# Obesity and brain topological organization differences throughout the lifespan.

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**Abstract – Life expectancy and obesity rates have drastically increased in recent years. An unhealthy weight is related to long-lasting biological deregulations that might compromise the normal course of development and jeopardize the so-called "successful aging". The aim of the current study was to test whether an obesity status could mimic or exacerbate the topological organization of an aged brain. Also, we explored potential differences in brain maturation in presence of an obesity status. Thus, the current study included adults with (N = 32, mean age 34.5 ± 6.49) and without obesity (N = 34, mean age 32.7 ± 6.79) as well as adolescents with obesity (N = 30, mean age 15.3 ± 2.64) and normal-weight (N = 31, mean age 15.6 ± 2.60). A sample of stroke-free non-obese and non-demented seniors was also entered (N = 32, mean age 66.1 ± 7.43). Participants underwent resting-state MRI acquisition and graph-based measurements of segregation, integration and robustness (i.e., mean degree and strength) were calculated. Our results showed that adults with obesity displayed increases in whole-brain weakening (i.e., lower mean degree and strength) when compared to healthy-weight adults and seniors, as well as increases in network segregation relative to elders. No interaction emerged when exploring the transition from childhood to adulthood accounting for body-weight status. Altogether, this pattern might negatively affect network-resilience and pave the way to an unsuccessful aging of the brain.**

**Obesity | Aging | Maturation | Resting-state | Graph-theory**
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## Introduction

Our life expectancy is longer than it has ever been before. Above 30% of the population from Western developed countries will be older than 60 years by 2050 (WHO, 2015). For this reason, research on the psychobiological factors that have an impact on the so-called "successful aging" is rapidly gaining popularity. One of such factors is obesity. The World Health Organization (WHO) estimates that the prevalence of obesity has tripled in the last decades (WHO, 2017). This numbers are particularly virulent among youngsters, as in 2016 over 340 million children and adolescents were overweight or obese (WHO, 2018). The consequences of obesity involve several chronic conditions, such as type II diabetes, cardiovascular diseases and cancer (Wade, Carslake, Sattar, Davey Smith, & Timpson, 2018). On a similar note, obesity could accelerate brain aging (Ronan et al., 2016; Tzanetakou, Katsilambros, Benetos, Mikhailidis, & Perrea, 2012), increasing the risks of suffering late-onset dementia, such as Alzheimer's disease and vascular dementia (Bischof & Park, 2015). The neurobiological mechanisms behind this, however, remain largely elusive. Neuroanatomical studies suggest that obesity is associated with reductions in gray matter (GM) volume (García-García et al., 2018) and alterations in white matter (WM) microstructure (Repple et al., 2018; Zhang et al., 2018). Likewise, yet to a lesser extent, changes within these tissues can also be observed in child and adolescents (Kennedy, Collins, & Luciana, 2016; Ou, Andres, Pivik, Cleves, & Badger, 2015). Therefore, morphologically at least, an obesity status could induce changes in the brain that resemble those prompted by aging.

The functional organization of the brain is intricate. Distinct and anatomically distant regions interact with each other contributing to cognitive function. Graph-based indexes could serve as proxies of the complex rendering of large-scale networks. Measures of segregation, such as modularity, represent how topologically neighboring brain nodes tend to aggregate as independent clusters (Rubinov & Sporns, 2010). This community-based organization underpins the principle of brain economics where modules specialize onto processing certain sources of information, principally those of sensory nature (Wig, 2017). Integration indexes reflect instead to which extent a priori unrelated modules interchange information. A typical surrogate of integration is the characteristic path length. This parameter reflects the shortest path between modules (Rubinov & Sporns, 2010). Hence, the fewer the jumps, the greater the between-communities integration. Well-balanced short and long-range connections allow the rapid combination of resources necessary for higher cognitive activity. Finally, nodal degree and strength mirror the network integrity and efficiency by averaging the amount and the weight of connections a given node has with the rest of the brain (Rubinov & Sporns, 2010). Densely interconnected nodes are metabolically costly and commonly referred

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to as "hubs" as they exert as bridges coupling remote networks (van den Heuvel & Sporns, 2013).

Aging is associated with losses in the differentiation between well-defined circuits. In other words, nodes that belong to independent communities in younger adults tend to enhance their communications in older adults. These losses in network discreteness could expose either the recruitment of age-related compensatory mechanisms (Geerligs, Renken, Saliasi, Maurits, & Lorist, 2015), the decreases in the number of nodes and short-range connections (Sala-Llonch et al., 2014), or both. Similarly, during childhood and adolescence, the developing brain progressively steps from highly clustered and randomly wired communities towards less modular ones with an optimal number of connections (Boersma et al., 2013). These are thought to reflect age-related changes in GM/WM tissue (i.e., axonal pruning, cell-shrinkage) (Cao et al., 2014).

To date, and to the best of our knowledge, only three studies have explored the brain functional organization in obese individuals with graph-theoretical parameters. Two works reported lower modularity in individuals with obesity when compared to healthy-weight subjects (Baek, Morris, Kundu, & Voon, 2017; Chao et al., 2018). A third study described global brain connectivity decreases mainly within prefrontal circuits (Geha, Cecchi, Todd Constable, Abdallah, & Small, 2017). The current study had two aims. The first and main objective was to explore whether an obesity status is linked to brain connectivity patterns similar to those present in elders. To achieve this, we matched adults with and without obesity and non-obese healthy seniors. The second aim was to examine if an obesity condition could differently shape the brain topological organization during maturation. To answer this, we tested for interactions between body-weight status in adults and adolescents.

## Methods

**Participants.** Two independently collected samples were included in this work. One sample comprised 32 non-obese healthy seniors (51-85 years old). The recruitment procedure of this group is fully described in Abós et al. (2017). Briefly, exclusion criteria consisted on presence of psychiatric or neurological comorbidity, low global intelligence quotient estimated by the WAIS-III Vocabulary subtest score (> 7 scalar score) (Wechsler, 1999), and a Mini-Mental state examination score below 25 (Folstein, Folstein, & McHugh, 1975). For the current work, senior participants with obesity (body mass index [BMI] equal to or higher than 30 kg/m$^2$) were excluded (N = 4) as well as those presenting MRI pathological findings such as white matter hyperintensities unrelated to the course of normal aging (N = 2).

