Food Characteristics Implicated in Biobehavioral Indicators of Addiction in Vulnerable Individuals

by

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LIST OF ACRONYMS

ACC: anterior cingulate cortex

AC-PC: anterior commissure-posterior commissure

ANOVA: analysis of variance

ART: artifact detection tools

BED: binge eating disorder

BMI: body mass index

BOLD: blood-oxygen-level dependent

dlPFC: dorsolateral prefrontal cortex

DSM: Diagnostic and Statistical Manual of Mental Disorders

EMA: ecological momentary assessment

fMRI: functional magnetic resonance imaging

FOV: field of view

FWHM: full width at half maximum

g: grams

GL: glycemic load

HLM: hierarchical linear modeling

MINI: Mini International Neuropsychiatric Interview

MRI: magnetic resonance imaging

OFC: orbitofrontal cortex

TE: echo time

TR: repetition time

YFAS (YFAS 2.0): Yale Food Addiction Scale (Yale Food Addiction Scale version 2.0)

ABSTRACT

This dissertation investigated if foods may vary in their ability to activate reward-related mechanisms implicated in addictive disorders and whether differences in these processes may be amplified for individuals who exhibit a phenotype consistent with an addiction to food. Specifically, this work examined 1) associations between various foods and food characteristics with to neural and behavioral reward responses, 2) differential relationships between food characteristics with reward responses for individuals with or without a food addiction phenotype, and 3) differential associations of subjective effect reports of nutritionally diverse food items with eating behavior for persons with or without a food addiction phenotype. Women with overweight and obesity (*N*=43), half of whom met criteria for food addiction (*n*=21), participated in an fMRI food cue reactivity task of 34 nutritionally diverse foods, reported on wanting and liking for each food after the scan, engaged in a taste test task that assessed facets of subjective experience for 14 of the foods, and had the opportunity to consume these 14 foods during a 15-minute ad libitum consumption period. Individuals with food addiction exhibited greater activation in the precuneus, a region implicated in compulsive use of addictive substances, in response to highly processed food cues, suggesting that the food addiction phenotype may represent a more severe, compulsive phenotype within obesity. Further, highly processed foods were associated with subjective effect reports indicative of elevated abuse liability, which were uniquely related to consumption for persons with food addiction. Across all three study aims, ambivalence emerged as a likely contributor to both biological and behavioral reward responses

to food. This research has important implications for informing future work exploring mechanisms involved in food addiction, intervention efforts for addictive-like eating and obesity, and food-related public policy initiatives.

CHAPTER 1

INTRODUCTION

1.1 Overview

In the past 30 years, the food environment has changed significantly, as highly processed foods, with added amounts of fat, refined carbohydrates, and/or salt, (e.g., pizza, chocolate) have become increasingly available in large portion sizes for affordable prices (Gearhardt, Grilo, DiLeone, Brownell, & Potenza, 2011). In concert, the rates of obesity and eating-related problems like binge eating have also risen (Y. Wang, Beydoun, Liang, Caballero, & Kumanyika, 2008; Yanovski, 2003a). Some individuals seem to overconsume highly processed foods despite experiencing negative health consequences (e.g., diabetes) and reporting a desire to cut down, paralleling behavioral features of substance-use disorders (American Psychiatric Association, 2013a). As a result, it has been suggested that some persons may experience an addictive-like response to highly processed foods in a manner akin to drugs of abuse (Gearhardt, Corbin, & Brownell, 2009a, 2009b; Schulte, Avena, & Gearhardt, 2015). Yet, unlike the investigation of the addictive agent in drugs of abuse, few prior studies have focused on identifying the foods or food characteristics that may be capable of triggering this potential addictive-like process. It is essential to understand which foods may exhibit an addictive potential, as all individuals must eat to maintain life. Thus, a focus is needed on which food characteristics may be most closely implicated in addictive-like responses and which individuals may be vulnerable to a phenotype consistent with addictive-like eating. If foods vary in their ability to activate processes implicated in substance-use disorders, then this research may have significant implications for the development of novel intervention programs for eating-related problems and informing food policy initiatives.

While there is no agreed upon definition to classify who meets criteria for a "food addiction," The Yale Food Addiction Scale (YFAS) is the only existing tool that has been validated to assess for markers of addictive-like eating (Gearhardt et al., 2009b; Gearhardt, Corbin, & Brownell, 2016b). The YFAS is based on the diagnostic criteria for substance-related and addictive disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM) like loss of control over consumption and craving (American Psychiatric Association, 2013b). Though the "food addiction" phenotype has been controversial (Corsica & Pelchat, 2010; Corwin & Hayes, 2014; Ziauddeen, Farooqi, & Fletcher, 2012; Ziauddeen & Fletcher, 2013), existing evidence has suggested biological (Davis et al., 2013; Gearhardt, Yokum, et al., 2011) and behavioral (Gearhardt, White, Masheb, & Grilo, 2013; Gearhardt et al., 2012; Gearhardt, Yokum, et al., 2011; Meule, Lutz, Vogele, & Kubler, 2012; Murphy, Stojek, & MacKillop, 2014; Pivarunas & Conner, 2015) similarities between individuals endorsing indicators of addictive-like eating on the YFAS and persons with substance-use disorders.

Mechanistic parallels between food addiction, measured by the YFAS, and substance-use disorders have been identified, but little research has examined whether foods are differentially associated with addictive-like eating. Highly processed foods have been hypothesized to have the greatest addictive potential, as these foods contain added amounts ("doses") of rewarding ingredients like fat, and/or refined carbohydrates, and the refined carbohydrates may be rapidly absorbed into the body (e.g., high glycemic load (GL)). In support, animal model studies have demonstrated that consumption of highly processed foods (e.g., cheesecake, Oreo cookies) is associated with key biological and behavioral indicators of addiction, such as binge consumption, changes in reward-related neural systems akin to prolonged heroin or cocaine access, increased motivation to obtain the food, and cross-sensitization with addictive substances (Avena & Hoebel, 2003; Avena, Rada, & Hoebel, 2008, 2009; Johnson & Kenny, 2010a; M. J. Robinson et al., 2015). Additionally, when sugar has been removed from a rat's diet, withdrawal symptoms like anxiety and teeth chattering have been observed (Avena, Rada, et al., 2008).

