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# Do Shape and Volume of Subcortical Neural Structures Involved in Reward Processing Correlate with Body Mass and Food Reward in Adolescent Females?

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A thesis submitted to the faculty of
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Master of Science

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# ABSTRACT

## Do Shape and Volume of Subcortical Neural Structures Involved in Reward Processing Correlate with Body Mass and Food Reward in Adolescent Females?

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Background: The prevalence of adolescent obesity has increased drastically in the last few decades, spurring research examining causes and consequences of this chronic health condition. Neuroimaging techniques are being used to determine possible neural correlates of obesity that could help inform research in this field. However, the research among adolescents is not as abundant and findings so far are contradictory. This study sought to examine the association of the shape and volume of subcortical brain structures involved in reward processing with weight status in adolescent females. Additionally, this study sought to determine if the shape and volume of these structures were correlated with the Power of Food Scale (PFS), a self-report measure of food reward sensitivity.

Method: The shape and volume of the nucleus accumbens (NAc) and amygdala were examined in 89 adolescent females ranging from normal weight to obese. MR scans were acquired using a high-resolution T1-weighted (MPRAGE) sequence. Shape was estimated using Large Deformation Diffeomorphic Metric Mapping. Seemingly unrelated regression models (SUM) were used for both brain structures with shape and volume as outcome variables and zBMI as the predictor variable. Pairwise correlation coefficients were determined for PFS score and both regions of interest (ROI).

Results: SUM results revealed that zBMI was significantly associated with the shape of the left amygdala ($\beta$ = -1.1, $p$<.021, 95% confidence interval [CI] = -2.02, -.16). When we controlled for age on the relationship between zBMI and left amygdala shape, we found the following partial correlation: $r$ = -.24, $p$ = .03. The PFS was found to have weak correlations with the volume and shape of the right NAc that approached significance ($r$ = .20, $p$ = .06; $r$ = .19, $p$ = .08, respectively).

Conclusions: Our study suggests that there is an association between higher zBMI and aberrations in the shape of the left amygdala. We did not find associations between zBMI and the shape of our other reward-related ROIs, nor did we find any associations with zBMI and ROI volume. These findings suggest that variation in the shape of certain ROIs implicated in reward processing is associated with weight status in adolescents. Our findings also suggest that the shape and volume of the NAc could be a neural correlate of the PFS warranting further investigation. These findings may elucidate an important neural link between weight status and reward processing that could help to inform obesity research in adolescents.



Keywords: neuroimaging, obesity, adolescence, reward, amygdala, nucleus accumbens

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**Do Shape and Volume of Subcortical Neural Structures Involved in Reward Processing Correlate with Body Mass and Food Reward in Adolescent Females?**

Prevalence of adolescent obesity has increased drastically in the last few decades, spurring research examining possible causes and consequences of this chronic health condition (Skinner et al., 2018). Neuroimaging methodologies have been utilized to explore the underlying neural mechanisms involved in obesity and feeding behaviors. Functional magnetic resonance imaging (fMRI) studies have found differential neural activation in adolescents with obesity/ overweight compared to their normal weight peers in response to food images (Yokum, et al., 2011; Duraccio et al., 2019).

Magnetic resonance imaging (MRI) has also explored the mechanisms involved in obesity and feeding behaviors, but there are some contradictory findings, especially regarding the differences between adult and pediatric populations. For example, some studies have found differences in frontal cortical thickness and gray matter volume in adults and adolescents with overweight/obesity compared to their normal weight peers (Marques-Iturria et al., 2013; Ross et al., 2015). In contrast, one study found that there were no differences in cortical thickness in adolescents with obesity despite these differences being present among adults (Sharkey et al., 2015).

Neuroimaging has brought new and interesting perspectives to health psychology, but much of the literature in pediatric populations with obesity/overweight is conflicting, likely due in part to small sample sizes and differences in how the data is processed and analyzed. The literature on this topic in general is also not as abundant in the adolescent population, thus requiring further investigation.

In the last decade, obesity research has implicated brain circuits, other than those involved in satiety and hunger, in food consumption and obesity; specifically, limbic structures such as the nucleus accumbens, amygdala, and basal ganglia are thought to be involved in the rewarding effects of food (Volkow et al., 2011). While the literature linking diminished cognitive functioning in domains such as reward processing with adult obesity is quite abundant, less is known about these processes in pediatric populations. Nevertheless, based on the research conducted in this population, findings suggest that adolescents with obesity appear to have differing neurocircuitry involved in inhibitory control and reward processing than their normal weight counterparts (Liang et al., 2014). Subcortical structures involved in processes such as reward sensitivity have also been identified in the pediatric obesity literature. Haghighi and colleagues (2013) found amygdala volume to be inversely correlated with fat intake, suggesting a possible association of brain structure and eating behaviors. Additionally, Perlaki and colleagues (2018) found volume of reward system structures, namely the amygdala and the nucleus accumbens, to be correlated with BMI in children.

