# From the reward network to whole-brain metrics: structural connectivity in adolescents and young adults according to body mass index and genetic risk of obesity

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**Abstract**

**Background:** Obesity is a multifactorial condition. Genetic variants, such as the fat mass and obesity related gene (FTO) polymorphism, may increase the vulnerability of developing obesity by disrupting dopamine signaling within the reward network. Yet, the association of obesity, genetic risk of obesity, and structural connectivity of the reward network in adolescents and young adults remains unexplored. We investigate, in adolescents and young adults, the structural connectivity differences in the reward network and at the whole-brain level according to body mass index (BMI) and FTO rs9939609 polymorphism.

**Methods:** One hundred thirty-two adolescents and young adults (age range: 10 – 21 years, BMI z-score range: -1.76 – 2.69) were included. Genetic risk of obesity was determined by the presence of the FTO A allele. Whole-brain and reward network structural connectivity were analyzed using graph metrics. Hierarchical linear regression was applied to test the association between BMI-z, genetic risk of obesity, and structural connectivity.

**Results:** Higher BMI-z was associated with higher ($B$ = 0.76, 95% CI = [0.30, 1.21], P = 0.0015) and lower ($B$ = -0.003, 95% CI = [-0.006, -0.00005], $P$ = 0.048) connectivity strength for fractional anisotropy at the whole-brain level and of the reward network, respectively. The FTO polymorphism was not associated with structural connectivity nor with BMI-z.

**Conclusions:** We provide evidence that, in healthy adolescents and young adults, higher BMI-z is associated with higher connectivity at the whole-brain level and lower connectivity in the reward network. We did not find the FTO polymorphism to correlate

with structural connectivity. Future longitudinal studies with larger sample sizes are needed to assess how genetic determinants of obesity change brain structural connectivity and behavior.

**Key words:** adolescence, reward network, structural connectivity, FTO, obesity, BMI

## Introduction

Obesity is a complex condition caused by a combination of biological, social, psychological, and environmental factors (1). Genetic variants, with heritability estimates of 40-70%, may underlie the inter-individual variation in the susceptibility to the obesogenic environment. The fat mass and obesity related gene (FTO), the first gene to emerge from body mass index (BMI) genome-wide association studies, has been consistently associated with obesity. The most representative single nucleotide polymorphism in the first intron of the FTO gene is rs9939609 (2).The effect of FTO on BMI is relatively large (0.35 $kg/m^2$ per A allele), although the underlying biological mechanisms have not yet been fully elucidated (3).

In humans, variations in the FTO gene may exert an effect on BMI by modulating food intake rather than energy expenditure (4). Polymorphisms in the FTO may regulate the activity of dopaminergic neurons in the reward circuit, thus affecting reward sensitivity within the reward network (5). The reward network comprises interconnected cortical and subcortical structures (lateral and medial orbitofrontal cortices, nucleus accumbens, caudate nucleus and putamen) that are involved in reward processing, learning, motivation and self-regulation (6). Evidence suggests that a disruption in this network may increase food cravings and preference for high-calorie food, as well as impair reward learning and impulse control, thus changing feeding behavior and producing weight gain (7).

Various neuroimaging approaches have been used to assess the structural and functional neurobiology of obesity. A compromised (lower) structural connectivity within the

reward network has been associated with obesity (6,8,9). However, other studies showed contradictory results, describing both higher and lower structural connectivity between the ventral striatum and the frontal cortex (10,11). Gray matter volume in the reward network has also been studied in the context of obesity. In a recent meta-analysis, greater volumes of the nucleus accumbens were associated with higher BMI in adolescents, whereas the opposite result was found in adults (12).

Importantly, not only is weight status associated with the reward network, but also having a genetic risk of developing obesity. A functional neuroimaging study suggested a positive and additive relationship between obesity genetic factors and striatal activation (13). Similarly, another study (14) revealed disrupted structural connectivity in the nucleus accumbens and the thalamus in homozygous participants for the FTO A allele, while another study found increased structural connectivity between the ventral tegmental area/substantia nigra and the nucleus accumbens in FTO A allele carriers (7).

While other studies have investigated the relationship between FTO polymorphisms and brain structural connectivity in children and adults with diverse BMI values (7,9,14,15), to our knowledge, the associations of structural connectivity with BMI and genetic risk of obesity in adolescents and young adults remain unexplored. Since changes in the reward network connectivity might stem from adverse effects of obesity (i.e., metabolic burden) or arise from predisposing factors (i.e., genetics), in this study we investigate, in a sample of adolescents and young adults, the structural connectivity differences in the reward network according to (i) BMI and (ii) being carrier of the FTO rs9939609 A allele. Based on previous literature, we hypothesized that (i) higher BMI and (ii) the presence

of the FTO rs9939609 A allele may be related to lower connectivity in the reward network. Using an exploratory approach, we also investigated the same hypotheses at the whole-brain level.

## Methods

### Participants selection and procedure

Potential participants from public primary care centers of the Consorci Sanitari de Terrassa were randomly contacted by telephone and invited to take part in the study. If they agreed, they underwent a telephonic screening interview to assess the adequacy of their participation. Inclusion criterion was being aged between 10 and 21 years (16). Exclusion criteria were: (i) underweight, (ii) psychiatric, neurological, developmental (e.g., attention-deficit/hyperactivity disorder, autism spectrum disorder), cardiometabolic (e.g., diabetes, metabolic syndrome, hypo/hyperthyroidism), or systemic (e.g., cancer, lupus) diagnosis, and (iii) global cognitive impairment or bulimia-like behaviors. Additionally, the medical doctor explored with the participants their medical history to ensure the suitability of their inclusion.

The first day, 144 potential candidates were cited to undergo a medical evaluation and a blood sample extraction at the Hospital de Terrassa – Consorci Sanitari de Terrassa (n = 89), or to undergo an at-home medical visit and blood sample extraction (after SARS-Cov-2 breakdown, n = 55). Pubertal stage was determined according to the Tanner scale of sexual maturity. The second day, we further assessed exclusion criteria with specific questionnaires: a scalar score <7 in the Weschler Adults Intelligence Scale-III/Weschler Intelligence Scale for Children-IV vocabulary subtest determined global cognitive

impairment, and meeting criteria for bulimia nervosa at the Mini International Neuropsychiatric Interview for Bulimia or a score ≥20 in the Bulimia Inventory Test of Edinburgh determined bulimia-like behaviors. Three participants were excluded for presenting bulimia-like behaviors (n = 2 assessed with the Bulimia Inventory Test of Edinburgh and n = 1 with the Mini International Neuropsychiatric Interview for Bulimia). Bulimia was not assessed using the same questionnaire for all participants due to a change in the protocol. Anxiety and depression symptoms were also assessed using the Hospital Anxiety and Depression Scale. Recruitment and data collection were carried out between 2010 and 2022. Some of the participants in the present study were already included in previous works (17,18).

Participants without claustrophobia or metal protheses also underwent a brain magnetic resonance imaging (MRI) acquisition on a 3T MAGNETON (Siemens, Germany) at the Centre de Diagnòstic per la Imatge Clínica at the Hospital Clínic de Barcelona. One participant was excluded during the MRI acquisition due to the detection of a low-grade glioma and was immediately referred to neurology and oncology services. Eight more participants were excluded after the neuroimaging quality control (see imaging preprocessing and connectome reconstruction section). This led to a final sample size of 132 adolescents and young adults, of which two had missing genetic data.

This study was approved by the Ethics Committee for Clinical Research of the Consorci Sanitari de Terrassa, and Institutional Ethics Committee of the University of Barcelona (Institutional Review Board IRB00003099, assurance number FWA00004225). The research was conducted in accordance with the Helsinki Declaration. Written informed

consent was obtained from all participants, or their legal guardian in underage participants, prior to entry in the study.

**Anthropometric measurement**

Anthropometric measures were obtained by a trained nurse from participants in light clothing without shoes. Height was measured with two different devices (n = 81: Holtan Limited Harpenden Stadiometer, and n = 51: Längenmessstab 5003-Soehnle Professional). Weight was also measured with two different devices (n = 81: Seca 704s, and n = 51: Tanita InnerScan-V). T-tests were performed and no differences in height and weight measurements were observed (P>0.05). BMI was calculated as kilograms/meters$^2$, and then transformed into BMI z-score using the R package *cdcanthro.* Since BMI-z values can be calculated for participants up to 20 years, for those participants aged 20 and 21, their BMI z-score was calculated as if they were 19 years and 11 months (19). For descriptive purposes, we classified participants as normal-weight or overweight/obesity using the BMI cut-offs from Cole and Lobstein (20) for underage participants, and the 25kg/m2 BMI cut-off from the World Health Organization (21) for participants aged 18-21.

**Genotyping**

Peripheral blood samples were obtained from 130 participants and genomic DNA was extracted automatically using the MagNaPure Compact Instrument (Roche Applied Science, Barcelona, Spain). The FTO polymorphism rs9939609 was genotyped in 70 participants using polymerase chain reaction and Sanger Sequencing (primers and conditions available on request). On the other 60 patients, rs9939609 was genotyped

using the Flex Six GT Integrated Fluidic Circuit and SNP Type assays according to the manufacturer's protocol using the genotyping platform Fluidigm Juno System and Biomark HD (Fluidigm Corp, South San Francisco, CA, USA). The risk allele of this variant is the A allele. The genotype counts in our sample were $n_{TT}$ = 39, $n_{AT}$ = 68, $n_{AA}$ = 23 (minor allele frequency = 0.44, test for Hardy–Weinberg equilibrium $Chi^2$ = 0.33, df = 1, P = 0.56). Two participants had missing genetic data. Participants were mostly White and Spaniard (n = 124). Six participants had American Latino ancestry, and for two participants race or ethnicity was not reported. For the analysis, we grouped together carriers of at least one risk allele (A) vs. non-carriers, and we controlled for the batch effect by adding a covariate indicating which laboratory genotyped the FTO polymorphism.