The other sample included 61 adolescents (12-21 years old) and 66 adults (22-48 years old) from public health care centers belonging to the *Consorci Sanitari de Terrassa*. This sample was recruited in the context of a broader line of research revolving around obesity and brain function. Part of this sample was used in previous works (Ariza et al., 2012; Caldú et al., 2019; García-García et al., 2013a, 2013b, 2013c, 2015; Marqués-Iturria et al., 2013, 2014, 2015; Ottino-González et al., 2017, 2018, 2019). Thirty-two adults were considered as obese and 34 as healthy weight (BMI < 24.9 kg/m$^2$). Following the cut-offs established by the WHO (2012), 30 adolescents above the gender-based 95$^{th}$ BMI percentile were categorized as obese, and 31 teens oscillating between the 5$^{th}$ and the 84$^{th}$ percentile, were categorized as healthy-weight (Cole, Flegal, Nicholls, & Jackson, 2007). Thirty-four individuals with overweight (i.e., BMI 25 kg/m$^2$ to 29.9 kg/m$^2$, or between the 85$^{th}$ and 94$^{th}$ percentiles for adolescents) were not included in this study since we were only interested in addressing the two extremes of the BMI continuum.

As in previous work, we excluded participants with cardiometabolic comorbidities (i.e., type II diabetes, hypercholesterolemia, hypertension), as well as those with past or present neurological or psychiatric disorders. Individuals underwent three visits. The first consisted of a fasting blood sample extraction and a medical exploration. The second visit included an extensive neuropsychological evaluation in which subjects with a Vocabulary subtest scalar score below 7 were discarded (WAIS-III or WISC-IV) (Wechsler, 1999, 2007). The third and last visit comprised a magnetic resonance imaging (MRI) acquisition at the *Hospital Clínic de Barcelona*. Additionally, participants from all five groups exhibiting excessive head motion were discarded (N = 16). Excessive movement was defined as (1) mean interframe head motion greater than 0.3 mm translation or 0.3° rotation, and (2) maximum interframe head motion greater than 1 mm translation or 1° rotation.

**MRI acquisition.** Images were acquired with a 3T Siemens scanner (MAGNETOM Trio, Siemens, Germany). Each participant underwent a T1-weighted structural image for co-registration and parcellation purposes with the MPRAGE-3D protocol [echo time (TE) = 2.98 ms; repetition time (TR) = 2300 ms; inversion time = 900 ms; 256 mm field of view [FOV]; matrix size = 256 x 256; voxel size = 1.0 x 1.0 x 1.0 mm$^3$). Resting-state volumes in adolescents and adults were collected using a multi-slice gradient-echo EPI sequence covering the whole brain (TE = 19 ms; TR = 2000 ms; 3 mm slice thickness; 90° flip angle; 220 mm FOV; voxel size = 1.7 x 1.7 x 3.0 mm$^3$). Resting-state images in the elders were obtained with the following parameters: TE = 28 ms, TR = 2500 ms, 80° flip angle, 3 mm slice thickness, 240 mm FOV, voxel size = 1.7 x 1.7 x 3.0 mm$^3$.

**Image pre-processing.** Basic functional image preprocessing, using AFNI (http://afni.nimh.nih.gov/afni) and FSL (https://www.fmrib.ox.ac.uk/fsl) tools, included: discarding the first five volumes to allow magnetization stabilization, despiking, motion correction, brain extraction, grand-mean scaling, linear detrending, and high-pass filtering (maintaining frequencies above 0.01 Hz). Functional images and T1-weighted volumes were co-registered and then non-linearly normalized to the MNI ICBM152 template. Then, images were non-linearly transformed to MNI space at 3 x 3 x 3 mm$^3$ voxel size using SPM (http://www.fil.ion.ucl.ac.uk/spm/).

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To remove the effects of head motion and other non-neural sources of signal variation from the functional data sets, we used an independent component analysis (ICA)-based strategy for Automatic Removal of Motion Artifacts (ICA-AROMA) (Pruim et al., 2015). This method uses individual resting-state data to perform ICAs and automatically identify artifact-related independent components. The time courses of components considered as artifactual were stored to be used as regressors during network computation.

The six motion parameters obtained from the realignment procedure, as well as the average white matter and cerebrospinal fluid signals were stored to serve as regressors in network reconstruction. To generate the corresponding white matter and cerebrospinal fluid (lateral ventricle) masks, T1-weighted structural images were segmented using FreeSurfer (https://surfer.nmr.mgh.harvard.edu/). The resulting binary masks were linearly transformed from structural to native functional space using FSL-FLIRT (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FLIRT). To prevent these masks from extending to the adjacent gray matter due to resampling blur in linear transformation, white matter masks were then "eroded" by applying a threshold of 0.9, while ventricular masks were thresholded at 0.3.

**Connectivity matrix computation.** To reconstruct the functional connectome, the brain needs to be divided into a set of nodes; network edges connecting pairs of nodes are then defined as a measure of relationship between their respective time courses. In this work, we used the Brainnetome atlas (Fan et al., 2016), a cross-validated connectivity-based parcellation scheme that divides the cerebrum into 210 cortical and 36 subcortical gray matter regions, taken as network nodes. The first eigenvariates of the time series of all voxels included in each region mask were extracted using *fslmeants* and taken as the time course of the corresponding nodes.

Individual 246 x 246 connectivity matrices were then reconstructed by calculating the standardized regression coefficient between the time courses of nodes $i$ and $j$, while also entering the ICA-AROMA artifact time courses, six motion parameters, and white matter and cerebrospinal fluid mean time courses as regressors. This produces fully connected and undirected brain networks with 30,135 unique edges with values ranging between -1 and 1. Moreover, a group temporal-concatenation spatial ICA was performed using FSL's MELODIC (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC) with a predetermined dimensionality of 15 independent components. The spatial and power spectral characteristics of the resulting components were inspected to identify 10 well-established networks (Griffanti et al., 2017): two primary visual networks (PVN and PVN2), secondary visual network (SVN), default mode network (DMN), dorsal attentional network (DAN), anterior default mode network (aDMN), right and left frontoparietal networks (FPN), sensory-motor network (SMN) and the salience network (SN) (see Supplementary Figure 1). Two additional networks were identified as the medial temporal network (MTN) (including the hippocampus and the amygdala) and the striatal-thalamic network (STN).

