Neural Correlates of Food Addiction in Adolescents, as Assessed by Inhibitory Control and the YFAS-C

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Abstract

Introduction

Neural correlates of food addiction in adults have been found in studies using the Yale Food Addiction Scale (YFAS) in conjunction with fMRI, and inhibitory control has been used as a behavioral proxy in the addiction literature. However, research combining these methods to consider adolescent food addiction has yet to be conducted. This project aims to investigate the relationship between inhibitory control, addictive-like eating, and brain regions implicated in executive functioning in an adolescent population. It is predicted that adolescents demonstrating weaker inhibitory control will endorse food addiction symptomatology, as opposed to adolescents demonstrating stronger inhibitory control.

Methods

Seventy-six right-handed participants, aged 8.2 to 17.8 years, were recruited from the Michigan Longitudinal Study (MLS). Participants performed a go/no-go task during fMRI and completed the YFAS for Children (YFAS-C), after which they were categorized into two groups according to their YFAS-C scores. Individual analysis was completed using a general linear model; the main contrast of interest was correct no-go versus correct go trials, calculated for second-level group analysis.

Results

A two-sample *t*-test revealed significant group differences for CRvsGO ($p < 0.001$; uncorrected with a cluster-wise threshold of $p < 0.05$ FWE) in three primary clusters when comparing the Control and YFAS-C groups, all exclusively in the left hemisphere: the middle temporal gyrus/occipital gyrus, the precuneus/calcarine sulcus, and the inferior frontal gyrus. Specially, the YFAS-C group showed deactivation in these clusters.

Discussion

Differences in inhibitory control are apparent in food addicted adolescents, as determined by the YFAS-C and as visualized in the middle temporal gyrus, posterior cingulate, and inferior frontal gyrus. While these differences are perhaps due to task demands, developmental changes in inhibitory control circuitry have more explanatory power.

Keywords: Response inhibition; food addiction; development; adolescence; left middle temporal gyrus; left middle occipital gyrus; left precuneus; left calcarine sulcus; left posterior cingulate, left inferior frontal gyrus

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Neuroscience Honors Thesis

Introduction

What is food addiction?

Drug seeking behavior in humans is not habitual; it is goal-directed, motivated action (Robinson, 2017). Research on consumptive addictions, as in the abuse of alcohol (Tiffany & Conklin, 2000) and tobacco (Hatsukami, Stead, & Gupta, 2008), and non-consumptive addictions, like excessive gaming (Ding et al., 2014) and internet usage (Young, 1998), have shown this to be true. In recent years, food has been regarded in a similar way, but separately from binge eating disorders, with which there is only partial overlap (Gearhardt et al., 2012). Since the publication of the inaugural paper by Gearhardt, Corbin, and Brownwell (2009), the notion that food could have addictive properties analogous to alcohol and other substances has been given serious attention, and is being rigorously studied by the scientific community.

While food is different from drugs in that the former is needed for survival (Smith & Robbins, 2013), food addiction is assessed according to the same diagnostic criteria as other substance dependencies, including considerations of tolerance, withdrawal, loss of control, failure to reduce or stop consumption, excessive time investment, foregoing important activities, and continued use despite physical or psychological problems, among others. The diagnostic threshold is set at the presentation of three or more of these symptoms (Gearhardt et al., 2009). The parallels continue; just as classical addictions have demonstrated neural correlates, food addiction research has produced analogous results. For instance, elevated activation of reward circuitry in response to food cues, reduced activation of inhibitory regions in response to food intake, and different activity for high food addiction in terms of palatable food intake has been reported in adults (Gearhardt et al., 2011). Additionally, a positive correlation exists between the number of food addiction symptoms and greater activation of the orbitofrontal cortex (OFC), caudate, amygdala, thalamus, midbrain, and insula in response to food cues (Gearhardt et al., 2011). Many of these regions are implicated in other consumptive addictions, like nicotine, alcohol, or illicit drug abuse (see De Ridder et al. [2016] for a comparison between food and alcohol; see Pelchat [2009] for a comparison between food and drugs). Furthermore, markers of vulnerability for other classical addictions, like heavy alcohol use, include particular neurocognitive performance and neural response patterns during inhibition, working memory,

and reward processing (Squeglia & Gray, 2016). These appear to translate to food addiction, as seen in (Gearhardt et al., 2011), and the current study chooses to focus on inhibitory control.

It is important to acknowledge that while we are using the term 'food addiction' here, there is not a consensus amongst the scientific community that this is in fact the proper terminology. Nonetheless, the foods that we are concerned with are rich in sugars and fats; these have become the standard, addictive material amongst researchers employing the term 'food addiction' (Gearhardt et al., 2009). Drewnowski, Krahn, Demitrack, Nairn, & Gosnell (1995) showed that these specific, palatable food types are addictive -- as opposed to vegetables, for example -- because high fat sweets can cause endogenous opiates to be released in the brain. Furthermore, their consumption can be reduced in obese and lean binge eaters with Naloxone, an opiate blocker (Drewnowski et al., 1995). Since nutrient-poor and calorie-dense foods induce the diagnostic symptoms for addiction as seen in the DSM-V, which was reflected in the development of the YFAS, there is validity in using the term 'food addiction' for our purposes.

To be clear, there is a distinction between food addiction and disordered eating. However, it is worth noting that there exists phenotypic overlap between food addiction and binge eating disorder (BED; Schulte, Grilo, & Gearhardt, 2016). Additionally, there is a higher comorbidity with BED for food addicted individuals than controls (Davis et al., 2011). To elaborate, there are demonstrated co-contributors for food addiction and BED, including reward dysfunction, craving, emotional dysregulation, and impulsivity, though it is unclear which of these came first: the addiction or disorder, or the underlying mechanisms (Schulte et al., 2016). Nonetheless, it is still important to recognize the behaviors and the overlap between food addiction and BED. In an examination of food addicted individuals with BED, Gearhardt et al., (2012) observed associations between the YFAS, emotion dysregulation, and low self-esteem, but did not report a relationship with restraint. The authors found that the impulsivity subscale of the Difficulties in Emotion Regulation Scale had the strongest specific relationship with YFAS food addiction, which is consistent with the literature, supporting the involvement of impulsivity in both substance use and eating disorders. Overall, individuals with BED and YFAS food addiction appear to suffer from greater eating disorder psychopathology and associated difficulties with negative affect and emotional dysregulation (Gearhardt et al., 2012).

It is also important to emphasize that are differences between food addiction and other consumptive disorders. Unlike alcohol or cocaine, food is not an intoxicant in the same way that

the word is typically defined. For instance, food addiction is fundamentally divergent from alcohol use disorders in that the former does not produce similar neurotoxicity; with alcohol use disorders, the cortex often deteriorates, and cognitive deficits appear (Bowden, Crews, Bates, Fals-Stewart, & Ambrose, 2001). Food also acts via different molecular mechanisms. Namely, the consumption of foods that are high in fats and carbs reduces anxiety via feedback to the hypothalamic pituitary adrenal axis (Dallman et al., 2003). In other words, comfort foods aid in the shutdown of the stress response by regulating the release of corticotropin releasing factor, which seems to make individuals with disordered eating syndromes feel better (Dallman et al., 2003). Since it has been shown that YFAS food addiction is strongly associated with Major Depressive Disorder (Gearhardt et al., 2012), the role of mood in eating behaviors and habitual comfort food use warrants appreciation and attention.

Why do we care if adolescents are addicted to food?

