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Deficits in executive function and suppression of default mode network in obesity

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ABSTRACT

Background: Although nutritional and metabolic factors are well established in obesity, neurocognitive determinants are less understood. Using data from the Human Connectome Project, this study concurrently investigated neurocognitive performance, neural activation during a working memory task, and cortical brain morphometry in relation to obesity in a group of young adults, 22–35 years old.

Methods: Using a case-control design, obese individuals (n = 243, body mass index [BMI] ≥ 30 kg/m^2) were compared to a control group of lean BMI individuals (n = 469, BMI = 18–24.9 kg/m^2). Performance tests comprised a battery of behavioral neurocognitive assessments. Neural activity was measured as blood-oxygenation-level-dependent (BOLD) activity during an N-Back task using functional magnetic resonance imaging (fMRI). Cortical morphometry included indices of volume, thickness, and surface area.

Results: Relative to the control group, the obese group exhibited significantly worse performance in terms of the National Institutes of Health Toolkit (NIH) 9-Hole Peg Board, Penn Working Memory Test, Delay Discounting, Penn Progressive Matrices, NIH Picture Vocabulary Test, Dimensional Change Card Sort Test and the in-scanner N-Back working memory test (FDR-corrected $ps < 0.05$; ds = 0.231–0.405). The obese group also exhibited significantly greater BOLD activation in N-Back task-negative regions, including the ventromedial prefrontal cortex, posterior cingulate, and right precentral gyrus (FDR-corrected $ps < 0.05$). Supplemental functional connectivity analyses provided evidence that the implicated regions were part of the default mode network. Significant differences in morphometry were present in the medial orbitofrontal cortex, rostral anterior cingulate cortex, inferior and superior parietal gyri, and temporal pole (FDR-corrected $p < 0.001$). A data-driven integrative model classified 73.8% of participants correctly.

Conclusions and Relevance: This multimodal investigation suggests diverse aspects of neurocognition are associated with obesity, particularly implicating deficits in executive function and ineffective suppression of the default mode network.

1. Introduction

Obesity poses a substantial public health problem, conferring significant medical, psychosocial, and economic consequences (Ogden et al., 2014). Estimates from the World Health Organization suggest that the prevalence of obesity in the world has tripled since 1975, with 650 million meeting criteria for obesity in 2016 (World Health Organization 2018). Established medical consequences of obesity include diabetes mellitus, cardiovascular risk, cerebrovascular risk, and cancer (Hruby and Hu, 2014). Indeed, obesity is an established 'upstream' antecedent of the most common 'downstream' forms of morbidity and mortality in developed nations (Malik et al., 2013).

Metabolic, dietary, and physical activity factors are well established as determinants of obesity, but neurocognitive processes are increasingly being examined and implicated (Prickett et al., 2015). For

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example, recent results suggest that the most robust associations between obesity and cognitive impairment is present in tests of executive functioning, specifically in the areas of planning, problem solving, mental flexibility (Yang et al., 2018), and concept formation and set shifting (Boeka and Lokken, 2008; Fagundo et al., 2012; Lokken et al., 2010). Studies also reveal that obesity is associated with impairment in processing speed (Cournot et al., 2006; Etou et al., 1989; Sargénius et al., 2017), verbal memory (Cournot et al., 2006; Davis et al., 2010; Gunstad et al., 2006a), complex attention (Fergenbaum et al., 2009), inhibition and decision making (Fagundo et al., 2012; Davis et al., 2010; Pignatti et al., 2006). Finally, obesity has also been associated with delay discounting, or the tendency to discount larger future rewards in place of smaller immediate rewards, a behavioral economic measure of impulsivity (Jarmolowicz et al., 2014). However, the existing studies in aggregate have produced mixed findings across domains, which may be attributable to. the scarcity of literature in a number of neurocognitive domains and often small sample sizes because of the experimental demands of neurocognitive testing.

Beyond behavioral performance on cognitive tasks, a small number of studies have implicated functional and structural differences in brain regions responsible for mediating cognition in general (executive functioning, working memory) and with specific relevance to addictive behavior (reward valuation, delay discounting) in obesity. In obese adults, it has been reported that impaired working memory performance may be mediated by white matter alterations in the left inferior longitudinal fasciculus relative to age-matched controls ($n = 152$) (Alarcón et al., 2015), and it has also been linked to poor academic performance in obese children ($n = 159$) (Wu et al., 2017). In women specifically, one study reported that obese women preferred immediate rewards despite negative long-term consequences relative to lean BMI controls ($n = 122$) (Horstmann, 2011). Moreover BMI was positively correlated with gray matter volume in the left dorsal striatum; emphasizing the potential role of dysregulated reward valuation on mediating obesity and weight gain (Horstmann, 2011). Studies also suggest that decreased functional activation in brain regions associated with executive functioning during difficult vs. easy delay discounting trials may predictive of weight gain over the following 1–3 years in obese women ($n = 19$) (Kishinevsky et al., 2012).

In a small number of studies investigating brain structure and obesity, lower gray matter density has been detected in frontal regions, such as the frontal operculum and middle frontal gyrus ($n = 24$) (Pannacciulli et al., 2006), and the orbitofrontal cortex ($n = 42$) (Shott et al., 2014), brain areas that are associated with decision making and executive function more generally. Cortical thinning in obese BMI compared to lean BMI individuals and individuals who lost weight and maintained their weight loss was also reported in cognitive control regions ($n = 53$) (Hassenstab et al., 2012). A negative correlation between the thickness of the right ventromedial prefrontal cortex and the left lateral occipital cortex and BMI was also reported in a comparatively large sample of individuals ($n = 202$) (Medic et al., 2016). Higher BMI and body fat percentage has been associated with decreased volumes of white matter tracts associated with activity in default mode, central executive and salience networks (Figley et al., 2016). Obesity has also been shown to impact large scale brain networks (Ronan et al., 2016) and associated with increased brain age in midlife (Bischof and Park, 2015).

Collectively, the preceding findings individually implicate diverse aspects of neurocognitive performance, task-related neural activity, and brain morphometry in obesity. However, inconsistencies have been also present, perhaps due to small sample sizes. In addition, no studies to date have concurrently examined neurocognitive, functional, and structural changes in obesity. Thus, the current literature does not address independent roles or the potential overlap among these domains. To address these issues, the present study used a multi-modal approach to investigate the neurocognitive correlates of obesity in the Human Connectome Project (Van Essen et al., 2013), a large 'open science' investigation of human brain connectomics. Using a case-control design, obese individuals (i.e., BMI of over 30 kg/m^2) were compared to lean BMI control participants (BMI: 18–24.9 kg/m^2). Cognitive functioning was tested using a battery of well-validated neurocognitive tests, neural activity during a working memory task was assessed using functional magnetic resonance imaging (fMRI), and cortical morphometry was measured from high-resolution T1-weighted MRI images, providing indices of volume, thickness, and surface area. Finally, integrative models were used to examine the implicated processes concurrently. The superordinate hypothesis was that obesity would be associated with deficits in tasks and brain regions associated with executive functioning.

