by crossing the midline at the genu and rostrum of corpus callosum [Thomas et al., 2011; Gobbi et al., 2014; Mamiya et al., 2018]. Previous studies have demonstrated an association between the microstructural properties of forceps minor, measured with the DTI technique, and the control of attention skills [Mamiya et al., 2018]. For instance, *Qiu et al.* [Qiu et al., 2011] found lower FA values in the forceps minor of children with attention-deficit-hyperactivity disorder (ADHD) compared to HS. Similarly, lower FA values were also observed in the forceps minor of patients with frontotemporal dementia when compared to HS [Lillo et al., 2012]. More recently, *He et al.* [He et al., 2018] demonstrated that altered integrity of the forceps minor may lead to poor interhemispheric communication across frontal cortices, potentially underlying some of the documented functional and structural abnormalities in patient affected by obsessive-compulsive disorder (OCD), a psychiatric disorder characterized by reduced cognitive regulation, included impairments in emotional responses [Ferreira et al., 2020]. This finding was further supported more recently by *Dikmeer et al.* [Dikmeer et al., 2021], who demonstrated that patients with OCD exhibited lower FA and higher RD values in the anterior cingulum and forceps minor when compared to HS. Additionally, a study by *Gobbi et al.* [Gobbi et al., 2014] observed a reduction in FA of the forceps minor in patients with multiple sclerosis, which was associated with concurrent depression and fatigue, suggesting that the status of forceps minor could also be involved in the regulatory mechanisms of other neuropsychological functions. As for depression, a recent exploratory study by Vasavada et al. [Vasavada et al., 2016], which described the variation between responders and no-responders after medical treatment during an episode of major depression, found significant differences in tract-based diffusion metrics between the two groups. Specifically, non-responders showed reduced FA, increased RD, and reduced MD in the forceps minor. These results highlight how variations in FA and other diffusion metrics, including RD and MD, in fronto-limbic pathways linking brain regions associated with mood regulation and emotion may not only reflect an anatomical status but also may assist in predicting treatment response.

In this study, we tested the hypothesis of the existence of a correlation between CR function (measured with the CR ERQ score) and the shape and microstructural properties of the forceps minor (analyzed usinmg the DTI technique). The results confirmed our initial hypothesis, revealing a mild statistically significant positive correlation between FA and CR ERQ score, a weak negative correlation between MD and CR ERQ score, and a mild negative correlation between RD and CR ERQ score. However, no statistically significant correlations were found between CR ERQ score and AD, volume, and mean diameter. These findings suggest an association between CR ERQ scores and the microstructural status of the forceps minor WM. Specifically, although the exact interpretation of DTI metrics is still a matter of debate [Figley et al., 2022], it would appear that individuals with better emotion regulation abilities tend to exhibit a higher degree of myelination in the forceps minor, regardless of the shape metrics.

The results of our study are consistent with those found in other recent DTI studies that have analyzed the association between CR and WM status of various association fiber bundles within the CR network in HS, particularly the uncinate fasciculus [d'Arbeloff et al., 2018], and the superior longitudinal fasciculus [Enrico et al., 2022]. Furthermore, these results do not seem to contradict previous studies that have examined the microstructural properties of forceps minor in several psychiatric conditions such as ADHD, OCD, and depression. All of these studies share a common finding, namely the demonstrated association between a reduction in FA of the forceps minor and impaired control of emotion and attention skills. Based on the aforementioned evidence, we can speculate an "anatomical" hypothesis wherein individuals with a higher degree of myelination and integrity in the PFC WM tend to exhibit better emotion regulation through the CR process. In this context, a higher degree of myelination of forceps minor bundles would facilitate a more efficient communication between the cerebral regions of the PFC implied in CR mechanism and in attention control. At the same time, it is important to consider that CR is an adaptive skill that tends to develop through experience during growth and can be trained to modulate several aspects of emotional responding, including self-reported negative emotions [McRae et al., 2012]. Additionally, a growing body of literature suggests that WM microstructural development is a dynamic process that occurs not only during development and aging but also in response to phenomena such as experience and learning [Zatorre et al., 2012; Lebel et al., 2018; Williamson et al., 2018], with mechanisms partly mediated by neuronal activity [Lundgaard, 2013; Walhovd et al., 2014]. Considering these findings, it is reasonable to propose an additional, purely speculative "adaptive" hypothesis, according to which CR development through experience and/or pharmacological and non-pharmacological therapies [Kazantis et al., 2018; Feeser et al., 2014] could influence PFC WM microstructure, including the forceps minor. However, due to the exploratory cross-sectional nature of the study and its exclusive focus on forceps minor, both the “anatomical” and “adaptive” hypotheses remain confined to the realm of pure speculation and require further investigation in future studies.

