Neural and behavioral endophenotypes of obesity.

Selin Neseliler[1], Uku Vainik[1,2], Mahsa Dadar[1], Yvonne H.C. Yau[1], Isabel Garcia-Garcia[1], Stephanie G. Scala[1], Yashar Zeighami[1], D. Louis Collins[1] and Alain Dagher[1]

1. Montreal Neurological Institute, McGill University, Montréal, Canada
2. Institute of Psychology, University of Tartu, Estonia

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Abstract

Background

Impulsivity is a risk factor for obesity. It has different underlying facets that can be assessed using questionnaires. Impulsivity can be further refined by the use of food-specific questionnaires, which measure a tendency to uncontrolled eating. We examined how these impulsivity measures relate to each other, to obesity, and to brain anatomy.

Methods

We assessed students in their first year of university - a risky period for weight gain- at the beginning (N = 2214) and at the end of the school year (N = 1145) using questionnaire measures of impulsivity, personality, stress reactivity and eating-specific traits. A subset of participants (N = 72) underwent T1-weighted MRI to investigate the brain correlates of impulsivity.

Results

Using factor analysis, we show that impulsivity can be stratified into three domains, which we label stress reactivity, reward sensitivity and self-control, while eating questionnaires resolve into a single latent factor - uncontrolled eating. A watershed model shows that uncontrolled eating mediates the effect of impulsivity traits on BMI. Self-control and stress reactivity scores are associated with a thinner lateral orbitofrontal cortex. In addition, stress reactivity correlates positively with amygdala and negatively with hippocampal volume. Longitudinally, lack of self-control, not uncontrolled eating, correlates with weight gain, while stress reactivity correlates with weight loss in male students.

Conclusions

The brain-impulsivity-obesity relationship is hierarchical. Structural brain differences relate to differences in impulsivity domains which affect BMI via uncontrolled eating. However,

longitudinally, low self-control, not uncontrolled eating, is a predictor of weight gain in this sample.

Introduction

Obesity is a neurobehavioral disorder that stems from a vulnerable brain in a disease-promoting environment (1). Its risk factors can be studied as endophenotypes - intermediate phenotypes that link biological processes to observable outcomes (2, 3). Broadly, the neurobehavioral endophenotypes associated with obesity can be categorized as domain-general and eating-specific (4). The main domain-general endophenotype identified to date is impulsivity, defined as a tendency to act without full consideration of the consequences. Impulsivity is a multifaceted trait that has been associated with pathological gambling, substance abuse, and obesity (5, 6). Meta-analysis of impulsivity questionnaires revealed that impulsivity can further be subdivided into three domains that align with personality factors (5): 1) low *conscientiousness*, reflecting self-control ; 2) *neuroticism*, a reflection of an individual's sensitivity to stress and aversive events, and 3) *extraversion*, reflecting an individual's sensitivity to rewards (7–9). The magnitude and directionality of the association between impulsivity and obesity have been inconsistent (4, 10, 11). This inconsistency could be explained by different impulsivity measures and domains used across studies (4, 5, 11), and to weak effect sizes relating general impulsivity to BMI (12). Therefore, eating specific impulsivity questionnaires may better capture the vulnerability endophenotype.

Eating-specific impulsivity constructs include emotional eating (13), disinhibited eating (14) and power of food (15). Scores on all these questionnaires consistently and strongly correlate with BMI (4, 16) and with each other (17). Different eating behavior questionnaires may be depicting a common underlying latent factor for eating specific impulsivity (16, 18). This can be labelled uncontrolled eating (UE). While both general impulsivity traits and UE have been linked to

increased BMI, the relationships between different impulsivity domains, UE and obesity remain to be tested (i.e. some impulsivity traits might be associated with eating-specific impulsive behavior which in turn will be linked to BMI (11, 12, 19)). Statistically, if true, this hypothesis implies a complete mediation of general impulsivity traits on BMI via eating-specific impulsivity. However, so far, comprehensive models have not been built for all impulsivity domains and eating questionnaires, and have not been applied to the prediction of weight gain.

There is considerable overlap between the brain regions associated with obesity and the brain regions associated with impulsivity (10, 20, 21). Scores from both general impulsivity and conscientiousness scales are inversely correlated with the thickness of the lateral prefrontal cortex (PFC) (8, 22–25) - a region that has been related to cognitive control. Neuroticism is positively correlated with amygdala volume and negatively correlated with hippocampal volume and prefrontal cortex thickness (26–29). Extraversion and sensation seeking correlate positively with medial orbitofrontal cortex (mOFC) and ventromedial PFC (vmPFC) volume (8, 30, 31), a region associated with the computation of value (32). These results support a model where the impulsivity endophenotype might be mapped to the brain as reduced cortical thickness in the prefrontal cortex and increased gray matter volume in brain structures (e.g. amygdala, OFC, mPFC) associated with reward and value computation (33). Such a brain endophenotype has also been associated with obesity (4, 10, 21). Differences in brain morphometry and function might underlie differences in impulsivity and might thereby be associated with obesity.

If impulsivity (either general or eating-specific) is a risk factor for obesity, people with these risk endophenotypes will have higher BMI and will gain more weight compared to their peers with

non-risk endophenotypes. So far, most analyses have been conducted on cross-sectional datasets making it difficult to say if impulsivity is a risk factor or a consequence of obesity (4). The freshman year of university creates an ideal time period to test these hypotheses both cross-sectionally and longitudinally. During this time, students transition into a new environment with access to similar food and exercise options, allowing underlying vulnerability to express itself. Weight gain often happens in this short period of time and affects approximately 50-60% of students (34–40). Of the risk factors for weight gain, eating specific behaviors that revolve around the concept of impulsivity have been most commonly studied, but the results have been contradictory (38, 41–44).

We used structural brain imaging measures, general and eating-specific impulsivity questionnaires, and measures of BMI and weight gain in freshman students to test the hypothesis that the relationship between brain, impulsivity and obesity is hierarchical. We utilized a hierarchical statistical framework referred to as a 'watershed model' to study the relationship between impulsivity endophenotypes. This methodological framework has previously proven useful to study the relationships between age, brain structure and intelligence (2, 45, 46). From this perspective, brain structure will influence impulsivity measures which could affect eating-specific impulsivity (namely, UE) that is associated with over-eating. We predicted that UE would mediate the relationship between general impulsivity and BMI domains, and act as a risk factor for weight gain during the freshman year of university.

Methods and Materials

Participants

Participants were first year McGill university students, at least 18 years of age, recruited via an advertisement sent to the incoming class electronic mailing list. Participants provided their consent online and data were collected using the online survey tool LimeSurvey (https://www.limesurvey.org) over three consecutive years. The study was approved by the Montreal Neurological Institute Research Ethics Board. Participants for the brain imaging experiment gave additional consent before participating.

