Title: Elevated Body Mass Index is associated with reduced integration of sensory-driven with internally-guided resting-state functional brain networks

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Running title: Effect of body mass index on brain functional organization

Abstract

Elevated body mass index (BMI) is associated with increased multi-morbidity and mortality. The investigation of the relationship between BMI and brain organization has the potential to provide new insights relevant to clinical and policy strategies for weight control. Here, we quantified the association between increasing BMI and the functional organization of resting-state brain networks in a sample of 496 healthy individuals that were studied as part of the Human Connectome Project. We demonstrated that higher BMI was associated with dysconnectivity of the Default-Mode (DMN), Central Executive (CEN), Sensorimotor (SMN) and Visual (VN) Networks and their constituent modules. In siblings discordant for obesity, we showed that person-specific factors contributing to obesity are linked to compromised cohesiveness of the sensory networks (SMN and VN). We conclude that higher BMI is associated with widespread disruption in brain networks that balance sensory-driven (SMN, VN) and internally-guided states (DMN, CEN) which may augment sensory driven behavior leading to overeating and subsequent weight gain. Our results suggest the need for wider societal policies that incorporate modifications to eating environments (including exposure and proximity to food) and to the visual presentation and branding of food products.

Keywords: body mass index, brain networks, functional connectivity, resting-state, siblings.

Introduction

The prevalence of overweight and obesity is increasing worldwide (Ng M et al. 2014). This is concerning because overweight, as measured by the Body Mass Index (BMI; the weight in kilograms divided by the square of the height in meters), is reliably associated with increased morbidity and all-cause mortality (Aune D et al. 2016). The rise in BMI has been attributed to multiple interacting factors relating to the increased availability of calorie dense food (Chandon P and B Wansink 2011; Egger G et al. 2012) and to genetic (Curran JE et al. 2013; Locke AE et al. 2015) and neurobiological mechanisms (Ziauddeen H et al. 2012; Vainik U et al. 2013) that regulate individual behavior. BMI shows significant heritability, estimated between 0.58 and 0.87 (Elks CE et al. 2012; Min J et al. 2013). However, the familial contribution to BMI reduces over the lifespan (Silventoinen K and J Kaprio 2009) and person-specific factors account for nearly half of the variance in BMI changes during adulthood (Romeis JC et al. 2004). Behavioral evidence suggests that higher BMI is associated with reduced inhibitory control and increased responsiveness to food-related stimuli (Davis C and J Fox 2008; Smith E et al. 2011; Vainik U *et al.* 2013). Higher BMI may therefore reflect dysfunction in brain networks that balance sensory-driven and internally-guided states. Congruent with this notion, higher BMI has been associated with abnormal activity and connectivity in brain regions involved in sensory processing and reward valuation of food stimuli (Wang GJ et al. 2002; Grill HJ et al. 2007; Stice E et al. 2008; Garcia-Garcia I et al. 2013). Further, higher BMI has been linked to abnormal brain activity (Volkow ND et al. 2009; Willeumier K et al. 2012) and functional connectivity (Kullmann S et al. 2012) of core regions of the default-mode network (DMN) and the central executive network (CEN),

two internally-guided networks that are involved the integration of cognitive control with information about somatic and emotional states (Bressler SL and V Menon 2010).

These findings suggest the need for a better understanding of the influence of BMI on brain organization as a means to develop neuroscience-informed public health and clinical interventions for the prevention and treatment of obesity. To this aim we used the rich dataset of the Human Connectome Project (HCP) comprising publically released sociodemographic, cognitive and neuroimaging data from 496 participants, including 209 fully-related sibling pairs (Van Essen DC and DM Barch 2015). Using resting-state functional magnetic resonance imaging (rs-fMRI) data we identified four major networks corresponding to the DMN, CEN, Sensorimotor (SMN) and Visual (VN) Networks and their constituent modules. We tested two hypotheses. First, we predicted that higher BMI would disrupt the functional integration of networks involved in the sensory processing of external stimuli (SMN, VN) and in the representation of internal states and goals (DMN, CEN). Second, we tested the contribution of familial and person-specific factors by comparing siblings discordant for obesity. The results presented here have direct implications for clinical and policy interventions for weight control. First, they suggest that interventions that target cognition and behavior (dietary restriction, recommendations for exercise) need to be expanded to include modifications to individuals' eating environment (visibility of and proximity to food). We also argue that our findings point to the need of public policy strategies to address how food, especially calorie dense food, is displayed, advertised and packaged.