We acknowledge several limitations in our study. The first limitation is related to the small size and composition of the study population. The study included only young HS of both sexes aged between 20 and 35. This choice was made to prioritize the homogeneity of the study population based on the dataset's characteristics, specifically the absence of subjects in the age range of 35-59 [Babayan et al., 2019]. Additionally, the selection of study population was based on specific strict criteria to minimize confounding factors such as the presence of psychiatric disorders, severe systemic disorders, or other conditions known to influence WM properties, including smoking [Hudkins et al., 2012].

Furthermore, due to the exploratory nature of the study and the small study population, we decided not to apply any multiple test corrections in the statistical analysis to minimize type II statistical errors [Bender et al., 2001]. Consequently, larger studies with a more extensive study population are needed to confirm these findings.

Another limitation to note is that the frontal lobe can experience susceptibility distortion during the acquisition of diffusion-weighted imaging (DWI) sequences [Le Bihan et al., 2006]. As the forceps minor, located in the frontal lobe, is involved in the study, the quality of its tracking could be affected. However, two volumes with reversed phase encoding (AP and PA) were acquired after the DWI sequence in order to limit the geometric distortion in the LEMON dataset [Babayan et al., 2019]. Furthermore, an automated technique for standardizing the tracking method was used in the DTI analysis to minimize tracking bias, and the quality of the tracking of all the data was accurately checked by an expert neuroradiologist.

Attention should also be given when interpreting the results. As mentioned at the beginning of this discussion, the interpretation of DTI metric results remains a subject of debate and ongoing research due to the inherent complexity of WM structure [Figley et al., 2022]. However, our study focused solely on the forceps minor, a WM region characterized by a relatively homogeneous composition and simple geometry, with very few crossing fibers [Figley et al., 2022; Fitsiori et al., 2011]. Consequently, the interpretation of the results can be reasonably considered more straightforward in this case [Figley et al., 2022].

Lastly, we did not explore the association of our findings with cerebral activity, in particular the interhemispheric connectivity.

All the aforementioned limitations affect the generalizability of the study. In particular, we focus our attention on a population of young HS, and we did not investigate the presence or absence of these correlations in pathological conditions and/or during aging and development. Furthermore, the DTI metrics are sensitive to the MRI scanner used for the analysis and the scanner acquisition parameters [Barrio-Arranz et al, 2015]. However, this study could serve as a topic for consideration for further consideration in future studies aimed at understanding the impact of WM microstructure on CR mechanisms.

5. Conclusions

This exploratory study confirmed the existence of a correlation between the CR, measured with the CR ERQ score, and the microstructural properties of forceps minor measured with the DTI technique in physiological conditions in a population of HS, similarly to what observed in other association fibers within the cerebral circuits involved in CR mechanism. While we are not allowed to draw firm conclusions at this stage and further confirmatory studies are needed, the findings of this research have the potential to provide valuable insight and serve as starting point for future research aimed at gaining a deeper understanding of the anatomical and physiological mechanisms underlying CR. Consequently, this research could help researchers identify therapeutic targets and/or biological markers of treatment response for psychological and psychiatric disorders characterized by impaired emotional responses.