In humans, only one study has systematically examined which foods may be associated with YFAS indicators of addictive-like eating. Consistent with animal research, the study concluded that highly processed foods (e.g., pizza, chocolate, chips) were most closely linked to addictive-like eating based on participants self-report (Schulte et al., 2015). Further, food characteristics like elevated fat content and GL predicted whether a food was reported as associated with behavioral indicators of addictive-like eating assessed by the YFAS (Schulte et al., 2015). This provides preliminary support that the added amounts (higher "doses") of rewarding ingredients (e.g., fat, refined carbohydrates) that may be rapidly absorbed into the system (e.g., high GL) may increase the possible addictive potential of highly processed foods. However, this preliminary study was limited to self-report data and provides only initial insight for the role of processing, fat content, and GL in the presentation of a phenotype consistent with an addictive-like response to food.

Thus, the first aim of the current study evaluated whether foods with diverse characteristics varied in their ability to activate biological and behavioral mechanisms that contribute to the development and maintenance of substance-use disorders. Specifically, neural responses (obtained with functional magnetic resonance imaging (fMRI) techniques) to food cues with varying characteristics (e.g., fat content, GL) and behavioral reports of wanting and liking were examined. Cue reactivity fMRI paradigms have been utilized in the examination of substance-use disorders and found elevated reward-related neural response to drug cues to be associated with increased craving, motivation, and wanting for the drug (Schacht, Anton, & Myrick, 2013; Yalachkov, Kaiser, & Naumer, 2012). Wanting assesses the motivational process of drug seeking behavior in substance-use disorders, which appears to contribute to compulsive patterns of consumption (Berridge & Robinson, 1995b; T. E. Robinson & Berridge, 2000). Among individuals with substance-use disorders, drug-specific cues can couple with the addictive substance, and the cues can become strong triggers of wanting for the drug (Berridge & Robinson, 1995a; T. E. Robinson & Berridge, 2000). In addition to wanting, liking for the effects of the drug has been identified as an important component of reward, though wanting and liking seem to reflect differential, separable processes (Berridge, Robinson, & Aldridge, 2009). While wanting, or motivation to seek out the drug, may increase over the course of addiction, liking tends to be more stable or even diminish (Berridge et al., 2009; T. E. Robinson & Berridge, 2001). Further, liking may be less predictive of compulsive drug use as wanting (T. E. Robinson & Berridge, 1993).

Given the individual differences (e.g., genetic variability) that may contribute to a person's propensity to develop an addictive disorder, previous studies have examined the biological and behavioral processes associated with drugs of abuse in individuals with the substance-use disorder (McBride, Barrett, Kelly, Aw, & Dagher, 2006; Sell et al., 2000; Tapert et al., 2003). With respect to drugs of abuse, it has been essential to assess their addictive potential with individuals who experience an addictive-like response to the drug, as the majority of individuals who consume an addictive substance do not develop a substance-use disorder

(McBride et al., 2006; Sell et al., 2000; Tapert et al., 2003). Similarly, the present project recruited individuals who exhibit an addictive-like eating phenotype, as measured by the YFAS. This approach allowed for the examination of whether certain foods are particularly associated with addictive-like reward responses within a vulnerable group of individuals experiencing behavioral indicators of addictive-like eating. Thus, the second aim of this study examined whether individuals with indicators of addictive-like eating behavior on the YFAS experienced elevated biological (e.g., neural response to food cues) and behavioral (e.g., wanting and liking) indicators of reward for certain foods (e.g., highly processed foods), relative to individuals who do not exhibit YFAS symptoms of food addiction.

Finally, previous studies examining the addictive potential of substances have assessed subjective experience (e.g., appeal, intentions to use again) while consuming the drug as a measure of the drug's reinforcing nature (Henningfield & Keenan, 1993; Jasinski & Henningfield, 1989; Jasinski, Johnson, & Henningfield, 1984). The reinforcing potential of a drug, as evaluated in laboratory settings, has been a reliable indicator of its addictive potential in the natural environment (Comer et al., 2008; Haney, 2009). In addition, subjective experience has been associated with self-administration of the substance in laboratory and real-world contexts (Comer et al., 2008; Products, 2012). Thus, evaluating the subjective experience and eating behaviors associated with nutritionally diverse foods is an essential next step to investigate which foods (e.g., highly processed foods) and food characteristics (e.g., fat content, GL) may exhibit an addictive potential. Thus, the third aim of the present study implemented methodology adapted from the addiction literature and investigated subjective effect reports to nutritionally diverse food items and ad libitum food consumption. Further, between-group differences in subjective experience and eating behavior were assessed for individuals who exhibit YFAS indicators of addictive-like eating, relative to those who do not.

Evidence of certain foods and food characteristics being implicated in biobehavioral processes of addictive disorders, especially for those who exhibit markers of addictive-like eating, may contribute to the development of novel treatment programs and inform food-related public policy initiatives. Unlike other addictions, food is necessary for survival. Thus, differentiating which foods may have an addictive potential and for whom these foods may be most problematic may allow the public to make more informed choices about what to eat and which foods to feed their children. Additionally, identifying foods with an elevated addictive potential may lead to policies, such as preventing these foods from being marketed to children. Finally, exploring the clinical utility of the food addiction phenotype, measured by the YFAS, may provide insight into whether treatment approaches for substance-use disorders (e.g., craving management) may be effective interventions for addictive-like eating behavior.

1.2 Summary of Specific Aims

1. The investigation of foods' differential ability to activate neural (fMRI cue reactivity) and behavioral (wanting, liking) reward mechanisms implicated in addictive disorders. Highly processed foods were hypothesized to be most capable of triggering mechanisms that parallel reward responses to drugs of abuse.

2. The examination of whether biobehavioral reward responses (fMRI cue reactivity, behavioral wanting and liking) to nutritionally diverse food items varied for individuals who exhibit a phenotype consistent with an addiction to food, relative to those who do not. Reward responses for highly processed foods were hypothesized to be particularly elevated for individuals who reported indicators of addictive-like eating.

3. The evaluation of whether an individual's presentation of addictive-like eating was differentially associated with subjective experience and eating behavior for nutritionally diverse food items. Highly processed foods were expected to be most closely associated with subjective response patterns related to addictive substances and consumed in elevated quantities, particularly by individuals who exhibited indicators of food addiction.