Questionnaires

Participants filled out the following online questionnaires: "Big Five" personality dimensions (Openness/ Imagination, Conscientiousness, Agreeableness, Extraversion, and Neuroticism) from the International Personality Item Pool (IPIP) (47), two subscales (lack of perseverance and sensation seeking) of the UPPS Impulsive Behavior Scale (48), Cohen's Perceived Stress Scale (PSS) (49), and Rosenberg Self Esteem Scale (50) as well as eating specific questionnaires such as the disinhibition subscale of Three-Factor Eating Questionnaire (TFEQ)(14), emotional eating subscale of Dutch Eating Behavior Questionnaires (DEBQ) (13), and all subscales of Power of Food Scale (PFS) (15) (Table 1). A subset (N=1145) of our initial population completed a follow-up questionnaire in the spring for longitudinal assessment. Our questionnaire included two "catch" questions and three "catch-match" questions as a measure of the level of participants' attention in completing the survey. Participants with total catch scores above three were excluded. An additional exclusion criterion was BMI under 15 or above 45, resulting in a sample of 2213 participants (Males N= 752; Females N= 1461). Only after completion of the

158 questionnaire, participants were asked to visit our laboratory to have their BMI measured in both
159 the fall and spring. BMI was measured from 333 participants in the fall, and from 209
160 participants in the spring semester (N =115 overlap with the fall group) using a medical scale and
161 a stadiometer. Reported BMI was highly correlated with measured BMI in the fall ($r = 0.91$,
162 $p<10^{-5}$) and in the spring ($r = 0.92$, $p<10^{-5}$). We replaced the reported BMI with measured BMI
163 in the analyses for higher accuracy. BMI was further residualized for age, sex and a covariate to
164 account for whether it was reported or measured. Brain imaging was conducted on a subset of
165 participants (N=72) selected from this sample in the fall.
166
167 Magnetic Resonance Imaging parameters and preprocessing
168 High-resolution T1-weighted anatomical images with voxel size = 1x1x1 mm were obtained (TR
169 = 2.3 s; TE = 2.98 ms; FOV phase=93.8°; FOV = 256mm) with a Siemens Magnetom Trio 3T
170 MRI scanner at the Montreal Neurological Institute (MNI).
171
172 Pre-processing of T1-weighted MRIs included denoising using optimized non-local means
173 filtering (51), correction for intensity inhomogeneity (52) and linear intensity scaling using
174 histogram matching to the ICBM-MNI152 template. The images were linearly registered to
175 ICBM-MNI152 template (9 parameter registration) (53). A mask of the brain was generated
176 using BEaST, a nonlocal segmentation method applied to the linearly registered images in
177 stereotaxic space (54).
178
179 Deformation Based Morphometry

Deformation Based Morphometry is utilized to calculate the local difference in tissue volume between subjects (55). Each MRI was non-linearly transformed to the stereotaxic ICBM-MNI152 template. The local deformation, a measure of tissue expansion or shrinkage, was then computed at each voxel. We utilized Deformation Based Morphometry as it is suggested to be the most sensitive morphometric method for studying subcortical anatomy (as explained in (56)).

Cortical Thickness

All T1-weighted MRI images were processed using the CIVET pipeline (version 2.1; http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET). Native T1-weighted MRI scans were first corrected using the N3 algorithm, underwent brain masking, and registration to ICBM-MNI152 template. Images were then segmented into gray matter (GM), white matter (WM), cerebrospinal fluid (CSF) and background using a neural net classifier. The white matter (inner) and gray matter (outer) cortical surfaces were extracted using the Constrained Laplacian-based Automated Segmentation with Proximities algorithm (CLASP). The resulting surfaces were resampled to a stereotaxic surface template to provide vertex-based measures of cortical thickness. All resulting images went through a stringent quality control by two inspectors in which 69 of 72 images were accepted for further analysis. Cortical thickness was then measured in MNI space using the linked distance between the two surfaces across vertices and a 20mm surface smoothing kernel was applied to the data. The Desikan–Killiany–Tourville (DKT) atlas was used to parcellate the surface into 64 cortical regions (57). Cortical thickness was averaged over all vertices (left and right) in each region of interest (ROI) for each subject. The subject mean cortical thickness was regressed out from the ROIs before further analysis.

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204 Factor Analysis

205 Factor analysis was carried out in order to (i) understand the shared variance of the measured
206 variables, which can be attributed to latent factor(s) and (ii) reduce the collinearity between the
207 questionnaire scores. The correlation matrix of the impulsivity traits is shown in Figure S2.
208 Questionnaire scores were z-scored for this group and entered into the factor analysis.
209 Exploratory Factor Analysis was carried out first in order to identify the underlying factor
210 structure of our set of observed variables. All of the statistical analyses are carried out in R
211 version 3.3 (58).To account for missing values, we used the R "Amelia" library to impute data
212 (59). We conducted our exploratory factor analysis on the split half of our population of 2213
213 participants (N=1107) to create our model. Factor selection was conducted using parallel
214 analysis via the fa.parallel function from the Psych package in R (60). The generated pattern
215 matrix of standardized loadings suggested the existence of a 3-factor latent structure (Table S1).

216

217 Afterwards, confirmatory factor analysis (CFA) was utilized to test the relationship between our
218 observed variables and their underlying latent factors in both split-halves of the sample (61). All
219 structural equation models were fit using package Lavaan 0.5 (62). BMI was log transformed to
220 increase normality. Models were fit using full information maximum likelihood (FIML) using
221 robust standard errors. Model fit was assessed with the chi-square test (X^2), the Comparative Fit
222 index (CFI), Root Mean Square Error of Approximation (RMSEA) and the standardized root
223 mean squared residuals (SRMR). The following guidelines were utilized for judging good fit:
224 CFI>0.95; RMSEA<0.08 and SRMR <0.10 (63). The hierarchical relationship between
225 impulsivity, UE and BMI was tested using the watershed framework (see supplementary

material, also explained in (46)). Only variables that survived multiple comparisons with False Discovery Rate (FDR) are displayed as significant. The *p* values reported are FDR corrected.

Results

Eating-specific impulsivity factor uncontrolled eating is correlated with BMI

Participant characteristics are listed in Table 1. We first tested if UE emerged as a latent factor that captures the covariance between the eating questionnaires, namely Disinhibition (TFEQ), Power of Food, and Emotional Eating (DEBQ) (Figure 1-A). We created the model in the first split-half sample, and verified it in the second split-half. Both models resulted in good fits and returned similar loadings (Table S2). Following the best practices in structural equation modeling (64), here we report our model in the full sample. A single factor confirmatory factor analysis for UE provided a good fit for our data. Figure 1-B shows that UE correlated with BMI ($ß = 0.37$, $p<10^{-5}$) and explained 9.2% of the variance in BMI ($F(1, 2206) = 223.7$, $p<10^{-5}$).

General impulsivity traits can be explained with a three-factor latent structure and are correlated with BMI

We next tested the relationship between general impulsivity measures and UE and BMI. A data driven exploratory factor analysis in a split-half of the data suggested a three-factor latent factor structure for impulsivity traits (Table S1). The first factor had a negative loading from the Rosenberg self-esteem questionnaire and positive loadings from Neuroticism (IPIP) and the Perceived Stress Scale (PSS). We labelled this factor 'Stress Reactivity (STRESS)'. The second factor had a positive loading from Lack of Perseverance (UPPS) and a negative loading from Conscientiousness (IPIP). We labelled this latent factor 'Lack of Self Control'. The third factor

was named 'Reward Sensitivity' (REWARD) and it was characterized by positive loadings from the Extraversion (IPIP) and Sensation Seeking (UPPS) subscales (Table 1). We next tested if these general impulsivity domains were associated with BMI. Using confirmatory factor analysis, we showed that there is a small but significant correlation between STRESS and BMI (β = 0.08, p=0.028), and REWARD and BMI (β=0.09, p = 0.028) (Figure 1-C).

The relationship between general impulsivity, uncontrolled eating, and BMI

General impulsivity traits might exert their effects on BMI via UE, eating-specific impulsivity. To test this, we fit the full watershed model integrating the general impulsivity latent factors, the UE latent factor and BMI (Figure 1-D). Our model satisfied the predictions of the watershed model (46, see supplementary materials). These results showed that the relationship between general impulsivity, UE and BMI is hierarchical. Furthermore, our watershed model was selective for eating behaviors. For example, when alcohol intake (i.e. how many alcoholic beverages do you consume a week?) was utilized as the outcome variable in the watershed model, general impulsivity factors, but not UE, explained 25.6% of the variance in alcohol intake (Figure S3).

UE mediates the relationship of stress reactivity and reward sensitivity to BMI

We additionally utilized mediation analysis to test if UE mediates the relationships between STRESS and BMI and REWARD and BMI. Using the structural equation model framework, we simultaneously modelled two pathways: UE mediates (i) the effect of REWARD on BMI and (ii) the effect of STRESS on BMI. The analysis confirmed that the effects of STRESS and REWARD on BMI were mediated by UE (76% mediation; Figure 2; Table S3).

