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Neurobehavioural Correlates of Obesity are Largely Heritable

Short title: Heritable neurobehavioural correlates of obesity

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Abstract

Recent molecular genetic studies have shown that the majority of genes associated with obesity are expressed in the central nervous system. In other studies, obesity has been associated with neurobehavioural factors like brain morphology, cognitive performance, and personality. Here, we tested whether these neurobehavioural factors were associated with the heritable variance in obesity measured by body mass index (BMI) in the Human Connectome Project (N = 895 siblings). Cortical thickness findings supported the "right brain hypothesis" for obesity. Namely, increased BMI associated with decreased cortical thickness in right frontal lobe and increased thickness in the left frontal lobe. In addition, lower thickness and volume in entorhinal-parahippocampal structures, and increased thickness in parietal-occipital structures in obese subjects supported the role of visuospatial function in obesity. Brain morphometry results were supported by cognitive tests, which outlined obesity's negative association with visuospatial function, verbal episodic memory, and cognitive flexibility. Personality-obesity correlations were small. We then aggregated the effects for each neurobehavioural factor for a behavioural genetics analysis and demonstrated their genetic overlap with obesity. Namely, all aforementioned neurobehavioural factors had 0.22-0.52 genetic correlations with obesity and the phenotypic correlations were 80%-100% explained by genetic factors. In a separate analysis, brain morphology effects were partly accounted for by the aggregated personality and cognitive factors, as they mediated 8-12% of brain morphology effects on obesity. In summary, obesity has considerable genetic overlap with neurobehavioural factors, which may inform intervention strategies.

Significance Statement

Obesity is a widespread heritable health condition. Evidence from psychology, cognitive neuroscience, and genetics has proposed links between obesity and the brain. The current study tested whether the heritable variance in obesity is explained by brain and behavioural factors in a large brain imaging cohort that included multiple related individuals. We found that the heritable variance in obesity had genetic correlations 0.22 - 0.52 with cognitive abilities, personality factors, cortical thickness, and regional brain volume. In particular, obesity was associated with frontal lobe asymmetry and differences in temporal-parietal perceptual systems. Further, brain

morphology effects were partly explained by cognitive and personality factors. In summary, the genetic vulnerability to obesity is expressed in the brain. This can inform intervention strategies.

Introduction

Obesity is a widespread condition leading to increased mortality (1) and economic costs (2). Twin and family studies have shown that individual differences in obesity are largely explained by genetic variance (3). Gene enrichment patterns suggest that obesity-related genes are preferentially expressed in the brain (4). While it is unclear how these brain-expressed genes lead to obesity, several lines of research show that neural, cognitive, and personality differences have a role in vulnerability to obesity(5, 6). Here we seek to test whether these neurobehavioral factors could explain the genetic variance in obesity.

Diverse neurobehavioural effects have been found. In the personality literature, obesity is most often negatively associated with Conscientiousness (exhibiting self-discipline and orderliness) and positively with Neuroticism (a tendency towards negative affect) (7, 8). In the cognitive domain, tests capturing executive function, inhibition, and attentional control have a negative association with obesity (5, 6, 8–10). Neuroanatomically, obesity seems to have a negative association with the grey matter volume of prefrontal cortex, and to a lesser extent the volume of parietal and temporal lobes, as measured by voxel based morphometry (11). It has also been suggested that structural and functional asymmetry of the prefrontal cortex might underlie overeating and obesity (12). For genetic analysis, cortical thickness estimates of brain structure have been preferred over volumetric measures (13). So far, cortical thickness patterns associated with obesity have been inconsistent (14, 15). As a prerequisite to our goal of ascertaining the heritability of brain-based vulnerability to obesity, we sought to extend these neurobehavioural findings in a large multi-factor dataset from the Human Connectome Project. Since cortical thickness measurement is limited to cortex only, we also included volumetric estimates of medial temporal lobe and subcortical structures, which have been implicated in appetitive control (e.g., 16).

The first goal was to assess whether the outlined obesity-neurobehavioural associations are of genetic or environmental origin. Recent evidence from behavioural and molecular genetics suggests that there is considerable genetic overlap between obesity, cognitive ability, and brain imaging findings (17–19). However, the evidence so far is not comprehensive across all neurobehavioural factors discussed. A recent paper has assessed the heritability of obesity-

associated brain structures themselves and found them varying (20). However, that study did not analyse the heritability of the association between brain and obesity. The latter analysis is crucial for understanding whether brain anatomy and obesity could have a genetic overlap, which would suggest that the heritability of vulnerability to obesity is expressed in the brain.

The second goal is to test whether psychological measures from personality questionnaires and cognitive tests mediate any brain morphology-obesity associations. Since variance in psychological measures seems to originate from the brain (e.g., 21), performance in the cognitive tests and questionnaires could be expected to mediate brain-obesity associations (6). This hypothesis has rarely been tested. Within a normal population, only one study has suggested a cognitive measure of inhibition to mediate the association between thickness of right superior prefrontal cortex and obesity (22).

Establishing the mediation role of psychological measures in the associations between cortical thickness and obesity would be beneficial in several ways. First, it would provide more concrete meaning to the outlined brain-obesity associations, and support the theory that weight gain is mostly caused by the behavioral and cognitive manifestations of brain variability. Second, if psychological measures partly explain the effect of brain-obesity associations, the psychological measures could be used as proxies for brain phenotypes (6)

Taken together, the goal of the current analysis is to use a large multifactor dataset to analyse the heritability of the associations between obesity and brain/behavior. We further test whether personality and cognitive phenotypes mediate the relation between brain and body mass index (BMI).

Results

Background

We analysed data from 895 participants from the Human Connectome Project (23), consisting of 111 pairs of monozygotic twins and 189 pairs of dizygotic twins and siblings. Univariate heritability using an AE (A: additive genetics and E: unique environment) model on twin and sibling data revealed that BMI heritability was A = 70% [95% CI: 59%;77%], which is close to

the published meta-analytic estimate (A = 75% [74%; 76%] 3). Most control variables, such as age, gender, race, ethnicity, education, income, as well as family structure had considerable influence on BMI (SI Results: Control variables, Figure S2). Therefore, the effect of control variables is accounted for in all analyses reported below.

Cognitive and Personality Factors

Log-transformed and residualized BMI was negatively correlated with several cognitive tests capturing visuospatial ability, verbal memory and cognitive flexibility (Figure 1A). Tests measuring reading abilities and lack of impulsivity (Delay Discounting) also showed a negative trend, which was not significant at the false discovery rate (FDR) corrected level. No personality test surfaced when FDR correction was applied (Figure 1B). Trendwise, there were effects of Agreeableness, Aggression and Fear: somatic symptoms.

Brain Morphology

Cortical thickness was estimated from each T1-weighted MRI using CIVET 2.0 software (24). Parcel-based analysis identified negative associations with BMI in right inferior lateral frontal cortex, and bilateral entorhinal-parahippocampal cortex (Figures 2A & 3A). Positive associations were found with the left superior frontal cortex, left inferior lateral frontal cortex, and bilateral parietal cortex parcels.