Materials and Methods

Study Sample

We used data from 496 participants (291 women) of the Human Connectome Project (HCP) database (http://www.humanconnectome.org). The study sample included 209 full sibling pairs (50 monozygotic twin pairs and 159 full fraternal sibling pairs). Participants had a mean age of 29 years (range 22–37 years) and mean BMI of 26.6 (range 16.8 to 47.8). When categorizing participants according to BMI, we followed the world health organization definitions for obesity (BMI>30.0), overweight (BMI 25.0-29.9), normal weight (BMI 18.5-24.9) and underweight (BMI<18.5) (Organization WH 2013). Based on this definition, the sample comprised 109 obese and 165 overweight individuals, 213 normal-weight participants and 9 underweight individuals.

Data used in this work were obtained from the MGH-USC HCP database (https://ida.loni.usc.edu/login.jsp).

HCP Non-imaging Subject Measures

The HCP database includes structural and functional imaging data and non-imaging data on demographic characteristics (e.g., age, sex), physical health, lifestyle and personality measures (e.g., smoking, drug use) and neurocognitive measures derived from tests included in the National Institute of Health (NIH) Toolbox (http://www.nihtoolbox.org) and HCP-specific tests (details at wiki.humanconnectome.org). We focused on variables relating to sex, age, smoking and alcohol use that are known to affect brain function independent of BMI and on stimulating thyroid levels as they may independently affect BMI. Based on previous

literature (Vainik U *et al.* 2013), we also examined the relationship of BMI to performance on Regional Taste Intensity test and on the Flanker Inhibitory Control and Attention Task, both from the NIH Toolbox. The former measures perceived intensity of quinine (a bitter tastant) and salt, administered in liquid solutions. The latter tests the executive control of attention, measured by the ability to ignore distracting flanker stimuli, and response inhibition, measured by the ability to suppress responses to task-incongruent stimuli. To ensure completeness, we also examined univariate correlations between BMI and 103 non-imaging measures for which we had no a priori hypothesis (Fig. S1-S4). As functional connectivity is related to brain structural integrity we also examined correlations between BMI and brain volumes (Fig. S5). These measures extracted by the HCP team and are available to download from http://www.humanconnectomeproject.org/data/.

Neuroimaging Acquisition and Preprocessing

Resting-state functional magnetic resonance imaging data were acquired on a Siemens Skyra 3T scanner using “left-to-right” phase encoding; image matrix = 104 x 90; number of volumes = 1200; pixel resolution = 2.0 mm isotropic; slice thickness = 2.0 mm; repetition time = 720 ms; echo time = 33.1 ms; field of view = 208 x 180 mm; flip angle = 52 degrees. Data were de-identified prior to release as described by van Essen and Barch (Van Essen DC and DM Barch 2015). Also, the influence of potential head movement artefacts was minimized in the functional data by using strict inclusion criteria regarding head motion as well as strict overall quality control (Van Essen DC and DM Barch 2015). Termemon et al. (Termenon M et al. 2016) recently showed that when

considering more than 100 subjects, 600 volumes from the HCP rs-fMRI data were as reliable as the full 1200 volumes available. Therefore, for each individual, 600 resting-state fMRI volumes were preprocessed using Statistical Parametric Mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm/software/spm12). A six-parameter variance cost function rigid body affine registration was used to realign all images to the first volume. Motion regressors were computed and later used as regressors of no interest. To maximize mutual information, coregistration between the functional scans and the average anatomical T1 scan was carried out using six iterations and resampled with a 7th-Degree B-Spline interpolation. Functional images were then normalized into standard space (MNI) and segmented into gray matter, white matter (WM), and cerebrospinal fluid (CSF). All normalized images were smoothed by convolution with a Gaussian kernel, with a full width at half maximum of 6 mm in all directions.