Obesity is a public health concern in the United States, and to a lesser extent, throughout the world. There are a number of obesity-related health maladies, including diabetes, hypertension, and liver disease (Smith & Robbins, 2013). The concern is even greater for children because the incidence of obesity has only seemed to grow within the last 30 years. In light of the 'obesity epidemic,' it is important to determine risk factors for early detection so that resources are allocated toward appropriate treatment, rather than exhaustive and fruitless dieting, as adolescents develop. However, it should be noted that the relationship between food addiction and bodily markers is not entirely clear. On one hand, food addiction has shown to be strongly correlated with obesity in adults, given its positive relationship with relevant measurements like body mass index (BMI) and body fat percentage (Pedram et al., 2013). On the other, there is literature arguing that there is no correlation between YFAS scores and BMI (Gearhardt et al., 2011). This is a discrepancy that certainly requires further research.

Adolescent neurodevelopment also reflects a critical period of greater vulnerability for experimentation with substances and subsequent acquisition of substance use disorders (Chambers, Taylor, & Potenza, 2003). Systems mediating motivation and goal-directed behavior are amongst the neurocircuitry undergoing maturation during adolescence, which may be reflected in the YFAS-C responses seen in the current study (Chambers et al., 2003).

What is the method of testing inhibitory control? Why is inhibitory control a valid proxy for food addiction?

Previous literature has used inhibitory control as a proxy for addiction in adults (see Kamarajan et al. [2005] for an example of alcohol use disorder as assessed by event-related potentials [ERPs]), including in fMRI studies (see Kaufman, Ross, Stein, & Garavan [2003] for an example of cocaine use and fMRI). Participants often complete the go/no-go task, where better performance is indicative of higher response inhibition. The lack thereof is classically linked to addictive tendencies because of the parallel that exists between the reduced ability to control go/no-go responses and alcohol consumption and tobacco use; in other words, response inhibition is higher in control groups than in use groups, which means that the no-go error rate is lower for the control groups than for the use groups (Easdon, Izenberg, Armilio, Yu, & Alain, 2005; Sofuoglu, Herman, Li, & Waters, 2012). More generally, in studies of alcohol addiction, it has been shown that response inhibition, and underlying neural correlates, predict the onset of substance use and abstinence (Moeller, Bederson, Alia-Klien, & Goldstein, 2016). Further, increased response inhibition and less activation during exertion of inhibitory control predicted a better clinical outcome (Moeller et al., 2016). This makes intuitive sense upon examination of the relationship between impulsivity and inhibitory control; that is, reaction time to the 'go' signal does not vary with impulsivity, but estimated stop-signal reaction time is longer in more impulsive subjects (Logan, Schachar, & Tannock, 1997).

Not surprisingly (given the neurodevelopmental changes described in forthcoming subsections), inhibitory control is dynamic; it increases with age, and is a critical temperamental underpinning of internalization (Kochanska, Murray, Jacques, Koenig, & Vandegeest, 1996).

What is the method of testing food addiction?

The YFAS was initially developed for the assessment of food addiction in adults and has since been adapted for children (YFAS-C). The translation of the scale was important because a) children are perhaps more vulnerable to addictive tendencies, b) addictive eating in children has been shown to be related to elevated BMI, and c) addictive eating in children may also be related to reduced satiety (Gearhardt, Roberto, Seamans, Corbin, & Brownell, 2013).

How do these measures differ between children and adults?

While many aspects of cognitive control are similar between adolescents and adults, these two groups differ in terms of response inhibition and working memory. Inhibitory responses are present as early as infancy, but the rate of correctness improves throughout development, especially during mid-to-late adolescence (Luna, Padmanabhan, & O'Hearn,

2010). The brain matures in a number of ways throughout adolescence, including through synaptic pruning and enhanced myelination, which contribute to improved executive processing (Luna, 2009). These molecular, cellular, and systemic changes allow for behavior to become more controlled and voluntary as existing executive processes are refined (Luna, 2009). The improved flexibility to inhibit responses is due to the top-down modulation of behavior throughout adolescence, during which prefrontal connectivity to the rest of the brain coincides with more widely distributed circuitry (Luna, 2009).

What are some other demographic considerations?

Inhibitory control and impulse control circuitry differ amongst certain demographic groups. For instance, there is ERP evidence for gender differences in behavioral inhibitory control in a two-choice oddball task (Yuan, He, Qinglin, Chen & Li, 2008), as well as in the go/no-go task, as used in the current study (Fillmore & Weafer, 2004). Fillmore & Weafer (2004) compared men and women in terms of the degree to which a moderate dose of alcohol impairs inhibitory control of behavior and found that men displayed more failures to inhibit responses to no-go targets under the influence of alcohol than women. Since these gender differences may be due to the subjectively stimulant and sedative effects of alcohol, it is worth considering whether food addiction in particular bears any relation to the patterns of response inhibition seen in previous literature.

Apart from inhibitory control, it has been reported that women are at a higher risk for food addiction than men (Pedram et al., 2013). However, Pedram et al. (2013) reported an unmatched sample of men and women, all of whom were older than 19 years old. The present study aims to expand upon the current understanding of food addiction by using matched populations of adolescent boys and girls.

Why can we not generalize food addiction findings from adults to adolescents?

There is extensive evidence suggesting that adolescent brains undergo not only structural and functional changes across the entire organ, but individual brain regions demonstrate unique and asynchronous developmental trajectories as well (Plate, Richards, & Ernst, 2016). The developmental changes have been used to explain typical adolescent behaviors like cognitive impulsivity, risk seeking, emotional intensity and lability, and social reorientation (Plate et al., 2016). Furthermore, Geier, Terwilliger, Teslovich, Velanova, & Luna (2009) posited that brain maturation is incomplete until the mid-20s, which means that adolescent neurocircuitry is

inherently different from that of adults. For instance, adolescents are capable of inhibiting impulsive responses like adults can, but it takes the younger age group more effort to be successful. Additionally, adolescents are over-sensitive to reward and under-sensitive to outcome (risk, in particular). While these differences in sensitivity may be evolutionarily advantageous, they might cause addictive-like behavior in the modern age. Therefore, it is unreasonable to assume that addictive eating behaviors have identical foundations in adults and adolescents, and thus we cannot entirely generalize the current neural correlate literature in adults (e.g. Gearhardt et al., 2011) to adolescent populations.

Why is it important to consider adolescence as a period in development?

"The developmental mismatch hypothesis proposes that, in humans, subcortical structures involved in processing affect and reward develop earlier than cortical structures involved in cognitive control, and that this mismatch in maturational timing is most exaggerated during adolescence" (Mills, Goddings, Clasen, Giedd, & Blakemore, 2014). There have been numerous fMRI studies that use the developmental mismatch model (e.g. Mills et al., 2014), and the model has been supported for certain brain regions. For instance, Mills et al. (2014) demonstrated developmental mismatch in structural maturity most prevalently between the amygdala and the prefrontal cortex (PFC) -- at the group level -- during adolescence. Furthermore, they found that the amygdala matures during adolescence, and the nucleus accumbens and PFC both change structurally into the third decade. However, the authors also reported high variation at the individual level, suggesting that reward and cognitive control are perhaps more nuanced than this model allows. Nonetheless, the model is reasonably robust, and warrants acknowledgement and discussion here.

While the current study does not have a comparison population of adults, it responds to the lack of differentiation between adult and adolescent food addicted individuals in the literature. Namely, this project not only recognizes that there is a difference in processing between children and adults, but stipulates that this is an important distinction, and uses the YFAS-C and fMRI as techniques for quantification. Findings in adults, especially correlations between neurological activity and behavioral self-reports, cannot be generalized to younger populations.

In accordance with the developmental mismatch hypothesis, it has been proposed that the gap in maturity between prefrontal and subcortical regions increases the risk for affectively

driven behaviors during adolescence (Somerville, Jones, & Casey, 2010). This is relevant to the current study because not only are eating behaviors colloquially emotional, but there is scientific literature to support this affective correspondence as well (e.g. Gearhardt et al., 2012).