We formally tested the effect of frontal lobe asymmetry on BMI. We averaged all frontal parcels (Frontal section in Figure 2A) into left and right frontal lobes. Cortical thickness of the left frontal lobe correlated positively with BMI ($r = 0.17$, $p<0.001$), and right frontal lobe thickness correlated negatively with BMI ($r = -0.10$, $p = 0.021$). This correlation difference was highly significant ($z = 4.27$, $p<0.001$)(25). The areas demonstrating the greatest asymmetry effect were in the inferior frontal gyrus (Figure 2A & Figure 3A).

Brain volume was measured for estimation of brain morphology-obesity associations in brain structures not covered by the cortical thickness algorithm. Namely, medial temporal lobe and subcortical volumes were individually segmented and measured by registering each brain to a labelled atlas using ANIMAL software (26). Volumetric results supported the role of entorhinal

cortex and also highlighted a positive association of left amygdala volume with BMI (Figures 2B & 3B). No subcortical region had a significant association with BMI.

Creating poly-phenotype scores

We performed dimension reduction for heritability and mediation analyses to reduce measurement noise and avoid multiple testing with redundant measures. We used the weights of each individual neurobehavioural factor (Figures 1 & 2) to create an aggregate BMI risk score or *poly-phenotype score (PPS).* This approach is similar to polygenic approach in genetics, where the small effects of each polymorphism are aggregated to yield a total effect score (e.g., 27). We used the correlation values as weights to multiply each participant's scaled measurements, and aggregated the results into a single composite variable, the PPS. The PPS reflects the total association of a given factor with BMI. PPS-s were created separately for cognition (correlation with BMI: $r = 0.18$, $p<0.001$), personality ($r = 0.17$, $p<0.001$), cortical thickness (r = 0.33, $p<0.001$), medial temporal brain volume (r = *0*.28, $p<0.001$), and subcortical brain volume ($r = 0.07$, $p = 0.034$). Ten-fold cross-validation showed that in out-of-sample data, the effect sizes dropped but stayed significant if the PPS has significant individual phenotype weights (cognition r = 0.12, $p<0.001$; cortical thickness r = 0.26, $p<0.001$; medial temporal lobe volume r = 0.19, $p<0.001$, see SI Results: Overview of PPS-obesity associations). While the PPS-obesity effect sizes are likely overestimated, it is less of a concern in the current analysis, as we focus on the proportion of the PPS-obesity association explained by genetic factors, and by mediation models. For the heritability analysis, we used PPSs not residualized for family structure, education, or income, as this information is needed for modelling heritability.

Heritability

In the bivariate heritability analysis, we preferred the AE model that does not model the shared environment (C) because it had lower Akaike Information Criteria (AIC) values than the classic ACE model (Figure 4A, SI Table S4). All PPSs were found to be highly heritable, with the A component explaining 37-80% of the variance (Figure 4B, SI Table S5). Genetic correlations (r_g) between BMI and neurobehavioural factors ranged from $r_g = 0.25$ to $r_g = 0.51$, suggesting considerable genetic overlap between the heritable variances of BMI and each factor, with the

exception of subcortical structures (r_g = 0.06, Figure 4C, SI Table S6). As expected from high heritability of the traits and high genetic correlations, the phenotypic BMI-PPS correlations described in the previous sections were 86-100% explained by genetic factors (Figure 4D, SI Table S5).

Mediation

We used a mediation model to test whether the PPSs of cognition and personality mediated the brain morphology effects on BMI. For cortical thickness (Figure 5A), personality and cognition in total mediated 7.5% (p = 0.002) of the effects on BMI (Figure 5D). On their own, cognition mediated 4.5% (p = 0.012), and personality 3% (p = 0.06) of the effect. For medial temporal lobe, personality and cognition in total mediated 11.7% (p<0.001), with personality mediating 6.3% (p = 0.009) and cognitive score mediating 5.4% (p = 0.017) of the effect (Figure 5B, Figure 5D). The association between subcortical volume and BMI was not mediated (Figure 5C, Figure 5D). We were unable to replicate a previously suggested mediation model where inhibition task performance mediates the effect of right Superior Frontal Gyrus on BMI (22)(SI Methods: Mediation).

Discussion

Cortical thickness, medial temporal lobe volume, and cognitive and personality measures all had covariation with BMI, and their effect on BMI was almost entirely heritable. The effects of cortical thickness and medial temporal lobe volume on BMI were 8-12% explained by variation in cognitive abilities and personality traits. Together, our results from a large sample support the role of brain and psychological constructs in explaining genetic variance in obesity.

BMI correlated with increased cortical thickness in the left prefrontal cortex and decreased thickness in the right prefrontal cortex, supporting the right brain hypothesis for obesity (12). The effect was most prominent in the inferior frontal gyrus (Figures 2A and 3A). Only preliminary support for the right brain hypothesis has been previously available (15). Right prefrontal cortex has been implicated in inhibitory control (21) and possibly bodily awareness (12). Many neuromodulation tasks aimed at increasing self-regulation capacity often target right prefrontal cortex. On the other hand, effects have also been demonstrated in studies targeting left prefrontal

cortex (28).

Cortical thickness results also highlighted the role of temporo-parietal perceptual structures in obesity. Namely, obesity was associated with bilaterally decreased thickness of the parahippocampal and entorhinal cortices, and with mostly right-lateralised increased thickness of parietal and occipital lobes. Volumetric results within the medial temporal lobe supported the role of entorhinal cortex and also suggested that obesity is positively associated with the volume of left amygdala. Emergence of the effects of the right parietal structures together with right prefrontal structures hint at the role of ventral frontoparietal network (29), whereas the parahippocampal cortex is associated with episodic memory and context mediation (30). The amygdala is implicated in emotional and appetitive responses to sensory stimuli, including food cues (31).

Integrating these findings, one could envision a model where obesity is associated with a certain cognitive profile (32). The model starts with a hyperactive visual attention system attributing heightened salience to food stimuli, implicating the ventral visual stream and amygdala. These signals are then less optimally tied into relevant context by the parahippocampal structures, and less well moderated (or filtered) by the prefrontal executive system. This could result in consummatory behavior more likely driven by the presence of appetitive food signals that are ubiquitous in the obesogenic environment. An impaired response inhibition and salience attribution model of obesity has been suggested based on the functional neuroimaging literature (reviewed in 5, 31, 33). Functional MRI studies have consistently identified obesity to associate with heightened salience response to food cues, coupled with reduced activation in prefrontal and executive systems involved in self-regulation and top-down attentional control. A similar conclusion emerged from a recent resting state network analysis of a subset of the HCP data (34), in which obesity was associated with alterations in perceptual networks and decreased activity of default mode and central executive networks.