2. Methods

2.1. Design and participants

We intentionally elected to use a case-control design over a dimensional design (examining BMI as a continuous variable) because we were specifically interested in neurocognitive correlates of the clinical condition of obesity. Individuals who are defined as overweight (BMI $>25<30$) are a clinically ambiguous group insofar as their overweight status may reflect a prodrome to obesity or a more transient elevation that may prompt an individual to initiate a weight-loss regimen. In other words, in understanding neurocognition in relation to obesity, overweight individuals represented a gray area, whereas a case-control comparison of obese individuals versus healthy weight individuals was anticipated to bring differences into sharper relief. Cases and controls were extracted from the total S1200 Release of the Human Connectome Project (HCP). Overall, HCP participants were young adults (ages 22–35), with no significant history of neurological disorder, cardiovascular disease, or Mendelian genetic disease, and no contraindications for MRI. General HCP information can be found in Van Essen et al. (2013). The goal of the overall HCP project was to systematically assess the role of macro-level neuronal connections in a large sample of generally healthy young adults. Participants were recruited in Missouri and Minnesota. All participants gave informed consent and all aspects of the protocol were approved by the Washington University School of Medicine Institutional Review Board. Participants were categorized into two groups according to their BMI (obese: > BMI of over 30 kg/m^2; lean BMI: 18–24.9 kg/m^2). Individuals with a BMI between 18 and 25 were excluded to create two separate groups of individuals with clinically significant differences in BMI, as were individuals with BMI < 18 to exclude underweight individuals. The total sample comprised 712 participants (Obese, $n = 243$, lean BMI controls, $n = 469$; Table 1). Consistent with the intentions of the design, the two groups differed very substantially in terms of BMI

Table 1
Participant characteristics ($n = 712$).

	Obese Group ***N* = =243*M (SD)***	Control Group ***N* = =469*M (SD)***	*P*
BMI	34.40 (3.61)	22.36 (1.55)	<0.001
Height, inches	67.17 (3.96)	67.09 (3.53)	0.99
Weight, pounds	221.24 (31.9)	143.73 (19.65)	<0.001
M/F	103/140	184/285	0.46
Age (SD), years	29.29 (3.62)	28.46 (3.67)	0.004
Race	163 (67.1%)	360 (76.7%)	<0.001
Handedness	66.6	66.65	0.943
Income	4.60 (1.99)	5.25 (2.18)	<0.001
Alcohol Use	4.11 (6.22)	3.99 (5.71)	0.804
Smokers (number,%)	23 (9.5%)	29 (6.2%)	0.148

NOTE: Income was defined according to SSAGA income score - Total household income: <$10,000 = 1, 10K-19,999 = 2, 20K-29,999 = 3, 30K-39,999 = 4, 40K-49,999 = 5, 50K-74,999 = 6, 75K-99,999 = 7, >=100,000 = 8.

(d = 4.33; Table 1). Reflecting this, the two groups had almost identical height but differed in weight by ~80lbs. There were no significant differences in sex, height, Latino ethnicity, drug use, alcohol use, or smoking between groups. Age, income, and racial diversity were significantly different between groups, and were used as covariates.

2.2. Neurocognitive assessment

Neurocognitive functioning was examined across several cognitive domains, including both out-of-scanner and fMRI behavioral assessments of working memory. Out-of-scanner tasks included the NIH 9-Hole Peg Board, measuring psychomotor dexterity; the Penn Working Memory Test (Form A), measuring working memory; the Delay Discounting Task, measuring impulsivity; Penn Progressive Matrices, measuring fluid intelligence; NIH Toolbox Picture Vocabulary Test, measuring language and vocabulary comprehension; the NIH Toolbox Dimensional Change Card Sort, measuring cognitive flexibility; the Short Penn Continuous Performance Task, measuring behavioral inhibition; the NIH Toolbox List Sort Working Memory Test, measuring working memory; the NIH Toolbox Flanker Inhibitory Control and Attention Test, measuring inhibition and attention; and the NIH Pattern Processing Comparison Processing Speed Test, measuring processing speed.

For task fMRI, we specifically selected the N-Back working memory paradigm because decrements in working memory are among the most consistent neurocognitive correlates of obesity (for a meta-analysis, see Yang et al., 2018) (Yang et al., 2018). Furthermore, the paradigm was best suited for characterizing higher order cognitive processing, as opposed to social cognition or emotion processing (Owen et al., 2005). The N-back fMRI paradigm was presented to participants in blocks of trials with stimuli that consisted of places, tools, faces, and body parts. Within each run, the 4 different stimulus types were presented in separate blocks. Each of two runs contained 8 N-back task blocks (27.5 s each), consisting of four 0-back blocks and four 2-back blocks, and four resting/eye fixation blocks (15 s each). A 2.5 s cue was presented at the beginning of each block to inform participants which task followed (i.e., 0-back or 2-back), 10 trials of 2.5 s each were included in each block. On each trial, the stimulus was presented for 2 s, followed by a 500 ms inter-trial interval. During 0-back task blocks, participants were presented with a target cue and then instructed to identify any stimuli that matched the target. During 2-back task blocks, the subject was required to identify stimuli that matched the stimulus presented two trials prior. For a full description of fMRI task see (Barch et al., 2013). Functional MRI data was collected during the N-Back paradigm across two 5.01 min imaging runs using a 3T Siemens Skyra (Seimens AG, Erlanger, Germany) with a 32-channel head coil with the following acquisition parameters: TR = 720 ms, TE = 33.1 ms, flip angle = 52°, FOV = 208 × 180 mm, 72 2mm-thick coronal slices, 2.0 mm isotropic voxels. A multi-band acceleration factor of 8 was used. One imaging run was acquired with left to right phase encoding, and the other was acquired with right to left phase encoding. Data were preprocessed by HCP scientists using the minimal preprocessing pipeline (Glasser et al., 2013) that includes gradient unwarping, motion correction, field-map based EPI distortion correction, brain boundary-based registration of EPI to the structural scan, registration into MNI152 space, and grand-mean intensity normalization.