Moreover, food reward sensitivity, or how one determines a food to be desirable, is positively correlated with adolescent body mass index (BMI) as indicated by the Power of Food Scale (PFS), a measure of appetite and reward sensitivity to palatable foods (Duraccio et al., 2019; Lowe et al., 2009). Moreno-Lopez et al. (2012) explored structural brain correlates of reward sensitivity in adolescents with normal weight and excess weight. They discovered an increase in right hippocampal gray matter volume in individuals with excess weight. They also found secondary somatosensory cortex related with reward sensitivity in lean controls, but not in excess weight individuals, possibly due to the relatively small sample used. The current study

aims to explore reward sensitivity in a similar manner; however, with a focus on how the volume and shape of a priori selected subcortical brain structures relates with the PFS, a measure of food reward, as well as BMI ranging from normal to obese. By using both behavioral and neuroanatomical measures, reward processing and its effects on pediatric obesity is explored in a multidimensional approach.

Yokum et al. (2011) found that BMI was positively correlated with neural activation in brain regions associated with food reward for adolescent females. Furthermore, significant sex differences were observed in cognitive functioning in adolescents, with females displaying greater responses to visual food stimuli than males and increased activation in sensory processing-related brain regions (Jensen et al., 2016; Varley-Campbell et al., 2018). Sex differences such as these have also been demonstrated in research examining brain structure, where differences in the left dorsal striatum and right dorsolateral prefrontal cortex were found among women with obesity but not men (Horstmann et al., 2011). Due to the inherent biological and physical sex differences in obesity and emotional responses to food, the current study sought to examine the relationship between reward processing and obesity/overweight in an exclusively female adolescent population.

In this study we used MRI procedures to assess integrity of deep brain nuclei involved in reward processing and appetite in adolescents ranging from normal weight to obese. The aim of the study was twofold: first, to characterize the morphology of the amygdala and nucleus accumbens (NAc) in this adolescent sample. Second, to examine whether various shape features of the amygdala and NAc related to body mass and appetite for foods as measured by the PFS. To our knowledge, the PFS has not been examined as a correlate with reward-related subcortical brain structures in an obese/overweight population. We selected these specific subcortical

structures based on previous research that implicated them in reward processing related to obesity and feeding behaviors, with the desire to gain insight into potential brain-behavior relationships. This study is among the first to analyze subcortical shape, as well as volume, in an obese/overweight adolescent population. We hypothesized that BMI would predict differences in subcortical neural shape and volume in adolescents. Additionally, we hypothesize that scores on the PFS would strongly relate with volume and shape of the selected brain structures.

## Methods

### Participants

Eighty-nine adolescent females (Mean age = 16.41, *SD* = 1.48) ranging from normal weight to obese (BMI ranging from 16.6 to 49.42) were recruited from multiple studies on adolescence at the same research site. All participants were recruited from local middle and high schools in Utah County, Utah.

Additionally, height and weight were measured in all study procedures, which included calculations for BMI. Exclusion criteria were consistent across studies: use of weight loss medication, history of bariatric surgery, use of medications that affect salivation (e.g., antihistamines, antidepressants), binge eating, left handedness, psychiatric conditions (e.g., epilepsy, traumatic brain injury, schizophrenia, bipolar disorder), food allergies and standard MRI contraindications (e.g., pregnancy, ferrous implants, and claustrophobia). In two of the four studies included, participants also had met criteria for overweight or obesity (BMI%ile $\geq 85$) to participate. In one study that required the participants to exercise, individuals were also excluded if they were "aerobically trained", operationally defined to mean that they engage in moderate to vigorous physical activity for more than 3 hours per week.

### Measures

***Food Reward***

The Power of Food Scale (PFS) is a self-report measure of the appetite-related thoughts, feelings, and motivations towards palatable foods (Lowe et al., 2009). Questions include "If I see or smell a food I like, I get a very strong desire to have some," or "Just before I taste a favorite food, I get very excited." The measure comprises three factors of food proximity: food available (i.e., reactions to the widespread availability of palatable foods in the environment), food present (i.e., reactions to food that are physically present), and food tasted (i.e., reactions to food when they are first tasted but not yet consumed). The PFS is only meant to be used in food-abundant environments where food is not only eaten out of need for survival, but also out of factors such as desirability and appetite. The PFS purports to measure the rewarding and appetite-related attitudes and reactions towards food and not actual food consumption (Cappelleri et al., 2009). The current study examined the outcomes of this measure as it relates to food reward (i.e., desire and motivation to taste food; Rogers & Hardman, 2015). Questions are rated on a 5-point Likert-type scale and participants were asked to respond in reference to the previous week. A higher score on the PFS is considered to reflect stronger emotional reactions to food and more motivation for eating based on needs other than hunger alone (Lowe et al., 2009).