This brain morphology-derived model has some support from cognitive tests. The role of prefrontal executive control is outlined by obesity's negative association with cognitive flexibility. Surprisingly, there was no effect of motor inhibition as measured by the Flanker inhibitiory task. A relation between obesity and reduced motor inhibition, while often mentioned,

has been inconsistent even across meta analyses (8, 9). More intriguingly, obesity was found to be negatively associated with spatial orientation and verbal episodic memory, tasks that tap into the key functions associated with entorhinal and parahippocampal regions implicated in our study (30). Therefore, both cognitive tests and brain morphology measures propose that the increased salience of food stimuli could be facilitated by dysregulated context representation and executive control in obesity.

Regarding personality, we were unable to find any questionnaire-specific effects, notably with respect to Neuroticism and Conscientiousness, both often thought to be associated with obesity (5, 6). There are potential explanations for this discrepancy. First, the meta-analytical effects of Neuroticism and Conscientiousness are small ($r \approx 0.1$, 8), for which we might have been underpowered after p-value correction. Second, controlling for family structure likely further reduced the effect sizes (35). Third, the personality-obesity associations tend to pertain to more specific facets and nuances than broad factors (36), therefore, further analysis with more detailed and eating-specific personality measures is needed. Still, using the PPS approach, we were able to uncover a general personality risk score that aggregated the multiple small effects, which we used in subsequent analyses.

All the associations discussed were largely due to shared genetic variance between neurobehavioural factors and BMI. This is in accordance with recent molecular genetics evidence that 75% of obesity related genes express preferentially in the brain (4). The current evidence further supports the brain-gene association with obesity vulnerability.

A possible interpretation here is pleiotropy – the existence of a common set of genes that independently influence variance in both obesity and brain function. However, our results could also support a causal relationship – that the genetic correlation is due to a persistent effect of heritable brain factors on over-eating and hence BMI. For instance, we could hypothesize that the heritable obesity-related cognitive profile introduces overeating when high-calorie food is available. As high-calorie food is abundant, the cognitive profile could lead to repeated overeating providing an opportunity for genetic obesity-proneness to express. Such longitudinal environmental effects of a trait need not to be large, they just have to be consistent (37, see discussion in 38). Of course, a reverse scenario is also possible – obesity leads to alterations in

cortical morphology due to the consequences of cardiometabolic complications, including inflammation, hypertension, and vascular disease (reviewed in 11, 39). However, we find this less plausible in our study for two reasons. First, the reviews outline that reported consequence of chronic visceral adipose tissue accumulation is often global brain atrophy. In contrast, current data suggests focal brain effects – vascular or inflammatory atrophy would not explain the left-right asymmetry in the prefrontal cortex. Second, the same reviews suggest that global brain atrophy is mostly seen in older participants, whereas in current sample had a mean age of 29. Young adults often experience "healthy or transitional obesity", where clinical inflammation levels (40) and other cardiometabolic comorbidities have not yet developed (41). Further, a recent mendelian randomisation study suggested that low genetic potential for education (proxy for cognitive ability, Figure S3B) leads to high risk for cardiovascular disease, whereas high genetic risk for cardiovascular disease does not lead to low education (42). Therefore, this indirect evidence suggests that the genetic neurobehavioural factors described here lead to higher risk of obesity.

The mediation models provide evidence that the brain structure associations with BMI are partly explained by cognitive abilities and personality traits. While we were unable to replicate a previous specific effect implicating poor inhibitory control and the lateral prefrontal cortex (22), our PPS-based analysis suggested that the general principle is true – brain structure effects were partly mediated by cognitive and personality factors. Granted, the effects were small so cognitive tests cannot fully replace brain structure measures yet. While a more focused analysis on psychological measures and brain regions that had strong effects in current analysis might have yielded higher mediation effects, we abstained from such analysis to avoid "double dipping" (43).

From a practical point of view, current evidence suggests that evidence from psychology and neuroscience can be used to design intervention strategies for people with higher genetic risk for obesity. One way would be modifying neurobehavioural factors, e.g. with cognitive training, to improve people's ability resist the obesogenic environment (28, 32). Another path could be changing the immediate environment to be less obesogenic (e.g., 44) so that individual differences in neurobehavioural factors would be less likely to manifest. In any case, current evidence highlights that obesity interventions should not only focus on diet, but also take into account that obesity is genetically intertwined with variation in neurobehavioural profiles.

The current analysis has limitations. Due to the cross-sectional nature of the dataset, mediation models are only suggestive – longitudinal designs would enable better insight into the causal associations between brain morphology, psychological measures, and BMI or weight gain. While the measurement of cognitive abilities and personality was exhaustive, it lacked some common behavioural tasks like the stop-signal task, or common questionnaires measuring self-control, impulsivity, and eating-specific behaviours (5, 6), that have been previously associated with body weight. Particularly, the common eating-specific behaviours such as uncontrolled eating (45) are likely better candidates for explaining brain morphology-BMI associations as they are more directly related to the hypothesized underlying behaviour. Ideally, the PPSs should be applied not to same data but to new data for unbiased estimates of PPS-obesity effect sizes. This is feasible, as cross-validation analysis showed that the weights obtained are mostly generalizable to new data, albeit with slightly smaller effect sizes. However, as the current study does not address the effect size of PPS-obesity associations, but the relative proportion of effect explained by genetic factors or mediation models, the possible overestimation of effect size is not a major concern.

One has to be careful in translating individual differences in cortical thickness in normal population to underlying neural mechanisms. Diverse biological processes have been suggested to influence MRI-based cortical thickness measures, ranging from synaptic density to apparent thinning due to synaptic pruning and myelination (summarised in 46, 47). A definitive model of the underlying mechanism that links normal variations in cortical thickness to differences in brain function cannot be given, as cortical thickness has not been mapped with both MRI and histology in humans (47). Similarly, BMI is a crude proxy for actual eating behaviours or health status. At the same time, the associations between brain morphology and BMI were also present in out-of-sample cross-validation, suggesting that the pattern is robust. Our conceptual interpretation has support from measures of both brain structure and cognitive function. Still, future hypothesis-driven studies have to elucidate the neurobehavioural mechanisms behind obesity proneness.

In summary, the current analysis provides comprehensive evidence that the obesity-related differences in brain structure, cognitive abilities, and personality traits are largely due to shared genetic factors. Mediation analysis using aggregate scores for each factor outlined that, in principle, the brain morphology-obesity associations are partly mediated by personality traits and cognitive abilities. We hope that increasingly larger longitudinal data sets, dedicated studies, and

more sophisticated methods will help to outline more specific neurobehavioural mechanisms for a better understanding of obesity, and providing a basis for designing informed interventions.

Methods

Data were provided by the Human Connectome Project (23). Certain people were excluded due to missing data or not fulfilling typical criteria. Exclusion details, demographics and family structure are summarized in SI Methods: Participants and Table S1. See Table S2 for a complete list of 22 questionnaires and 18 cognitive tests used in our analysis. Software pipelines for obtaining cortical thickness, quality control, and brain parcellation are described in SI Methods: Measures. Analysis scripts are available on request from the first author.