**MRI data acquisition**

MRI acquisition was performed using a 3T Siemens Magnetom Trio (n = 72) and a 3T Siemens Magnetom Prisma (n = 60). T1-weighted images were acquired with the following parameters for the Trio scanner: inversion time = 900 ms, repetition time = 2300 ms, echo time = 2.98 ms; flip angle = 9º, band width = 240 Hz/Px, field of view = 256x256x240 $mm^3$, voxel size = 1 x 1 x 1 $mm^3$ , slices = 240, total scan time = 7:48 minutes; and with these parameters for the Prisma scanner: inversion time = 1000 ms, repetition time = 2400 ms, echo time = 2.22 ms; flip angle = 8º, band width = 220 Hz/Px, field of view = 256x240x167 $mm^3$, voxel size = 0.8 x 0.8 x 0.8 $mm^3$, slices = 208, total scan time = 6:38 minutes.

Diffusion-weighted images (DWI) were acquired with the following parameters for the Trio scanner: repetition time = 7700 ms, echo time = 89 ms , field of view = 244 × 244 x 120 $mm^3$, diffusion directions = 30, slice thickness = 2 mm, number of slices = 60, max *b*

value = 1000 s/mm$^2$, total scan time = 4:23 minutes; and these parameters for the Prisma scanner: repetition time = 3230 ms, echo time = 89.2 ms, field of view = 210 x 210 x 138 mm$^3$, diffusion directions = 99, slice thickness = 1.5 mm, number of slices = 92, max *b* value = 3000 s/mm$^2$, total scan time = 5:41 minutes.

**Imaging preprocessing and connectome reconstruction**

DWI data were denoised using MRtrix's tool *dwidenoised* (22) and corrected for distortions (n = 40 Brainsuite registration-based distortion correction (23), n = 92 FSL *topup* (24)) and eddy-current and head motion (25), while performing outlier detection and replacement (26). Quality control was performed using e*ddyqc* (FSL) output (27). Two participants were excluded for having large ventricles and 6 participants were excluded for excessive (>3SD) head motion. The final sample size included 132 participants.

DWI were resampled to 2mm isotropic resolution and rotated to align with the anterior commissure – posterior commissure line. The diffusion data were reconstructed using generalized q-sampling imaging (28) with a diffusion sampling length ratio of 2. Deterministic whole-brain fiber tracking was implemented in DSI Studio using a modified fiber assignment by continuous tracking algorithm (29). For each subject, 1.000.000 streamlines with a length between 30-300mm were initiated. Fiber tracking was performed with randomized angular threshold, step size and anisotropy threshold values. Fractional anisotropy (FA) was calculated for each reconstructed streamline.

Brain parcellation was performed using DSI Studio's built-in Freesurfer Desikan-Killiany Cortical and Subcortical atlases, with 80 regions of interest that were transformed to each participant's native space. For every participant, structural weighted and undirected connectivity matrices were constructed by using 80 cortical and subcortical regions as nodes, and connectivity weights between the regions as edges. Two types of connectivity weights were evaluated: the total number of connecting streamlines touching two regions and the mean FA across voxels included in these streamlines.

**Reward network analyses**

The reward network was reconstructed based on ten bilateral regions (Figure 1): lateral and medial orbitofrontal cortex, nucleus accumbens, caudate nucleus and putamen (6). Again, such regions were defined as nodes, and the number of streamlines (NOS) and average FA between regions as edges. We calculated graph metrics using the Brain Connectivity Toolbox (Matlab) implemented in DSI Studio. The organization of the reward network was analyzed by means of connectivity strength (CS), that describes the overall strength of connections between regions both quantitatively (NOS) and qualitatively (FA), and clustering coefficient (CC), that measures local organization as the average probability of neighboring nodes in the network to be interconnected. The resulting network metrics (NOS CS, NOS CC, FA CS, FA CC) were normalized by the whole brain connectivity metrics (6,9) and harmonized between-scanners and protocols using ComBat (see Figure S1), a batch-effect correction tool that removes the unwanted variation by site and preserves biological variability (30).

**Data treatment and statistical analysis**

Prior to conducting the analyses, we registered our analysis plan in Open Science Framework: https://osf.io/nfyha. Data manipulation and statistical procedures were performed in R statistical package v.4.0.5 and RStudio v.2022.02.3. Mann–Whitney U and Chi-square tests were used to analyze between-group differences in sample demographic characteristics. Assumptions of linear regression were visually checked for all models using R's *check_model* in package *performance.* If the assumptions were not met, we log-transformed the variables.

*Main analysis*

We performed hierarchical linear regression analyses to assess the relationship between reward network (REW) metrics (NOS CS, NOS CC, FA CS, FA CC) and different predictors, which were entered in the models by steps. We used F-tests and associated P values from ANOVA to compare the models.

To assess the first hypothesis – whether higher BMI may be related to lower connectivity in the reward network –, we tested the null model 1a: REW metric ~ age + sex + estimated intracranial volume (eTIV) vs. the full model 1b: REW metric ~ age + sex + eTIV + BMI-z). For the second hypothesis – whether the FTO rs9939609 A allele is related to lower connectivity in the reward network – we used the same approach (null model 2a: REW metric ~ age + sex + eTIV + batch effect; full model 2b: REW metric ~ age + sex + eTIV + batch effect + FTO). Additionally, we investigated whether the FTO locus explained variance in BMI-z (null model 3a: BMI-z ~ age + sex + batch effect; full model 3b: BMI-z ~ age + sex + batch effect + FTO). Unstandardized betas were reported. To assess whether the results were consistent despite possible confounders, we repeated the analyses of

hypotheses (1) and (2) controlling for pubertal stage (prepubescent or pubertal), and the anxiety and depression scores of the Hospital Anxiety and Depression Scale. We based the inference of whether the effect was still present on the uncorrected p-values of the model comparison. A sensitivity analysis without controlling for eTIV can be found in Supplementary Material.

*Exploratory analysis*

We further performed an exploratory analysis that was not included in the registration of the study. Hypotheses (1) and (2) were explored at the whole-brain level using the same predictors and structure described above (model 4a: whole-brain metric ~ age + sex + eTIV; model 4b: whole-brain metric ~ age + sex + eTIV + BMI-z; model 5a: whole-brain metric ~ age + sex + eTIV + batch effect; model 5b: whole-brain metric ~ age + sex + eTIV +batch effect + FTO), as well as repeating the analyses controlling for possible confounders. A sensitivity analysis without controlling for eTIV can be found in Supplementary Material.

Multiple comparison correction

Using R studio, we applied a false discovery rate (FDR) correction to 17 models: REW metrics and BMI-z (4 models), REW metrics and FTO (4 models), whole-brain metrics and BMI-z (4 models), whole-brain metrics and FTO (4 models), and BMI-z and FTO (1 model). Significance was set at FDR-corrected p-value<0.05. When testing if the results were consistent after controlling for possible confounders (anxiety, depression, pubertal stage), we reported the results at an uncorrected level.

## Results

Descriptive characteristics of the sample according to BMI (n = 132) and FTO status (n = 130) are detailed in Table 1. A histogram of age distribution is provided in Figure S2.

### Main analysis: reward network results

When testing if the variables of interest (BMI-z or FTO A allele carrier) explained variance in the graph metrics of the reward network, we did not find significant results (FDR>0.05; Supplementary Table S1). After controlling for possible confounders, we observed that higher BMI-z was associated with lower FA CS (beta = -0.003, F = 3.97, uncorrected *P* = 0.048, Table 2). That is, with a lower white matter integrity among the white matter tracts that interconnect the reward network brain regions (lateral and medial orbitofrontal cortex, nucleus accumbens, caudate nucleus and putamen). Additionally, we investigated whether the FTO polymorphism explained variance in BMI-z, and found no significant results (beta = 0.11, F = 0.0026, FDR>0.05).

### Exploratory analysis: whole-brain results

Furthermore, we investigated differences in the whole-brain structural connectivity according to BMI-z and genetic risk of obesity. We observed that higher BMI-z was associated with higher FA CS (beta = 0.77, F = 11.34, FDR = 0.017, Supplementary Table S2). After controlling for confounders (Table 3), this relationship was still significant (beta = 0.76, F = 10.49, uncorrected *P* = 0.0015). No significant associations were found regarding whole-brain structural connectivity and FTO variants.

## Discussion

In this pre-registered study of adolescents and young adults, we examined the relationship between the structural connectivity of the reward network, BMI-z, and the genetic risk of obesity. Here, a higher BMI-z was significantly associated with lower structural connectivity of the reward network. Specifically, a higher BMI-z was associated with lower FA CS. Interestingly, when exploring the direction of the results at the whole-brain level, we found that a higher BMI-z was significantly related to higher FA CS. Regarding the FTO polymorphism, we did not observe genetic associations with measures of structural connectivity neither in the reward network nor at the whole-brain level. Moreover, the FTO polymorphism was not associated with BMI-z differences.

### BMI-z and FTO

In our sample, the FTO polymorphism was not statistically significantly associated with BMI-z yet, the association was in the expected direction. This is contrary to the results of a meta-analysis (31) that assessed, in children and adolescents of diverse ethnicities, the effect of FTO risk alleles on obesity. We hypothesize that such unexpected results might be explained by both methodological considerations and the presence of confounders. First, it is possible that we could not detect the effect due to the relatively small sample size and low power. Further, our approach for the FTO analysis (carriers of the risk allele vs. non carriers; instead of differentiating between homozygous and heterozygous genotypes) might also have influenced the results. Additionally, it is worth considering that other factors such as developmental stage, socioeconomic status, and epigenetics might modify the effects of the FTO polymorphism on BMI in this group. Regarding developmental status, a previous study suggested that the influence of a

genome-wide polygenic score of obesity on BMI trajectories was more pronounced as development advanced and adulthood was reached (32). Thus, the genetic effect of FTO might be age-dependent (33), and the impact of FTO on BMI in our sample might be blurred due to the wide age range of our participants (10 to 21 years old), probably via the endocrinological and physiological changes present during midpuberty that might temporarily diminish the association between BMI-z and FTO (34). There is also evidence of the interaction between socioeconomic status and FTO, and how a higher socioeconomic status exerts a protective effect regarding obesity in both children (35) and adults (36). Although the socioeconomic status was an intended question of our protocol, 65% of the sample did not provide information about their monthly family income. Thereby, this variable was not included in the analyses. However, we stress the importance of including social determinants in genetic studies. Additionally, lifestyle variables (e.g., diet, physical activity, sleeping patterns, and alcohol intake) and environmental exposure to endocrine disruptors (e.g., bisphenol A or organophosphate pesticides) are known to contribute to obesity via alterations in DNA methylation, histone modification, and non-coding RNAs (37). Thus, and although we did not include these variables in our study, epigenetics might explain BMI variance and should be considered in future studies.

