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Brain and behavioral correlates of insulin resistance in youth with depression and obesity

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ABSTRACT

Depression, together with insulin resistance, is increasingly prevalent among youth. These conditions have traditionally been compartmentalized, but recent evidence suggests that a shared brain motivational network underlies their co-occurrence. We posit that, in the context of depressive symptoms, insulin resistance is associated with aberrant structure and functional connectivity in the Anterior Cingulate Cortex (ACC) and hippocampus. This motivational neural circuit underlies dysfunctional behavioral responses and increased sensitivity to rewarding aspects of ingesting high calorie food that lead to disinhibition of eating even when satiated. To investigate this shared mechanism, we evaluated a sample of forty-two depressed and overweight (BMI > 85th %) youth aged 9 to 17. Using ACC and hippocampus structural and seed-based regions of interest, we investigated associations between insulin resistance, depression, structure (ACC thickness, and ACC and hippocampal area), and resting-state functional connectivity (RSFC). We predicted that aberrant associations among these neural and behavioral characteristics would be stronger in insulin resistant compared to insulin sensitive youth. We found that youth with greater insulin resistance had higher levels of anhedonia and more food seeking behaviors, reduced hippocampal and ACC volumes, and greater levels of ACC and hippocampal dysconnectivity to fronto-limbic reward networks at rest. For youth with high levels of insulin resistance, thinner ACC and smaller hippocampal volumes were associated with more severe depressive symptoms, whereas the opposite was true for youth with low levels of insulin resistance. The ACC-hippocampal motivational network that subserves depression and insulin resistance separately, may represent a critical neural interaction that *link* these syndromes together.

1. Introduction

1.1. Shared brain mechanisms of depression and insulin resistance

Depression combined with insulin resistance, a precursor to diabetes in which cells fail to respond to the normal actions of the hormone insulin, is increasing in youth worldwide (Merikangas et al., 2010; Neef et al., 2013) and is leading to progressively severe, atypical, and treatment refractory forms of depression (Lamers et al., 2010; Penninx et al., 2013; Ramasubbu, 2002; Takeuchi et al., 2013). Traditionally, these syndromes have been compartmentalized as separate emotional and physical health conditions. However, recent evidence in adults (McIntyre et al., 2009, 2010; Ryan et al., 2012; Soczynska et al., 2011) and youth (Shomaker et al., 2011) suggests fundamental neurobehavioral disruptions that may bidirectionally link these syndromes (Beydoun et al., 2016; Gunnell et al., 2016; Hiles et al., 2016), implying a shared underlying mechanism (Buhl et al., 2010; Rasgon et al., 2010) that may mediate the progressive worsening of depressive symptoms (Al Mamun et al., 2007; Ernersson et al., 2010; McElroy et al., 2004; Pott et al., 2010). To have the greatest impact on early intervention efforts to mitigate the progression of depressive symptoms (Hills et al., 2007), it is essential to clarify *when* and *how* the neurobehavioral disruptions underlying these syndromes emerge. Characterizing these disruptions early in development in children and adolescents provides a unique opportunity to understand how depression and insulin resistance interact during the earliest stages of risk.

1.2. Depression is a stress risk factor for insulin resistance

Depression has metabolic consequences across the lifespan (McIntyre et al., 2009; Rasgon and Kenna, 2005; Rasgon and McEwen, 2016). Among children and adolescents, obesity and insulin resistance

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have been attributed to an overactive stress response that accompanies depression (Pervanidou and Chrousos, 2012). The hypothalamic-pituitary-adrenal (HPA) axis, which modulates the production of the stress hormone cortisol, is hyperactive in 40–60% of individuals with Major Depressive Disorder. Excess circulating cortisol and its disruption of glucoregulatory mechanisms is thought to lead to hyperinsulinemia and insulin resistance, which promotes the development of diabetes and cardiovascular disease (Brown et al., 2004). Indeed, animal and human studies have suggested that exposure to maternal stress even in the prenatal period may represent very early modifiable risk factors during fetal and infant development that predispose offspring to cardiovascular disease in adult life; these risk factors are targets for prevention (van Dijk et al., 2010). Early and serious stress exposure is increasingly being shown to result in metabolic consequences. A recent compelling study among healthy youth in Australia demonstrated that early and even preclinical symptoms of depression increase insulin resistance, independent of adiposity (Olive et al., 2017). Alternatively, the correlation between depressive symptomatology and insulin resistance could be explained by maladaptive lifestyle choices associated with depression such as physical inactivity and poor dietary habits that increase the risk of developing insulin resistance (Pearson et al., 2010). In youth at high-risk for obesity, higher levels of depression severity in childhood were associated with the development of insulin resistance six years later, independent of changes in body mass index (BMI), implicating a direct pathophysiological link between depression and insulin resistance (Shomaker et al., 2011).

1.3. Insulin resistance is a risk factor for worsening depression

There is substantial evidence both that depression can promote insulin resistance and that insulin resistance is a risk factor for the worsening of existing depressive symptoms. Insulin receptors are ubiquitous throughout the central nervous system, and central insulin resistance is linked to a variety of cognitive impairments across the lifespan (Akın et al., 2017; Liu et al., 2014; McIntyre et al., 2015). Importantly, insulin receptors are expressed in key reward regions (Figlewicz, 2016), and insulin signals a reward behavior through mechanisms such as enhanced dopamine release (Eisenstein et al., 2015; Khanh et al., 2014; Stouffer et al., 2015) and GABA inhibition (Williams, 2015). Collectively, these studies implicate a role of insulin in the regulation of reward behaviors. Similarly, there are a variety of brain regions that are both sensitive to insulin and implicated in the pathophysiology of depression (Ryan et al., 2012). These common brain regions contribute to reward-related cognitions and behaviors that most likely lead to depression symptom expression and progression (McIntyre et al., 2010). Specifically, aberrant reward-seeking behaviors likely drive the vicious cycle between depression and insulin resistance leading to the progression of worsening depressive symptoms over time. This process begins when depressed youth initially experience pleasure from eating unhealthy or “comfort” foods to improve their mood, which consequently reinforces motivation for eating (Weltens et al., 2014). Overeating then becomes more frequent due to a reinforced drive for food, and the cues associated with food also produce a reward response, which further strengthens the neural reward pathway associated with food consumption (Christensen and Pettijohn, 2001). Over time, responses to actual food receipt diminish and may drive continued overeating in an attempt to experience the previous level of pleasure, resulting in weight gain and insulin resistance (Anthony et al., 2006). This reward prediction error, defined as the discrepancy between an expected reward and an actual reward, is central to the progression of depressive symptoms in overweight youth (Gradin et al., 2011; Huys et al., 2013; Kumar et al., 2008; Singh, 2014).

There are other behavioral and brain findings that link insulin resistance to worsening of depression. Individuals with insulin resistance are more likely to be obese and, therefore, more likely to behaviorally experience peer victimization (Nemiary et al., 2012), which is well established to be strongly related to depression (Hawker and Boulton, 2000). Youth with obesity are also more likely to experience body dissatisfaction, negative self-esteem, and anhedonia (Goldfield et al., 2010). Obese adolescents demonstrate brain structural abnormalities in orbitofrontal and anterior cingulate cortices (Yau et al., 2014), reduced hippocampal volumes (Yau et al., 2012), and functional abnormalities in addiction related neural pathways in frontotemporal and parietal cortices (Feldstein Ewing et al., 2016). However, there is limited understanding of how these brain abnormalities relate to insulin resistance in the context of depression. Moreover, to our knowledge, there are no studies that have evaluated whether brain structural or functional abnormalities in youth vary with fasting versus post-glucose challenge measurements of insulin resistance. A comprehensive assessment of behavioral and brain correlates of insulin resistance in fasting and post-glucose challenge states would clarify early brain mechanisms of insulin resistance that have not to date been well characterized.

1.4. Using the approach motivation construct in childhood to investigate early relations between depression and insulin resistance

Compelling data separately in pediatric onset mood disorders (Gabbay et al., 2013; Singh et al., 2013, 2014) and insulin resistance (Adam et al., 2013; Androutsos et al., 2014; Anthony et al., 2006; Kullmann et al., 2012; Ryan et al., 2012) suggest neurobehavioral disruptions in the Research Domain Criteria (RDoC) construct of *approach motivation*, which involves mechanisms or processes that regulate the pursuit of desired rewards and goals in the environment. Aberrant reward sensitivity may explain the relation between reward processing and mood symptoms. For example, decreased approach motivation is a defining characteristic of classic unipolar depression, in which reward *hypo*sensitivity is associated with motivational deficits in anhedonia (Nusslock and Alloy, 2017). In the combined phenotype of depression and insulin resistance (Androutsos et al., 2014; Ryan et al., 2012), maladaptive behaviors such as inactivity and compensatory overeating may be represented by neurobiological disruptions in function, structure, and connectivity in the reward network; these disruptions lead, in turn, to subsequent worsening of depressive symptoms. We posit that such disruptions are localized to two central regulatory regions in the neural reward network: the Anterior Cingulate Cortex (ACC) (Foland-Ross et al., 2015, p.; Pruessner et al., 2010; Ryan et al., 2012; Teh et al., 2010; Wozniak et al., 2012) and the hippocampus (Chantiluke et al., 2012; Hulvershorn et al., 2011; Keding and Herringa, 2015; Marusak et al., 2017), which each play key roles in emotion, stress, and insulin regulation.

There are several reasons why the ACC and hippocampus are likely key players in the neuroendocrine and clinical consequences of sedentary behaviors and overeating among depressed youth. First, as illustrated above, aberrant structure and function in these regions are reproducible and consistently implicated uniquely and jointly to the pathophysiology of both pediatric depression and insulin resistance syndromes. Insulin is a potent anorexigenic hormone. Prior fMRI studies suggest differential activation during feeding states of a complex neural network that regulates appetite through the hypothalamus, thalamus, limbic (hippocampus) and paralimbic (insular cortex, anterior cingulate gyrus, and the orbitofrontal cortex) regions (Pliquett et al., 2006). Second, both the ACC and hippocampus play a critical role in stress regulation throughout development, and departures from typical developmental trajectories for these regions can lead to depressive symptoms. For example, modified developmental changes in intrinsic functional networks that proceed from the ACC affect key self-regulatory processes, which, when vulnerable, then increase adolescent risk for depression (Jalbrzikowski et al., 2017; Lichenstein et al., 2016). Third, the ACC and hippocampus are highly connected (de Kwaasteniet et al., 2013; James et al., 2017; Ye et al., 2016; Zeng et al., 2012) and the interdependence between these regions are implicated in

understanding mesostriatal dopaminergic disturbances in approach motivation in depression (Hamilton et al., 2011). Moreover, aberrant connectivity between these regions may be mediated by oxidative stress, particularly in early stages of depressive illness (Hermens et al., 2017). Compellingly, downregulation of cingulate-hippocampal connectivity may represent a treatment biomarker for persistent and treatment refractory forms of depression (Argyelan et al., 2016; Wong et al., 2016) which are common among individuals with insulin resistance (Lamers et al., 2016).