Figure S1 provides a schematic pipeline for data analysis. Details of each data analysis step are outlined in SI Methods: Data analysis. We discuss missing data handling, and how cross-validation was applied to test the robustness of PPS-based results. We further describe the main principles of twin and sibling based heritability analysis and model selection. Finally, the software and packages used are listed.

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Figures

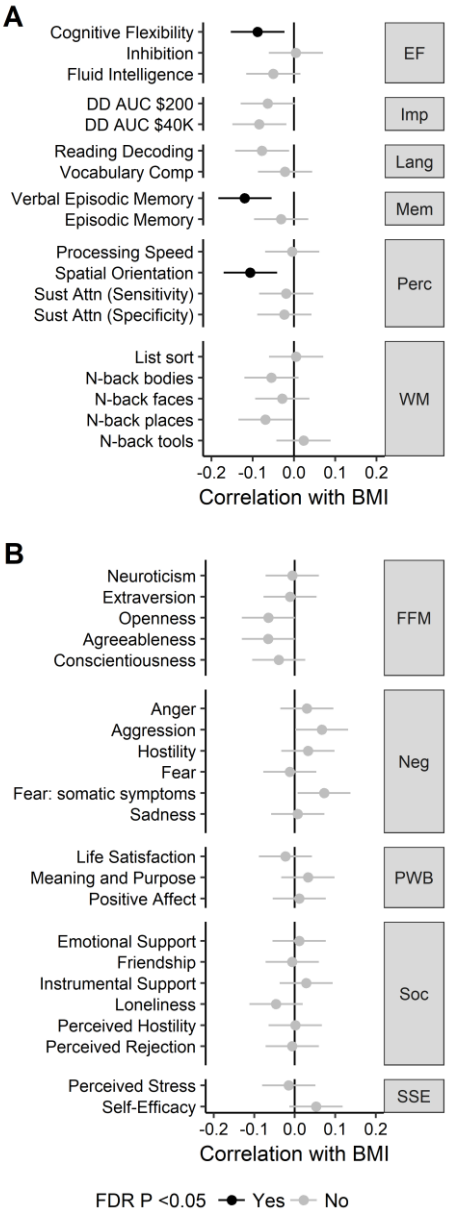

Figure 1. Associations between body mass index (BMI), cognitive ability (A), and personality traits (B). Error bars mark 95% confidence intervals. See Table S2 for explanation of cognitive test names. Numerical values are reported in Table S3. EF = executive function; FFM = Five-Factor Model; FDR = false discovery rate; Imp = (lack of) impulsivity; Lang = language; Mem = memory; Neg = negative affect; Perc = perception; PWB = psychological well-being; Soc = social Relationships; SSE = stress and self efficacy; WM = working memory

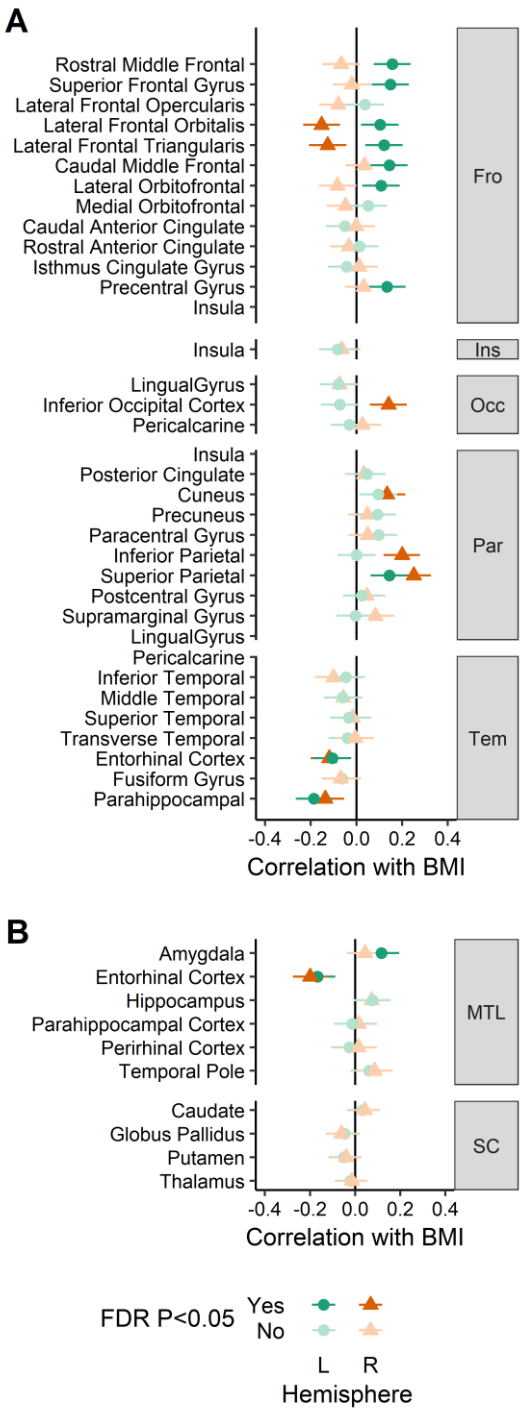

Figure 2. Associations between body mass index (BMI), cortical thickness (A) and regional brain volume (B). Error bars mark 95% confidence intervals. Numerical values are reported in SI Table S2. FDR = false discovery rate; Fro = frontal, Ins = insula; Occ = occipital; Par = parietal; Tem = temporal; MTL = medial temporal lobe; SC = subcortical.

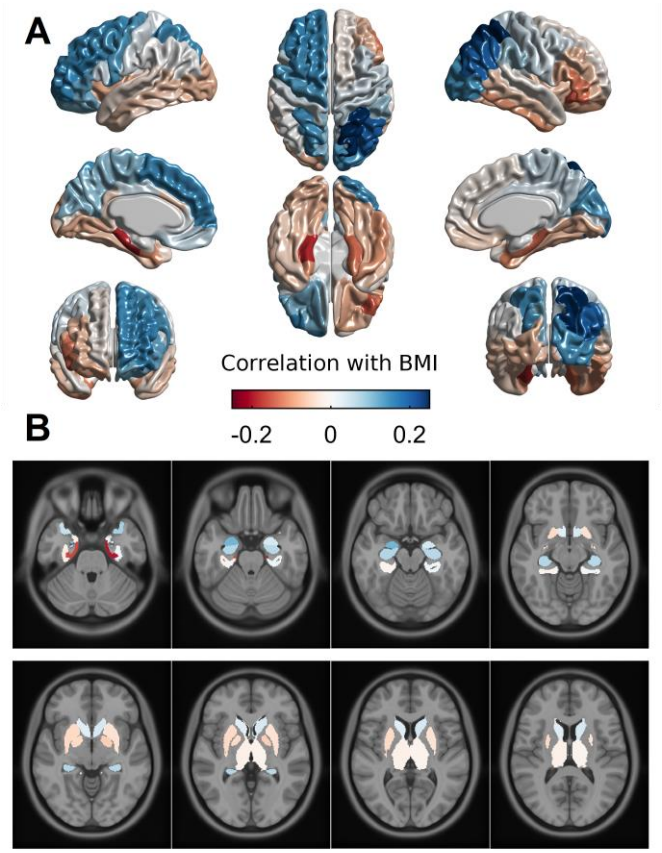

Figure 3. Associations between body mass index (BMI), cortical thickness (A) and brain volume (B) on a brain template. Values are the same as in Figure 2. Colour bar applies to both sub-plots.