Prefrontal and subcortical brain structures are associated with impulsivity traits

We hypothesized that structural brain measures might be related to the latent impulsivity factors. To test this hypothesis, we included brain regions that have been linked to impulsivity traits and obesity in the full model. Cortical regions were measured using cortical thickness (CT) and anatomical differences in subcortical regions were measured using deformation-based morphometry. We found that STRESS was positively associated with amygdala volume (β = 0.29, p = 0.035) and inversely with hippocampal volume (β = -0.33, p = 0.021) and lateral OFC thickness (β = -0.31, p = 0.035). Lack of self-control inversely correlated with lateral OFC cortical thickness (β = -0.33, p = 0.041). Independent of these relationships, superior frontal gyrus thickness inversely correlated with BMI (β = -0.38, p = 0.014).

Longitudinal Predictors of Weight Gain

We next looked for predictors of change in body weight in the first year of university (Figure 4-A). Our results revealed that students gained on average 0.51 kg (SD ± = 3.22) in the first year of university (August/September to April/May), which is a small but significant effect (t = 5.4, df = 1133, p-value = $p<10^{-5}$, %95 CI = 0.32-0.68). We utilized percent BMI change as the outcome variable to account for the initial BMI. Our model explained 1.5 % of the variance in percent BMI change (Figure 4-A). According to our model, UE did not significantly predict BMI change in this sample (β = 0.03, p = 0.57) . Among the impulsivity factors, Lack of Self Control predicted weight change (β = 0.10, p = 0.028), while stress reactivity predicted weight loss (β = -0.13, p = 0.028). A post-hoc regression analysis of the relationship between stress reactivity and weight change revealed that this negative correlation was driven by males. In male students,

295 STRESS explained 2% of the variance in weight reduction (β = - 0.17, p = 0.0053, N= 360, R^2 =
296 0.02). No significant correlation emerged for female students (β = - 0.061, p = 0.15, N = 788, R^2
297 = 0.001) (Figure 4-B).
298
299 **Discussion**
300 The purpose of the current study was twofold (i) to provide a comprehensive link between brain
301 structure, impulsivity and obesity, and (ii) to characterize the temporal relationship between
302 impulsivity and weight changes. We utilized a large sample size (N>2000) of first-year students
303 and accounted for the multidimensional nature of impulsivity to study these relationships. The
304 models were developed in the first split-half of the sample and replicated in the second.
305
306 We first stratified impulsivity into two domains: general and eating-specific, and then tested the
307 relationship between these two domains. We showed that the variance of different eating-specific
308 questionnaires can be captured by a general underlying latent factor (UE). UE had a strong
309 relationship to BMI. This result was consistent with previous studies suggesting that different
310 food questionnaires are measuring different severity levels of a common latent factor: eating-
311 specific impulsivity (16, 18). Next, we demonstrated that the commonly used general impulsivity
312 questionnaires can be explained in a three-factor structure that align with the general personality
313 domains of neuroticism (stress sensitivity), conscientiousness (self-control), and extraversion
314 (reward sensitivity) (Figure 1-C). This result is in agreement with the previously published meta-
315 analysis of impulsivity factor structure (5), and highlights the multifaceted nature of impulsivity.
316

We hypothesized that people with general impulsivity traits might also exhibit eating-specific impulsivity, and that the relationship between general personality domains, UE and BMI would be hierarchical. Using the hierarchical watershed model, we first showed that each general impulsivity domain had an independent and positive correlation with UE (Figure 1-D). While stress reactivity and reward sensitivity weakly correlated with BMI, we showed that this was mediated by UE (Figure 2). This mediation was specific for BMI. For example, increased scores in each general impulsivity domain, but not UE, were linked to increased alcohol intake (Figure S3). This suggests eating-specific impulsivity (UE) captures the relationship between impulsivity and obesity.

Differences in brain structure might underlie differences in impulsivity domains (20). We next tested if brain morphometry related to impulsivity or if it had an independent correlation with BMI. Our results showed that cortical thickness in lateral OFC is inversely related to the self-control and stress reactivity latent factor scores (Figure 3). This is in line of the role of lateral OFC in maintaining goal-oriented focus by suppressing irrelevant information (65–67). Furthermore, lateral OFC and its neighboring ventrolateral PFC have also been implicated in emotional regulation, particularly in the reduction of negative affect (66, 68, 69). Lateral OFC thickness has been shown to be lower in adults with obesity (70). Our results add to this literature and suggest that reduced lateral OFC thickness might affect impulsivity and thereby appetite control and obesity.

Both amygdala and hippocampus have been implicated in the control of food intake as well as in stress reactivity (71–74). In this study we showed that a personality dimension related to stress

reactivity was associated with greater amygdala volume and lower hippocampal volume, consistent with previous reports (26, 27, 75). Our results suggest that differences in amygdala and hippocampal volumes might relate to increased stress reactivity which can lead to UE and obesity. Independent of these relationships, we showed that superior frontal gyrus thickness was inversely related to BMI consistent with the literature (70, 76, 77). This suggests that some brain regions might be important in overeating and obesity independent of impulsivity.

Finally, we tested the hypothesis UE underlies vulnerability for weight gain. We utilized the transition period into university that is associated with high risk of weight gain to study this hypothesis. In our sample, the average weight gain was small, but significant, and was similar to previously reported studies (40). However, in this sample we failed to find that UE was a predictor of weight gain. This could be due to limited duration of the study. Furthermore, the directionality of the UE-BMI relationship could contribute to this result: changes in body weight might lead to longitudinal variations in eating-specific impulsivity. For instance, scores in different uncontrolled eating scales decrease after bariatric surgery (78–81) or voluntary weight loss (82, 83). In this study, weight changes correlated with changes in disinhibition score from TFEQ (has the highest loading UE) between spring and fall semesters ($\beta = 0.088$, $p = 0.02$, $N = 660$), supporting this view.

Our results support a model in which weight gain results from lack of self-control. Upon transitioning into a new environment, difficulties in self-control could compromise the maintenance of behaviors that promote healthy weight. High scores on conscientiousness have been consistently linked to a lower risk of having and developing obesity across independent

363 samples (84, 85). These results are generally derived from sample populations with a higher
364 mean age than ours, suggesting that self-control deficits may be more associated with BMI as
365 individuals age and start making their own food decision. Our findings thus point to self-control
366 deficits as risk factors for future weight gain in young populations.
367
368 Higher stress reactivity correlated with longitudinal weight loss in our study. This result is
369 surprising, and yet, it is consistent with the existence of bidirectional effects of stress on eating
370 behaviors. Stress is associated both with weight-gain and weight-loss longitudinally (86, 87).
371 This bidirectional relationship might be partly mediated by sex differences, since there seem to
372 be biological and psychological variations in stress responses among sexes (88). Male
373 participants that report distress at the transition from high school to university tend to lose weight
374 (89) and decrease their food intake compared to female participants (90). In a similar vein, our
375 post hoc analysis revealed that stress reactivity was associated with weight loss only in male
376 students. Conversely, the stress reactive endophenotype was associated with higher BMI,
377 possibly due to differences in the effects of chronic versus acute stress on appetite and weight
378 gain (91).
379
380 The results of our study should be considered with regards to its limitations. Although we had a
381 large sample group, whereby we were able to detect and replicate results from meta-analyses,
382 most of our measures were self-reported. In addition, brain imaging was conducted with a
383 smaller subset from the sample. Therefore, the relationship between impulsivity and brain
384 morphometry were only tested in regions of interest based on the literature. This limits the
385 generalizability of the brain imaging results.