High resolution T1-weighted structural images were acquired using the same MR scanner and head coil with a resolution of 0.7 mm^3 isotropic (FOV = 224 × 240, matrix = 320 × 320, 256 sagittal slices; TR = 2400 ms, TE = 2.14 ms). Further details of MRI data acquisition parameters and data preprocessing are in Glasser et al. (2013) and Van Essen et al. (2012). All scans were subject to rigorous quality control. To ensure images were of the highest quality, all images were checked by a scanning technician immediately following acquisition. Scans were rated on a scale from 1–4 (poor to excellent) for image quality based on the crispness of the image, blurriness, motion accuracy of defacing and other artifacts. Scans rated 3 (good) or below were reacquired, meaning all structural images were of the highest quality (excellent, level 4). Details of the HCP quality control approach are in Marcus et al. (2013).

2.3. Data analysis

There was little missing data, with no individual neurocognitive test missing scores for any more than 6 participants; fMRI data was missing from 32 participants; and no participants were missing structural MRI data. Age-adjusted scores on neurocognitive tests were used where available. As noted, age, income, and racial diversity were used as covariates Specifically, for race, as white participants were more common in the lean BMI group, White/Non-white status was used as a dichotomous covariate. In addition, because the cohort oversampled for twins, monozygotic and dizygotic twin status were covaried per Pagliaccio et al. (2015). For behavioral performance on neurocognitive tasks, difference between groups was examined using analysis of covariance (ANCOVA) with the aforementioned covariates. Functional MRI data was downloaded after preprocessed by the minimal preprocessing pipeline described above (Glasser et al., 2013). Additional fMRI data processing and analysis were then conducted using the Analysis of Functional NeuroImages software (Cox, 1996). Data were spatially smoothed using a 6 mm full width half maximum Gaussian filter. General linear modeling was completed using regressors for the time course of blocks of each condition (2-back, 0-back, and instruction screens), six nuisance regressors to account for observed head motion (x, y, z, roll, pitch, yaw), and regressors for linear, quadratic, and cubic trends. Activation associated with the 2-back was measured relative to an active control baseline of activation during the 0-back task, which is matched on most visual/behavioral/cognitive characteristics (except WM demands) and is effectively a task of sustained attention. A whole brain voxelwise GLM analysis, with a two-tailed false discovery rate correction (Benjamini and Hochberg, 1995) of q = 0.05 to reduce inflation of type I error rate, was used to quantify the unique association between the 2-back time course and the observed BOLD signal in each voxel after accounting for the 0-Back and other covariates. For further details of the N-back analysis, see Owens et al. (2018). The measure of WM performance was accuracy on the 2-back, which was tested for its association with GLM effects in clusters exhibiting significant brain response during the 2-back task. Preprocessing of T1-weighted MRI data was completed using a modified version of the FreeSurfer pipeline, available in the FreeSurfer Image Analysis Suite version 5.3 (Fischl et al., 1999; Fischl and Dale, 2000) and using Rorden's DICOM to NIFTI conversion software (Li et al., 2016) Cortical thickness was extracted from 68 regions defined by the Desikan et al. (2006). For structural brain analyses, correlations between bilateral regions from the Desikan atlas were examined and those sharing >50% variance were consolidated to reduce type 1 error rate inflation. Group differences were then compared using an ANCOVA with the previous covariates and also total intracranial volume to account for head size and corrected with false discovery rate, q = 0.05. Finally, integrative analyses examined all three domains of indicators concurrently to characterize unique contributions and potential overlap using a data-driven approach. Zero-order associations among the neurocognitive tests, BOLD signal regions, and cortical thickness regions that differentiated obese from control individuals were examined using a partial correlation matrix, incorporating with aforementioned covariates. Then, the differentiating variables were entered into a binary logistic regression using the fixed covariates and backward conditional inclusion of the implicated variables to determine which variables uniquely significantly discriminated between obese and control groups when considered in concert. Finally, two machine learning approaches, supervised vector machines using a linear kernel and random forest classification, were employed to attempt to improve prediction of group status.

Table 2
Neurocognitive performance for obese participants compared to lean BMI control participants.

Neurocognitive Test	ControlM (SD)	ObeseM (SD)	F	*P*	*d*
NIH 9-Hole Peg Board	102.02 (9.51)	97.77 (9.35)	26.112357	4.16E-07	0.405
Penn Working Memory Test (Form A)	36 (2.78)	35.03 (3.10)	15.470938	0.000092	0.312
Delay Discounting	0.4130 (0.22)	0.3353 (0.21)	13.158289	0.000307	0.287
Penn Progressive Matrices	16,357.079 (9229)	13,901.378 (8365)	10.638344	0.001162	0.258
NIH Picture Vocabulary Test	111.48 (14.66)	105.28 (16.25)	13.281877	0.000288	0.289
Dimensional Change Card Sort	102.83 (9.38)	100.06 (10.57)	8.536461	0.003593	0.231
Short Penn Continuous Performance Task	470.72 (46.27)	470.44 (44.49)	0.266824	0.605635	0.041
List Sort Working Memory Test	103.67 (12.98)	101.81(14.15)	0.292984	0.588487	0.043
NIH Toolbox Flanker Inhibitory Control and Attention Test	101.71 (9.94)	101.13 (9.92)	0.000179	0.989338	0.001
NIH Pattern Processing Comparison Processing Speed Test	104.35 (19.68)	102.69 (19.67)	0.048476	0.8258	0.017
N-Back Test Accuracy	84.83 (10.28)	80.96 (11.15)	7.696634	0.005686	0.22

3. Results

3.1. Behavioral neurocognitive assessment

Relative to controls, the obese group exhibited significantly worse performance on the 9-Hole Peg Board, Penn Working Memory Test, Delay Discounting, Penn Progressive Matrices, Picture Vocabulary Test and Dimensional Change Card Sort Test (Table 2). Effect sizes were generally small to medium in magnitude (*ds* = 0.231–0.405). There was no difference in performance on the Short Penn Continuous Performance Test, List Sort Working Memory Test, Flanker Inhibitory Control and Attention Test or Pattern Processing Comparison Processing Speed Test ($ps > 0.05$).

