

Left-lateralized reduced white matter structural connectivity in young women with obesity: analysis of graph theory applied to inter-tract correlation matrices

José Gerardo Suárez-García^a, Eduardo Moreno-Barbosa^a, Javier M. Hernández-López^a, Jorge Velázquez-Castro^a and
Benito de Celis-Alonso^{a*}

^a Faculty of Physical and Mathematical Sciences, Benemérita Universidad Autónoma de Puebla (BUAP), Puebla,
México

*Correspondence author

E-mail address: bdca@fcfm.buap.mx (B. de Celis-Alonso)

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Abstract

Objective: Differences in WM structural connectivity were sought by comparing graph measures from young women with normal weight (D_{norm}) and obesity (D_{over}), studying FA-based inter-tract correlation matrices.

Methods: Undirected binary adjacency matrices were created from WM inter-tract correlation matrices. Sixteen global graph measures were compared between the D_{norm} and D_{over} groups. At the nodal level, four graph measures were compared. Optimal community structures were calculated using the Louvain community detection algorithm. This was done considering all network, as well as the left and right hemispheres separately.

Results: At the global level and considering all network, the D_{over} group had significantly reduced global efficiency compared to the D_{norm} group. Considering only the right hemisphere, none of the graph measures were significantly different between the two groups. Studying only the left hemisphere, the D_{over} group obtained significantly reduced measures compared to the D_{norm} group in five global graph measures. At the nodal level, the D_{over} group obtained significantly reduced graph measures in WM tracts when studying all network and the left hemisphere separately. These tracts were mainly involved in the reward network. The optimal community structures calculated were consistent with the results reported.

Conclusion: The D_{over} group showed altered and reduced structural connectivity in WM tracts compared to the D_{norm} group. The reported tracts are involved in reward processing, inhibitory control, executive decision-making, and cognitive processing. In addition to obtaining results consistent with those reported in the literature, it was additionally observed that the results were lateralized to the left hemisphere.

1. Introduction

Obesity has become a major global public health and economic problem, having been declared a global epidemic by the World Health Organization (WHO) [1]. Around one third of the world's population is overweight or obese. Obesity is known to be associated with various cardiovascular, metabolic, and neuronal diseases. In the neurological context, several studies have found relationships between obesity and the structure and function of brain gray matter (GM) and white matter (WM) [2–6], by analyzing different magnetic resonance imaging (MRI) modalities, such as T1- and T2-weighted, positron emission tomography (PET), single-photon emission computed tomography (SPECT), or diffusion tensor imaging (DTI). Regarding WM, DTI allows the study of tract integrity and coherence through measures such as mean diffusivity (MD), fractional anisotropy (FA), radial diffusivity (Dr), and axial diffusivity (Da) [7]. In particular, FA measures the water diffusivity along axons that form WM tracts. High FA values represent highly organized and normally myelinated axon structures, while low FA values are interpreted as a loss of coherence in the preferred main diffusion direction, resulting in a deficit in WM integrity [8]. Therefore, FA is highly sensitive to WM microstructural changes, making it the most widely used DTI measure to quantify WM features in voxel-based analysis (VBA) and tract-based spatial statistics (TBSS) [9].

A commonly used tool to analyze brain structural and functional connectivity is based on so-called connectomes, which model the complex networks of the human brain, allowing the study of segregation and integration of information processing [10]. Their analysis is based on topology and graph theory, which provides a quantitative method for identifying nodes, edges, and disparate topological parameters, such as clustering coefficient, characteristic path length, and small-worldness (i.e., high levels of local clustering among nodes of a network and short paths that globally link all nodes of the network) [11]. This approach is based on the evidence that large-scale brain networks are intrinsically organized like graphs and show corresponding properties.

Using these tools, several studies have analyzed changes in WM structural connectivity associated with obesity. For example, Chen et al. [12] created structural connectivity matrices through DTI and generalized q-sampling imaging to identify altered brain networks associated with obesity. The authors reported a lower amount of network connections observed in obese subjects compared with non-obese controls. Topological measures of clustering coefficient, local efficiency, global efficiency, and transitivity were significantly lower among obese

subjects. Similarly, three sub-networks were identified to have decreased structural connectivity among frontal–temporal regions in obese subjects.

In another study, Beyer et al. [13] investigated the association of obesity, related genetic variants, and structural connectivity of the dopaminergic reward network, using a graph-theoretic approach to investigate the strength and organization of this network. The connectivity matrices studied were created from DWI data using 82 (sub)cortical regions as nodes and connectivity weights between regions as edges. The weights were evaluated in two ways: one equal to the total number of connecting streamlines touching both regions, and the other equal to the mean FA between voxels included in these streamlines. The authors provided evidence that higher BMI correlates with lower structural connectivity of the reward network.

Studies in healthy subjects have shown that diffusion properties correlate between tracts, and these correlations reflect known phylogenetic development and interhemispheric (a)symmetries [14–16]. For example, Wahl et al. [15] analyzed microstructural correlations between WM tracts and established that there are significant inter-tract correlations across normal adults in tract-based measures of FA, MD, AD and RD. Also, other works have studied WM connectivity by analyzing inter-tract correlations with graph theory in different topics of interest. For example, Dean et al sought to compare the regional interrelatedness of WM microstructure in children with autism spectrum disorder with respect to children with typical development. They reported significant interregional correlations within the WM of both groups, while the strength and clustering configuration of those microstructural correlations were found to be different, being reduced in the autism spectrum disorder group. Recently, Matijevic et al. [17], investigated whether increasing age has a homogenizing effect on DTI measures of WM microstructural integrity between tracts. They compared inter-tract correlation matrices and general WM factors across age groups, observing greater shared variance between DTI tract measures in older adults compared to younger adults.

Although different approaches have been used to investigate whether there are differences in WM structural connectivity between obese subjects compared to normal-weight subjects, to the best of our knowledge, WM connectivity has not been studied by analyzing the regional interrelationship of WM microstructural integrity by comparing FA-based inter-tract correlation matrices. Therefore, in the present work, we aimed to evaluate whether there are topological alterations in WM structural connectivity by analyzing inter-tract correlations in a group of young women with obesity compared to their normal-weight counterparts. Graph theory analysis was

applied at both the global and nodal levels, considering the entire network, as well as the left and right hemispheres separately.

2. Methodology

2.1 Database

In this work, the freely accessible Amsterdam Open MRI Collection (AOMIC) database was used [18]. This database consists of high-quality multimodal 3T MRIs with demographic and psychometric details from a large set of healthy subjects. In particular, a database within AOMIC called ID-1000 was studied. This database contains data representative of the general Dutch population (445 men and 483 women) in terms of educational level (as defined by the Dutch government) but limited to the age range of 19–26 years to minimize the effect of aging on any brain-related covariates. ID-1000 contains raw data as well as preprocessed data from well-established preprocessing and quality control pipelines. Among the different MRI modalities available, preprocessed diffusion-weighted MRI (DWI) was studied in this work, from which derived data consisting of fractional anisotropy (FA) maps were analyzed. For the analysis of WM tracts, the ICBM-DTI-81 white matter labels atlas [19] was used, which is composed of 50 tracts. Considering the FA maps, for each tract, the median FA value of the voxels that comprise it was calculated according to the atlas used. These tract measurements were subsequently analyzed using graph theory.

2.1.1 MRI Scanning protocol

Based on the description included in the database [18], data from ID1000 dataset were scanned on a Philips 3T scanner (Philips, Best, the Netherlands), on the Intera version using a 32-channel head coil. A low-resolution survey scan was made to determine the location of the field-of-view. Three T1-weighted scans, three diffusion-weighted scans, and one functional (BOLD) MRI scan were recorded. For all diffusion scans, the slice stack was not angled. Three scans were obtained with the SE-DWI technique with a b_0 image, 32 diffusion-weighted directions, a half sphere sampling scheme, and DWI b -value equal to 1000 s/mm^2 . Voxel size was equal to $2 \times 2 \times 2 \text{ mm}$, matrix size of

112×112, FOV of 224×224×120, TR = 6370 ms and TE = 75 ms, 60 slices with no slice gap, water-fat shift of 12,861 pixels, flip angle of 90 degrees, bandwidth equal to 33.8 Hz/pixel.