The three factors of food proximity (food available, food present, food tasted) that comprise the PFS were found to be highly correlated and supported the use of a total scale score (all 15 items). In an adult population, the PFS has excellent internal consistency ($\alpha = 0.91$), and four-month test-retest reliability is adequate ($r = 0.77$; Cappelleri et al., 2009). The PFS has also been recently shown to have good internal consistency in adolescent samples ($\alpha = 0.86$ to $0.95$, $\alpha = 0.93$ to $0.95$; Duraccio et al., 2019; Mitchell et al., 2016).

Content validity of the PFS was found to be acceptable according to expert rater assessments (Cappelleri et al., 2009). The PFS is moderately correlated with the Disinhibition and Hunger subscales of the Three Factor Eating Questionnaire and the Emotional Eating and External Eating subscales of the Dutch Eating Behavior Questionnaire. Forman and colleagues (2007) tested the validity of the PFS by asking participants to abstain from eating any chocolate after being given a transparent box of chocolate kisses to store in their home. Participants who gave in and ate the kisses had significantly higher PFS scores than those who did not, suggesting that the PFS is an adequate representation of differing motivations to eat and desirability of food.

As mentioned previously, the PFS was originally designed to measure thoughts, feelings, and motivations towards palatable foods. Since the creation of the PFS, many studies have utilized it as a measure of food reward, but the extent to which this measure is accurately measuring this construct continues to be explored. A recent review of food reward and its measurement by the PFS suggests that the PFS is considered to be closely related to motivation to consume palatable foods as well as the occurrence of loss-of-control eating episodes. The PFS has not been found to be predictive of the amount of food consumed but scores have been shown to decline over time among patients undergoing behavioral weight loss or other treatments for overweight/obesity. Thus, food reward as measured by the PFS can fluctuate depending on learned food and weight related behaviors (Espel-Huynh et al., 2018). This same review article expressed the need to further explore the PFS as it relates to food reward through measures such as neuroimaging. The current study will attempt to link the PFS with food reward by exploring brain structures thought to be involved in reward processing.

**Procedures**

Participants came to the Brigham Young University MRI Research Facility and checked in with staff at the reception area. Trained research personnel obtained informed consent and again conducted a pre-screening for MRI contraindications to ensure safety during scanning. The Power of Food Scale (PFS) questionnaire was administered to all participants across studies. Three of the four studies administered the PFS in an appointment prior to the scanning appointment along with a demographic questionnaire and other questionnaires that varied depending on the individual aims of each study. One of the studies involved two scanning appointments that were a month apart where the PFS was administered after scanning on each occasion. The PFS score collected from the first scanning appointment was used for the current study.

In each study, MRI procedures were nearly identical. Participants were debriefed before entering the scanner on what to expect. They were provided ear protection and prepared to enter the scanner room. While in the scanner, the structural scan was the first scan across studies. Participants were asked to remain completely still while the structural MR image was acquired. The scanning time for this portion of the imaging procedure was seven minutes. The fMRI task used in three of the four studies was a food go/no-go task that lasted an additional 14 minutes (Jensen et al., 2019; Jensen & Kirwan, 2015). In one study the fMRI task was a social evaluation simulation where participants were told whether or not a peer was interested in chatting with them that lasted approximately 25 minutes. While fMRI data was previously collected and analyzed from these studies, the current study analyzed the structural images for the first time. All data were de-identified and are currently stored on a secure university server. Preprocessing scripts written for the current study will be shared publicly so results can be replicated.

**MRI Data Acquisition**

Imaging was conducted using a Siemens TIM Trio 3T MRI scanner equipped with a 12-channel head coil. A high-resolution T1-weighted structural brain scan (MPRAGE) was obtained using the following parameters: TE = 2.26ms; TR = 1900ms; FOV = 218 × 250mm; acquisition matrix = 215 × 256; slice thickness = 1mm; voxel size = 0.98 × 0.98 × 1mm.

**Volume and Shape of Subcortical Structures**

Subcortical structures make up highly complex systems that vary across individuals, making it difficult to analyze human brain structure. In order to address this complexity, a collection of coordinate systems has been developed to represent neuroanatomical structures. These systems consist of landmark points (0D), curves (1D), surfaces (2D), and subvolumes (3D). By generating diffeomorphic transformations from these coordinate systems, we are able to better represent the variability that is inevitable among individuals (Grenander & Miller, 1994, 1998; Joshi et al., 1997). Templates are created from the images generated by diffeomorphic transformations and these templates are detailed enough that shape and volume of subcortical structures can be identified. Under this assumption, subcortical structures are considered to be enclosed by a single surface. Although an oversimplification of human brain anatomy, a great deal of information can be obtained regarding abnormalities by analyzing subcortical brain structures in this way (Csernansky et al., 2004).