BMI and structural connectivity

Our results suggested a divergence in the structural connectivity patterns in adolescents and young adults with higher BMI-z. In the reward network, and consistent with other studies (6,9,38), BMI-z was associated with less structural connectivity, whereas the opposite relationship was found at the whole-brain level, similar to the results reported

by Augustijn et al. (39). While these findings (at an uncorrected level) in the reward network agreed with our hypothesis, the finding of higher global FA CS related to higher BMI-z values was unexpected. We presume that the contrary findings in our study may evidence that the obesity-related alterations of white matter integrity are not widespread across the brain, but that distinct brain regions may not be affected equally by BMI. Specifically, we hypothesize that lower FA CS values in the reward network may explain the alterations in the reward processing of food seen in obesity states (40). However, in supplementary analyses, we found that higher BMI was not significantly related to FA CS when using raw (not normalized) values. This might indicate that the relationship was to some extent driven by the positive association of BMI and whole brain FA CS (Supplementary Section A and Supplementary Figure 3). Moreover, it is possible that differences in brain development due to age and sex may moderate the relationship between FA CS and BMI (41,42). Longitudinal sex-stratified approaches are required to assess how the obese physiological state affects structural connectivity during development. Importantly, since our sample size was small and our results regarding the reward network were significant at an uncorrected level, they should be considered preliminary. Validating these results in an independent cohort (e.g., ABCD dataset) is advised to confirm our findings. Additionally, it would be interesting to assess if body fat percentage – which highly correlates with BMI but may be a more specific measure of adiposity and probably more relevant in the context of adolescence – has a stronger relationship with structural connectivity in the reward network and at the whole-brain level.

FTO and structural connectivity

In our study, and consistent with the results of Beyer et al. (9), we did not find an association between the FTO polymorphism and structural connectivity. Few studies have assessed the effect of the FTO gene on brain structure and function. One study found that high-risk FTO genotype carriers had greater activation by high energy dense food in the ventral tegmental area/substantia nigra, amygdala, and ventral striatum, suggesting that allelic variations in FTO may disturb satiety processing (43). Another study found that the FTO risk allele was associated with lower nucleus accumbens volumes, indicating possible impairment of dopaminergic projections in the reward network (44). Overall, it is still unclear whether FTO really exerts its obesity risk via reward network structures. We suggest that using polygenic risk scores in larger sample sizes might elucidate with greater predictive power the relationship between the FTO gene and the reward network structural connectivity.

Adolescence and reward system neurodevelopment

The dopamine system undergoes significant changes across development. Dopamine-rich regions, such as frontal and striatal regions, undergo maturational processes during adolescence. At the functional level, the reward system becomes hyper-responsive to reward and incentives, and rewarding events may result in a larger dopamine release that can contribute to a cycle of reward-seeking behavior (45). The asynchrony between a heightened bottom-up reward-related drives and a not fully matured top-down cognitive control may underpin the adolescents' sub-optimal decision-making regarding risk and health behaviors (e.g., substance use or overconsumption of palatable foods) (46,47). Structurally, the reported increases in white matter volumes during adolescence

474 are accompanied by progressive increases in white matter integrity – such as FA –, that
475 may reflect the continuous axonal myelination that undergoes during this
476 developmental window (48). However, both higher BMI categories and high fat diets may
477 affect early myelinization, either via disruption of essential fatty acid production or
478 oligodendrocytes impairment (49). Thus, it is possible that individual differences in white
479 mater maturation (50) condition the effect of biological insults, such as having
480 overweight/obesity.
481
482 Strengths and Limitations
483 Strengths of our study include a high-resolution MRI protocol and the application of
484 ComBat harmonization. Further, we pre-registered our hypotheses and thereby increase
485 transparency and reliability of human neuroimaging. Limitations include that we could
486 not assess potential mediating factors (see the registered analysis plan to check the
487 conditions in which the mediation analyses would have been performed:
488 https://osf.io/nfyha). Second, the sample size used might have been underpowered to
489 detect the effect of the FTO polymorphism on brain connectivity. Third, lifestyle factors
490 (51,52) and cardiometabolic or inflammatory variables that could help to better define
491 our sample were not included in our study. Fourth, we preregistered using normalized
492 graph metrics of the reward network, but this made it difficult to understand whether
493 reward vs. whole-brain changes drove the effect. Future studies should study those
494 independently or use other metrics to adjust for whole-brain effects.
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Conclusions

We provide evidence that, in healthy adolescents and young adults, higher BMI-z is associated with higher connectivity at the whole-brain level. Using an uncorrected threshold, we show that higher BMI-z is associated with lower structural connectivity of the reward network. Such findings may be indicative of specific anatomical alterations associated with obesity in adolescents and young adults. We did not find the FTO polymorphism to correlate with structural connectivity, suggesting that the genetic contribution of this variant to white matter microstructure patterns is small and not a plausible mechanism through which obesity risk is conferred. Future longitudinal studies with larger sample sizes are needed to assess how genetic determinants of obesity may change brain structural connectivity and its behavioral implications.

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manuscript. All authors critically reviewed the manuscript, approved its final version for publishing, and agreed to be accountable for all aspects of such work.

**Conflict of interest:** The authors declare that they have no conflict of interest.

**Data availability:** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**References**


1. Safaei M, Sundararajan EA, Driss M, Boulila W, Shapi'i A. A systematic literature review on obesity: Understanding the causes & consequences of obesity and reviewing various machine learning approaches used to predict obesity. Comput Biol Med. 2021;136(104754):1–17.
2. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, et al. A Common Variant in the FTO Gene Is Associated with Body Mass Index and Predisposes to Childhood and Adult Obesity. Science (80- ). 2007;316:889–94.
3. Loos RJF, Yeo GSH. The genetics of obesity: from discovery to biology. Nat Rev Genet. 2022;23(2):120–33.
4. Speakman JR. The "Fat Mass and Obesity Related" (FTO) gene: Mechanisms of Impact on Obesity and Energy Balance. Curr Obes Rep. 2015;4(1):73–91.
5. Hess ME, Hess S, Meyer KD, Verhagen LAW, Koch L, Brönneke HS, et al. The fat mass and obesity associated gene (Fto) regulates activity of the dopaminergic midbrain circuitry. Nat Neurosci. 2013;16(8):1042–8.
6. Marqués-Iturria I, Scholtens LH, Garolera M, Pueyo R, García-García I, González-

Tartiere P, et al. Affected connectivity organization of the reward system structure in obesity. Neuroimage. 2015;111:100–6.

7. Edwin Thanarajah S, Hanssen R, Melzer C, Tittgemeyer M. Increased meso-striatal connectivity mediates trait impulsivity in FTO variant carriers. Front Endocrinol (Lausanne). 2023;14:1130203.

8. Adise S, Allgaier N, Laurent J, Hahn S, Chaarani B, Owens M, et al. Multimodal brain predictors of current weight and weight gain in children enrolled in the ABCD study ®. Dev Cogn Neurosci. 2021;49(100948):1–14.

9. Beyer F, Zhang R, Scholz M, Wirkner K, Loeffler M, Stumvoll M, et al. Higher BMI, but not obesity-related genetic polymorphisms, correlates with lower structural connectivity of the reward network in a population-based study. Int J Obes. 2021;45:491–501.

10. Gupta A, Mayer EA, Sanmiguel CP, Van Horn JD, Woodworth D, Ellingson BM, et al. Patterns of brain structural connectivity differentiate normal weight from overweight subjects. NeuroImage Clin. 2015;7:506–17.

11. Riederer JW, Shott ME, Deguzman M, Pryor TL, Frank GKW. Understanding Neuronal Architecture in Obesity through Analysis of White Matter Connection Strength. Front Hum Neurosci. 2016;10:271.

12. García-García I, Morys F, Dagher A. Nucleus accumbens volume is related to obesity measures in an age-dependent fashion. J Neuroendocrinol. 2020;32(12):1–12.

13. Lancaster TM, Ihssen I, Brindley LM, Linden DE. Preliminary evidence for genetic overlap between body mass index and striatal reward response. Transl Psychiatry. 2018;8(19):1–9.

14. Olivo G, Latini F, Wiemerslage L, Larsson EM, Schiöth HB. Disruption of accumbens and thalamic white matter connectivity revealed by diffusion tensor tractography in young men with genetic risk for obesity. Front Hum Neurosci. 2018;12(75):1–10.

15. Lugo-Candelas C, Pang Y, Lee S, Cha J, Hong S, Ranzenhofer L, et al. Differences in brain structure and function in children with the FTO obesity-risk allele. Obes Sci Pract. 2020;6(4):409–24.

16. Sawyer SM, Azzopardi PS, Wickremarathne D, Patton GC. The age of adolescence. Lancet Child Adolesc Heal. 2018;2(3):223–8.

17. Prats-Soteras X, Jurado MA, Ottino-González J, García-García I, Segura B, Caldú X, et al. Inflammatory agents partially explain associations between cortical thickness, surface area, and body mass in adolescents and young adulthood. Int J Obes. 2020;44(7):1487–96.