2.1.2 DWI standardization, preprocessing and FA image computing

Preprocessing was already implemented on the database by creators which consists of the following. Data were converted to BIDS, including file renaming, conversion to compressed nifti, and defacing and extraction of metadata. The three DWI scans per participant, the diffusion gradient table, and b-value information were concatenated. Preprocessing was applied to the data using tools from MRtrix3 and FSL. This consisted of denoising the diffusion-weighted data using *dwidenoise* [20,21], removing Gibbs ringing artifacts using *mrdegibbs* [22], and performing eddy current and motion corrections using *dwipreproc*. Within the eddy, a quadratic first-level and linear second-level model and outlier replacement with default parameters were used. Bias correction and brain mask extraction were also performed. To validate the consistency in the data preprocessing steps using MRtrix3 and FSL software, specifically regarding checking the orientation of the diffusion gradient table, the database authors used *dwigradcheck* to correct possible problems of improperly rotated diffusion gradient orientations in diffusion weighted MRI. This algorithm is based on the method proposed by Jeurissen et al. [23]. A diffusion tensor model on the preprocessed diffusion-weighted data using weighted linear least squares with 2 iterations was fit using *dwi2tensor* [24]. From the estimated tensor image, a fractional anisotropy (FA) image was computed and a map with the first eigenvectors was extracted using *tensor2metric*.

2.1.3 Affine aligned into MNI152 standard space

In the present work, an additional affine alignment of the FA images into MNI152 standard space was carried out through two FSL scripts available online (developed originally to perform TBSS) [25]. The first script was *tbss_2_reg*, used to align all FA images to a 1x1x1 mm standard space by performing nonlinear registration and considering the adult-derived target image FMRIB58_FA. The second script was *tbss_3_postreg*, which made nonlinear transformations to bring the images into MNI152 standard space.

2.1.4 Subjects included in the study

Only right-handed young adult women of normal weight and overweight according to their body mass index (BMI) were studied. From the total number of overweight women available in the ID-1000F database (57 subjects with $IBM \geq 30 \text{ kg/m}^2$), a group of subjects called D_{over} was created. Moreover, since the total number of normal-weight women available (273 subjects with $IBM < 25 \text{ kg/m}^2$) was greater than the number of overweight women, 57 normal-weight women were randomly selected, thus creating a group of subjects called D_{norm} , such that both groups had the same number of subjects. Information about the D_{norm} and D_{over} group is shown in Table 1.

	D_{norm}	D_{over}
Subjects	57	57
Age (years)	22.41 ± 1.60	23.07 ± 1.66
BMI (kg/m^2)	21.47 ± 1.88	34.46 ± 4.27

Table 1. Information about D_{norm} and D_{over} groups. The number of subjects according to their weight classification in each group, as well as average age and BMI are shown.

2.1.5 Inter-tract correlation matrix

For each group D_{norm} and D_{over} , a correlation matrix was calculated with entries equal to the Spearman correlation coefficient between the median FA values of pairs of tracts. When all tracts were considered, the matrix had dimensions of 50×50 , with values on its diagonal equal to 1, representing the correlations of a tract with itself. When only the left or right hemisphere was considered, the matrix had dimensions of 22×22 . From the correlation matrices, undirected binary adjacency matrices were constructed for subsequent graph analysis. For their construction, a correlation threshold had to be chosen above which the entries of the matrices were replaced by binary values. That is, if the input was less than the threshold, then it was changed to 0, and if the input was greater than or equal to the threshold, then the input was changed to 1. The nodes of the adjacency matrices corresponded

to the white matter tracts, and the edges to the correlation connections between pairs of tracts after applying the threshold and binarizing the matrix. Therefore, this threshold has an important impact on the topological characteristics of a network, since the higher the threshold, the more dispersed the network would become, and vice versa. The following were considered to choose the appropriate threshold. In order to measure small-worldness characteristics, the graph characteristic called the mean degree of the network had to meet the condition that its value had to be greater than the natural logarithm of the number of edges in the graph. When all 50 tracts were considered, the mean degree of the respective network had to be greater than $\ln(50) = 3.91$. However, when only the left or right hemisphere was considered, the mean degree had to be greater than a $\ln(22) = 3.09$. Since the mean degree value depends on the chosen threshold, adjacency matrices were created with different thresholds, and their respective mean degrees were calculated. The threshold chosen was the largest value such that the required condition was met for both the D_{norm} and D_{over} matrices. Since the entire network, the right hemisphere, and the left hemisphere were studied separately, a separate threshold was chosen for each.

The calculated graph characteristics were the most commonly studied [12,26–28], which were: mean degree, mean cluster coefficient, mean local efficiency, modularity, assortativity, density, edges, transitivity, global efficiency, radius, diameter, mean flow coefficient, and characteristic path length. Three small-world parameters, known as lambda, gamma, and sigma, were also calculated. The small-world parameters were calculated as follows. From the matrices of the groups D_{norm} and D_{over} , the graph measures called clustering coefficient (CC_g) and characteristic path length (CPL_g) were calculated and compared with those of 500 pairs of random graphs, each with the same number of nodes, mean degree, and degree distribution, respectively. Then, the small-world parameters were calculated as $\gamma = \frac{CC_g}{CC_r}$, $\lambda = \frac{CPL_g}{CPL_r}$ and $\sigma = \frac{\gamma}{\lambda}$, where CC_r and CPL_r were the average clustering coefficient and average characteristic path length of the 500 random graphs respectively. A small-world network should satisfy the conditions $\gamma > 1$, $\lambda \sim 1$ and $\sigma > 1$, where small-worldness is a characteristic that represents the balance between global integration and local processing. To compare the graph characteristics of the network of the sets D_{norm} and D_{over} , a permutation test with 5,000 permutations was performed.

At the same time, a graph analysis was performed on each node (or tract) of the network, calculating the following graph measures for each: degree, clustering coefficient, local efficiency, and flow coefficient. Furthermore, the optimal community structure was also calculated using the Louvain community detection algorithm. This structure is a subdivision of the network into groups of non-overlapping nodes, maximizing the number of edges

within the group and minimizing the number of edges between groups. Both the graph characteristics of each node and the optimal community structures were compared between groups by applying a permutation test with 5,000 permutations. Unless otherwise stated, algorithms were developed in MATLAB R2024b, using a conventional computing system (Intel Core i7-12700H, NVIDIA GeForce RTX 3070 Ti, 32 GB RAM). Graph measures were calculated within MATLAB using the freely available Brain Connectivity Toolbox [29].

3. Results

Fig. 1 shows the variation in the threshold applied to the correlation matrices and the calculation of the network's mean degree. This was done to choose the threshold that would allow the calculation of small-worldness variables, fulfilling the condition that the mean degree be greater than the natural logarithm of the number of nodes. For the entire network, there were 50 nodes, and the threshold chosen was 0.53. For the right and left hemispheres, the number of nodes was 22, with thresholds chosen at 0.45 and 0.47, respectively.

The correlation matrices of the D_{norm} and D_{over} groups are shown in Fig. 2(a) and (b), considering the complete network of 50 tracts. The undirected binary adjacency matrices considering a threshold equal to 0.53 are shown in Fig. 2(c) and (d) respectively. Similarly, the correlation matrices and adjacency matrices of the D_{norm} and D_{over} groups are shown in Figs. 3 and 4, considering 22 tracts from the right and left hemispheres using thresholds equal to 0.45 and 0.47 respectively.

Table 2 shows the results of comparing the graph measures of the D_{norm} and D_{over} groups considering the entire network composed of 50 tracts. The significance of the comparisons was obtained after performing a permutation test with 5,000 permutations. Of the 16 graph measures calculated, only global efficiency showed significant differences ($p < 0.05$) between the two study groups. Table 3 shows the results of the graph measures considering only the right hemisphere. No measurement obtained significant differences after comparing the results of both study groups after the permutation test. Table 4 shows the results considering the left hemisphere. In this case, mean degree, mean clustering coefficient, density, number of edges and the small-worldness parameter lambda showed significant differences ($p < 0.05$) between the D_{norm} and D_{over} groups.