386

387 ***Conclusions***

388 The present study provides a comprehensive characterization of the relationships between
389 different facets of impulsivity and obesity. We show that structural brain differences relate to
390 differences in impulsivity domains which affect BMI via eating-specific impulsivity (UE).
391 However, predictors of weight gain, at least in the short-term, are different than the risk factors
392 associated with increased BMI. Deficits in self-control, not UE, predict longitudinal weight gain,
393 while higher stress reactivity predicts weight loss in the first year of university (in males). These
394 findings highlight the role of self-control deficits in longitudinal weight gain. Our results might
395 inform future clinical strategies aimed at fostering self-control abilities to prevent and/or treat
396 unhealthy weight gain.

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665 **Table 1. Descriptive statistics of the study variables.**

666 2214 Students (34% Males) filled the questionnaires in the fall semester. Out of the 2214
667 students, 1145 answered the questionnaires in the spring. There were no significant
668 differences in the variables of interest between participants who completed only fall and
669 who completed both fall and spring questionnaires (Figure S1). Paired t-tests revealed that
670 BMI in the spring (mean difference 0.15 kg/m^2; t = 4.40, p-value = $1.5*10^{-5}$, 95% Cl: 0.08 -
671 0.22) and weight in the spring (mean difference 0.51 kg; t = 5.32, p< 10^{-5}, 95% Cl: 0.32 -
672 0.70) were significantly different from the fall values. 95% Cl refer to 95 percent
673 confidence intervals. UE: Uncontrolled Eating.

674

Variables	Mean	SD (±)	min	max
Age	19.8	3.4	18.0	52.0
BMI (kg/m^2)	22.2	3.4	15.5	42.8
Spring BMI (kg/m^2)	22.3	3.3	14.7	44.3
Disinhibition (Three-Factor Eating Questionnaire (14))	6.4	3.4	0.0	16.0
Emotional Eating (Dutch Eating Behavior Questionnaire (13))	2.5	0.7	1.0	4.8
Power of Food (PFS) (15)	12.4	3.7	5.0	25.0
Lack of Perseverance (the UPPS Impulsive Behavior Scale (48))	1.9	0.4	1.0	3.7
Sensation Seeking (the UPPS Impulsive Behavior Scale (48))	2.8	0.6	1.0	4.0
Rosenberg Self Esteem (50)	29.9	5.0	13.0	40.0
Cohen's Perceived Stress Scale (49)	24.5	7.2	2.0	52.0

Neuroticism (International Personality Item Pool (47))	11.6	2.9	4.0	20.0
Agreeableness (International Personality Item Pool(47))	15.6	2.8	4.0	20.0
Imagination (International Personality Item Pool(47))	15.2	2.7	4.0	20.0
Conscientiousness (International Personality Item Pool (47))	14.0	2.9	4.0	20.0
Extraversion (International Personality Item Pool(47))	12.1	3.5	4.0	20.0
Change in weight in first year (kg)	0.51	3.22	-13.0	15.0

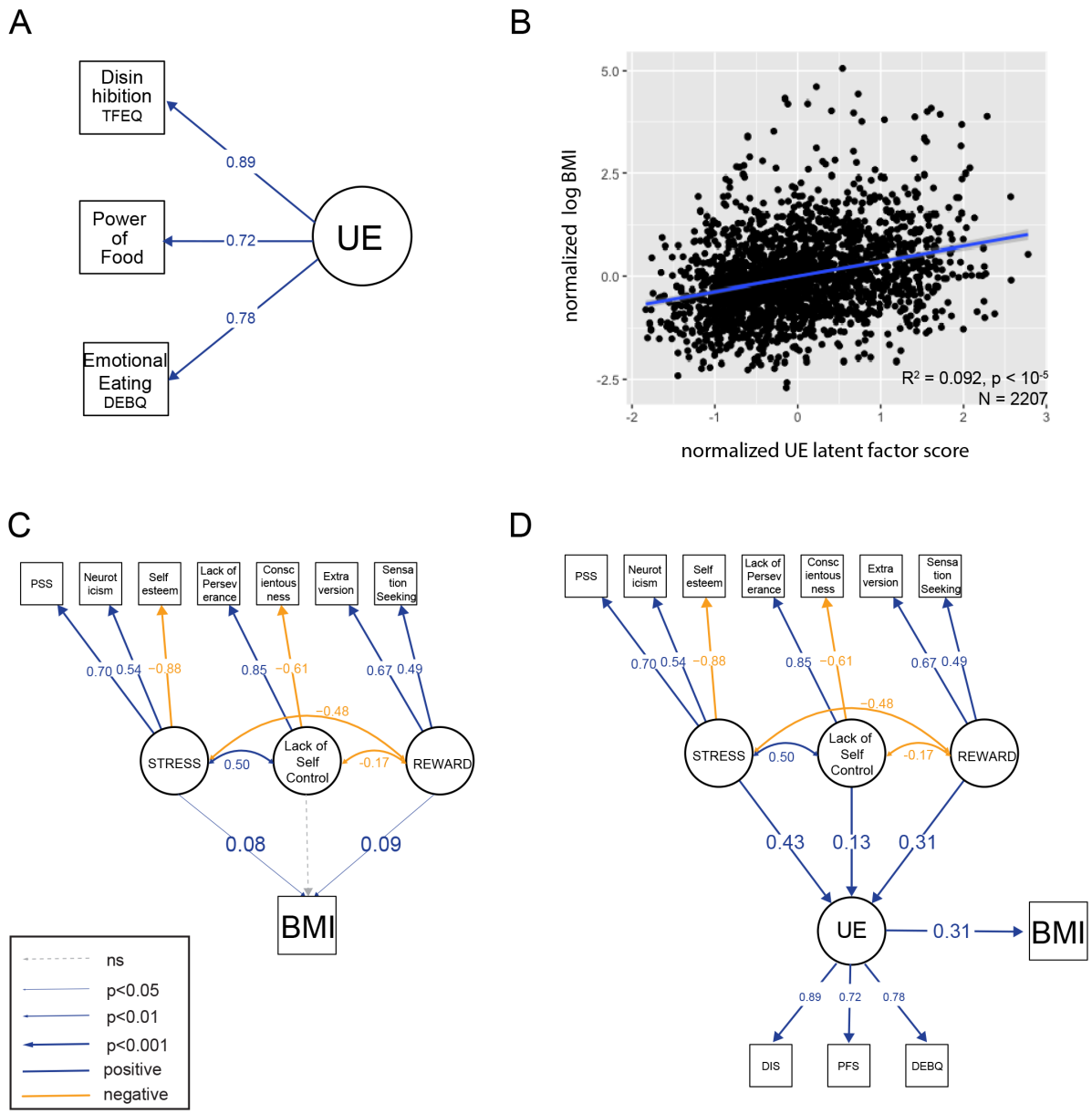
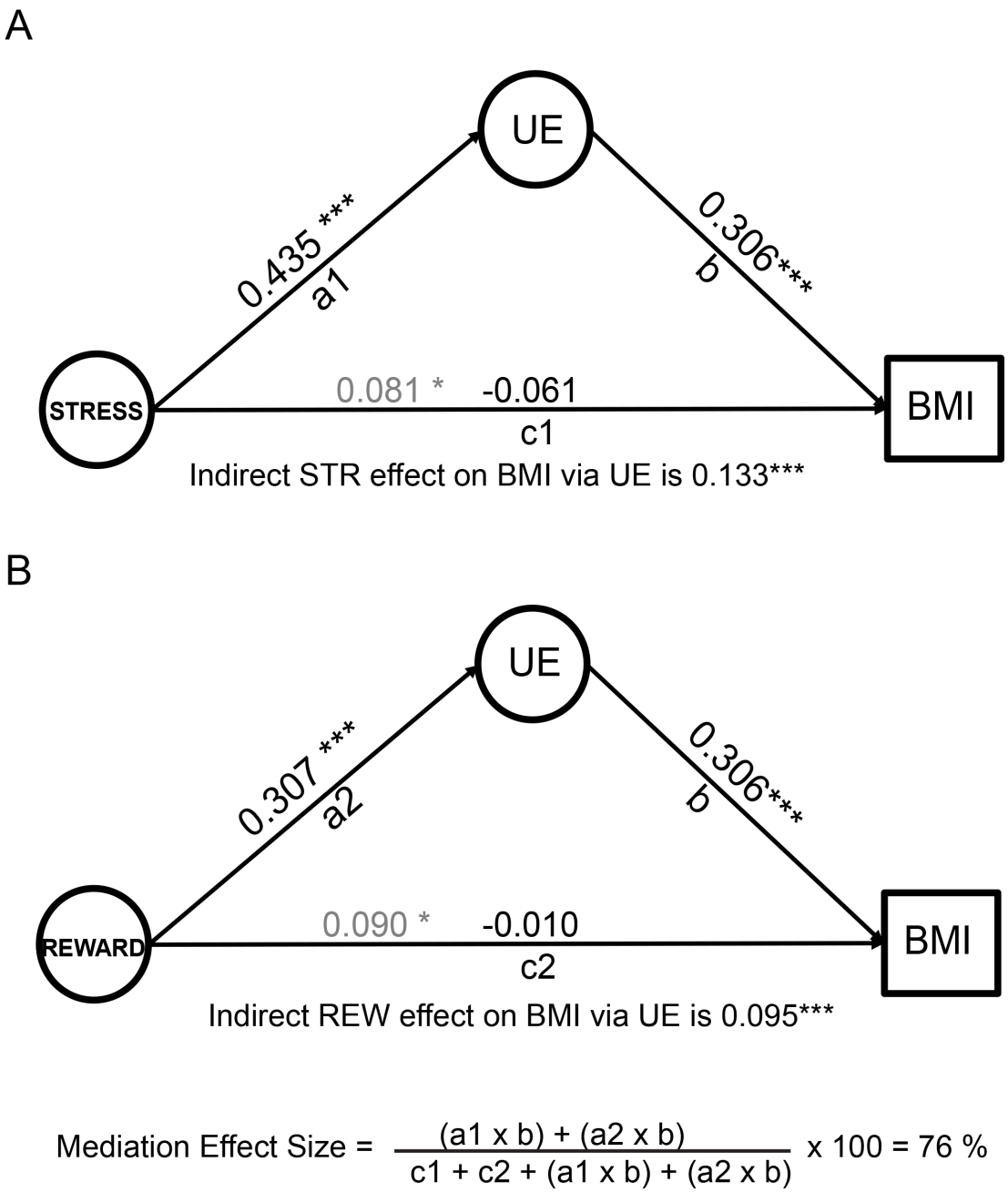