1.3 Aim 1: Evaluating the Addictive Potential of Food

1.3.1 Introduction

Evidence is growing for the idea that some individuals may experience an addictive-like response to certain foods. Previous studies have concluded that similar patterns of reward-related neural activity may underlie addictive disorders and eating-related problems (D. W. Tang, L. K. Fellows, D. M. Small, & A. Dagher, 2012; Tomasi & Volkow, 2013; Volkow, Wang, Fowler, & Telang, 2008; Volkow, Wang, Fowler, Tomasi, & Baler, 2012; Volkow, Wang, Tomasi, & Baler, 2013) and shared mechanisms (e.g., impulsivity, emotion dysregulation) seem to contribute to an individual's propensity to develop a substance-use disorder or addictive-like eating behavior (Dallman, 2010; L. H. Epstein et al., 2014; Grilo, Shiffman, & Wing, 1989; Nederkoorn, Braet, Van Eijs, Tanghe, & Jansen, 2006; Nederkoorn, Smulders, Havermans, Roefs, & Jansen, 2006). While prior literature has suggested biological and behavioral parallels between addictive disorders and food addiction, the food addiction theory specifically parallels substance-use disorders, positing that certain foods play a direct role in triggering behavioral indicators of addiction (e.g., loss of control) in a similar manner as drugs of abuse. Yet, little research has examined which foods or food characteristics (e.g., fat content) may have an elevated addictive potential.

Given that no foods or food characteristics have been identified as addictive to date, the term ‘food addiction’ remains broad. However, the food addiction perspective suggests that certain foods, particularly highly processed foods, may be most closely implicated in addictive-like eating behaviors (Gearhardt et al., 2009b; Gearhardt, Davis, Kuschner, & Brownell, 2011). Preliminary studies exploring the addictive potential of highly processed foods have defined these foods as having added fats and/or refined carbohydrates (Polk, Schulte, Furman, & Gearhardt, 2017; Schulte et al., 2015). However, the addictive potential of salt has also been discussed (Cocores & Gold, 2009), and a recent study observed that foods with added salt but not added fat or refined carbohydrates (e.g., bacon, cheese) clustered with foods categorized as highly processed on subjective experience indicators of abuse liability (Schulte, Smeal, & Gearhardt, 2017). Further, many foods defined as highly processed due to having added fats and/or refined carbohydrates also contain added salt (e.g., cheeseburger, pizza, French fries, chips). Thus, in the present study, the term highly processed foods referred to foods with added amounts of fats, refined carbohydrates (e.g., white flour, sugar), and/or salt.

Highly processed foods can be made by combining ingredients that create a new food item with added amounts of fats, refined carbohydrates, and/or salt (e.g., cookies, white pasta, pizza), relative to foods in their natural states. Highly processed foods can also be created by adding fat, refined carbohydrates, and/or salt to a food in its natural state (e.g., adding caramel to apples, adding salt to cure bacon). Further, highly processed foods may be purchased in a store (e.g., Pillsbury chocolate chip cookies) or may be created at home (e.g., making cookies with butter and sugar). While processing may occur through cooking (e.g., grilling, baking) or by adding ingredients to enhance the nutritional value (e.g., vitamins) or shelf life (e.g., preservatives), the current definition only considered a food to be highly processed if fat, refined carbohydrates, and/or salt are added when making the food item. In contrast, a minimally processed food was defined in the current work as a food without added fat, refined carbohydrates, or salt (e.g., fruits, vegetables, steak, nuts).

It has been suggested that highly processed foods may be most associated with a phenotype consistent with addictive-like eating, as highly processed foods exhibit characteristics that elevate the rewarding nature of drugs of abuse (Schulte et al., 2015). The addictive potential of a substance may be increased by adding a greater dose of the addictive agent, which is rapidly absorbed by the body. For example, a 1.5oz shot of hard liquor may have a greater addictive potential than a 12oz light beer. The hard liquor has a larger dose of ethanol, the addictive agent in alcohol, than the light beer (35% versus 3.2% alcohol by volume) and is concentrated in a manner that increases the rate that the ethanol is absorbed by the system. While dose and rate of absorption are important pharmacokinetic properties that elevate the addictive potential of drugs of abuse, there seems to be an optimal dose and rate of absorption for hedonic reward. For instance, individuals with alcohol-use disorders do not seek out 100% ethanol solutions (highest possible dose) to administer intravenously (high rate of absorption). Thus, other facets of reward (e.g., enjoyment of the effects of the drug) may also contribute importantly to a substance's addictive potential.

Similarly, highly processed foods contain added amounts of rewarding ingredients like fat, refined carbohydrates, and/or salt. For example, while some minimally processed foods are naturally high in fat (e.g., nuts, avocado) or sugar (e.g., bananas), no minimally processed foods are naturally high in both fat and sugar. Further, minimally processed foods do not typically contain a high salt content. Thus, highly processed foods may be particularly rewarding as they often have an added amount, or elevated "dose," of both fat and refined carbohydrates like white flour or sugar (e.g., chocolate, cake) and, in many cases, significant added salt content (e.g., cheeseburger, French fries, pizza). Additionally, the refined carbohydrates in highly processed foods are more rapidly absorbed into the body than foods naturally high in sugar. For example, the natural sugars in bananas are coupled with water and fiber in the fruit, which reduces the GL or blood sugar spike of the food. In contrast, sugar is added to make highly processed foods (e.g., chocolate) while simultaneously stripping out ingredients that slow digestion (e.g., water), which leads to a higher GL and greater blood sugar spike for these foods. Thus, highly processed foods may be most capable of triggering an addictive-like response in vulnerable individuals due to shared characteristics with drugs of abuse, such as added amounts (higher "dose") of rewarding ingredients that may be more rapidly absorbed into the system, relative to minimally processed foods (e.g., fruits, vegetables). Notably, like drugs of abuse, there is likely an optimal dose and rate of absorption that maximizes the hedonic effects of highly processed foods compared to the consumption of pure fat, refined carbohydrates like sugar, or salt.