For the analysis of graph measures for individual nodes (or tracts), considering the entire network of 50 nodes, Table 5 contains information on the tracts that showed significant differences when comparing the D_{norm} and D_{over} groups after performing a permutation test with 5,000 permutations. For the degree, cluster coefficient, local efficiency, and flow coefficient measures, the number of tracts that obtained significant differences was equal to 10, 5, 6, and 4, respectively. Considering only 22 nodes from the left hemisphere, Table 6 shows the tracts that obtained significant differences for the four node graph measures mentioned above. In this case, 5, 1, 2, and 1 tracts, respectively, showed significant differences. Similarly, Table 7 shows information considering 22 nodes from the right hemisphere. Only one tract (Tapetum R) obtained significant differences when measuring the node's cluster coefficient, local efficiency, and flow coefficient.

After calculating the optimal community structures using the Louvain community detection algorithm, considering the entire network of 50 nodes, Figs. 4(a) and (b) show the 5 and 6 communities formed for the D_{norm} and D_{over} groups, respectively, such that the number of edges within a community is maximized and the number of edges between communities is minimized, all without overlap. Similarly, considering the nodes in the right hemisphere, Figs. 5(a) and (b) show the 3 and 4 communities formed for the D_{norm} and D_{over} groups, respectively. Figs. 6(a) and (b) show the 2 and 3 communities formed for the D_{norm} and D_{over} groups, respectively, considering only the left hemisphere.

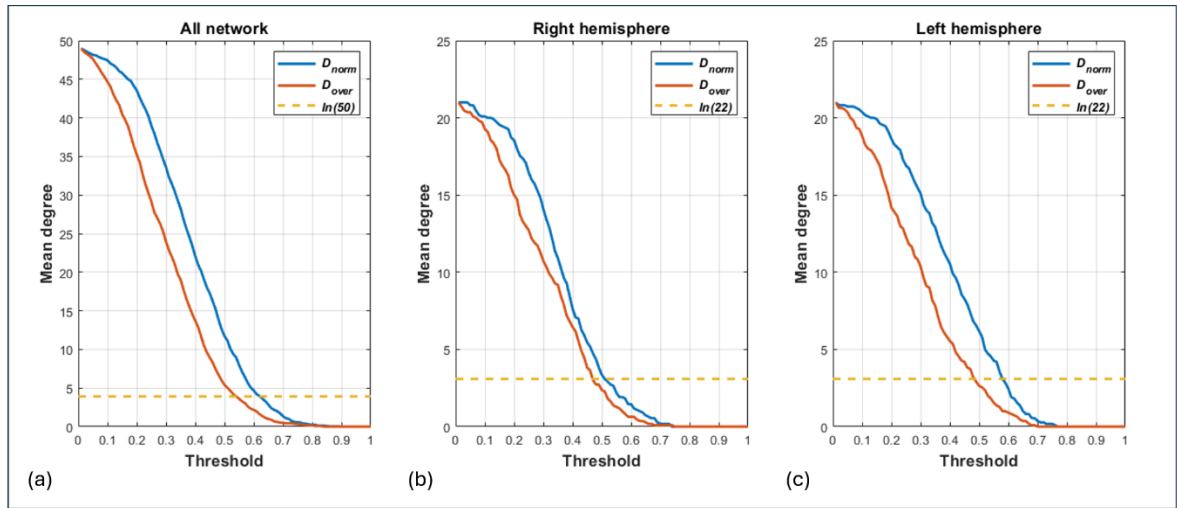


Figure 1. Mean degree vs. threshold. (a) By varying the threshold applied to the correlation matrices, the condition that the mean degree of the D_{norm} and D_{over} groups be greater than $\ln(50) = 3.91$ throughout the network was met with a threshold of 0.53. For the right (b) and left (c) hemispheres, considering the value of $\ln(22) = 3.09$, the condition was met with thresholds equal to 0.45 and 0.47 respectively.

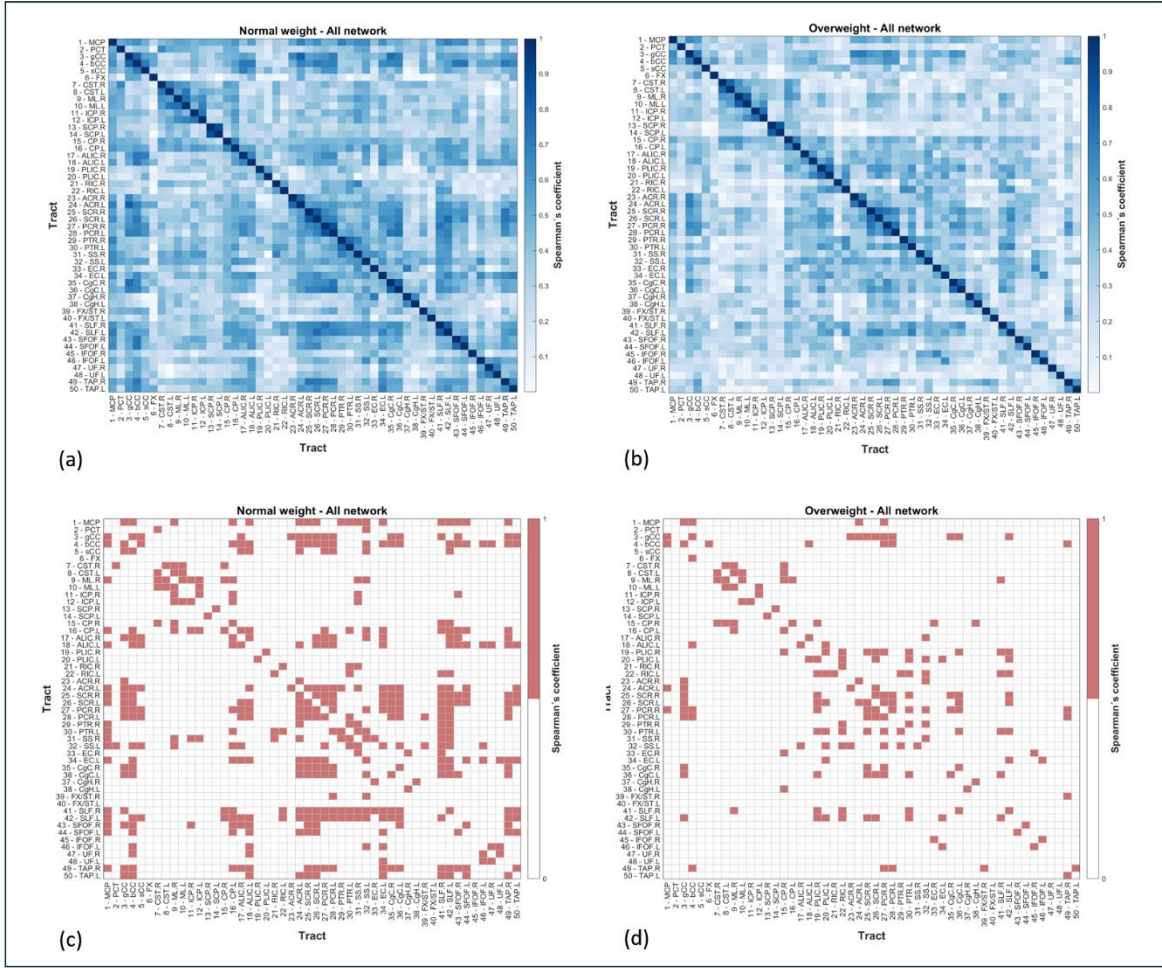


Figure 2. All network matrices. The correlation matrices of the (a) D_{norm} and (b) D_{over} groups are shown, considering the complete network composed of 50 tracts, and whose entries were the Spearman correlation coefficients between pairs of tracts. Undirected binary adjacency matrices of the (c) D_{norm} and (d) D_{over} groups respectively, using a threshold equal to 0.53.