.

Financial disclosure

This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Author contributions

Conceptualization, M.P., L.C.; Methodology M.P.; Validation M.P., L.C.; Data Curation M.P., R.C.; Investigation M.P., L.C.; Writing – Original Draft, M.P., L.C., R.C., L.S.; Writing – Review and Editing, L.S., J.S.S., L.M., K.I.P., Y.Q., M.M.; Supervision, L.S., J.P., Y.Q, K.I.P..

Declaration of Interests

The authors declare no conflict of interests.

Ethical approval

The ethical approval was not required because the study was performed exploiting the public dataset "Leipzig Study for Mind-Body-Emotion Interactions" (LEMON) [Babayan et al., 2019].

Data availability statement

The dataset analyzed during the current study derives from the public dataset "Leipzig Study for Mind-Body-Emotion Interactions" (LEMON) [Babayan et al., 2019]; in the publication is reported the link to the data repository.

All data generated specifically for the analyses of this study are included in this published article (and its supplementary information file).

Figure legends

Figure 1: Example of Forceps Minor tracking; A) sagittal view; B) axial view.

Figure 2: Graphs representing the relationships between the variables of the statistically significant correlations found in the two-tailed non-parametric partial correlation analysis: positive correlation between CR ERQ score and FA (on the left), and negative correlation between CR ERQ score and MD (in the center), and RD (on the right). MD and RD values are expressed in 10^{-3} mm^2/s.

.

Table legends

- **Table 1**: Details of the population study selection process. ERQ = Emotion Regulation Questionnaire; MP2RAGE = Magnetization Prepared 2 Rapid Acquisition; FLAIR = Fluid Attenuated Inversion Recovery; SWI = Susceptibility-Weighted Imaging; DWI = Diffusion Weighted Imaging.
- **Table 2**: Demographic statistics of the study population.
- **Table 3**: Statistics of the reappraisal scores of the ERQ test [Gross & John, 2003; Abler & Kessler, 2009]. ERQ = Emotion Regulation Questionnaire.
- **Table 4**: Statistics of the DTI metrics of forceps minor.
- **Table 5**: Statistics of the Shapiro-Wilk test.
- **Table 6**: Results of the non-parametric two-tailed partial correlation analysis. ρ = correlation coefficient; ERQ = Emotion Regulation Questionnaire; p = p-value; N = Number of subjects; FA = Fractional Anisotropy; MD = Mean Diffusivity; AD = Axial Diffusivity; RD = Radial Diffusivity.

Supplementary table legend

- **Supplementary table**: Complete demographic and DTI data (included shape metrics) of the population study. ID (identification number of the subject according to the LEMON dataset [Babayan et al., 2019]; FA = Fractional Anisotropy; MD = Mean Diffusivity; AD = Axial Diffusivity; RD = Radial Diffusivity; MD = Mean Diffusivity; CR ERQ = score of the CR subscale of the german version of the Emotion Regulation Questionnaire.

.

References:

1. Abler, B., Hofer, C., Walter, H., Erk, S., Hoffmann, H., Traue, H. C., & Kessler, H. (2010). Habitual emotion regulation strategies and depressive symptoms in healthy subjects predict fMRI brain activation patterns related to major depression. Psychiatry research, 183(2), 105–113. https://doi.org/10.1016/j.pscychresns.2010.05.010
2. Abler, B., & Kessler, H. (2009). Emotion Regulation Questionnaire—Eine deutschsprachige Fassung des ERQ von Gross und John [Emotion Regulation Questionnaire—A German version of the ERQ by Gross and John]. Diagnostica, 55(3), 144–152. https://doi.org/10.1026/0012-1924.55.3.144
3. Aldao, A., Nolen-Hoeksema, S., & Schweizer, S. (2010). Emotion-regulation strategies across psychopathology: A meta-analytic review. Clinical psychology review, 30(2), 217–237. https://doi.org/10.1016/j.cpr.2009.11.004
4. Amstadter A. (2008). Emotion regulation and anxiety disorders. Journal of anxiety disorders, 22(2), 211–221. https://doi.org/10.1016/j.janxdis.2007.02.004
5. Assaf, Y., & Pasternak, O. (2008). Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. Journal of molecular neuroscience : MN, 34(1), 51–61. https://doi.org/10.1007/s12031-007-0029-0
6. Babayan, A., Erbey, M., Kumral, D., Reinelt, J. D., Reiter, A., Röbbig, J., Schaare, H. L., Uhlig, M., Anwander, A., Bazin, P. L., Horstmann, A., Lampe, L., Nikulin, V. V., Okon-Singer, H., Preusser, S., Pampel, A., Rohr, C. S., Sacher, J., Thöne-Otto, A., Trapp, S., … Villringer, A. (2019). A mind-brain-body dataset of MRI, EEG, cognition, emotion, and peripheral physiology in young and old adults. Scientific data, 6, 180308. https://doi.org/10.1038/sdata.2018.308
7. Barrio-Arranz, G., de Luis-García, R., Tristán-Vega, A., Martín-Fernández, M., & Aja-Fernández, S. (2015). Impact of MR Acquisition Parameters on DTI Scalar Indexes: A Tractography Based Approach. PloS one, 10(10), e0137905. https://doi.org/10.1371/journal.pone.0137905
8. Bender, R., & Lange, S. (2001). Adjusting for multiple testing--when and how?. Journal of clinical epidemiology, 54(4), 343–349. https://doi.org/10.1016/s0895-4356(00)00314-0
9. Boucher, S., Arribarat, G., Cartiaux, B., Lallemand, E. A., Péran, P., Deviers, A., & Mogicato, G. (2020). Diffusion Tensor Imaging Tractography of White Matter Tracts in the Equine Brain. Frontiers in veterinary science, 7, 382. https://doi.org/10.3389/fvets.2020.00382
10. Buhle, J. T., Silvers, J. A., Wager, T. D., Lopez, R., Onyemekwu, C., Kober, H., Weber, J., & Ochsner, K. N. (2014). Cognitive reappraisal of emotion: a meta-analysis of human neuroimaging studies. Cerebral cortex (New York, N.Y. : 1991), 24(11), 2981–2990. https://doi.org/10.1093/cercor/bht154
11. Catani, M., & Thiebaut de Schotten, M. (2008). A diffusion tensor imaging tractography atlas for virtual in vivo dissections. Cortex; a journal devoted to the study of the nervous system and behavior, 44(8), 1105–1132. https://doi.org/10.1016/j.cortex.2008.05.004
12. Corbalán, F., Beaulieu, S., & Armony, J. L. (2015). Emotion regulation in bipolar disorder type I: an fMRI study. Psychological medicine, 45(12), 2521–2531. https://doi.org/10.1017/S0033291715000434
13. Cutuli D. (2014). Cognitive reappraisal and expressive suppression strategies role in the emotion regulation: an overview on their modulatory effects and neural correlates. Frontiers in systems neuroscience, 8, 175. https://doi.org/10.3389/fnsys.2014.00175
14. d'Arbeloff, T. C., Kim, M. J., Knodt, A. R., Radtke, S. R., Brigidi, B. D., & Hariri, A. R. (2018). Microstructural integrity of a pathway connecting the prefrontal cortex and amygdala moderates the association between cognitive reappraisal and negative emotions. Emotion (Washington, D.C.), 18(6), 912–915. https://doi.org/10.1037/emo0000447
15. Collins, D. L., Neelin, P., Peters, T. M., & Evans, A. C. (1994). Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. Journal of computer assisted tomography, 18(2), 192–205.
16. Dikmeer, N., Besiroglu, L., Di Biase, M. A., Zalesky, A., Kasal, M. I., Bilge, A., Durmaz, E., Polat, S., Gelal, F., & Zorlu, N. (2021). White matter microstructure and connectivity in patients with obsessive-compulsive disorder and their unaffected siblings. Acta psychiatrica Scandinavica, 143(1), 72–81. https://doi.org/10.1111/acps.13241