The current study uses a fully-automated brain segmentation method to define the morphology of specific brain regions involved in reward processing, namely the NAc and amygdala. Although fully-automated methods have not been widely used in past research due to issues of reliability and accuracy, combining the probabilistic-based FreeSurfer (FS) method with the Large Deformation Diffeomorphic Metric Mapping (LDDMM)-based label-propagation

method increases reliability and accuracy as well as maintains smoothness and detail that might otherwise be lost, which is especially important for shape analysis. This method (FS+LDDMM) has been shown to have statistically significant improvement of accuracy over traditional FreeSurfer methods used for subcortical brain segmentation (Khan et al., 2008).

The first step in the FS+LDDMM pipeline was the generation of the FreeSurfer subcortical labels. The FreeSurfer pipeline consisted of five stages: an affine registration with template space, an initial volumetric labeling, bias filed correction, non-linear alignment to the template space, and final labeling of the volume (Fischl et al., 2002). Using the labels generated from the FreeSurfer pipeline, the LDDMM is computed on regions of interest (ROIs), which are used to bound the structures of interest rather than looking at the brain as a whole. By selecting ROIs, we are more likely to meet the assumption that the images can be mapped with an invertible transformation, which is crucial for the reliability and accuracy of the LDDMM computation. The subcortical structures of interest were then registered to the template image to ensure that they were contained within the ROIs (Khan et al., 2008). Two coders performed quality assurance checks for all participants and rated accuracy of boundaries for the NAc and amygdala. Reliability between raters was found to range from good to excellent. The average measure ICC was .93 for the NAc and .86 for the amygdala.

From this point, we were able to characterize the structures by volume and shape. The template we created allows us to compare differences among subjects. Analysis of volume and shape of subcortical structures using an automated FreeSurfer method has been shown to have high test-retest reliability ($r = 0.81$ to $r = 0.98$). The amygdala and NAc have relatively lower test-retest reliability likely due to their small size but are still adequate ($r = 0.86$ & $r = 0.81$, respectively; Madan & Kensinger, 2017).

**Statistical Analyses**

Statistical analyses were completed using Stata 15 (Stata Corp, 2017). Descriptive statistics were used to summarize demographic information including age, race, and BMI as well as PFS scores. BMI standard deviation scores (z-scores; zBMI) were used in our analysis since they are adjusted measurements of BMI for child/teen age and sex which better represents our adolescent sample (Must & Anderson, 2006). Two multivariate models were used to allow for correlations of the right and left hemispheres for both volume and shape of the ROIs. Specifically, two seemingly unrelated regression (SUR) models were used for volume and shape in order to carry out multiple linear regressions and avoid spurious results due to multiple comparisons. The SUR analysis allows for cross-equation error correlation. The regression equations used in the primary SUR analyses included the following:

1) $Right\_Amyg\_Vol_i = \beta_0 + \beta_{zbmi} + \beta_{age} + \varepsilon_i$
2) $Left\_Amyg\_Vol_i = \beta_0 + \beta_{zbmi} + \beta_{age} + \varepsilon_i$
3) $Right\_NA\_Vol_i = \beta_0 + \beta_{zbmi} + \beta_{age} + \varepsilon_i$
4) $Left\_NA\_Vol_i = \beta_0 + \beta_{zbmi} + \beta_{age} + \varepsilon_i$

1) $Right\_Amyg\_Shape_i = \beta_0 + \beta_{zbmi} + \beta_{age} + \varepsilon_i$
2) $Left\_Amyg\_Shape_i = \beta_0 + \beta_{zbmi} + \beta_{age} + \varepsilon_i$
3) $Right\_NA\_Shape_i = \beta_0 + \beta_{zbmi} + \beta_{age} + \varepsilon_i$
4) $Left\_NA\_Shape_i = \beta_0 + \beta_{zbmi} + \beta_{age} + \varepsilon_i$

To address our first aim, the SUR models were used to investigate how BMI is predictive of volume and shape of the NAc and amygdala with age as a covariate. Regarding shape, a principal component analysis (PCA) was conducted during the preprocessing phase of the data. Multiple eigenvectors were derived from the PCA, with the first eigenvector containing the majority of the variance in the model. This principal component eigenvector represented shape as one of our dependent variables in our SUR model. Due to the ambiguity in interpreting the shape outcome variable, a semi-partial correlation was conducted to determine effect size for shape.

Volume of subcortical structures was also determined in preprocessing and acted as our second dependent variable. A follow-up exploratory group analysis was also conducted for volume and shape using two-way repeated measures analyses of variance (ANOVAs) in order to better understand the relationship of these structures with weight status (See Table 1).