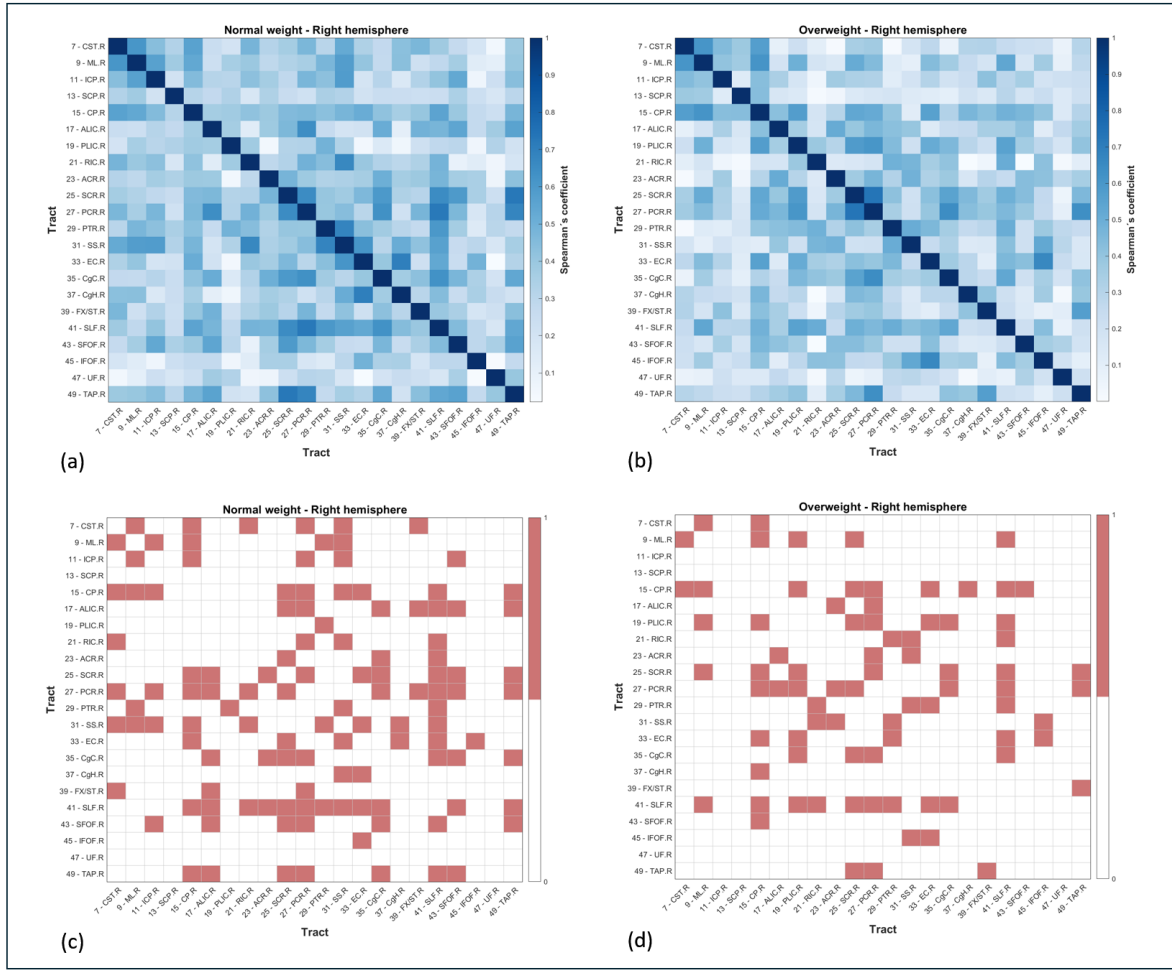


Figure 3. Right hemisphere matrices. The correlation matrices of the (a) D_{norm} and (b) D_{over} groups are shown, considering the right hemisphere composed of 22 tracts, and whose entries were the Spearman correlation coefficients between pairs of tracts. Undirected binary adjacency matrices of the (c) D_{norm} and (d) D_{over} groups respectively, using a threshold equal to 0.45.

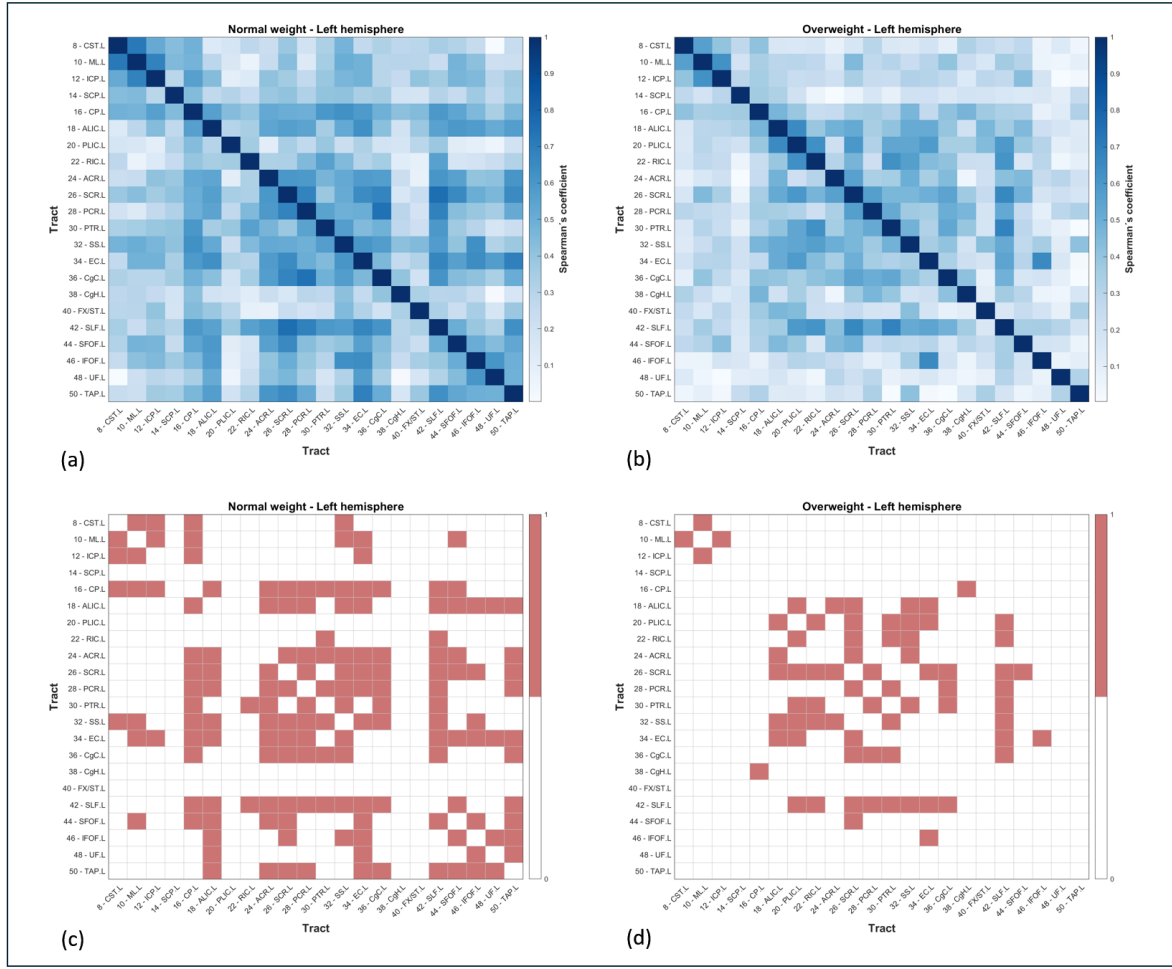


Figure 4. Left hemisphere matrices. The correlation matrices of the (a) D_{norm} and (b) D_{over} groups are shown, considering the left hemisphere composed of 22 tracts, and whose entries were the Spearman correlation coefficients between pairs of tracts. Undirected binary adjacency matrices of the (c) D_{norm} and (d) D_{over} groups respectively, using a threshold equal to 0.47.

