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2   Classification:

3   Biological Sciences

4   Neuroscience

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7   **Neurobehavioural Correlates of Obesity are Largely Heritable**

8   **Short title: Heritable neurobehavioural correlates of obesity**

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Abstract

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23   Recent molecular genetic studies have shown that the majority of genes associated with obesity

24   are expressed in the central nervous system. Obesity has also been associated with

25   neurobehavioural factors such as brain morphology, cognitive performance, and personality.

26   Here, we tested whether these neurobehavioural factors were associated with the heritable

27   variance in obesity measured by body mass index (BMI) in the Human Connectome Project

28   (N=895 siblings). Phenotypically, cortical thickness findings supported the "right brain

29   hypothesis" for obesity. Namely, increased BMI associated with decreased cortical thickness in

30   right frontal lobe and increased thickness in the left frontal lobe, notably in lateral prefrontal

31   cortex. In addition, lower thickness and volume in entorhinal-parahippocampal structures, and

32   increased thickness in parietal-occipital structures in obese participants supported the role of

33   visuospatial function in obesity. Brain morphometry results were supported by cognitive tests,

34   which outlined obesity's negative association with visuospatial function, verbal episodic

35   memory, impulsivity, and cognitive flexibility. Personality-obesity correlations were inconsistent.

36   We then aggregated the effects for each neurobehavioural factor for a behavioural genetics

37   analysis and demonstrated the factors' genetic overlap with obesity. Namely, cognitive test scores

38   and brain morphometry had 0.25 - 0.45 genetic correlations with obesity, and the phenotypic

39   correlations with obesity were 77-89% explained by genetic factors. Neurobehavioural factors

40   also had some genetic overlap with each other. In summary, obesity has considerable genetic

41   overlap with brain and cognitive measures. This supports the theory that obesity is inherited via

42   brain function, and may inform intervention strategies.

Significance Statement

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44   Obesity is a widespread heritable health condition. Evidence from psychology, cognitive

45   neuroscience, and genetics has proposed links between obesity and the brain. The current study

46   tested whether the heritable variance in obesity is explained by brain and behavioural factors in a

47   large brain imaging cohort that included multiple related individuals. We found that the heritable

48   variance in obesity had genetic correlations 0.25 - 0.45 with cognitive tests, cortical thickness,

49   and regional brain volume. In particular, obesity was associated with frontal lobe asymmetry and

50   differences in temporal-parietal perceptual systems. Further, we found genetic overlap between

51   certain brain and behavioural factors. In summary, the genetic vulnerability to obesity is

52   expressed in the brain. This may inform intervention strategies.

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Introduction

56   Obesity is a widespread condition leading to increased mortality (1) and economic costs (2).

57   Twin and family studies have shown that individual differences in obesity are largely explained

58   by genetic variance (3). Gene enrichment patterns suggest that obesity-related genes are

59   preferentially expressed in the brain (4). While it is unclear how these brain-expressed genes lead

60   to obesity, several lines of research show that neural, cognitive, and personality differences have

61   a role in vulnerability to obesity (5, 6). Here we seek to test whether these neurobehavioural

62   factors could explain the genetic variance in obesity.

63   In the personality literature, obesity is most often negatively associated with Conscientiousness

64   (self-discipline and orderliness) and positively with Neuroticism (a tendency towards negative

65   affect) (7). In the cognitive domain, tests capturing executive function, inhibition, and attentional

66   control have a negative association with obesity (5–8). Neuroanatomically, obesity seems to have

67   a negative association with the grey matter volume of prefrontal cortex, and to a lesser extent the

68   volume of parietal and temporal lobes, as measured by voxel based morphometry (9). It has also

69   been suggested that structural and functional asymmetry of the prefrontal cortex might underlie

70   overeating and obesity (10). For genetic analysis, cortical thickness estimates of brain structure

71   from Magnetic Resonance Imaging (MRI) have been preferred over volumetric measures (11).

72   However, to date, reports of cortical thickness patterns associated with obesity have been

73   inconsistent (12, 13). As a prerequisite to our goal of ascertaining the heritability of brain-based

74   vulnerability to obesity, we sought to extend previous neurobehavioural findings in a large multi-

75   factor dataset from the Human Connectome Project (HCP). Since cortical thickness measurement

76   is limited to cortex only, we also measured volumetric estimates of medial temporal lobe and

77   subcortical structures, which have been implicated in appetitive control (e.g., 14).

78   The main goal was to assess whether the outlined obesity-neurobehavioural associations are of

79   genetic or environmental origin. Recent evidence from behavioural and molecular genetics

80   suggests that there is considerable genetic overlap between obesity, cognitive test scores, and

81   brain imaging findings (15–20). However, the evidence so far is not comprehensive across all

82   neurobehavioural factors discussed. A recent paper assessed the heritability of obesity-associated

83   regional brain volumes (21). However, the study did not analyze the heritability of the association

84 between brain and obesity. The latter analysis is crucial for understanding whether brain anatomy

85 and obesity could have a genetic overlap, which would suggest that the heritability of

86 vulnerability to obesity is expressed in the brain.

87 In addition, we sought to estimate the genetic overlap between the different BMI-related

88 neurobehavioural factors. On one hand, performance on cognitive tests and personality must

89 originate from the brain (e.g., 22), and therefore personality and cognition could be expected to

90 explain brain-morphometry associations with BMI (6). On the other hand, brain-behaviour

91 associations are far from certain (23), and even different measurement traditions in both

92 behaviour (personality and cognitive tests) and brain morphometry (cortical thickness or brain

93 volume) are often conceptualized as providing independent sources of information (7, 11).

94 Documenting the degree of genetic overlap between behavioural and brain measures would shed

95 light on whether similar underlying processes lead to obesity's associations with different

96 neurobehavioural factors.

97 Taken together, the goal of the current analysis was to use a large multifactor dataset to analyze

98 the heritability of the associations between obesity and brain/behaviour. We further tested genetic

99 overlap between the different neurobehavioural factors themselves.

100 **Results**

101 **Background**

102 We analyzed data from 895 participants from the Human Connectome Project S900 release (24),

103 including 111 pairs of monozygotic twins and 188 pairs of dizygotic twins and siblings. Similarly

104 to many previous reports (3) we modelled BMI heritability with the AE model (A: additive

105 genetics and E: unique environment), as opposed to the ACE model (C: common environment),

106 as AE had the lowest Akaike Information Criterion (Table S10). BMI heritability was A=71%

107 [95% CI: 61%;78%], which is close to the published meta-analytic estimate (A=75%, 3).

108 In all analyses below, we controlled for age, gender, race, ethnicity, handedness, and evidence of

109 drug consumption on day of testing, which mostly associated with BMI (SI Results, Figure S2).

110 When presenting and interpreting phenotypic associations, we controlled for family structure to

111   avoid inflated effect sizes and standard errors (e.g., 25). The behavioural genetics analysis did not

112   control for family structure, since this information is needed for modelling heritability. As socio-

113   economic status (SES) is intertwined with cognitive test scores (26), personality (27), and brain

114   morphometry (28), we also present phenotypic associations controlling for SES (education and

115   income) in the supplementary material. All in-text p-values are provided without correcting for

116   multiple comparisons. False discovery rate (FDR) correction was applied when screening for

117   features within cognitive, personality, and brain factors (Figures 1,2,5).

Cognitive and Personality Factors

119   BMI was negatively correlated with these tests of executive function: cognitive flexibility, fluid

120   intelligence, inability to delay gratification, reading abilities, and working memory. Intriguingly,

121   the strongest effects were present for non-executive tasks measuring visuospatial ability and

122   verbal memory (Figure 1A). These tasks remained associated with BMI after controlling for SES;

123   controlling for SES reduced the number of executive function tests involved with BMI to

124   cognitive flexibility and inability to delay gratification (SI Figure S3A left). No personality test

125   score correlated with BMI when FDR correction was applied (Figure 1B).

Brain Morphology

127   Cortical thickness was estimated from each T1-weighted MRI using CIVET 2.0 software (29).

128   Parcel-based analysis identified negative associations with BMI in right inferior lateral frontal

129   cortex, and bilateral entorhinal-parahippocampal cortex (Figures 2A & 3A). Positive associations

130   with BMI were found with the left superior frontal cortex, left inferior lateral frontal cortex, and

131   bilateral parietal cortex parcels. Controlling for SES did not change these results (Figure S4A

132   left). The frontal lobe asymmetry in the BMI association (thinner on the right, thicker on the left)

133   mostly involved the inferior lateral prefrontal areas, such as inferior frontal gyrus.

134   Regional brain volumes were measured for estimation of brain morphology-obesity associations

135   in brain structures not covered by the CIVET cortical thickness algorithm. Medial temporal lobe

136   and subcortical volumes were individually segmented and measured by registering each brain to a

137   labelled atlas using ANIMAL software (30). Volumetric results demonstrated an association

138   between BMI and lower volume of the entorhinal cortex bilaterally, and a positive association of

139   left amygdala volume with BMI (Figures 2B & 3B). No subcortical region had a significant

140   association with BMI, and results did not change when controlling for SES (Figure S4B left).

141   **Creating poly-phenotype scores**

142   We performed dimension reduction for heritability analyses to reduce measurement noise and

143   avoid multiple testing with redundant measures. Similarly to other recent papers, (20, 27), we

144   used the weights of each individual feature within a neurobehavioural factor (personality test,

145   cognitive test, brain parcel) to create an aggregate BMI risk score or *poly-phenotype score (PPS).*

146   This is similar to the polygenic score approach in genetics, where the small effects of several

147   polymorphisms are aggregated to yield a total effect score (15, 19, 20, 27). We used the

148   correlation values as weights to multiply each participant's scaled measurements, and aggregated

149   the results into a single composite variable, the PPS. The PPS reflects the total association of

150   each neurobehavioural factor with BMI. To avoid overfitting, we assigned each 10% of

151   participants the PPS weights obtained from the other 90% (see SI: Data analysis for details).