These data-driven spatial maps were used to assign the Brainnetome's nodes to specific brain networks for further regional graph-based measurements calculation, using in-house MATLAB scripts. Specifically, the Z-maps generated by MELODIC corresponding to the 12 networks of interest were thresholded at $Z \geq 2$. Subsequently, each Brainnetome node was considered to belong to a network if over 60% of its voxels overlapped with this network's thresholded map. When this overlap occurred for more than one network, the sum of the Z-values across all overlapping voxels was considered, and the node was assigned to the network with the highest Z-value sum. In total, 153 of the 246 Brainnetome nodes were ascribed to one of the 12 networks of interest, as shown in Supplementary Table 1.

**Global and regional graph-theory parameters estimation.** Global network parameters were computed using the Brain Connectivity Toolbox (Rubinov & Sporns, 2010) and in-house MATLAB scripts. As non-normalized global parameters, we assessed two complementary metrics: the mean network degree (average number of positive connections linked to a node, across all brain nodes) and the mean network strength (average of unthresholded connection strength across all edges, positive and negative), both of which can be understood as measures of network efficiency and integrity. Regional parameters such as nodal degree and strength were calculated by averaging the total number of connections and weights between nodes ascribed to each ICA-based network and the rest of the brain.

The modularity coefficient, another non-normalized global measure, was estimated using the Louvain algorithm and indicating the degree to which a network can be subdivided into well-defined modules with few intermodular connections.

Normalized weighted global measures were computed by averaging the ratio between the actual measure and those obtained through randomly rewiring the connectivity matrix 500 times using a degree-preserving algorithm. Thus, after setting negative edge weights to zero, we computed the characteristic path length, defined as the average minimum number of edges that need to be traversed between each pair of network nodes (Rubinov & Sporns, 2010).

## Statistical analysis

Sociodemographic variables as well as the mean interframe translational and rotational movements of the head were examined across groups. Non-parametrical tests were applied when data assumptions were violated. All comparisons, including post-hoc pairwise contrasts, of global and regional graph-based measures were conducted with permutation-based tests (10,000 permutations).

One-factor univariate general linear models (GLMs) were conducted in adults and seniors. To avoid comparisons of non-interest, differences in adolescents were tested in independent models. Post-hoc pairwise t-tests were performed for contrasts that emerged as statistically significant. Cumulative odds for false-positive results were prevented with Bonferroni-adjustments. Here, the raw p-values were multi-

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plied by k variables for omnibus tests (i.e., by 4 for global graph-based measures, and by 12 for regional degree and strength parameters), and by n contrast of interest (3) in post-hoc comparisons. Statistical significance was set at adjusted p-value < 0.05. Likewise, effect sizes (i.e., Cohen's d or eta-partial square [$\eta p^2$]) and bias-corrected and accelerated bootstrap (10,000 simulations) confidence intervals (CI 95%, or 90% for $\eta p^2$) were calculated for each significant contrast.
Moreover, to explore for differences in the transition from young to adulthood in both global and regional graph-related indexes, we sought for interactions between body-weight status (i.e., healthy-weight vs. obesity) and age (i.e., adolescent vs. adult) with two-factor univariate GLMs. All statistical analyses were performed with *R* version 3.5.0 (R Core Team, 2018).

## Results

**Sociodemographics.** As expected, groups differed in age ($F_{(4,153)}$ = 420, p < 0.001) and years of education ($F_{(4,153)}$ = 24.62 p < 0.001). Post-hoc tests revealed no significant differences between adults with and without obesity in age (p-adjusted = 0.674) or education (p-adjusted = 0.854). Similarly, healthy-weight and obese adolescents were comparable in terms of age (p-adjusted = 0.999) and years of education (p-adjusted = 0.732). All five groups were equally distributed for sex ($x^2$ = 1.22, p = 0.875) (Table 1).

**Table 1.** Sociodemographics across groups (mean and standard deviation)

| Groups | Age | Education | N/Females |
|---|---|---|---|
| OB adult | 34.53 (6.49) | 13.88 (2.92) | 32/20 |
| HW adult | 32.68 (6.79) | 14.62 (2.75) | 34/18 |
| Senior | 66.13 (7.43) | 11.22 (4.26) | 32/17 |
| OB young | 15.27 (2.64) | 8.57 (2.45) | 30/15 |
| HW young | 15.64 (2.60) | 9.52 (2.19) | 31/16 |

OB = participant with obesity, HW = healthy-weight individual.

**MRI quality check.** Rotational movements of the head did not diverge between groups ($H_{(4)}$ = 4.32, p = 0.364). By contrast, head translational movements proved different among groups ($H_{(4)}$ = 38.90, p < 0.001), with post-hoc analyses revealing that such displacements were more marked for elders and adults with obesity, as both of them differed from the other groups yet not from each other. Consequently, head translational movements were controlled for all further graph-theoretical analyses, either by introducing it as a covariate or by regressing out its effects from each variable of interest.

**Global graph-based results.** Adults and seniors exhibited differences in modularity ($F_{(3,94)}$ = 5.71, p-adjusted = 0.020), mean degree ($F_{(3,94)}$ = 5.56, p-adjusted = 0.024), and mean strength ($F_{(3,94)}$ = 4.81, p-adjusted = 0.039).
Post-hoc analyses exposed that the contrast between adults with obesity and without did not pass the Bonferroni adjustment (raw p-value = 0.024). Still, individuals with obesity showed lower mean degree (t = 2.69, p-adjusted = 0.012, d = -0.66; $CI_{bca}$95% [-1.11, -0.19]) and mean strength (t = 2.74, p-adjusted = 0.015, d = -0.68; $CI_{bca}$95% [-1.10, -0.21]) when compared to their normal-weight counterparts.
Relative to seniors, adults with obesity presented greater modularity (t = -3.94, p-adjusted = 0.002, d = 0.99; $CI_{bca}$95% [0.45, 1.55]), as well as lower mean degree (t = 3.38 , p-adjusted = 0.007, d = -0.85; $CI_{bca}$95% [-1.32, -0.37]) and strength (t = 2.81, p-adjusted = 0.025, d = -0.70; $CI_{bca}$95% [-1.16, -0.22]).
Normal-weight adults did not differ from non-obese elders for any of the abovementioned. Results are depicted below in Figure 1.