1.3.2 Existing Evidence for the Foods Associated with Addictive-Like Eating

Animal model research has provided key preliminary support for the idea that highly processed foods or ingredients added to highly processed foods (e.g., sugar) are most closely associated with an addictive-like response. Rats with prolonged access to highly processed foods (e.g., cheesecake) or a diet high in both fat and sugar have exhibited biological changes in the reward system, such as downregulation of dopamine, that are similarly implicated in extended drug consumption (Alsio et al., 2010; Johnson & Kenny, 2010b). Rats have also engaged in behavioral indicators of addiction in response to highly processed foods (e.g., Oreo cookies) or ingredients added to highly processed foods (e.g., sugar), such as binge consumption, craving, use despite negative consequences, withdrawal, and cross-sensitization with drugs of abuse

(Avena, Bocarsly, Rada, Kim, & Hoebel, 2008; Avena & Hoebel, 2003; Avena, Rada, et al., 2008; Boggiano et al., 2007; Johnson & Kenny, 2010b; Oswald, Murdaugh, King, & Boggiano, 2011). Notably, rats have not demonstrated these characteristics with nutritionally balanced chow, even despite implementation of circumstances that may elevate risk for overeating (e.g., intermittent access to the chow) (Johnson & Kenny, 2010b; Oswald et al., 2011). Thus, previous studies using animal models have importantly suggested that not all foods are associated with biological and behavioral features of an addictive-like response, and highly processed foods may be most closely implicated in a phenotype consistent with food addiction.

In human studies, highly processed foods have been closely associated with intense craving (Gendall, Joyce, & Sullivan, 1997; Gilhooly et al., 2007; Ifland et al., 2009; Weingarten & Elston, 1991; White & Grilo, 2005; Yanovski, 2003b; Zellner, Garriga-Trillo, Rohm, Centeno, & Parker, 1999), loss-of-control (Arnow, Kenardy, & Agras; Vanderlinden, Dalle Grave, Vandereycken, & Noorduin, 2001; Waters, Hill, & Waller, 2001) and binge eating (Rosen, Leitenberg, Fisher, & Khazam, 1986; Vanderlinden et al., 2001; Yanovski et al., 1992), and consumption in response to negative affect (Epel, Lapidus, McEwen, & Brownell, 2001; Oliver & Wardle, 1999; Oliver, Wardle, & Gibson, 2000; Zellner et al., 2006). While highly processed foods have been related to problematic eating behavior, only one previous study systematically examined which foods may be implicated in addictive-like eating behavior. Schulte and colleagues (2015) asked participants to complete the Yale Food Addiction Scale (YFAS), which operationalizes addictive-like eating using the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for addictive disorders like loss of control and continued use despite negative consequences (American Psychiatric Association, 2013b). Then, participants reported how likely they were to experience problems, described by the YFAS, with 35 nutritionally diverse foods (Schulte et al., 2015). It was observed that highly processed foods (e.g., pizza, chocolate, chips) were most closely implicated in eating-related problems described by the YFAS, but this association was particularly strong for individuals who endorsed experiencing elevated YFAS symptoms of addictive-like eating (Schulte et al., 2015). Further, fat content and GL emerged as food characteristics that positively predicted whether a food was likely to be associated with YFAS eating-related problems[1]. Notably, foods with a high GL (e.g., high blood sugar spike) were especially problematic for individuals who reported exhibiting addictive-like eating behavior on the YFAS, whereas fat content was similarly problematic for all participants (Schulte et al., 2015). This study supports that highly processed foods may be most closely associated with a food addiction phenotype, perhaps due to features that increase the addictive potential of drugs of abuse, such as added amounts ("doses") of rewarding ingredients (fat, refined carbohydrates) that may be rapidly absorbed by the body (high GL).

Three other studies have also provided insight about the relationship between highly processed foods and addictive-like eating behaviors indicated by the YFAS. Pursey and colleagues (2015) observed that individuals who reported experiencing indicators of addictive-like eating on the YFAS also self-reported increased dietary intake of highly processed foods, such as baked sweet products (e.g., cake, cookies), take-out (e.g., pizza, French fries), and candy (e.g., chocolate). Curtis and Davis (2014) utilized qualitative methods to conclude that individuals who self-identified as "addicted" to food (not measured by the YFAS) reported feeling "addicted" uniquely to highly processed foods, particularly those with both added fats and refined carbohydrates (e.g., chocolate, ice cream). Lastly, Schulte and colleagues (2017)

[1] Salt was highly correlated with fat content in this study ($r=.62$, $p<.001$) and thus unique associations of salt with addictive-like eating could not be investigated.

observed that YFAS food addiction was associated with greater reported consumption of trans fats and added sugars among African-American adolescents with obesity.

In summary, previous studies in animals and humans have provided support for the idea that highly processed foods, or ingredients added to highly processed foods (e.g., sugar), may be most closely associated with a phenotype consistent with addictive-like eating. However, to date, the existing evidence for which foods may be addictive in human samples has been limited to self-report data. Thus, the current study addressed an essential next step in this line of research by examining biological and behavioral responses to further elucidate whether highly processed foods may be most capable of engaging reward-related mechanisms in a manner similar to drugs of abuse.

1.3.3 Cue Reactivity in Addictive Disorders and Eating-Related Problems

Reward dysfunction is a mechanism that seems to contribute to both substance-use disorders and problematic eating behavior (Schulte, Grilo, & Gearhardt, 2016), as evidenced by overlapping neural processes. Previous studies have observed that food and drugs may similarly increase dopamine signaling and activation of mesocorticolimbic brain regions (e.g., striatum) (Volkow, Fowler, & Wang, 2002; G. J. Wang, Volkow, & Fowler, 2002). Further, fMRI studies have frequently utilized cue reactivity paradigms to examine reward responsiveness to food and drugs and have found similar patterns of activation for food and drug cues in reward-related regions, such as the amygdala, insula, orbitofrontal cortex (OFC), and striatum (Kelley & Berridge, 2002; Pelchat, 2002; Pelchat, Johnson, Chan, Valdez, & Ragland, 2004; D. Tang, L. Fellows, D. Small, & A. Dagher, 2012). Thus, existing evidence suggests that certain foods may be capable of activating reward-related systems in a similar manner as drugs of abuse, which may contribute to the development and maintenance of compulsive eating behavior for some individuals.