Here, we systematically investigated reward sensitivity by evaluating the neurobehavioral disruptions in approach motivation in depressed youth with varying levels of insulin resistance. Our study aimed to characterize overweight or obese youth with depression for behavioral, neurostructural, and neurofunctional disruptions in approach motivation and the relation of such disruptions to a clinical assessment of insulin resistance and depression severity. We predicted that youth with higher, compared with lower, levels of insulin resistance would exhibit evidence of impaired approach motivation: behaviorally, through more anhedonia and more food seeking behaviors, neurostructurally, through reductions in volume in the hippocampus and ACC, and neurofunctionally, through greater levels of ACC and hippocampal dysconnectivity to the fronto-limbic reward networks while at rest. Further, we predicted that insulin-related brain and behavioral measures of aberrant approach motivation would correlate with depression severity. Finally, we predicted these findings would be consistent across two related indices of insulin resistance: fasting insulin and insulin measured after an oral glucose challenge.

2. Materials and methods

2.1. Study participants, screening procedures, and analytic approach to behavioral correlates of insulin resistance

Forty-two overweight or obese youth between the ages of 9 to 17 years with currently untreated depressive symptoms were recruited for this study. All adolescent participants provided written assent and at least one parent or legal guardian provided written informed consent prior to all study procedures. This study was approved by Stanford University's Institutional Review Board. Participants were recruited from pediatric mood and weight control programs, and community advertisements.

Children and adolescents were included if their body mass index (BMI) was at the 85th percentile or higher for their age and sex based on the Center for Disease Control and Prevention BMI calculator for children and teens (https://nccd.cdc.gov/dnpabmi/calculator.aspx). During the screening visit, height (with accuracy of 0.1 cm) and weight (with accuracy of 0.1 kg) were measured with the Seca 284, an electronic measuring station, after the removal of shoes and jackets. Two measures of height were obtained and averaged. Participants were also evaluated for at least moderate levels of depression severity using the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski et al., 1984) administered separately to parents and youth by a study clinician or trained coordinator. Participants were included if their raw CDRS-R summary score was > 35, signifying at least moderate levels of depression severity at the time of enrollment. All youth in this sample were treatment seeking for active unremitted symptoms that were early in the course of their depressive illness.

Individuals were assessed for current and lifetime psychiatric disorders with the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (KSADS-PL) (Kaufman et al., 1997). Youth were excluded if they were currently being treated for a mood disorder when evaluated at the screening visit. Youth were also excluded if they had type 1 or type 2 diabetes, were taking medication that affected their weight or metabolism, had a contraindication for an MRI (e.g. metal in their body or anterior-posterior diameter > 46 cm) or if their Full-4 IQ score on the Wechsler Abbreviated Scale of Intelligence (WASI) (Psychological Corporation, 1999) was < 70.

We used the CDRS-R as our primary clinical assessment of depressive symptoms in youth. This clinician-administered interview with parents and children captured depression symptom severity and its impact on multiple areas of functioning. There were several advantages of using the CDRS-R over self-report measures of depressive symptoms: (i) it provided the presence or resolution of a comprehensive list of approach motivation-related symptoms that may have differential associations with insulin resistance (Austin et al., 2014), their levels of severity, and their impact on function (ii) it only takes 10 min to complete by the clinician; (iii) it is empirically derived and validated; and (iv) it is administered to both parent and child to provide multi-informant data. We also used the Snaith Hamilton Pleasure Scale (SHPS) (Snaith et al., 1995), the Temporal Experience of Pleasure Scale (TEPS) (Ho et al., 2014), and the Three-Factor Eating Questionnaire (TFEQ) (Shearin et al., 1994) as behavioral measures of approach motivation. The SHPS is a 14-item scale of hedonic function self-reported by the youth participants. Higher SHPS values represent high levels of anhedonia. The TEPS assesses consummatory and anticipatory approach motivation of the child as assessed by the parent with higher scores denoting higher levels of anticipatory and consummatory pleasure. The TFEQ is an easy self-rated instrument completed by youth that measures 3 aspects of eating behavior: cognitive restraint, uncontrolled eating or eating disinhibition, and emotional eating. It has been extensively studied and has been shown to be valid and reliable in youth.

2.2. Assessment of insulin resistance

After the screening visit, eligible youth were assessed for insulin resistance and neural markers of approach motivation using structural and functional magnetic resonance imaging (MRI) scans. Serum markers of insulin resistance were assessed using a 2-hour oral glucose tolerance test (OGTT). After a 10-hour fasting period and an initial fasting blood draw, participants consumed 75 g of oral glucose and had their blood drawn every 30 min for 2 h to measure insulin and glucose. Insulin values were measured by immunoassay. Insulin resistance was determined by fasting insulin measures and with the Matsuda Index, calculated with the following formula: Matsuda = $10{,}000 / (G_0 \times I_0 \times G_{mean} \times I_{mean})^{1/2}$ where G_0 is fasting glucose, I_0 is fasting insulin, G_{mean} is average serum glucose across entire OGTT period, and I_{mean} is mean insulin across entire OGTT period (Matsuda and DeFronzo, 1999). Fig. 1 depicts average blood insulin levels over time after glucose ingestion.

2.3. Neuroimaging data acquisition

After participants were familiarized with the scanning environment in an MRI simulator, whole-brain images were acquired on a 3T GE Signa Excite (General Electric Co., Milwaukee, WI) scanner equipped with an 8-channel head coil. Functional images were collected at rest using a spiral pulse sequence with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle (FA) = 80°, field of view (FOV) = 22 cm, number of slices = 30 slices in the axial plane, and slice thickness = 4 mm with a gap of 1 mm. The first four volumes of each participant's resting-state scan were discarded at the scanner to allow for stabilization of longitudinal magnetization. High-order shimming was used before acquisition of resting-state data to improve field homogeneity. High-resolution structural images were also collected to assist in registration of functional data to standard space using a fast spoiled gradient recalled (3D FSPGR) pulse sequence with the following parameters: TR = 8.5 ms, TE = 3.32 ms, TI = 400 ms, flip angle = 15°, field of view (x) = 25.6 cm, matrix of 256 × 256, number of slices = 186 slices in the axial plane, and a slice thickness of 1 mm.

2.3.1. Structural MRI data processing

Scans were processed using FreeSurfer to produce measures of

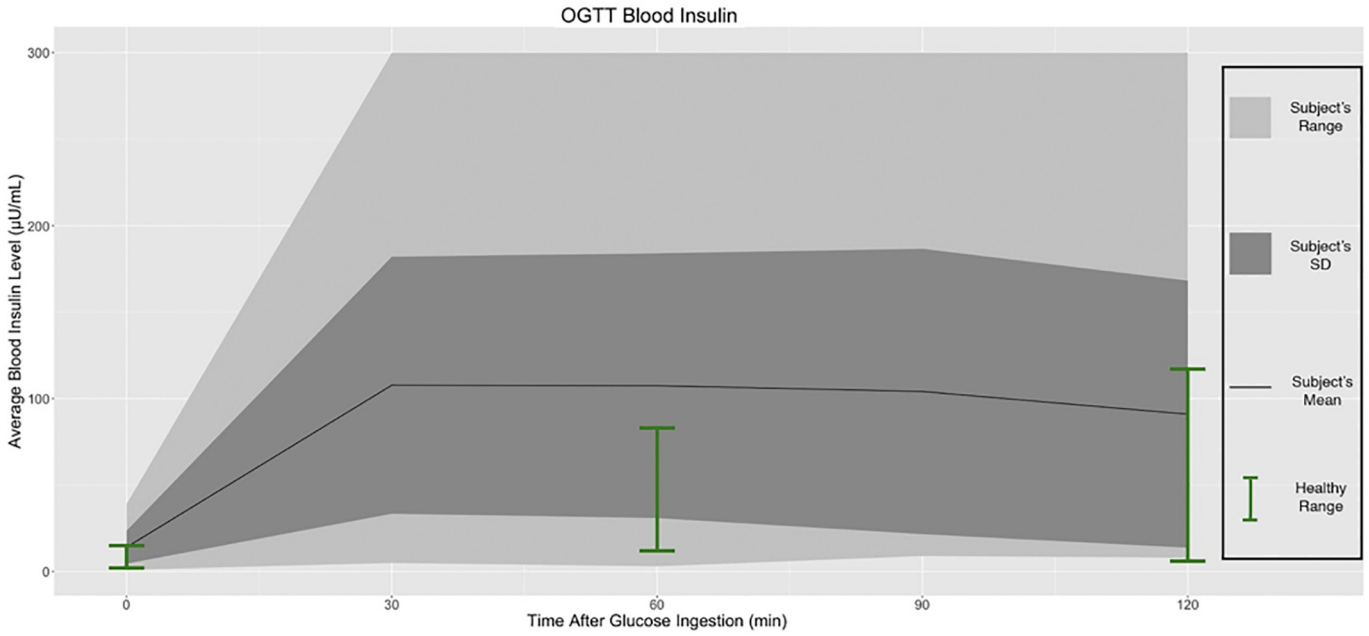

Fig. 1. Average blood insulin level across time after glucose challenge.

cortical gray matter thickness version 5.3, (http://surfer.nmr.mgh.harvard.edu) (Fischl and Dale, 2000; Salat et al., 2004). To ensure the accuracy of gray/white matter segmentation, exclusion of scalp and other non-brain tissue, and the inclusion of brain tissue and cortical surfaces were visually inspected by an expert (YVZ). Manual corrections were performed by this rater where appropriate, in accordance with previously established procedures (Black et al., 2012; Mazaika et al., 2016). ACC cortical thickness and area (rostral and caudal regions combined together from the Desikan-Killiany Atlas), along with bilateral hippocampus, with left and right hemispheres averaged together, were assessed to test study hypotheses. Given that adolescents with depression may show differential topography in subregions of the ACC (Schmaal et al., 2017), to maximize our ability to detect subtle aberrations in neuronal architecture, we measured and report on both ACC cortical thickness and area.

2.3.2. Hypothesis testing for structural MRI data

There is a critical need in this nascent field to understand how levels of insulin map on to neural and behavioral correlates of insulin resistance and to provide biological plausibility for cut-offs that are otherwise unresolved or controversial in youth (Brambilla et al., 2007; van der Aa et al., 2017). We theorized that the yet untested relation between depression and aberrant brain structure differs depending on level of insulin resistance. Moreover, relations among these continuous variables are nonlinear (de la Torre-Luque et al., 2016; Jani et al., 2014). We used a well-known trichotomized collapsing method to maximize the information learned from these nonlinearly related continuous variables (Gelman and Park, 2009). This collapsing method was especially important to improve power in our moderately sampled study. Thus, to reveal the effect of very low and high insulin levels, we dichotomized insulin-related variables (fasting insulin and Matsuda Index) in two different ways. First, they were dichotomized into two categories: bottom 1/3 (low = 1) and the rest (low = 0), defined by a fasting insulin < 10 or a Matsuda < 2.54, and top 1/3 (high = 1) and the rest (high = 0), defined by a fasting insulin ≥16 or a Matsuda ≥3.88. Among the total sample of 42 youth and based on the first categorization (low vs. rest), 14 was categorized as having low insulin and 28 as moderate to high. Based on the second categorization (high vs. rest), 14 was categorized as having high insulin and 28 as low to moderate. Second, we compared the correlation between depression and neural structure in the ACC and hippocampus across the two categories for each dichotomization. Specifically, we used a multiple group comparison approach implemented in Mplus (Muthén and Muthén, 1998) using maximum likelihood estimation with robust standard errors. For graphical purposes, significant relations between structure and depression severity were depicted using partial correlation coefficients in SPSS v.22 with age, sex, and Matsuda Index as covariates.