Figure 1. Eating-specific impulsivity UE correlates with general impulsivity traits and with BMI. A) A single-factor confirmatory factor analysis for uncontrolled eating fits the data well (X^2=30.28, df=4, p<.001, CFI=.992, RMSEA=.054, SRMR=.015). B) Linear fit of UE with log BMI. C) Confirmatory factor analysis analysis of impulsivity traits with three latent factors fit the data well (X^2=147.277, df=14, p<.001, CFI=.963, RMSEA=.066, SRMR=.03). After multiple comparison correction, STRESS and REWARD are weakly correlated with BMI. D) The full watershed model that links general impulsivity traits to UE and UE to BMI fits the data

well. (X^2=328.03, df=34, p<.001, CFI=.957, RMSEA=.063, SRMR=.035) REWARD: Reward Sensitivity; STRESS: Stress Reactivity; UE: Uncontrolled Eating. B-D represent normalized scores that have been residualized for age and sex. DEBQ: Emotional eating from DEBQ scale; DIS: Disinhibition from TFEQ; PFS: Power of Food Scale; PSS: Perceived Stress Scale; Self-esteem: Rosenberg Self Esteem Scale. Significant relationships after FDR correction for multiple comparisons are shown in blue or yellow based on the directionality of the relationship.



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722 **Figure 2. Mediation model for BMI.** The mediation model tests the hypothesis that the effect
723 of general personality traits- STRESS and REWARD- on BMI is mediated by UE. In mediation
724 models, there are three paths, a, b and c, between the variables. Full mediation will result in the
725 direct relationship between the independent variable and the dependent variable (path c) to
726 become insignificant when taking the mediator into account (path a). The mediation models were

fit together in structural equation model framework but displayed on separate figures as A and B. REWARD: Reward Sensitivity; STRESS: Stress Reactivity; UE: Uncontrolled Eating. Gray numbers represent the regression coefficients between general impulsivity traits and BMI without UE as shown in Figure 1-C. *P<0.05, **P<0.01, ***P<0.001.