18. Prunell-Castañé A, Jurado MÁ, Ottino-González J, Prats-Soteras X, Sánchez Garre C, Cano Marco N, et al. Beyond BMI: cardiometabolic measures as predictors of impulsivity and white matter changes in adolescents. Brain Struct Funct. 2023;228(3):751–60.

19. Must A, Anderson SE. Body mass index in children and adolescents: Considerations for population-based applications. Int J Obes. 2006;30(4):590–4.

20. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. Pediatr Obes. 2012;7:284–94.

21. Organization WH. World Health Organization. Obesity and overweight [Internet]. Available from: https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight

22. Veraart J, Novikov DS, Christiaens D, Ades-aron B, Sijbers J, Fieremans E. Denoising of diffusion MRI using random matrix theory. Neuroimage. 2016;142:394–406.
23. Bhushan C, Haldar JP, Joshi AA, Leahy RM. Correcting Susceptibility-Induced Distortion in Diffusion-Weighted MRI using Constrained Nonrigid Registration. Signal Inf Process Assoc Annu Summit Conf APSIPA Asia Pac. 2012;
24. Andersson JLR, Skare S, Ashburner J. How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. Neuroimage. 2003 Oct;20:870–88.
25. Andersson JLR, Sotiropoulos SN. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. Neuroimage. 2016;125:1063–78.
26. Andersson JLR, Graham MS, Zsoldos E, Sotiropoulos SN. Incorporating outlier detection and replacement into a non-parametric framework for movement and distortion correction of diffusion MR images. Neuroimage. 2016;141:556–72.
27. Bastiani M, Cottaar M, Fitzgibbon SP, Suri S, Alfaro-Almagro F, Sotiropoulos SN, et al. Automated quality control for within and between studies diffusion MRI data using a non-parametric framework for movement and distortion correction. Neuroimage. 2019;184:801–12.
28. Yeh FC, Wedeen VJ, Tseng WYI. Generalized q-Sampling Imaging. IEEE Trans Med Imaging. 2010;29(9):1626–35.
29. Yeh FC, Verstynen TD, Wang Y, Fernández-Miranda JC, Tseng WYI. Deterministic diffusion fiber tracking improved by quantitative anisotropy. PLoS One. 2013;8(11):1–16.

30. Fortin JP, Parker D, Tunç B, Watanabe T, Elliott MA, Ruparel K, et al. Harmonization of multi-site diffusion tensor imaging data. Neuroimage. 2017;161:149–70.

31. da Silva TER, Andrade NL, Cunha D de O, Leão-Cordeiro JAB, Vilanova-Costa CAST, Silva AMTC. The FTO rs9939609 polymorphism and obesity risk in teens: Evidence-based meta-analysis. Obes Res Clin Pract. 2018;12:432–7.

32. Khera A V., Chaffin M, Wade KH, Zahid S, Brancale J, Xia R, et al. Polygenic Prediction of Weight and Obesity Trajectories from Birth to Adulthood. Cell. 2019;177(3):587–96.

33. Ganeff IMM, Bos MM, Van Heemst D, Noordam R. BMI-associated gene variants in FTO and cardiometabolic and brain disease: Obesity or pleiotropy? Physiol Genomics. 2019;51:311–22.

34. Rutters F, Nieuwenhuizen AG, Bouwman F, Mariman E, Westerterp-plantenga MS. Associations between a Single Nucleotide Polymorphism of the FTO Gene ( rs9939609 ) and Obesity-Related Characteristics over Time during Puberty in a Dutch Children Cohort. J Clin Endocrinol Metab. 2011;96(6):939–42.

35. Foraita R, Günther F, Gwozdz W, Reisch LA, Russo P, Lauria F, et al. Does the FTO gene interact with the socioeconomic status on the obesity development among young European children? Results from the IDEFICS study. Int J Obes. 2015;39(1):1–6.

36. Rask-Andersen M, Karlsson T, Ek WE, Johansson Å. Gene-environment interaction study for BMI reveals interactions between genetic factors and physical activity, alcohol consumption and socioeconomic status. PLoS Genet. 2017;13(9):1–20.

641 37. Mahmoud AM. An Overview of Epigenetics in Obesity: The Role of Lifestyle and
642 Therapeutic Interventions. Int J Mol Sci. 2022;23(3).
643 38. Tan Z, Hu Y, Ji G, Li G, Ding Y, Zhang W, et al. Alterations in Functional and
644 Structural Connectivity of Basal Ganglia Network in Patients with Obesity. Brain
645 Topogr. 2022;35(4):453–63.
646 39. Augustijn MJCM, Di Biase MA, Zalesky A, Van Acker L, De Guchtenaere A,
647 D'Hondt E, et al. Structural connectivity and weight loss in children with obesity:
648 a study of the "connectobese." Int J Obes. 2019;43:2309–21.
649 40. Meng X, Huang D, Ao H, Wang X, Gao X. Food cue recruits increased reward
650 processing and decreased inhibitory control processing in the
651 obese/overweight: An activation likelihood estimation meta-analysis of fMRI
652 studies. Obes Res Clin Pract. 2020;14(2):127–35.
653 41. Carbine KA, Duraccio KM, Hedges-Muncy A, Barnett KA, Kirwan CB, Jensen CD.
654 White matter integrity disparities between normal-weight and
655 overweight/obese adolescents: an automated fiber quantification tractography
656 study. Brain Imaging Behav. 2020;14:308–19.
657 42. Ma J, Mcglade EC, Id RSH, Lyoo IK, Renshaw F, Yurgelun-todd DA. Overweight /
658 Obesity-related microstructural alterations of the fimbria-fornix in the ABCD
659 study : The role of aerobic physical activity. PLoS One. 2023;18(7):1–16.
660 43. Melhorn SJ, Askren MK, Chung WK, Kratz M, Bosch TA, Tyagi V, et al. FTO
661 genotype impacts food intake and corticolimbic activation. Am J Clin Nutr.
662 2018;107(2):145–54.
663 44. De Groot C, Felius A, Trompet S, De Craen AJM, Blauw GJ, Van Buchem MA, et
664 al. Association of the fat mass and obesity-associated gene risk allele,

rs9939609A, and reward-related brain structures. Obesity. 2015;23:2118–22.

45. Galvan A. Adolescent development of the reward system. Front Hum Neurosci. 2010;4:1–9.

46. Reichelt AC. Adolescent maturational transitions in the prefrontal cortex and dopamine signaling as a risk factor for the development of obesity and high fat/high sugar diet induced cognitive deficits. Front Behav Neurosci. 2016;10:1–17.

47. Geier CF. Adolescent cognitive control and reward processing: Implications for risk taking and substance use. Horm Behav. 2013;64(2):333–42.

48. Blakemore SJ. Imaging brain development: The adolescent brain. Neuroimage [Internet]. 2012;61(2):397–406. Available from: http://dx.doi.org/10.1016/j.neuroimage.2011.11.080

49. Sadler JR, Thapaliya G, Ranganath K, Gabay A, Chen L, Smith KR, et al. Paediatric obesity and metabolic syndrome associations with cognition and the brain in youth: Current evidence and future directions. Pediatr Obes. 2023;18(8):1–27.

50. Stiles J, Jernigan TL. The basics of brain development. Neuropsychol Rev. 2010;20(4):327–48.

51. Loos RJF, Yeo GSH. The bigger picture of FTO - The first GWAS-identified obesity gene. Nat Rev Endocrinol. 2014;10(1):51–61.

52. Jiang Y, Mei H, Lin Q, Wang J, Liu S, Wang G, et al. Interaction effects of FTO rs9939609 polymorphism and lifestyle factors on obesity indices in early adolescence. Obes Res Clin Pract. 2019;13(4):352–7.

**Table 1. Demographic characteristics of the BMI and FTO groups**.

| | BMI groups | | | | | | | | FTO groups | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NW (n = 62) | | | OW/OB (n = 70) | | | Test | P | TT (n = 39) | | | AT/AA (n = 91) | | | Test | P |
| | Mean (sd) | Min | Max | Mean (sd) | Min | Max | | | Mean (sd) | Min | Max | Mean (sd) | Min | Max | | |
| Age (years old) | 15.6 (2.63) | 10 | 21 | 15.2 (2.68) | 10 | 21 | 2381[a] | 0.34 | 15.7 (2.65) | 11 | 21 | 15.3 (2.69) | 10 | 21 | 1935[a] | 0.42 |
| Prepubescents (n) | 4 | | | 2 | | | 0.32[b] | 0.57 | 3 | | | 3 | | | 0.41[b] | 0.52 |
| Sex (n females) | 32 | | | 32 | | | 0.25[b] | 0.61 | 21 | | | 43 | | | 0.25[b] | 0.62 |
| BMI z-score | -0.1 (0.62) | -1.76 | 0.89 | 1.79 (0.4) | 0.95 | 2.69 | 0[a] | <0.001 | 0.85 (1.11) | -0.98 | 2.61 | 0.96 (1.04) | -1.76 | 2.69 | 1648[a] | 0.52 |
| Anxiety | 5.92 (3.17) | 0 | 13 | 5.24 (3.26) | 0 | 14 | 2436[a] | 0.22 | 5.31 (3.15) | 0 | 13 | 5.75 (3.25) | 0 | 14 | 1614[a] | 0.41 |
| Depression | 2.71 (2.24) | 0 | 12 | 3.04 (2.53) | 0 | 9 | 2037[a] | 0.54 | 3.13 (2.55) | 0 | 12 | 2.82 (2.34) | 0 | 9 | 1893[a] | 0.54 |
| Estimated intelli-gence | 11.2 (2.44) | 7 | 19 | 11 (2.47) | 7 | 19 | 2269[a] | 0.65 | 10.9 (2.51) | 7 | 17 | 11.2 (2.44) | 7 | 19 | 1719[a] | 0.78 |
| FTO A Carrier (n) | 43 | | | 48 | | | 0.04[b] | 0.85 | ---- | | | ---- | | | ---- | ---- |

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690 Test statistics: a Mann–Whitney U test; b Chi Squared Test. BMI: body mass index; Estimated intelligence: calculated
691 using the Weschler Adults Intelligence Scale-III/Weschler Intelligence Scale for Children-IV vocabulary subtest; FTO:
692 fat mass and obesity related gene; NW: normal-weight; OW/OB: overweight/obesity.