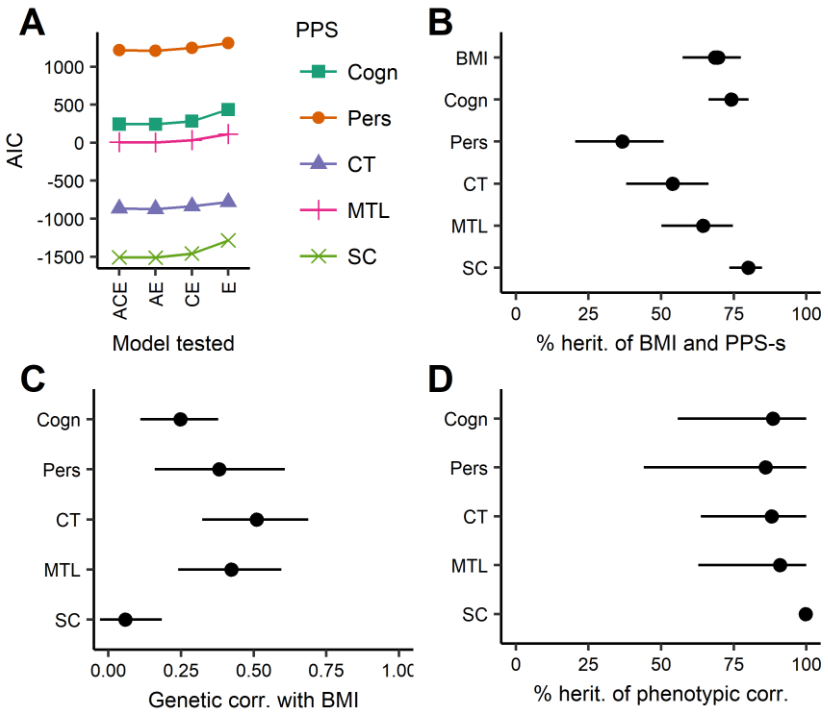

Figure 4. Heritability analysis of the association between poly-phenotype scores (PPS) and body mass index (BMI). (A) Akaike Information Criterion values for different model decompositions. The AE model was chosen for subsequent analyses. (B) Heritability of each trait. BMI has multiple estimates, since it was entered into a bivariate analysis with each other PPS separately. The effect of unique environment (E) is not shown, since E = 100-A. (C) Genetic correlations between BMI and each PPS. The genetic correlations are positive, because the PPSs are designed to positively predict BMI. None of the environmental correlations were significant and therefore not shown. (D) Heritability of the phenotypic correlation between BMI and PPS. Horizontal lines depict 95% confidence intervals. Confidence intervals were not estimated for subcortical structures, because the genetic and phenotypic correlations with BMI were very small. AIC = Akaike Information Criterion; Cogn = PPS of cognitive tests; CT = PPS of cortical thickness; MTL = PPS of medial temporal lobe volume; Pers = PPS of personality tests; SC = PPS of subcortical structure volumes

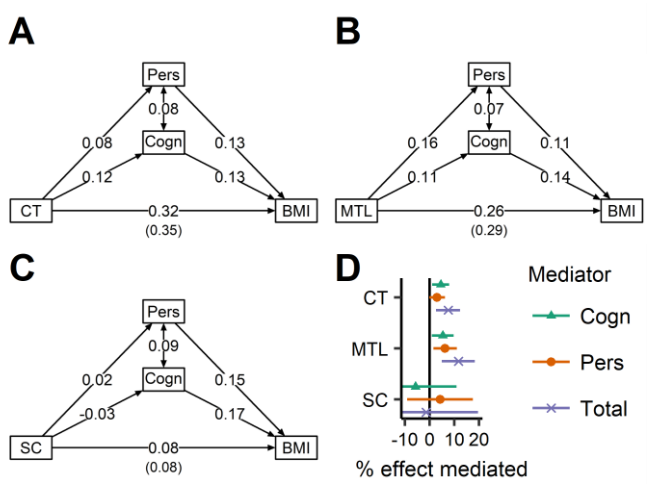

Figure 5. Summary of mediation models. (A-C) The role of cognition and personality in mediating brain effects on body mass index (BMI). Path strengths greater or equal to 0.07 have *p* <0.05. Total effect (c) is in brackets. (D) Summary of % mediated effect size [(a+b)/c]. Error bars mark 95% confidence intervals. Cogn = PPS of cognitive tests; CT = PPS of cortical thickness; MTL = PPS of medial temporal lobe volume; Pers = PPS of personality tests; SC = PPS of subcortical structures' volume; Total = personality + cognition effect.

Supporting information

SI Methods

Participants

Data were provided by the Human Connectome Project (23) WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657, RRID:SCR_008749) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University,

Background, personality and cognitive data were analysed from 970 participants (S900 data release). Participant relatedness information was updated from the S1200 data release. For the current analysis, we applied the following exclusion criteria, as these they might confound brain-obesity associations: people with missing values on crucial variables, such as age, BMI, education, income, gender, race, and ethnicity (n = 6), hypo/hyper thyroidism (n = 4), other endocrine problems (n = 16), underweight (BMI < = 18, n = 9), women who had recently given birth (n = 9). In addition, as we used family information control for participants' relatedness, we excluded participants that were half-siblings to other participants (n = 31).

The final dataset analysed consisted of 895 participants, demographics of which are summarised in Table 1. The sample had good gender balance and reasonable variation in BMI and income. As limitations, the sample was relatively young and well educated. Most people were white and non-Hispanic, however other races-ethnicities were also represented. The participants were nested into 383 families, typically having 1-3 siblings in the dataset.

Table S1. Descriptive statistics of sample analysed.