Like all classical addictions, dependent food behaviors are also sensation-seeking. Addictive foods are typically dense in flavor and energy (Gearhardt et al., 2009), and much more sensation-provoking than healthier options. As introduced above, Mills et al. (2014) used a longitudinal study of structural MRI scans to test the developmental mismatch hypothesis in terms of brain maturation and self-reported risk-taking and sensation-seeking behaviors during adolescence. We are not predicting that food addicted adolescents will also be risk takers. In fact, as noted previously, food addiction is different from classical addictions in that it does not carry the legal ramifications that alcohol abuse and drug dependence do. However, the possibility of addiction transfer requires further attention. Negative associations have been revealed when looking at the co-prevalence of both: a) food addiction and smoking, and b) food addiction and alcohol misuse, suggesting that a mediator -- like impulsivity -- may play a role in addiction transfer between food addiction and other consumptive abuses (Meule & Gearhardt, 2014). Without knowing how these addictive behaviors interact, we need to consider how identifying food addicted adolescents may allow us to predict their drug and alcohol use, or lack thereof. Thus, the peak age of risk taking (13 to 18 years; Mills et al., 2014) in other classical addictions is relevant. High risk takers tend to be higher sensation seeking, and -- again -- although risk in the conventional sense is not relevant to the current project, sensation seeking certainly is.

Hypothesis

The present study aims to investigate the relationship between inhibitory control behavior and food addiction in an adolescent population. Inhibitory control is assessed with the go/no-go paradigm, and food addiction is measured according to the YFAS-C. We predict that adolescents demonstrating weaker inhibitory control will score higher on the YFAS-C than adolescents demonstrating stronger inhibitory control.

Methods

Participants

Seventy-six right-handed individuals (44 males, 32 females) aged 8.2–17.8 years participated in the study. Participants were recruited from the MLS, an ongoing, prospective study of families with high levels of parental alcohol use disorder (AUD) and a contrast sample

of nonalcoholic families (Zucker et al., 1996; 2000). Parental AUD diagnosis was based on DSM-V criteria, and assessed by way of the Diagnostic Interview Schedule–Version 4 (Robins et al., 1981; 2001), supplemented with the Drinking and Drug History Questionnaire (Zucker & Fitzgerald, 1994). Participants in the current study came from families with and without a family history of AUD (see Table 1). For a further discussion on demographics, there is a historical difference between the number of males and females included in the MLS because the study was originally only open to males.

Exclusionary criteria from this study included: neurological, acute, uncorrected, or chronic medical illness; current or recent (within 6 months) treatment with centrally active medications; and history of psychosis or schizophrenia in first-degree relatives. The presence of Axis I psychiatric or developmental disorders, which would interfere with the interpretation of the data, was also exclusionary; this did not include past history of mood disorder or current unmedicated mood disorder, or current or past history of conduct or attention deficit disorders (ADHD). Diagnosis was determined using the Diagnostic Interview Schedule–Child (Costello et al., 1984). Families in which the target child displayed evidence of fetal alcohol effects were excluded from the original ascertainment.

As part of the MLS, all offspring were assessed annually on substance use and related problems (Zucker et al., 1996). All participants were told to abstain from alcohol and illicit substances for 48 hours prior to the fMRI scan. For participants age 15 years and older, urine drug screens were conducted immediately prior to the fMRI scan; positive results were exclusionary. In participants age 14 years and younger, we relied on verbal confirmation of drug and alcohol abstinence of the day of the scan. No participants had to be excluded from the current study due to a positive drug screen or affirmative self-report of alcohol or drug use. All participants gave written consent/assent after explanation of the experimental protocol, as approved by the local institutional review board. Since participants were under the age of 18, at least one parent gave written informed consent. Height (in) and weight (lbs) for each participant were collected at the time of the scan. Table 1 contains participant information.

Participants were categorized into one of two groups (Control, YFAS) based on their scores on the YFAS-C (Gearhardt et al., 2013), described below. Groups were matched on age, sex, and family history of AUD since these characteristics have demonstrated differences in inhibitory control, as mentioned in the introduction (see Kochanska et al. [1996] for age

differences, Yuan et al. [2008] for sex differences, and Hardee et al. [2014] for family history differences).

Yale Food Addiction Scale for Children

The YFAS-C was used to measure addictive-like eating behaviors in participants (Gearhardt et al., 2013). The YFAS-C is a 9-item measure that applies the diagnostic criteria for substance-use disorders to consumption of certain foods, namely highly palatable foods such as ice cream, pizza, and chocolate. The YFAS-C has two scoring options: 1) a continuous summary of the number of symptoms endorsed, and 2) a dichotomous diagnostic threshold based on the DSM-IV criteria. For the current study, the symptom count method was used, as younger samples may be less likely to meet full diagnostic criteria for eating disorders (Decaluwé & Bract, 2003). Each question can achieve a score of 1 or 0, based on whether substance dependence criterion have been met for that question. See Table 2 for more information. Groups were formed based on symptom count scores; the Control group contained participants who scored 0 on the YFAS-C (n=41), and the YFAS-C group contained participants who scored ≥ 1 on the YFAS-C (n=35), indicating the participant demonstrated symptoms of food dependence.

fMRI Task

A go/no-go task (Durston et al., 2002) was used to probe response inhibition. Participants were instructed to respond to target stimuli (letters other than X) by pressing a button (go trials) but make no response to infrequent non-target stimuli (letter X; no-go trials). A visualization is given in Figure 1. Stimulus duration was 500 ms, followed by 3500 ms of fixation. There were 5 runs of 49 trials, each run lasting 3 minutes and 2 sec and containing 11, 12, or 13 no-go trials for a total of 60 no-go trials out of 245 trials. Reaction times for correct go responses (Hit RT), accuracy for correct go trials (Hit), accuracy for false alarms (FA), and reaction times for false alarms (FA RT) were calculated as performance measures. Before the fMRI scan, all participants had a practice session of 49 trials on a desktop computer.

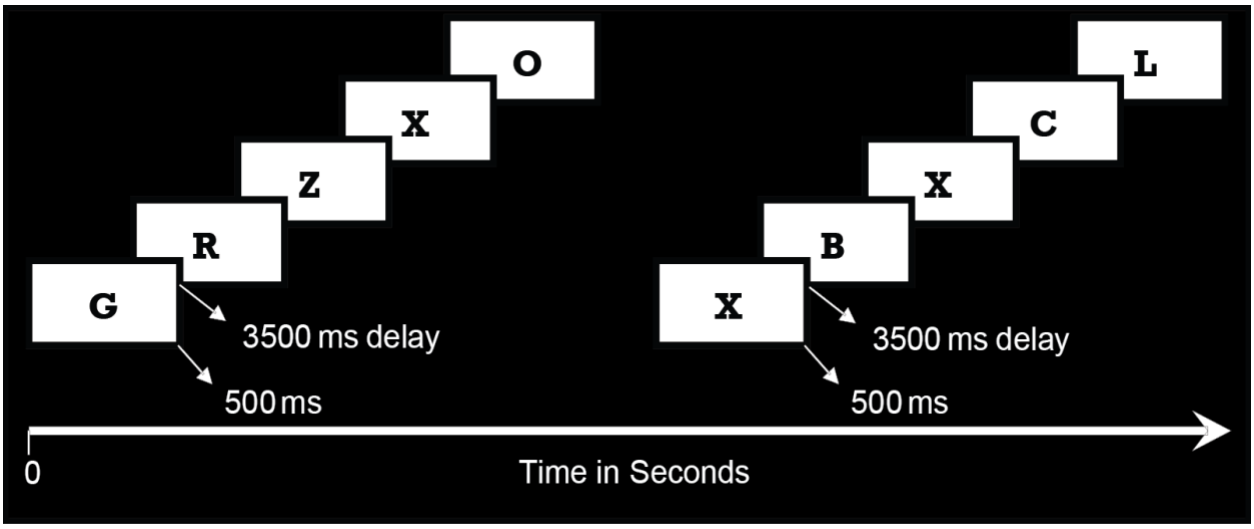

Figure 1. Schematic for the the go/no-go task.