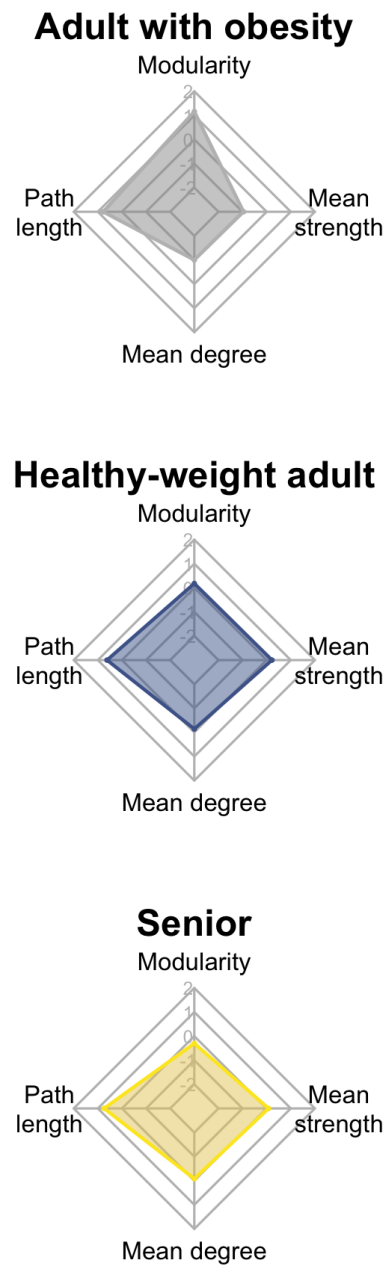


**Figure 1**. Network profiles of adults with obesity, healthy-weight adults and seniors.

While analogous to adults, differences in adolescents in modularity, mean degree and strength did not survive multiple comparison correction (0.049, 0.029 and 0.033, raw p-values) (see Figure 2). Additionally, mean and standard deviation across groups for graph-based parameters are included in the Supplementary Table 2.

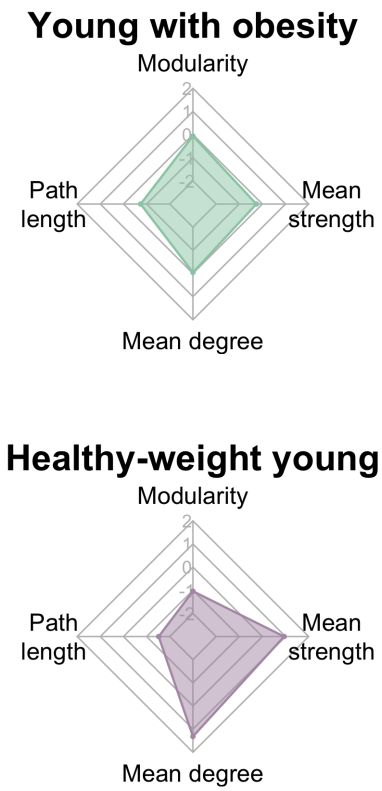


**Figure 2**. Network profiles of adolescents with and without obesity.

**Regional nodal degree and strength results.** Adults and seniors diverged in the average number of inward and outward connections in the DMN ($F_{(3,94)}$ = 5.97, p-adjusted = 0.048). Here, adults with obesity displayed lesser regional degree than healthy-weight adults (t = 3.21, p-adjusted = 0.008, d = -0.79; $CI_{bca}$95% [-1.26, -0.33]) and seniors (t = 3.15, p-adjusted = 0.007, d = -0.79; $CI_{bca}$95% [-1.26, -0.28]).

Groups also diverged in the strength of such links $F_{(3,94)}$ = 7.02, p-adjusted = 0.022). Adults with obesity demonstrated lower strength when rivalled against their healthy-weight peers (t = 3.67, p-adjusted = 0.001, d = -0.90; $CI_{bca}$95% [-1.33, -0.44]) and non-obese elders (t = 2.57, p-adjusted = 0.031, d = -0.64; $CI_{bca}$95% [-1.03, -0.17]). Healthy-weight adults did not prove different from seniors neither for degree nor strength in the DMN. Results are available in Figure 3.

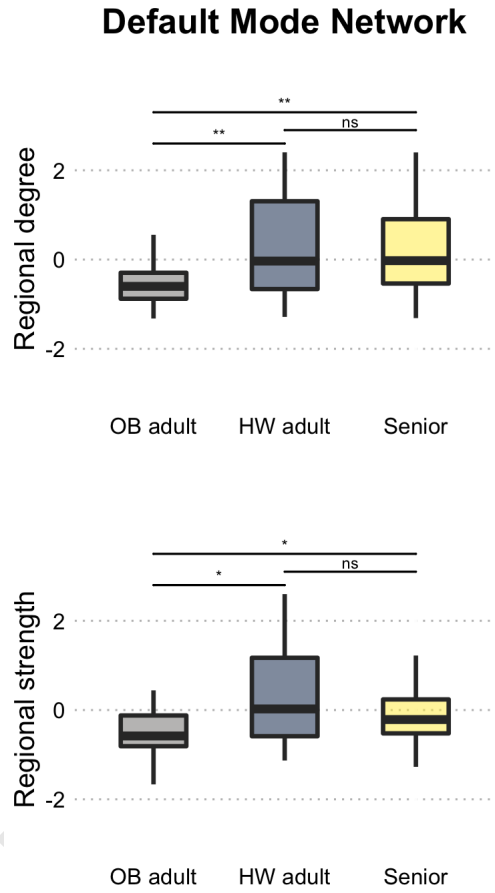


**Figure 3**. Group comparison for DMN regional degree and strength. OB = participants with obesity, HW = healthy-weight individuals, *<0.05, **<0.01, ns = non-significant.