2.3.3. Functional MRI pre-processing

Pre-processing of resting-state data was carried out using FEAT Version 6.00 within FSL (FMRIB's Software Library; www.fmrib.ox.ac.uk/fsl). Each participant's 210-volume functional dataset was realigned to compensate for small head movements using MCFLIRT (Jenkinson et al., 2002), skull-stripped using the Brain Extraction Tool (BET) (Smith, 2002); spatially smoothed using a Gaussian kernel of 5 mm FWHM, intensity normalized by a single multiplicative factor, and band-pass filtered to correct for baseline drift and high frequency noise (high-pass temporal filter: Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 s; low-pass temporal filter: Gaussian with sigma = 2.8 s). Functional images were registered to participants' corresponding high-resolution T1-weighted structural images and then normalized to Montreal Neurological Institute (MNI) space using a 12-parameter transformation. Masks of white matter and cerebrospinal fluid (CSF) generated from each subject's anatomical images were applied to the functional data to extract white matter and CSF time-series. These time-series were used together with 6 motion parameters as nuisance regressors in a voxel-wise regression of the fMRI data. Data scrubbing was also performed following the method of Power et al. (2014), excluding any volume in which either the value for DVARS (the root mean squared change in BOLD signal from the prior volume) or the value for framewise displacement exceeded the upper boxplot threshold (the 75th percentile plus 1.5 times the interquartile range), along with the previous volume and the 2 following volumes. All participants in this study had < 33% of the volumes requiring removal, enabling inclusion in this analysis. Residuals of the voxel-wise regression were used in subsequent seed-based connectivity analyses.

2.3.4. Hypothesis testing for functional MRI data

The Harvard-Oxford cortical and subcortical atlases were used to

define anatomical regions, using a probability threshold of 25%. The anterior cingulate and bilateral hippocampus were selected as seed regions. ROIs were registered to the preprocessed fMRI data, and the mean time series of voxels in these regions were extracted and used as a primary regressor in a GLM analysis of all other voxel time series, resulting in whole-brain ACC and hippocampus RSFC maps.

At the group level, inter-subject differences in functional connectivity were investigated using a voxel-wise GLM analysis that modeled each insulin measure as a covariate of interest and age and sex as covariates of no interest. Gaussian random field theory was used to correct for multiple comparisons with a cluster threshold of $z > 2.3$ and $p < 0.025$ (to compare for multiple comparisons with 2 seeds). These higher-level analyses generated thresholded *Z*-statistic maps of those voxels exhibiting significant insulin-related variation in coactivation for each seed. To further investigate the associations between RSFC and insulin measures in significant clusters resulting from the voxel-wise test, parameter estimates (proportional to fMRI signal change) of BOLD signal response were extracted using featquery. Pearson correlations were used in exploratory analyses to assess the relation between parameter estimates from the emergent clusters and depression severity (CDRS-R) scores.

3. Results

3.1. Demographic and clinical characteristics

Demographic and clinical characteristics of the participants are summarized in Table 1. 62% of youth in this sample were female, with diverse ethnic backgrounds (55% Caucasian), with above average IQ (103.88 ± 15.03), with an average BMI in the obese range (29.89 ± 5.69), and with moderate to severe depression severity (CDRS-R = 70.32 ± 7.17). Imaging results remained significant after covarying for BMI, but given the wide age range and known sexual dimorphism in depression and insulin resistance, age and sex were covaried in subsequent analyses. Fasting insulin and Matsuda Index are highly inversely correlated ($r = 0.79$, $p < 0.001$). The relation between fasting insulin and Matsuda Index in all participants is depicted in Fig. 2.

3.2. Behavioral correlates of insulin resistance

Relations between clinical depression severity and behavioral measures of approach motivation were explored with post-glucose challenge and fasting measurements of insulin resistance. Higher levels of anhedonia ($r = -0.408$, $p = 0.009$) and eating disinhibition ($r = -0.341$, $p = 0.03$) correlated inversely with the Matsuda Index, where lower values denote insulin resistance. Higher levels of consummatory pleasure correlated with a higher Matsuda Index denoting insulin sensitivity ($r = 0.323$, $p = 0.045$). No behavioral measures correlated with fasting insulin, and depression severity measured by the CDRS-R was not directly related to either measure of insulin resistance (Table 2).

Table 1
Demographic, behavioral, & clinical summary statistics.

Variable	N (%) or mean (SD)
Age (mean, SD)	14.82 ± 1.86
Female (N, %)	26 (62%)
Caucasian race (N, %)	23 (55%)
Intellectual quotient (IQ), (mean, SD)	103.88 ± 15.03
Body mass index (BMI) (mean, SD)	29.89 ± 5.69
Depression severity (CDRS-R) (mean, SD)	70.32 ± 7.17
Snaith Hamilton Pleasure Scale (SHPS) (mean, SD)	1.21 ± 1.28
Temporal Experience of Pleasure Scale (TEPS)	
Anticipatory pleasure (mean, SD)	42.86 ± 8.28
Consummatory pleasure (mean, SD)	38.46 ± 5.77
Three Factor Eating Questionnaire (TFEQ)	
Cognitive Restraint (mean, SD)	9.40 ± 4.70
Disinhibition (mean, SD)	7.33 ± 3.82
Hunger (mean, SD)	7.14 ± 3.55
Fasting insulin, (mean, SD)	14.83 ± 9.55
Matsuda index, (mean, SD)	3.52 ± 1.70

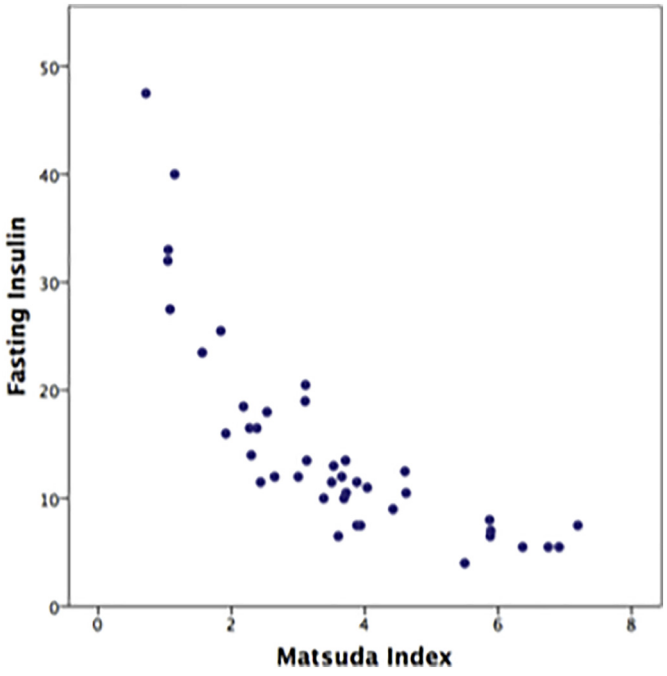

Fig. 2. Relation between fasting insulin and Matsuda Index (after glucose challenge).

3.3. Brain structural correlates of insulin resistance

The analysis results summarized in Table 3 show how the correlations between depression severity (CDRS-R) and brain structure vary depending on the level of fasting insulin. We first examined the relation between depression and abnormal neural structure, focusing on the role of very high fasting insulin (high vs. rest). Individuals with low to moderate insulin levels showed significantly positive correlation between CDRS-R and anterior cingulate thickness, whereas anterior cingulate area showed negative correlations with CDRS-R. None of these correlations were statistically significant among individuals with high insulin, which is partly due to the small sample of the group (n = 14). Interestingly, correlation between CDRS-R and anterior cingulate thickness showed sizable effects in both groups (correlation of 0.37 and −0.41), although with opposite directions, negative among those with high insulin and positive among those with low to moderate insulin. We then examined the relation between depression and abnormal neural structure focusing on the role of low fasting insulin (low vs. rest). Anterior cingulate thickness was negatively correlated with CDRS-R in both groups. We did not find any significant group differences (i.e., interaction) based on this categorization.

The analysis results summarized in Table 4 show how the correlation between depression severity (CDRS-R) and brain structure vary depending on the level of insulin measured by Matsuda Index. We first examined the relation between depression and abnormal neural structure focusing on the role of very high insulin (high vs. rest). Anterior cingulate area was negatively correlation with CDRS-R in both groups (Fig. 3). None of the correlations showed statistically significant group differences based on this categorization. We then examined the relation between depression and neural structure focusing on the role of very low insulin (low vs. rest). Among those with low insulin, hippocampus volume was positively correlated with CDRS-R. Among those moderate

Table 2
Age and sex adjusted correlations between clinical and behavioral measures of approach motivation and insulin resistance.

Insulin measure	CDRS-R	SHPS anhedonia scale	TEPS anticipatory pleasure	TEPS consummatory pleasure	TFEQ cognitive restraint	TFEQ eating disinhibition	TFEQ hunger
Fasting insulin	r = 0.112, p = 0.490	r = 0.254, p = 0.113	r = 0.058, p = 0.721	r = −0.198, p = 0.227	r = 0.101, p = 0.534	r = 0.209, p = 0.196	r = 0.179, p = 0.270
Matsuda Index	r = −0.094, p = 0.563	r = −0.408, **p = 0.009**	r = 0.075, p = 0.644	r = 0.323, **p = 0.045**	r = −0.232, p = 0.150	r = −0.341, **p = 0.031**	r = −0.192, p = 0.236

to high insulin, anterior cingulate area was negatively correlated with CDRS-R. A group difference was quite prominent based on this categorization of Matsuda Index. Anterior cingulate thickness showed sizable correlations with CDRS-R in both groups, but with opposite signs (−0.36 vs. 0.31), resulting in a significant difference between the two groups. Hippocampus volume was positively correlated with CDRS-R among those with low insulin, but negatively correlated with CDRS-R among those with moderate to high insulin, resulting in significant group differences.

3.4. Brain functional connectivity correlates of insulin resistance

Differences in fasting insulin levels among subjects were related to variation in intrinsic connectivity between the ACC and two limbic clusters encompassing regions of the left hippocampus, amygdala, temporal pole, brainstem, subcallosal cortex, orbitofrontal cortex (OFC), and nucleus accumbens (Nacc), as well as an occipital cluster centered in the intracalcerine cortex. Higher fasting insulin levels correlated positively with stronger connectivity between the ACC and the two limbic clusters, and negatively with connectivity between the ACC and the intracalcerine cortex (Table 5; Fig. 4).

Inter-individual fasting insulin levels were associated with differences in intrinsic connectivity between the hippocampus and the bilateral ACC, left MFG, left frontal pole, brainstem, cerebellum, and right lateral occipital cortex. Higher fasting insulin levels correlated positively with hippocampus-ACC and hippocampus-left frontal functional connectivity. Estimates of functional connectivity between the hippocampus and the brainstem, cerebellum, and lateral occipital cortex were correlated negatively with higher fasting insulin (Table 5; Fig. 4).