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**Table 2. Results from the hierarchical multiple regression analysis of BMI-z, FTO and reward network structural connectivity after controlling for confounders.**

| REW metric | Model | Multiple regression | | Model comparison | | Variable of interest | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Adj $R^2$ | *P* model | F | $P_{uncorrected}$ | | *b* | 95% CI | *P* |
| CC NOS (log) | 1c | 0.007 | 0.27 | ---- | ---- | BMI-z | ---- | ---- | ---- |
| | 1d | -0.002 | 0.45 | 0.62 | 0.61 | | ---- | ---- | ---- |
| | 1e | -0.009 | 0.57 | 0.03 | 0.86 | | 0.004 | (-0.04, 0.05) | 0.87 |
| | 2c | 0.006 | 0.32 | ---- | ---- | FTO | ---- | ---- | ---- |
| | 2d | -0.0004 | 0.44 | 0.74 | 0.53 | | ---- | ---- | ---- |
| | 2e | -0.0003 | 0.44 | 1 | 0.32 | | -0.06 | (-0.17, 0.06) | 0.32 |
| CS NOS | 1c | -0.013 | 0.74 | ---- | ---- | BMI-z | ---- | ---- | ---- |
| | 1d | -0.023 | 0.81 | 0.58 | 0.63 | | ---- | ---- | ---- |
| | 1e | -0.03 | 0.85 | 0.29 | 0.59 | | -0.01 | (-0.05, 0.03) | 0.59 |
| | 2c | -0.02 | 0.81 | ---- | ---- | FTO | ---- | ---- | ---- |
| | 2d | -0.03 | 0.83 | 0.65 | 0.58 | | ---- | ---- | ---- |
| | 2e | -0.03 | 0.85 | 0.56 | 0.45 | | -0.037 | (-0.13, 0.06) | 0.45 |
| CC FA | 1c | 0.06 | 0.012 | ---- | ---- | BMI-z | ---- | ---- | ---- |
| | 1d | 0.06 | 0.026 | 1.2 | 0.31 | | ---- | ---- | ---- |
| | 1e | 0.07 | 0.026 | 1.64 | 0.2 | | -0.01 | (-0.03, 0.005) | 0.2 |
| | 2c | 0.05 | 0.025 | ---- | ---- | FTO | ---- | ---- | ---- |
| | 2d | 0.06 | 0.037 | 1.31 | 0.27 | | ---- | ---- | ---- |
| | 2e | 0.06 | 0.04 | 1.2 | 0.27 | | 0.02 | (-0.02, 0.06) | 0.27 |
| CS FA | 1c | -0.005 | 0.52 | ---- | ---- | BMI-z | ---- | ---- | ---- |
| | 1d | -0.0009 | 0.44 | 1.23 | 0.3 | | ---- | ---- | ---- |
| | 1e | 0.02 | 0.2 | 3.97 | 0.048* | | -0.003 | (-0.006, -0.00005) | 0.048* |
| | 2c | -0.01 | 0.62 | ---- | ---- | FTO | ---- | ---- | ---- |
| | 2d | -0.003 | 0.47 | 1.32 | 0.27 | | ---- | ---- | ---- |
| | 2e | 0.003 | 0.48 | 0.99 | 0.32 | | 0.004 | (-0.004, 0.01) | 0.32 |

Model 1c: REW metric ~ age + sex + eTIV; model 1d: REW metric ~ age + sex + eTIV + prepubescent + anxiety + depression; model 1e: REW metric ~ age + sex + eTIV + prepubescent + anxiety + depression + BMI-z; model 2c: REW metric ~ age + sex + eTIV + batch effect; model 2d: REW metric ~ age + sex + eTIV + batch effect + prepubescent + anxiety + depression; model 2e: REW metric ~ age + sex + eTIV + batch effect + prepubescent + anxiety + depression + FTO. Unstandardized betas were reported.

Abbreviations: BMI-z: body mass index z-score; CC: clustering coefficient; CS: connectivity strength; eTIV: estimated total intracranial volume; FA: fractional anisotropy; FTO: fat mass and obesity related gene (A-allele carrier vs. non carrier); NOS: number of streamlines; REW: reward network.

**Table 3. Results from the hierarchical multiple regression analysis of BMI-z, FTO and whole-brain structural connectivity after controlling for confounders.**

| Whole-brain metric | Model | Multiple regression | | Model comparison | | Variable of interest | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Adj $R^2$ | P model | F | $P_{uncorrected}$ | | *b* | 95% CI | *P* |
| CC NOS | 4c | 0.001 | 0.37 | ---- | ---- | BMI-z | ---- | ---- | ---- |
| | 4d | -0.003 | 0.47 | 0.82 | 0.49 | | ---- | ---- | ---- |
| | 4e | 0.001 | 0.42 | 1.58 | 0.21 | | 0.0002 | (-0.0001, 0.0006) | 0.21 |
| | 5c | 0.21 | 0.0000009 | ---- | ---- | FTO | ---- | ---- | ---- |
| | 5d | 0.19 | 0.00002 | 0.12 | 0.95 | | ---- | ---- | ---- |
| | 5e | 0.2 | 0.00002 | 2.05 | 0.15 | | 0.0006 | (-0.0002, 0.001) | 0.15 |
| CS NOS | 4c | -0.01 | 0.7 | ---- | ---- | BMI-z | ---- | ---- | ---- |
| | 4d | -0.02 | 0.8 | 0.55 | 0.65 | | ---- | ---- | ---- |
| | 4e | -0.009 | 0.57 | 2.73 | 0.1 | | 0.038 | (-0.007, 0.08) | 0.1 |
| | 5c | -0.018 | 0.8 | ---- | ---- | FTO | ---- | ---- | ---- |
| | 5d | -0.03 | 0.85 | 0.56 | 0.64 | | ---- | ---- | ---- |
| | 5e | -0.02 | 0.67 | 2.39 | 0.12 | | 0.09 | (-0.02, 0.2) | 0.12 |
| CC FA | 4c | 0.014 | 0.19 | ---- | ---- | BMI-z | ---- | ---- | ---- |
| | 4d | 0.016 | 0.24 | 1.1 | 0.35 | | ---- | ---- | ---- |
| | 4e | 0.036 | 0.12 | 3.61 | 0.06 | | 0.004 | (-0.0001, 0.009) | 0.06 |
| | 5c | 0.006 | 0.31 | ---- | ---- | FTO | ---- | ---- | ---- |
| | 5d | 0.01 | 0.29 | 1.26 | 0.29 | | ---- | ---- | ---- |
| | 5e | 0.005 | 0.38 | 0.03 | 0.85 | | 0.001 | (-0.01, 0.01) | 0.85 |
| CS FA | 4c | 0.1 | 0.0006 | ---- | ---- | BMI-z | ---- | ---- | ---- |
| | 4d | 0.11 | 0.002 | 1.22 | 0.31 | | ---- | ---- | ---- |
| | 4e | 0.17 | 0.00007 | 10.49 | 0.0015* | | 0.76 | (0.30, 1.21) | 0.0015* |
| | 5c | 0.1 | 0.002 | ---- | ---- | FTO | ---- | ---- | ---- |
| | 5d | 0.1 | 0.004 | 1.3 | 0.28 | | ---- | ---- | ---- |
| | 5e | 0.1 | 0.007 | 0.27 | 0.6 | | 0.3 | (-0.84, 1.44) | 0.6 |

Model 4c: whole-brain metric ~ age + sex + eTIV; model 4d: whole-brain metric ~ age + sex + eTIV + prepubescent + anxiety + depression; model 4e: whole-brain metric ~ age + sex + eTIV + prepubescent + anxiety + depression + BMI-z; model 5c: whole-brain metric ~ age + sex + eTIV + batch effect; model 5d: whole-brain metric ~ age + sex + eTIV + batch effect + prepubescent + anxiety + depression; model 5e: whole-brain metric ~ age + sex + eTIV + batch effect + prepubescent + anxiety + depression + FTO. Unstandardized betas were reported.

Abbreviations: BMI-z: body mass index z-score; CC: clustering coefficient; CS: connectivity strength; eTIV: estimated total intracranial volume; FA: fractional anisotropy; FTO: fat mass and obesity related gene (A-allele carrier vs. non carrier); NOS: number of streamlines; REW: reward network.