3.2. Working memory and associated brain activity

Significant behavioral differences in 2-Back accuracy between the two groups was present (Table 2), with obese individuals exhibiting worse N-Back performance compared to control individuals. For BOLD signal, significant activation or deactivation was present in the medial frontal gyrus, superior frontal gyrus, ventromedial prefrontal cortex, supplementary motor area, precentral gyrus, inferior parietal lobule, precuneus, posterior cingulate, and cerebellum (Fig. 1). All regions were significantly positively or negative correlated with task performance (Table 3), suggesting both task-positive and task-negative roles (i.e., either recruitment or suppression for successful task performance). Moreover, in obese individuals compared to controls, BOLD activation during the 2-Back was significantly increased in the ventromedial prefrontal cortex, posterior cingulate, and precentral gyrus (Table 3), all of which were significantly inversed correlated with task performance ($ps < 0.01$). This suggests less attenuation of task-negative brain regions among obese individuals, implying inadequate suppression of the default mode network (DMN).

3.3. Brain morphometry

In comparison to controls, the obese group exhibited decreased cortical thickness in the right entorhinal cortex, and right and left temporal pole (Table 4; $p < 0.001$, FDR-corrected). In contrast, compared to controls, obese individuals exhibited greater cortical thickness in the right medial orbital frontal cortex, right and left rostral anterior cingulate cortex, and bilateral inferior and superior parietal gyri (Table 4; $p < 0.001$, FDR-corrected).

3.4. Integrative analysis

Associations among the indicators differentiating the obese group and the control group varied considerably, from negligible to large magnitude (Fig. 2). When entered into a binary logistic regression, variables predicted 73.8% (control = 89.0%; obese = 44.3%) of group status correctly (Cox & Snell $R^2 = 0.207$; Nagelkerke $R^2 = 0.286$). Beyond the covariates, the final model included 9-Hole Pegboard Dexterity Test, Penn Progressive Matrices, Dimensional Change Card Sort Test, Delay Discounting, right temporal pole thickness, left rostral anterior cingulate thickness, left temporal pole thickness, bilateral superior parietal thickness and BOLD signal in the left posterior cingulate cortex during the NBack WM task (Table 5). Machine learning accuracy of the differentiating indicators did not improve accuracy in cross-validated solutions: SVM = 71.94% and Random Forest = 72.32%.

3.5. Supplementary connectivity and co-activation analysis

Coordinates from the task-negative ROIs in the working memory paradigm were examined further for clarification. Specifically, functional connectivity of the implicated ROIs that are most associated with the DMN (PCC, vmPFC) were investigated in the full Human Connectome Project ($n = 1003$) (Fig 3). Although this sample contained individuals from a range of BMI, we considered it optimal to understand the functional significance of the ROIs. The patterns of activity in both cases was consistent with the ROI being part of the DMN. In addition, to further clarify whether task-negative regions of interest (PCC and vmPFC) are part of the DMN, functional connectivity co-activation analyses were completed using NeuroSynth, an open science meta-analytic functional connectivity platform (www.neurosynth.org). The PCC showed functional co-activation with regions consistent with the default mode network, including the medial prefrontal cortex (including the vmPFC), inferior parietal lobule and the medial temporal lobe. Similarly, the vmPFC also showed functional co-activation with the default mode network; the medial prefrontal cortex (including the vmPFC), inferior parietal lobule and the medial temporal lobe (Fig 4).

4. Discussion

The current study examined the neurocognitive correlates of obesity in three major domains - neurocognitive performance in behavioral tasks, neural activity during an fMRI working memory task, and cortical morphometry – and did so in the largest case-control study to date. When taken together, the results reveal numerous aspects of neurocognition that are implicated in obesity. In particular, the results highlight that, compared to controls, obese individuals exhibited worse neurocognitive test performance in cognitive flexibility, impulsivity, verbal memory, fluid intelligence, language and vocabulary comprehension, and psychomotor dexterity. Common themes were deficits in attention, memory and executive function, the mental processes that underlie higher-order cognition such as deliberation and decision making. Reduced capacity in these domains may lead to a reduction in overall self-regulatory control needed to maintain a healthy lifestyle, giving rise to overeating in ways that are parallel to overconsumption of addictive drugs (Volkow et al., 2012; Filbey and Yezhuvath, 2016). A growing body of literature suggests that neurocognitive impairment and dysregulated self-control seen in obesity may mirror that seen in addictive disorders (Amlung et al., 2016a). Particularly consistent with