With respect to substance-use disorders, the relationship between cue reactivity and indicators of drug-seeking behavior has been substantially examined. Individuals with substance-use disorders have exhibited elevated reactivity to drug cues in reward-related brain regions associated with increased craving, reward-based learning, and motivation to seek out a drug (e.g., dorsal striatum, dorsolateral prefrontal cortex (dlPFC)) (Brody et al., 2002; Goldstein & Volkow, 2011; Schacht et al., 2013; Volkow et al., 2006; Yang et al., 2009), and reward responsiveness may be heightened when the cued drug is primed to be accessible or available (Carter & Tiffany, 2001; Jasinska, Stein, Kaiser, Naumer, & Yalachkov, 2014). Cue reactivity fMRI paradigms have also been associated with relevant clinical outcomes (Goldstein & Volkow, 2011). For instance, greater drug cue reactivity in the mesocorticolimbic system has been related to severity of drug use (Vingerhoets et al., 2016; Yalachkov, Kaiser, & Naumer, 2009) and future drug use (Grusser et al., 2004). Further, activation in response to drug cues in neural regions associated with emotion and interoceptive awareness (e.g., insula, anterior cingulate cortex (ACC)) has predicted increased relapse-vulnerability in quit attempts (Janes et al., 2010). In summary, fMRI cue reactivity paradigms have been an integral methodology for investigating the reinforcing nature of drugs of abuse and the drugs' potentials to activate reward-related circuitry associated with drug-seeking behavior. Thus, this task seemed to be an appropriate methodological approach to elucidate which foods may be most capable of activating reward-related mechanisms implicated in substance-use disorders.

In previous studies examining food cue reactivity, preliminary evidence has suggested that food may vary in their ability to engage reward-related neural circuitry. Relative to low-calorie food cues (e.g., fruits, vegetables), cues for high-calorie foods (e.g., cake, chips) have been related to greater activation in reward and prefrontal regions (e.g., ACC, OFC, dlPFC) (Dimitropoulos, Tkach, Ho, & Kennedy, 2012; Killgore et al., 2003; Stoeckel et al., 2008), and a food's energy content may modulate the striatal response to visual food cues (Van der Laan, De Ridder, Viergever, & Smeets, 2011). While no studies have yet examined whether food cue reactivity may vary based on certain food characteristics (e.g., fat content), one previous study observed that consumption of a high-sugar/low-fat milkshake was more effective at activating mesolimbic reward circuitry, whereas consumption of a low-sugar/high-fat milkshake was related to oral somatosensory activation, which may reflect the pleasantness of fat's mouthfeel and texture (Stice, Burger, & Yokum, 2013). Thus, foods may vary in their ability to activate reward-related neural circuitry based on certain characteristics. However, neural activation while consuming rewards (e.g., drugs, food) has differed significantly from reward-related responses to cue exposure (e.g., motivation to seek out the reward), particularly for individuals who exhibit the addictive phenotype (Martinez et al., 2005; Volkow et al., 2006). Given that elevated cue reactivity has been associated with a number of relevant clinical outcomes (e.g., problem severity) with respect to drugs of abuse, the examination of whether foods and food characteristics may similarly activate this mechanism was warranted.

In summary, cue reactivity tasks have provided important insight into how drugs of abuse implicate reward-related neural mechanisms in a manner that may drive compulsive consumption for some individuals. While few studies have observed that high versus low calorie food cues are more capable of activating the reward system, no research had evaluated whether food cues varying in certain characteristics (e.g., fat content, high GL) may differentially engage reward-related brain regions. Thus, the current study examined cue reactivity to 34 foods that encompassed a wide range of characteristics, such as calories, processing categorization (e.g., highly processed food), fat, salt, and GL. From an addiction perspective, highly processed food cues were hypothesized to be most effective at activating reward-related mechanisms in a similar manner as drugs of abuse. Further, food cues with added amounts ("doses") of rewarding ingredients (e.g., fat content, refined carbohydrates, salt) that may be rapidly absorbed into the body (e.g., high GL) were expected to be positively correlated with greater reward-related neural activity.

1.3.4 Wanting and Liking as Behavioral Measures of Reward

In addition to the investigation of whether foods vary in their ability to activate addictive-like biological reward processes, the present study also included behavioral measures of reward. In the addiction literature, the incentive sensitization theory has provided a framework of two separable reward-related processes, wanting and liking, that may contribute to the development and maintenance of problematic substance use. Wanting reflects one's craving and motivation to seek out the substance, whereas liking is associated with enjoying the effects of the drug (Berridge & Robinson, 1995a; Berridge et al., 2009; T. E. Robinson & Berridge, 2000). Over the course of an individual's substance-use disorder, liking may be stable or diminish, whereas wanting increases and appears to be associated with continued, compulsive drug use (Berridge, 2009; T. E. Robinson & Berridge, 1993, 2001). Further, for individuals with substance-use disorders, drug-related cues may become coupled with the reinforcing nature of the addictive substance, and the drug cues may become triggers of wanting for the substance (Berridge & Robinson, 1995a; T. E. Robinson & Berridge, 2000). Relatedly, elevated drug cue reactivity in reward-related regions has been associated with greater reports of craving and wanting (Schacht et al., 2013; Yalachkov et al., 2009).

The incentive sensitization theory has also been applied to natural rewards, such as food. The theory similarly posits that wanting, but not necessarily liking, may contribute to an elevated motivation to consume certain foods in a way that may become compulsive for some individuals (Berridge, 1996, 2009). Previous studies in animal models have suggested that rats with sensitized dopamine systems exhibit elevated wanting (measured by reward motivation behaviors) but not liking (indexed by pleasantness of facial expression) for sucrose (sugar) (Berridge, 2009; Pecina, Cagniard, Berridge, Aldridge, & Zhuang, 2003; Wyvell & Berridge, 2000). In humans, there is some evidence that wanting and liking are distinct reward-related mechanisms and engage different brain regions with respect to food (Born et al., 2011; Pelchat & Schaefer, 2000; Yokum, Ng, & Stice, 2011). Thus, it has been suggested that individuals with problematic eating behavior may exhibit a neutral or decreased liking for certain foods over time, while also experiencing an elevated wanting, or motivational drive to seek out the food (Berridge, 2009; Yokum et al., 2011). However, there are a number of complexities that need to be explored in order to determine whether certain foods are capable of sensitizing the reward system in a similar manner as addictive substances, such as the role of the food's palatability and an individual's hunger (Berridge, 2009). Further, no previous studies have examined whether foods and food cues with varying characteristics are differentially related to wanting and liking in a way that resembles drugs of abuse.