What is more, differences in the regional degree ($F_{(3,94)}$ = 6.61, p-adjusted = 0.008) emerged in the SMN. In contrast to healthy-weight adults, adults with obesity revealed lesser nodal degree (t = 3.45, p-adjusted = 0.005, d = -0.85; $CI_{bca}$95% [-1.35, -0.36]). The contrast from non-obese seniors and adults with obesity did not survive Bonferroni adjustment (raw p-value = 0.041).

Groups also differed in the SMN strength ($F_{(3,94)}$ = 6.23, p-adjusted = 0.031). Adults with obesity did also show lesser strength than healthy-weight adults (t = 3.54, p-adjusted = 0.002, d = -0.87; $CI_{bca}$95% [-1.37, -0.38]). The contrast between this group and elders did not emerge as statistically significant. Adults without obesity did not differ from seniors for any measure of the SMN. Results are displayed in Figure 4.

Adolescents with and without obesity only proved different in the regional degree ($F_{(2,58)}$ = 8.98, p-adjusted = 0.035, $\eta p^2$ = 0.13; [0.02, 0.27]) and strength ($F_{(2,58)}$ = 9.92, p-adjusted = 0.043, $\eta p^2$ = 0.15; [0.02, 0.30]) of the PVN (see Figure 5).

**Body-weight status and age interaction.** There were no significant interactions between body-weight status and age for any graph-theoretical measurement as presented in Figure 6. No interaction emerged for regional indexes either.

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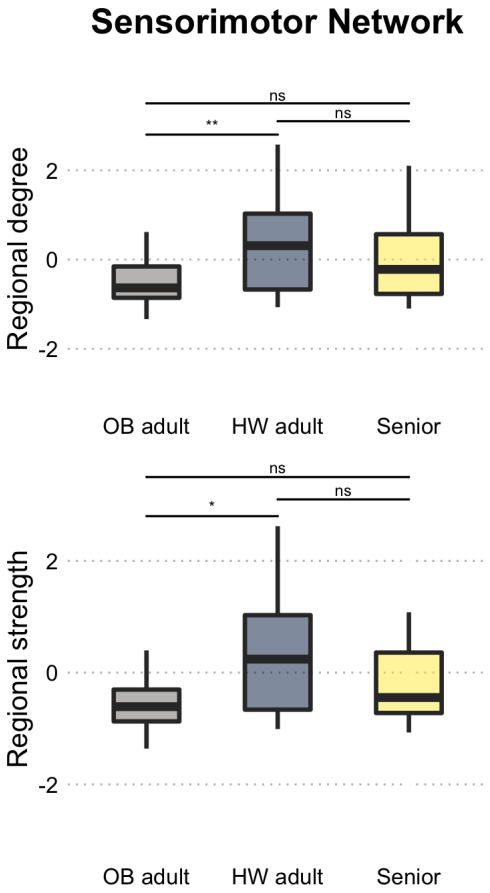


**Figure 4**. Group comparison for SMN regional degree and strength. OB = participants with obesity, HW = healthy-weight individuals, *<0.05, **<0.01, ns = non-significant.

## Discussion

The current work aimed to shed a broader light on whether an obesity status could relate to differences in how the brain topological organization is shaped at two relevant time windows: senescence and adolescence. Adults with obesity exhibited increased lower mean degree and mean strength when compared to healthy-weight adults and non-obese elders. Moreover, this group also demonstrated greater modularity in comparison to the later. These results did partially stand in line with our hypothesis of an obesity status mimicking an aged brain. This pattern of increased segregation and lesser robustness could represent a caveat for successful aging in the future, which is further discussed. Strikingly, normal-weight adults did not diverge from seniors for any graph-theoretical parameter. Moreover, and despite differences between adolescents did not survive multiple comparison correction for global graph-based indexes, they did show differences in the regional properties of visual-related networks. Lack of results in global-based parameters will be disclosed separately for this group. Finally, no interaction emerged as significant between body-weight status and age for any of the abovementioned.

**Modularity.** This index can be generally regarded as a proxy of network segregation, which stands for how clustered the brain is in terms of sharing and processing information (Sporns, 2013). As the brain ages, modularity tends to decrease as a result of the progressive scattering of intra-network pairwise connections (Geerligs et al., 2015; Sala-Llonch, Bartrés-Faz, & Junqué, 2015; Sala-Llonch et al., 2014). Adults with obesity showed a pattern of enhanced modularity relative to seniors (and healthy-weight adults to some extent) which is the opposite to what was originally hypothesized. An increase in such parameter reflects that the information is densely handled within clusters rather than be generally distributed. Although this could benefit the processing of sensory-specific information, higher-level cognitive activity may in turn deteriorate (Sporns, 2013). An increase in modularity could also allow a second negative reading as it might entail a risk factor for cardiovascular-related disconnection syndromes (Siegel et al., 2018).

**Global and regional mean degree and strength.** These parameters, respectively, echo the number of edges connected to a given node and the average weight of such links. Therefore, both return a global reading of the network integrity and efficiency, or robustness. Our results showed that adults with obesity presented a lower mean degree and mean network strength when compared to healthy-weight adults. These results are partially in line with the study conducted by Geha et al. (2017). In this work, the authors served a mea-