To address our second aim, pairwise correlation coefficients were determined for PFS score and the corresponding ROIs from our analysis for aim 1. The syntax used to perform these analyses in Stata for aim 1 and 2 is as follows:

Aim 1 Stata Syntax:

```
sureg (vol_amyg_l zbmi age) (vol_amyg_r zbmi age) (vol_na_l zbmi age) (vol_na_r zbmi age)

sureg (pc_amyg_r_01 zbmi age) (pc_amyg_l_01 zbmi age) (pc_na_l_01 zbmi age) (pc_na_r_01 zbmi age)
```

Aim 2 Stata Syntax:

```
pwcorr pfs vol_amyg_l vol_amyg_r vol_na_l vol_na_r prob_amyg prob_na, sig
```

**Sensitivity Power Analysis**

The sample size for the current study is fixed at 89 because data was pulled from several studies that had been conducted previously and no additional data was collected. Using G*Power (Erdfelder, Faul, & Buchner, 1996), a sensitivity power analysis was performed to find the smallest possible population correlation that can be detected considering our sample size restrictions. Results found that with a sample of 89 and a type I error rate of 0.05, we have 80% power to detect a population correlation of $r = 0.26$ or greater. With an increase of 20 participants, a correlation as small as $r = 0.23$ could be detected with 80% power. Conversely, if some of the data were to be lost or excluded due to complications in preprocessing, a correlation as small as $r = 0.27$ could be detected with a decrease of 10 participants (see Figure 1). Nevertheless, our sample of 89 appears to be adequate for addressing our research question. A study examining adolescents and brain structure with a sample of 120 found correlations between BMI and limbic brain region that ranged from $r = -0.31$ to $r = -0.35$ (Alosco et al.,

2014). Another study with a sample of 80 obese adults with a somewhat similar design to the current study reported a correlation between amygdala volume and sensation seeking behaviors of $r$ = -0.41 (Wang et al., 2017). Thus, the current study appears to have sufficient power and sample size to detect possible correlations as outlined by preexisting literature.

## Results

### Data Screening

No data were missing from our analysis. A priori data screening guidelines defined outliers as any subject with values outside the median plus/minus twice the interquartile range. Six total outliers were discovered across the different shape and volume values. Extreme scores for the subjects were recoded to the upper/lower limit of the range.

To determine whether or not both hemispheres (LH and RH) would be included in our regression model for volume, paired samples t-tests were performed on the structures. Volume and shape of the left and right hemispheres for the NAc and amygdala were found to be significantly different from each other and were both included in our model. The first eigenvector derived from the PCA was used to represent shape in our analysis. The first eigenvector for the left and right hemisphere of the amygdala accounted for 35.9% of the total variance and the first eigenvector for the left and right hemisphere of the NAc accounted for 32.7% of the total variance.

### Aim 1

Characterize the morphology of specific subcortical brain structures involved in reward processing and appetite, specifically the amygdala and NAc in an adolescent population.

#### *Prediction of NAc and Amygdala Shape/Volume*

SUM results revealed that zBMI was significantly associated with the morphology of the left amygdala ($\beta$ = -1.1, $p$<.021, 95% confidence interval [CI] = -2.02, -.16; See Table 2). When we controlled for age on the relationship between zBMI and left amygdala shape, we found the

following partial correlation: $r$ = -.24, $p$ = .03 (see Table 3). There appeared to be a relationship between zBMI and left amygdala shape. zBMI was not found to be associated with the volume of any of our ROIs (See Table 4).

***Exploratory Group Analysis of Shape***

To better understand these results, repeated measures two-way analyses of variance (ANOVAs) were utilized for analysis of shape, with group status (overweight/obese vs. normal) as the fixed effect, hemisphere (LH and RH) as the repeated measure, and age as a covariate in the model. Results from this analysis revealed a main effect of group on amygdala shape ($F(3, 86)$ = 4.67, $p < .03$). No main effect of group was found on NAc shape.

Post-hoc paired samples t-tests between groups were conducted for left and right amygdala shape. This analysis revealed that the means between these groups were significantly different ($p$ = .03) for the left amygdala, but not for the right amygdala. The average shape value for left amygdala in the normal weight group was -11.69 and the average shape value for the overweight/obese group was -13.63. Thus, an increase in zBMI predicts a decrease in shape value. The shape of the left amygdala for overweight/obese individuals is significantly different from normal weight individuals.

***Exploratory Group Analysis of Volume***

To follow-up our original analysis, we also conducted ANOVAs for analysis of volume, with group status as the fixed effect, hemisphere (LH and RH) as the repeated measure, and age as a covariate in the model. No significant between group differences were found for NAc or amygdala volume.

**Aim 2**

Relate volume and shape of these subcortical structures to body mass and appetite for foods as measured by the PFS.

### *Correlation of PFS with NAc and Amygdala Shape/Volume*

The rewarding effect of food determined by total scores on the PFS was found to have weak correlations with the volume and shape of the right NAc that approached significance ($r$ = .20, $p$ = .06; $r$ = .19, $p$ = .08, respectively; see Figure 2). All other correlations between PFS score and shape/volume of NAc and amygdala were very small.