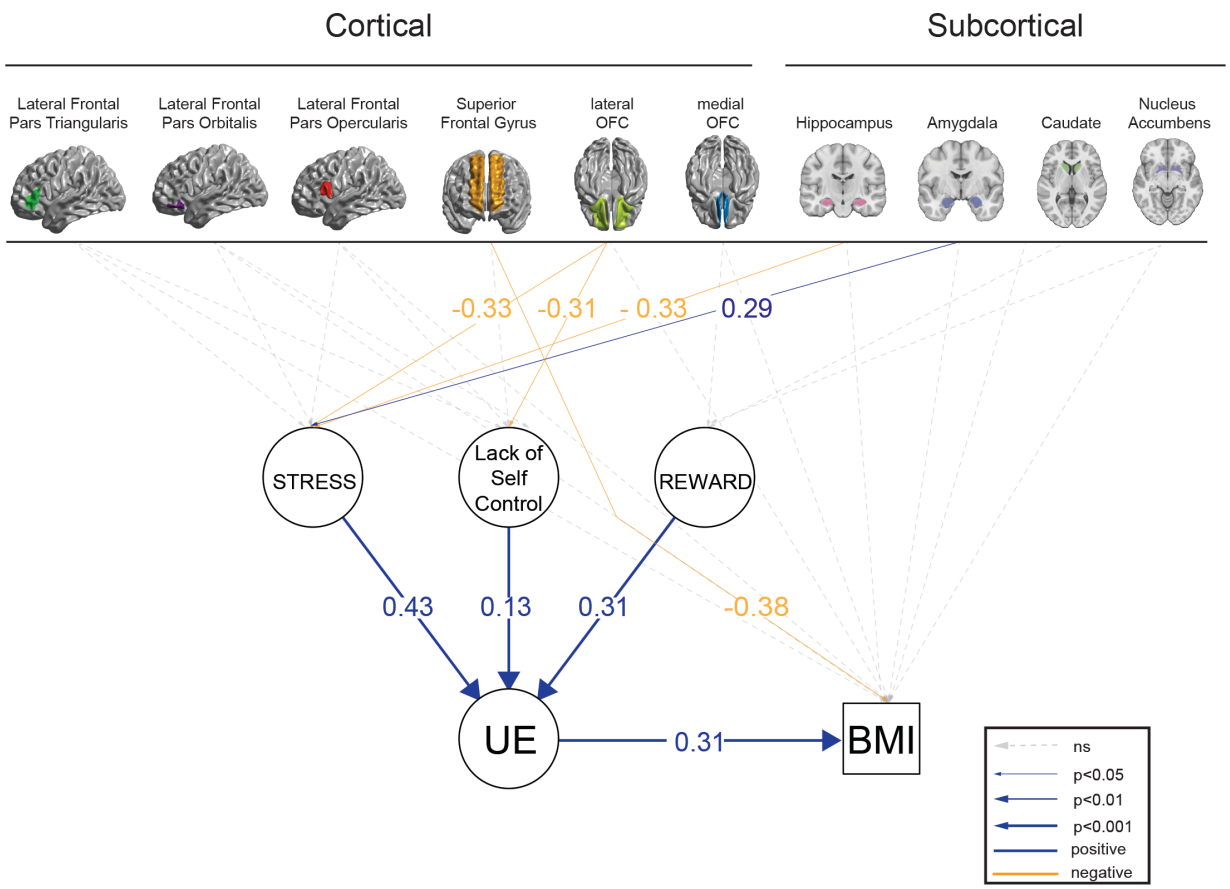
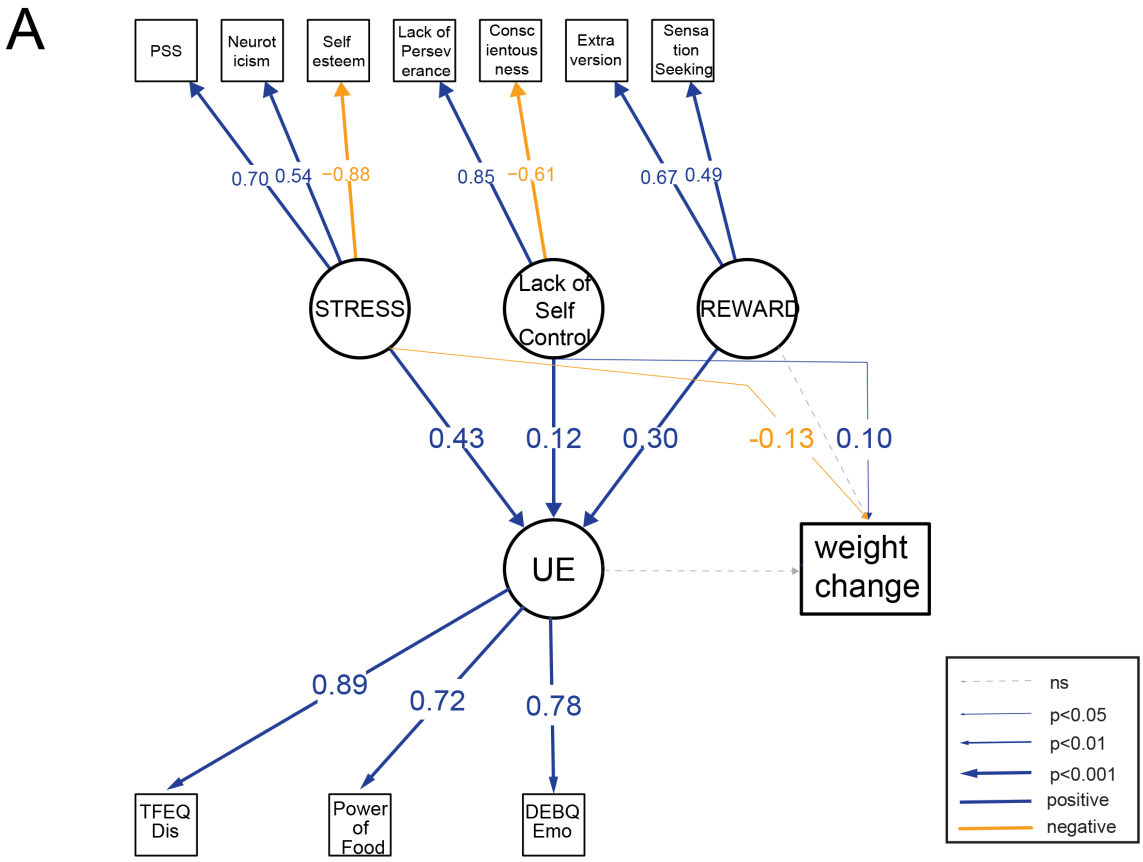


Figure 3. The full watershed model with structural brain parameters. This model fits the data well (X^2= 440.485, df=120, p<.001, CFI=.954, RMSEA=.035, SRMR=.07). All of the numbers shown reflect parameters that are standardized and residualized for age and sex. The correlations within the latent factors and within the brain parameters are allowed but not shown for simplicity. Significant relationships after FDR correction for multiple comparisons are shown in blue or yellow based on the directionality of the relationship. Dashed lines represent tested nonsignificant regressions. REWARD: Reward Sensitivity; STRESS: Stress Reactivity; UE: Uncontrolled Eating.