152   The associations between BMI and the PPS-s for cognition (correlation with BMI: $r=0.16$,

153    $p<0.001$, $n=798$) and personality ($r=0.08$, $p=0.017$, $n=888$) are slightly higher than the meta-

154   analytic estimates of the pooled association between BMI and cognitive test scores ($r=0.10$, ref:

155   8) and personality factors ($r=0.05$, ref: 8). BMI had stronger associations with the PPS-s for

156   cortical thickness ($r=0.26$, $p<0.001$, $n=591$), and medial temporal brain volume ($r=0.23$, $p<0.001$,

157    $n=594$). There was no association between BMI and subcortical brain volume ($r=-0.05$, $p=0.169$,

158    $n=828$). To test the generalizability of the PPS approach, we used weights obtained from the full

159   S900 release (Figures S3 right and S4 right) to test PPS-BMI correlation amongst the unseen

160   additional participants in the S1200 release (referred to as S1200n, n=236). Cortical thickness

161   PPS had essentially unchanged effect size when correlated with BMI in S1200n (SI Results,

162   Figure S7). At the same time, cognitive and personality PPS-s were less stable (SI Results, Figure

163   S7), likely because the smaller effect sizes of individual features need larger training datasets to

164   reduce inaccuracies, or that the true PPS-BMI effect size was too small to be found just within

165   the S1200n sample.

Heritability

167   Bivariate heritability was similarly conducted with the AE model, since the main goal was to

168   explain variance in BMI, for which AE was the best model. All PPS-s were found to be highly

169   heritable, with the A component explaining 36-79% of the variance (Figure 4A, SI Table S11.

170   Significant genetic correlations (r_g) were found between BMI and cognitive test scores (r_g=0.25

171   (p=0.002), cortical thickness (r_g=0.45, p<0.001), and medial temporal brain volume (r_g=0.36,

172   p<0.001) (Figure 4B, SI Table S12). The personality PPS genetic correlation with BMI was not

173   significant (r_g=0.22, p=0.052). Molecular evidence relying on linkage disequilibrium score

174   regression has reported effects of similar magnitude between higher cognitive test scores and

175   BMI (rg=-0.22, ref: , 15, rg=-0.18, ref: , 18). Environmental correlations (i.e. correlations

176   between environmental variances) were small and not significant (SI Table S12). As expected

177   from high heritability of the traits and high genetic correlations, the phenotypic BMI-PPS

178   correlations described in the previous sections were 77-89% explained by genetic factors (Figure

179   4C, SI Table S11). The results broadly replicated when repeating the analysis with just the top

180   features within a PPS, suggesting that PPS based findings summarize the effects of the

181   underlying individual features (Figure S8). We further replicated the heritability patterns in a

182   separate analysis focused only on the additional participants from the S1200 HCP release (Figure

183   S9).

Genetic overlap between neurobehavioural factors

185   Phenotypically, certain PPS-s had small but significant intercorrelations (Figure S10 upper

186   triangle). After FDR correction, we were able to find two genetic correlations between PPS-s of

187   cognition and cortical thickness (r_g=0.35), as well as cognition and personality (r_g=0.33, Figure

188   S10 lower triangle). Taken together, while the neurobehavioural factors have mostly independent

189   effects on BMI, cognitive test scores have small genetic overlap with brain structure and

190   personality.

191

Discussion

192

193   Cortical thickness, medial temporal lobe volume, and cognitive measures all had covariation with

194   BMI, and their effect on BMI was almost entirely heritable. Similarly, we found genetic

195   correlations between obesity risk scores of cognition, cortical thickness and personality.

196   Together, our results from a large sample support the role of brain and psychological constructs

197   in explaining genetic variance in obesity.

198   BMI correlated with increased cortical thickness in the left prefrontal cortex and decreased

199   thickness in the right prefrontal cortex, supporting the "right brain" hypothesis for obesity (10).

200   The effect was most prominent in the inferior frontal gyrus (Figures 2A and 3A). Only

201   preliminary support for the right brain hypothesis has been previously available (13). Right

202   prefrontal cortex has been implicated in inhibitory control (22) and possibly bodily awareness

203   (10). Many neuromodulation interventions (e.g. transcranial magnetic stimulation) aimed at

204   increasing self-regulation capacity often target right prefrontal cortex. On the other hand, effects

205   have also been demonstrated in studies targeting left prefrontal cortex (31).

206   Cortical thickness results also highlighted the role of temporo-parietal perceptual structures in

207   obesity. Namely, obesity was associated with bilaterally decreased thickness of the

208   parahippocampal and entorhinal cortices, and with mostly right-lateralized increased thickness of

209   parietal and occipital lobes. Volumetric results within the medial temporal lobe supported the role

210   of entorhinal cortex and also suggested that obesity is positively associated with the volume of

211   left amygdala. Emergence of the effects of the right parietal structures together with right

212   prefrontal structures hint at the role of the ventral frontoparietal network, thought to be especially

213   important for detection of behaviourally relevant visual stimuli (32). The parahippocampal and

214   entorhinal cortex are associated with episodic memory and context mediation (33). Similarly, the

215   hippocampus has been associated with the modulation of food cue reactivity by homeostatic and

216   contextual information, and hippocampal dysfunction is postulated to promote weight gain in the

217   western diet environment (34). The amygdala is implicated in emotional and appetitive responses

218   to sensory stimuli, including food cues (35).

219   Integrating these findings, one could envision a model where obesity is associated with a certain

220   cognitive profile (36). The model starts with a hyperactive visual attention system attributing

221   heightened salience to food stimuli, implicating the ventral visual stream and amygdala. These

222   signals are then less optimally tied into relevant context by the parahippocampal and entorhinal

223   structures, and less well moderated (or filtered) by the prefrontal executive system. This could

224   result in consummatory behaviour driven by the presence of appetitive food signals, which are

225   ubiquitous in our obesogenic environment. An impaired response inhibition and salience

226   attribution model of obesity has been suggested based on the functional neuroimaging literature.

227   Namely, functional MRI studies have consistently identified obesity to associate with heightened

228   salience response to food cues, coupled with reduced activation in prefrontal and executive

229   systems involved in self-regulation and top-down attentional control (e.g., 35). A similar

230   conclusion emerged from a recent resting state network analysis of the HCP data (37), in which

231   obesity was associated with alterations in perceptual networks and decreased activity of default

232   mode and central executive networks.

233   This brain morphology-derived model has some support from cognitive tests. The role of

234   prefrontal executive control is outlined by our finding of obesity's negative association with

235   scores on several executive control tasks. Surprisingly, there was no effect of motor inhibition as

236   measured by the Flanker inhibitory task. A relation between obesity and reduced motor

237   inhibition, while often mentioned, has been inconsistent even across meta analyses (7, 8). On the

238   other hand, we found a relationship between decisional impulsivity, measured by delay-

239   discounting, and BMI, replicating previous literature (6, 7, 18). While controlling for education

240   reduced the number of executive tasks associated with BMI, the overall pattern remained the

241   same, suggesting that education level is a proxy for certain executive function abilities.

242   Intriguingly, obesity was found to be negatively associated with spatial orientation and verbal

243   episodic memory. These tasks tap into the key functions associated with entorhinal and

244   parahippocampal regions implicated in our study (33). Therefore, both cognitive and brain

245   morphology features propose that the increased salience of food stimuli could be facilitated by

246   dysregulated context representation in obesity.

247   Regarding personality, we were unable to find any questionnaire-specific effects, notably with

248   respect to Neuroticism and Conscientiousness, both often thought to be associated with obesity

249 (5–7). There are potential explanations for this discrepancy. First, the meta-analytical association

250 between various personality tests and BMI is small (r=0.05, ref: 7), for which we might have

251 been underpowered after p-value correction. Second, controlling for family structure likely

252 further reduced the effect sizes (25). Third, the personality-obesity associations tend to pertain to

253 more specific facets and nuances than broad personality traits (38), therefore, further analysis

254 with more detailed and eating-specific personality measures is needed in larger samples.

255 All the associations discussed here were largely due to shared genetic variance between

256 neurobehavioural factors and BMI. This is in accordance with recent molecular genetics evidence

257 that 75% of obesity related genes express preferentially in the brain (4). Similarly, the genetic

258 correlation between cognition and BMI uncovered in our sample is at the same magnitude as

259 molecular estimates of associations between more specific cognitive measures and BMI (15, 18).

260 The current evidence further supports the brain-gene association with obesity vulnerability.

261 A possible explanation of the genetic correlations is pleiotropy – the existence of a common set

262 of genes that independently influence variance in both obesity and brain function. However, our

263 results could also support a causal relationship – that the genetic correlation is due to a persistent

264 effect of heritable brain factors on overeating and hence BMI. For instance, we could hypothesize

265 that the heritable obesity-related cognitive profile promotes overeating when high-calorie food is

266 available. As high-calorie food is abundant and inexpensive, the cognitive profile could lead to

267 repeated overeating providing an opportunity for genetic obesity-proneness to express. Such

268 longitudinal environmental effects of a trait need not to be large, they just have to be consistent

269 (39, see discussion in 40). Of course, a reverse scenario is also possible – obesity leads to

270 alterations in cortical morphology due to the consequences of cardiometabolic complications,

271 including low-grade chronic inflammation, hypertension, and vascular disease (reviewed in 9,

272 41). However, we find this hypothesis less plausible in our study for two reasons. First, the

273 reviews outline that the reported consequence of chronic visceral adipose tissue accumulation is

274 typically global brain atrophy. In contrast, the current data implicate focal brain effects – vascular

275 or inflammatory neurodegenerative effects would not explain the left-right asymmetry in the

276 prefrontal cortex, nor the many areas of gray matter increase with BMI. Second, the same

277 reviews suggest that global brain atrophy due to metabolic syndrome is mostly seen in older

278 participants, whereas the current sample had a mean age of 29. Young adults often experience

279   "healthy or transitional obesity", where clinical inflammation levels (42) and other

280   cardiometabolic comorbidities have not yet developed (43). Further, a recent mendelian

281   randomisation study suggested that low genetic potential for education (a proxy for cognitive test

282   score, compare Figure 1A with Figure S3A left) leads to high risk for cardiovascular disease,

283   whereas high genetic risk for cardiovascular disease (outcome of high BMI) does not lead to low

284   education (44). A likely explanation of these findings is that even if the cardiovascular disease

285   (and BMI) genes have effects on cognition via neurodegenerative mechanisms, these genes have

286   an effect later in life, when people have completed their education. Taken together, the focality of

287   the cortical thickness patterns and young age of the participants suggest that the genetic

288   neurobehavioural factors described here lead to a higher risk of obesity.