Previous studies have underscored the importance of correcting for participant head motion (Power JD et al. 2012; Satterthwaite TD et al. 2012) and physiological noise (Chang C and GH Glover 2009) in functional connectivity studies to avoid spurious correlations between brain regions. Therefore, additional temporal preprocessing steps were performed to regress out the effects of participant motion (i.e., the six realignment parameters from rigid-body registration) and physiological motion (i.e., the time-courses of WM and CSF masks). For each individual, the time-courses of both WM and CSF were estimated in the relevant brain tissue classes defined at the segmentation step.

Head motion effect

In addition to regressing out the head motion from the data, we took great care in minimizing potential movement artifacts by including strict inclusion criteria based on

maximal head motion: less than 2 mm translation or 0.5 degree rotation, resulting in the exclusion of 5 individuals. We also examined the relation between obesity and relative head motion and did not find any significant difference in average or maximum head motion between obese, overweight individuals and normal-weight individuals ($p>0.05$, Bonferroni corrected) (Table S1). Lastly, no significant correlation was found between head motion and BMI, in any direction ($|r|\leq 0.1$, $p>0.05$, Bonferroni corrected).

Functional Network Construction

In each individual, we averaged regional mean blood oxygenation level-dependent time series from each of 638 cortical and subcortical regions (Zalesky A et al. 2010; Crossley NA et al. 2013) that were used as nodes in our network modeling. We applied a wavelet decomposition to the raw time series to extract information in the frequency interval of approximately 0.01 to 0.11 Hz, as wavelet-based methods have significant advantages in terms of denoising (Fadili MJ and ET Bullmore 2004), robustness to outliers (Achard S et al. 2006), and utility in null model construction (Breakspear M et al. 2004). This frequency scale was chosen to minimize the impact of high frequency physiological noise (i.e., heartbeat, respiration) while maximizing the degrees of freedom available for wavelet correlation (Lo CY et al. 2015). In the specific frequency interval, all-pairwise functional connections between these nodes were estimated using Pearson correlation coefficients, which were then Fisher r-to-z transformed, resulting in 638*638 connectome matrix for each participant. Using *k*-means clustering algorithm, we partitioned the functional connectome of each participant into groups of densely functionally interconnected brain regions. The objective function optimized in the estimation is defined in terms of time course similarity in each subset:

$$J = \sum_{v=1}^{V} d^2\left(y_v, m_{k(v)}\right),$$

where y_v is the time course of voxel v, $m_{k(v)}$ is the mean time course of the voxel's assigned cluster, and d^2 is the squared distance function [defined as: $1 - r(x,y)$]. This formulation leads to a non-linear optimization problem that is solved iteratively. This method minimizes the within-cluster sums of point-to-cluster-centroid distances and can identify consistent networks based on the fMRI data rather than any regularization property of a particular clustering method (Golland Y et al. 2008). We employed a robust estimation procedure in determining the mean time course of each network during clustering. In each reiteration of the *k*-means algorithm, all voxels assigned to a particular network participate in the initial estimate of its mean time course. The final partition was defined using a commonly used approach of defining similarity between time courses based on their correlation coefficient:

$$r(x,y) = \frac{\sum_{t=1}^{T}(x[t] - \bar{x})(y[t] - \bar{y})}{\sqrt{\sum_{t=1}^{T}(x[t] - \bar{x})^2 \sum_{t=1}^{T}(y[t] - \bar{y})^2}},$$

where x and y are the time courses of length T, and $\bar{x}$ and $\bar{y}$ are the mean value of vectors x and y, respectively. Identification of network was performed both at the individual and at the group level. For the latter, we used the average functional connectivity matrix of all participants as the input of the *k*-means algorithm. The average group partition was used in further analysis as the normative reference partition.