All network - 50 tracts					
Graph measure	<i>D_{norm}</i>		<i>D_{over}</i>		p-value
	Mean	SD	Mean	SD	
Mean degree	9.826	0.910	3.241	0.442	0.0690
Mean clustering coefficient	0.530	0.034	0.256	0.038	0.0580
Mean local efficiency	0.459	0.033	0.242	0.039	0.1786
Modularity	0.240	0.029	0.518	0.047	0.0934
Assortativity	0.093	0.062	0.301	0.076	0.2388
Density	0.201	0.019	0.066	0.009	0.0690
Number of edges	245.638	22.755	81.032	11.038	0.0690
Transitivity	0.577	0.032	0.378	0.038	0.0802
Global efficiency	0.566	0.022	0.377	0.026	0.0384
Radius	1.001	0.054	1.285	0.829	0.8872
Diameter	5.334	0.737	8.288	1.209	0.2566
Mean flow coefficient	0.386	0.051	0.384	0.050	0.2068
Characteristic path length	2.193	0.134	3.540	0.338	0.0714
Small-worldness					
λ	1.036	0.070	1.237	0.100	0.2046
γ	1.288	0.140	2.788	0.719	0.1706
σ	1.183	0.151	2.385	0.719	0.2188

Table 2. Graph measures considering all network. The results obtained by comparing the graph measures of the D_{norm} and D_{over} groups after performing a permutation test with 5,000 permutations are shown. The mean, standard deviation (SD), and significance (p-value) for each graph measure are indicated. The shaded row indicates the measure that obtained significant differences ($p < 0.05$).

Right hemisphere - 22 tracts					
Graph variable	D_{norm}		D_{over}		p-value
	Mean	SD	Mean	SD	
Mean degree	6.262	0.910	2.967	0.513	0.2706
Mean clustering coefficient	0.552	0.053	0.327	0.067	0.2670
Mean local efficiency	0.561	0.043	0.350	0.067	0.3006
Modularity	0.233	0.043	0.373	0.063	0.4374
Assortativity	-0.137	0.077	0.057	0.108	0.3358
Density	0.300	0.043	0.140	0.024	0.2624
Number of edges	68.881	10.011	32.640	5.648	0.2706
Transitivity	0.531	0.048	0.398	0.053	0.3246
Global efficiency	0.639	0.037	0.508	0.036	0.2932
Radius	1.815	0.408	2.913	0.508	0.3618
Diameter	3.666	0.550	5.352	0.807	0.3772
Mean flow coefficient	0.360	0.071	0.358	0.070	0.3818
Characteristic path length	1.855	0.134	2.488	0.255	0.3182
Small-worldness					
λ	1.087	0.055	1.021	0.056	0.4948
γ	1.893	0.616	1.269	0.144	0.4564
σ	1.825	0.853	1.216	0.138	0.4542

Table 3. Graph measures considering the right hemisphere. The results obtained by comparing the graph measures of the D_{norm} and D_{over} groups after performing a permutation test with 5,000 permutations are shown. The mean, standard deviation (SD), and significance (p-value) for each graph measure are indicated. No measure obtained significant differences ($p < 0.05$).

Left hemisphere - 22 tracts					
Graph variable	D_{norm}		D_{over}		p-value
	Mean	SD	Mean	SD	
Mean degree	7.123	0.537	2.524	0.369	0.0436
Mean clustering coefficient	0.629	0.050	0.248	0.055	0.0474
Mean local efficiency	0.577	0.039	0.269	0.043	0.0722
Modularity	0.177	0.030	0.344	0.051	0.2382
Assortativity	-0.133	0.090	0.130	0.103	0.2696
Density	0.338	0.026	0.120	0.017	0.0456
Number of edges	78.018	6.011	27.811	4.017	0.0456
Transitivity	0.628	0.042	0.399	0.053	0.1620
Global efficiency	0.650	0.038	0.544	0.041	0.2878
Radius	2.702	0.587	1.467	0.543	0.3854
Diameter	4.006	0.698	4.882	0.954	0.6294
Mean flow coefficient	0.321	0.073	0.317	0.071	0.3686
Characteristic path length	1.874	0.159	2.309	0.255	0.3616
Small-worldness					
λ	1.179	0.110	0.894	0.106	0.0304
γ	1.119	0.113	1.714	0.364	0.3158
σ	1.031	0.124	2.110	0.568	0.1084

Table 4. Graph measures considering the left hemisphere. The results obtained by comparing the graph measures of the D_{norm} and D_{over} groups after performing a permutation test with 5,000 permutations are shown. The mean, standard deviation (SD), and significance (p-value) for each graph measure are indicated. The shaded rows indicate the measures that obtained significant differences ($p < 0.05$).

All network					
Tract	D_{norm}		D_{over}		p-value
	Mean	SD	Mean	SD	
Degree					
4 - Body of corpus callosum	23.660	1.637	6.547	1.868	0.0318
19 - Posterior limb of internal capsule R	1.031	0.406	11.813	1.969	0.0448
24 - Anterior corona radiata L	19.983	1.745	3.161	0.891	0.0348
31 - Sagital stratum R	13.720	2.374	0.960	0.777	0.0200
34 - External capsule L	18.322	2.538	1.475	0.730	0.0484
43 - Superior fronto-occipital fasciculus R	13.952	1.984	1.070	0.442	0.0372
44 - Superior fronto-occipital fasciculus L	13.399	2.002	1.631	0.720	0.0396
47 - Uncinate fasciculus R	4.757	1.068	0.064	0.246	0.0404
49 - Tapetum R	17.304	1.954	2.696	1.077	0.0184
50 - Tapetum L	11.917	1.782	0.417	0.515	0.0024
Cluster coefficient					
16 - Cerebral peduncle L	0.224	0.174	0.858	0.183	0.0412
17 - Anterior limb of internal capsule R	0.816	0.084	0.015	0.052	0.0274
23 - Anterior corona radiata R	0.976	0.069	0.280	0.108	0.0182
27 - Posterior corona radiata R	0.724	0.072	0.309	0.084	0.0346
44 - Superior fronto-occipital fasciculus L	0.898	0.061	0.010	0.037	0.0206
Local efficiency					
17 - Anterior limb of internal capsule R	0.901	0.035	0.001	0.011	0.0254
18 - Anterior limb of internal capsule L	0.831	0.042	0.004	0.027	0.0280
23 - Anterior corona radiata R	0.959	0.073	0.234	0.143	0.0162
27 - Posterior corona radiata R	0.824	0.047	0.458	0.115	0.0316
44 - Superior fronto-occipital fasciculus L	0.944	0.028	0.000	0.000	0.0190
49 - Tapetum R	0.831	0.073	0.100	0.123	0.0370
Flow coefficient					
17 - Anterior limb of internal capsule R	0.166	0.094	0.976	0.063	0.0186
18 - Anterior limb of internal capsule L	0.192	0.169	0.840	0.169	0.0466
23 - Anterior corona radiata R	0.007	0.032	0.693	0.067	0.0166
27 - Posterior corona radiata R	0.275	0.071	0.689	0.081	0.0344

Table 5. Graph measures for individual nodes considering all network. The results obtained for four nodal measures are shown after performing a permutation test with 5,000 permutations. All tracts contained in the table obtained significant differences ($p < 0.05$). Blue shaded cells indicate the highest mean values when comparing D_{norm} and D_{over} groups

Left hemisphere					
Tract	D_{norm}		D_{over}		p-value
	Mean	SD	Mean	SD	
Degree					
16 - Cerebral peduncle L	14.354	1.175	1.120	0.760	0.0350
44 - Superior fronto-occipital fasciculus L	9.918	1.330	0.826	0.733	0.0368
46 - Inferior fronto-occipital fasciculus L	7.899	1.201	1.005	0.219	0.0378
48 - Uncinate fasciculus L	4.795	1.045	0.021	0.142	0.0390
50 - Tapetum L	10.375	0.518	0.000	0.000	0.0016
Cluster coefficient					
26 - Superior corona radiata L	0.816	0.091	0.269	0.085	0.0120
Local efficiency					
16 - Cerebral peduncle L	0.860	0.073	0.030	0.063	0.0204
26 - Superior corona radiata L	0.844	0.057	0.366	0.093	0.0310
Flow coefficient					
26 - Superior corona radiata L	0.184	0.091	0.731	0.085	0.0120

Table 6. Graph measures for individual nodes considering the left hemisphere. The results obtained for four nodal measures are shown after performing a permutation test with 5,000 permutations. All tracts contained in the table obtained significant differences ($p < 0.05$). Blue shaded cells indicate the highest mean values when comparing D_{norm} and D_{over} groups

