Neurobehavioural Correlates of Obesity are Largely Heritable

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Abstract

Recent molecular genetic studies have shown that the majority of genes associated with obesity are expressed in the nervous system. In other studies, obesity has been associated with various 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). We found that obesity was associated with various neurobehavioural factors: cortical thickness findings supported Alonso-Alonso and Pascual-Leone's "right brain hypothesis" for obesity. Increased BMI associated with decreased cortical thickness in right frontal lobes and increased thickness in the left frontal lobes. 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. Also, cognitive tests revealed that obesity was associated with reduced visuospatial function, in addition to reduced cognitive flexibility and increased impulsivity. Personality-obesity correlations were small. We then aggregated the effects for each neurobehavioural factor for 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 represented by the aggregated personality and cognitive factors, as they mediated 8-12% of brain morphology effects on obesity. In summary, the genetic vulnerability to obesity is expressed in various neurobehavioural factors, which 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. Here we seek to test whether these neurobehavioral factors could explain the genetic variance in obesity.

Diverse brain-based phenotypes have been associated with obesity, as assessed by personality questionnaires, cognitive tests, and brain imaging (5, 6). 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). Cortical thickness estimates of brain structure have been preferred over volumetric measures in genetic analysis (13), but cortical thickness patterns associated with obesity have so far 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 right 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).

For estimation of brain morphology-obesity associations in brain structures not covered by the cortical thickness algorithm, 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 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: Robustness of 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. Using the PPSs significantly reduced the number of mediation models to be made, as otherwise several psychological measures would have to be tested as mediators of several brain regions. 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 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 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 all parts of 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. 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 heightened salience response to food cues, coupled with reduced activation in prefrontal and executive systems involved in self-regulation and top-down attentional control, in obesity. 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 and positive association with decisional impulsivity (measured by delay discounting). On the other hand, there was no effect of motor impulsivity 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 largely 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=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 leads a person to have difficulty to avoid eating in response to high-calorie food availability. This 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, as the reported consequence of chronic visceral adipose tissue accumulation is global, not focal, brain atrophy and is mostly seen in older participants (11, 39). In contrast, here we see focal brain effects, and the participants had a mean age of 29. Also, vascular or inflammatory atrophy would not explain the left-right asymmetry in the prefrontal cortex. 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 so that individual differences in neurobehavioural factors would be less likely to manifest (e.g., 44). 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, 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 clarify 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 and analysis scripts are available on request.

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

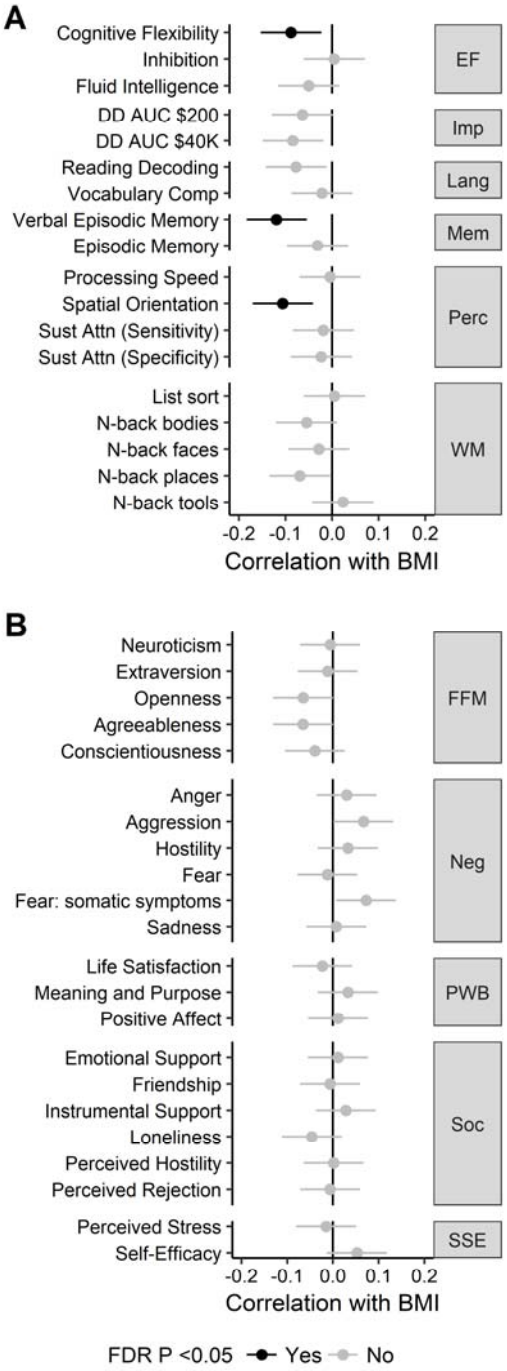

Figure 1. Associations between body mass index (BMI), cognitive ability (A), and personality traits (B). Error bars mark 95% confidence intervals. See Table S2 for explanation of cognitive test names. Numerical values are reported in Table S3. EF= executive function; FFM = Five-Factor Model; FDR=false 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