The current study measured wanting and liking following the fMRI cue reactivity task, as participants rated each food cue on how intensely they typically 1) want and 2) like the taste of each of the food items. Hunger was measured before the cue reactivity for inclusion as a covariate in analyses. From an addiction perspective, highly processed foods, with added amounts ("doses") of rewarding ingredients (e.g., fat, refined carbohydrates, salt) that may be rapidly absorbed by the system (e.g., high GL), were hypothesized to be most closely associated with patterns of wanting and liking observed in response to addictive substances.

1.3.5 Conclusion

The first aim of this study investigated whether foods varied in their ability to activate neural (fMRI cue reactivity) and behavioral (wanting, liking) reward mechanisms implicated in addictive disorders. The food addiction theory posits that certain foods exhibit an addictive potential that directly drives forward addictive-like eating behavior in vulnerable individuals. While it has been suggested that highly processed foods, with added fats, refined carbohydrates and/or salt, may be most closely associated with addictive-like eating, previous studies have been limited to self-report data. The current study represents an essential next step in this line of research by investigating which foods and food characteristics may trigger biobehavioral reward-related responses in a similar manner as drugs of abuse. Given the proposed similarities between highly processed foods and addictive substances, as added amounts ("doses") of rewarding ingredients that may be rapidly absorbed by the system, highly processed foods and the food characteristics of fat content and GL were hypothesized to be particularly related to addictive-like reward responses. Akin to prior work (Schulte et al., 2015), fat and salt content were highly correlated (r=.50, p=.002). Thus, while foods with added salt were categorized as highly processed (cheese, bacon), the unique associations of salt with neural and behavioral reward responses were not examined.

Overall, the present work contributes to progress in identifying whether certain foods may be addictive (e.g., highly processed foods) and which characteristics may elevate addictive potential (e.g., GL). Notably, unlike other addictive disorders, humans must eat to sustain life. Thus, the identification of which foods are of greatest risk for vulnerable individuals is essential for informing public policy. For example, in the modern food environment, there is an abundance of cues that signal the availability of highly processed foods in large quantities for affordable prices. If cues for highly processed foods activate motivational reward processes similar to drugs of abuse, then policies may aim to reduce the saturation of cues in vulnerable populations, such as restricting marketing of highly processed foods to children.

1.4 Aim 2: Differential Susceptibility to Addictive-Like Responses to Food

1.4.1 Introduction

Previous research has supported that similar mechanisms may contribute to addictive disorders and eating-related problems, such as impulsivity, emotion dysregulation, and reward dysfunction (Schulte et al., 2016). Further, phenotypic overlap of symptoms (e.g., loss of control) in substance-use disorders and some forms of disordered eating (e.g., binge eating) has been observed (Gold, Frost-Pineda, & Jacobs, 2003; Schulte et al., 2016). Given these shared features, it has been suggested that some individuals may experience an addictive-like response to certain foods, which may contribute to problematic, overeating behavior (Gearhardt et al., 2009a, 2009b). An essential next step in evaluating the validity and clinical utility of a food addiction phenotype is the investigation of which foods or food characteristics may exhibit an addictive potential and for whom these foods may be most problematic.

Given that individual differences (e.g., genetic variability) contribute to a person's susceptibility to develop an addiction, prior work has examined the addictive potential of drugs of abuse in individuals with the substance-use disorder (McBride et al., 2006; Sell et al., 2000; Tapert et al., 2003). This has been an essential methodological approach when evaluating whether a substance may exhibit an addictive potential, as most individuals who try an addictive substance do not develop indicators of an addictive process. For example, approximately 90% of persons in the United States consume an alcoholic beverage within their lifetime but only 5-10% of the population meet the criteria for an alcohol-use disorder (American Psychiatric Association, 2000; Grant, 1997). If previous studies evaluated whether alcohol has an addictive potential in the majority of individuals who do not experience an addictive-like response to it, researchers may have concluded that alcohol is not an addictive substance. Thus, the second aim of this study similarly explored which foods and food characteristics may activate addictive-like processes in individuals who exhibit a food addiction phenotype.

1.4.2 Rationale for the Current Sample

The Yale Food Addiction Scale (YFAS) (Gearhardt et al., 2009b, 2016b) is the only validated tool to operationalize addictive-like eating and is based on the DSM criteria for substance-use disorders (American Psychiatric Association, 2013b). The YFAS has demonstrated good internal consistency (α = .76-.92), convergent validity with assessments of eating pathology (e.g., emotional eating, food craving), and incremental validity in predicting binge eating frequency above and beyond existing measures (for a review see (Meule & Gearhardt, 2014)). The current version of the YFAS (YFAS 2.0) consists of 35-item self-report items that assess for the eleven criteria of substance-related and addictive disorders in the DSM-5 when the substance is food (Gearhardt et al., 2016b) (see Appendix A). Individuals can meet criteria for a “diagnostic” threshold of food addiction by endorsing clinically significant impairment or distress plus at least two DSM-5 criteria, though varying “diagnostic” severity levels are associated with different criteria requirements (mild: 2-3, moderate: 4-5, severe: 6-11) (Gearhardt et al., 2016b). The current study compared biobehavioral responses to various foods in individuals who met for moderate or severe YFAS 2.0 food addiction, relative to individuals who endorsed 0-1 criteria and no clinically significant impairment or distress on the YFAS 2.0.