17. Dixon, M. L., Thiruchselvam, R., Todd, R., & Christoff, K. (2017). Emotion and the prefrontal cortex: An integrative review. Psychological bulletin, 143(10), 1033–1081. https://doi.org/10.1037/bul0000096
18. Fagerland M. W. (2012). t-tests, non-parametric tests, and large studies--a paradox of statistical practice?. BMC medical research methodology, 12, 78. https://doi.org/10.1186/1471-2288-12-78
19. Feeser, M., Prehn, K., Kazzer, P., Mungee, A., & Bajbouj, M. (2014). Transcranial direct current stimulation enhances cognitive control during emotion regulation. Brain stimulation, 7(1), 105–112. https://doi.org/10.1016/j.brs.2013.08.006
20. Ferreira, S., Pêgo, J. M., & Morgado, P. (2020). A Systematic Review of Behavioral, Physiological, and Neurobiological Cognitive Regulation Alterations in Obsessive-Compulsive Disorder. Brain sciences, 10(11), 797. https://doi.org/10.3390/brainsci10110797
21. Figley, C. R., Uddin, M. N., Wong, K., Kornelsen, J., Puig, J., & Figley, T. D. (2022). Potential Pitfalls of Using Fractional Anisotropy, Axial Diffusivity, and Radial Diffusivity as Biomarkers of Cerebral White Matter Microstructure. Frontiers in neuroscience, 15, 799576. https://doi.org/10.3389/fnins.2021.799576
22. Filley, C. M., & Fields, R. D. (2016). White matter and cognition: making the connection. Journal of neurophysiology, 116(5), 2093–2104. https://doi.org/10.1152/jn.00221.2016
23. Fitsiori, A., Nguyen, D., Karentzos, A., Delavelle, J., & Vargas, M. I. (2011). The corpus callosum: white matter or terra incognita. The British journal of radiology, 84(997), 5–18. https://doi.org/10.1259/bjr/21946513
24. Gobbi, C., Rocca, M. A., Pagani, E., Riccitelli, G. C., Pravatà, E., Radaelli, M., Martinelli-Boneschi, F., Falini, A., Copetti, M., Comi, G., & Filippi, M. (2014). Forceps minor damage and co-occurrence of depression and fatigue in multiple sclerosis. Multiple sclerosis (Houndmills, Basingstoke, England), 20(12), 1633–1640. https://doi.org/10.1177/1352458514530022
25. Goldin, P. R., Manber-Ball, T., Werner, K., Heimberg, R., & Gross, J. J. (2009). Neural mechanisms of cognitive reappraisal of negative self-beliefs in social anxiety disorder. Biological psychiatry, 66(12), 1091–1099. https://doi.org/10.1016/j.biopsych.2009.07.014
26. Goldstein, A., Covington, B. P., Mahabadi, N., & Mesfin, F. B. (2022). Neuroanatomy, Corpus Callosum. In StatPearls. StatPearls Publishing.
27. Gross J. J. (1998). Antecedent- and response-focused emotion regulation: divergent consequences for experience, expression, and physiology. Journal of personality and social psychology, 74(1), 224–237. https://doi.org/10.1037//0022-3514.74.1.224
28. Gross, J. J., & John, O. P. (2003). Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. Journal of personality and social psychology, 85(2), 348–362. https://doi.org/10.1037/0022-3514.85.2.348
29. He, X., Steinberg, E., Stefan, M., Fontaine, M., Simpson, H. B., & Marsh, R. (2018). Altered frontal interhemispheric and fronto-limbic structural connectivity in unmedicated adults with obsessive-compulsive disorder. Human brain mapping, 39(2), 803–810. https://doi.org/10.1002/hbm.23883
30. Hudkins, M., O'Neill, J., Tobias, M. C., Bartzokis, G., & London, E. D. (2012). Cigarette smoking and white matter microstructure. Psychopharmacology, 221(2), 285–295. https://doi.org/10.1007/s00213-011-2621-9
31. Jenkins, L. M., Barba, A., Campbell, M., Lamar, M., Shankman, S. A., Leow, A. D., Ajilore, O., & Langenecker, S. A. (2016). Shared white matter alterations across emotional disorders: A voxel-based meta-analysis of fractional anisotropy. NeuroImage. Clinical, 12, 1022–1034. https://doi.org/10.1016/j.nicl.2016.09.001
32. John, O. P., & Gross, J. J. (2004). Healthy and unhealthy emotion regulation: personality processes, individual differences, and life span development. Journal of personality, 72(6), 1301–1333. https://doi.org/10.1111/j.1467-6494.2004.00298.x
33. Kazantzis, N., Luong, H. K., Usatoff, A. S., Impala, T., Yew, R. Y., & Hofmann, S. G. (2018). The processes of cognitive behavioral therapy: A review of meta-analyses. Cognitive Therapy and Research, 42(4), 349–357. https://doi.org/10.1007/s10608-018-9920-y