289   We found neurobehavioural PPS-s to have occasional phenotypic and genetic correlations with

290   each other. Here, it is hard to argue against pleiotropy playing a role. While one could reasonably

291   expect that at least part of the variation in cognitive performance would be shaped by brain

292   morphometry (22), it is also the case that engaging in education leads to improvement in

293   cognitive test scores (26) and might also lead to changes in cortical thickness (45). The small

294   genetic overlap between cognition, cortical thickness and personality can probably be explained

295   by common pleiotropic roots. At the same time, integrating morphometry and cognitive findings

296   is difficult with this dataset.

297   From a practical point of view, our work suggests that evidence from psychology and

298   neuroscience can be used to design intervention strategies for people with higher genetic risk for

299   obesity. One way would be modifying neurobehavioural factors, e.g. with cognitive training, to

300   improve people's ability resist the obesogenic environment (31, 36). Another path could be

301   changing the immediate environment to be less obesogenic (e.g., 46) so that individual

302   differences in neurobehavioural factors would be less likely to manifest. In any case, current

303   evidence highlights that obesity interventions should not focus solely on diet, but also take into

304   account that obesity is genetically intertwined with variation in neurobehavioural profiles.

305   The current analysis has limitations. Due to the cross-sectional nature of the dataset, causality

306   between neurobehavioural factors and obesity is only suggestive – longitudinal designs would

307   enable better insight into the causal associations between brain morphology, psychological

308   measures, and BMI or weight gain. BMI is a crude proxy for actual eating behaviours or health

309   status. In addition, there were more normal-weight than obese participants. However, the 25%

310   obesity rate in this sample is close to the published obesity rate of the state of Missouri (31.7%)

311   and the US (36.5%, ref: , 47). Also, we expect that BMI itself and the neurobehavioural

312   mechanisms behind it are continuum processes, therefore all variation in the range from normal-

313   weight to obesity is likely helping to uncover underlying associations. While the measurement of

314   cognition and personality was exhaustive, it lacked some common behavioural tasks like the

315   stop-signal task, or common questionnaires measuring self-control, impulsivity, and eating-

316   specific behaviours that have been previously associated with body weight (5, 6). Particularly, the

317   common eating-specific behaviours such as uncontrolled eating (48) are likely better candidates

318   for explaining brain morphology-BMI associations as they are more directly related to the

319   hypothesized underlying behaviour.

320   One has to be careful in translating individual differences in cortical thickness in normal

321   populations to underlying neural mechanisms. Diverse biological processes have been suggested

322   to influence MRI-based cortical thickness measures, ranging from synaptic density to apparent

323   thinning due to synaptic pruning and myelination (summarized in 49, 50). A definitive model of

324   the underlying mechanism that links normal variations in cortical thickness to differences in brain

325   function cannot be given, as cortical thickness has not been mapped with both MRI and histology

326   in humans (50). Still, the associations between cortical thickness and BMI in one sample were

327   able to predict BMI in a new separate sample, suggesting that the pattern is robust. Our

328   conceptual interpretation of the meaning of cortical thickness patterns has support from measures

329   of both brain structure and cognitive function.

330   Relying on PPS-s prevented us from analyzing detailed interactions between cortical thickness

331   and cognitive function in their genetic overlap with each other. However, given the relatively

332   small associations between PPS-s, and the number of candidate measures that could be expected

333   to interact with one another, we believe it would have been hard to find an association that would

334   have survived multiple testing correction. Future, focused, hypothesis-driven studies have to

335   further elucidate the neurobehavioural mechanisms behind obesity proneness.

336   In summary, the current analysis provides comprehensive evidence that the obesity-related

337   differences in brain structure and cognitive tests are largely due to shared genetic factors. Genetic

338   factors also explain occasional overlap between neurobehavioural factors. We hope that

339   increasingly larger longitudinal data sets and dedicated studies will help to outline more specific

340   neurobehavioural mechanisms that confer vulnerability to obesity, and provide a basis for

341   designing informed interventions.

342   **Methods**

343   Data were provided by the Human Connectome Project (24). Certain people were excluded due

344   to missing data or not fulfilling typical criteria. Exclusion details, demographics and family

345   structure are summarized in SI Methods and Table S1. Software pipelines for obtaining features

346   of cortical thickness and brain volume are described in SI Methods. Analysis scripts to reproduce

347   results presented are available at: osf.io/htx7u.

348   Figure S1 provides a schematic pipeline for data analysis. Details of each data analysis step are

349   outlined in SI Methods. We describe how PPS weights are obtained through cross-validation and

350   how the weights generalize to a separate dataset (S1200n). We further describe the main

351   principles of twin and sibling-based heritability analysis and replication of these findings using

352   individual features instead of PPS-s, and replication in a separate dataset (S1200n). Finally, the

353   software and packages used are listed.

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467 **Figures**
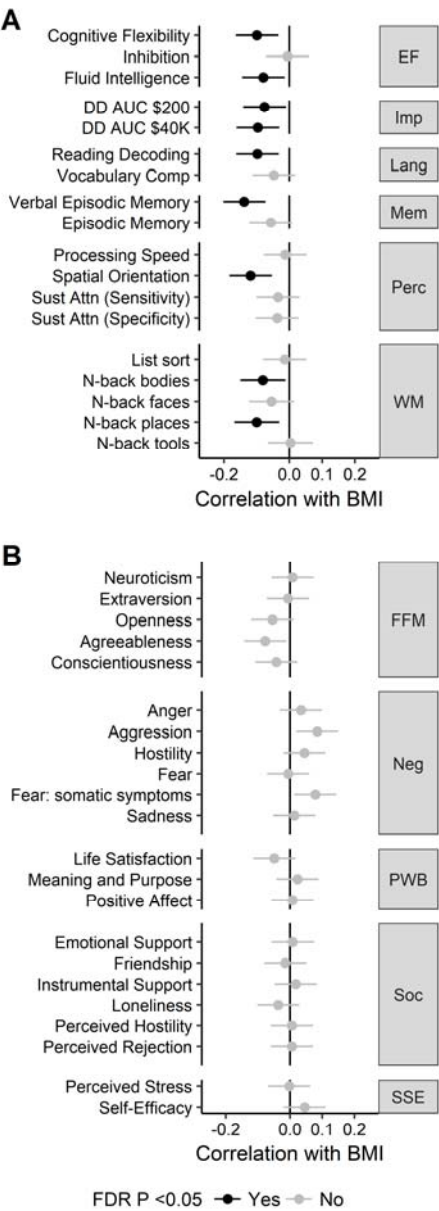
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469 Figure 1. Associations between body mass index (BMI) and (A) cognitive test scores, and (B)

470 personality traits (B). Error bars represent 95% confidence intervals. See Table S2 for

471 explanation of cognitive tests. Numerical values are reported in Table S3. EF=executive function;

472 FFM=Five-Factor Model; FDR=false discovery rate; Imp=(lack of) impulsivity; Lang=language;

473 Mem=memory; Neg=negative affect; Perc=perception; PWB=psychological well-being;

474 Soc=social relationships; SSE=stress and self efficacy; WM=working memory.
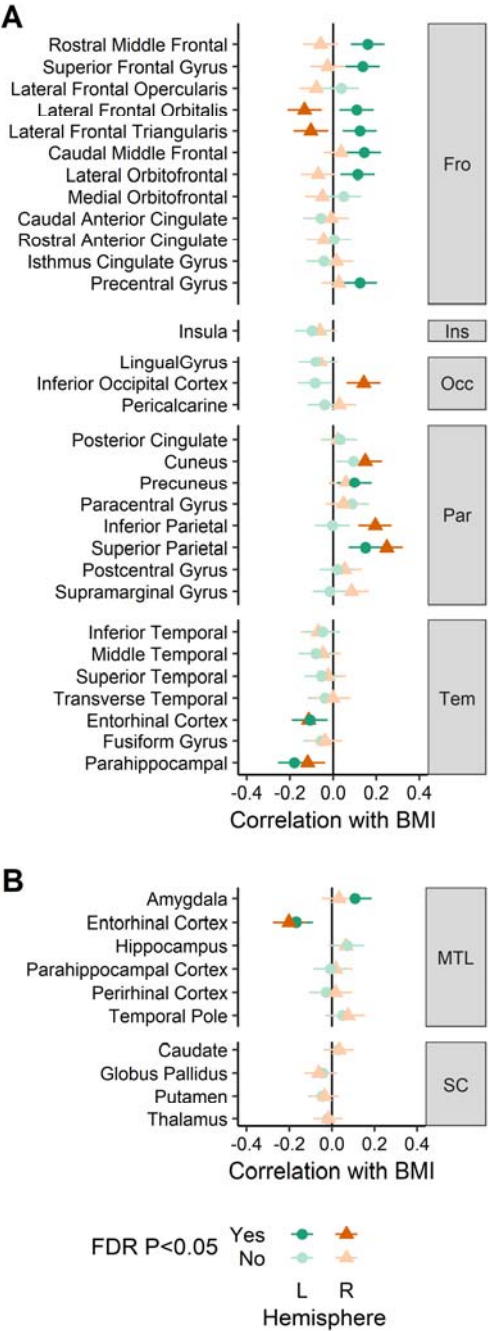
Figure 2. Associations between body mass index (BMI) and brain morphometry. (A) cortical thickness. (B) medial temporal and subcortical regional brain volume. Error bars represent 95% confidence intervals. Numerical values are reported in SI Table S2. FDR=false discovery rate; Fro=frontal, Ins=insula; L=left; Occ=occipital; Par=parietal; R=right; Tem=temporal; MTL=medial temporal lobe; SC=subcortical.