For each individual, we calculated two global properties: (1) the variance in network size to test whether the networks were similarly sized; (2) the index of spatial similarity (Z-score of Rand Coefficient; *Z-Rand*) to evaluate the consistency of partitions (Traud A et al. 2011). We also calculated two local properties to examine the roles of each network

within the global brain architecture: (1) the within-network connectivity (a measure of functional cohesion of a network) and (2) the between- network connectivity (a measure of functional integration of a network). The within-network connectivity measures the mean strength of functional connectivity between all nodes in a given network. The between-network connectivity measures the mean strength of functional connectivity between the nodes of one network and the nodes of all the others (Gu S et al. 2015).

Statistical Analyses

The effect of BMI on functional brain organization was examined using non-parametric correlations. Analyses were conducted with and without potential confounders (age and education); the latter were retained if they contributed to the results. The network metrics tested were variance in network size, Z-Rand and within- and between- network functional connectivity; the threshold for statistical significance was set at $P<0.05$ using False Discovery Rate (FDR) correction.

We used correlations and tests of group differences, as appropriate, to examine the relationship of BMI to age, sex, smoking status (current smokers vs. non-smokers), alcohol use (number of alcoholic drinks per day), the regional taste intensity test and the Flanker Test. As these variables were determined a priori the level of statistical significance was $P < 0.05$. We conducted exploratory correlations between BMI and variables relating to cognition, personality, health, lifestyle and brain structure that were available through the HPC database; correlations of at least moderate strength (i.e., correlation coefficient > 0.2) that were significant at $P<0.05$, uncorrected, were considered potentially informative (Hinkle DE et al. 2006).

Sibling analyses

We estimated the familial similarity in BMI in sibling pairs using the intraclass correlation coefficient (ICC). We tested the relative contribution of familial and person-specific factors to obesity (BMI>30) based on the extent to which the mean BMI of the full siblings of obese individuals regresses to the rest of the population mean (n=395). This approach has been used to determine familial vs. person-specific contributions to complex quantitative traits such as height (Chan Y et al. 2011) and cognitive ability (Reichenberg A et al. 2016). If the mean BMI of siblings of obese participants (BMI>30) was comparable to the mean BMI of the total sample that would indicate the relative predominance of person-specific as opposed to familial factors to the etiology of obesity. If the mean BMI of the siblings of obese individuals was significantly higher than the mean BMI of the total sample that would indicate the relative importance of familial factors for obesity. Finally, we used the discordant sibling pair paradigm to examine the contribution of familial and person-specific factors to BMI-related rs-fMRI changes by comparing the network configuration of sibling pairs in which one sibling was obese (BMI≥30) and the other was of normal weight (BMI 18-25), using paired t-tests. To allow potentially meaningful moderator effects to be considered in future study designs, the threshold for statistical significance for this analysis was set at $P<0.05$.

Results

BMI association with non-imaging and brain structural subject measures

Here we report on a priori considered correlations based on previous literature between non-imaging measures and BMI relating to age, sex, thyroid function, substance use, taste perception and executive function (Davis C and J Fox 2008; Smith E *et al.* 2011; Vainik U *et al.* 2013; Ng M *et al.* 2014; Aune D *et al.* 2016). BMI was associated with age ($r=0.1$, $p=0.03$) and level of education ($r=-0.16$, $p=3.10^{-4}$) but not with sex (men: 26.9±4.5; women: 26.4±5.8; $p=0.2$), level of thyroid stimulating hormone ($r=0.04$, $p=0.5$) and number of alcoholic drinks per week ($r=-0.06$, $p=0.38$). The difference in BMI between current smokers (22% of the sample) and non-smokers was just below the conventional threshold of statistical significance ($p=0.08$). We found no correlation with task performance on either the regional taste intensity test ($r=-4.10^{-3}$, $p=0.9$) nor the Flanker Inhibitory Control and Attention Task ($r=-0.03$, $p=0.6$). Additionally, no differences in either test (both $p>0.2$) were identified when obese participants (BMI>30) were compared to the rest of the sample.