Right hemisphere					
Tract	D_{norm}		D_{over}		p-value
	Mean	SD	Mean	SD	
Cluster coefficient					
49 - Tapetum R	0.870	0.156	0.251	0.181	0.0392
Local efficiency					
49 – Tapetum R	0.863	0.093	0.125	0.147	0.0254
Flow coefficient					
49 – Tapetum R	0.092	0.131	0.706	0.161	0.0346

Table 7. Graph measures for individual nodes considering the right hemisphere. The results obtained for nodal measures are shown after performing a permutation test with 5,000 permutations. The tract contained in the table obtained significant differences ($p < 0.05$). Blue shaded cells indicate the highest mean values when comparing D_{norm} and D_{over} groups

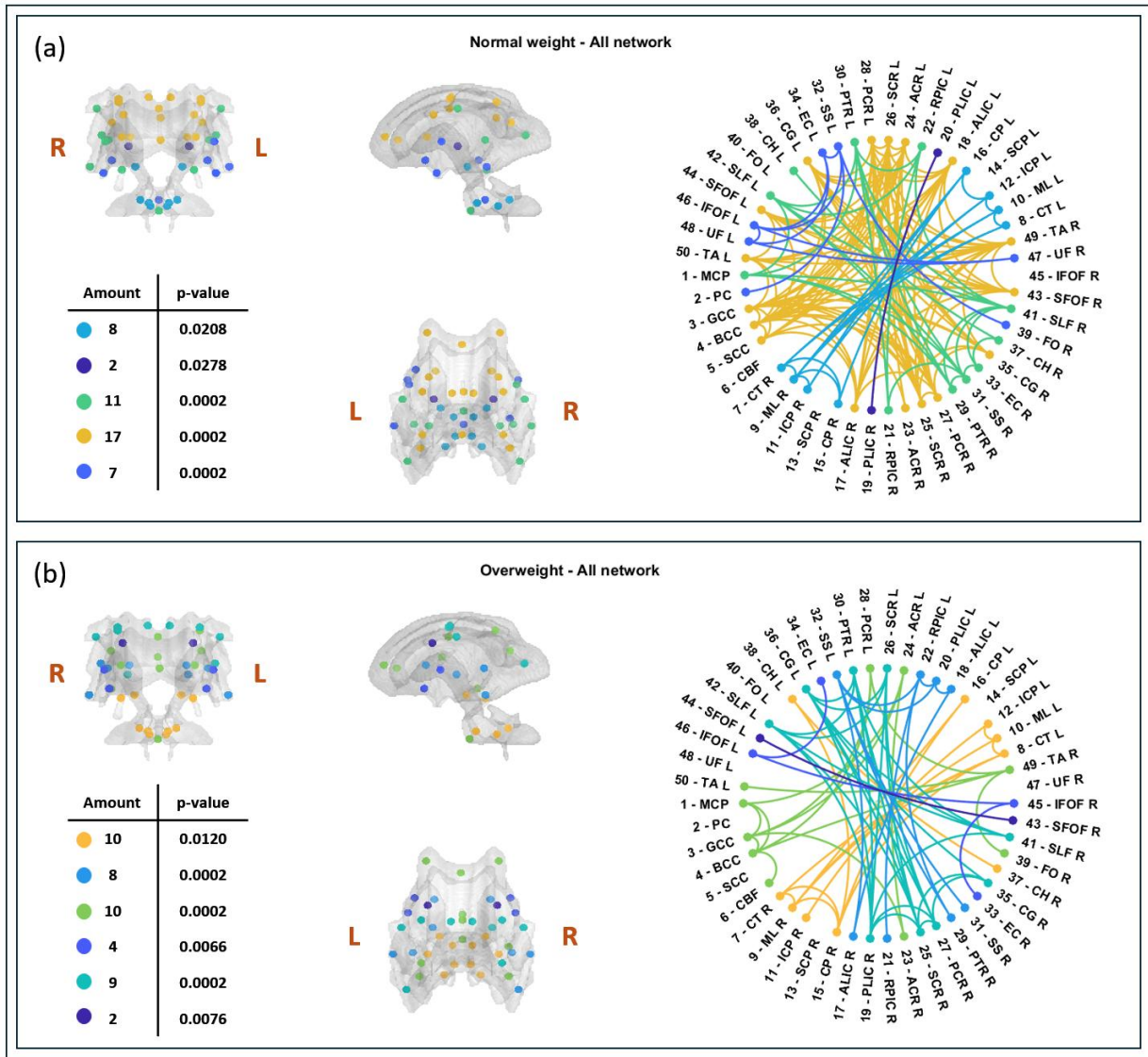


Figure 4. Optimal community structures considering all network. After applying the Louvain community detection algorithm to the network, the 5 and 6 communities formed are shown for groups (a) D_{norm} and (b) D_{over} groups, respectively. The amount of tracts that comprise each community and their significance after applying a permutation test with 5,000 permutations are indicated. All communities shown were significant ($p < 0.05$). Colored dots indicate the location of the centroid of the tracts included in the communities on three WM views. A connectome indicates the connections between pairs of tracts, differentiated by colors according to the community to which they belong. The connections are based on the undirected binary adjacency matrix of each group.