Variable	Summary
Age	$\bar{x}$ = 28.83 (SD = 3.67) years
BMI	$\bar{x}$ = 27.28 (SD = 5.77) kg/m^2
Education	$\bar{x}$ = 14.85 (SD = 1.82) years

Ethnicity	Not Hispanic/unknown: 819 (91.51%) Hispanic/Latino: 76 (8.49%)
Family structure	381 families. 1 sibling: 82 (21.41%) 2 siblings: 112 (29.24%) 3 siblings: 150 (39.16%) 4 siblings: 35 (9.14%) 5 siblings: 4 (1.04%)
Gender:	Men: 420 (45.85%) Women with birth control: 146 (15.94%) Women without birth control: 350 (38.21%)
Handedness	Laterality score: $\bar{x}$ = 64.84, SD = 45.39
Income	<$10,000: 66 (7.37%) 10K-19,999: 79 (8.83%) 20K-29,999: 115 (12.85%) 30K-39,999: 104 (11.62%) 40K-49,999: 99 (11.06%) 50K-74,999: 180 (20.11%) 75K-99,999: 119 (13.3%) > = 100,000: 133 (14.86%)
Race	White: 665 (74.3%) Asian, native Hawaiian, or other Pacific islander: 45 (5.03%) Black or African American: 144 (16.09%) American or Alaskan native, more than one race, or other/unknown: 41 (4.58%)

For the heritability analysis between each neurocognitive factor and BMI, we randomly chose one sibling pair per family, ensuring that the pair had complete data. Non-twin sibling pairs were considered equivalent to dizygotic twin pairs with respect to heritability analyses once data was residualized for age and gender. If multiple sibling pairs within a family had complete data, we prioritized choosing monozygotic twin pairs and dizygotic twin pairs over non-twin sibling pairs. Depending on the neurocognitive factor, the heritability analysis was conducted on 64-111 pairs of monozygotic twins (median = 105) and 65-189 pairs of dizygotic twins and siblings (median = 160).

Measures

Psychological measures.

Participants completed an extensive set of questionnaires and cognitive tests (see 48, 49 for an overview). In the current analysis, we included 22 questionnaires and 18 cognitive tests (see Figure 2 and Table S2 for complete list). We named the set of questionnaires personality variables, as personality encompasses various patterns of what people want, say, do, feel, or believe (50). Based on our previous review (6) we chose cognitive tests capturing aspects of executive function, memory, and language.

Cortical thickness.

All T1-weighted MRI images were processed using the CIVET pipeline (version 2.0) (24, 51, 52). Processing was executed on the Canadian Brain Imaging Network (CBRAIN) High Performance Computing platform for collaborative sharing and distributed processing of large MRI datasets (53). Briefly, native T1-weighted MRI scans were corrected for non-uniformity using the N3 algorithm (54). The corrected volumes were masked and registered into stereotaxic space, and then segmented into gray matter (GM), white matter (WM), cerebrospinal fluid (CSF) and background using a neural net classifier (55). The white matter and gray matter surfaces were extracted using the Constrained Laplacian-based Automated Segmentation with Proximities algorithm (56, 57). The resulting surfaces were resampled to a stereotaxic surface template to provide vertex based measures of cortical thickness (58). All resulting images were visually inspected for motion artefacts by experienced personnel and then subsequently processed through a stringent quality control protocol, which only 559 of the 879 participants in our initial cohort passed. For those participants who passed, cortical thickness was then measured in native space using the linked distance between the two surfaces across 81924 vertices and a 20mm surface smoothing kernel was applied to the data (59). The Desikan–Killiany–Tourville (DKT) atlas was used to parcellate the surface into 64 cortical regions (60). Cortical thickness was averaged over all vertices in each region of interest for each subject (61) and the effect of mean cortical thickness was regressed to allow for regional analysis (62).

Volumetric estimates.

Because our cortical thickness method does not cover all medial temporal and subcortical structures, we used volumetric estimates for these brain regions. For subcortical volumetric estimation, T1-weighted scans of the subjects were pre-processed through a computerized pipeline (n = 897). Image denoising (63), intensity non-uniformity correction (54), and image intensity normalization into range (0-100) using histogram matching were performed. After preprocessing, all images were first linearly (using a 9-parameter rigid registration) and then nonlinearly registered to an average template (MNI ICBM152) as part of the ANIMAL software (26, 64). The subcortical structures, i.e., thalamus, putamen, caudate, and globus pallidus were segmented using ANIMAL by warping segmentations from ICBM152 back to each subject using the obtained nonlinear transformations. The medial temporal lobe structures, i.e. hippocampi, amygdala, temporal pole, and parahippocampal, entorhinal and perirhinal cortices, were segmented using an automated patch-based label-fusion technique (65). The method selects the most similar templates from a library of labelled MRI template images, and combines them with a majority voting scheme to assign the highest weighted label to every voxel to generate a discrete segmentation. Quality control was performed on the individual registered images as well as the automated structure segmentations by visual inspection, and inaccurate results were discarded. The final results included data from n = 827, 8 parcels per subjects for the subcortical structures, and n = 591, 12 parcels for the medial temporal lobe structures.

Data Analysis

A schematic pipeline of the analysis is displayed in Figure S1. Data from all neurocognitive factors were first residualized for control variables (age, education, ethnicity, gender, handedness, income, race) using a linear mixed model, adding a random intercept for family (Figure S1). Using a random intercept for family resulted in very similar results, as compared to using the theoretical genetic relatedness matrix to account for family effects. As BMI was skewed (long-tail at the upper end of the scale), it was log-transformed to achieve a normal-like distribution. Handedness was reversed and also log normalised.

As some psychological measures had missing responses, but psychological tasks often correlate, missing data were replaced using multiple imputation, taking the mean of 100 simulated datasets.

For each factor category (cognition, personality, cortical thickness, medial temporal volume, subcortical volume), factor-BMI relationships were assessed using univariate correlation between each brain parcel or test score and BMI. We initially also tried using a partial least squares (PLS) correlation approach, which is a multivariate technique suited to handling correlated predictors (66, 67). However, the PLS estimates were extremely close to univariate correlations, and univariate correlations were preferred for simplicity. As a result, we received an estimate of the relative contribution (weight) of each predictor within a given factor.

Estimates used in this study are presented in Table S3. In that table, type enables filtering a certain factor, (eg “ct” for cortical thickness), and control variables used. “_reg” stands for regular control variables (e.g. all mentioned variables). Other types include weights without controlling for education and income (“_neiyf”), and without controlling for education, income, and family structure (“_neinf”). Finally, we also ran the correlation in 10 different combinations of 90% subsets of the data and took the average of these estimates. Estimates obtained this way were very close to full sample estimates and had little variation (Table S3, columns “rmean_cv90” and “rsd_cv”).

Using these weights, we created an aggregate BMI risk score or *poly-phenotype score (PPS)* for each neurocognitive factor. This approach is inspired by polygenic risk score approach, where the effects of single-nucleotide polymorphisms are added up to a total genetic score (27). Specifically, we used the correlation-derived weights to multiply each participant's measured values, and aggregated the results into a single composite variable for a given factor, the PPS. A PPS would reflect the total association that a given factor has with BMI. Similarly to polygenic scores, we do not apply a p-value threshold (68).

To get a sense of robustness of the PPSs, we ran ten-fold cross-validation on the BMI-PPS correlations. Namely, we estimated the correlations on 90% of the data, and used the correlation weights obtained to build PPSs both in the same 90% of data and in the 10% out of sample data. The estimates obtained from 10 folds of 90% data were averaged. The estimates obtained from 10 folds of 10% data were put together, and a global estimate for 10% folds was found. When

creating the 10% folds, we created folds for each factor separately, as each factor has a different number of available data points, ensuring that folds were as equal in size as possible. We also ensured siblings from the same family were in the same fold. Therefore, no data from family members were used in calculating both the correlation weights and performing out of sample predictions.