## Discussion

The present study sought to examine the relationship between reward-related subcortical brain regions and zBMI in adolescent females. To further investigate these structures as they relate specifically to the rewarding effects of food, we examined the PFS, a self-report measure of hedonic hunger, as a possible neural correlate with the NAc and amygdala.

Our first aim was to characterize the integrity of the NAc and amygdala using surface-based approaches of shape and volume in adolescent females ranging from normal weight to obese. We hypothesized that zBMI would be associated with variations in shape and volume of the NAc and amygdala in adolescents when we control for age. We found a significant association of zBMI with left amygdala shape. A recent study found cardiorespiratory fitness, controlling for BMI, to be predictive of the shape of several subcortical structures including the left/right amygdala and the left NAc (but not the right NAc) in children (Ortega et al., 2017). These findings, despite the differences in research aims and analysis, are relatively consistent with what we have found in our study regarding shape. Granted, research in this field with adolescents remains under-explored and the current study sought to add to this literature.

While the shape value derived from our PCA is meant to represent overall variation in morphology, it was difficult to interpret what this effect could mean without following up our analysis with an exploratory group comparison of overweight/obese and normal weight

adolescents. We found that there was a significant difference between the mean shape values for these groups for the left amygdala shape, which informed the directionality of our SUR results. An increase in zBMI was associated in a significant decrease in shape compared to the normal weight group. These results suggest that aberrations in amygdala shape are associated with greater zBMI in our adolescent sample.

In the extant literature, volumetric differences of the whole brain and other regions of the brain such as the frontal and temporal lobes have been found between overweight/obese and normal weight groups in adults (Gunstad et al., 2008; Raji et al., 2010). Studies conducted with children and adolescents are much less abundant, but differences in volume corresponding to weight categories have been found in some regions of the brain among adolescents (e.g., orbitofrontal cortex). However, our findings suggest that there are not differences in the volume of reward-related subcortical regions of the brain between overweight/obese and normal weight groups. This is somewhat inconsistent with findings from one study that found lower amygdala volume was negatively correlated with fat intake in adolescents (Haghighi et al., 2013). And yet, similar to our study, Haghighi and colleagues did not find any correlations with the NAc. Another study found both the amygdala and the NAc to be positively correlated with zBMI (Perlaki et al., 2018), further highlighting the inconsistency of results in this population and the need for continued exploration. Small subcortical structures such as the amygdala and NAc can be challenging to measure, and possible differences present between these structures can be difficult to detect (Fischl et al., 2002). More research needs to be conducted in adolescents to better understand possible differences in these specific structures and how they relate to the rewarding effects of food.

Our second aim was to determine if the PFS, a measure of the rewarding effect of food, is correlated with the morphology of the NAc and amygdala. We hypothesized that PFS scores would be correlated with the shape/volume of NAc and amygdala, such that higher scores would be related to variations in these structures. Espel-Huynh et al. (2018) expressed the need to examine the PFS as it relates to the rewarding effects of food through methodologies such as neuroimaging. Discovering a possible neural correlate for the PFS could improve validity and clarify that it is measuring what it purports to measure about human behavior.

Our study is among the first to explore how reward-related regions of the brain may be related to the PFS. While we did not find statistically significant correlations of our ROIs with the PFS, the shape and volume of the right NAc had the strongest correlations with the measure compared to the other structures examined. Rapuano and colleagues (2017) found increased genetic risk for obesity predicted higher NAc volume in children. Children with this genetic risk also showed stronger reward-related responses to food cues. These findings are relatively consistent with the positive correlations we found of NAc volume and the PFS. The positive correlation of the PFS and the shape of the right NAc suggests certain variations in the shape of the NAc that could be implicated specifically in the rewarding effect of food, such that greater PFS scores are associated with greater shape abnormalities.

The NAc is thought to play a key role in mediating reward behavior and is implicated directly in addictive behaviors (Russo et al., 2010). The PFS is specifically targeting the rewarding or even possibly “addicting” effects of food which might help explain why it is more strongly correlated with the NAc than it is the amygdala, even though these two structures are often related in their functions. Further exploration of the relationship between reward-related

regions of the brain, specifically the NAc as implicated by this study, is warranted to better understand how these structures are related to the rewarding effects of food.

The literature on BMI and neural correlates in adolescents is scant and existing findings are inconsistent. Additionally, much of the research in the field examines group differences between individuals with normal weight and individuals with overweight/obese. The current study was designed to add to the research being done with this population and methodology by using zBMI ranging from normal weight to overweight/obese as a continuous predictor of brain shape/volume. Other studies have used BMI to predict brain morphology, specifically volume, in children and adults (Kennedy et al., 2016). Our study is the first, to our knowledge, to examine the association of zBMI and subcortical shape in adolescents.