Inter-individual Matsuda Index scores were associated with differences in intrinsic connectivity between the hippocampus and two frontal clusters with peak coordinates in the left middle frontal gyrus, frontal pole, and precentral gyrus. Matsuda Index scores were also associated with differences in intrinsic functional connectivity between the hippocampus and occipital regions, including the lingual gyrus and intracalcerine cortex. Higher Matsuda Index scores negatively correlated with connectivity between the Hippocampus and the left MFG, precentral cortex, and frontal pole. A positive correlation was observed between Matsuda Index scores and resting-state connectivity of the hippocampus with the right lingual gyrus (Table 5; Fig. 4). No regions of coactivation were found to relate significantly with the ACC seed and Matsuda Index.

Depression severity (CDRS-R) was found to positively correlate with fasting insulin-associated RSFC between the ACC and the subcallosal cortex. Depression severity also positively correlated with Matsuda Index-associated functional connectivity between the hippocampus and the left MFG. A negative correlation was seen between depression severity and hippocampus-right lingual RSFC (Table 5; Fig. 4).

4. Discussion

4.1. Discussion and limitations

Aberrant approach motivation may be a critical early vulnerability factor for persistent, lifelong depression. In the current study, we documented empirical support for our hypotheses that with higher insulin resistance, youth with depression and obesity exhibit behavioral, brain structural, and brain functional evidence of aberrant approach motivation. Across all behavioral and neural units of analysis, insulin resistance and depression severity, although uncorrelated with each other, showed synergistic relations to an ACC-hippocampal approach motivation network. Importantly, our results demonstrate specific brain structure and function patterns during fasting versus post-glucose challenge insulin assessments in youth with depression and obesity. Understanding the differential brain structural and functional characteristics relative to fasting and post-glucose challenge states is critical to elucidating the pathophysiology of the combined syndrome of depression and insulin resistance.

Behaviorally, greater insulin resistance was associated with higher levels of anhedonia, decreased consummatory pleasure, and greater disinhibition in food seeking behaviors. These behavioral characteristics were present in post-glucose challenge but not during fasting insulin states, suggesting state but not trait dependent interactions between approach motivation and early insulin resistance. Anhedonia or decreased consummatory pleasure may also represent focal and early risk markers for the development of insulin resistance and chronic depression (Carter and Swardfager, 2016). Disinhibition in food seeking was also associated with more insulin resistance (lower Matsuda Index),

Table 3
Fasting insulin and association between depression and brain structure.

Correlation of CDRS with	Fasting insulin		Group difference
	High = 0 (n = 28, bottom 2/3)	High = 1 (n = 14, top 1/3)	
Anterior cingulate thickness	**0.365 (p = 0.045)**	−0.409 (p = 0.054)	**0.774 (p = 0.016)**
Anterior cingulate area	**−0.465 (p = 0.009)**	−0.230 (p = 0.197)	−0.235 (p = 0.242)
Hippocampus volume	−0.215 (p = 0.234)	0.228 (p = 0.176)	−0.443 (p = 0.073)

Correlation of CDRS with	Fasting insulin		Group difference
	Low = 1 (n = 14, bottom 1/3)	Low = 0 (n = 28, top 2/3)	
Anterior cingulate thickness	0.425 (p = 0.051)	−0.009 (p = 0.965)	0.434 (p = 0.204)
Anterior cingulate area	**−0.427 (p < 0.001)**	**−0.380 (p = 0.002)**	−0.047 (p = 0.880)
Hippocampus volume	−0.124 (p = 0.562)	0.028 (p = 0.841)	−0.152 (p = 0.572)

Table 4
Matsuda Index and association between depression and brain measures.

Correlation of CDRS-R with	Matsuda Index		Group difference
	High = 0 (n = 28, bottom 2/3)	High = 1 (n = 14, top 1/3)	
Anterior cingulate thickness	0.269 (p = 0.250)	−0.045 (p = 0.864)	0.314 (p = 0.373)
Anterior cingulate area	**−0.352 (p = 0.045)**	**−0.472 (p < 0.001)**	0.120 (p = 0.801)
Hippocampus volume	0.108 (p = 0.420)	−0.327 (p = 0.139)	0.435 (p = 0.108)

Correlation of CDRS-R with	Matsuda Index		Group difference
	Low = 1 (n = 14, bottom 1/3)	Low = 0 (n = 28, top 2/3)	
Anterior cingulate thickness	−0.362 (p = 0.133)	0.310 (p = 0.147)	**−0.672 (p = 0.042)**
Anterior cingulate area	−0.306 (p = 0.119)	**−0.436 (p = 0.009)**	0.130 (p = 0.309)
Hippocampus volume	**0.344 (p = 0.034)**	−0.253 (p = 0.130)	**0.597 (p = 0.009)**

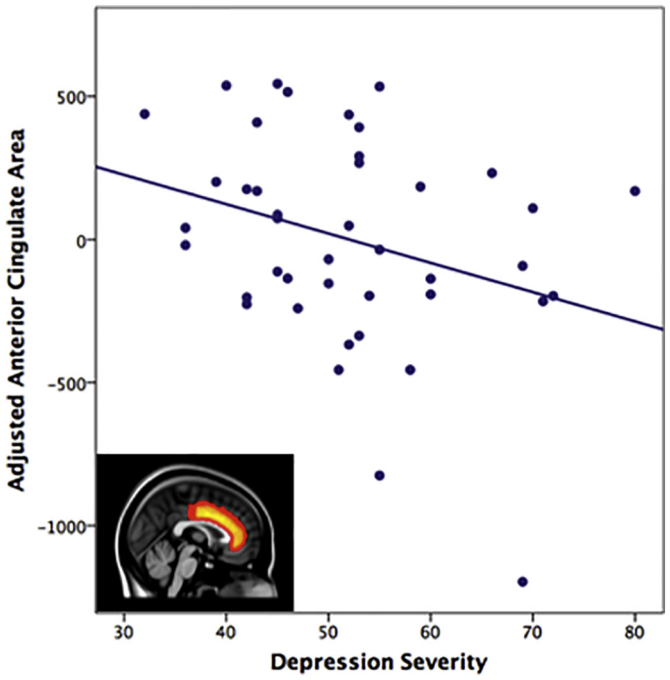

Fig. 3. Age, sex, and Matsuda Index adjusted Anterior Cingulate Cortex Area correlated with depression severity (CDRS-R score).

consistent with previously reported relations to BMI in adolescents (Gallant et al., 2010), which is frequently used as a proxy marker of insulin resistance. Importantly, depression severity did not directly relate to insulin in either fasting or post-glucose challenge states. This may be due to the heterogeneity of depression (Young et al., 2016) or due to the complex and interlinked mediators of depression (Wolkowitz et al., 2011) that dynamically interact with insulin secretion leading to aberrant neurodevelopment (Pervanidou and Chrousos, 2012). Although depression scores may have previously informed efficacy and adherence in weight loss interventions (Somerset et al., 2011), longitudinal follow up in these youth over time and into adulthood will aide in understanding how approach motivation-related behavioral markers may be used to develop innovative and selective treatment targets.

Structurally, youth with depression and obesity showed predicted depression-related reductions in volume in the ACC and hippocampus that is consistent with the extant literature for these syndromes as discrete entities in similar pediatric populations (Bauer et al., 2015; MacMaster et al., 2008; Pannekoek et al., 2014; Wang et al., 2017), as well as in adults (Rasgon et al., 2011). To our knowledge, this is the first study to demonstrate these findings in youth with both depression and obesity. Our study also adds new data about the specific relations between insulin resistance, depression severity, and the prefrontal-limbic network. For youth with high levels of fasting insulin, smaller ACC volumes were associated with more severe depressive symptoms, whereas the opposite was true for youth with low levels of fasting insulin. Indeed, high fasting insulin has been associated with reduced ACC volumes in adults (Castro et al., 2016; Raji et al., 2010), which may explain why the significant relation between ACC volume and depressive symptoms was present in youth with high relative to low fasting insulin levels. For youth with high levels of insulin after a glucose challenge (low Matsuda Index), thinner ACC and smaller hippocampal volumes were associated with more severe depressive symptoms, whereas the opposite was true for youth with a high Matsuda Index. Reduced hippocampal volume with more depression severity in

Table 5
Resting state functional connectivity results.

Seed region of interest (ROI)	Insulin measure	Region	Cluster size	Peak MNI coordinates			p-Value	Correlation with CDRS-R	
				x	y	z		r	p
Anterior Cingulate Cortex (ACC)	Fasting insulin	Brainstem + hippocampus + temporal pole + amygdala	1046	−2	−14	−16	< 0.001	0.023	0.886
		Subcallosal cortex + OFC + NAcc	465	−10	12	−14	0.0133	0.416	**0.006**
		Intracalcerine cortex + cuneal cortex	1872	16	−74	14	< 0.001	−0.258	0.100
Hippocampus	Fasting insulin	ACC	802	−6	−2	34	< 0.001	0.272	0.081
		Left middle frontal gyrus + frontal pole	437	−38	34	28	0.0158	−0.027	0.865
		Brainstem + cerebellum	682	0	−22	−44	0.00076	0.049	0.76
		Right lateral occipital cortex	563	36	−66	0	0.00316	−0.087	0.585
Hippocampus	Matsuda Index	Left middle frontal gyrus + frontal pole	469	−34	12	32	0.0104	−0.033	0.836
		Left middle frontal gyrus + precentral	436	−38	34	28	0.0161	0.311	**0.045**
		Right lingual gyrus + intracalcerine cortex	606	14	−86	0	0.00188	−0.331	**0.032**