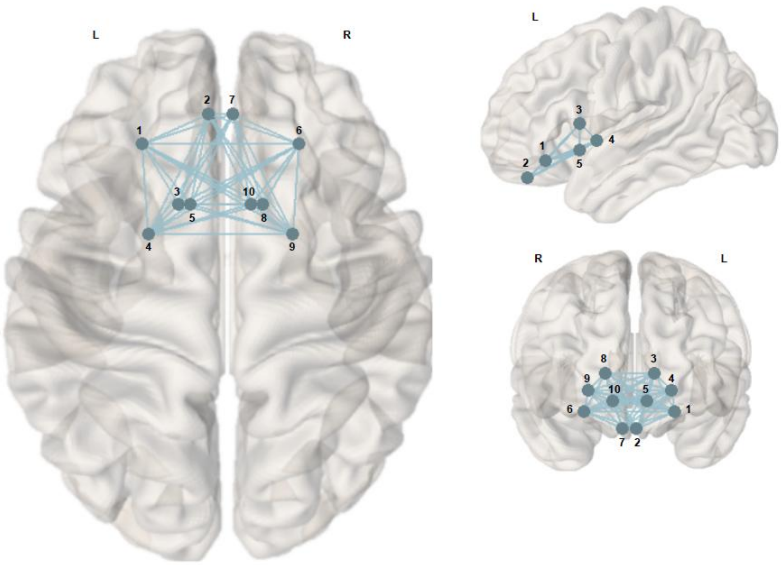
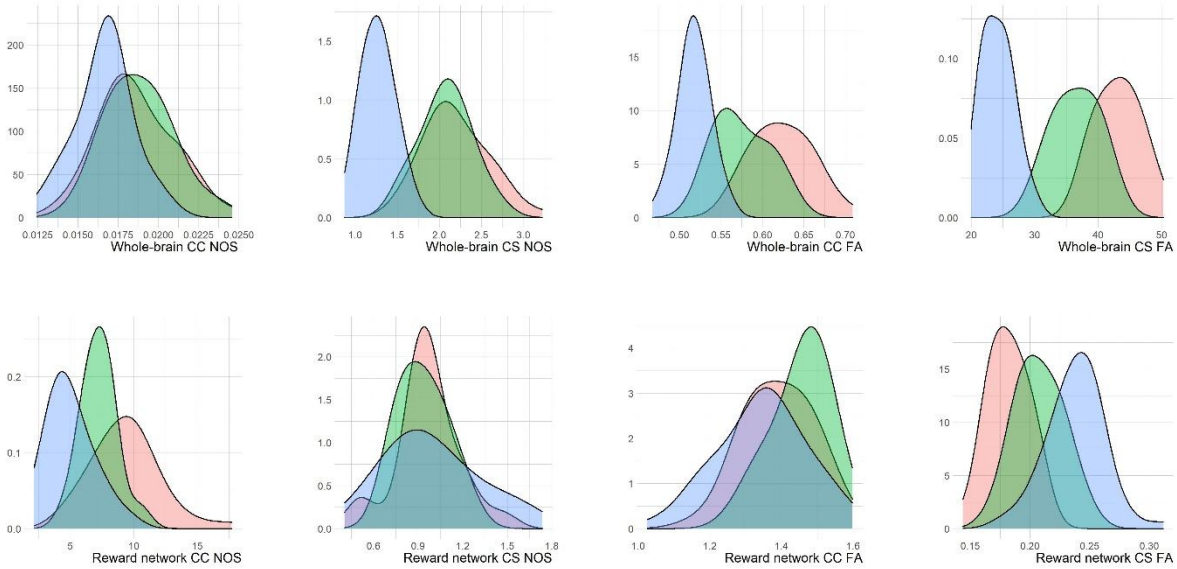



**Figure 1.** Reconstruction of the reward network using R's package *brainconn.* Dots refer to hubs of the lateral (1,6) and medial orbitofrontal cortex (2,7), caudate nucleus (3,8), putamen (4,9), and nucleus accumbens (5,10). Lines indicate structural connections.

## SUPPLEMENTARY MATERIAL

We provide a single PDF where the reader can find a figure of the ComBat harmonization application for the graph metrics, a histogram of the age distribution of our sample, an exploratory analysis and figure of the relationship between BMI-z and connectivity strength measures, as well as 2 tables displaying the results of the main analysis without controlling for confounders, and 4 tables showing the results of the sensitivity analysis.

Not harmonized




Harmonized

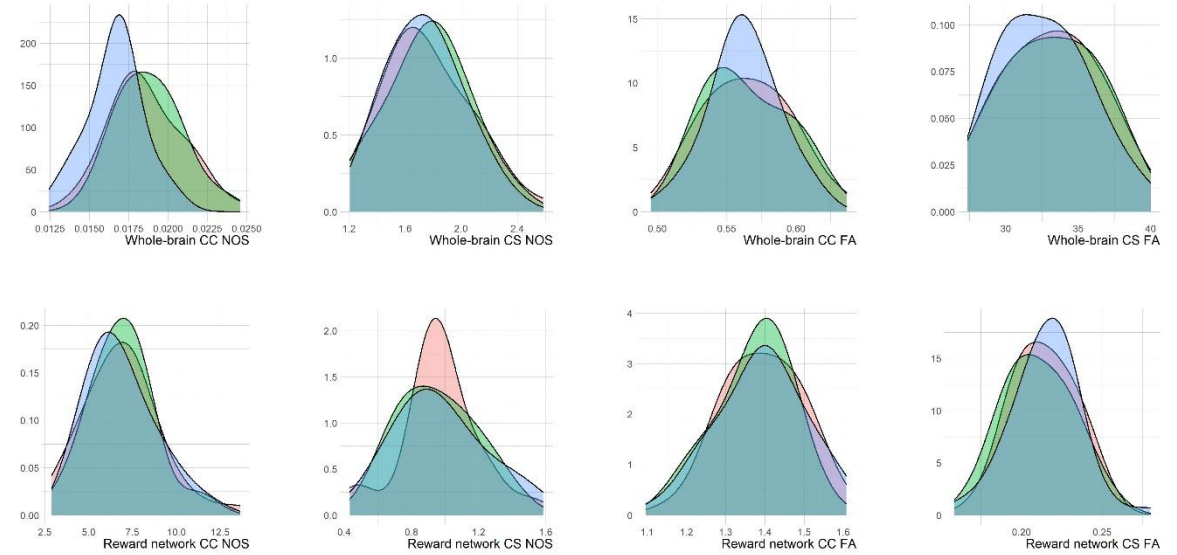



**Figure S1. Graph metrics (NOS CS, NOS CC, FA CS, FA CC) with and without ComBat harmonization application. Each color represents a different neuroimaging protocol acquisition. Abbreviations: CC: clustering coefficient; CS: connectivity strength; FA: fractional anisotropy; NOS: number of streamlines.**

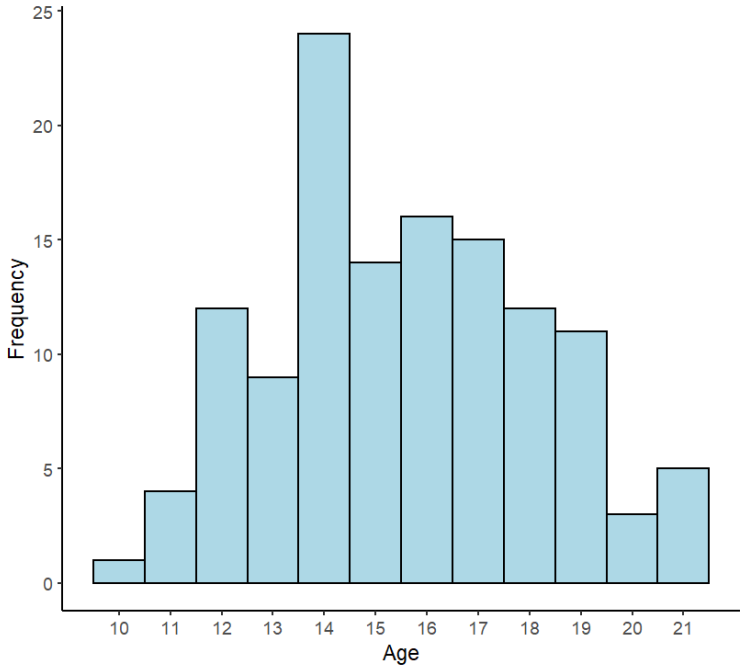



**Figure S2. Histogram of age distribution.**

### A) Testing the effect of BMIz on whole-brain CS FA and reward network CS FA

We performed an exploratory analysis and regressed both whole-brain and reward network FA CS on BMIz (BMz ~ whole-brain CS FA + reward network CS FA). We used the raw values for reward network FA CS because the normalized reward network FA CS depends on whole brain FA CS. We found that whole-brain FA CS was positively associated with BMIz (beta = 0.11, 95% CI = (0.05, 0.17), P = 0.0009), whereas the coefficient for the reward network FA CS was negative but not significant (beta = -0.14, 95% CI = (-0.52, 0.33), P = 0.44).

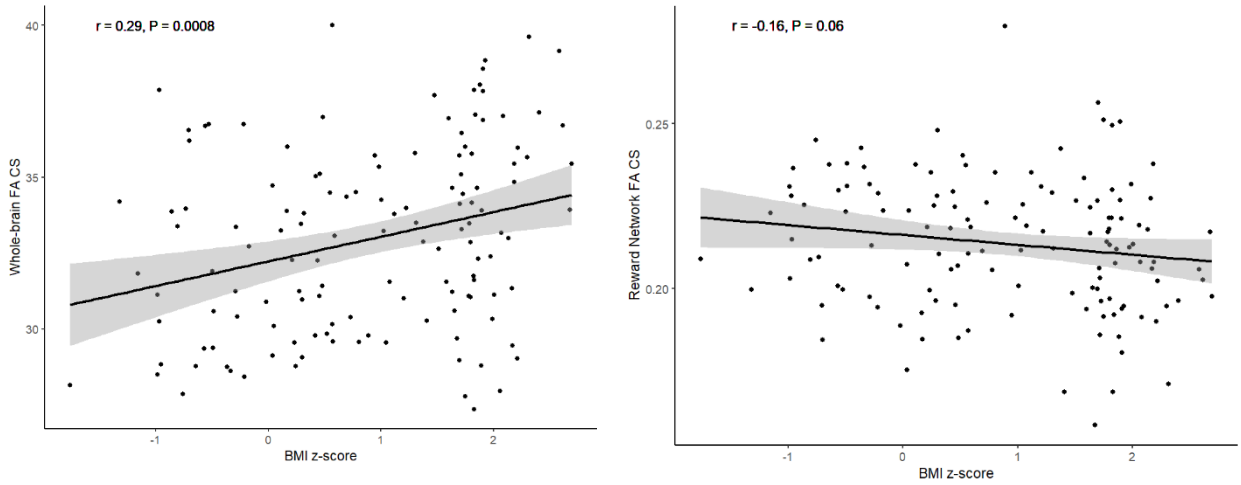



**Figure S3. Association between BMI-z and whole-brain FA CS (left), and BMI-z and reward network FA CS (right). FA CS is defined as the sum of FA values that connect the nodes either for the whole-brain cortical and subcortical structures (n = 80), or the nodes of the reward network (n = 10). Abbreviations: BMI-z: body mass index z-score, FA: fractional anisotropy, CS: connectivity strength.**