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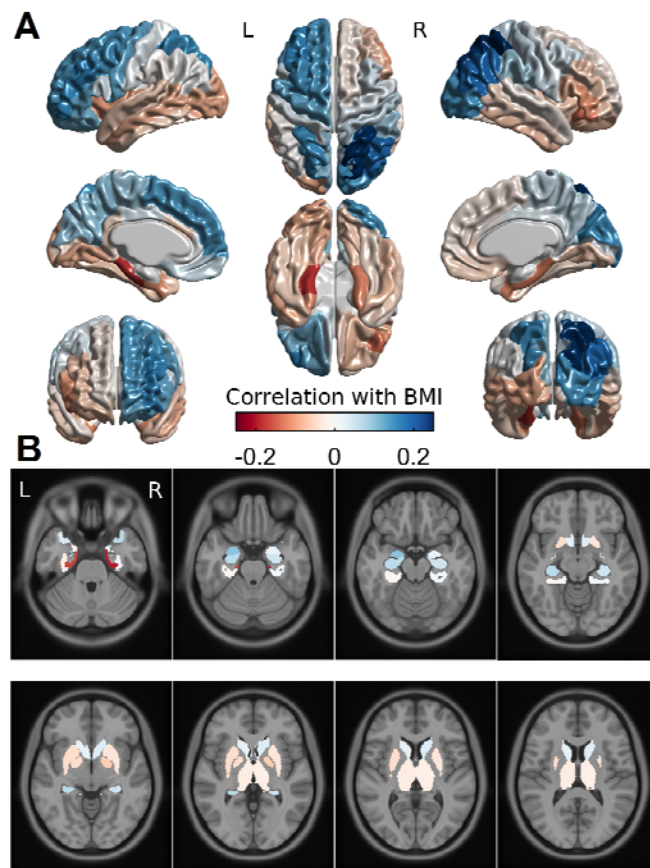
Figure 3. Brain maps of the associations between body mass index (BMI) and (A) cortical thickness and (B) medial temporal and subcortical regional brain volume on a standard brain template in MNI space. Values are the same as in Figure 2. Colour bar applies to both sub-plots. L=left; R=right.

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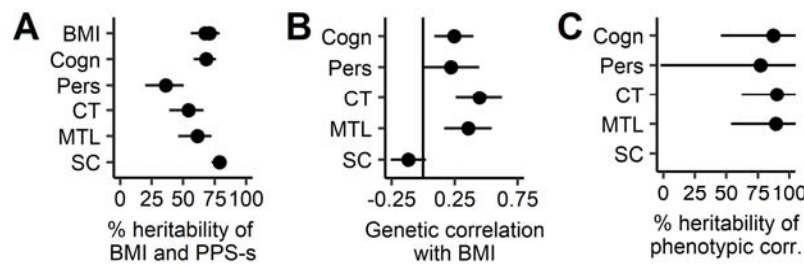
Figure 4. Heritability analysis of the association between poly-phenotype scores (PPS) and body mass index (BMI). (A) Heritability of each trait. BMI has multiple estimates, since it was entered into a bivariate analysis with each PPS separately. (B) Genetic correlations between BMI and each PPS. The genetic correlations are positive, because the PPS-s are designed to positively predict BMI. (C) Heritability of the significant phenotypic correlation between BMI and PPS. Horizontal lines depict 95% confidence intervals. Cogn=PPS of cognitive tests; corr=correlation; CT=PPS of cortical thickness; MTL=PPS of medial temporal lobe volume; Pers=PPS of personality tests; SC=PPS of subcortical structure volumes.

497

498   # Supplementary Information for

499

500   ## Neurobehavioural Correlates of Obesity are Largely Heritable

501   Uku Vainik , Travis Baker , Mahsa Dadar , Yashar Zeighami, Andréanne Michaud, Yu Zhang,
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507

508   **This PDF file includes:**

509

510   Supplementary text

511   Figs. S1 to S11

512   Tables S1

513   References for SI reference citations

514

515   **Other supplementary materials for this manuscript include the following:**

516

517   Tables S2-S13

518

519
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521

522   **Supplementary Information Text**

523   **Methods**

524   <u>Participants</u>

525   Data were provided by the Human Connectome Project (24) WU-Minn Consortium (Principal

526   Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657, RRID:SCR_008749)

527   funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience

528   Research; and by the McDonnell Center for Systems Neuroscience at Washington University,

529   The analyzed data were split between S900 data release (964 participants) and S1200 data release

530   (236 additional participants). We treated the S900 as the main analysis sample and results from

531   this sample are reported throughout the paper. At times, we used unique participants from the

532   S1200 release for replication, referred to as S1200n. For the main analysis sample, we applied the

533   following exclusion criteria, as these might confound brain-obesity associations: people with

534   missing values on crucial variables, such as age, BMI, education, income, gender, race, and

535   ethnicity (n=6), hypo/hyper thyroidism (n=4), other endocrine problems (n=16), underweight

536   (BMI <=18, n=9), and women who had recently given birth (n=9). In addition, as we used family

537   information to control for participants' relatedness, we excluded participants that were half-

538   siblings to other participants (n=31). The same exclusions were applied to S1200n (n=11).

539   The final main analysis dataset consisted of 895 participants, demographics of which are

540   summarized in Table 1. The sample had good gender balance and variation in BMI and income.

541   As limitations, the sample was relatively young and well educated, and BMI distribution was

542   slightly less obese compared to current prevalence estimates for Missouri or the US as a whole

543   (MO: 31.7%, US: 36.5%, ref: , 47). Most people were white and non-Hispanic, however other

544   races-ethnicities were also represented. The participants were nested into 384 families, typically

545   having 1 to 3 siblings in the dataset. For comparison, we also provide the same statistics for the

546   S1200n sample, as well as a subset of S1200n sample in which no participant is related to the

547   S900 sample.

548   For the heritability analysis between each neurocognitive factor and BMI, we randomly chose

549   one sibling pair per family, ensuring that the pair had complete data. Non-twin sibling pairs were

550   considered equivalent to dizygotic twin pairs with respect to heritability analyses once data was

551   residualized for age and gender. If multiple sibling pairs within a family had complete data, we

552   prioritized choosing monozygotic twin pairs and dizygotic twin pairs over non-twin sibling pairs.

553   Depending on the neurocognitive factor, the heritability analysis was conducted on 46-111 pairs

554   of monozygotic twins (median=97) and 60-202 pairs of dizygotic twins and siblings

555   (median=176).

556   <u>Measures</u>
557   Psychological measures.
558   Participants completed an extensive set of questionnaires and cognitive tests (see 51, 52 for an

559   overview). In the current analysis, we included 22 questionnaires and 18 cognitive tests (see

560   Figure 2 and Table S2 for complete list). Here we refer to the set of questionnaire results as

561   personality variables, as personality encompasses various patterns of what people want, say, do,

562   feel, or believe (53). Based on our previous review (6) we chose cognitive tests capturing aspects

563   of executive function, memory, and language.

564   Cortical thickness.
565   All T1-weighted MRI images were processed using the CIVET pipeline (version 2.0) (29, 54,

566   55). Processing was executed on the Canadian Brain Imaging Network (CBRAIN) High

567   Performance Computing platform for collaborative sharing and distributed processing of large

568   MRI datasets (56). Briefly, native T1-weighted MRI scans were corrected for non-uniformity

569   using the N3 algorithm (57). The corrected volumes were masked and registered into stereotaxic

570   space, and then segmented into gray matter (GM), white matter (WM), cerebrospinal fluid (CSF)

571   and background using a neural net classifier (58). The white matter and gray matter surfaces were

572   extracted using the Constrained Laplacian-based Automated Segmentation with Proximities

573   algorithm (59, 60). The resulting surfaces were resampled to a stereotaxic surface template to

574   provide vertex based measures of cortical thickness (61). All resulting images were visually

575   inspected for motion artefacts by experienced personnel and then subsequently processed through

576   a stringent quality control protocol, which only 641 of the 894 participants in our initial cohort

577   passed. In the S1200n, 144 of the 214 passed. For those participants who passed, cortical

578   thickness was then measured in native space using the linked distance between the two surfaces

579   across 81924 vertices and a 20mm surface smoothing kernel was applied to the data (62). The

580   Desikan–Killiany–Tourville (DKT) atlas was used to parcellate the surface into 64 cortical

581   regions (63). Cortical thickness was averaged over all vertices in each region of interest for each

582   subject (64) and the effect of mean cortical thickness was regressed to allow for regional analysis

583   (65). After participant exclusions, data was available for 591/137 participants in the S900/S1200n

584   samples.

585   Volumetric estimates.

586   Because the CIVET cortical thickness method does not cover all medial temporal and subcortical

587   structures, we used volumetric estimates for these brain regions. For subcortical volumetric

588   estimation, T1-weighted scans of the subjects were pre-processed through a computerized

589   pipeline (n=899). Image denoising (66), intensity non-uniformity correction (57), and image

590   intensity normalization into range (0-100) using histogram matching were performed. After

591   preprocessing, all images were first linearly (using a 9-parameter rigid registration) and then

592   nonlinearly registered to an average template (MNI ICBM152) as part of the ANIMAL software

593   (30, 67). The subcortical structures, i.e., thalamus, putamen, caudate, and globus pallidus were

594   segmented using ANIMAL by warping segmentations from ICBM152 back to each subject using

595   the obtained nonlinear transformations. The medial temporal lobe structures, i.e. hippocampi,

596   amygdala, temporal pole, and parahippocampal, entorhinal and perirhinal cortices, were

597   segmented using an automated patch-based label-fusion technique (68). The method selects the

598   most similar templates from a library of labelled MRI template images, and combines them with

599   a majority voting scheme to assign the highest weighted label to every voxel to generate a

600   discrete segmentation. Quality control was performed on the individual registered images as well

601   as the automated structure segmentations by visual inspection, and inaccurate results were

602   discarded. In S900, 648 participants passed the quality control for medial temporal lobe

603   structures, ad 895 for subcortical structures. Within S1200n, of the 214 participants, 212 passed

604   the quality control for subcortical structures, and 174 passed the quality control for medial

605   temporal lobe. After exclusions, the S900/S1200n samples included data from n=828/204, 8

606   parcels per subjects for the subcortical structures, and n=594/166, 12 parcels for the medial

607   temporal lobe structures.

608   Data Analysis

609   Analyzing each feature

610   A schematic pipeline of the analysis is displayed in Figure S1. Data from all neurocognitive

611   factors were first residualized for control variables (age, ethnicity, gender, handedness, race)

612   using linear multiple regression. When presenting phenotypic associations, we used a linear

613   mixed model, adding a random intercept for family (Figure S1), and also varied the involvement

614   of income and education. As BMI was skewed (long-tail at the upper end of the scale), it was log-

615   transformed to achieve a normal-like distribution. Handedness was also log normalized.