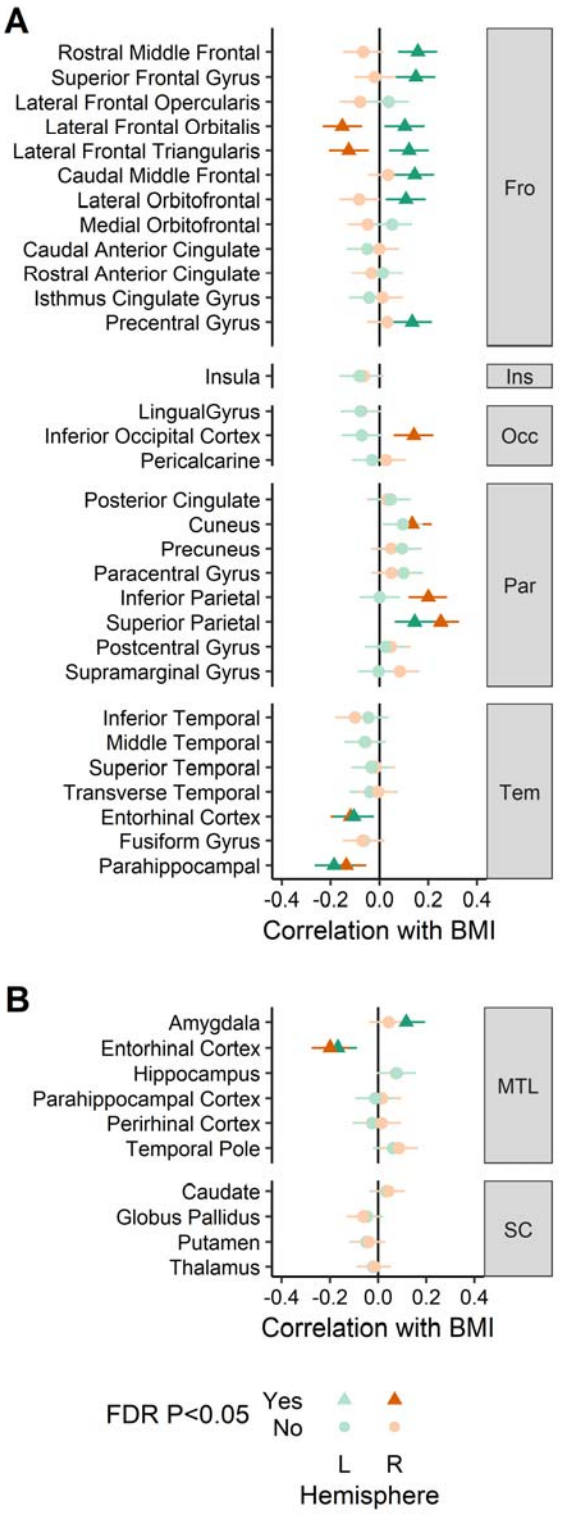

Figure 2. Associations between body mass index (BMI), cortical thickness (A) and regional brain volume (B). Error bars mark 95% confidence intervals. Numerical values are reported in SI Table S2. FDR=false discovery rate; Fro=frontal, Ins=insula; Occ=occipital; Par=parietal; Tem=temporal; MTL=medial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