.

34. Krogsrud, S. K., Fjell, A. M., Tamnes, C. K., Grydeland, H., Mork, L., Due-Tønnessen, P., Bjørnerud, A., Sampaio-Baptista, C., Andersson, J., Johansen-Berg, H., & Walhovd, K. B. (2016). Changes in white matter microstructure in the developing brain--A longitudinal diffusion tensor imaging study of children from 4 to 11years of age. NeuroImage, 124(Pt A), 473–486. https://doi.org/10.1016/j.neuroimage.2015.09.017
35. Lebel, C., & Deoni, S. (2018). The development of brain white matter microstructure. NeuroImage, 182, 207–218. https://doi.org/10.1016/j.neuroimage.2017.12.097
36. Le Bihan, D., Poupon, C., Amadon, A., & Lethimonnier, F. (2006). Artifacts and pitfalls in diffusion MRI. Journal of magnetic resonance imaging : JMRI, 24(3), 478–488. https://doi.org/10.1002/jmri.20683
37. Li, Z., Wu, X., Zhang, L., & Zhang, Z. (2017). Habitual Cognitive Reappraisal Was Negatively Related to Perceived Immorality in the Harm and Fairness Domains. Frontiers in psychology, 8, 1805. https://doi.org/10.3389/fpsyg.2017.01805
38. Lillo, P., Mioshi, E., Burrell, J. R., Kiernan, M. C., Hodges, J. R., & Hornberger, M. (2012). Grey and white matter changes across the amyotrophic lateral sclerosis-frontotemporal dementia continuum. PloS one, 7(8), e43993. https://doi.org/10.1371/journal.pone.0043993
39. Lundgaard, I., Luzhynskaya, A., Stockley, J. H., Wang, Z., Evans, K. A., Swire, M., Volbracht, K., Gautier, H. O., Franklin, R. J., Charles Ffrench-Constant, Attwell, D., & Káradóttir, R. T. (2013). Neuregulin and BDNF induce a switch to NMDA receptor-dependent myelination by oligodendrocytes. PLoS biology, 11(12), e1001743. https://doi.org/10.1371/journal.pbio.1001743
40. Mamiya, P. C., Richards, T. L., & Kuhl, P. K. (2018). Right Forceps Minor and Anterior Thalamic Radiation Predict Executive Function Skills in Young Bilingual Adults. Frontiers in psychology, 9, 118. https://doi.org/10.3389/fpsyg.2018.00118
41. Martinez-Heras, E., Grussu, F., Prados, F., Solana, E., & Llufriu, S. (2021). Diffusion-Weighted Imaging: Recent Advances and Applications. Seminars in ultrasound, CT, and MR, 42(5), 490–506. https://doi.org/10.1053/j.sult.2021.07.006
42. McKay, N. S., Iwabuchi, S. J., Häberling, I. S., Corballis, M. C., & Kirk, I. J. (2017). Atypical white matter microstructure in left-handed individuals. Laterality, 22(3), 257–267. https://doi.org/10.1080/1357650X.2016.1175469
43. McRae, K., & Gross, J. J. (2020). Emotion regulation. Emotion (Washington, D.C.), 20(1), 1–9. https://doi.org/10.1037/emo0000703
44. McRae, K., Gross, J. J., Weber, J., Robertson, E. R., Sokol-Hessner, P., Ray, R. D., Gabrieli, J. D., & Ochsner, K. N. (2012). The development of emotion regulation: an fMRI study of cognitive reappraisal in children, adolescents and young adults. Social cognitive and affective neuroscience, 7(1), 11–22. https://doi.org/10.1093/scan/nsr093
45. Nelson, B. D., Fitzgerald, D. A., Klumpp, H., Shankman, S. A., & Phan, K. L. (2015). Prefrontal engagement by cognitive reappraisal of negative faces. Behavioural brain research, 279, 218–225. https://doi.org/10.1016/j.bbr.2014.11.034
46. Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. Trends in cognitive sciences, 9(5), 242–249. https://doi.org/10.1016/j.tics.2005.03.010
47. Ochsner, K. N., Silvers, J. A., & Buhle, J. T. (2012). Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. Annals of the New York Academy of Sciences, 1251, E1–E24. https://doi.org/10.1111/j.1749-6632.2012.06751.x
48. Porcu, M., Cocco, L., Puig, J., Mannelli, L., Yang, Q., Suri, J. S., Defazio, G., & Saba, L. (2021). Global Fractional Anisotropy: Effect on Resting-state Neural Activity and Brain Networking in Healthy Participants. Neuroscience, 472, 103–115. https://doi.org/10.1016/j.neuroscience.2021.07.021
49. Porcu, M., Cocco, L., Cau, R., Suri, J. S., Mannelli, L., Puig, J., Qi, Y., Paraskevas, K. I., & Saba, L. (2022). Mid-term effects of carotid endarterectomy on cognition and white matter status evaluated by whole brain diffusion tensor imaging