MRI data acquisition

Whole-brain blood oxygenated level-dependent images were acquired on a 3.0 Tesla GE Signa scanner (Milwaukee, WI) using a T2*-weighted single-shot combined spiral in-out sequence (Glover & Law, 2001) with the following parameters: TR = 2000 ms; TE = 30 ms; flip angle = 90º; FOV = 200 mm; 64 x 64 matrix; in-plane resolution = 3.12 x 3.12 mm; slice thickness = 4 mm; 29 slices. A high-resolution anatomical T1 scan was obtained for spatial normalization (three-dimensional spoiled gradient-recalled echo; TR = 25 ms; min TE; FOV= 25 cm; 256 x 256 matrix; slice thickness = 1.4 mm). Participant head motion was minimized using foam pads placed around the head along with a forehead strap. In addition, the importance of keeping as still as possible was emphasized.

Data Analysis

Demographics, Performance, and Substance Use Variables

Independent-sample *t*-tests were used to look for group differences for age, IQ, family history of AUD, BMI, and each of the performance variables: Hit, Hit RT, and FA. Fisher's Exact Test was used to look for group differences for sex. The number of participants for each group who reported any substance use before their fMRI scan is reported in Table 1, and Fisher's Exact Test was used to look for group differences between individuals who reported having a first drink, first been drunk, a first use of marijuana, a first use of cigarettes, a first use of illicit drugs, or any combination of these (use of multiple substances) prior to their fMRI scan. For

diagnoses, Fisher's Exact Test was run for ADHD as no other diagnoses (conduct disorder, generalized anxiety disorder, or depressive disorder) were present in this sample.

fMRI Data

Functional images were reconstructed using an iterative algorithm (Sutton, Noll, & Fessler, 2003; Noll, Fessler, & Sutton, 2005). Subject head motion was corrected using FSL 5.0.2.2. (Analysis Group, FMRIB, Oxford, United Kingdom) (Jenkinson, Bannister, Brady, & Smith, 2002). Analysis of estimated of motion parameters confirmed that overall head motion within each run did not exceed 3 mm translation or 3º rotation in any direction. All remaining image processing (including slice timing correction) and statistical analysis were completed using statistical parametric mapping (SPM8; Wellcome Institute of Cognitive Neurology, London, United Kingdom). Functional images were spatially normalized to a standard stereotaxic space as defined by the Montreal Neurological Institute. A 6 mm full-width half-maximum Gaussian spatial smoothing kernel was applied to improve signal-to-noise ratio and to account for differences in anatomy.

Individual analysis was completed using a general linear model. Three regressors of interest (correct no-go trials, failed no-go, and correct go) were convolved with the canonical hemodynamic response function, with event durations of 4 seconds from stimulus presentation. Motion parameters were modeled as nuisance regressors to remove residual motion artifacts. The main contrast of interest was correct no-go (correct reject) versus correct go trials (CRvsGO). This was calculated for second-level group analysis by linearly combining parameter estimates over all five runs of the task. To confirm that the go/no-go task elicited the expected activation, a one-sample *t*-test was run using the entire sample (N = 76) for the contrast of interest (CRvsGO). Areas of activation were deemed significant if they reached a threshold of $p < 0.001$, uncorrected with a cluster-wise threshold of $p < 0.05$ FWE. While FWE and Bonferroni are both ways to combat error by controlling for false positives, FWE corrections are better for our purposes because Bonferroni corrections assume independence between voxels; because we smoothed the data during preprocessing, we made nearby voxels more similar to each other, and thus interdependent. Furthermore, the brain is living tissue and no tissue is distinct from its surrounds, thus reaffirming our decision beyond the acknowledgement our noise-reduction methods.

The main hypothesis of interest was tested on a whole-brain basis using a two-sample *t*-test. Values from significant clusters were extracted using MarsBaR Region of Interest toolbox

(Brett, Anton, Valabregue, & Poline, 2002). Extracted values were then imported into SPSS (Version 24, IBM Corp, Armonk, NY) for graphical purposes and post-hoc analyses. Associations among scan age, BMI, YFAS-C group, and three clusters were also investigated using independent-samples *t*-tests or Pearson's correlations.

Results

Participant Characteristics

There were no significant differences (i.e., all *p*s > .05) between groups on sex, age at fMRI scan, IQ, family history of AUD, BMI, or ADHD diagnosis. There were also no significant differences between the groups for substance use initiation prior to fMRI scan. Age was significantly positively correlated with BMI, $r = .34$, $p = .002$. See Table 1 for statistics.

Task Performance

There were no significant differences between groups on task performance measures—Hits, Hit RT, FAs, and FA RT. See Table 3 for statistics.

fMRI Data

Task effect

See Tables 4 and 5 and Figure 2 for task effect coordinates and statistics.

Group differences

A two-sample *t*-test revealed a significant group difference for CRvsGO at $p < 0.001$, uncorrected with a cluster-wise threshold of $p < 0.05$ FWE, when comparing Control to the YFAS-C group, in three clusters: 1) in the left middle temporal gyrus, extending into the middle occipital gyrus, 2) in the left precuneus/left calcarine sulcus, extending into the posterior cingulate, and 3) in the left inferior frontal triangularis/opercularis region (Figure 2). See Table 4 for coordinates and statistics. In all three regions-of-interest (ROIs), the YFAS-C group showed a marked deactivation during inhibitory control compared to the Control group (Figure 3). The Control group activated during inhibitory control in the left middle temporal gyrus and the left inferior frontal gyrus ROIs, but slightly deactivated during inhibitory control in the left precuneus ROI (Figure 3). Activation in the three clusters was not significantly correlated with age (all *p*s > .436) or BMI (all ps > .329).

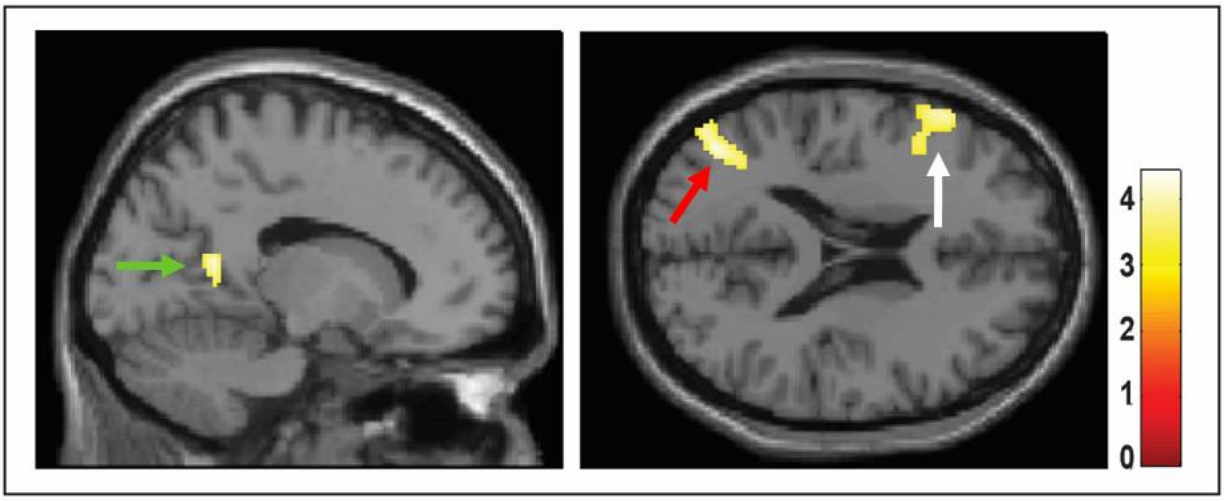

Figure 2. Regions displaying a significant difference for the no-go versus go contrast at $p <$ 0.001, uncorrected with a cluster-wise threshold of $p < 0.05$ FWE. Three regions of interested pass criteria: ROI 1 encompassed the left middle temporal and occipital gyrus (red arrow); ROI 2 encompassed the left precuneus and calcarine sulcus (green arrow); ROI 3 encompassed the left inferior frontal gyrus – pars triangularis and pars opercularis (white arrow). See Table 4 for full coordinates.