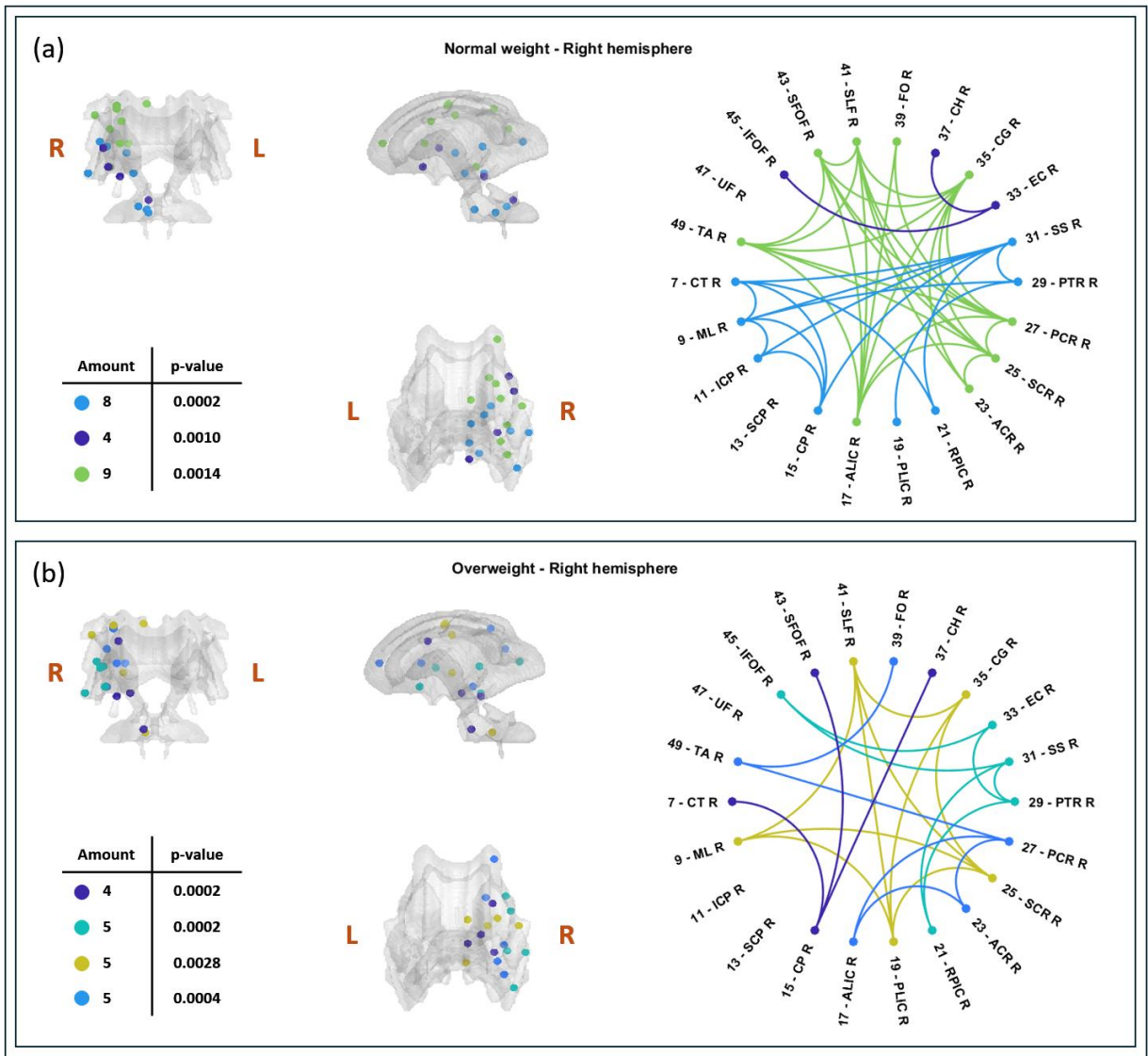


Figure 5. Optimal community structures considering the right hemisphere. After applying the Louvain community detection algorithm to the network, the 3 and 4 communities formed are shown for groups (a) D_{norm} and (b) D_{over} groups, respectively. The amount of tracts that comprise each community and their significance after applying a permutation test with 5,000 permutations are indicated. All communities shown were significant ($p < 0.05$). Colored dots indicate the location of the centroid of the tracts included in the communities on three WM views. A connectome indicates the connections between pairs of tracts, differentiated by colors according to the community to which they belong. The connections are based on the undirected binary adjacency matrix of each group.

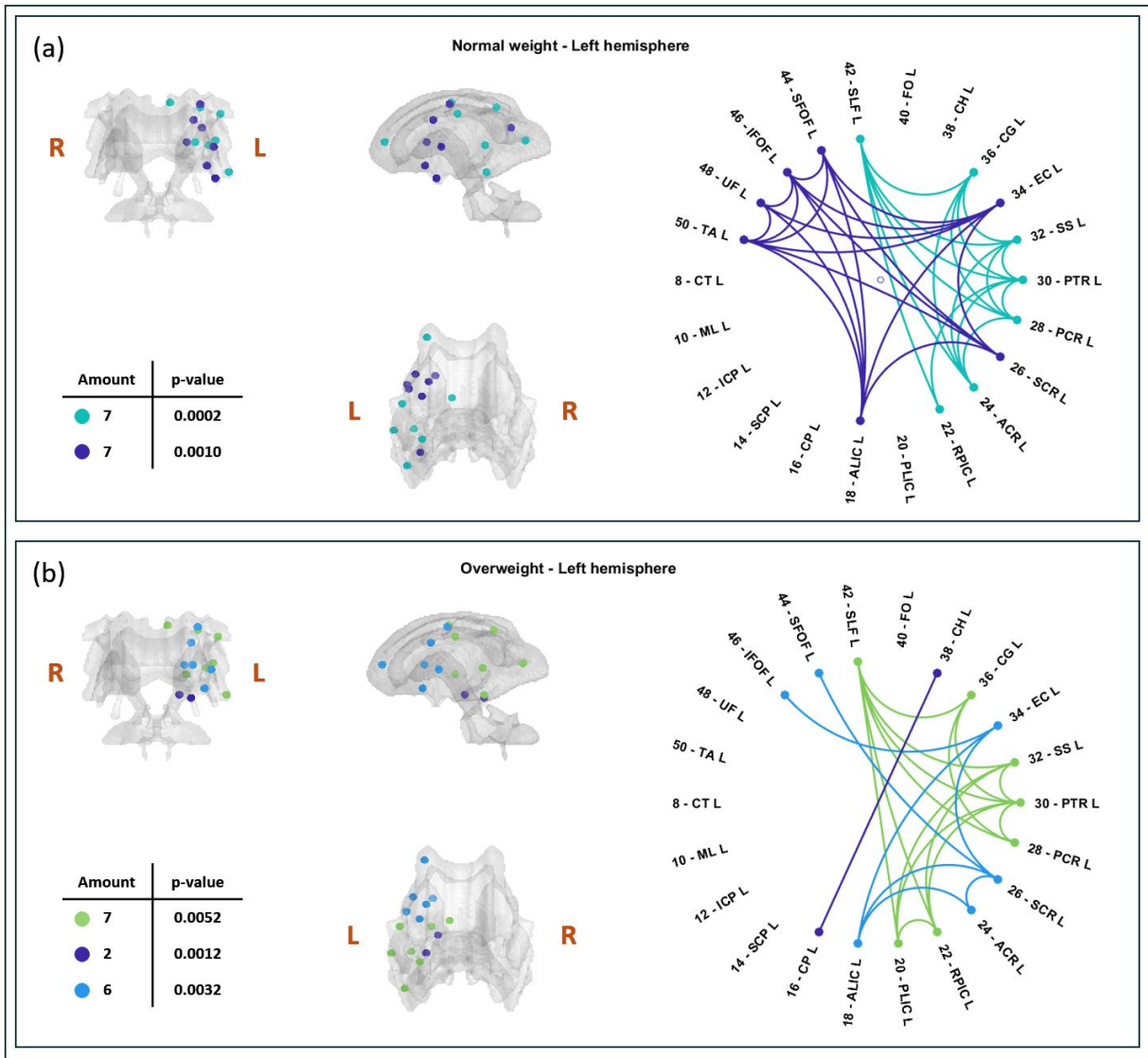


Figure 6. Optimal community structures considering the left hemisphere. After applying the Louvain community detection algorithm to the network, the 2 and 3 communities formed are shown for groups (a) D_{norm} and (b) D_{over} groups, respectively. The amount of tracts that comprise each community and their significance after applying a permutation test with 5,000 permutations are indicated. All communities shown were significant ($p < 0.05$). Colored dots indicate the location of the centroid of the tracts included in the communities on three WM views. A connectome indicates the connections between pairs of tracts, differentiated by colors according to the community to which they belong. The connections are based on the undirected binary adjacency matrix of each group.

4. Discussion

In this study, we aimed to investigate whether there were differences in WM structural connectivity between young women with obesity (D_{over} group) and those with normal weight (D_{norm} group). To this end, inter-tract correlation matrices were analyzed using a measure of WM integrity known as FA and applying graph theory to analyze the topological characteristics of the network at the global and nodal levels, considering all network, as well as the right and left hemispheres separately.

4.1 Global level

4.1.1 All network

At the global level and considering all network, the results obtained in this work indicated that the D_{over} group showed significantly reduced global efficiency compared to the D_{norm} group. Global efficiency characterizes the efficiency of a network transporting information in parallel [27]. Thus, the results obtained demonstrated that the D_{over} group was characterized by lower efficiency in information transfer across the entire network compared to the D_{norm} group. Although both groups exhibited small-worldness characteristics in the FA-based networks ($\gamma > 1$, $\lambda \sim 1$ and $\sigma > 1$), none of the network parameters showed significant differences when comparing the D_{norm} and D_{over} groups.

4.1.2 Right and left hemispheres

When considering only the right hemisphere, none of the graph measures studied showed significant differences between the two groups. On the other hand, when considering only the left hemisphere, the D_{over} group showed a significant reduction in the mean degree, mean clustering coefficient, and the density and number of edges in the network. Regarding small-worldness characteristics, the D_{over} group showed a reduction in the Lambda parameter

compared to the D_{norm} group. The mean degree of a network is the average number of links connected to an individual node and provides a measure of network density. The mean clustering coefficient represents an average measure of the local connectivity of the network. Small-worldness characteristics represent an optimal balance between global integration and local processing [26]. Thus, the results indicated that the D_{over} group showed a greater left lateralized imbalance between connectivity and structural organization compared to the D_{norm} group.