metrics: A preliminary analysis. European journal of radiology, 151, 110314. https://doi.org/10.1016/j.ejrad.2022.110314

50. Qiu, M. G., Ye, Z., Li, Q. Y., Liu, G. J., Xie, B., & Wang, J. (2011). Changes of brain structure and function in ADHD children. Brain topography, 24(3-4), 243–252. https://doi.org/10.1007/s10548-010-0168-4
51. Schilling, K. G., Yeh, F. C., Nath, V., Hansen, C., Williams, O., Resnick, S., Anderson, A. W., & Landman, B. A. (2019). A fiber coherence index for quality control of B-table orientation in diffusion MRI scans. Magnetic resonance imaging, 58, 82–89. https://doi.org/10.1016/j.mri.2019.01.018
52. Thomas, C., Humphreys, K., Jung, K. J., Minshew, N., & Behrmann, M. (2011). The anatomy of the callosal and visual-association pathways in high-functioning autism: a DTI tractography study. Cortex; a journal devoted to the study of the nervous system and behavior, 47(7), 863–873. https://doi.org/10.1016/j.cortex.2010.07.006
53. Vasavada, M. M., Leaver, A. M., Espinoza, R. T., Joshi, S. H., Njau, S. N., Woods, R. P., & Narr, K. L. (2016). Structural connectivity and response to ketamine therapy in major depression: A preliminary study. Journal of affective disorders, 190, 836–841. https://doi.org/10.1016/j.jad.2015.11.018
54. Vitolo, E., Diano, M., Giromini, L., & Zennaro, A. (2022). Markers of emotion regulation processes: A neuroimaging and behavioral study of reappraising abilities. Biological psychology, 171, 108349. https://doi.org/10.1016/j.biopsycho.2022.108349
55. Yeh F. C. (2020). Shape analysis of the human association pathways. NeuroImage, 223, 117329. https://doi.org/10.1016/j.neuroimage.2020.117329
56. Walhovd, K. B., Johansen-Berg, H., & Káradóttir, R. T. (2014). Unraveling the secrets of white matter--bridging the gap between cellular, animal and human imaging studies. Neuroscience, 276(100), 2–13. https://doi.org/10.1016/j.neuroscience.2014.06.058
57. Wang, Y. X., & Yin, B. (2023). A new understanding of the cognitive reappraisal technique: an extension based on the schema theory. Frontiers in behavioral neuroscience, 17, 1174585. https://doi.org/10.3389/fnbeh.2023.1174585
58. Williamson, J. M., & Lyons, D. A. (2018). Myelin Dynamics Throughout Life: An Ever-Changing Landscape?. Frontiers in cellular neuroscience, 12, 424. https://doi.org/10.3389/fncel.2018.00424