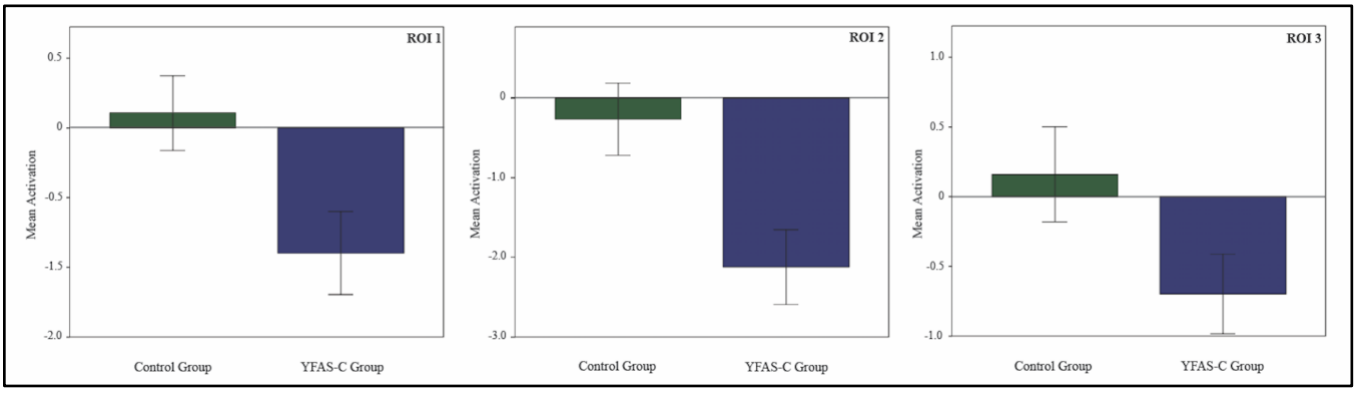

Figure 3. Mean activations extracted from each ROI from the no-go versus go contrast from Figure 2 in the Control and YFAS-C groups. See Table 4 for ROI labels and coordinates.

Discussion

The purpose of this study was to investigate the relationship between inhibitory control and food addiction in an adolescent population using the go/no-go paradigm and the YFAS-C. Here we find that there is a significant difference between Control and YFAS-C groups -- in three clusters -- such that adolescents demonstrating weaker inhibitory control reported

addictive-like eating behaviors, as opposed to individuals demonstrating relatively stronger inhibitory control that did not endorse such behaviors.

In terms of previous work, the neural correlates of food addiction have been identified in adults using a reward task and fMRI (Gearhardt et al., 2011), and the neural correlates of internet gaming addiction have been located in adolescents using the go/no-go task and fMRI (Ding et al., 2014). Therefore, there exists a match in the literature between our food addiction pursuits and an essentially analogous study for another emerging addiction. However, the neural underpinnings of food addiction in adolescents with any proxy has yet to be undertaken, making the current project necessary and important. We chose to use inhibitory control as our behavioral assessment for addiction, but as discussed below, the role of reward circuitry should also be considered for adolescents.

Curiously, all of our ROIs are located in the left hemisphere, specifically the left middle temporal gyrus (extending into the middle occipital gyrus), the left precuneus/left calcarine sulcus (extending into the posterior cingulate), and the left inferior frontal triangularis/opercularis. Below, two potential explanations for this pattern are presented.

Task Demands

The specific version of the go/no-go task used in the current experiment could account for the unilateral activation seen in Table 1. In general, there is evidence for task-dependent changes in activation, even when the experimental paradigm changes in nuanced ways. For instance, in a meta-analysis of go/no-go tasks using fMRI in healthy adults, where the correctly rejected no-go trials were contrasted against baseline, Simmonds, Pekar, and Mostofsky (2008) found that response inhibition varies for the specific go/no-go paradigm employed. The authors included 11 studies in their analysis; ‘simple’ go/no-go tasks (5 total) demonstrated different neural activation than ‘complex’ go/no-go tasks (6 total), the latter of which relied on working memory for successful response inhibition. Furthermore, the working memory demands of the complex tasks seem to favor right-lateralized prefrontal-parietal circuits; this is in contrast to the current study, which is a simple go/no-go procedure. However, all tasks showed overlapping activation in the pre-supplementary motor area (SMA), which is considered to be crucial for response inhibition. This justifies why the current results do not show between-group differences in the pre-SMA; all participants, regardless their of their YFAS-C scores, require this region for correct reject performance.

The explanation for exclusively left hemisphere activation could be simple; the go/no-go task prompted participants to respond 'go' to all non-X letters and to inhibit their button-pressing response to all Xs displayed. Since the stimuli were all language-related, perhaps the correlates of inhibitory control were all localized to the language-dominant left hemisphere. Another potentially concise explanation could regard the current study's use of an event related design as opposed to a blocked design. Since blocked go/no-go studies require maintaining a task set across a period of time, they have the potential to demonstrate different patterns of activation (Swick, Ashley, & Turken, 2011).

In summary, it is necessary to acknowledge that a fair amount of neural variability exists for different versions of the go/no-go task. These nuances may be strong enough to account for the unilateral activation reported in the current study. However, exclusively left hemisphere activation is more likely due to inherent characteristics of the comparison groups. In particular, a proposed theory for the development of response inhibition circuitry and an argument for (early) elevated BMI neural markers are presented below.

Developmental Change

The results show different activation to that typically reported in food addiction and inhibitory control neuroimaging studies in adults; perhaps this is because of developmental differences. After all, the PFC is not the only region changing (or potentially even driving the change) in cognitive and impulse control (Mills et al., 2014). Since maturation in these skills is not attributed solely to PFC, other subcortical structures can also be involved. These appear to develop earlier than the PFC, leading to the developmental mismatch hypothesis (see Introduction). In terms of task-specific differences, it has been shown that the volume of activation is significantly greater for children relative to adults when performing the no-go condition of the go/no-go task (Casey et al., 1997).

Interestingly, for the CRvsGO condition, for control versus YFAS-C groups, we did not see any differential activity in the dorsolateral PFC (dlPFC), orbitofrontal cortex, or amygdala, which have been shown to be implicated in goal selection, self-regulation (preventing impulsive or perseverative behaviors), and the triggering of cravings, respectively (Crews & Boettiger, 2009). We also do not report significant activation in the anterior cingulate cortex; perhaps this is because its recruitment in response inhibition increases with development, while our population is of adolescents (Luna et al., 2010). Finally, we do not note any basal forebrain activity, though

its neuronal inhibition has been shown to enable rapid behavioral stopping (Mayse, Nelson, Avila, Gallagher, & Lin, 2015).

As explained by Mills et al. (2014), "The PFC is a large, functionally and anatomically heterogeneous region. For this reason, it is difficult to compare the developmental trajectories of specific prefrontal regions of interest (ROIs) across studies, unless other studies have used the same parcellation method. [...] a variety of studies have found different PFC regions involved in tasks entailing risky decision making, reward processing and emotion processing, with inconsistent developmental patterns." Due to this lack of clarity in methodological reporting, after closer inspection, our findings may not be terribly unique from previous literature. For instance, our ROI in the inferior frontal gyrus may not be as distinct from published activity in the dlPFC (e.g. Crews & Boettiger, 2009).