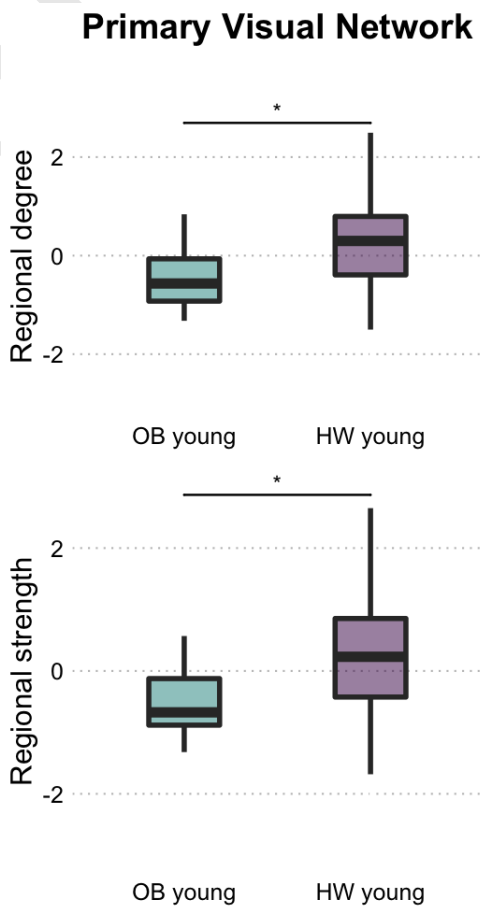


**Figure 5**. Group comparison for PVN regional degree and strength. OB = participants with obesity, HW = healthy-weight individuals, *<0.05.

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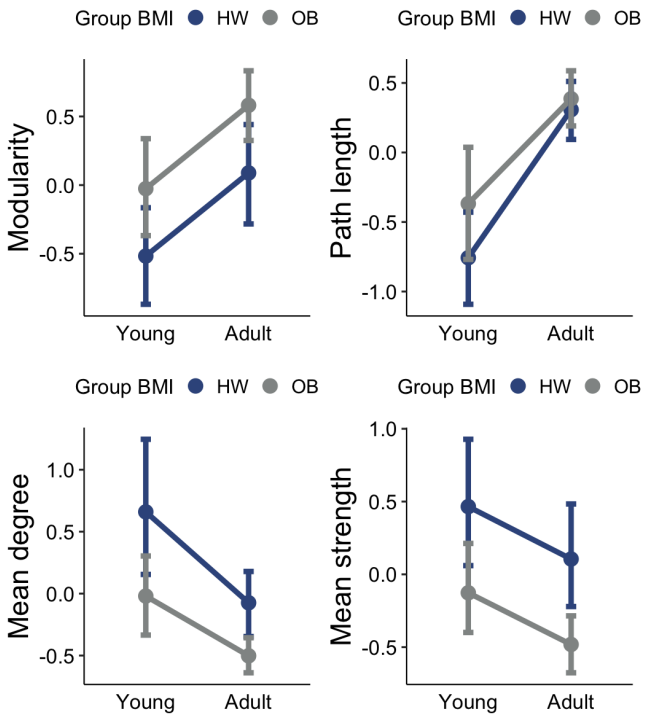


**Figure 6**. Age and body-weight status interactions for global graph-related indexes. OB = participants with obesity, HW = healthy-weight individuals.

sure of global brain connectivity, defined as the number of connections each node has with others. Moreover, one of the consequences of aging on the brain is the trimming of short-range edges and the scattering of nodes (Sala-Llonch et al., 2014). Adults with obesity also displayed lesser global degree and strength than non-obese seniors, which might point towards an accelerated course of age-related changes. This finding supports the hypothesis of an obesity status as an escalator of brain aging.

What is more, when examined regionally, we found group differences in sensory-driven circuits (i.e., SMN), as well as in task-negative networks (i.e., DMN) between the three groups. Overall, these ratify the idea of a global weakening in whole-brain network-resilience. Also, adolescents with obesity presented lower degree and strength in primary-visual networks (i.e., PVN). Sensory-processing circuits (e.g., SMN and PVN), are naturally engaged during the handling of domain-specific information. Subjects with obesity feature alterations within tactile and visual-processing networks (Doucet et al., 2017; García-García et al., 2013; Geha et al., 2017). The DMN, the most typical task-negative network, is considered to be a biomarker for pathological aging and dementia (Buckner, Andrews-Hanna, & Schacter, 2008; Palmqvist et al., 2017). This network is also extremely vulnerable to the negative effects of obesity-related disorders such as type II diabetes (Wang, Ji, Lu, & Zhang, 2016), hypertension (Haight et al., 2015), and dyslipidemia (Spielberg et al., 2017). To date, very few studies have described alterations in the DMN relative to an obesity status (Beyer et al., 2017; Doucet et al., 2017; Figley, Asem, Levenbaum, & Courtney, 2016; Tregellas et al., 2011).

Obesity is a preventable health problem associated with the development of long-lasting cardiometabolic disorders (Wade et al., 2018) and increases the risk of developing late-onset dementia (Bischof & Park, 2015; Deckers, van Boxtel, Verhey, & Köhler, 2017). Relative to non-obese elders, adults with obesity exhibited a pattern of enhanced segregation and loses in network robustness (i.e., mean degree and strength). Altogether, this picture could jeopardize the so-called "successful aging" in the face of cardiovascular insults taking place in the mark of this condition. Besides the acquired vulnerability to disconnection syndromes (e.g., stroke-induced aphasia) (Siegel et al., 2018), this network profile of fragile and overly clustered communities could also hinder cognitive performance. High-order cognitive functions depend on the balance between network segregation and integration (Sporns, 2013). Excessively isolated clusters will not be able to exchange information efficiently if there are no improvements in their communications (i.e., decreases in path length). This, in turn, may relate to the increment in the processing times and the background noise that can be observed in the cognitive performance of elders and subjects with obesity (Deckers et al., 2017; Sala-Llonch et al., 2014).

Interestingly, no meaningful differences were found among healthy-weight adults and seniors. Literature is consistent in signaling towards reductions in modularity in elders (Geerligs et al., 2015; Song et al., 2014), a finding that we failed to replicate as both groups showed similar scores. Equally, reductions in robustness neither emerged as significant for this particular contrast. It is important to remark that none of the participants in the senior group presented obesity, a condition that alone (Beyer et al., 2017; Doucet et al., 2017), or in conjunction with its medical complications (Haight et al., 2015; Spielberg et al., 2017; Wang et al., 2016), is linked to changes in the brain functional organization. This criterion is usually ignored in healthy-aging literature. However, and although more research is needed, we cannot rule out the possibility that the sample of elders served in this study might not be representative of their population. Therefore, some of the results hereby presented should be taken with caution.