Our study was not without limitations. The cross-sectional design of our study is such that we are unable to make any causal inferences about the results presented. Due to the paucity of research on this subject broadly and the inconsistency of findings in the field, we were not able to form directional hypotheses for our analyses. Additionally, since our data was pooled from several different studies, we had to use what was common among these studies and thus were only able to include one behavioral measure of food reward (PFS). While BMI is widely used in the literature as a correlate and predictor of health outcomes, future studies could benefit by incorporating other biomarkers such as visceral fat and waist adiposity in their analyses of brain-behavior relationships. Lastly, our sample was not racially or ethnically diverse and is therefore not completely representative of the broader population.

As we come to understand the associations of the brain with weight status, we are able to create more targeted treatments. By narrowing analysis to specific regions of the brain implicated in the rewarding effects of food, we can make sense of why certain eating patterns exist.

Moreover, neural correlates for the measures we use to assess for these behaviors can also help to establish validity. More research should be conducted in adolescent populations to understand the brain during this critical period of development. If weight status impacts brain development, it would become even more crucial to target eating behaviors from a young age. Longitudinal research is necessary to understand the causal relationship of weight status on brain volume and shape in adolescents.

**Conclusion**

Our study suggests that there is an association between higher zBMI and aberrations in the shape of the left amygdala. However, we did not find associations between zBMI and the shape of our other reward-related ROIs, nor did we find any associations with zBMI and ROI volume. These findings suggest that variations in the shape of certain ROIs implicated in reward processing is associated with weight status in adolescents.

We also examined whether these ROIs were correlated with the PFS, a measure of the rewarding impact of food. While no significant correlations were found, the shape and volume of the right NAc had the highest correlation with the PFS compared to the other ROIs. Our findings suggest that the shape and volume of the NAc could be a neural correlate of the PFS warranting further investigation.

These findings add to the neuroimaging literature in an adolescent population, which is sparse and contradictory. More research is necessary in this population, specifically in understanding the impact of neural shape abnormalities on weight status and feeding behaviors. These findings may elucidate an important neural link between weight status and reward processing that could help to inform obesity research in adolescents.

Table 1. Subject Characteristics by Weight Category

| | Overweight/Obese, n = 54 | Normal Weight, n = 35 |
|---|---|---|
| Mean (SD) age in years | 16.5 (1.2) | 16.3 (1.9) |
| Mean (SD) BMI | 31.9 (5.4) | 21.4 (2.3) |
| Mean (SD) PFS score | 34.6 (12.2) | 41.5 (12.2) |

Table 2. Seemingly Unrelated Regression (SUR) for Shape

| Subcortical Morphology | | Coefficient | Standard Error | P-value | 95%CI |
|---|---|---|---|---|---|
| Right Amygdala Shape | | | | | |
| | zBMI | -.51 | .52 | .324 | -1.5, .51 |
| | Age | -.02 | .02 | .195 | -.05, .01 |
| Left Amygdala Shape | | | | | |
| | zBMI | -1.10* | .48 | .021 | -2.0, -.16 |
| | Age | .23 | .30 | .443 | -.35, .81 |
| Right NAc Shape | | | | | |
| | BMI | -.58 | .44 | .181 | -1.4, .27 |
| | Age | .01 | .02 | .478 | -.02, .05 |
| Left NAc Shape | | | | | |
| | zBMI | -.41 | .35 | .239 | -1.1, .27 |
| | Age | -.18 | .22 | .396 | -.61, .24 |

*indicates $p<.05$

Table 3. Semi-Partial Correlation for Left Amygdala

| | Semi-partial correlation | Significance value |
|---|---|---|
| Left Amygdala Shape | | |
| zBMI | -.24 | .03 |
| Age | .08 | .45 |

Table 4. Seemingly Unrelated Regression (SUR) for Volume

| Subcortical Morphology | Coefficient | Standard Error | P-value | 95%CI |
|---|---|---|---|---|
| Right Amygdala Volume | | | | |
| zBMI | 14.91 | 18.18 | .412 | -20.73, 50.55 |
| Age | 2.71 | 11.29 | .811 | -19.42, 24.82 |
| Left Amygdala Volume | | | | |
| zBMI | 2.98 | 20.06 | .882 | -36.34, 42.30 |
| Age | 3.15 | 12.45 | .800 | -21.25, 27.56 |
| Right NAc Volume | | | | |
| BMI | -1.30 | 4.54 | .771 | -10.22, 7.58 |
| Age | -2.57 | 2.82 | .362 | -8.09, 2.96 |
| Left NAc Volume | | | | |
| zBMI | .35 | 4.49 | .937 | -8.45, 9.16 |
| Age | -4.83 | 2.79 | .083 | -10.30, .63 |