De Ridder et al. (2016) used electroencephalogram (EEG) to identify 'addiction neural brain activity' by comparing food-addicted and non-food-addicted obese individuals with alcohol-addicted and non-alcohol-addicted lean controls. The authors found the addiction activity to consist of the dorsal and pregenual anterior cingulate cortex, parahippocampal area, and precuneus, which are partially distinct from the 'obesity neural brain activity' reported (De Ridder et al., 2016). Again, our only shared finding was that of the left precuneus in ROI 2, but our participants were adolescents and were not necessarily obese.

While we did not identify some of the common correlates of addiction in adults, much of our ROIs have shown to be implicated in language processing (see further discussion below), and because all of our ROIs are located in the left hemisphere (which is known to dominate language processing), the following developmental trajectory is proposed:

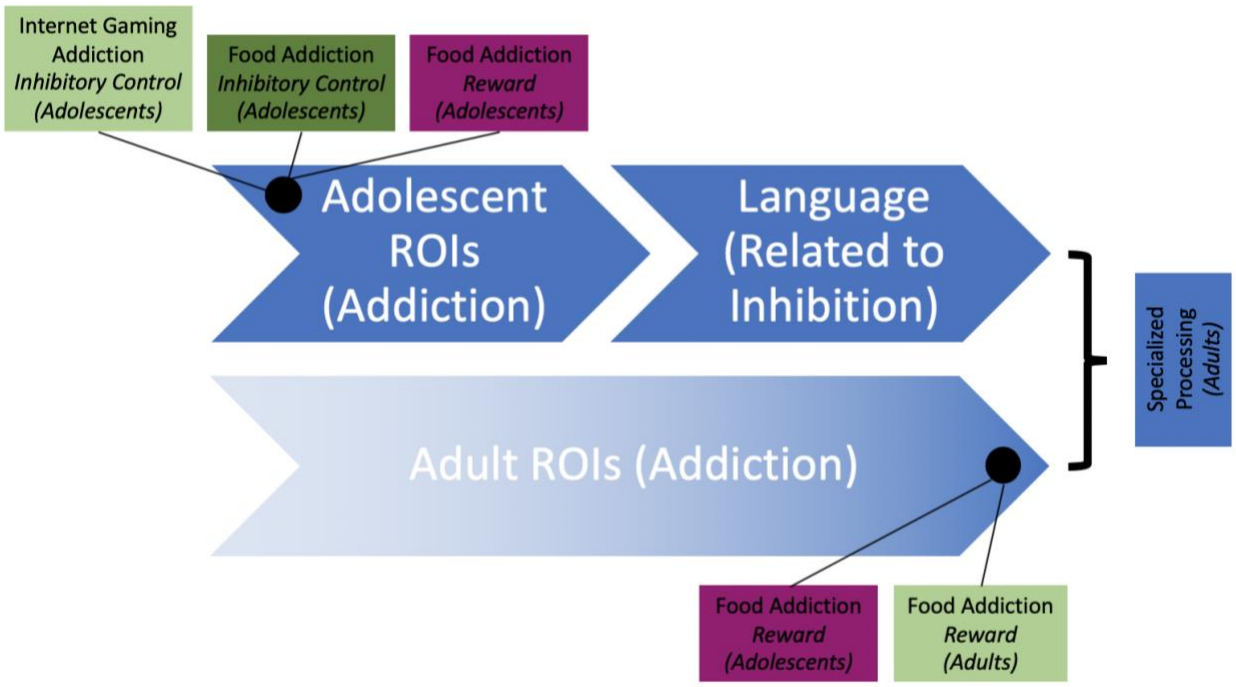

Figure 4. Generalized adolescent inhibitory control circuitry (as conceptualized here with addictive behaviors) perhaps becomes more specialized over time.

We are suggesting that inhibitory control circuitry, especially in terms of addiction, differs between adolescents and adults, with the adolescent regions developing into language areas that choose between competing selections. Therefore, the adolescent regions persist as mitigators of conflicting choices, but more mature inhibitory control circuitry emerges in adults to account for arguably greater conflicts, like addictive tendencies. Of course, further research is necessary in order to be confident in this conclusion/interpretation. Evidence for this plausible conclusion is laid out below, divided according to ROI for the CRvsGO condition, in control versus YFAS-C groups. However, before the evidence is summarized and a final argument is made, findings in the addiction and inhibitory control literature -- whose ROIs overlap with those reported here -- are discussed.

ROI 1: left middle temporal gyrus

The middle temporal gyrus plays an important role in executive functioning overall, perhaps in ways that are not entirely understood. For instance, it has been identified as part of the widely distributed circuitry known to underlie working memory (Luna et al., 2010), as well as a region with less activation in youth who later transitioned in heavy alcohol use (Moeller et al., 2016). In an investigation of online gaming addiction, the group addicted to a particular video

game (World of Warcraft) showed activation in the left middle temporal gyrus, as opposed to the non-heavy internet usage control group (Ko et al., 2009). Another internet addiction study, but in an adolescent population, found significant hypoactivity in the middle temporal gyrus during no-go trials for the internet gaming addicted group (Ding et al., 2014). However, while ROI 1 has been reported in the previous addiction literature (as cited above), activation of the middle temporal region has also shown a positive correlation with success of interference suppression in children (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002). This study noted the same correlation for the lingual gyrus in ROI 3.

Since the middle temporal region and lingual gyrus normally act as suppressors in children, but the middle temporal gyrus was less active for Ding et al.'s (2014) experimental group, we can infer that activity is depressed in children with various addictions, including internet gaming and, from the current study, food.

ROI 2: left precuneus/calcarine sulcus/lingual gyrus

In abstinent -- but dependent -- heroin subjects, Xie et al. (2011) identified an altered anticorrelated intrinsic amygdala functional connectivity network. This network is connected to the precuneus, and significant reduction in this region may contribute to a loss of impulse control.

Aron & Paulus (2007) showed that the precuneus also faces decreased activation during a decision-making task for methamphetamine-dependent subjects, and that the left precuneus was activated less with longer subject use of methamphetamine. Further, in studies with healthy volunteers, the precuneus has been identified as a neural substrate of inhibition during go/no-go performance (Aron & Paulus, 2007).

In terms of the calcarine sulcus, decreased cortical thickness for heroin dependent individuals has been found (Li et al., 2014). Further relationships between our ROI and addiction studies have not been frequently identified.

Finally, for the left lingual gyrus, In a voxel-based morphometry study, lower gray matter density for internet addicted adolescents was found (Zhou et al., 2011). The authors also noted that interpreting gray matter volume in this area is difficult because this region plays an unclear role in schizophrenia. To elaborate, cortical thickness seems to be a common theme, as thicknesses of the precuneus and lingual gyrus correlated with the duration of online gaming addiction; interestingly, this anatomical trend did not affect performance on the color-word

Stroop task (Yuan et al., 2013). It was concluded that cortical thickness abnormalities may thus be implicated in online gaming addiction.

ROI 3: left inferior frontal gyrus - pars triangularis and pars opercularis

Converging methodologies have shown that the left inferior frontal gyrus is critical for successful inhibitory control of motor responses (Swick, Ashley, & Turken, 2008). This strong body of evidence lends support to our findings that the YFAS-C group demonstrated less inhibition on no-go trials because of diminished activation in this region.