616   For each factor category (cognition, personality, cortical thickness, medial temporal volume,

617   subcortical volume), factor-BMI relationships were assessed using univariate correlation between

618   each brain parcel or test score and BMI. We initially also tried using a partial least squares (PLS)

619   correlation approach, which is a multivariate technique suited to handling correlated predictors

620   (69, 70). However, the PLS estimates were extremely close to univariate correlations, therefore

621   univariate correlations were preferred for simplicity. As a result, we received an estimate of the

622   relative contribution (weight) of each predictor within a given factor. Estimates used in this study

623   are presented in Table S3.

624   Creating poly-phenotype scores
625   To summarize effects for each neurocognitive factor, we created an aggregate BMI risk score or

626   *poly-phenotype score (PPS)* for each neurocognitive factor. This was inspired by the polygenic

627   risk score approach, where the effects of single-nucleotide polymorphisms are added up to form a

628   total genetic score (71). Specifically, we used the correlation-derived weights to multiply each

629   participant's measured values, and aggregated the results into a single composite variable for a

630   given factor, the PPS. A PPS would reflect the total association that a given factor has with BMI.

631   Even though only some features within a neurobehavioural factor had significant effects on BMI,

632   and certain features correlated with each other (see SI Tables S4-S8), both our testing (see SI

633   Results) and recommendations by others (72) lead us to not apply p-value cutoffs, clumping, or

634   pruning, as excluding these steps does not hurt predictive ability and improves transparency (72).

635   PPS-s have a mean of 0 but varying standard deviation, depending on the number of features and

636   their effect sizes (Table S9).

637   We used cross-validation principles to avoid and test for overfitting. Namely, we divided

638   participants into 10% folds. Each 10% fold received the correlation weights from the remaining

639   90% of the sample. As the result, we received one PPS vector for each factor, where each

640   participant's score was based on out-of-sample prediction. When creating the 10% folds, we

641   created folds for each factor separately, as each factor has a different number of available data

642   points, ensuring that folds were as equal in size as possible. We also ensured that siblings from

643   the same family were in the same fold. Therefore, no data from family members were used in

644   calculating both the correlation weights and performing out of sample predictions.

645   To test the robustness of PPS-s, we first tested the impact of not pruning and applying p-value

646   cutoffs. In a pruned PPS, features are omitted that a) correlate above criterion to another feature

647   and b) have lower correlation with BMI than the other feature (73). In a PPS with p-value cut-off,

648   features are omitted that have an above-criterion uncorrected p-value when correlated with BMI

649   Neither pruning nor a p-value cutoff improved the predictive ability of the PPS-s (see SI Results).

650   We further tested the predictive ability of PPS scores by applying the weights created on the full

651   S900 release to predict BMI in the S1200n release (new participants only), which we did not

652   touch before predicting. As 101 participants within the S1200n were related to participants in the

653   S900, we also tested the predictive ability in the subset of S1200 that was not related to S900

654   (n=124).

655   Heritability analysis
656   In the heritability analysis, a typical behavioural genetics decomposition uses relatedness

657   assumptions between individuals to divide variance in a trait to the following components:

658   genetic variance (A, additive and interactive effects), shared environmental variance (C, family

659   and shared school effects), and unique environmental variance (E, unique experience and

660   measurement error). The assumptions are: 100% of genetic variance shared between

661   monozygotic twins, 50% of genetic variance shared between dizygotic twins and sex-and gender

662   residualized siblings, 100% of family environment shared by all siblings, 0% unique variance

663   shared between siblings. Such decomposition is called univariate heritability.

664   Besides establishing univariate heritability, one can also conduct heritability analysis on the

665   covariance between two traits. For instance, a genetic correlation is the correlation between the A

666   components of trait 1 and trait 2. A bivariate heritability analysis decomposes the phenotypic

667   correlation between trait 1 and trait 2 into A, C, and E components.

668   Heritability analysis was conducted on PPS scores not residualized for family structure, as this

669   information is used in heritability modelling. We then ran bivariate heritability analyses

670   separately between each PPS and BMI, which provided univariate heritability estimates of the

671   PPS-s and BMI, genetic and environmental correlations between the univariate estimates of PPS-

672   s and BMI, and bivariate decomposition of the phenotypic correlation between each PPS and

673   BMI. We used the AE model, since BMI was best explained by an AE model, as opposed to an

674   ACE model, based on Akaike Information Criterion (AIC) (Table S10). Similar AIC patterns

675   were present for bivariate models (Figure S11, Table S13). We report only standardized A

676   estimates in the main results, as in the univariate and bivariate analysis of the AE model, E=100-

677   A. Also, no environmental correlations were significant. All standardized and unstandardized

678   estimates are reported in the supplementary materials (Tables S11-S12).

679   Analysis software
680   Analysis reported in paper was conducted in Microsoft R Open 3.4.0 (74), using May 2017

681   version of packages abind, car, caret, cowplot, corrplot, ggplot2, lme4, MuMIn, pbkrtest, plyr,

682   psych, synthpop, tidyr, WriteXLS (75–90). Cortical thickness was plotted using Surfstat (91) in

683   MATLAB (92). Heritability analysis was conducted using OpenMX (93), adapting scripts

684   provided by the Colorado International Twin Workshop (94).

685   **SI Results**
686   Control variables
687   Age, gender and race related to BMI, demonstrating the need for residualizing (Figure S2).

688   Marginal R^2 explaining only fixed effects was 0.07, and conditional R^2 explaining both fixed and

689   random effects was 0.38, highlighting the effect of family structure. When controlling for

690   education and income, education was a significant additional predictor, with total model R^2 being

691   0.09 and conditional R^2 0.37. Further, controlling for family structure in a nested model as

692   random intercept improved model fit (AIC dropped from 7006 to 6895 / 6978 to 6885 when

693   controlling for education and income), suggesting that family nesting needs to be taken into

694   account.

695   Robustness of PPS-s
696   Similarly to genetic literature (72), we found that pruning features or applying a p-value threshold

697   does not change the predictive ability of the PPS-s (Figures S5 & S6).

698   To test the generalizability of the PPS approach, we used weights obtained from the full S900

699   release (Figures S3 right and S4 right) to predict the BMI of new participants in the S1200 release

700   (S1200n, n=236), which were not used in any of the initial assessments. As certain participants in

701   the S1200n release were related to participants in the S900, we also tested the PPS performance

702   when they were excluded. As can be seen in Figure S7, cortical thickness estimates are very

703   similar, no matter the training or testing dataset. Cognition PPS effect sizes were similar to each

704   other, but did not reach statistical significance in the replication sample (S1200n). Personality

705   PPS had unexpectedly high correlation with BMI in the new data. Further research is needed to

706   determine if such effect sizes would further replicate. Medial temporal lobe PPS-s also did not

707   replicate.

708   Heritability replication

709   We tested whether the PPS-based bivariate analysis patterns would replicate in the S900 dataset,

710   but using unaggregated top individual features within the PPS-s. We chose the 5 individual

711   features from the top predictors of cognition and cortical thickness. As shown in Figure S8, the

712   individual tasks are comparable with the PPS-s in terms of univariate heritability, genetic

713   correlations, and heritability of phenotypic correlation. However, with genetic correlations, the

714   estimates are non-significant (Figure S8 B1&B2), suggesting that we are not powered to establish

715   significance of the smaller correlations. Further, the standardized estimates for heritability of the

716   phenotypic correlations (Figure S8 C1&C2) are noisier and the estimator often failed at

717   estimating standardized confidence intervals. Such failures at individual feature levels highlight

718   the value of PPS-s, which provide more stable estimates at these sample sizes.

719   We further used participants only in the S1200n release to replicate the bivariate heritability

720   analysis results in new data. PPS weights were obtained from the S900 release. We focused only

721   on participants who did not have siblings in the S900 release. Granted, the power is low because

722   of fewer complete twin pairs available (29 MZ pairs and 30 DZ pairs). The univariate estimate

723   for BMI heritability was [A=64% [95% CI: 41%;79%]. In the bivariate analysis, we were also

724   able to replicate the patterns seen in the main dataset (Figure S9), however the confidence

725   intervals were often covering 0 or not estimated, likely due to small sample size.

726

727 **Figures**

728

729
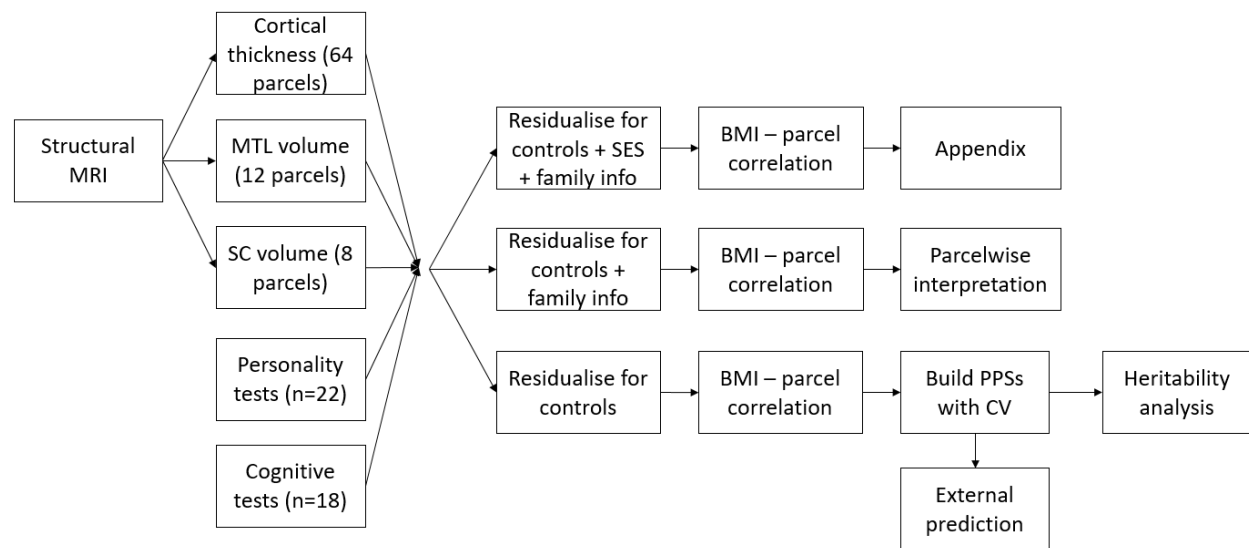
730   Fig. S1. A schematic diagram of the analysis pipeline. All steps were conducted on all