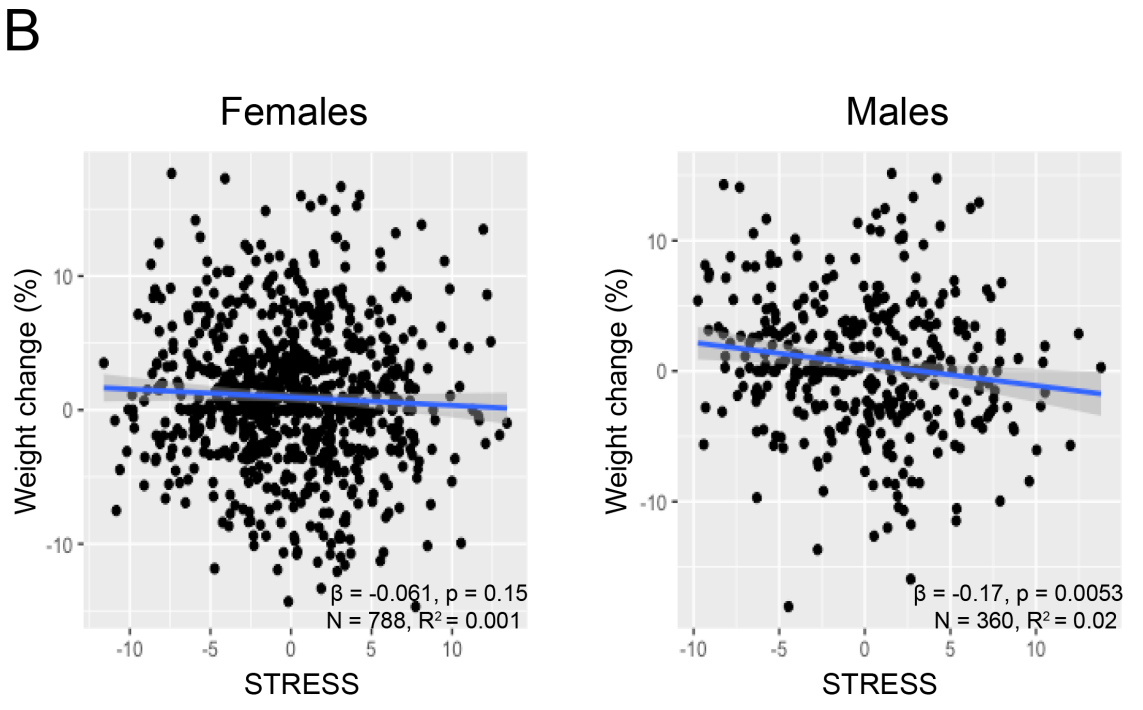


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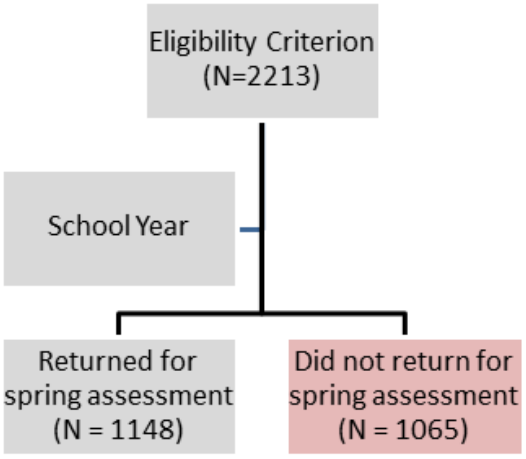
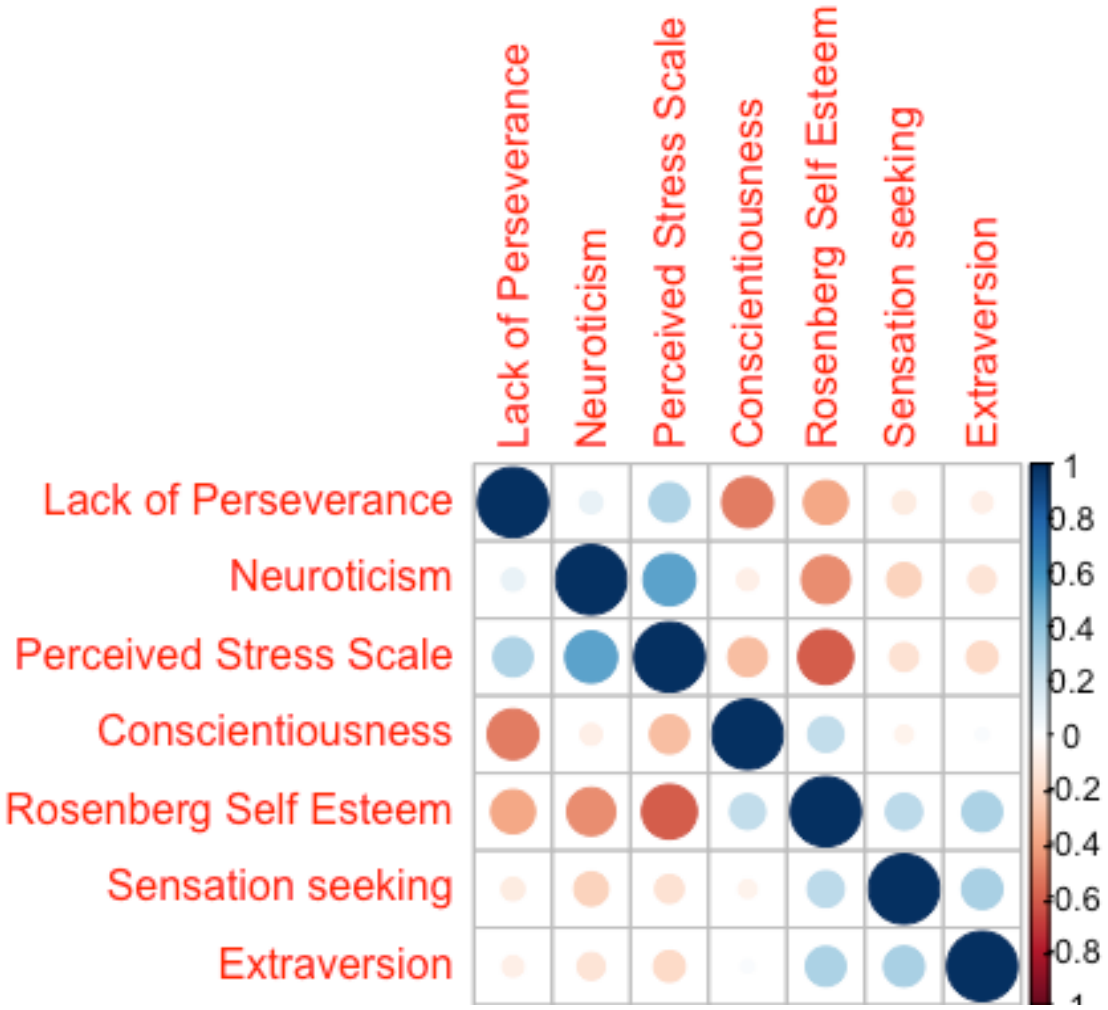
Figure 4. Predictors of weight gain in first year university students. A) This model represents the whole watershed model with percent BMI change as the outcome variable in (N = 1134). The data fits this model well (X^2=124.855, df=34, p<.001, CFI=.972, RMSEA=.048, SRMR=.03). All of the numbers shown reflect parameters that are standardized and residualized for age and sex. Significant relationships after FDR correction for multiple comparisons are shown in blue or yellow based on the directionality of the relationship. B) Regression analysis of STRESS endophenotype with weight change is only significant in male students. Raw data is plotted in panel B. UE: Uncontrolled Eating; STRESS: Stress Reactivity; REWARD: Reward Sensitivity.

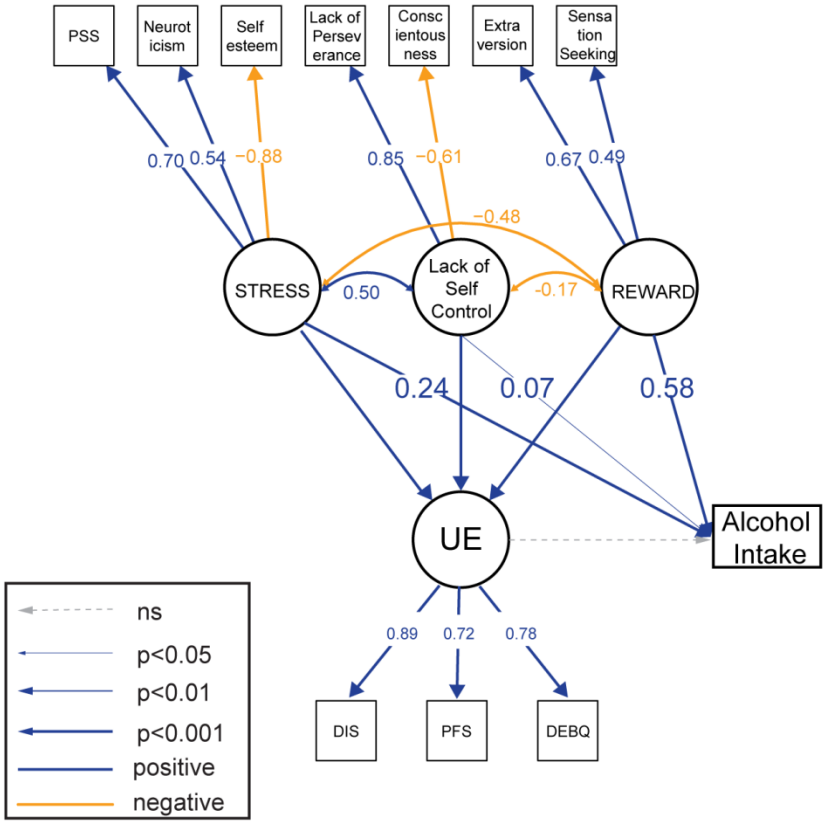


	Mean	SD (+/-)	Mean	SD (+/-)	p
Age	19.7	3.4	19.9	3.4	0.65
BMI (kg/m^2)	22.2	3.3	22.3	3.6	0.65
Disinhibition (from TFEQ)	6.4	3.4	6.4	3.2	0.99
Emotional Eating (from DEBQ)	2.4	0.8	2.5	0.7	0.11
Power of Food (PFS)	12.4	3.8	12.3	3.5	0.89
Lack of Perseverance (from UPPS)	1.9	0.5	1.9	0.4	0.89
Sensation Seeking (from UPPS)	2.8	0.6	2.8	0.5	0.89
Rosenberg Self Esteem (RES)	29.7	5.3	30.1	4.6	0.23
Perceived Stress Scale (PSS)	24.8	7.4	24.2	6.9	0.23
Neuroticism (from IPIP)	11.6	3.2	11.7	2.7	0.65
Agreeableness (from IPIP)	15.7	3.0	15.5	2.6	0.65
Imagination (from IPIP)	15.2	2.9	15.2	2.5	0.98
Conscientiousness (from IPIP)	14.0	3.2	14.0	2.7	0.98
Extraversion (from IPIP)	11.9	3.7	12.2	3.3	0.11

Supplementary Figure 1. Descriptive statistics of participants who completed only the first session in the fall and who completed both sessions. There were no significant differences in the variables of interest between participants between these groups after FDR correction.



Supplementary Figure 2. Correlation plot of the impulsivity traits used in the exploratory factor analysis. Blue colors refer to positive correlations, red refer to negative correlations. The size of the circle is modulated by the correlation coefficient value. The correlation is shown only for the split half of the data.