While we did not seek any gender differences in the activation of the left inferior frontal gyrus (since we matched for gender in the Control and YFAS-C groups), it is important to acknowledge this has been found in prior work, even though this difference was explained in terms of speech development and lateralization of language (Blanton et al., 2004). In particular, the authors noted that there is continued modification of the inferior frontal gyrus during normal development in boys, in addition to significant gender differences in inferior frontal gyrus gray matter between boys and girls.

It is also worth discussing our population; the inferior frontal gyrus is shown to increase in activation with age (Luna et al., 2010). Furthermore, children have been shown to display significantly weaker top-down modulatory influences coming from the inferior frontal area (Bitan et al., 2006). Again, this was a language study, and the results were explained in terms of adult language processing involving greater top-down cognitive control compared to children, meaning that adults had less interference from task-irrelevant information. However, we know that top-down control also plays a role in the inhibition of motor responses; perhaps the inferior frontal gyrus is responsible for this more general capacity in adolescents.

In summary, ROI 3 provides the strongest evidence for the developmental trajectory in Figure 4. Zhang, Feng, Fox, Gao, & Tan (2004) showed that the left inferior frontal gyrus is generally involved in selection, and not just in semantic retrieval tasks, as previously assumed. Since selection is one of the critical functions of the PFC, it makes sense that selection behavior would change throughout development since the PFC certainly does (as discussed throughout this thesis). We can see the relationship between selection and response inhibition in the broader theme of executive control in the addiction literature as well. For instance, Moeller et al. (2016) explained that, in general, depressed activation of key regions in the frontal cortex, including in the inferior frontal gyrus, during response inhibition predicted not only the onset of substance

use, but also better abstinence-related outcomes among individuals already addicted. Since the inferior frontal gyrus has been shown to be reliably engaged during inhibitory control (Moeller et al., 2016) we can conclude that it plays an important role for the participants in the present study, regardless of developmental changes.

Implications

The activation explanations presented above certainly prioritize future studies in different ways. However, the societal treatment of the results should remain consistent; the current study identifies neural correlates of food addiction in an adolescent population. While food addiction may or may not be relevant contributor to the obesity epidemic (see Introduction for further discussion), healthy eating behaviors are necessary for other positive outcomes.

As we proceed with this information, it is important to consider that not all addictions are treated the same; for instance, consider the characterization of -- and stereotypes surrounding -- alcohol and tobacco use (Gearhardt et al., 2009). If future public health policy for highly palatable foods mirrors that of nicotine, then marketing campaigns for unhealthy foods will certainly change. While it is certainly beneficial to reduce adolescent exposure to palatable choices via popular media, we risk framing food addiction in the context of the disease model. By doing so, we open the door to the ramifications of allocating responsibility away from problematic food (Gearhardt et al., 2009). Needless to say, the way in which this data is presented and circulated should be done with great care in order to best support food-addicted individuals and provide data-driven, forthcoming treatments. This sentiment especially holds true when considering an adolescent population, since formative food attitudes and behaviors are at stake.

Future Directions

While this study proposes a way to enhance understanding of food addiction in children, more work is necessary to paint a complete picture of food addiction in adults, in children, and the (potential) difference between those populations. A schematic for the research that has been completed, and the gaps remaining, is shown below:

Figure 5. Current foci and future directions for food addiction research.

The opaque colors (also marked by an asterix) are the projects which have not been undertaken. Reward processing in adults was investigated in Gearhardt et al. (2011), where the authors investigated the neural correlates of food addiction using the YFAS and an adult population. Specifically, the authors designed a 'milkshake paradigm' to examine neural activation in response to consumption and anticipated consumption of palatable food. In this case, the desirable food was a chocolate milkshake and the control food was a neutral stimulus that the mimicked the natural taste of saliva. Since little support was found for the presence of abnormal reward response to food intake driving addiction -- and instead the highly food addicted group demonstrated neural activation patterns that indicated reduced inhibitory control -- more work is needed to explore these often-overlapping addiction predictors. Particularly, because these results were found in adults, research in adolescents is necessary to determine whether this mechanism differs in younger populations, especially because children demonstrate reduced inhibitory control and enhanced reward sensitivity (e.g. Heitzeg, Cope, Martz, & Hardee, 2015). If an analogous study (an fMRI investigation that considers reward circuitry in food addicted versus non-food addicted individuals) were to be conducted and activation patterns match that of Gearhardt et al.'s (2011) adults, then we can infer that reward processing is similar between food addicted adolescents and adults. If the activation were to significantly differ, then we can consider the ways in which reward circuitry changes its role in addictive-like eating behaviors over the lifespan.

It would be appropriate to study reward circuitry using Monetary Incentive Delay since the milkshake paradigm is highly domain-specific, and it is thus difficult to relate this data to studies of classical addictions. Such comparisons are important to draw because there is a limited body of literature regarding food addiction in children, and if it can be contextualized in terms of other, classically consumptive addictions, public health policy change may be more apt to occur. Aside from task-specific details, reward should be the next focus because of the continual affirmation that inhibitory control and reward are perhaps the most integral to addictive behaviors; this claim is elaborated below.

There is extensive evidence suggesting that adolescent brains undergo not only structural and functional changes across the entire organ, but individual brain regions demonstrate unique and asynchronous developmental trajectories as well (Plate et al., 2016). The developmental changes have been used to explain typical adolescent behaviors like cognitive impulsivity, risk seeking, emotional intensity and lability, and social reorientation (Plate et al., 2016). One perspective for adolescent neurodevelopment is proposed and defended by Plate et al. (2016): the triadic model. This model suggests that there are three interacting networks – underlying (1) reward, (2) emotion, and (3) regulatory function – which are responsible for certain behavioral patterns. In their review, the authors identified corresponding brain regions for these networks, including (1) the striatum, (2) the amygdala, and (3) the PFC.

In a review of neuroimaging risk markers for substance abuse, Heitzeg et al. (2015) focused on a subset of the networks in the triadic network. Instead of identifying three primary networks, these authors emphasize inhibitory control and reward circuitry when considering risk factors for substance use disorders because they tend to be involved in risk-taking behaviors, which are known to be heightened in adolescence. Since the Heitzeg et al. review (2015), as well as related literature (discussed throughout this thesis), highlight the enhanced reward sensitivity in youth, it is clear that adolescents are an important population to study. Evidence of enhanced reward sensitivity "suggests that, in at-risk youth, cognitive control and reward networks are not appropriately dissociated, and appetitive brain regions are not appropriately integrated" (Heitzeg et al., 2015).

In time, the full breadth of research projects presented in Figure 5 above should be undertaken so that the field can realize which aspects of addiction are subject to developmental change, since we know that executive control processes are much different between adolescents

and adults. Once the full range of measures have been considered, a more robust interpretation of food addiction neural correlates will be possible. From there, more informed public health policy decisions will be in reach, with the aim of creating more effective treatments for obesity, all while reducing the stigma of addictive-like eating behavior. Specifically, given the characteristic sensitivity to reward in adolescents and the disruptive functioning in classically addicted groups, a finer-grained analysis of their interplay should be conducted so as to better characterize adolescent addictive-eating tendencies. As the field moves forward, the following questions should be considered: Are the behaviors of interest more similar to those of addicted adults, or are there no differences between the YFAS-C and control groups, such that all adolescents have similarly immature reward, habit-forming, and/or craving circuitry, regardless of their addiction classification?