731   neurocognitive factors separately. BMI=body mass index; CV=cross-validation; MTL=medial

732   temporal lobe; MRI=magnet resonance image; PPS=poly-phenotype score; SC=subcortical;
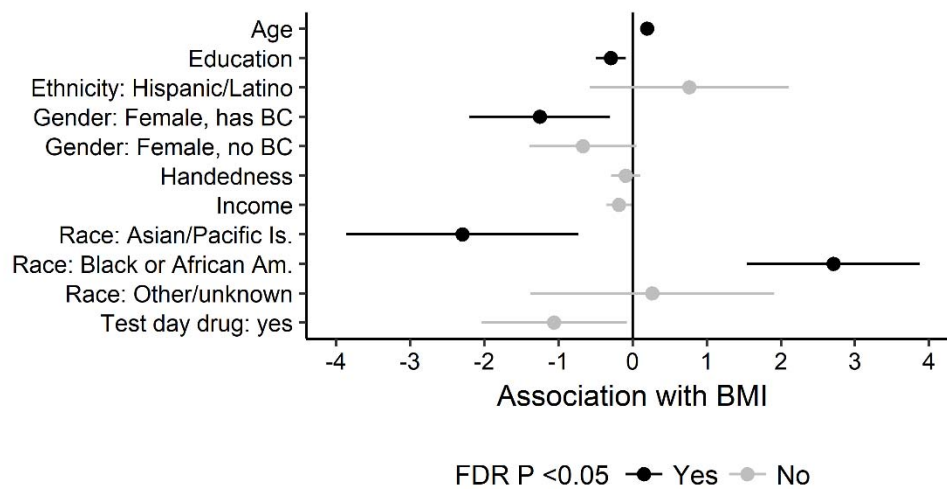
733   SES=socio-economic status (education and income).

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Fig. S2. Regression weights of a 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

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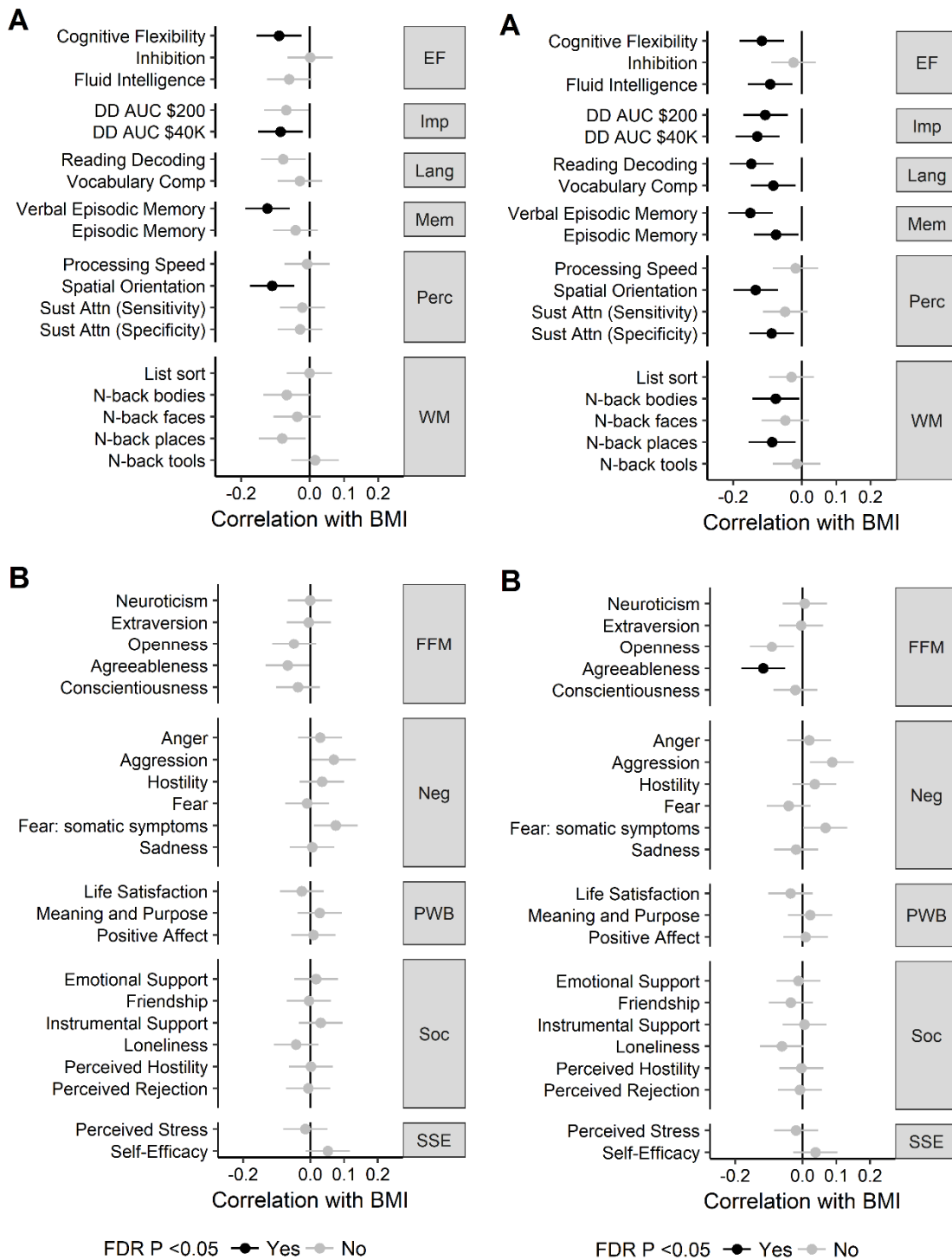
Fig. S3. Associations between body mass index (BMI), cognitive test scores (A), and personality traits (B), either when controlling for education, income, and family structure (left), or not controlling for these variables (right). Error bars mark 95% confidence intervals. See Table S2

746   for explanation of cognitive test names. Numerical values are reported in Table S3. EF=executive

747   function; FFM=Five-Factor Model; FDR=false discovery rate; Imp=(lack of) impulsivity;

748   Lang=language; Mem=memory; Neg=negative affect; Perc=perception; PWB=psychological

749   well-being; Soc=social relationships; SSE=stress and self efficacy; WM=working memory.

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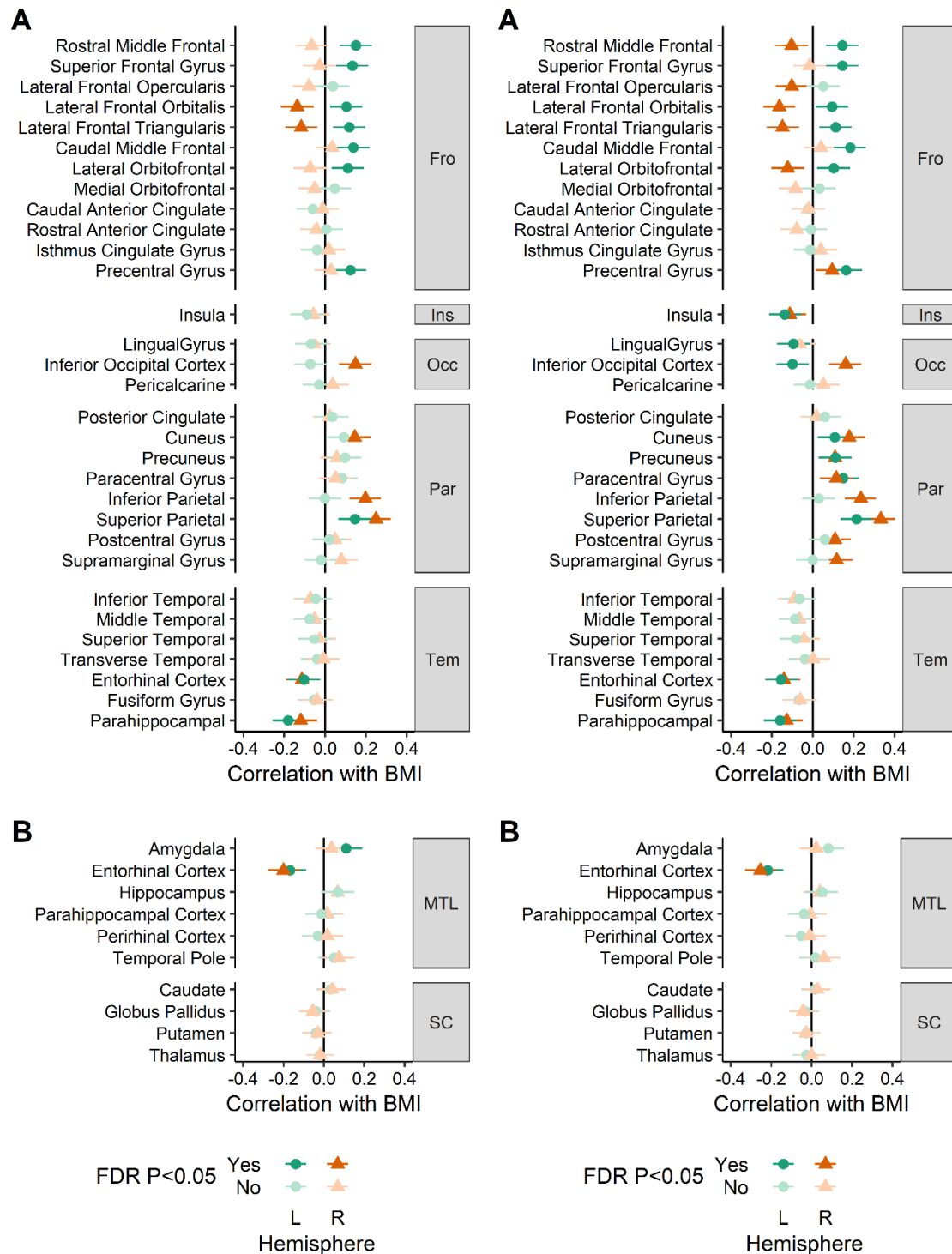
Fig. S4. Associations between body mass index (BMI), cortical thickness (A) and regional brain volume (B), either when controlling for education, income, and family structure (left), or not controlling for these variables (right). Error bars mark 95% confidence intervals. Numerical

755   values are reported in SI Table S3. FDR=false discovery rate; Fro=frontal, Ins=insula; L=left;