**Table S1. Results from the hierarchical multiple regression analysis of BMI-z, FTO and reward network structural connectivity**

| REW metric | Model | Multiple regression | | Model comparison | | Variable of interest | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Adj $R^2$ | *P* model | F | FDR | | *b* | 95% CI | *P* |
| CC NOS (log) | 1a | 0.007 | 0.27 | ---- | ---- | | ---- | ---- | ---- |
| | 1b | 0.0001 | 0.41 | 0.09 | 0.93 | BMI-z | 0.007 | (-0.04, 0.05) | 0.76 |
| | 2a | 0.006 | 0.32 | ---- | ---- | | ---- | ---- | ---- |
| | 2b | 0.008 | 0.31 | 1.28 | 0.4 | FTO | -0.06 | (-0.18, 0.05) | 0.26 |
| CS NOS | 1a | -0.01 | 0.74 | ---- | ---- | | ---- | ---- | ---- |
| | 1b | -0.02 | 0.84 | 0.13 | 0.93 | BMI-z | -0.007 | (-0.05, 0.03) | 0.71 |
| | 2a | -0.02 | 0.81 | ---- | ---- | | ---- | ---- | ---- |
| | 2b | -0.02 | 0.81 | 0.66 | 0.59 | FTO | -0.04 | (-0.13, 0.06) | 0.42 |
| CC FA | 1a | 0.06 | 0.01 | ---- | ---- | | ---- | ---- | ---- |
| | 1b | 0.06 | 0.02 | 1.39 | 0.4 | BMI-z | -0.009 | (-0.02, 0.006) | 0.24 |
| | 2a | 0.05 | 0.02 | ---- | ---- | | ---- | ---- | ---- |
| | 2b | 0.06 | 0.02 | 1.78 | 0.4 | FTO | 0.02 | (-0.01, 0.06) | 0.18 |
| CS FA | 1a | -0.005 | 0.52 | ---- | ---- | | ---- | ---- | ---- |
| | 1b | 0.01 | 0.2 | 3.76 | 0.31 | BMI-z | -0.003 | (-0.006, 0.00003) | 0.05 |
| | 2a | -0.01 | 0.62 | ---- | ---- | | ---- | ---- | ---- |
| | 2b | -0.006 | 0.52 | 1.59 | 0.4 | FTO | 0.005 | (-0.003, 0.01) | 0.21 |

Model 1a: REW metric ~ age + sex + eTIV; model 1b: REW metric ~ age + sex + eTIV + BMI-z; model 2a: REW metric ~ age + sex + eTIV + batch effect; model 2b: REW metric ~ age + sex + eTIV + batch effect + FTO. Unstandardized betas were reported.

Abbreviations: BMI-z: body mass index z-score; CC: clustering coefficient; CS: connectivity strength; eTIV: estimated total intracranial volume; FA: fractional anisotropy; FTO: fat mass and obesity related gene (A-allele carrier vs. non carrier); NOS: number of streamlines; REW: reward network

**Table S2. Results from the hierarchical multiple regression analysis of BMI-z, FTO and whole-brain structural connectivity**

| Whole-brain metrics | Model | Multiple regression | | Model comparison | | Variable of interest | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Adj $R^2$ | *P* model | F | FDR | | *b* | 95% CI | *P* |
| CC NOS | 4a | 0.001 | 0.37 | ---- | ---- | | ---- | ---- | ---- |
| | 4b | 0.004 | 0.34 | 1.45 | 0.4 | BMI-z | 0.0002 | (-0.0001, 0.0006) | 0.23 |
| | 5a | 0.2 | $9.49 \times 10^{-7}$ | ---- | ---- | | ---- | ---- | ---- |
| | 5b | 0.21 | $1.23 \times 10^{-6}$ | 2.1 | 0.4 | FTO | 0.0006 | (-0.0002, 0.001) | 0.15 |
| CS NOS | 4a | -0.01 | 0.7 | ---- | ---- | | ---- | ---- | ---- |
| | 4b | 0.001 | 0.39 | 2.75 | 0.4 | BMI-z | 0.038 | (-0.007, 0.08) | 0.1 |
| | 5a | -0.02 | 0.8 | ---- | ---- | | ---- | ---- | ---- |
| | 5b | -0.01 | 0.6 | 2 | 0.4 | FTO | 0.078 | (-0.03, 0.19) | 0.16 |
| CC FA | 4a | 0.01 | 0.19 | ---- | ---- | | ---- | ---- | ---- |
| | 4b | 0.04 | 0.06 | 4.29 | 0.31 | BMI-z | 0.004 | (0.0002, 0.009) | 0.04 |
| | 5a | 0.006 | 0.31 | ---- | ---- | | ---- | ---- | ---- |
| | 5b | -0.001 | 0.44 | 0.02 | 0.94 | FTO | -0.0008 | (-0.01, 0.01) | 0.88 |
| CS FA | 4a | 0.1 | 0.0006 | ---- | ---- | | ---- | ---- | ---- |
| | 4b | 0.17 | 0.00001 | 11.34 | **0.017** | BMI-z | 0.77 | (0.32, 1.22) | 0.001 |
| | 5a | 0.1 | 0.002 | ---- | ---- | | ---- | ---- | ---- |
| | 5b | 0.09 | 0.004 | 0.04 | 0.94 | FTO | 0.11 | (-1.01, 1.24) | 0.84 |

Model 4a: whole-brain metric ~ age + sex + eTIV; model 4b: whole-brain metric ~ age + sex + eTIV + BMI-z; model 5a: whole-brain metric ~ age + sex + eTIV + batch effect; model 5b: whole-brain metric ~ age + sex + eTIV + batch effect + FTO. Unstandardized betas were reported.

Abbreviations: BMI-z: body mass index z-score; CC: clustering coefficient; CS: connectivity strength; eTIV: estimated total intracranial volume; FA: fractional anisotropy; FTO: fat mass and obesity related gene (A-allele carrier vs. non carrier); NOS: number of streamlines; REW: reward network.

## Sensitivity analysis

**Table S3. Results from the hierarchical multiple regression analysis of BMI-z, FTO and reward network structural connectivity *without* controlling for estimated total intracranial volume.**

| REW metric | Model | Multiple regression | | Model comparison | | Variable of interest | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Adj $R^2$ | *P* model | F | *P* uncorrected | | *b* | 95% CI | *P* |
| CC NOS (log) | 1c | 0.01 | 0.14 | ---- | ---- | | ---- | ---- | ---- |
| | 1d | 0.007 | 0.27 | 0.07 | 0.79 | BMI-z | 0.006 | (-0.04, 0.05) | 0.79 |
| | 2c | 0.01 | 0.19 | ---- | ---- | | ---- | ---- | ---- |
| | 2d | 0.01 | 0.2 | 1.25 | 0.26 | FTO | -0.06 | (-0.17, 0.05) | 0.26 |
| CS NOS | 1c | -0.008 | 0.62 | ---- | ---- | | ---- | ---- | ---- |
| | 1d | -0.01 | 0.76 | 0.2 | 0.65 | BMI-z | -0.009 | (-0.05, 0.03) | 0.65 |
| | 2c | -0.01 | 0.7 | ---- | ---- | | ---- | ---- | ---- |
| | 2d | -0.01 | 0.73 | 0.57 | 0.45 | FTO | -0.04 | (-0.13, 0.06) | 0.45 |
| CC FA | 1c | 0.07 | 0.004 | ---- | ---- | | ---- | ---- | ---- |
| | 1d | 0.07 | 0.007 | 1.35 | 0.25 | BMI-z | -0.009 | (-0.02, 0.006) | 0.25 |
| | 2c | 0.06 | 0.01 | ---- | ---- | | ---- | ---- | ---- |
| | 2d | 0.07 | 0.01 | 1.68 | 0.20 | FTO | 0.02 | (-0.01, 0.06) | 0.2 |
| CS FA | 1c | 0.002 | 0.33 | ---- | ---- | | ---- | ---- | ---- |
| | 1d | 0.02 | 0.11 | 3.85 | 0.052 | BMI-z | -0.003 | (-0.006, -0.000004) | 0.05 |
| | 2c | -0.003 | 0.45 | ---- | ---- | | ---- | ---- | ---- |
| | 2d | 0.002 | 0.38 | 1.55 | 0.21 | FTO | 0.005 | (-0.003, 0.01) | 0.22 |

Model 1a: REW metric ~ age + sex; model 1b: REW metric ~ age + sex + BMI-z; model 2a: REW metric ~ age + sex + batch effect; model 2b: REW metric ~ age + sex + batch effect + FTO. Unstandardized betas were reported.

Abbreviations: BMI-z: body mass index z-score; CC: clustering coefficient; CS: connectivity strength; FA: fractional anisotropy; FTO: fat mass and obesity related gene (A-allele carrier vs. non carrier); NOS: number of streamlines; REW: reward network.