Previous studies investigating parallels between substance-use disorders and eating-related issues have often utilized obesity as a proxy for problematic eating behavior (Kenny, 2011; Trinko, Sears, Guarnieri, & DiLeone, 2007; Volkow et al., 2008; Volkow et al., 2012; Volkow et al., 2013; Volkow & Wise, 2005). While greater endorsement of addictive-like eating behavior on the YFAS has been correlated with elevated body mass index (BMI) (Gearhardt et al., 2016b), YFAS food addiction has been observed across weight classes (Gearhardt et al., 2009b; Gearhardt, Corbin, & Brownell, 2016a; Gearhardt, Yokum, et al., 2011). Further, the prevalence rate of YFAS food addiction "diagnosis" in obese samples has been estimated at 20% (Burmeister, Hinman, Koball, Hoffmann, & Carels, 2013; Davis et al., 2011; Davis et al., 2013; Eichen, Lent, Goldbacher, & Foster, 2013), which demonstrates that obesity is not a necessary nor sufficient condition for the presence of addictive-like eating behavior. Further, the nature of obesity is multifactorial and may not reflect eating patterns (e.g., medication side effects) (Schwartz, Nihalani, Jindal, Virk, & Jones, 2004; Wright & Aronne, 2012). Thus, the present study recruited individuals who exhibit the behavioral phenotype of addictive-like eating for the examination of which foods may be most implicated in this response. Given the association of YFAS food addiction diagnoses with elevated BMI, it was expected that the sample would consist of more individuals with overweight or obesity than persons of healthy weight. In order to increase the likelihood that between-group differences were attributed to the presence of addictive-like eating behavior rather than weight class, only individuals with overweight or obesity were included and recruitment was targeted to ensure non-significant differences in BMI between the two participant groups.

It has also been debated whether food addiction, measured by the YFAS, is distinct from binge eating disorder (BED), given the high degree of phenotypic overlap between indicators of addictive-like eating binge eating (e.g., loss of control over consumption) (Gold et al., 2003). Previous studies have found, on average, that approximately 50% of individuals with BED meet for a “diagnosis” of food addiction measured by the YFAS (Gearhardt et al., 2013; Gearhardt et al., 2012). It appears that individuals with BED and a food addiction “diagnosis” may represent a more severe presentation of disordered eating, evidenced by more frequent binge eating episodes, more intense cravings, and elevated depressive symptoms, relative to persons with only a BED diagnosis (Davis & Carter, 2009; Gearhardt et al., 2012). Additionally, the endorsement of greater YFAS food addiction symptoms has been related to binge eating episode frequency beyond measures of disordered eating (e.g., dietary restraint) and negative affect (Gearhardt et al., 2013; Gearhardt et al., 2012). While the YFAS has been associated with symptoms in BED, a BED diagnosis is also not a sufficient or necessary condition for YFAS food addiction. Notably, individuals who endorsed greater indicators of addictive-like eating on the YFAS but do not meet criteria for any DSM-5 eating disorder (e.g., BED, bulimia nervosa) have exhibited clinically significant functional impairment and distress, such as depressive symptoms, impulsivity, and negative affect (Gearhardt, Boswell, & White, 2014).

Further, there are two key differences between symptomology and theoretical underpinnings of BED and YFAS indicators of addictive-like eating. First, a binge-eating episode is defined by consuming an objectively large amount of food within a two-hour time period, at least once weekly (American Psychiatric Association, 2013b). In contrast, an addiction perspective suggests that problematic consumption can occur within a short period of time (e.g., binge drinking) and also in a more constant, grazing pattern (e.g., chain smoking). Thus, addictive-like eating behavior may occur in a bingeing pattern or by consuming highly processed foods in a compulsive manner throughout the day.

Second, there are fundamental differences between theoretical perspectives of addictive disorders and eating disorders. Traditional explanations of eating disorders like BED have suggested that cognitive restraint and shape/weight concern may cause and maintain symptomology, which contrasts substance-use disorders (e.g., cognitive restraint of cigarette usage has not been thought to cause nicotine-use disorder). Further, an addiction perspective applied to eating may encompass mechanisms not relevant within eating disorder frameworks, such as withdrawal, tolerance, and the addictive potential of the food (Schulte et al., 2016). Thus, food addiction, assessed by the YFAS, may represent a unique phenotype of problematic eating behavior. The present study excluded individuals diagnosed with BED, bulimia nervosa, and anorexia nervosa in order to specifically investigate between-group differences in biobehavioral responses to certain foods for persons who meet for YFAS food addiction, relative to controls who do not exhibit addictive-like eating behavior.

1.4.3 Reward Responsiveness and YFAS Food Addiction

One previous study to date has investigated neural responses associated with YFAS food addiction (Gearhardt, Yokum, et al., 2011). This work provided preliminary evidence for differential responses to food rewards among individuals who report three or more YFAS indicators of food addiction, relative to persons who endorse zero or one symptoms of addictive-like eating behavior. Individuals with three or more YFAS markers of food addiction exhibited increased responses in mesocorticolimbic reward regions (e.g., dlPFC, caudate) while anticipating a highly processed food reward (chocolate milkshake), but diminished activation of inhibitory control neural structures (e.g., OFC) during consumption of the highly processed food (Gearhardt, Yokum, et al., 2011), relative to persons endorsing zero or one YFAS criteria. These patterns have been observed in individuals with substance-use disorders with respect to the anticipation and receipt of drug-specific rewards (Martinez et al., 2005; Volkow et al., 2006). Thus, this study provided initial insight that neural patterns of reward dysfunction may contribute to YFAS food addiction in a similar manner as substance-use disorders.

However, this study had several limitations that warrant attention in the present work. Most notably, Gearhardt and colleagues (2011) were not able to categorize participants into those with or without YFAS food addiction, as only two participants in the sample endorsed clinically significant impairment or distress. It is unknown how individuals with elevated symptoms but no impairment/distress may vary from individuals who meet for the full YFAS criteria, although it is likely that Gearhardt and colleagues' (2011) study represented a conservative test of food-related reward responses. Thus, the current study explored between-group differences in neural responses to food cues in individuals who met either the moderate or severe thresholds of YFAS food addiction, indicated by endorsement of at least four symptoms plus clinically significant impairment or distress (Gearhardt et al., 2016b). Further, Gearhardt and colleagues (2011) investigated reward-related responses to one highly processed food (chocolate milkshake). The present study expanded on this work through measurement of neural responses to 34 nutritionally diverse food cues and the investigation of which foods or food characteristics (e.g., fat content, GL) may be most associated with elevated reward reactivity for individuals exhibiting YFAS indicators of food addiction. Finally, Gearhardt and colleagues (2011) stated that future studies should include additional, behavioral addiction-relevant indexes to help elucidate how the observed reward responses may contribute to addictive-like food consumption. Thus, in addition to the fMRI food cue reactivity paradigm, the current protocol included measures of wanting and liking in order to examine behavioral reward responses to various food items and whether between-group differences exist for individuals with versus without a "diagnosis" of YFAS food addiction.