Similarly, differences between adolescents with and without obesity did not survive multiple comparison correction for global-theoretical parameters. It is possible that with a less-restrictive threshold or with an enough-powered sample size group differences would emerge as such. On another note, the body-weight status did not influence the transition from childhood to adulthood as hypothesized. Adolescents and adults with obesity shared the same pattern of enhanced modularity and network-weakening in comparison to their healthy-weight peers. Hence, obesity-related network alterations might already be noticeable at earlier developmental stages. Still, this inference, as preliminary as it is, should be properly confirmed with a longitudinal approach.

In line with the earlier exposed, the current work has limitations that should be addressed in future studies. First, its cross-sectional nature prevents to draw any conclusion upon causality. Longitudinal approaches would help disentangle

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whether the transition from childhood to adulthood and to elderhood is different in the presence of an unhealthy weight. Second, our modest sample size (N = 159) might have limited our statistical power to catch any subtle difference. Third, to have had a group of elders with obesity would have allowed exploring the impact of such condition across all possible age ranges. Fourth, the resting-state acquisition in the senior cohort were slightly different from the rest of the groups. Particularly, the echo-time was different in this group, which might have resulted in a difference in the sensitivity to the BOLD signal. Thus, further works should compare subjects with equal MRI parameters. By contrast, a strong point of this work was the strict criteria that ruled out participants with neurological or psychiatric comorbidities likely prompting network-related differences.

In sum, adults with obesity have showed differences in graph-based measures of network organization. Concretely, and compared to healthy-weight adults and non-obese seniors, volunteers with obesity demonstrated a pattern of losses in network integrity and efficiency. What is more, adults with obesity exhibited increases in brain segregation relative to seniors. Overall, these preliminary findings could point towards a weakening in network resilience that might jeopardize the so-called "successful aging".

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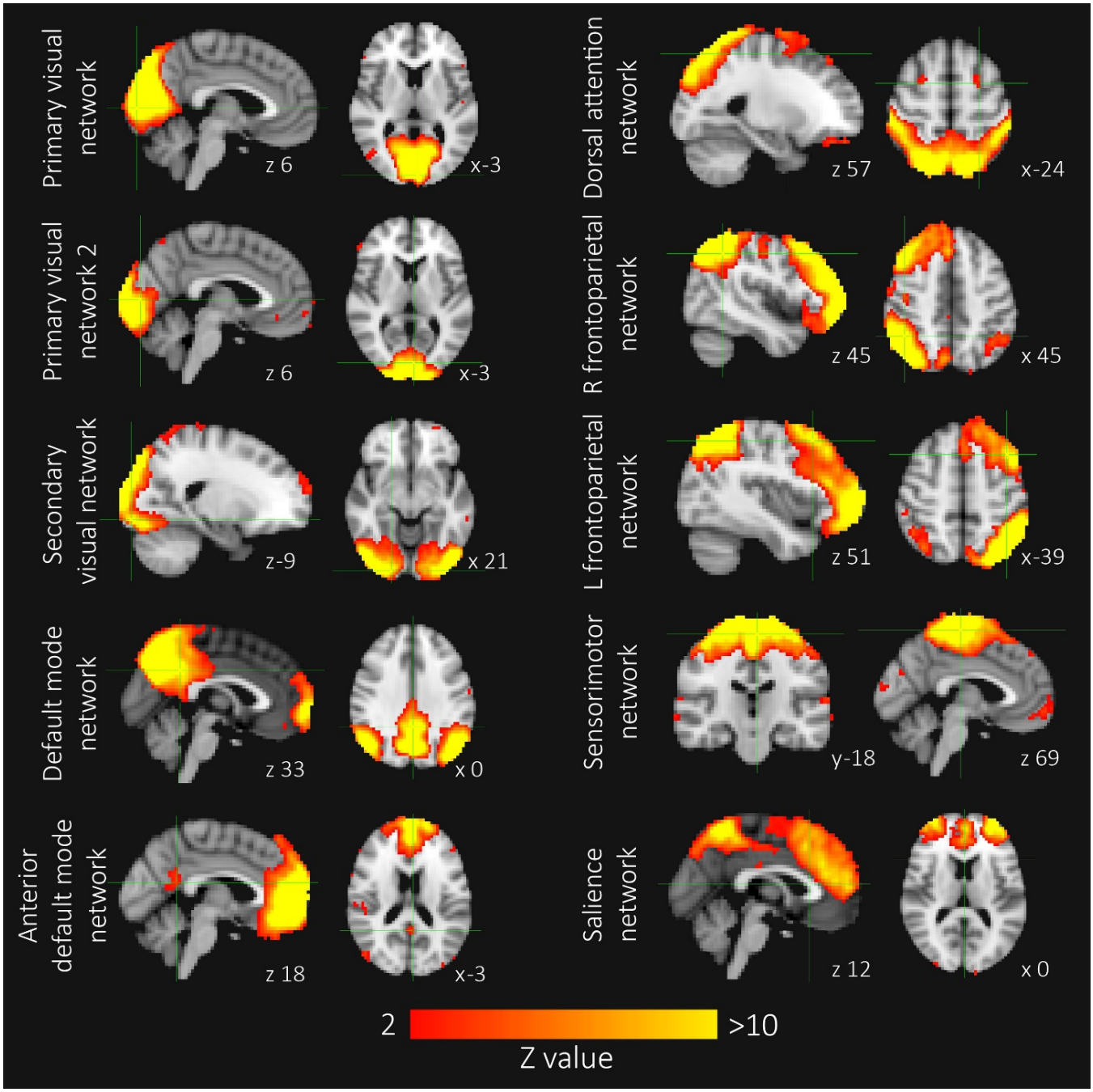
## Supplementary Material




**Supplementary Figure 1**. Plots disclose the spatial maps corresponding to 10 networks of interest characterized through independent component analysis. The x, y or z MNI coordinates of the slices shown are indicated. In coronal and axial slices, the right hemisphere is displayed on the left side of the image. R: right; L: left.