To capitalize on the rich phenotypic information available through the HCP we conducted exploratory analyses of 103 non-imaging cognitive, personality, lifestyle and physical health variables as shown in Figures S1-S4. Significant correlations were only found between BMI and systolic ($r=0.36$, $p=7.10^{-17}$) and diastolic ($r=0.31$, $p=4.10^{-12}$) blood pressure and age at menarche ($r=-0.3$, $p=2.10^{-7}$), which accord with prior findings (Fernandez-Rhodes L et al. 2013; Prentice P and RM Viner 2013) (Fig. S1). Additionally, we explored correlations between BMI and brain morphological variables provided by the HCP (http://www.humanconnectomeproject.org/data/). Given, the variability in the extant literature (Curran JE *et al.* 2013; Medic N et al. 2016) we had no

a priori hypotheses but we found that BMI showed negative but minimal correlations with all whole brain and regional gray and white matter volumes tested (Fig. S5).

Networks and constituent modules

We used rs-fMRI data acquired from 496 HCP participants to estimate functional connectivity (edges) between 638 cortical and subcortical brain regions (nodes) and applied k-means algorithm to partition the functional connectome of each participant into networks. We identified four major networks corresponding to the Default Mode Network (DMN), Central Executive Network (CEN), Somatosensory Network (SMN) and Visual Network (VN) (Fig. 1). We further decomposed these networks into their constituent modules (Fig. 2). Consistent with previous literature (Andrews-Hanna JR 2012), the DMN partitioned in four modules comprising the anterior DMN (including the anterior medial prefrontal and the anterior cingulate cortex), the posterior DMN (including the ventral precuneus and posterior cingulate cortex), the medial temporal DMN centered in the middle temporal cortex, and the dorsal medial prefrontal cortical DMN (also including the angular gyrus and the inferior temporal gyrus). The CEN partitioned into the salience, lateral frontoparietal and subcortical modules (Seeley WW et al. 2007; Bressler SL and V Menon 2010). The SMN partitioned into the dorsal (hand) and ventral (oral) module. The VN partitioned into four modules centered in the lateral and medial occipital cortex, and in the dorsal central and posterior precuneus.

Disrupted Network reconfiguration with increasing BMI

We tested the effect of BMI on the consistency of network configuration using the Z-Rand which is the Z-score of the Rand Coefficient (i.e., a measure of the similarity between data clusters). We found a negative correlation between BMI and Z-Rand for all four networks (ρ=-0.14; p=0.009) and for their constituent modules (ρ=-0.18; p=0.001), confirming that elevated BMI disrupts the composition of functional brain networks.

Altered network connectivity with increasing BMI

We then tested whether the BMI-associated disruption in network configuration observed above was driven by alterations in the functional cohesion (within-network connectivity) or the functional integration (between-network connectivity) of brain networks. We found that higher BMI was associated with reduced functional cohesion of the DMN (ρ =-0.12, p=0.02) coupled with increased between-network connectivity of the DMN (ρ =0.15, p=0.008) and the SMN (ρ=0.11, p=0.02). Analyses at the level of the constituent modules provided further evidence for an effect of BMI on the DMN and yielded additional findings regarding the CEN and VN. Within the DMN, higher BMI was associated with reduced cohesion of the anterior (ρ=-0.15, p=0.007) and posterior (ρ=-0.17, p=0.001) DMN modules and increased between-network connectivity of the dorsal medial prefrontal (ρ=0.11, p=0.04) and anterior DMN (ρ =0.14, p=0.01) modules. In the CEN and VN, we found evidence of reduced within-network connectivity of the salience (ρ =-0.18, p=0.001), frontoparietal (ρ =-0.13, p=0.02) and medial occipital (ρ =-0.13, p=0.02) modules.