756   Occ=occipital; Par=parietal; R=right; Tem=temporal.

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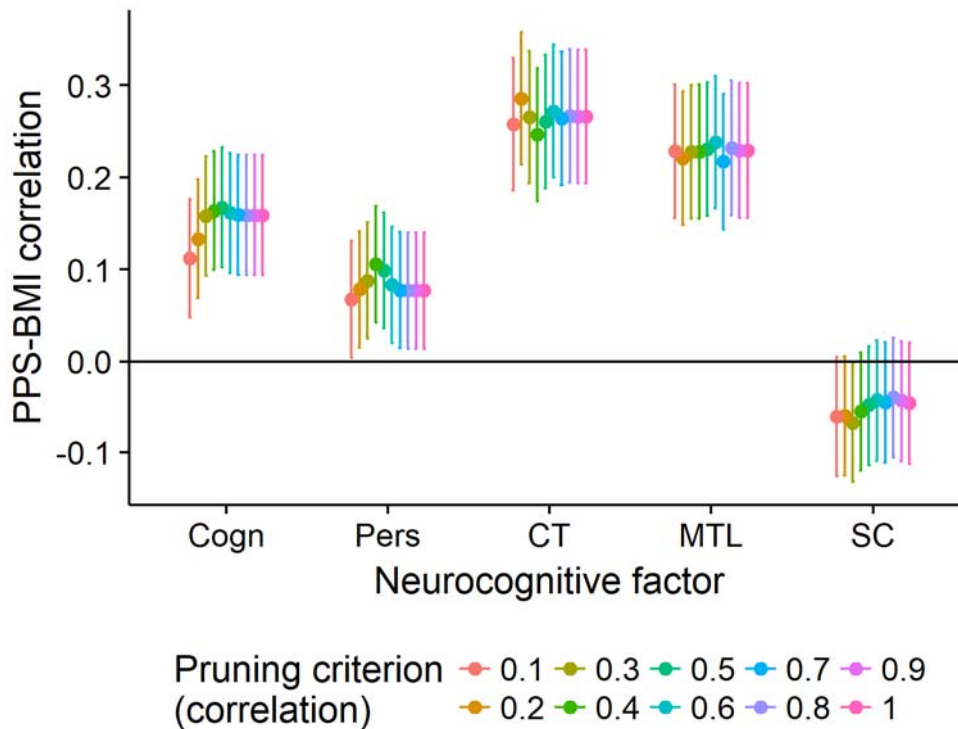
Fig. S5. Low impact of pruning to the poly-phenotype scores' (PPS) associations with BMI. PPS-s were trained and tested within the Human Connectome Project's S900 release, using cross-validation. Pruning means excluding features that have a higher correlation than set criterion with another feature that associates with BMI. A pruning criterion equal to 1 means no pruning was done. Cogn=PPS of cognitive tests; CT=PPS of cortical thickness; MTL=PPS of medial temporal lobe volume; Pers=PPS of personality tests.

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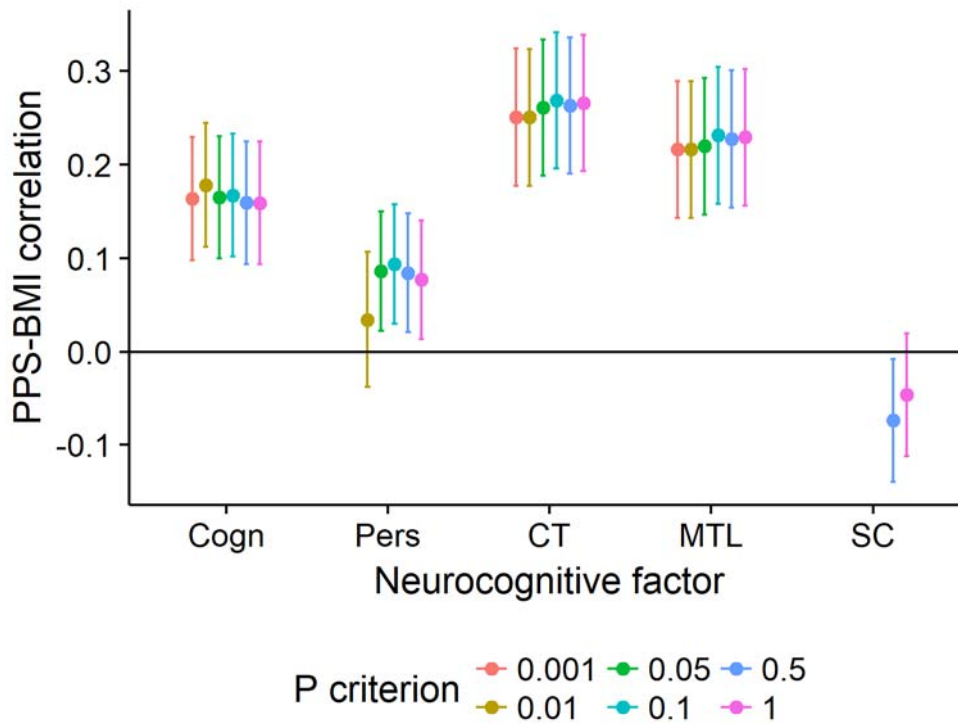
Fig. S6. Low impact of excluding features by p value to the poly-phenotype scores' (PPS)
associations with BMI. PPS-s were trained and tested within the Human Connectome Project's
S900 release, using cross-validation. Features with a p value higher than criterion were excluded
from the PPS. A p criterion of 1 means no exclusion was done. Cogn=PPS of cognitive tests;
CT=PPS of cortical thickness; MTL=PPS of medial temporal lobe volume; Pers=PPS of
personality tests.

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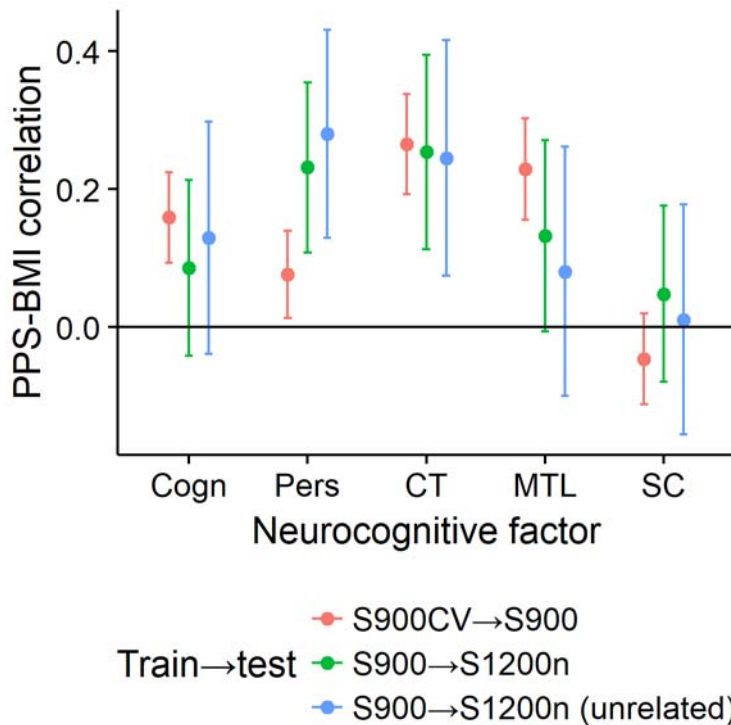
Fig. S7. Comparison of poly-phenotype scores' (PPS) performance in correlating with BMI, depending on training data and test data.

S900CV→S900: PPS-s within S900 release trained and tested with cross-validation to avoid bias. These PPS-s are used in heritability analysis.

S900→S1200n: PPS-s trained on S900 and tested in full S1200n sample.

S900→S1200n (unrelated): PPS-s trained on S900 and tested in S1200n sample not related to S900.

Cogn=PPS of cognitive tests; CT=PPS of cortical thickness; CV=cross-validated; MTL=PPS of medial temporal lobe volume; Pers=PPS of personality tests; S900 – Participants in Human Connectome Project's S900 release; S1200n – participants only in the S1200 release; SC=PPS of subcortical structure volumes.

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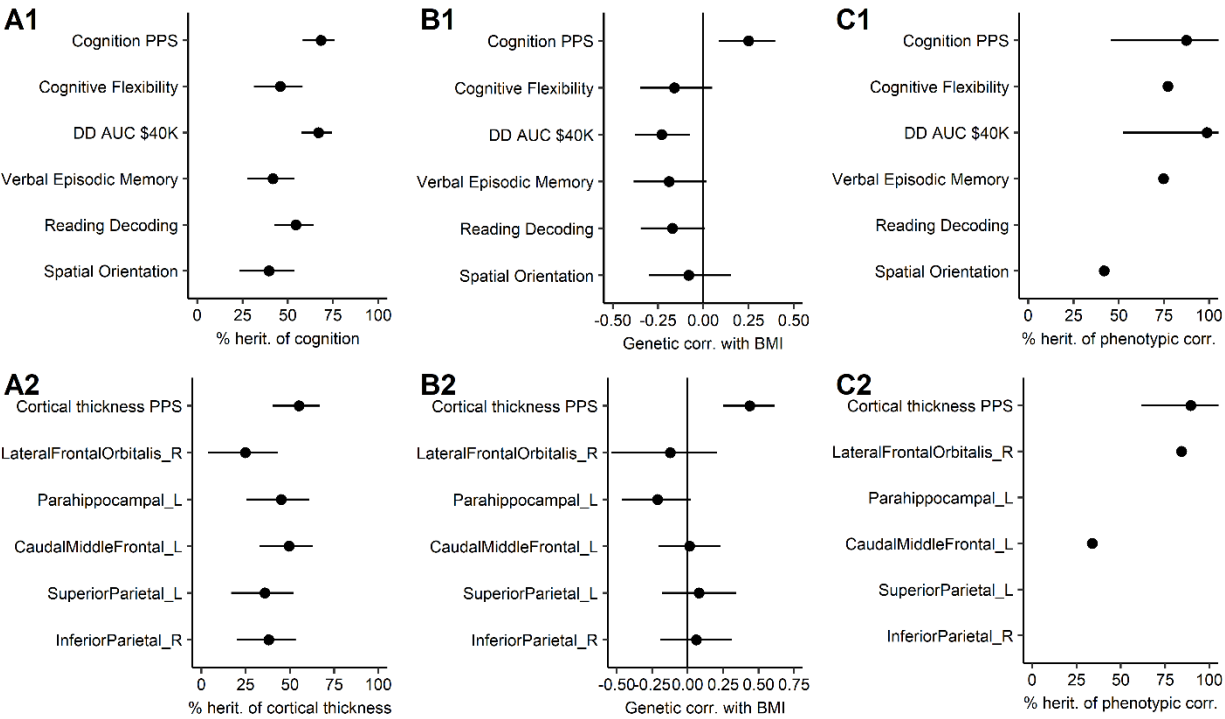
Fig. S8. Heritability analysis of the association between poly-phenotype scores (PPS) of cognitive test scores (A1-C1) and cortical thickness (A2-C2), compared with most significant individual features of each PPS. (A) Heritability of each trait. The effect of unique environment (E) is not shown, since E=100-A. (B) Genetic correlations between BMI and each PPS or between BMI and each feature. The PPS-based genetic correlations are positive, because the PPS-s are designed to positively predict BMI. However, individual features can have negative genetic correlations. (C) Heritability of the phenotypic correlation between BMI and PPS or between BMI and each feature. Horizontal lines depict 95% confidence intervals. The estimator failed at estimating certain features. Corr=correlation; L=Left hemisphere; herit=heritability; R=right hemisphere.