| | | | | | |
|---|---|---|---|---|---|
| **Primary visual network** | | | | | |
| Cun_L_5_2 | Cun_L_5_4 | Cun_L_5_5 | Cun_R_5_2 | Cun_R_5_3 | Cun_R_5_5 |
| sOcG_L_2_1 | sOcG_R_2_1 | | | | |
| **Primary visual network 2** | | | | | |
| Cun_L_5_1 | Cun_L_5_3 | Cun_R_5_1 | OcG_R_4_3 | | |
| **Secondary visual network** | | | | | |
| FuG_L_3_2 | FuG_R_3_2 | OcG_L_4_1 | OcG_L_4_2 | OcG_L_4_3 | OcG_L_4_4 |
| OcG_R_4_1 | OcG_R_4_2 | OcG_R_4_4 | sOcG_L_2_2 | | |
| **Anterior default mode network** | | | | | |
| CG_L_7_7 | CG_R_7_7 | OrG_L_6_1 | OrG_L_6_4 | OrG_R_6_1 | SFG_L_7_3 |
| SFG_L_7_7 | SFG_R_7_7 | | | | |
| **Dorsal attention network** | | | | | |
| IPL_L_6_1 | IPL_R_6_1 | IPL_R_6_3 | ITG_L_7_5 | ITG_R_7_2 | ITG_R_7_5 |
| sOcG_R_2_2 | SPL_L_5_1 | SPL_L_5_2 | SPL_L_5_4 | SPL_R_5_1 | SPL_R_5_2 |
| SPL_R_5_3 | SPL_R_5_5 | | | | |
| **Default mode network** | | | | | |
| CG_L_7_1 | CG_R_7_1 | IPL_L_6_5 | IPL_R_6_5 | Pcun_L_4_1 | Pcun_L_4_3 |
| Pcun_L_4_4 | Pcun_R_4_1 | Pcun_R_4_3 | Pcun_R_4_4 | pSTS_L_2_2 | |
| **Left frontoparietal network** | | | | | |
| IFG_L_6_1 | IFG_L_6_2 | IFG_L_6_3 | IFG_L_6_4 | IFG_L_6_6 | IPL_L_6_2 |
| ITG_L_7_2 | ITG_L_7_6 | MFG_L_7_2 | MFG_L_7_4 | MFG_L_7_5 | MFG_L_7_6 |
| OrG_L_6_2 | OrG_L_6_3 | OrG_L_6_6 | SFG_L_7_2 | SPL_L_5_5 | |
| **Right frontoparietal network** | | | | | |
| IFG_R_6_2 | IFG_R_6_3 | IPL_R_6_2 | ITG_R_7_6 | MFG_R_7_4 | MFG_R_7_5 |
| MFG_R_7_6 | MTG_R_4_1 | OrG_R_6_2 | OrG_R_6_3 | OrG_R_6_6 | SFG_R_7_2 |
| SFG_R_7_3 | | | | | |
| **Salience network** | | | | | |
| CG_L_7_3 | CG_R_7_3 | IPL_L_6_3 | IPL_L_6_4 | IPL_R_6_4 | MFG_L_7_1 |
| MFG_L_7_3 | MFG_R_7_1 | MFG_R_7_3 | PCL_R_2_1 | Pcun_L_4_2 | SFG_L_7_1 |
| SFG_L_7_6 | SFG_R_7_1 | SFG_R_7_6 | SPL_L_5_3 | | |
| **Sensorimotor network** | | | | | |
| PCL_L_2_1 | PCL_L_2_2 | PCL_R_2_2 | Pcun_R_4_2 | PoG_L_4_4 | PoG_R_4_4 |
| PrG_L_6_3 | PrG_L_6_4 | PrG_R_6_2 | PrG_R_6_3 | PrG_R_6_4 | SFG_L_7_4 |
| SFG_L_7_5 | SFG_R_7_4 | SFG_R_7_5 | SPL_R_5_4 | | |
| **Medial temporal network** | | | | | |
| Amyg_L_2_1 | Amyg_L_2_2 | Amyg_R_2_1 | Amyg_R_2_2 | Hipp_L_2_1 | Hipp_L_2_2 |
| Hipp_R_2_1 | Hipp_R_2_2 | | | | |
| **Striatal thalamic network** | | | | | |
| Str_L_6_1 | Str_L_6_2 | Str_L_6_3 | Str_L_6_4 | Str_L_6_5 | Str_L_6_6 |
| Str_R_6_1 | Str_R_6_2 | Str_R_6_3 | Str_R_6_4 | Str_R_6_5 | Str_R_6_6 |
| Tha_L_8_1 | Tha_L_8_2 | Tha_L_8_3 | Tha_L_8_4 | Tha_L_8_5 | Tha_L_8_6 |
| Tha_L_8_7 | Tha_L_8_8 | Tha_R_8_1 | Tha_R_8_2 | Tha_R_8_3 | Tha_R_8_4 |
| Tha_R_8_5 | Tha_R_8_6 | Tha_R_8_7 | Tha_R_8_8 | | |

**Supplementary Table 1**. Brainnetome atlas regions (http://atlas.brainnetome.org/) assigned to each of the 12 brain networks of interest.

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| | OB adult | HW adult | Senior | OB young | HW young |
|---|---|---|---|---|---|
| *Modularity* | 0.58 | 0.09 | -0.15 | -0.03 | -0.52 |
| | (0.75) | (1.09) | (0.74) | (1.06) | (1.04) |
| *Path length* | 0.39 | 0.31 | 0.37 | -0.39 | -0.76 |
| | (0.59) | (0.64) | (0.99) | (1.15) | (1.02) |
| *Mean degree* | -0.50 | -0.07 | -0.04 | -0.02 | 0.66 |
| | (0.44) | (0.79) | (0.64) | (0.91) | (1.56) |
| *Mean strength* | -0.48 | 0.11 | 0.04 | -0.13 | 0.47 |
| | (0.60) | (1.06) | (0.86) | (0.91) | (1.26) |

**Supplementary Table 2.** Mean and standard deviation of graph-based parameters across groups (z-scores; adjusted for mean translational movements). OB = Participants with obesity, HW = Healthy-weight individuals.

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