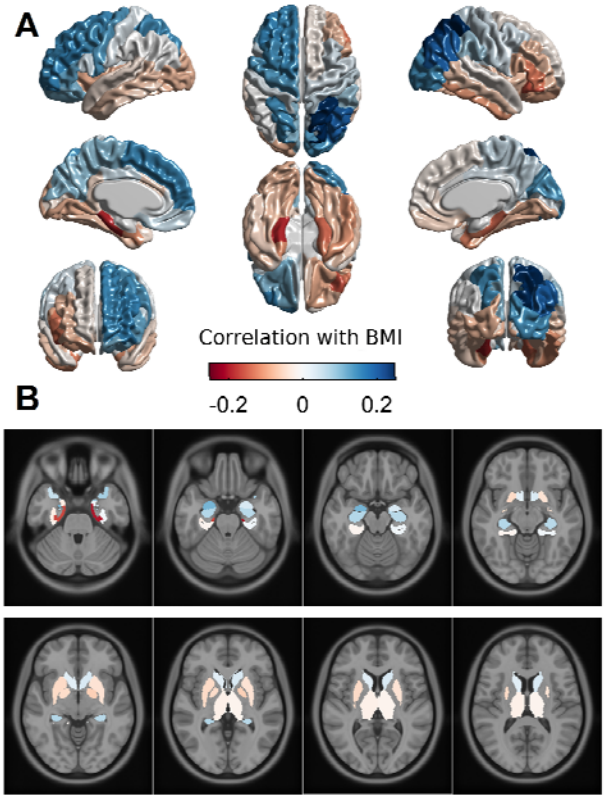

Figure 3. Associations between body mass index (BMI), cortical thickness (A) and brain volume (B) on a brain template. Values are the same as in Figure 2. Colour bar applies to both sub-plots.

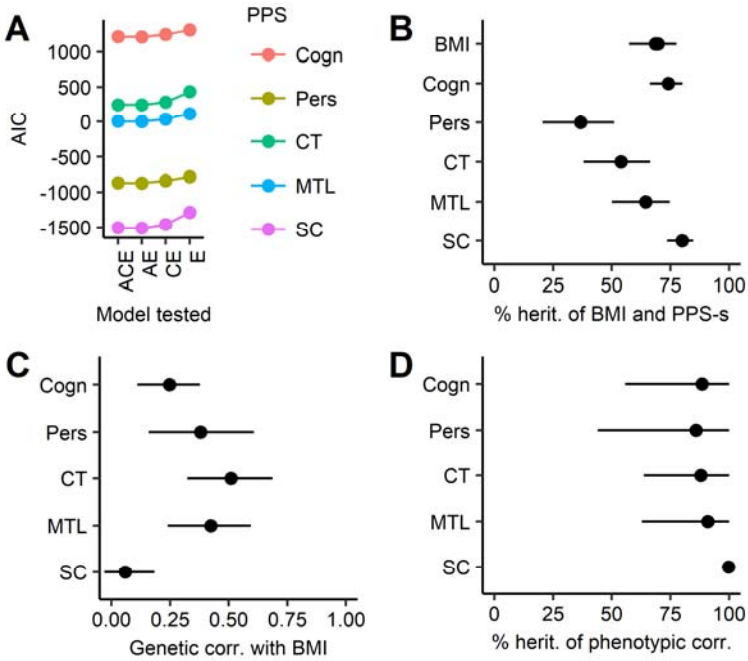

Figure 4. Heritability analysis of the association between poly-phenotype scores (PPS) and body mass index (BMI). (A) Akaike Information Criterion values for different model decompositions. The AE model was chosen for subsequent analyses. (B) Heritability of each trait. BMI has multiple estimates, since it was entered into a bivariate analysis with each other PPS separately. The effect of unique environment (E) is not shown, since E=1-A. (C) Genetic correlations between BMI and each PPS. The genetic correlations are positive, because the PPSs are designed to positively predict an outcome. 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=AkaikeInformation 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

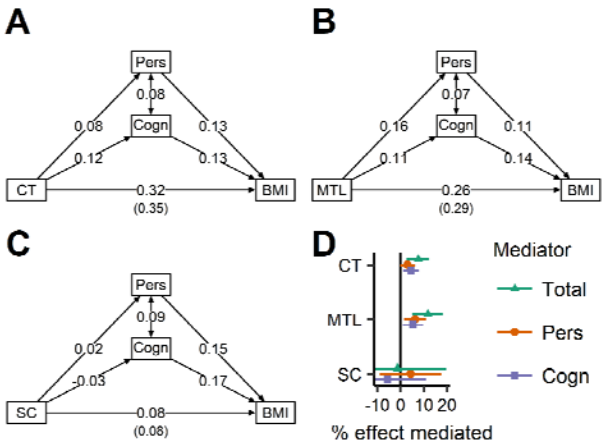

Figure 5. Summary of mediation models. (A-C) The role of cognition and personality in mediating brain effects on body mass index (BMI). Path strengths greater or equal to 0.07 have p <0.05. Total effect (c) is in brackets. (D) Summary of % mediated effect size [(a+b)/c]. Error bars mark 95% confidence 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.