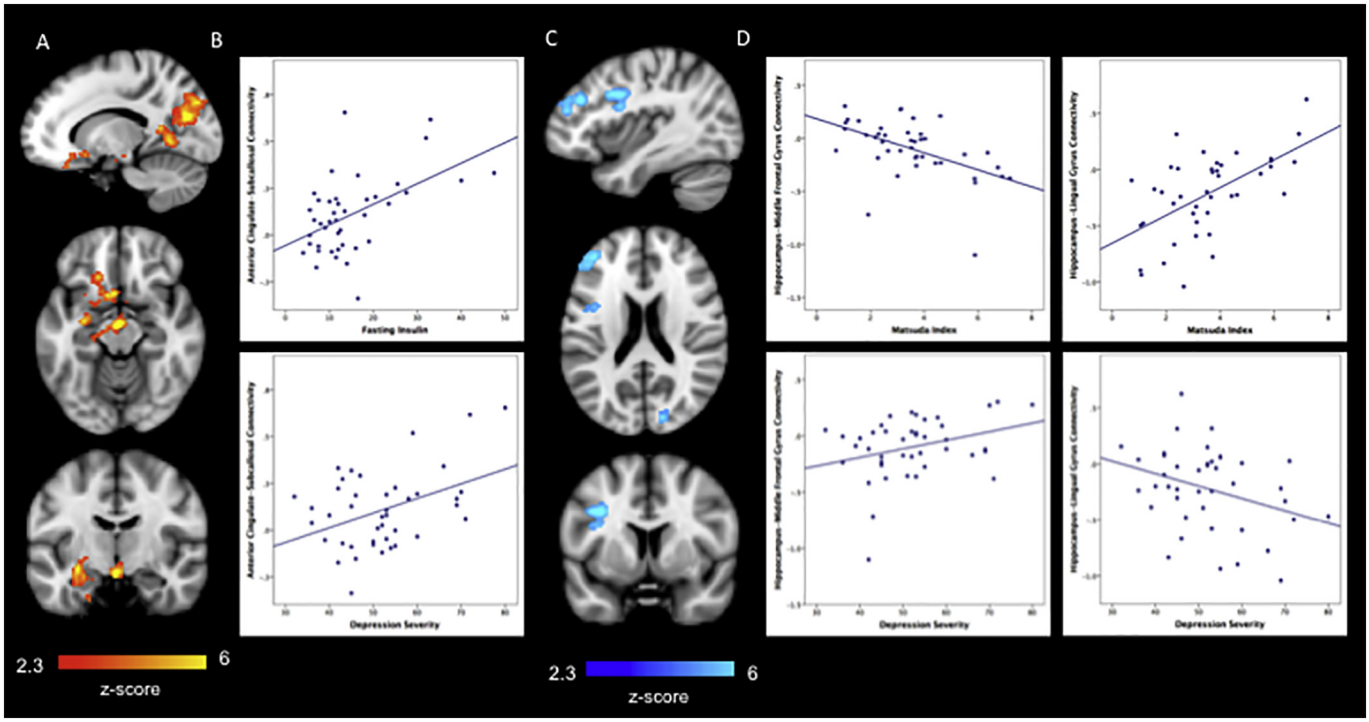

Fig. 4. Significant insulin and depression related resting state functional connectivity A. Orange clustered regions of significant insulin-correlated connectivity with the Anterior Cingulate Cortex (ACC) seed. B. ACC-Subcallosal connectivity estimates correlated with fasting insulin and with depression severity (CDRS-R scores). C. Blue clustered regions of significant Matsuda Index-correlated connectivity with the Hippocampus seed. D. Hippocampus-Middle Frontal Gyrus connectivity estimates correlated with Matsuda Index and with depression severity. Hippocampus-Lingual Gyrus connectivity estimates correlated with Matsuda Index and with depression severity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the presence of insulin resistance after an oral glucose challenge may be due to a number of potential mechanisms including oxidative stress, impaired vascular reactivity, neuroinflammation or abnormal lipid metabolism (Yates et al., 2012). In contrast to the hippocampus, reduced volume and cortical thinning of the ACC was found to be associated with insulin resistance in both fasting and post-glucose challenge states. Structural deficits in the ACC may occur sooner than in the hippocampus, be vulnerable to the effects of depression as a stress syndrome at critical sensitive windows in development (Charmandari et al., 2003; Pervanidou and Chrousos, 2012), or represent a mechanism of stress regulation to preserve subcortical function (Teh et al., 2010).

Finally, contrary to our prediction, greater ACC and hippocampal connectivity to fronto-limbic reward networks while at rest were associated with higher levels of insulin resistance. A stronger medial prefrontal-hippocampal intrinsic connectivity with high fasting insulin levels may represent a neuroregulatory response to high levels of insulin in youth. This homeostatic response has been well described as a cognitive control response during a fasting state in obese (Lips et al., 2014) and aging (Kenna et al., 2013) women. Similar to the structural results, fasting insulin drove connectivity results within the ACC seed, and the Matsuda Index drove connectivity results within the hippocampal seed. Moreover, depression severity followed predicted patterns of worsening with insulin resistance. Strikingly, ACC and hippocampal seeds both led to significant correlations with each other, demonstrating a bidirectional relation between their regions, and supporting the idea that these regions form a network to subserve their regulatory functions. Regional correlations may be replicable and internally consistent due to some compounded effect of depression combined with obesity. Task-based functional MRI may provide some more direct in vivo clues about brain-behavioral relations in this sample. Nevertheless, intrinsic functional connectivity in youth with depression and obesity mirrors the structural results, are similar to neurobiological characteristics of addiction (Feldstein Ewing et al., 2016), and demonstrates the imbalance between prefrontal and limbic networks well characterized in depression and obesity (Page et al., 2013; Ryan et al., 2012; Rzepa and McCabe, 2016). Our results also demonstrate that the dynamics of intrinsic connectivity are strongly impacted by both insulin resistance and depression (Melasch et al., 2016). We have come closer to understanding the specific shared mechanisms between these syndromes and the commensurate neurofunctional markers that accompany them.

We should note a number of study limitations. First, we had a modest sample size for the multilevel assessments conducted; nevertheless, we found robust and consistent results across established behavioral and brain assessments of approach motivation. With full recognition that there are other candidate regions in the reward network to investigate, we took a hypothesis driven approach to mitigate multiple comparisons corrections and because we had limited but informed literature to guide our predictions. With larger sample sizes, we could investigate other candidate regions, as well as the role of moderators such as sex, family history of diabetes, and single versus multi-episode depression. Second, our cross-sectional design without a typically developing comparison group did not allow us to determine whether findings in the study represented markers of neural vulnerability versus neural adaptation. Comparing youth in our study to non-obese, non-depressed, or non-obese and depressed groups may be an important future direction. We tried to account for developmental differences and sexual dimorphism by covarying analyses for age and sex. Prospective studies are needed to determine whether aberrant approach motivation will predict the expected progressive worsening of depression outcomes. Third, self-report and parent questionnaires, rather than laboratory procedures, were used to assess behavioral measures of approach motivation in youth. However, few studies have directly examined brain effects of insulin resistance after an oral glucose challenge. Fourth, there is no single fool proof method for measuring insulin

resistance - the hyperinsulinemic euglycemic clamp is the “gold standard” (Hallschmid and Schultes, 2009); however, it is costly and time consuming. In order to best maximize our quantification of insulin resistance, we chose two commonly used measures (fasting insulin and Matsuda Index derived from the OGTT), each with their own advantages and disadvantages. Furthermore, the OGTT measurements of insulin that we derived are based on peripheral insulin levels, and there may be other endocrine changes associated with obesity that may contribute to the findings presented but were beyond the scope of the current study. Indeed, the relation between brain and peripheral insulin is complex, and our assessment of brain insulin resistance is limited, although it could be noted that this has been addressed in some of the pre-clinical literature. Future research that takes advantage of improved brain insulin biomarkers will be better positioned to unravel the precise role of insulin resistance in the pathophysiology of depression.

5. Conclusions

This study is the first to relate brain and behavioral correlates of approach motivation to pediatric depression and insulin resistance in fasting and post-glucose challenge states. Insulin resistance is represented consistently in an interdependent ACC-hippocampal mesocorticolimbic dopaminergic network. Insulin-related aberrant behavioral and neural approach motivation is evident among youth with depression and obesity as young as 9 years of age, implicating certain neural pathways already set into motion that may require early identification and treatment. Indeed, neuroendocrine, bio-energetic, oxidative, and inflammatory processes interact in the development of neuronal damage and deficits in dopaminergic function (Carter and Swardfager, 2016). Whether these processes are modifiable will require prospective assessment and critical evaluation of biological target engagement in future studies. Interactions between the brain and behavioral characteristics described in this study should also be examined directly using reward task-based functional MRI. Importantly, future studies should examine the longitudinal trajectory of approach motivation dysfunction and its ability to predict the progressive worsening toward chronic and lifelong forms of depression. Such research may facilitate the development of intervention strategies that leverage adaptive responses to stress that could prevent such progression.

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Conflicts of interest

Dr. Singh receives research support from Stanford's Child Health Research Institute, National Institute of Mental Health, National Institute of Aging, Neuronetics, Johnson and Johnson, and the Brain and Behavior Foundation. She is on the advisory board for Sunovion. Dr. Rasgon receives research support from the National Institute of Aging. No other authors report any conflicts of interest.

References

Adam, T.C., Tsao, S., Page, K.A., Hu, H., Hasson, R.E., Goran, M.I., 2013. Insulin sensitivity and brain reward activation in overweight Hispanic girls: a pilot study. Pediatr. Obes. http://dx.doi.org/10.1111/j.2047-6310.2013.00210.x.

Akın, O., Eker, İ., Arslan, M., Yavuz, S.T., Akman, S., Taşçılar, M.E., Ünay, B., 2017. Relation of insulin resistance to neurocognitive function and electroencephalography in obese children. J. Pediatr. Endocrinol. Metab. http://dx.doi.org/10.1515/jpem-2017-0186.

Al Mamun, A., Cramb, S., McDermott, B.M., O'Callaghan, M., Najman, J.M., Williams, G.M., 2007. Adolescents' perceived weight associated with depression in young adulthood: a longitudinal study. Obesity (Silver Spring) 15, 3097–3105. http://dx.doi.org/10.1038/oby.2007.369.

Androutsos, O., Moschonis, G., Mavrogianni, C., Roma-Giannikou, E., Chrousos, G.P., Kanaka-Gantenbein, C., Manios, Y., 2014. Identification of lifestyle patterns, including sleep deprivation, associated with insulin resistance in children: the Healthy Growth Study. Eur. J. Clin. Nutr. 68, 344–349. http://dx.doi.org/10.1038/ejcn.2013.280.

Anthony, K., Reed, L.J., Dunn, J.T., Bingham, E., Hopkins, D., Marsden, P.K., Amiel, S.A., 2006. Attenuation of insulin-evoked responses in brain networks controlling appetite and reward in insulin resistance: the cerebral basis for impaired control of food intake in metabolic syndrome? Diabetes 55, 2986–2992. http://dx.doi.org/10.2337/db06-0376.

Argyelan, M., Lencz, T., Kaliora, S., Sarpal, D.K., Weissman, N., Kingsley, P.B., Malhotra, A.K., Petrides, G., 2016. Subgenual cingulate cortical activity predicts the efficacy of electroconvulsive therapy. Transl. Psychiatry 6, e789. http://dx.doi.org/10.1038/tp.2016.54.

Austin, A.W., Gordon, J.L., Lavoie, K.L., Arsenault, A., Dasgupta, K., Bacon, S.L., 2014. Differential association of insulin resistance with cognitive and somatic symptoms of depression. Diabet. Med. http://dx.doi.org/10.1111/dme.12465.

Bauer, C.C.C., Moreno, B., González-Santos, L., Concha, L., Barquera, S., Barrios, F.A., 2015. Child overweight and obesity are associated with reduced executive cognitive performance and brain alterations: a magnetic resonance imaging study in Mexican children. Pediatr. Obes. 10, 196–204. http://dx.doi.org/10.1111/ijpo.241.

Beydoun, M.A., Fanelli-Kuczmarski, M.T., Shaked, D., Dore, G.A., Beydoun, H.A., Rostant, O.S., Evans, M.K., Zonderman, A.B., 2016. Alternative pathway analyses indicate bidirectional relations between depressive symptoms, diet quality, and central adiposity in a sample of urban US adults. J. Nutr. 146, 1241–1249. http://dx.doi.org/10.3945/jn.115.229054.