Sibling Analyses

The intraclass correlation coefficient of BMI was 0.82 and 0.6 in monozygotic twin and fraternal sibling pairs respectively. The mean BMI (mean=27.6; sd=4.8) of the siblings (n=96) of obese study participants was higher than that of the remaining sample (mean=24.6; sd=3.6) (Fig. 3). Confirming the influence of familial factors, the average BMI Z-score of the siblings of obese participants was 0.3 (95% CI: [0.1, 0.5]) while that of the rest of the sample was -0.4 (95% CI: [-0.4,-0.3]); this difference was significant ($t=-5.8$, $p< 0.001$).

We then tested for person-specific influences on BMI using a discordant sibling design. We identified 34 sibling pairs discordant for obesity (within the fraternal sibling pairs). Each pair consisted of an obese (BMI range: 30-44; mean BMI=34.1) and a normal-weight sibling (BMI range: [18-25]; mean BMI=22.6). The majority were same sex sibling pairs (41.7% females and 16.7% males). Of the remaining sibling pairs, 11.0% comprised of a normal-weight male and an obese female and 30.6% of a normal-weight female and an obese male. The discordant siblings did not differ in age ($p=0.3$), education ($p=0.8$), sex distribution ($p=0.2$), or head motion while scanned ($p>0.05$, Bonferroni corrected, for any directions). Compared to their normal-weight counterparts, obese siblings showed reduced spatial definition of network modules (Z-Rand; $p=0.001$, Cohen's $d=0.63$). In more detail, obese siblings showed reduced functional connectivity of medium effect size within the dorsal SMN ($p=0.003$, Cohen's $d=0.67$) and within the medial occipital VN module ($p=0.012$, Cohen's $d=0.49$) (Fig. 4). The functional connectivity of the DMN and CEN did not differ between obese and normal-weight siblings (both: $p>0.05$).

Discussion

We examined the effect of BMI on the functional architecture of the brain using rs-fMRI data from participants of the Human Connectome Project. We found that elevated BMI was associated with disrupted functional integration of sensory-driven (SMN, VN) with internally-guided (DMN, CEN) networks, implicating increased attention to sensory stimuli as a possible mechanism underpinning overeating and weight gain.

The effect of Body Mass Index on the Default Mode Network

The DMN is a robust resting-state network, that although characteristically more engaged during conditions of spontaneous mental activity (Raichle ME et al. 2001), plays a central role in the integration of information that underpins conscious processing during both spontaneous and task-related mental activity (Buckner RL et al. 2008; Andrews-Hanna JR 2012; Braga RM et al. 2013; Vatansever D et al. 2015). This is reflected in its functional profile which is defined by high within- and high between-network connectivity (Meunier D et al. 2009; Gu S *et al.* 2015). Based on these features, Gu et al. (Gu S *et al.* 2015) described the DMN as a "cohesive connector" system. The results presented here suggest that higher BMI alters the role of the DMN to that of an "incoherent connector" by reducing its differentiation and internal cohesiveness and increasing its integration with other networks. This change in status has been found to impair efficient processing of internal functions in obese individuals (Volkow ND *et al.* 2009; Willeumier K *et al.* 2012). For example, Garcia-Garcia and colleagues (Garcia-Garcia I *et al.* 2013) have shown that DMN dysfunction in obese

compared to normal-weight individuals, is associated with abnormal processing of food and non-food related reward. Abnormalities in the locus coeruleus/norepinephrine (LC-NE) system may offer a pathophysiological explanation for the observed reduction in DMN cohesion with increasing BMI (Corbetta M et al. 2008). DMN cohesion depends the tonic activity of the LC-NE system (Adan RA et al. 2008; Mittner M et al. 2016) which may be decreased in obesity based on recent findings of reductions in norepinephrine turnover and in norepinephrine transporter (NET) availability in obese individuals (Adan RA *et al.* 2008; Li CS et al. 2014; Melasch J et al. 2016).