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Appendix A:

Tables

Table 1. Participant Characteristics

	All Participants (*n* = 76)	Control Group (*n* = 41)	YFAS-C Group (*n* = 35)	Statistic	Significance
Males/Female (*n*)	44/32	26/15	18/17	—	$p = .35^{a}$
Age at fMRI scan	14.3 (2.8)	14.6 (2.9)	14.0 (2.8)	$t(74) = 0.89$	$p = .38^{b}$
Full-scale IQ*	101.8 (12.6)	102.5 (12.1)	100.9 (13.3)	$t(72) = 0.78$	$p = .57^{b*}$
Family history of AUD (*n*)	13/63	7/34	6/29	$t(74) = 0.01$	$p = .99^{b}$
BMI	21.8 (4.1)	22.1 (4.7)	21.5 (3.4)	$t(72) = 0.62$	$p = .54^{c}$
Substance Use at Time of fMRI Scan					
Used alcohol (*n*)	17	9	8	—	$p > .99^{a}$
Used cannabis (*n*)	12	7	5	—	$p > .99^{a}$
Used nicotine (*n*)	6	4	2	—	$p = .68^{a}$
Used other drugs (*n*)	4	3	1	—	$p = .62^{a}$
Used multiple substances (*n*)	10	6	4	—	$p > .99^{a}$
Lifetime Diagnosis (*n*; present)****					
Conduct disorder	0	—	—	—	—
ADHD	4	1	3	—	$p = .31^{a}$
Generalized anxiety disorder	0	—	—	—	—
Depressive disorder	0	—	—	—	—

Note. fMRI, functional magnetic resonance imaging; AUD, alcohol use disorder; BMI, body mass index; ADHD, attention deficit hyperactivity disorder. Numbers represent means, with standard deviations in parentheses, unless otherwise noted.

[a]Two-tailed Fisher's exact test.

[b]Two-tailed independent samples *t*-test, equal variances assumed

[c] Two-tailed independent samples *t*-test, equal variances not assumed

*One participant in each group was missing an IQ score

Table 2. YFAS Scoring Dichotomy and Scale

In the last year (past 12 months):	**Never**	**Rarely**	**Sometimes**	**Very Often**	**Always**
I eat foods even when I am not hungry	0 *n* = 12	0 *n* = 23	0 *n* = 32	0 *n* = 8	**1** *n* = 1
I feel tired a lot because I eat too much	0 *n* = 39	0 *n* = 29	0 *n* = 8	**1** *n* = 0	**1** *n* = 0
I avoid places where I cannot eat the food I want	0 *n* = 32	0 *n* = 25	**1** *n* = 12	**1** *n* = 6	**1** *n* = 1
I eat certain foods to stop from feeling upset or sick	0 *n* = 32	0 *n* = 20	0 *n* = 17	**1** *n* = 6	**1** *n* = 1
The way I eat makes me really unhappy	0 *n* = 51	0 *n* = 15	0 *n* = 8	**1** *n* = 1	**1** *n* = 1
The way I eat causes me problems (for example, problems at school, with my parents, with my friends)	0 *n* = 61	0 *n* = 13	0 *n* = 1	**1** *n* = 0	**1** *n* = 1
In the last years (past 12 months):				**No**	**Yes**
I eat in the same way even though it is causing problems				0 *n* = 70	**1** *n* = 6
I need to eat more to get the food feelings I want (for example, for happy, calm, relaxed)				0 *n* = 66	**1** *n* = 10
I am unable to cut down on certain foods				**1** *n* = 6	0 *n* = 70

Symptom count scoring dichotomy is represented by top number (0 or 1). Number in bold is number that contributes to symptom count. Bottom number represents number of participants who answered that question with that particular response (i.e. never, rarely, etc.).

Table 3. Go/No-Go Task Performance by Group

	Control Group	YFAS-C Group	Statistic	Significance
Hits (%)	96.8 (3.2)	96.3 (4.0)	$t(74) = 0.52$	$p = .60$
Hit RT (ms)	429.7 (59.2)	438.2 (58.4)	$t(72) = -0.63$	$p = .53$[a]
False Alarms (%)	41.1 (20.7)	44.5 (19.8)	$t(74) = -0.72$	$p = .47$
False Alarm RT (ms)	388.2 (58.3)	392.3 (49.8)	$t(74) = -0.34$	$p = .75$

Note. ms, milliseconds. For *Control* and *YFAS-C* columns, the numbers given are means, with standard devotion in parentheses. *Statistic* and *significance* columns refer to two-tailed independence samples *t*-tests.
[a]Degrees of freedom reduction reflects equal variances not assumed.

Table 4. CRvsGO contrast from two-sample *t*-test of Control vs YFAS-C Groups

	% ROI	*x*	*y*	*z*	*k*	*t*-value	FWE *p*-value
ROI 1		-40	-66	16	257	4.42	0.034
Left Middle Temporal Gyrus	53.7%						
Left Occipital Gyrus	26.1%						
Outside (not identified)	20.2%						
ROI 2		-14	-52	12	236	4.10	0.046
Left Precuneus	40.3%						
Left Calcarine Sulcus	30.5%						
Outside (not identified)	13.6%						
Lingual Gyrus	9.8%						
Vermis 4/5	5.9%						
ROI 3		-56	24	20	312	3.86	0.016
Left Inferior Frontal Gyrus - Pars Triangularis	68.3%						
Left Inferior Frontal Gyrus – Pars Opercularis	31.7%						

ROI, region of interest; k, cluster size
Coordinates are in Montreal Neurological Institute (MNI) space.

Table 5. Task effect activation from one-sample *t*-test for CRvsGO. Areas of activation were deemed significant if they reached a threshold of $p<0.001$, FWE-corrected for multiple comparisons.

	% ROI	*x*	*y*	*z*	*k*	*t*-value	FWE *p*-value
ROI 1		30	50	24	8008	8.09	0.001
Right Middle Frontal Gyrus - Pars Orbitalis	34.5%						
Right Inferior Frontal Gyrus - Pars Triangularis	11.1%						
Right Amygdala	10.8%						
Right Inferior Frontal Gyrus - Pars Orbitalis	8.9%						
Right Superior Frontal Gyrus - Pars Orbitalis	8.0%						
Remaining areas	>5% each						
ROI 2		58	-44	30	6219	7.43	0.001
Right Inferior Temporal Gyrus	28.1%						
Right Middle Temporal Gyrus	15.8%						
Right Angular Gyrus	15.7%						
Right Rolandic Operculum	13.1%						
Right Putamen	12.2%						
Right Supramarginal Gyrus	10.2%						
Remaining areas	>5% each						
ROI 3		6	-20	26	5851	6.42	0.001
Right Posterior Cingulate	17.5%						
Right Superior Frontal Gyrus	15.6%						
Left Superior Frontal Gyrus - Medial	14.7%						
Right Paracentral Lobule	12.0%						
Left Middle Cingulate	8.7%						
Right Middle Cingulate	8.0%						
Left Anterior Cingulate	6.4%						
Remaining areas	>5% each						

Table 5. Cont.

	% ROI	*x*	*y*	*z*	*k*	*t*-value	FWE *p*-value
ROI 4		-60	-58	34	2031	5.54	0.001
Left Angular Gyrus	24.2%						
Left Supramarginal Gyrus	16.6%						
Left Middle Temporal Gyrus	15.8%						
Left Rolandic Operculum	15.7%						
Left Putamen	9.9%						
Left Insula	6.7%						
Remaining areas	>5% each						
ROI 5		-30	42	28	935	5.30	0.001
Left Middle Frontal Gyrus - Pars Orbitalis	91.0%						
Left Middle Frontal Gyrus	5.2%						
Remaining areas	>5% each						
ROI 6		-30	4	-20	250	4.14	0.040
Left Inferior Frontal Gyrus - Pars Orbitalis	32.0%						
Left Amygdala	30.8%						
Left Putamen	8.8%						
Left Olfactory	6.0%						
Remaining areas	>5% each						

Appendix B:

Toolboxes

FSL: Software library used for preprocessing.

SPM: Software package used for preprocessing and analysis; MATLAB required.

Talairach Daemon: Database used to identify brain regions that correspond with given voxel numbers.