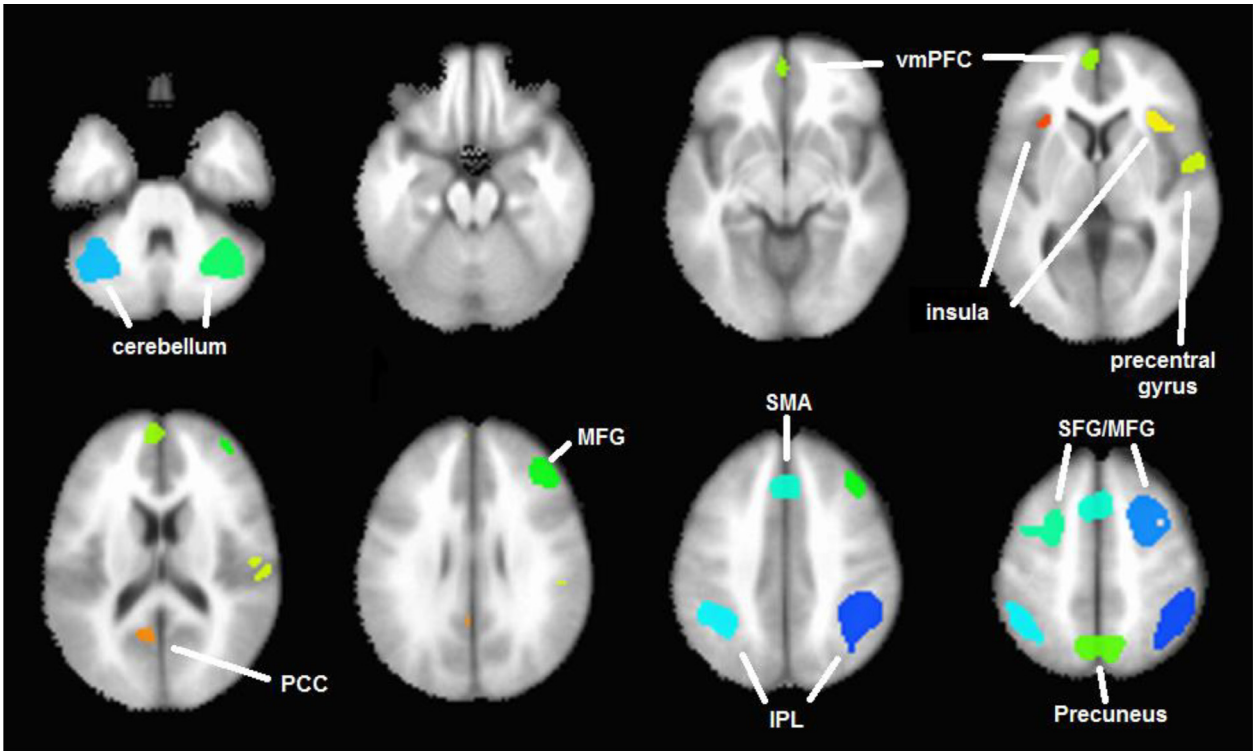

Fig. 1. Empirical regions of interest for the contrast of 2-Back vs 0-back during the N-Back Working Memory task. Note that the highlighted regions reflect spatial locations and do not denote signal intensity.
NOTE: IPL: inferior parietal lobule; SFG: superior frontal gyrus; MFG: middle frontal gyrus; SMA: sensory motor association cortex; vmPFC: ventromedial prefrontal cortex; PCC: precentral gyrus.

this perspective, obese individuals in the current study exhibited significantly greater preference for smaller immediate rewards compared to larger delayed rewards, which is both consistent with other studies obesity (Amlung et al., 2016a) and parallels individuals with addictive disorders (MacKillop et al., 2011; Amlung et al., 2016b).

Worse performance in the obese group relative to controls was also seen on the N-Back working memory test and this difference was associated with increased BOLD signal of in task-negative brain regions. Specifically, deficits in working memory performance corresponded with increased activation of several region of the default mode network including the medial prefrontal cortex, precentral gyrus, and posterior cingulate. These task-negative regions correspond to the default mode network, an interpretation that is further supported by the fact that their suppression was associated with better performance. The default mode network is responsible for spontaneous cognition and self-referential processing, and is typically deactivated during task-based activation and anti-correlated with brain networks associated with executive functioning (Andrews-Hanna et al., 2010; Buckner et al., 2008; Greicius et al., 2008). Heightened DMN activation in addition to worse N-Back performance than controls may reflect a decreased capacity for maintaining attention and focus, thereby leading to poor performance. Since we did not find lower BOLD signal in regions associated with

Table 3
2-Back vs 0-Back BOLD signal differences for obese participants compared to lean BMI controls. Clusters of differences in BOLD signal between obese and lean BMI controls. Correlation between BOLD signal and N-Back accuracy is seen in the Task Correlation column. Task Direction highlights whether N-Back task performance was negatively or positively correlated with brain activity.

Voxels	Peak X, Y, Z	Region	Task Correlation	P value	Task Direction	Obesity vs Control (*F*)	P	η_p^2
1425	+48.0 −44.0 + 54.0	right IPL	0.302	$P<0.001$	+	0.261	0.610	0.000
1086	+28.0 + 12.0 + 60.0	right SFG/MFG	0.375	$P<0.001$	+	0.449	0.502	0.000
931	−32.0 −60.0 −30.0	left cerebellum	0.281	$P<0.001$	+	2.505	0.114	0.004
813	−40.0 −56.0 + 54.0	left IPL	0.287	$P<0.001$	+	0.377	0.539	0.001
729	0.0 + 18.0 + 50.0	bilateral SMA	0.330	$P<0.001$	+	0.001	0.971	0.000
722	−26.0 + 8.0 + 62.0	left SFG/MFG	0.337	$P<0.001$	+	0.235	0.628	0.000
614	+32.0 −60.0 −30.0	right Cerebellum	0.309	$P<0.001$	+	0.012	0.913	0.000
588	+42.0 + 38.0 + 32.0	right MFG	0.331	$P<0.001$	+	0.002	0.969	0.000
497	+2.0 −68.0 + 50.0	bilateral Precuneus	0.380	$P<0.001$	+	0.667	0.414	0.001
346	−2.0 + 60.0 + 4.0	bilateral vmPFC	−0.276	$P<0.001$	–	**13.301**	**<0.001**	**0.019**
321	+60.0 0.0 + 6.0	right precentral gyrus	−0.187	$P<0.001$	–	**9.638**	**0.002**	**0.014**
249	+34.0 + 24.0 −2.0	right Insula	0.293	$P<0.001$	+	0.167	0.683	0.000
122	+40.0 −66.0 −52.0	right cerebellum	0.312	$P<0.001$	+	0.775	0.379	0.001
106	−2.0 −52.0 + 22.0	left PCC	−0.256	$P<0.001$	–	**21.283**	**<0.001**	**0.031**
98	−32.0 + 26.0 + 0.0	left insula	0.300	$P<0.001$	+	0.506	0.477	0.001
72	−44.0 + 30.0 + 34.0	left MFG	0.283	$P<0.001$	+	0.624	0.430	0.001

NOTE: IPL: inferior parietal lobule; SFG: superior frontal gyrus; MFG: middle frontal gyrus; SMA: sensory motor association cortex; vmPFC: ventromedial prefrontal cortex; PCC: precentral gyrus.

Table 4
Brain structural differences in cortical thickness in obese participants versus lean BMI control participants. Significant regions following FDR correction are reported. mOFC: medial orbital frontal cortex; ACC: anterior cingulate cortex.

Cortical Region	Control*M (SD)*	Obese*M (SD)*	F	*p*	*d*
Right mOFC	2.728 (0.14)	**2.751** (0.13)	8.816	0.003	0.235
Right rostral ACC	2.992 (0.09)	**3.037** (0.19)	8.996	0.002	0.238
Right Entorhinal Cortex	**3.433** (0.22)	3.372 (0.24)	6.490	0.01	0.202
Bilateral Inferior Parietal Gyrus	2.601 (0.09)	**2.624** (0.09)	16.587	0.00005	0.323
Right Temporal Pole	**3.680** (0.28)	3.593 (0.31)	10.041	0.001	0.251
Left rostral ACC	3.011 (0.17)	**3.062** (0.18)	18.642	0.00001	0.342
Bilateral Superior Parietal Gyrus	2.292 (0.25)	**2.322** (0.09)	22.718	0.000002	0.378
Left Temporal Pole	**3.460** (0.25)	3.363 (0.28)	19.522	0.00001	0.35

Table 5
Backward conditional logistic regression using covariates and implicated neurocognitive indicators in relation to group status (obese vs control group).