In the heritability analysis, a typical behavioural genetics decomposition uses relatedness assumptions between individuals to divide variance in a trait to the following components: genetic variance (A, additive and interactive effects), shared environmental (C, family and shared school effects), and unique environmental (E, unique experience and measurement error). The assumptions are:100% of genetic variance shared between monozygotic twins, 50% of genetic variance shared between dizygotic twins and sex-and gender residualized siblings, 100% of family environment shared by all siblings, 0% unique variance shared between siblings. Such decomposition is called univariate heritability.

Besides establishing univariate heritability, one can also conduct heritability analysis on the covariance between two traits. For instance, a genetic correlation is the correlation between A components of trait 1 and trait 2. A bivariate heritability analysis decomposes the phenotypic correlation between trait 1 and trait 2 into A, C, and E components.

Heritability analysis was conducted on PPS scores not residualized for education, income and family structure, as this information is used in heritability modelling. We first assessed the fit of different decomposition scenarios (ACE, AE, CE, E), and chose the one with the lowest Akaike Information Criterion (AIC). As AE had the lowest or close to the lowest AIC in all models, we opted for this decomposition (Table S4). We then ran bivariate heritability analysis separately between each PPS and BMI, which provided univariate heritability estimates of the PPSs and BMI, genetic and environmental correlations between the univariate estimates of PPSs and BMI, and bivariate decomposition of the phenotypic correlation between each PPS and BMI. We report only standardized A estimates in the main results, as in the univariate and bivariate analysis of the AE model, E = 100-A. Also, no environmental correlations were significant. All standardized and unstandardized estimates are reported in the supplementary materials (Tables S5-S6).

Most analysis was conducted in R (69), using packages Amelia, car, cocor, cowplot, corrplot, ggplot2, kinship2, lme4, MuMIn, pbkrtest, plyr, psych, R.matlab, rmatio, tidyr (70–84). PLS was applied using PLS Applications (85) in MATLAB (86). Heritability analysis was conducted using OpenMX (87), adapting scripts provided by the Colorado International Twin Workshop (88). Mediation analysis and multiple regression analysis was conducted with the lavaan package (89) using full information maximum likelihood for missing data.

SI Results

Control variables

Age, education, and race related to BMI, demonstrating the need for residualizing (Figure S2). Marginal R^2 explaining only fixed effects was 0.09, and conditional R^2 explaining both fixed and random effects was 0.35, highlighting the effect of family structure. Further, controlling for family structure in a nested model as random intercept improved model fit (AIC dropped from 5610 to 5539), suggesting that family nesting needs to be taken into account.

Overview of PPS-obesity associations

PPS-obesity associations are presented in Figure S4. The association between the cognition PPS and BMI was $r = 0.18$, $p<0.001$ ($R^2 = 0.03$) and the personality PPS-BMI association was $r = 0.17$, $p<0.001$ ($R^2 = 0.02$), cortical thickness PPS – BMI association was $r = 0.33$, $p<0.001$, ($R^2 = 0.11$), medial temporal lobe PPS – BMI association was $r = 0.28$, $p<0.001$ ($R^2 = 0.08$). The associations with subcortical structures were smaller (subcortical PPS – BMI: $r = 0.07$, $p = 0.034$, $R^2 = 0.01$). Leaving out random subsets of data did not change these correlations (Figure S4: CV90%). The PPS-obesity associations are likely overestimated because the PPS weights were created on and applied to same participants in current data. This was evidenced by out-of-sample cross validation estimates being smaller (Figure S4, CV 10%). PPSs with statistically significant single weights (Figures 1 and 2 in main text) seemed to be better generalizable to unseen data in cross-validation (Figure S4, CV 10%). All neurobehavioural PPSs had independent effects on BMI in a multiple regression (Figure S4, mult regr), suggesting that each factor has an independent effect on BMI (Figure S4). The R^2 for multiple regression was 0.21. For the heritability analysis, we used PPSs not residualized for family structure, education, or income, as this information is needed for modelling heritability. Not residualizing for these variables

increased the PPSs association with BMI (Figure S4, Heritability) (see also 35), and also with each other (compare Figure S3 left with S3 right).

Mediation

We sought to replicate the specific mediation model of Lavagnino et al (22), in which reduced inhibitory control mediated the effect of lateral prefrontal cortex function on BMI. Without control variables, the Flanker Inhibitory Control Task score had a slight negative association with BMI (r = -0.06, p = 0.061), and Right Superior Frontal Gyrus had a positive association (r = 0.08, p = 0.073). In the mediation model, where brain effects on BMI would be mediated by inhibition performance, the mediation effect was not significant. When we used variables residualized for control variables, no direct or mediated associations emerged.

SI Figures

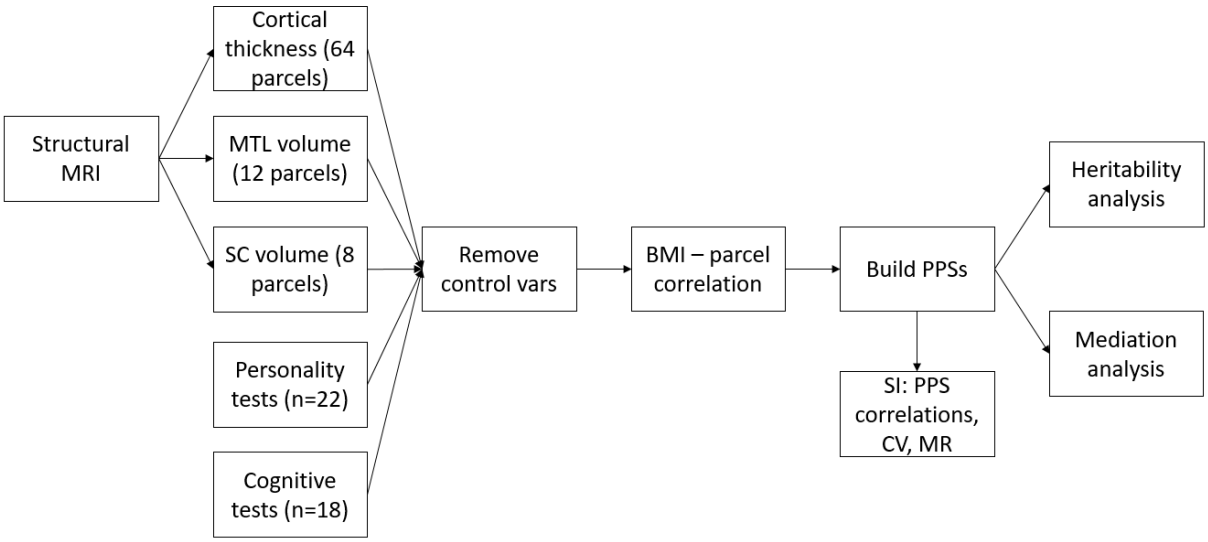

Figure S1. A schematic diagram of the analysis pipeline. All steps were conducted on all neurocognitive factors separately. BMI = body mass index; CV = cross-validation; MTL = medial temporal lobe; MR = multiple regression; MRI = magnet resonance image; PPS = poly-phenotype score; SC = subcortical; SI = supporting information.