Black, J.M., Tanaka, H., Stanley, L., Nagamine, M., Zakerani, N., Thurston, A., Kesler, S., Hulme, C., Lyytinen, H., Glover, G.H., Serrone, C., Raman, M.M., Reiss, A.L., Hoeft, F., 2012. Maternal history of reading difficulty is associated with reduced language-related gray matter in beginning readers. NeuroImage 59, 3021–3032. http://dx.doi.org/10.1016/j.neuroimage.2011.10.024.

Brambilla, P., Lissau, I., Flodmark, C.-E., Moreno, L.A., Widhalm, K., Wabitsch, M., Pietrobelli, A., 2007. Metabolic risk-factor clustering estimation in children: to draw a line across pediatric metabolic syndrome. Int. J. Obes. 2005 (31), 591–600. http://dx.doi.org/10.1038/sj.ijo.0803581.

Brown, E.S., Varghese, F.P., McEwen, B.S., 2004. Association of depression with medical illness: does cortisol play a role? Biol. Psychiatry 55, 1–9.

Buhl, E.S., Jensen, T.K., Jessen, N., Elfving, B., Buhl, C.S., Kristiansen, S.B., Pold, R., Solskov, L., Schmitz, O., Wegener, G., Lund, S., Petersen, K.F., 2010. Treatment with an SSRI antidepressant restores hippocampo-hypothalamic corticosteroid feedback and reverses insulin resistance in low-birth-weight rats. Am. J. Physiol. Endocrinol. Metab. 298, E920–929. http://dx.doi.org/10.1152/ajpendo.00606.2009.

Carter, J., Swardfager, W., 2016. Mood and metabolism: anhedonia as a clinical target in Type 2 diabetes. Psychoneuroendocrinology 69, 123–132. http://dx.doi.org/10.1016/j.psyneuen.2016.04.002.

Castro, M.G., Venutolo, C., Yau, P.L., Convit, A., 2016. Fitness, insulin sensitivity, and frontal lobe integrity in adults with overweight and obesity. Obesity (Silver Spring) 24, 1283–1289. http://dx.doi.org/10.1002/oby.21500.

Chantiluke, K., Halari, R., Simic, M., Pariante, C.M., Papadopoulos, A., Giampietro, V., Rubia, K., 2012. Fronto-striato-cerebellar dysregulation in adolescents with depression during motivated attention. Biol. Psychiatry 71, 59–67. http://dx.doi.org/10.1016/j.biopsych.2011.09.005.

Charmandari, E., Kino, T., Souvatzoglou, E., Chrousos, G.P., 2003. Pediatric stress: hormonal mediators and human development. Horm. Res. 59, 161–179. https://doi.org/69325.

Christensen, L., Pettijohn, L., 2001. Mood and carbohydrate cravings. Appetite 36, 137–145. http://dx.doi.org/10.1006/appe.2001.0390.

de Kwaasteniet, B., Ruhe, E., Caan, M., Rive, M., Olabarriaga, S., Groefsema, M., Heesink, L., van Wingen, G., Denys, D., 2013. Relation between structural and functional connectivity in major depressive disorder. Biol. Psychiatry 74, 40–47. http://dx.doi.org/10.1016/j.biopsych.2012.12.024.

de la Torre-Luque, A., Bornas, X., Balle, M., Fiol-Veny, A., 2016. Complexity and non-linear biomarkers in emotional disorders: a meta-analytic study. Neurosci. Biobehav. Rev. 68, 410–422. http://dx.doi.org/10.1016/j.neubiorev.2016.05.023.

Eisenstein, S.A., Gredysa, D.M., Antenor-Dorsey, J.A., Green, L., Arbeláez, A.M., Koller, J.M., Black, K.J., Perlmutter, J.S., Moerlein, S.M., Hershey, T., 2015. Insulin, central dopamine D2 receptors, and monetary reward discounting in obesity. PLoS One 10, e0133621. http://dx.doi.org/10.1371/journal.pone.0133621.

Ernersson, A., Frisman, G.H., Sepa Frostell, A., Nyström, F.H., Lindström, T., 2010. An obesity provoking behaviour negatively influences young normal weight subjects' health related quality of life and causes depressive symptoms. Eat. Behav. 11, 247–252. http://dx.doi.org/10.1016/j.eatbeh.2010.05.005.

Feldstein Ewing, S.W., Claus, E.D., Hudson, K.A., Filbey, F.M., Yakes Jimenez, E., Lisdahl, K.M., Kong, A.S., 2016. Overweight adolescents' brain response to sweetened beverages mirrors addiction pathways. Brain Imaging Behav. http://dx.doi.org/10.1007/s11682-016-9564-z.

Figlewicz, D.P., 2016. Expression of receptors for insulin and leptin in the ventral tegmental area/substantia nigra (VTA/SN) of the rat: historical perspective. Brain Res. 1645, 68–70. http://dx.doi.org/10.1016/j.brainres.2015.12.041.

Fischl, B., Dale, A.M., 2000. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc. Natl. Acad. Sci. U. S. A. 97, 11050–11055. http://dx.doi.org/10.1073/pnas.200033797.

Foland-Ross, L.C., Sacchet, M.D., Prasad, G., Gilbert, B., Thompson, P.M., Gotlib, I.H., 2015. Cortical thickness predicts the first onset of major depression in adolescence. Int. J. Dev. Neurosci. 46, 125–131. http://dx.doi.org/10.1016/j.ijdevneu.2015.07.