The effect of Body Mass Index on the Central Executive Network

Within the CEN, we show that increasing BMI was associated with diminished connectivity within the frontoparietal and salience modules. The frontoparietal network has been implicated in a wide range of functions that require cognitive control, including attention, working memory, performance monitoring, planning, and response inhibition (Niendam TA et al. 2012). In this study, BMI showed a minimal and non-significant negative correlation with task performance on the Flanker Task, the HPC measure of executive control of attention and response inhibition. It is possible that the Flanker Task is insensitive to subtle BMI-changes in brain connectivity or that executive dyscontrol related to BMI may be more evident in tasks that involve food-related stimuli.

We found diminished connectivity within the salience network that implicates abnormalities in the functional integration of its constituent brain regions that include the insula and dorsal anterior cingulate cortex (ACC). The insula is integral to food perception, regardless of body weight, as it forms part of the primary gustatory cortex

(Rolls ET 2006). Together with the ACC, it responds to the cognitive, homeostatic, or emotional salience of stimuli in order to guide behavior (Seeley WW *et al.* 2007; Menon V and LQ Uddin 2010). Elevated BMI has been shown to influence insula function leading to reduced connectivity at rest (Kullmann S *et al.* 2012) and increased activation and connectivity in response to food and food-related cues [reviewed by Frank et al. (Frank S et al. 2013)].

The effect of Body Mass Index on Somatosensory and Visual Networks

The VN and the SMN are reliably and robustly activated during perception of food images and tastes (Huerta CI et al. 2014). Typically, these sensory-driven networks have a competitive interaction with internally-guided networks (Doucet G et al. 2011; Huang S et al. 2015) and their optimal function within the brain connectome is characterized by high within-network and low between-network connectivity (Gu S *et al.* 2015). We found that higher BMI was associated with increased between-network connectivity of the SMN and reduced within-network connectivity of the VN and SMN, the latter being most evident in the discordant sibling analyses. We infer that these changes in SMN and VN connectivity, in conjunction with reduced DMN and CEN cohesiveness, may favor sensory-driven over internally-guided processing, consistent with reports of persistently increased responsiveness to food stimuli in obese individuals even when not hungry (Pursey KM et al. 2014). Our findings also provide indirect support for the popular concept of “see food” diet, which describes sensory-driven food consumption even when internal states (e.g., satiety) or goals (e.g., maintaining well-being) indicate the opposite action. Although our data do not allow us to test whether

increased sensory-driven responsiveness is a cause or consequence of elevated BMI (Stoeckel LE et al. 2016), prior studies suggest that sensory-driven food consumption is causally related to overeating as obese individuals behave in ways that make food more visible and more convenient to reach (Wansink B and CR Payne 2008; Wansink B and M Shimizu 2013; Wansink B et al. 2016).

Methodological Considerations

Despite this being the largest and most comprehensive assessment of the relationship between BMI and brain organization, the study has two important limitations. First, the cross-sectional design precludes conclusion about the direction of causality of the observed effects. Second, we did not have any measures of adiposity, other than BMI, so we could not examine whether the observed effects were associated or mediated by specific aspects of body fat distribution or other metabolic factors. However, as the HCP sample consists of healthy young adults we were able study the phenotypic relationship between BMI and brain and cognition unhindered by medical comorbidity. This is particularly important in terms of cognition where the association between elevated BMI and cognitive dysfunction appears, to a large extent, influenced by medical comorbidities (Elias MF et al. 2003; Cournot M et al. 2006; Gunstad J et al. 2007; Nilsson LG and E Nilsson 2009; Sabia S et al. 2009). We show that the average correlation between cognitive measures (number of variables considered=83) and BMI was 9.10^{-3} (Fig. S1-S4) which is low and consistent with that found in large population studies (Marioni RE et al. 2016) and meta-analyses of relevant data (Vainik U *et al.* 2013). Conversely, the HCP sample does not include elderly who are an age-group of