59. Winklewski, P. J., Sabisz, A., Naumczyk, P., Jodzio, K., Szurowska, E., & Szarmach, A. (2018). Understanding the Physiopathology Behind Axial and Radial Diffusivity Changes-What Do We Know?. Frontiers in neurology, 9, 92. https://doi.org/10.3389/fneur.2018.00092
60. Winston G. P. (2012). The physical and biological basis of quantitative parameters derived from diffusion MRI. Quantitative imaging in medicine and surgery, 2(4), 254–265. https://doi.org/10.3978/j.issn.2223-4292.2012.12.05
61. Wycoco, V., Shroff, M., Sudhakar, S., & Lee, W. (2013). White matter anatomy: what the radiologist needs to know. Neuroimaging clinics of North America, 23(2), 197–216. https://doi.org/10.1016/j.nic.2012.12.002
62. Xiao, D., Wang, K., Theriault, L., Charbel, E., & Alzheimer's Disease Neuroimaging Initiative (2022). White matter integrity and key structures affected in Alzheimer's disease characterized by diffusion tensor imaging. The European journal of neuroscience, 56(8), 5319–5331. https://doi.org/10.1111/ejn.15815
63. Yeh, F. C., Panesar, S., Fernandes, D., Meola, A., Yoshino, M., Fernandez-Miranda, J. C., Vettel, J. M., & Verstynen, T. (2018). Population-averaged atlas of the macroscale human structural connectome and its network topology. NeuroImage, 178, 57–68. https://doi.org/10.1016/j.neuroimage.2018.05.027
64. Yeh, F. C., Panesar, S., Barrios, J., Fernandes, D., Abhinav, K., Meola, A., & Fernandez-Miranda, J. C. (2019). Automatic Removal of False Connections in Diffusion MRI Tractography Using Topology-Informed Pruning (TIP). Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics, 16(1), 52–58. https://doi.org/10.1007/s13311-018-0663-y
65. Yeh, F. C., Verstynen, T. D., Wang, Y., Fernández-Miranda, J. C., & Tseng, W. Y. (2013). Deterministic diffusion fiber tracking improved by quantitative anisotropy. PloS one, 8(11), e80713. https://doi.org/10.1371/journal.pone.0080713

.

66. Zatorre, R. J., Fields, R. D., & Johansen-Berg, H. (2012). Plasticity in gray and white: neuroimaging changes in brain structure during learning. Nature neuroscience, 15(4), 528–536. https://doi.org/10.1038/nn.3045
67. Zhang, Y., & Burock, M. A. (2020). Diffusion Tensor Imaging in Parkinson's Disease and Parkinsonian Syndrome: A Systematic Review. Frontiers in neurology, 11, 531993. https://doi.org/10.3389/fneur.2020.531993