007.
Gabbay, V., Ely, B.A., Li, Q., Bangaru, S.D., Panzer, A.M., Alonso, C.M., Castellanos, F.X., Milham, M.P., 2013. Striatum-based circuitry of adolescent depression and anhedonia. J. Am. Acad. Child Adolesc. Psychiatry 52, 628–641.e13. http://dx.doi.org/10.1016/j.jaac.2013.04.003.
Gallant, A.R., Tremblay, A., Pérusse, L., Bouchard, C., Després, J.-P., Drapeau, V., 2010. The Three-Factor Eating Questionnaire and BMI in adolescents: results from the Québec family study. Br. J. Nutr. 104, 1074–1079. http://dx.doi.org/10.1017/S0007114510001662.
Gelman, A., Park, D.K., 2009. Splitting a predictor at the upper quarter or third and the lower quarter or third. Am. Stat. 63, 1–8. http://dx.doi.org/10.1198/tast.2009.0001.
Goldfield, G.S., Moore, C., Henderson, K., Buchholz, A., Obeid, N., Flament, M.F., 2010. Body dissatisfaction, dietary restraint, depression, and weight status in adolescents. J. Sch. Health 80, 186–192. http://dx.doi.org/10.1111/j.1746-1561.2009.00485.x.
Gradin, V.B., Kumar, P., Waiter, G., Ahearn, T., Stickle, C., Milders, M., Reid, I., Hall, J., Steele, J.D., 2011. Expected value and prediction error abnormalities in depression and schizophrenia. Brain J. Neurol. 134, 1751–1764. http://dx.doi.org/10.1093/brain/awr059.
Gunnell, K.E., Flament, M.F., Buchholz, A., Henderson, K.A., Obeid, N., Schubert, N., Goldfield, G.S., 2016. Examining the bidirectional relationship between physical activity, screen time, and symptoms of anxiety and depression over time during adolescence. Prev. Med. 88, 147–152. http://dx.doi.org/10.1016/j.ypmed.2016.04.002.
Hallschmid, M., Schultes, B., 2009. Central nervous insulin resistance: a promising target in the treatment of metabolic and cognitive disorders? Diabetologia 52, 2264–2269. http://dx.doi.org/10.1007/s00125-009-1501-x.
Hamilton, J.P., Chen, G., Thomason, M.E., Schwartz, M.E., Gotlib, I.H., 2011. Investigating neural primacy in Major Depressive Disorder: multivariate Granger causality analysis of resting-state fMRI time-series data. Mol. Psychiatry 16, 763–772. http://dx.doi.org/10.1038/mp.2010.46.
Hawker, D.S., Boulton, M.J., 2000. Twenty years' research on peer victimization and psychosocial maladjustment: a meta-analytic review of cross-sectional studies. J. Child Psychol. Psychiatry 41, 441–455.
Hermens, D.F., Hatton, S.N., Lee, R.S.C., Naismith, S.L., Duffy, S.L., Paul Amminger, G., Kaur, M., Scott, E.M., Lagopoulos, J., Hickie, I.B., 2017. In vivo imaging of oxidative stress and fronto-limbic white matter integrity in young adults with mood disorders. Eur. Arch. Psychiatry Clin. Neurosci. http://dx.doi.org/10.1007/s00406-017-0788-8.
Hiles, S.A., Révész, D., Lamers, F., Giltay, E., Penninx, B.W.J.H., 2016. Bidirectional prospective associations of metabolic syndrome components with depression, anxiety, and antidepressant use. Depress. Anxiety 33, 754–764. http://dx.doi.org/10.1002/da.22512.
Hills, A.P., King, N.A., Armstrong, T.P., 2007. The contribution of physical activity and sedentary behaviours to the growth and development of children and adolescents: implications for overweight and obesity. Sports Med. Auckl. 37, 533–545.
Ho, P.M., Cooper, A.J., Hall, P.J., Smillie, L.D., 2014. Factor structure and construct validity of the temporal experience of pleasure scales. J. Pers. Assess. 1–9. http://dx.doi.org/10.1080/00223891.2014.940625.
Hulvershorn, L.A., Cullen, K., Anand, A., 2011. Toward dysfunctional connectivity: a review of neuroimaging findings in pediatric major depressive disorder. Brain Imaging Behav. 5, 307–328. http://dx.doi.org/10.1007/s11682-011-9134-3.
Huys, Q.J., Pizzagalli, D.A., Bogdan, R., Dayan, P., 2013. Mapping anhedonia onto reinforcement learning: a behavioural meta-analysis. Biol. Mood Anxiety Disord. 3, 12. http://dx.doi.org/10.1186/2045-5380-3-12.
Jalbrzikowski, M., Larsen, B., Hallquist, M.N., Foran, W., Calabro, F., Luna, B., 2017. Development of white matter microstructure and intrinsic functional connectivity between the amygdala and ventromedial prefrontal cortex: associations with anxiety and depression. Biol. Psychiatry 82, 511–521. http://dx.doi.org/10.1016/j.biopsych.2017.01.008.
James, G.M., Baldinger-Melich, P., Philippe, C., Kranz, G.S., Vanicek, T., Hahn, A., Gryglewski, G., Hienert, M., Spies, M., Traub-Weidinger, T., Mitterhauser, M., Wadsak, W., Hacker, M., Kasper, S., Lanzenberger, R., 2017. Effects of selective serotonin reuptake inhibitors on interregional relation of serotonin transporter availability in major depression. Front. Hum. Neurosci. 11, 48. http://dx.doi.org/10.3389/fnhum.2017.00048.
Jani, B.D., Cavanagh, J., Barry, S.J.E., Der, G., Sattar, N., Mair, F.S., 2014. Revisiting the J shaped curve, exploring the association between cardiovascular risk factors and concurrent depressive symptoms in patients with cardiometabolic disease: findings from a large cross-sectional study. BMC Cardiovasc. Disord. 14, 139. http://dx.doi.org/10.1186/1471-2261-14-139.
Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. NeuroImage 17, 825–841.
Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., Ryan, N., 1997. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. J. Am. Acad. Child Adolesc. Psychiatry 36, 980–988. http://dx.doi.org/10.1097/00004583-199707000-00021.
Keding, T.J., Herringa, R.J., 2015. Abnormal structure of fear circuitry in pediatric post-traumatic stress disorder. Neuropsychopharmacology 40, 537–545. http://dx.doi.org/10.1038/npp.2014.239.
Kenna, H., Hoeft, F., Kelley, R., Wroolie, T., DeMuth, B., Reiss, A., Rasgon, N., 2013. Fasting plasma insulin and the default mode network in women at risk for Alzheimer's disease. Neurobiol. Aging 34, 641–649. http://dx.doi.org/10.1016/j.neurobiolaging.2012.06.006.
Khanh, D.V., Choi, Y.-H., Moh, S.H., Kinyua, A.W., Kim, K.W., 2014. Leptin and insulin signaling in dopaminergic neurons: relationship between energy balance and reward system. Front. Psychol. 5, 846. http://dx.doi.org/10.3389/fpsyg.2014.00846.
Kullmann, S., Heni, M., Veit, R., Ketterer, C., Schick, F., Häring, H.-U., Fritsche, A., Preissl, H., 2012. The obese brain: association of body mass index and insulin sensitivity with resting state network functional connectivity. Hum. Brain Mapp. 33, 1052–1061. http://dx.doi.org/10.1002/hbm.21268.
Kumar, P., Waiter, G., Ahearn, T., Milders, M., Reid, I., Steele, J.D., 2008. Abnormal temporal difference reward-learning signals in major depression. Brain J. Neurol. 131, 2084–2093. http://dx.doi.org/10.1093/brain/awn136.
Lamers, F., de Jonge, P., Nolen, W.A., Smit, J.H., Zitman, F.G., Beekman, A.T.F., Penninx, B.W.J.H., 2010. Identifying depressive subtypes in a large cohort study: results from the Netherlands Study of Depression and Anxiety (NESDA). J. Clin. Psychiatry 71, 1582–1589. http://dx.doi.org/10.4088/JCP.09m05398blu.
Lamers, F., Beekman, A.T.F., van Hemert, A.M., Schoevers, R.A., Penninx, B.W.J.H., 2016. Six-year longitudinal course and outcomes of subtypes of depression. Br. J. Psychiatry J. Ment. Sci. 208, 62–68. http://dx.doi.org/10.1192/bjp.bp.114.153098.
Lichenstein, S.D., Verstynen, T., Forbes, E.E., 2016. Adolescent brain development and depression: a case for the importance of connectivity of the anterior cingulate cortex. Neurosci. Biobehav. Rev. 70, 271–287. http://dx.doi.org/10.1016/j.neubiorev.2016.07.024.
Lips, M.A., Wijngaarden, M.A., van der Grond, J., van Buchem, M.A., de Groot, G.H., Rombouts, S.A.R.B., Pijl, H., Veer, I.M., 2014. Resting-state functional connectivity of brain regions involved in cognitive control, motivation, and reward is enhanced in obese females. Am. J. Clin. Nutr. 100, 524–531. http://dx.doi.org/10.3945/ajcn.113.080671.
Liu, C.S., Carvalho, A.F., McIntyre, R.S., 2014. Towards a “metabolic” subtype of major depressive disorder: shared pathophysiological mechanisms may contribute to cognitive dysfunction. CNS Neurol. Disord. Drug Targets 13, 1693–1707.
MacMaster, F.P., Mirza, Y., Szeszko, P.R., Kmiecik, L.E., Easter, P.C., Taormina, S.P., Lynch, M., Rose, M., Moore, G.J., Rosenberg, D.R., 2008. Amygdala and hippocampal volumes in familial early onset major depressive disorder. Biol. Psychiatry 63, 385–390. http://dx.doi.org/10.1016/j.biopsych.2007.05.005.
Marusak, H.A., Hatfield, J.R.B., Thomason, M.E., Rabinak, C.A., 2017. Reduced ventral tegmental area-hippocampal connectivity in children and adolescents exposed to early threat. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 2, 130–137. http://dx.doi.org/10.1016/j.bpsc.2016.11.002.
Matsuda, M., DeFronzo, R.A., 1999. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 22, 1462–1470.
Mazaika, P.K., Weinzimer, S.A., Mauras, N., Buckingham, B., White, N.H., Tsalikian, E., Hershey, T., Cato, A., Aye, T., Fox, L., Wilson, D.M., Tansey, M.J., Tamborlane, W., Peng, D., Raman, M., Marzelli, M., Reiss, A.L., Diabetes Research in Children Network (DirecNet), 2016. Variations in brain volume and growth in young children with type 1 diabetes. Diabetes 65, 476–485. http://dx.doi.org/10.2337/db15-1242.
McElroy, S.L., Kotwal, R., Malhotra, S., Nelson, E.B., Keck, P.E., Nemeroff, C.B., 2004. Are mood disorders and obesity related? A review for the mental health professional. J. Clin. Psychiatry 65, 634–651 (quiz 730).
McIntyre, R.S., Rasgon, N.L., Kemp, D.E., Nguyen, H.T., Law, C.W.Y., Taylor, V.H., Woldeyohannes, H.O., Alsuwaidan, M.T., Soczynska, J.K., Kim, B., Lourenco, M.T., Kahn, L.S., Goldstein, B.I., 2009. Metabolic syndrome and major depressive disorder: co-occurrence and pathophysiologic overlap. Curr. Diab. Rep. 9, 51–59.
McIntyre, R.S., Kenna, H.A., Nguyen, H.T., Law, C.W.Y., Sultan, F., Woldeyohannes, H.O., Adams, A.K., Cheng, J.S.H., Lourenco, M., Kennedy, S.H., Rasgon, N.L., 2010. Brain volume abnormalities and neurocognitive deficits in diabetes mellitus: points of pathophysiological commonality with mood disorders? Adv. Ther. 27, 63–80. http://dx.doi.org/10.1007/s12325-010-0011-z.
McIntyre, R.S., Xiao, H.X., Syeda, K., Vinberg, M., Carvalho, A.F., Mansur, R.B., Maruschak, N., Cha, D.S., 2015. The prevalence, measurement, and treatment of the cognitive dimension/domain in major depressive disorder. CNS Drugs 29, 577–589. http://dx.doi.org/10.1007/s40263-015-0263-x.
Melasch, J., Rullmann, M., Hilbert, A., Luthardt, J., Becker, G.A., Patt, M., Villringer, A., Arelin, K., Meyer, P.M., Lobsien, D., Ding, Y.-S., Müller, K., Sabri, O., Hesse, S., Pleger, B., 2016. The central nervous norepinephrine network links a diminished sense of emotional well-being to an increased body weight. Int. J. Obes. 2005 (40), 779–787. http://dx.doi.org/10.1038/ijo.2015.216.
Merikangas, K.R., He, J.-P., Burstein, M., Swanson, S.A., Avenevoli, S., Cui, L., Benjet, C., Georgiades, K., Swendsen, J., 2010. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication—Adolescent Supplement (NCS-A). J. Am. Acad. Child Adolesc. Psychiatry 49, 980–989. http://dx.doi.org/10.1016/j.jaac.2010.05.017.
Muthén, L., Muthén, B., 1998. Mplus User's Guide.
Neef, M., Weise, S., Adler, M., Sergeyev, E., Dittrich, K., Körner, A., Kiess, W., 2013. Health impact in children and adolescents. Best Pract. Res. Clin. Endocrinol. Metab. 27, 229–238. http://dx.doi.org/10.1016/j.beem.2013.02.007.
Nemiary, D., Shim, R., Mattox, G., Holden, K., 2012. The relationship between obesity and depression among adolescents. Psychiatr. Ann. 42, 305–308. http://dx.doi.org/10.3928/00485713-20120806-09.
Nusslock, R., Alloy, L.B., 2017. Reward processing and mood-related symptoms: an RDoC and translational neuroscience perspective. J. Affect. Disord. 216, 3–16. http://dx.doi.org/10.1016/j.jad.2017.02.001.
Olive, L.S., Telford, R.M., Byrne, D.G., Abhayaratna, W.P., Telford, R.D., 2017. Symptoms of stress and depression effect percentage of body fat and insulin resistance in healthy youth: LOOK longitudinal study. Health Psychol. http://dx.doi.org/10.1037/hea0000496.
Page, K.A., Chan, O., Arora, J., Belfort-Deaguiar, R., Dzuira, J., Roehmholdt, B., Cline, G.W., Naik, S., Sinha, R., Constable, R.T., Sherwin, R.S., 2013. Effects of fructose vs glucose on regional cerebral blood flow in brain regions involved with appetite and