Factor	B	S.E.	Sig.
Covariate			
Age in Years	.125	.029	.000
Race (White Status)	−0.418	.233	.072
Monozygotic Twin Status	−0.264	.229	.249
Dizygotic Twin Status	.133	.261	.611
Household Income	−0.115	.048	.016
Intracranial Volume	.000	.000	.006
Neurocognitive indicators			
9-Hole Peg Boars	−0.029	.010	.005
Penn Progressive Matrices	−0.053	.021	.014
Dimensional Change Card Sort Test	−0.019	.010	.055
Delay Discounting (mAUC)	−1.202	.442	.006
Right Temporal Pole Thickness	−0.664	.366	.069
Left Rostral ACC Thickness	1.948	.528	.000
Left Temporal Pole Thickness	−1.184	.403	.003
Bilateral Superior Parietal Thickness	4.408	1.039	.000
Left PCC Thickness	.018	.005	.000

NOTE: ACC: anterior cingulate cortex; PCC: posterior cingulate cortex.

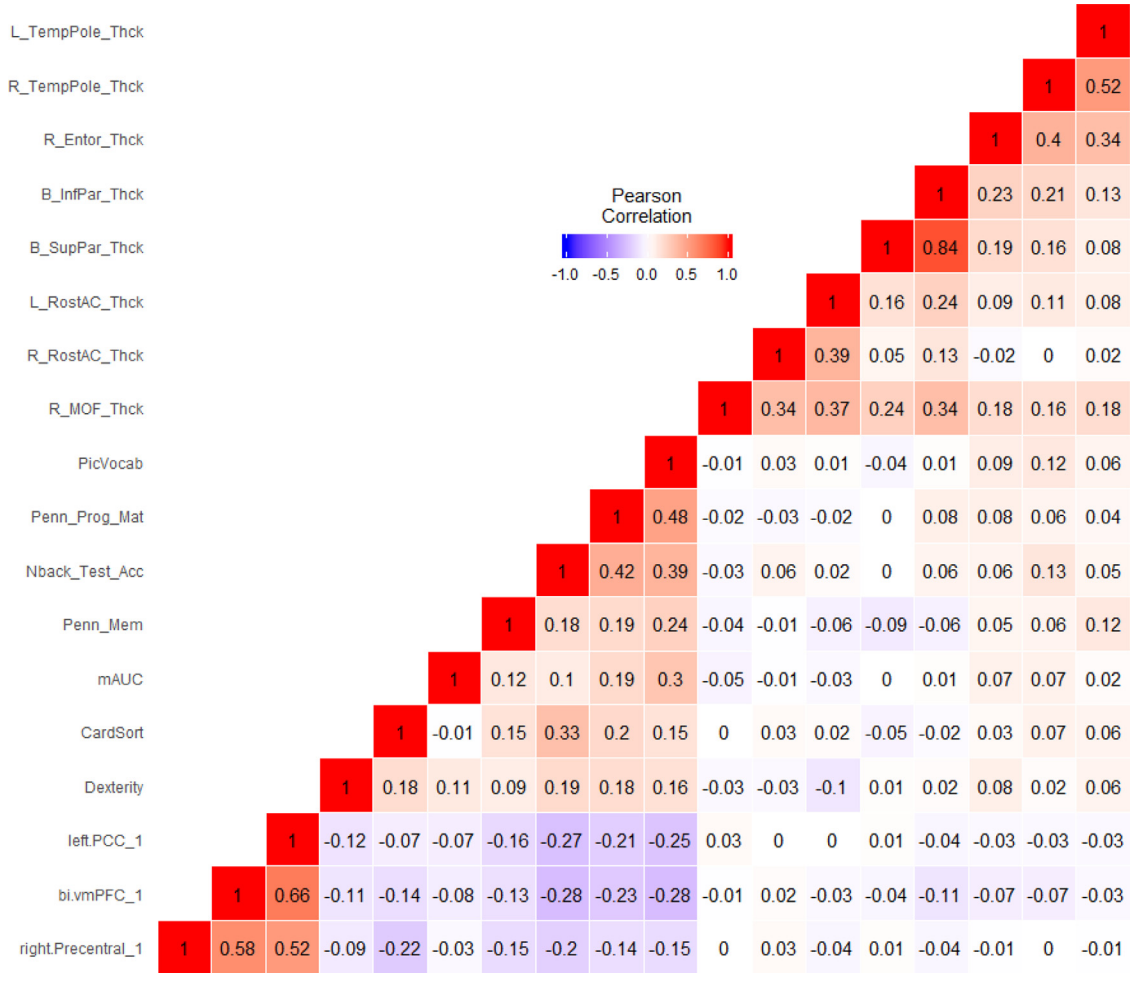

Fig. 2. Correlations among neurocognitive indicators associated with obesity status.
NOTE: Pearson correlations between variables showing significant differences between obese and control groups. L_TempPole_Thck: Left Temporal Pole Thickness; R_TempPole_Thck: Right Temporal Pole Thickness; R_Entor_Thck: Right Entorhinal Thickness; B_InfPar_Thck: Bilateral Inferior Parietal Thickness; B_SupPar_Thck: Bilateral Superior Parietal Thickness; L_RostAC_Thck: Left Rostral Anterior Cingulate Thickness; R_RostAC_Thck: Right Rostral Anterior Cingulate Thickness; R_MOF_Thck: Right Medial Orbital Frontal Thickness; PicVocab: Picture Vocabulary; Penn_Prog_Mat: Penn Progressive Matrices; NBack_Test_Acc: NBack Test Accuracy; Penn_Mem: Penn Working Memory Test; mAUC: Delay Discounting mean Area Under the Curve; CardSort: Dimensional Change Card Sort Test; Dexterity: 9-Hole Peg Board; left.PCC_1: Left Posterior cingulate cortex BOLD activity bi.vmPFC_1: Bilateral ventromedial prefrontal cortex BOLD activity; r.precentral_1: Right precentral gyrus BOLD activity.