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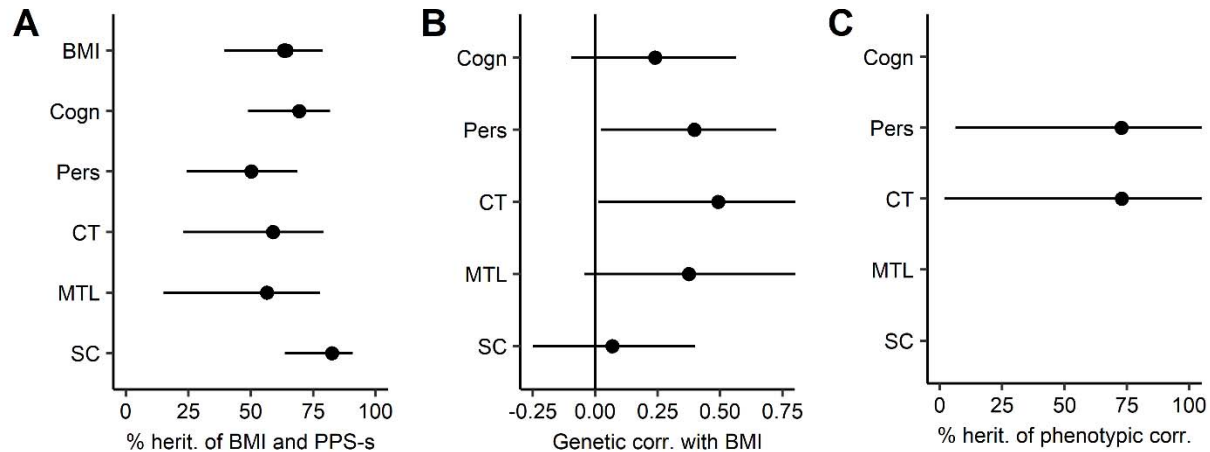
Fig. S9. Heritability analysis of the association between poly-phenotype scores (PPS) and body mass index (BMI) in the S1200n sample unrelated to S900. (A) Heritability of each trait. BMI has multiple estimates, since it was entered into a bivariate analysis with each PPS separately. The effect of unique environment (E) is not shown, since E=100-A. (B) Genetic correlations between BMI and each PPS. The genetic correlations are positive, because the PPS-s are designed to positively predict BMI. None of the environmental correlations were significant and therefore not shown. (C) Heritability of the phenotypic correlation between BMI and PPS. Horizontal lines depict 95% confidence intervals. Estimates not shown for PPS-s that did not have significant phenotypic association with BMI. Cogn=PPS of cognitive tests; corr=correlation; CT=PPS of cortical thickness; herit=heritability; MTL=PPS of medial temporal lobe volume; Pers=PPS of personality tests; SC=PPS of subcortical structure volumes.

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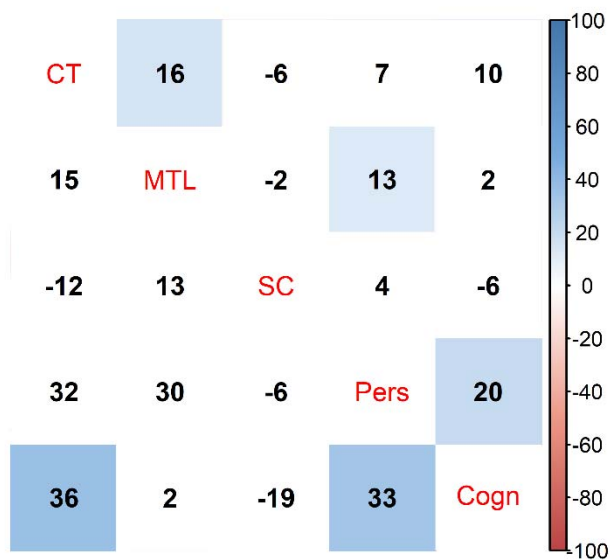
Fig. S10. Phenotypic (upper triangle) and genetic (lower triangle) correlations between poly-phenotype scores (PPS-s) used for heritability analysis. Phenotypic correlations account for family structure. FDR-corrected significant correlations are highlighted with color. Correlations are multiplied by 100 for clarity. Cogn=PPS of cognitive tests; corr=correlation; CT=PPS of cortical thickness; MTL=PPS of medial temporal lobe volume; Pers=PPS of personality tests; SC=PPS of subcortical structure volumes.

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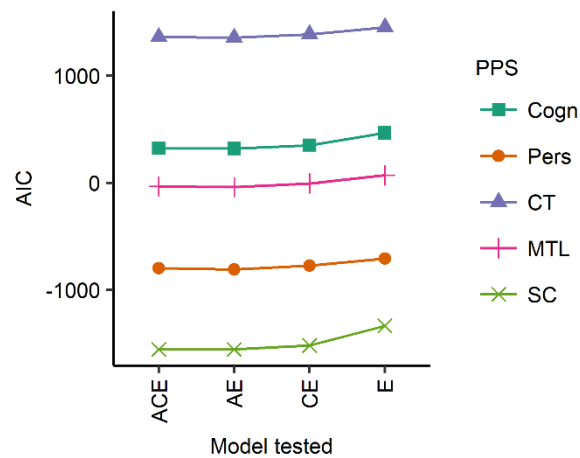
823   Fig. S11. Akaike Information Criteria (AIC) for BMI-PPS (poly-phenotype score) bivariate

824   heritability decompositions. Cogn=PPS of cognitive tests; corr=correlation; CT=PPS of cortical

825   thickness; MTL=PPS of medial temporal lobe volume; Pers=PPS of personality tests; SC=PPS of

826   subcortical structure volumes.

827

828   **Table S1. Descriptive statistics of samples analyzed.**

Variable	S900	S1200n	S1200n unrelated
N	895	225	124
Age (years)	$\bar{x}$=28.83 (SD=3.67)	$\bar{x}$=28.85 (SD=3.84)	$\bar{x}$=29.31 (SD=3.83)
BMI (kg/m^2)	$\bar{x}$=27.27 (SD=5.77)	$\bar{x}$=26.51 (SD=5.21)	$\bar{x}$=26.32 (SD=5.18)
BMI groups			
Normal weight (BMI 18-24.9)	375 (41.9%)	101 (44.9%)	56 (45.2%)
Overweight (BMI 25-29.9)	285 (31.8%)	74 (32.9%)	45 (36.3%)
Obese (BMI 30+)	235 (26.3%)	50 (22.2%)	23 (18.5%)
Drug test positive			
No	777 (86.8%)	195 (86.7%)	105 (84.7%)
Yes	118 (13.2%)	30 (13.3%)	19 (15.3%)
Education (years)	$\bar{x}$=14.85 (SD=1.82)	$\bar{x}$=15.06 (SD=1.72)	$\bar{x}$=14.83 (SD=1.8)
Ethnicity:			
Hispanic/Latino	819 (91.5%)	198 (88%)	114 (91.9%)
Not Hispanic/Latino/unknown	76 (8.5%)	27 (12%)	10 (8.1%)
Families	384	151	66
1 sibling	37 (10.4%)	19 (20%)	19 (28.8%)
2 siblings	107 (30.1%)	49 (51.6%)	36 (54.5%)
3 siblings	163 (45.9%)	20 (21.1%)	11 (16.7%)
4 siblings	43 (12.1%)	6 (6.3%)	0 (0%)

5 siblings	5 (1.4%)	1 (1.1%)	0 (0%)
Gender			
Male	413 (46.1%)	120 (53.3%)	61 (49.2%)
Female no birth control	143 (16%)	24 (10.7%)	16 (12.9%)
Female with birth control	339 (37.9%)	81 (36%)	47 (37.9%)
Handedness	x̄=65.07 (SD=45.13)	x̄=68.93 (SD=41.03)	x̄=70.73 (SD=36.97)
Income			
<$10,000	65 (7.3%)	16 (7.1%)	9 (7.3%)
10K-19,999	79 (8.8%)	12 (5.3%)	9 (7.3%)
20K-29,999	116 (13%)	24 (10.7%)	15 (12.1%)
30K-39,999	104 (11.6%)	30 (13.3%)	17 (13.7%)
40K-49,999	98 (10.9%)	23 (10.2%)	13 (10.5%)
50K-74,999	181 (20.2%)	46 (20.4%)	25 (20.2%)
75K-99,999	119 (13.3%)	28 (12.4%)	14 (11.3%)
>=100,000	133 (14.9%)	46 (20.4%)	22 (17.7%)
Race			
White	664 (74.2%)	176 (78.2%)	95 (76.6%)
Other/unknown	45 (5%)	21 (9.3%)	11 (8.9%)
Black or African Am.	145 (16.2%)	13 (5.8%)	8 (6.5%)
Asian/Nat. Hawaiian/Other Pacific Is.	41 (4.6%)	15 (6.7%)	10 (8.1%)

829   BMI=body mass index; Is=islander; Nat=native

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Additional Tables S2-S11 (separate file)

See first tab of file "SI_Tables_2-13.xlsx" for table of contents.

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