Supplementary Figure 3. Uncontrolled eating does not correlate with alcohol intake.

The full watershed model that links general impulsivity traits to UE and alcohol fits the data well (X^2=242.058, df=43, p<.001, CFI=.971, RMSEA=.046, SRMR=.032). This model explains 25.6 % of the variance in reported alcoholic beverages consumption per week. All of the numbers shown reflect parameters that are fully standardized and residualized for age and sex. Significant relationships after FDR correction for multiple comparisons are shown in blue or yellow based on t

he directionality of the relationship. UE: Uncontrolled Eating; STRESS: Stress Reactivity; REWARD: Reward Sensitivity.

Supplementary Table 1. Results of the exploratory factor analysis.

Parallel analysis is a technique that compares the scree plot of the observed data with that of a random data matrix of the same size as the original (Revelle). Sharp breaks in the scree plot, which plots successive eigenvalues, provide an estimation of the appropriate number of factors to extract. After analyzing the generated pattern matrix, we decided to exclude Imagination, Restraint, Agreeableness from our factor structure. These variables had poor communalities, meaning our factor structure explained a relatively low fraction of the variance for these variables. Re-running our parallel analysis suggested that the optimal number of factors = 3.

```
Parallel analysis suggests that the number of factors = 3
```

```
Factor Analysis using method =  minres
Call: fa(r = r, nfactors = 3, n.obs = nrow(means))
Standardized loadings (pattern matrix) based upon correlation matrix

                        item   MR1   MR2   MR3   h2   u2 com
Perceived Stress Scale     7  0.85             0.73 0.27 1.0
Neuroticism                6  0.70             0.46 0.54 1.1
Rosenberg Self Esteem      3 -0.56             0.60 0.40 1.6
Lack of Perseverance       1       -0.84       0.70 0.30 1.0
Conscientiousness          5        0.60       0.43 0.57 1.3
Sensation seeking          2              0.62 0.39 0.61 1.0
Extraversion               4              0.50 0.27 0.73 1.0
```

```
                        MR1  MR2  MR3
SS loadings           1.62 1.17 0.78
Proportion Var        0.23 0.17 0.11
Cumulative Var        0.23 0.40 0.51
Proportion Explained  0.45 0.33 0.22
Cumulative Proportion 0.45 0.78 1.00

 With factor correlations of
      MR1   MR2   MR3
MR1  1.00 -0.39 -0.36
MR2 -0.39  1.00  0.11
MR3 -0.36  0.11  1.00

Tucker Lewis Index of factoring reliability =  0.889
RMSEA index =  0.094  and the 90 % confidence intervals are  0.066 0.124
BIC =  10.88
Fit based upon off diagonal values = 1
Measures of factor score adequacy
```

Supplementary Table 2. Values from the CFA analysis of uncontrolled eating (UE) in the first and second split half of the sample.

	X^2	df	P value	CFI	RMSEA	SRMR
UE1	11.83	4	0.019	0.995	0.042	0.014
UE2	19.32	4	0.001	0.990	0.059	0.017

Supplementary Table 3. Mediation Analysis Results

```
lavaan (0.5-23.1097) converged normally after  43 iterations

                                                  Used       Total
  Number of observations                          2208        2213

  Number of missing patterns                         2

  Estimator                                         ML
  Minimum Function Test Statistic               328.032
  Degrees of freedom                                34
  P-value (Chi-square)                           0.000

Parameter Estimates:

  Information                                 Observed
  Standard Errors                             Standard

Latent Variables:
                   Estimate  Std.Err  z-value  P(>|z|)   Std.lv  Std.all
  STRESS =~
    PSS               1.000                               0.691    0.702
    Neuroticism       0.736    0.029   25.789    0.000    0.509    0.533
    Rosenberg        -1.248    0.054  -23.236    0.000   -0.863   -0.883
  Lack of Self Control =~
```

```
    Lack of Persever   1.000                                    0.830    0.846
     Conscientiousness -0.726    0.049  -14.704    0.000   -0.603   -0.609
  REWARD =~
     Extraversion       1.000                                    0.675    0.677
     SensationSeeking   0.701    0.064   10.987    0.000    0.473    0.492
  UE =~
     Disinhibition      1.000                                    0.845    0.886
     PFST               0.820    0.024   33.882    0.000    0.693    0.721
     DEBQ               0.864    0.024   36.314    0.000    0.730    0.780

Regressions:
                   Estimate  Std.Err  z-value  P(>|z|)   Std.lv  Std.all
  UE ~
     STRESS    (a1)    0.526    0.051   10.286    0.000    0.430    0.430
     LackofSC          0.140    0.035    4.034    0.000    0.137    0.137
     REWARD    (a2)    0.385    0.058    6.627    0.000    0.308    0.308
  logBMI ~
     STRESS    (c1)   -0.085    0.055   -1.555    0.120   -0.059   -0.061
     LackofSC         -0.025    0.034   -0.724    0.469   -0.021   -0.021
     REWARD    (c2)   -0.014    0.055   -0.257    0.797   -0.010   -0.010
     UE         (b)    0.352    0.031   11.289    0.000    0.297    0.309


Mediation  Parameters:
                     Estimate  Std.Err  z-value  P(>|z|)   Std.lv  Std.all
```

STRESS to BMI (a1)	-0.085	0.055	-1.555	0.120	-0.059	-0.061
REWARD to BMI (a2)	-0.014	0.055	-0.257	0.797	-0.010	-0.010
STRESS via UE (c1)	0.185	0.025	7.449	0.000	0.128	0.133
REWARD via UE (c2)	0.136	0.024	5.599	0.000	0.091	0.095
total effect	0.221	0.093	2.387	0.017	0.151	0.157
mediation effect	0.763	0.026	29.443	0.000	0.762	0.762

Watershed model

In order to study the endophenotypes that related to BMI in a watershed model, we needed to statistically satisfy three major criteria (as explained in 1, 2). 1) Higher statistical dimensionality

between upstream variables compared with downstream variables. The statistical dimensionality of the covariance pattern between all variables will increase as we move upstream in the model. The result will be that the upstream effects (i.e. brain or personality traits) cannot be fully captured by a single summary statistic. We tried to capture our cortical thickness variables as a single latent factor (not shown), but this model had a poor fit suggesting that upstream brain variables cannot be reduced to a single dimension. In addition, general impulsivity traits were only captured using three factors as opposed to one latent factor. Furthermore, the upstream effects were partially independent: all of the endophenotypes (i.e. STRESS, Lack of Self Control, REWARD) did better than each individual endophenotype (e.g. STRESS) in predicting the downstream outcome (i.e. UE). 2) Multiple realisability. According to the watershed model, there are multiple precursory causes for a complex endophenotype. In other words, a single behavioural dimension such as UE is likely to have multiple neural determinants. In an SEM framework, this means the variability in each endophenotype (i.e. STRESS, Lack of Self Control, REWARD) will make partially independent contributions to variability in UE endophenotype. 3) Hierarchical dependence. The watershed model should exhibit a hierarchical dependence. That means statistically there should be no residual, or direct, relationships between levels. In the present context this implies that the influence of general personality variables on BMI will be indirect, namely through UE. In the SEM formalization of this hypothesis, any direct paths between general impulsivity domains and BMI will be a source of model misfit, and mediation analysis will reveal either partial or no mediation.

1. Kievit RA, Davis SW, Griffiths J, Correia MM, Cam-Can, Henson RN (2016): A watershed model of individual differences in fluid intelligence. *Neuropsychologia*. 91: 186–198.

2. Kievit RA, Davis SW, Mitchell DJ, Taylor JR, Duncan J, Tyler LK, *et al.* (2014): Distinct

aspects of frontal lobe structure mediate age-related differences in fluid intelligence and multitasking. *Nat Commun*. 5: 5658.