particular interest since beyond the 6th decade of life higher BMI appears to mitigate against cognitive decline (Buchman AS et al. 2005; van den Berg E et al. 2007). Hsu and colleagues (Hsu CL et al. 2015) showed that obese adults aged 70-80 years had better preserved DMN and better cognitive performance at 12-month follow-up than their normal-weight peers. The underlying reasons are unclear but unintentional weight loss in old age is likely to reflect degenerative process affecting both body and brain (Grundman M et al. 1996) and contributing to general frailty (Rockwood K et al. 2007). Further studies are needed to examine BMI-related brain disorganization in underweight individuals (BMI<18.5) because only 9 HCP participants met this definition. Although we focus on resting-state brain networks, a sizable body of literature has used task-related fMRI to investigate brain responses to food-related stimuli (images, odors, actual food) [reviewed by Ziauddeen et al. (Ziauddeen H *et al.* 2012) and Vainik et al. (Vainik U *et al.* 2013)]. An important extension of this work would be the joint examination of resting-state connectivity with changes observed in fMRI datasets acquired while food-related information is actively processed. The interaction between intrinsic and task-related connectivity would complement our understanding of the neural mechanisms involved in regulating eating behaviors.

The influence of potential head movement artefacts was minimized in the functional data by using strict inclusion criteria regarding head motion as well as strict overall quality control (Van Essen DC and DM Barch 2015). Lastly, the construction of brain graphs from fMRI data entails multiple methodological choices regarding analyses. We therefore tested the robustness of our key results by examining the effect of BMI both on the spatial topology and the connectivity of brain networks.

Clinical and Translational Implications for addressing overweight and obesity

The current results provide a neurobiological context for understanding the association between BMI and brain functional organization while accounting for familial and person-specific influences. The widespread effect of elevated BMI on the intrinsic functional organization of the brain establishes overweight and obesity as multisystem challenges for healthcare. Of particular relevance to the planning of clinical and public health policies and interventions is the association of elevated BMI with disrupted integration of sensory-driven networks with networks that process internally generated states and goals. The results presented here suggest that weight control interventions should go beyond the current focus on individual cognitive and behavioral (dietary restriction, recommendations for exercise) modification. They underscore the role of the eating environment (visibility of and proximity to food) as an important moderator of eating behavior. Environmental modification could be implemented at the individual or household level (Wansink B *et al.* 2016) but should also include public policy strategies to address how food is displayed, advertised, packaged and priced.

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Figure Captions

Fig. 1: Brain functional organization into four major systems. Central Executive Network (CEN) is shown in blue; Default Mode Network (DMN) is shown in green; Somatosensory network (SMN) is shown in brown; Visual Network (VN) is shown in orange.

Fig. 2: Description of the 13 constituent modules composing the four major systems. (**A**) Default Mode Network (DMN), (**B**) Central Executive Network (CEN), (**C**) Visual Network (VN) and (**D**) Somatosensory network (SMN).

Fig. 3: Distribution of the Body mass index. Three groups are shown: siblings of obese individuals (light blue, mean BMI=27.6), obese study participants (dark blue, mean BMI=35.4), and the rest of the individuals (black, mean BMI=24.6).

Fig. 4: Within-Network connectivity in the discordant sibling pairs. Dark colors represent average within network connectivity in the normal-weight siblings (*left-sided bars*), light colors represent average within network connectivity in the obese siblings (*right-sided bars*). Error bars represent one standard-error. Name of each network community is described in Fig. 2. *: $p<0.05$; **: $p<0.005$.