**Table S4. Results from the hierarchical multiple regression analysis of BMI-z, FTO and whole-brain structural connectivity *without* controlling for estimated total intracranial volume.**

| Whole-brain metrics | Model | Multiple regression | | Model comparison | | Variable of interest | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Adj $R^2$ | *P* model | F | $P_{uncorrected}$ | | *b* | 95% CI | *P* |
| CC NOS | 4a | -0.009 | 0.67 | ---- | ---- | | ---- | ---- | ---- |
| | 4b | -0.001 | 0.42 | 2.03 | 0.16 | BMI-z | 0.0002 | (-0.0001, 0.0006) | 0.16 |
| | 5a | 0.21 | $4.34x10^{-7}$ | ---- | ---- | | ---- | ---- | ---- |
| | 5b | 0.22 | $5.21x10^{-7}$ | 2.51 | 0.11 | FTO | 0.0006 | (-0.0001, 0.001) | 0.12 |
| CS NOS | 4a | -0.005 | 0.52 | ---- | ---- | | ---- | ---- | ---- |
| | 4b | 0.009 | 0.24 | 2.88 | 0.09 | BMI-z | 0.04 | (-0.006, 0.08) | 0.09 |
| | 5a | -0.01 | 0.65 | ---- | ---- | | ---- | ---- | ---- |
| | 5b | -0.003 | 0.46 | 1.95 | 0.16 | FTO | 0.08 | (-0.03, 0.18) | 0.16 |
| CC FA | 4a | 0.01 | 0.16 | ---- | ---- | | ---- | ---- | ---- |
| | 4b | 0.04 | 0.04 | 4.95 | 0.03 | BMI-z | 0.005 | (0.0005, 0.009) | 0.03 |
| | 5a | 0.008 | 0.26 | ---- | ---- | | ---- | ---- | ---- |
| | 5b | 0.0005 | 0.4 | 0.07 | 0.78 | FTO | -0.001 | (-0.01, 0.009) | 0.78 |
| CS FA | 4a | 0.08 | 0.001 | ---- | ---- | | ---- | ---- | ---- |
| | 4b | 0.17 | 0.00001 | 13.31 | 0.0004 | BMI-z | 0.83 | (0.38, 1.28) | 0.0004 |
| | 5a | 0.08 | 0.003 | ---- | ---- | | ---- | ---- | ---- |
| | 5b | 0.07 | 0.008 | 0.002 | 0.96 | FTO | -0.03 | (-1.15, 1.1) | 0.96 |

Model 4a: whole-brain metric ~ age + sex; model 4b: whole-brain metric ~ age + sex + BMI-z; model 5a: whole-brain metric ~ age + sex + batch effect; model 5b: whole-brain metric ~ age + sex + batch effect + FTO. Unstandardized betas were reported.

Abbreviations: BMI-z: body mass index z-score; CC: clustering coefficient; CS: connectivity strength; FA: fractional anisotropy; FTO: fat mass and obesity related gene (A-allele carrier vs. non carrier); NOS: number of streamlines; REW: reward network.

**Table S5. Results from the hierarchical multiple regression analysis of BMI-z, FTO and reward network structural connectivity *without* controlling for estimated total intracranial volume *but controlling* for other confounders (pubertal stage and anxiety and depression scores).**

| REW metric | Model | Multiple regression | | Model comparison | | Variable of interest | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Adj $R^2$ | *P* model | F | *P* uncorrected | | *b* | 95% CI | *P* |
| CC NOS (log) | 1c | 0.01 | 0.14 | ---- | ---- | | ---- | ---- | ---- |
| | 1d | 0.006 | 0.33 | 0.63 | 0.6 | BMI-z | ---- | ---- | ---- |
| | 1e | -0.001 | 0.45 | 0.03 | 0.85 | | 0.004 | (-0.04, 0.05) | 0.85 |
| | 2c | 0.01 | 0.19 | ---- | ---- | | ---- | ---- | ---- |
| | 2d | 0.008 | 0.33 | 0.75 | 0.53 | FTO | ---- | ---- | ---- |
| | 2e | 0.008 | 0.34 | 1.03 | 0.31 | | -0.06 | (-0.17, 0.05) | 0.31 |
| CS NOS | 1c | -0.008 | 0.62 | ---- | ---- | | ---- | ---- | ---- |
| | 1d | -0.01 | 0.71 | 0.66 | 0.58 | BMI-z | ---- | ---- | ---- |
| | 1e | -0.02 | 0.77 | 0.34 | 0.56 | | -0.01 | (-0.05, 0.03) | 0.56 |
| | 2c | -0.01 | 0.7 | ---- | ---- | | ---- | ---- | ---- |
| | 2d | -0.02 | 0.74 | 0.69 | 0.56 | FTO | ---- | ---- | ---- |
| | 2e | -0.02 | 0.78 | 0.51 | 0.48 | | -0.03 | (-0.13, 0.06) | 0.48 |
| CC FA | 1c | 0.06 | 0.005 | ---- | ---- | | ---- | ---- | ---- |
| | 1d | 0.07 | 0.01 | 1.19 | 0.32 | BMI-z | ---- | ---- | ---- |
| | 1e | 0.07 | 0.01 | 1.51 | 0.22 | | -0.01 | (-0.02, 0.006) | 0.22 |
| | 2c | 0.06 | 0.01 | ---- | ---- | | ---- | ---- | ---- |
| | 2d | 0.07 | 0.02 | 1.28 | 0.28 | FTO | ---- | ---- | ---- |
| | 2e | 0.07 | 0.03 | 1.07 | 0.3 | | 0.02 | (-0.02, 0.06) | 0.3 |
| CS FA | 1c | 0.002 | 0.33 | ---- | ---- | | ---- | ---- | ---- |
| | 1d | 0.008 | 0.32 | 1.26 | 0.29 | BMI-z | ---- | ---- | ---- |
| | 1e | 0.03 | 0.13 | 3.92 | 0.05 | | -0.003 | (-0.006, -0.00003) | 0.05 |
| | 2c | -0.003 | 0.45 | ---- | ---- | | ---- | ---- | ---- |
| | 2d | 0.004 | 0.37 | 1.3 | 0.27 | FTO | ---- | ---- | ---- |
| | 2e | 0.004 | 0.39 | 0.9 | 0.34 | | 0.004 | (-0.004, 0.01) | 0.34 |

Model 1c: REW metric ~ age + sex; model 1d: REW metric ~ age + sex + prepubescent + anxiety + depression; model 1e: REW metric ~ age + sex + prepubescent + anxiety + depression + BMI-z; model 2c: REW metric ~ age + sex + batch effect; model 2d: REW metric ~ age + sex + batch effect + prepubescent + anxiety + depression; model 2e: REW metric ~ age + sex + batch effect + prepubescent + anxiety + depression + FTO. Unstandardized betas were reported.

Abbreviations: BMI-z: body mass index z-score; CC: clustering coefficient; CS: connectivity strength; FA: fractional anisotropy; FTO: fat mass and obesity related gene (A-allele carrier vs. non carrier); NOS: number of streamlines; REW: reward network.

**Table S6. Results from the hierarchical multiple regression analysis of BMI-z, FTO and whole-brain structural connectivity *without* controlling for estimated total intracranial volume *but controlling* for other confounders (pubertal stage and anxiety and depression scores).**

| Whole-brain metric | Model | Multiple regression | | Model comparison | | Variable of interest | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Adj $R^2$ | *P* model | F | *P* uncorrected | | *b* | 95% CI | *P* |
| CC NOS | 4c | -0.009 | 0.67 | ---- | ---- | BMI-z | ---- | ---- | ---- |
| | 4d | -0.005 | 0.50 | 1.2 | 0.31 | | ---- | ---- | ---- |
| | 4e | 0.003 | 0.38 | 1.99 | 0.16 | | 0.0003 | (-0.0001, 0.0006) | 0.16 |
| | 5c | 0.21 | $4.34x10^{-7}$ | ---- | ---- | FTO | ---- | ---- | ---- |
| | 5d | 0.19 | 0.00001 | 0.06 | 0.98 | | ---- | ---- | ---- |
| | 5e | 0.2 | 0.00001 | 2.50 | 0.12 | | 0.0006 | (-0.0001, 0.001) | 0.12 |
| CS NOS | 4c | -0.005 | 0.52 | ---- | ---- | BMI-z | ---- | ---- | ---- |
| | 4d | -0.01 | 0.69 | 0.59 | 0.62 | | ---- | ---- | ---- |
| | 4e | -0.002 | 0.45 | 2.7 | 0.1 | | 0.04 | (-0.007, 0.08) | 0.1 |
| | 5c | -0.01 | 0.65 | ---- | ---- | FTO | ---- | ---- | ---- |
| | 5d | -0.02 | 0.77 | 0.56 | 0.64 | | ---- | ---- | ---- |
| | 5e | -0.01 | 0.57 | 2.43 | 0.12 | | 0.09 | (-0.02, 0.2) | 0.12 |
| CC FA | 4c | 0.01 | 0.16 | ---- | ---- | BMI-z | ---- | ---- | ---- |
| | 4d | 0.01 | 0.22 | 1.17 | 0.32 | | ---- | ---- | ---- |
| | 4e | 0.04 | 0.08 | 4.14 | 0.04 | | 0.004 | (0.0002, 0.009) | 0.04 |
| | 5c | 0.008 | 0.26 | ---- | ---- | FTO | ---- | ---- | ---- |
| | 5d | 0.02 | 0.24 | 1.34 | 0.26 | | ---- | ---- | ---- |
| | 5e | 0.008 | 0.34 | 0.006 | 0.94 | | 0.0004 | (-0.01, 0.01) | 0.94 |
| CS FA | 4c | 0.08 | 0.001 | ---- | ---- | BMI-z | ---- | ---- | ---- |
| | 4d | 0.09 | 0.004 | 1.54 | 0.21 | | ---- | ---- | ---- |
| | 4e | 0.16 | 0.00007 | 12.15 | 0.0007 | | 0.81 | (0.35, 1.26) | 0.0007 |
| | 5c | 0.08 | 0.003 | ---- | ---- | FTO | ---- | ---- | ---- |
| | 5d | 0.09 | 0.005 | 1.53 | 0.21 | | ---- | ---- | ---- |
| | 5e | 0.09 | 0.01 | 0.09 | 0.76 | | 0.17 | (-0.96, 1.31) | 0.76 |

Model 4c: whole-brain metric ~ age + sex; model 4d: whole-brain metric ~ age + sex + prepubescent + anxiety + depression; model 4e: whole-brain metric ~ age + sex + prepubescent + anxiety + depression + BMI-z; model 5c: whole-brain metric ~ age + sex + batch effect; model 5d: whole-brain metric ~ age + sex + batch effect + prepubescent + anxiety + depression; model 5e: whole-brain metric ~ age + sex + batch effect + prepubescent + anxiety + depression + FTO. Unstandardized betas were reported.

Abbreviations: BMI-z: body mass index z-score; CC: clustering coefficient; CS: connectivity strength; FA: fractional anisotropy; FTO: fat mass and obesity related gene (A-allele carrier vs. non carrier); NOS: number of streamlines; REW: reward network