reward pathways. JAMA 309, 63–70. http://dx.doi.org/10.1001/jama.2012.116975.
Pannekoek, J.N., van der Werff, S.J.A., van den Bulk, B.G., van Lang, N.D.J., Rombouts, S.A.R.B., van Buchem, M.A., Vermeiren, R.R.J.M., van der Wee, N.J.A., 2014. Reduced anterior cingulate gray matter volume in treatment-naïve clinically depressed adolescents. NeuroImage Clin. 4, 336–342. http://dx.doi.org/10.1016/j.nicl.2014.01.007.
Pearson, S., Schmidt, M., Patton, G., Dwyer, T., Blizzard, L., Otahal, P., Venn, A., 2010. Depression and insulin resistance: cross-sectional associations in young adults. Diabetes Care 33, 1128–1133. http://dx.doi.org/10.2337/dc09-1940.
Penninx, B.W.J.H., Milaneschi, Y., Lamers, F., Vogelzangs, N., 2013. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. BMC Med. 11, 129. http://dx.doi.org/10.1186/1741-7015-11-129.
Pervanidou, P., Chrousos, G.P., 2012. Metabolic consequences of stress during childhood and adolescence. Metabolism 61, 611–619. http://dx.doi.org/10.1016/j.metabol.2011.10.005.
Pliquett, R.U., Führer, D., Falk, S., Zysset, S., von Cramon, D.Y., Stumvoll, M., 2006. The effects of insulin on the central nervous system—focus on appetite regulation. Horm. Metab. Res. 38, 442–446. http://dx.doi.org/10.1055/s-2006-947840.
Pott, W., Albayrak, O., Hebebrand, J., Pauli-Pott, U., 2010. Course of depressive symptoms in overweight youth participating in a lifestyle intervention: associations with weight reduction. J. Dev. Behav. Pediatr. 31, 635–640. http://dx.doi.org/10.1097/DBP.0b013e3181f178eb.
Power, J.D., Mitra, A., Laumann, T.O., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2014. Methods to detect, characterize, and remove motion artifact in resting state fMRI. NeuroImage 84, 320–341. http://dx.doi.org/10.1016/j.neuroimage.2013.08.048.
Poznanski, E.O., Grossman, J.A., Buchsbaum, Y., Banegas, M., Freeman, L., Gibbons, R., 1984. Preliminary studies of the reliability and validity of the children's depression rating scale. J. Am. Acad. Child Psychiatry 23, 191–197.
Pruessner, J.C., Dedovic, K., Pruessner, M., Lord, C., Buss, C., Collins, L., Dagher, A., Lupien, S.J., 2010. Stress regulation in the central nervous system: evidence from structural and functional neuroimaging studies in human populations - 2008 Curt Richter Award Winner. Psychoneuroendocrinology 35, 179–191. http://dx.doi.org/10.1016/j.psyneuen.2009.02.016.
Psychological Corporation, 1999. Wechsler Abbreviated Scale of Intelligence (WASI). Harcourt Brace & Company, San Antonio, TX.
Raji, C.A., Ho, A.J., Parikshak, N.N., Becker, J.T., Lopez, O.L., Kuller, L.H., Hua, X., Leow, A.D., Toga, A.W., Thompson, P.M., 2010. Brain structure and obesity. Hum. Brain Mapp. 31, 353–364. http://dx.doi.org/10.1002/hbm.20870.
Ramasubbu, R., 2002. Insulin resistance: a metabolic link between depressive disorder and atherosclerotic vascular diseases. Med. Hypotheses 59, 537–551.
Rasgon, N.L., Kenna, H.A., 2005. Insulin resistance in depressive disorders and Alzheimer's disease: revisiting the missing link hypothesis. Neurobiol. Aging 26 (Suppl. 1), 103–107. http://dx.doi.org/10.1016/j.neurobiolaging.2005.09.004.
Rasgon, N.L., McEwen, B.S., 2016. Insulin resistance-a missing link no more. Mol. Psychiatry 21, 1648–1652. http://dx.doi.org/10.1038/mp.2016.162.
Rasgon, N.L., Kenna, H.A., Williams, K.E., Powers, B., Wroolie, T., Schatzberg, A.F., 2010. Rosiglitazone add-on in treatment of depressed patients with insulin resistance: a pilot study. ScientificWorldJournal 10, 321–328. http://dx.doi.org/10.1100/tsw.2010.32.
Rasgon, N.L., Kenna, H.A., Wroolie, T.E., Kelley, R., Silverman, D., Brooks, J., Williams, K.E., Powers, B.N., Hallmayer, J., Reiss, A., 2011. Insulin resistance and hippocampal volume in women at risk for Alzheimer's disease. Neurobiol. Aging 32, 1942–1948. http://dx.doi.org/10.1016/j.neurobiolaging.2009.12.005.
Ryan, J.P., Sheu, L.K., Critchley, H.D., Gianaros, P.J., 2012. A neural circuitry linking insulin resistance to depressed mood. Psychosom. Med. 74, 476–482. http://dx.doi.org/10.1097/PSY.0b013e31824d0865.
Rzepa, E., McCabe, C., 2016. Decreased anticipated pleasure correlates with increased salience network resting state functional connectivity in adolescents with depressive symptomatology. J. Psychiatr. Res. 82, 40–47. http://dx.doi.org/10.1016/j.jpsychires.2016.07.013.
Salat, D.H., Buckner, R.L., Snyder, A.Z., Greve, D.N., Desikan, R.S.R., Busa, E., Morris, J.C., Dale, A.M., Fischl, B., 2004. Thinning of the cerebral cortex in aging. Cereb. Cortex 1991 (14), 721–730. http://dx.doi.org/10.1093/cercor/bhh032.
Schmaal, L., Yücel, M., Ellis, R., Vijayakumar, N., Simmons, J.G., Allen, N.B., Whittle, S., 2017. Brain structural signatures of adolescent depressive symptom trajectories: a longitudinal magnetic resonance imaging study. J. Am. Acad. Child Adolesc. Psychiatry 56, 593–601.e9. http://dx.doi.org/10.1016/j.jaac.2017.05.008.
Shearin, E.N., Russ, M.J., Hull, J.W., Clarkin, J.F., Smith, G.P., 1994. Construct validity of the Three-Factor Eating Questionnaire: flexible and rigid control subscales. Int. J. Eat. Disord. 16, 187–198.
Shomaker, L.B., Tanofsky-Kraff, M., Stern, E.A., Miller, R., Zocca, J.M., Field, S.E., Yanovski, S.Z., Hubbard, V.S., Yanovski, J.A., 2011. Longitudinal study of depressive symptoms and progression of insulin resistance in youth at risk for adult obesity. Diabetes Care 34, 2458–2463. http://dx.doi.org/10.2337/dc11-1131.
Singh, M., 2014. Mood, food, and obesity. Front. Psychol. 5, 925. http://dx.doi.org/10.3389/fpsyg.2014.00925.
Singh, M.K., Chang, K.D., Kelley, R.G., Cui, X., Sherdell, L., Howe, M.E., Gotlib, I.H., Reiss, A.L., 2013. Reward processing in adolescents with bipolar I disorder. J. Am. Acad. Child Adolesc. Psychiatry 52, 68–83. http://dx.doi.org/10.1016/j.jaac.2012.10.004.
Singh, M.K., Kelley, R.G., Howe, M.E., Reiss, A.L., Gotlib, I.H., Chang, K.D., 2014. Reward processing in healthy offspring of parents with bipolar disorder. JAMA Psychiat. http://dx.doi.org/10.1001/jamapsychiatry.2014.1031.
Smith, S.M., 2002. Fast robust automated brain extraction. Hum. Brain Mapp. 17, 143–155. http://dx.doi.org/10.1002/hbm.10062.
Snaith, R.P., Hamilton, M., Morley, S., Humayan, A., Hargreaves, D., Trigwell, P., 1995. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. Br. J. Psychiatry J. Ment. Sci. 167, 99–103.
Soczynska, J.K., Kennedy, S.H., Woldeyohannes, H.O., Liauw, S.S., Alsuwaidan, M., Yim, C.Y., McIntyre, R.S., 2011. Mood disorders and obesity: understanding inflammation as a pathophysiological nexus. NeuroMolecular Med. 13, 93–116. http://dx.doi.org/10.1007/s12017-010-8140-8.
Somerset, S.M., Graham, L., Markwell, K., 2011. Depression scores predict adherence in a dietary weight loss intervention trial. Clin. Nutr. Edinb. Scotl. 30, 593–598. http://dx.doi.org/10.1016/j.clnu.2011.04.004.
Stouffer, M.A., Woods, C.A., Patel, J.C., Lee, C.R., Witkovsky, P., Bao, L., Machold, R.P., Jones, K.T., de Vaca, S.C., Reith, M.E.A., Carr, K.D., Rice, M.E., 2015. Insulin enhances striatal dopamine release by activating cholinergic interneurons and thereby signals reward. Nat. Commun. 6, 8543. http://dx.doi.org/10.1038/ncomms9543.
Takeuchi, T., Nakao, M., Kachi, Y., Yano, E., 2013. Association of metabolic syndrome with atypical features of depression in Japanese people. Psychiatry Clin. Neurosci. 67, 532–539. http://dx.doi.org/10.1111/pcn.12104.
Teh, M.M., Dunn, J.T., Choudhary, P., Samarasinghe, Y., Macdonald, I., O'Doherty, M., Marsden, P., Reed, L.J., Amiel, S.A., 2010. Evolution and resolution of human brain perfusion responses to the stress of induced hypoglycemia. NeuroImage 53, 584–592. http://dx.doi.org/10.1016/j.neuroimage.2010.06.033.
van der Aa, M.P., Knibbe, C.A.J., de Boer, A., van der Vorst, M.M.J., 2017. Definition of insulin resistance affects prevalence rate in pediatric patients: a systematic review and call for consensus. J. Pediatr. Endocrinol. Metab. 30, 123–131. http://dx.doi.org/10.1515/jpem-2016-0242.
van Dijk, A.E., van Eijsden, M., Stronks, K., Gemke, R.J.B.J., Vrijkotte, T.G.M., 2010. Cardio-metabolic risk in 5-year-old children prenatally exposed to maternal psychosocial stress: the ABCD study. BMC Public Health 10, 251. http://dx.doi.org/10.1186/1471-2458-10-251.
Wang, H., Wen, B., Cheng, J., Li, H., 2017. Brain structural differences between normal and obese adults and their links with lack of perseverance, negative urgency, and sensation seeking. Sci. Rep. 7, 40595. http://dx.doi.org/10.1038/srep40595.
Weltens, N., Zhao, D., Van Oudenhove, L., 2014. Where is the comfort in comfort foods? Mechanisms linking fat signaling, reward, and emotion. Neurogastroenterol. Motil. 26, 303–315. http://dx.doi.org/10.1111/nmo.12309.
Williams, D.B., 2015. Inhibitory effects of insulin on GABAA currents modulated by the GABAA alpha subunit. J. Recept. Signal Transduct. Res. 35, 516–522. http://dx.doi.org/10.3109/10799893.2014.960935.
Wolkowitz, O.M., Reus, V.I., Mellon, S.H., 2011. Of sound mind and body: depression, disease, and accelerated aging. Dialogues Clin. Neurosci. 13, 25–39.
Wong, J.J., O'Daly, O., Mehta, M.A., Young, A.H., Stone, J.M., 2016. Ketamine modulates subgenual cingulate connectivity with the memory-related neural circuit-a mechanism of relevance to resistant depression? PeerJ 4, e1710. http://dx.doi.org/10.7717/peerj.1710.
Wozniak, J., Gönenç, A., Biederman, J., Moore, C., Joshi, G., Georgiopoulos, A., Hammerness, P., McKillop, H., Lukas, S.E., Henin, A., 2012. A magnetic resonance spectroscopy study of the anterior cingulate cortex in youth with emotional dysregulation. Isr. J. Psychiatry Relat. Sci. 49, 62–69.
Yates, K.F., Sweat, V., Yau, P.L., Turchiano, M.M., Convit, A., 2012. Impact of metabolic syndrome on cognition and brain: a selected review of the literature. Arterioscler. Thromb. Vasc. Biol. 32, 2060–2067. http://dx.doi.org/10.1161/ATVBAHA.112.252759.
Yau, P.L., Castro, M.G., Tagani, A., Tsui, W.H., Convit, A., 2012. Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. Pediatrics 130, e856–864. http://dx.doi.org/10.1542/peds.2012-0324.
Yau, P.L., Kang, E.H., Javier, D.C., Convit, A., 2014. Preliminary evidence of cognitive and brain abnormalities in uncomplicated adolescent obesity. Obesity (Silver Spring) 22, 1865–1871. http://dx.doi.org/10.1002/oby.20801.
Ye, M., Qing, P., Zhang, K., Liu, G., 2016. Altered network efficiency in major depressive disorder. BMC Psychiatry 16, 450. http://dx.doi.org/10.1186/s12888-016-1053-9.
Young, J.J., Silber, T., Bruno, D., Galatzer-Levy, I.R., Pomara, N., Marmar, C.R., 2016. Is there progress? An overview of selecting biomarker candidates for major depressive disorder. Front. Psych. 7, 72. http://dx.doi.org/10.3389/fpsyt.2016.00072.
Zeng, L.-L., Shen, H., Liu, L., Wang, L., Li, B., Fang, P., Zhou, Z., Li, Y., Hu, D., 2012. Identifying major depression using whole-brain functional connectivity: a multivariate pattern analysis. Brain J. Neurol. 135, 1498–1507. http://dx.doi.org/10.1093/brain/aws059.