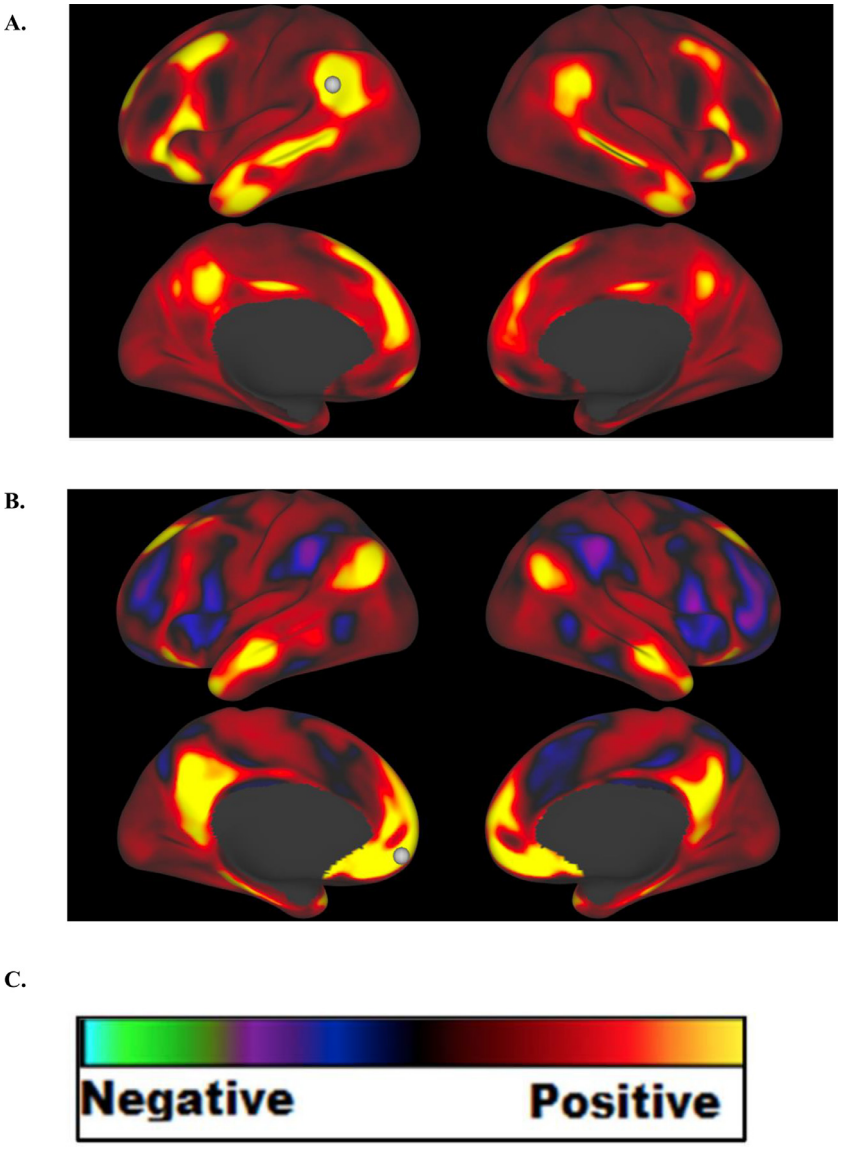

Fig. 3. Resting state functional connectivity for seed regions based on coordinates from the task-negative regions of interest in the N-Back Working Memory Paradigm in the Human Connectome Project (N = 1003) total sample. Each image shows a voxelwise correlation of all voxels on the cortical surface (no subcortical regions were shown) with a seed identified from the task-negative regions of interest identified from the N-Back Working Memory Paradigm between obese individuals and controls (white sphere). Seeds were A) posterior cingulate cortex and B) ventromedial prefrontal cortex. Panel C shows the colour scale used.

NBack performance in the obese group, the inability to disengage the default mode network during the N-Back Test suggests interference from inadequate default mode suppression, as opposed to specific deficits in the task-positive cognitive network. Alterations in DMN activity in obese individuals relative to controls has been reported at rest (Kullmann et al., 2011) and in response to overfeeding (Tregellas et al., 2011). In this capacity, increased DMN activation was suggested to reflect increased attention to internal states mediating appetite or gut signals (Tregellas et al., 2011). Deficient suppression of the default mode network during working memory tasks has been associated with a number of other psychiatric syndromes in which cognitive impairment is a hallmark, including early psychosis (Fryer et al., 2013) and major depressive disorder (Bartova et al., 2015). The hypothesis that inefficient DMN suppression could affect attentional processing is also supported by evidence ineffective default mode network suppression is linked to distractibility in attention deficit hyperactivity disorder and this inattention may contribute to poor decision making (Fassbender et al., 2009).

Significant differences in cortical morphometry were present bilaterally for the anterior cingulate, temporal pole, and the inferior and superior parietal gyrus, and localized in the right hemisphere for orbitofrontal cortex and entorhinal cortex. Further, our multimodal approach highlighted that obese individuals have a thinner cerebral cortex in regions associated with the limbic system, and a thicker cerebral cortex in regions associated with the default mode network, inhibition and salience network. Previous studies suggest that decreased cortical thickness in the temporal pole reflect impairment in emotional regulation, attention and decision making (Fernández-Jaén et al., 2014). When taken together, both increased BOLD activity and cortical thickness in regions associated with the default mode network may reflect enhanced interference of the DMN during task-based activity and, as a result, a decreased functional capacity.

Finally, in integrative analyses, it was notable that the data-driven logistic regression included variables from all three domains. Thus, it was not the case that any single set of neurocognitive findings was largely attributable to findings from another domain (e.g., all implicated behavioral performance indicators being attributable to differences in morphometry). An interesting collateral finding in the