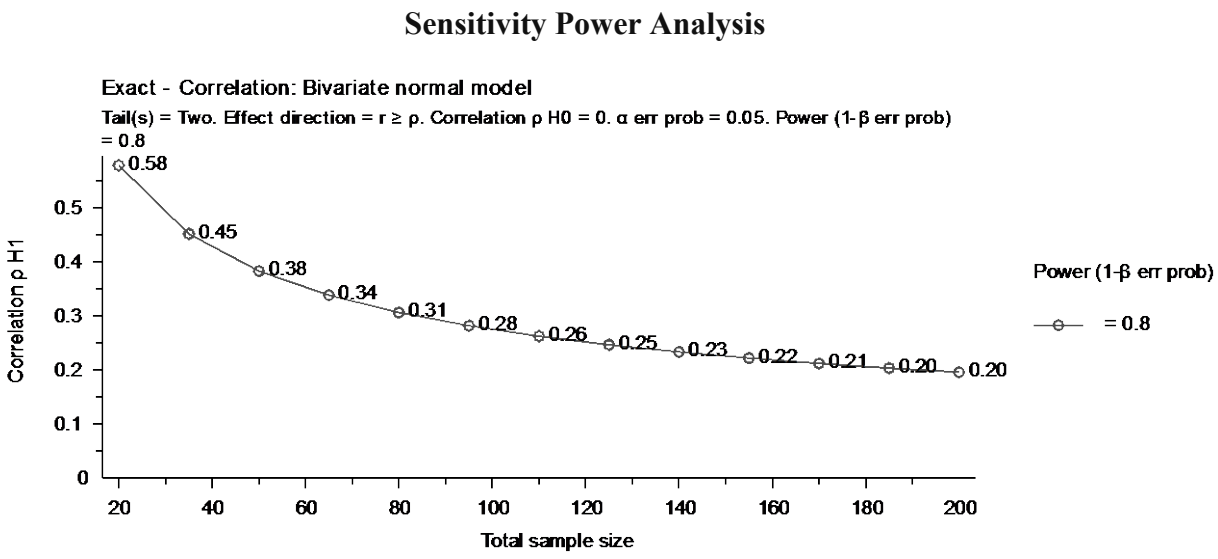


Figure 1. Detectable population correlations at 80% power, alpha of 0.05, and differing sample sizes

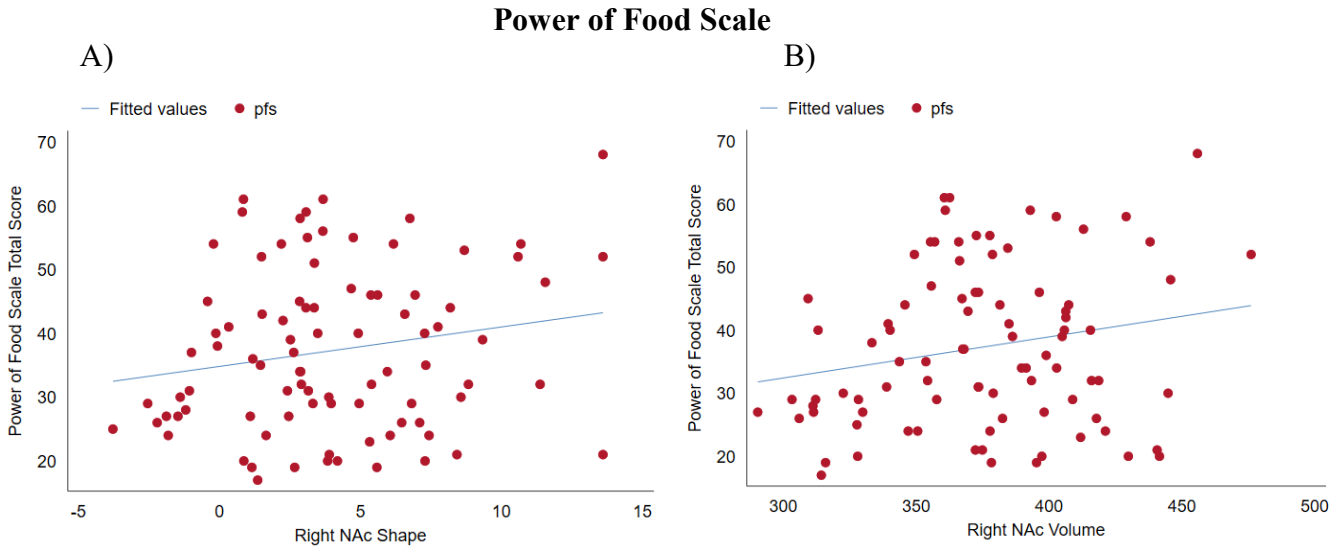


Figure 2. Correlations of right NAc shape and volume with the PFS. Higher PFS scores indicate stronger emotional reactions to food and more motivation for eating based on needs other than hunger alone. Higher volume values indicate greater structure size. Higher shape values indicate more variation in general structure shape.

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