These results are consistent with what has been reported by other works, which demonstrated in obese subjects lower structural connectivity between cortical regions of the left hemisphere. For example, Tan et al. [30] found altered structural and functional connectivity of the basal ganglia in obese patients. The basal ganglia play a key role in response to food cue stimulations in the control of eating behaviors and are heavily involved in inhibitory control. Specifically, through probabilistic tractography, the authors identified WM tracts between the left caudate (within the basal ganglia network) and the left dorsolateral prefrontal cortex, reporting lower structural connectivity measured with FA in obese patients. In another study, Li et al. [31], reported significant alterations in left lateralized functional connectivity within the default mode network (DMN), ventral attention network (VAN), and visual network (VN) in women with abdominal obesity. Specifically, in the DMN, they found reduced connectivity in the left precuneus, while in the VAN and VN, they found reductions in regions associated with attention control and visual processing, including the left inferior parietal gyrus, left inferior frontal gyrus, triangular part, and left calcarine fissure.

4.2 Nodal level

4.2.1 All network

In the analysis at nodal level considering all network, most of the tracts that showed significant differences ($p < 0.05$) in graph measures when comparing both groups, obtained reduced measures for the D_{over} group compared to the D_{norm} group. These measures were node degree, cluster coefficient and local efficiency. Opposite results were obtained for the flow coefficient, although it is consistent since the flow coefficient is inversely related to the cluster coefficient. Node degree is the number of links connected to the node. Clustering coefficient is the fraction of

triangles around a node and is equivalent to the fraction of neighbors that are neighbors of each other. Local efficiency is the overall efficiency calculated over a node's neighborhood. Flow coefficient is similar to betweenness centrality, but calculates centrality based on local neighborhoods [29]. Therefore, the D_{over} group obtained in the reported tracts a lower structural connectivity within their local network or neighborhood, in addition to being less efficient in transmitting information.

Among these tracts, the anterior limb of the internal capsule was found bilaterally. In this, the D_{over} group obtained a significant reduction in local efficiency and clustering coefficient (with the respective increase in flow coefficient), compared to the D_{norm} group. In the literature, it has been reported that the anterior limb of the internal capsule mediates the reward-guided learning by conducting fibers from the prefrontal cortex to the thalamus and brainstem [32]. Thus, this tract plays a vital role within the fronto-striatal network that is strongly involved in reward processing [33]. Moreover, it is known that obesity is associated with a reduction in the structural connectivity of the reward network. For example, it has recently been shown that in adolescents and young adults, higher BMI is associated with lower strength of structural connectivity for FA in the reward network [34]. Therefore, the result obtained in the present work on the anterior limb of internal capsule tract is consistent with what has been reported in the literature.

Among the tracts that showed reduced measures in the D_{over} group compared to the D_{norm} group considering all network, were the right anterior and posterior corona radiata, as well as the left cerebellar peduncle, with a significant reduction in local efficiency and clustering coefficient (with the respective increase in flow coefficient). The corona radiata is part of the limbic-thalamo-cortical circuitry that is critical for cognitive and reward processes [35], and it has been reported to be associated with eating disorders. Furthermore, the cerebellar peduncle originates primarily from the prefrontal cortex, which controls reward processing, inhibitory control, and executive decision-making [36].

4.2.2 Right and left hemispheres

When considering the left and right hemispheres separately, all tracts that showed significant differences in graph measures between the two groups indicated reduced measurements for the D_{over} group compared to the D_{norm} group. As observed, most of the reported tracts were found during the study of the left hemisphere (only the tapetum was

reported when studying only the right hemisphere). Thus, as observed during the global level analysis, studying the left and right hemispheres separately at the nodal level also yielded results that suggest a greater left-lateralized imbalance between connectivity and structural organization in the *D_{over}* group.

Among the tracts reported in the nodal analysis when studying only the left hemisphere was found again the left cerebellar peduncle, this time the left superior corona radiata (before were the right anterior y posterior corona radiata considering all network), in addition to the left uncinate fasciculus. In all these tracts, the *D_{over}* group obtained reduced graph measurements. It is worth mentioning that when considering the all network, the *D_{over}* group obtained reduced node degree also in the right uncinate fasciculus. The uncinate fasciculus is an association tract, connecting different cortical areas within the same hemisphere. This tract connects the temporal pole with the inferior frontal lobe and posterior orbitofrontal cortices, regions important for monitoring and learning the emotional (especially reward) value of stimuli [37]. Several studies have reported reduced FA in this tract associated with obesity [4].

Overall and as described before, the cerebellar peduncle, uncinate fasciculus, and superior corona radiata tracts are involved in networks that control reward processing, inhibitory control, and decision-making. Consistent with the results obtained in this study, a reduction in the structural connectivity of these tracts in obese individuals has been reported in the literature [38].

4.3 Optimal community structures

As mentioned before, the optimal community structures were calculated using the Louvain community detection algorithm. These structures are subdivisions of the network into groups maximizing the number of edges within the communities and minimizing the number of edges between communities. This process was done considering all network, as well as the left and right hemispheres separately.

4.3.1 Optimal all network and right hemisphere communities

Communities calculated considering the entire network and studying only the right hemisphere presented similar characteristics (Figs. 4 and 5). In both cases, the D_{norm} group, compared to the D_{over} group, obtained a smaller number of optimal community structures, containing a larger number of tracts, in addition to presenting a greater number of connections between them. Therefore, this was indicative that the D_{norm} group showed more efficient structural connectivity, with a smaller number of communities containing highly connected tracts.

4.3.2 Optimal left hemisphere communities

Observing the results obtained from the nodal-level analysis considering only the left hemisphere (Fig. 6), communities were calculated for the D_{norm} and D_{over} groups, which had tracts and connections in common for both groups. One of these common communities calculated for both groups included the following tracts from the left hemisphere: superior longitudinal fasciculus, cingulate gyrus, sagittal stratum, posterior thalamic radiation, posterior corona radiata, and retrolenticular part of internal capsule. However, in another common community calculated for both groups, although it also had some tracts and connections in common, the D_{over} group presented a lower number of tracts and connections. This second community included the following tracts from the left hemisphere: inferior and superior fronto-occipital fasciculus, external capsule, superior corona radiata, and anterior limb of internal capsule. Regarding the anterior limb of internal capsule, in the D_{over} group community, this tract did not present connections with the inferior and superior fronto-occipital fasciculus tracts, as it did in the community calculated for the D_{norm} group. Furthermore, in the D_{norm} group community, two other tracts were included: tapetum and uncinatus fasciculus, which also presented connections with the anterior limb of internal capsule. In the discussion of the nodal-level analysis considering only the left hemisphere, the D_{over} group showed lower structural connectivity compared to the D_{norm} group in different tracts, including the inferior and superior fronto-occipital fasciculus. This result was then reproduced when calculating the optimal community structures. Furthermore, as previously discussed, the D_{norm} group, unlike the D_{over} group, included the uncinatus fasciculus tract within its community, which was also connected to the inferior and superior fronto-occipital fasciculus tracts and the anterior limb of the internal capsule. These results demonstrate once again that the D_{over} group showed reduced and altered structural connectivity in key WM tracts involved in the reward-guided learning, and monitoring the emotional value of stimuli [32–34]. All this being, in addition, presented as left-lateralized results.

4.6. Limitations and future work

Among the limitations of this work were the sample sizes for the D_{norm} and D_{over} groups. Also, by studying only young women, there may have been a lack of generalizability by restricting the demographic variables of the subjects studied. Furthermore, subject classification was based solely on BMI measurement, which is sensitive to lean mass. It is now known that other obesity factors, such as the amount of visceral abdominal fat, can have a greater effect on brain covariates compared to lean mass; therefore, other obesity measures should be used in the future for subject classification. Further independent studies would need to reproduce the results obtained in the search for left lateralization in the differences in structural connectivity of WM associated with obesity, studying different databases with larger numbers of samples, in addition to obtaining results in other age ranges and including men.

5. Conclusions

Differences in WM structural connectivity were sought by comparing graph measures from young women with normal weight (D_{norm}) and obesity (D_{over}) using graph-theoretic analysis applied to undirected binary adjacency matrices from FA-based WM tract correlation matrices (this type of matrices not usually studied by other works). The D_{over} group showed altered and reduced structural connectivity in WM tracts compared to the D_{norm} group. The reported tracts are involved in reward processing, inhibitory control, executive decision-making, and cognitive processing. In addition to obtaining results consistent with those reported in the literature, there was the additional finding that the results were lateralized to the left hemisphere. All of the above should be useful in the future for developing new therapies to address and prevent the brain-related consequences observed in patients suffering from obesity.

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