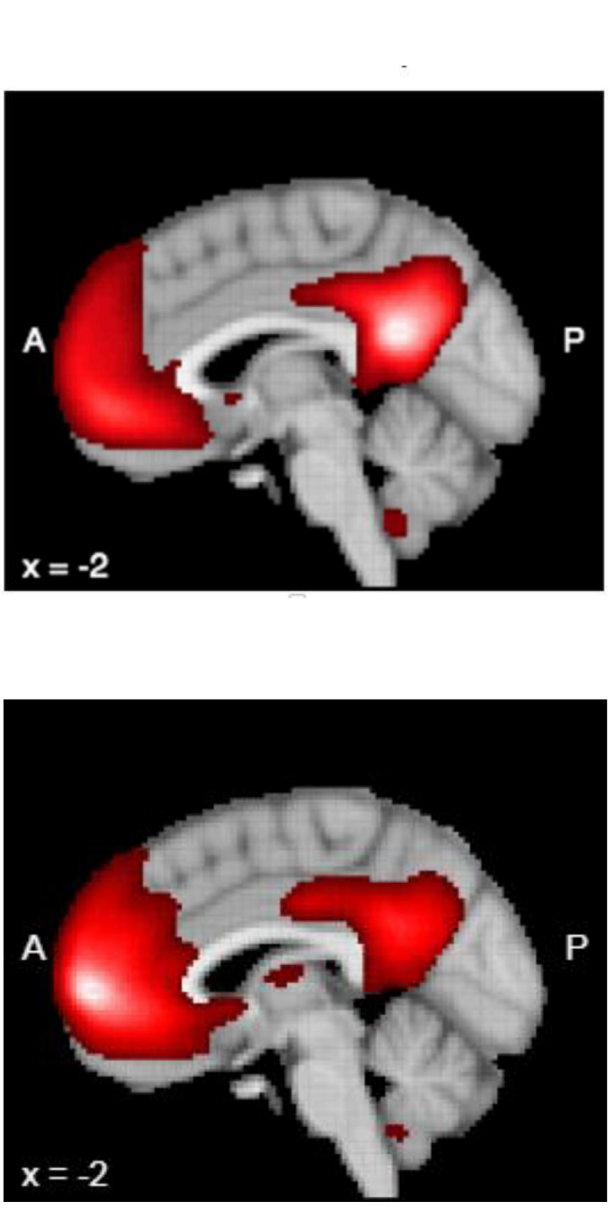

Fig. 4. Neurosynth co-activation meta-analysis of PCC and vmPFC, threshold at false discovery rate of $p \leq 0.05$. Neurosynth had 14,371 studies and 150 000 brain locations at the time of analysis (August 4, 2019). Red activation represents positive co-activation with seed region (white corresponds with the seed). Maps show co-activation in the sagittal plane of the following seed regions: A) PCC (−2.0 −52.0 + 22.0); B) vmPFC.(−2.0 + 60.0 + 4.0).

partial correlations was significant inverse associations between task-negative brain activation and neurocognitive test performance (other than delay discounting). This suggests that beyond the in-scanner N-Back paradigm, inadequate or inefficient suppression of default mode network is associated with poorer behavioral performance on multiple cognitive tasks and it suggests that, methodologically, assessing default mode network suppression on one task has relevance to others.

As a cross-sectional investigation, the current study cannot address whether the differences observed are causes or consequences of obesity. In particular, several hypotheses have emerged proposing a consequential relationship between high BMI and poor cognitive outcomes. Adiposity has been theorized to induce innate immune activation and low-grade inflammation in individuals with obesity (Yang et al., 2018; Miller and Spencer, 2014) and systemic low-grade inflammation may then translate to localized inflammation in brain regions responsible for mediating reward processing and cognitive functioning. Specifically, localized inflammation in these brain regions may impair neurogenesis, precipitate neuronal apoptosis and synaptic remodeling, and disrupt the integrity of the blood brain barrier (Miller and Spencer, 2014), ultimately giving rise to diminished cognitive capacity (Patel and Frey, 2015). On the other hand, it is equally possible that neurocognitive deficits play an etiological role, contributing to the development of obesity. In support of this, there is evidence that deficits in the domains implicated here have been shown to predict the development of substance abuse (Fernie et al., 2013; Audrain-McGovern et al., 2016). However, another important aspect to the association between obesity and subsequent lower brain performance may be the link between obesity and socioeconomic adversity (Puhl and Heuer, 2012). It is certainly credible that socioeconomic adversity decreases environmental enrichment and access to resources, leading to less brain stimulation and fewer opportunities for acquiring new knowledge (Puhl and Heuer, 2012). Moreover, due to decreased access to resources children that require additional support may not afford those valuable resources to aid in the resolution of maladaptive patterns of behaviour or learning difficulties. As an example, early life stress, an established risk-factor for subsequent obesity (Gunstad et al., 2006b), has also been linked to self-regulatory deficits also (Lovallo, 2013; Oshri et al., 2015). Low socioeconomic status and, probably as a result, lower expenditures on food has been linked to less-healthy eating choices (Drewnowski and Darmon, 2005). Equally, it is important to recognize that etiological or consequential roles may differentially apply to the indicators implicated. Longitudinal studies of neurocognitive factors and obesity will be essential to systematically address causal versus consequential roles.

Interestingly, the nature of obesity can also be explored through the lens of food addiction, as a growing body of literature suggests that food addiction can be thought of as a subtype of obesity or perhaps even an independent condition (Murphy et al., 2014; Epstein and Leddy, 2006). Specifically, there are neurobiological similarities between the effects of high palatability foods (high-sugar, high-salt, high-fat) and the effects of addictive drugs, insofar as high palatability foods similarly increase extracellular dopamine levels in the striatum (Fortuna, 2012). Behaviorally, like obese participants in this study, food addiction is associated with impulsive delay discounting (Murphy et al., 2014); indeed, food addiction has been found to mediate the link between delay discounting and obesity (Murphy et al., 2014). In this study, we focused exclusively on differences based on obesity status as no measure of food addiction was available, but concurrently probing the neurocognitive intersection (and lack thereof) of obesity and food addiction in future studies is clearly warranted.

The current study should be considered in the context of its strengths and limitations. Among its strengths are the fact it is the first study to use a multimodal approach to investigate the neurocognitive correlates of obesity and is the largest to date by several hundred participants. Further, the case and control groups were largely similar to each other in terms of age, sex distribution, income, and other substance use, differing most substantially in terms of their BMI. Furthermore, the obese individuals did not have obesity-related medical conditions that would potentially result in frank negative consequences on brain structure or function, or would significantly impact cognitive abilities (e.g., hyperlipidemia, diabetes mellitus, cerebrovascular disease). Therefore, the results in neurocognitive functioning and brain changes do not appear to be attributable to specific medical sequelae of obesity. A limitation of the current study is that it does not contain precise measures of adiposity, other anthropometrics, or metabolic functioning and thus solely relies on BMI as a measure of obesity, which is a relatively coarse measure. A further consideration is that most of the effect sizes were relatively small in absolute magnitude. However, when considered together, the classification was substantially improved, and the integrative analyses revealed that the neurocognitive indicators increased accuracy by almost a quarter of the maximum classification possible. Interestingly, although considered promising,

machine learning did not improve classification accuracy in this study. Finally, a further nuance was that the neurocognitive variables were better at classifying healthy individuals rather than obese individuals, perhaps suggesting greater cognitive heterogeneity within the obese group.

5. Conclusions

In sum, this multimodal study revealed numerous neurocognitive differences between individuals with obesity compared to controls. In behavior, brain activity, and brain structure, these differences collectively appeared to reflect deficits in executive functioning, memory, and attention; and insufficient suppression of default mode network. This may reflect early stage neuroinflammatory consequences of obesity on the brain, cognitive vulnerabilities that contribute to the development of obesity, or a combination of the two. Disentangling whether these differences reflect adverse consequences or etiological pathways is a high priority for future investigations.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

James MacKillop is a principal and senior scientist in BEAM Diagnostics, Inc. No other authors have declarations.

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