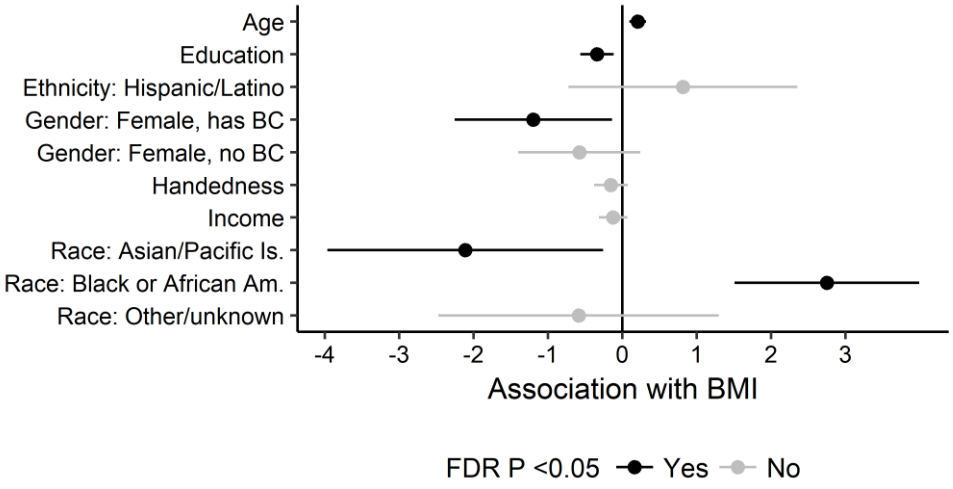

Figure S2. Regression weights of multilevel linear model nested for family. Lines mark standard 95% confidence intervals. Intercept is 27.37 (standard error: 2.16). For interpretability, regular BMI is unscaled here. Reference groups: gender – male, Race: white, Ethnicity: not Hispanic/unknown. Am. = American; BC = birth control; Is. = Islander

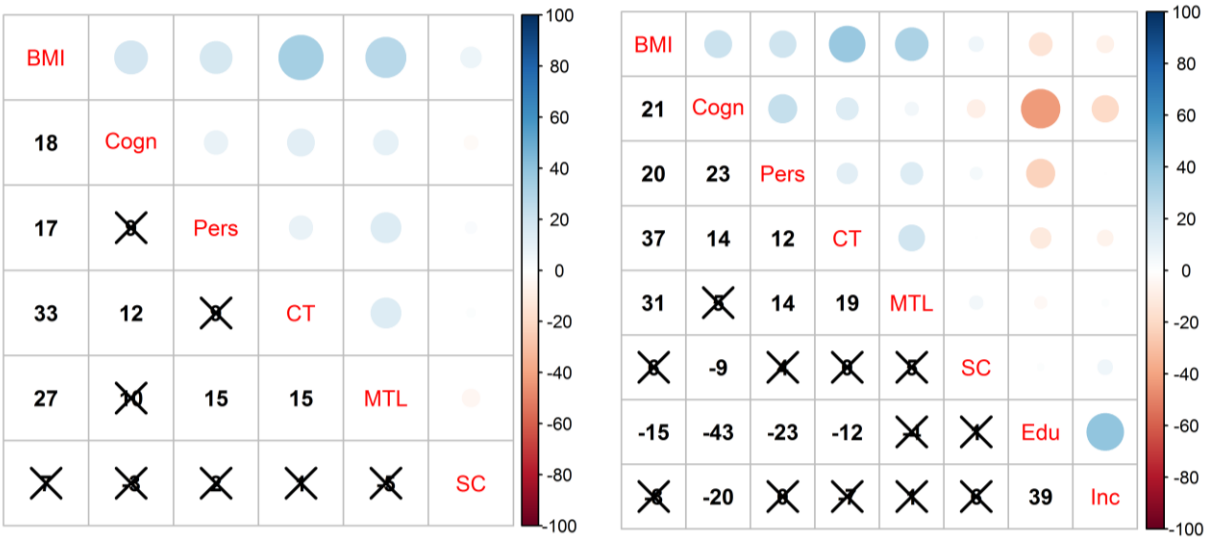

Figure S3. Correlations between BMI and modality poly-phenotype scores (PPS). (Left) correcting for all control variables. (Right) not correcting for education, income, and family nestedness. Correlations with p>0.01 are crossed out. Cogn = PPS of cognitive tests; CT = PPS of cortical thickness; MTL = PPS of medial temporal lobe volume; Pers = PPS of personality tests; SC = PPS of subcortical structures.

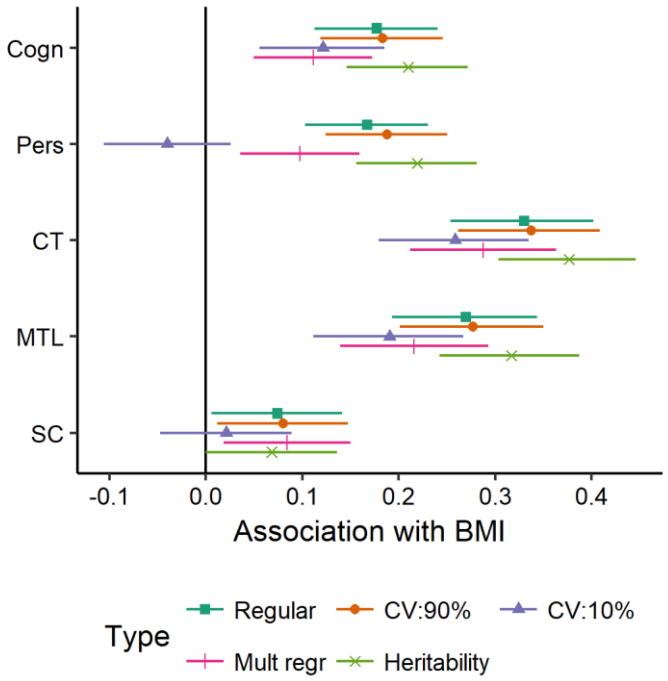

Figure S4. Standardized effect sizes of poly-phenotype scores' (PPS) associations with body mass index (BMI). Error bars mark 95% confidence intervals. Cogn = PPS of cognitive tests; CT = PPS of cortical thickness; CV = cross-validation; Heritability = correlations using variables not residualized for education, income, and family structure; MTL = PPS of medial temporal lobe volume; Mult regr = multiple regression; Pers = PPS of personality tests; Regular = regular correlations; SC = PPS of subcortical structures.

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