1.4.4 Wanting, Liking, and YFAS Food Addiction

As described earlier (see pages 15-17), wanting and liking have been differentially associated with reward (Berridge & Robinson, 1995a; Berridge et al., 2009; T. E. Robinson & Berridge, 2000). Previous studies have provided initial insight into how wanting and liking may be associated with behavioral indicators of food addiction, measured by the YFAS. Craving has been closely associated with wanting (T. E. Robinson & Berridge, 1993) and the focus of prior research using the YFAS. Greater endorsement of YFAS symptoms has been related to elevated food cravings (Davis et al., 2011; Gearhardt, Rizk, & Treat, 2014; Meule & Kubler, 2012), particularly for highly processed foods (Gearhardt, Rizk, et al., 2014). Though one prior study found that elevated reports of addictive-like eating on the YFAS was associated with both greater craving and liking for highly processed foods (Gearhardt, Rizk, et al., 2014), a recent study with a larger, more representative sample observed that greater YFAS symptoms were related to greater craving for highly processed foods but not liking (Polk et al., 2017). Additionally, Meule and Kubler (2012) found that individuals with elevated YFAS scores do not report an expectation to be positively reinforced by consuming foods they crave, which supports that persons with addictive-like eating behavior may experience elevated wanting without increased liking for certain foods. While existing findings have supported that food craving (wanting), but not necessarily liking, may be elevated for persons with YFAS food addiction symptomology, prior work has been limited to self-report data.

As described previously, the current study measured wanting and liking following the fMRI cue reactivity task, as participants rated each food cue on how much they typically 1) want and 2) like the taste of each of the food items. This provided a measure of an individual's general tendency of both wanting and liking associated with the food cues included in the fMRI cue reactivity paradigm.

1.4.5 Conclusion

The second aim of this study examined variance in biological (fMRI cue reactivity paradigm) and behavioral (wanting, liking) indexes of reward to nutritionally diverse food items for individuals with overweight or obesity with a phenotype consistent with an addiction to food, relative to those without. The current study paralleled addiction literature by, for the first time, examining reward responses to various foods in the population that exhibits the addictive-like profile of interest. In previous research, it has been essential to evaluate the addictive potential of substances within individuals who experience an addictive-like response to the drug (McBride et al., 2006; Sell et al., 2000; Tapert et al., 2003). Thus, the present sample was ideal for examining which foods or food characteristics may be potentially capable of activating reward-based mechanisms in a similar manner as drugs of abuse. Further, the examination of between-group differences for individuals who met the threshold of YFAS food addiction, relative to those who did not, may contribute to the understanding of individual susceptibility for addictive-like responses to food. Consistent with prior work in substance-use disorders, individuals who exhibit an addictive-like eating phenotype were hypothesized to have greater reward responses to certain foods (e.g., highly processed foods) and food characteristics (e.g., fat content, GL) that may share features with addictive substances (e.g., elevated dose, rapid rate of absorption), indexed by elevated neural reward responses to highly processed food cues and increased reports of wanting but not liking for these foods.[2]

In summary, the evaluation of not only which foods have elevated addictive potential but also for whom these foods may be most problematic followed as an essential extension of prior research. If certain foods may be more triggering for individuals who experience indicators of YFAS food addiction, then intervention approaches used to treat substance-use disorders may also be effective for this population. For example, techniques used to manage drug cravings may be beneficial as applied for reducing food cravings for individuals with addictive-like eating behavior, particularly if wanting appears to be an important reward response. Given that many individuals have not experienced success with existing treatments for obesity and eating-related problems (Brownley, Berkman, Sedway, Lohr, & Bulik, 2007; Grilo, Masheb, Wilson, Gueorguieva, & White, 2011; Vocks et al., 2010; Wadden, Butryn, & Byrne, 2004; G. T. Wilson, Wilfley, Agras, & Bryson, 2010), the present work may inform improvements to existing approaches or the development of novel interventions.

1.5 Aim 3: Subjective Experience of Food Consumption and Abuse Liability

1.5.1 Introduction

The scientific understanding of drugs and their effects has developed substantially in the past century (Jaffe & Jaffe, 1989). As new substances have been created, researchers have examined their addictive potential to determine the drug's abuse liability, defined as the likelihood that exposure to the substance will lead to continued use despite negative consequences (Henningfield & Nemeth-Coslett, 1988; Jaffe & Jaffe, 1989). Substances with a high abuse liability (e.g., morphine, methamphetamine) are greatly reinforcing and likely to lead

[2] As mentioned previously, fat and salt content were highly correlated (r=.50, p=.002) and thus could not be entered into the same model to explore the unique associations with salt. Akin to prior research, fat and GL were retained as the food characteristics of interest.

to problematic, compulsive consumption in individuals prone to addiction (Henningfield & Nemeth-Coslett, 1988; Jaffe & Jaffe, 1989). As such, studies that have evaluated the addictive potential of recreational or medicinal drugs have focused on indexing the reinforcing, rewarding nature of the substance and patterns of self-administration. In parallel, the present study adapted methodology from prior work on drug abuse liability for the investigation of which foods or food characteristics may have an addictive potential for vulnerable individuals.

1.5.2 Subjective Effect Reports as a Measure of Reinforcing Potential

The reinforcing potential of a drug reflects the probability that ingestion of the substance will lead to subsequent compulsive drug-taking behavior (Jaffe & Jaffe, 1989). Laboratory assessments have measured drug reinforcement through questions about individuals' subjective experience to consuming the substance (Henningfield & Keenan, 1993; Jasinski & Henningfield, 1989; Jasinski et al., 1984). For example, persons have reported on the appeal of the drug, averseness of the drug, desire to consume more, enjoyment of the drug's effects (e.g., euphoria), and satisfaction from consuming the drug. Several approaches exist for measuring subjective effect reports, such as visual analog scales (VAS) for individual items (e.g., enjoyment), adjective-based scales to assess feelings and responses associated with consumption of specific drugs (e.g., itchiness for opioids), and questionnaires that span effects of multiple classes of known addictive substances (e.g., alcohol, stimulants) (Fischman & Foltin, 1991; Fraser, Van Horn, Martin, Wolbach, & Isbell, 1961; Haertzen, 1966).

Preston and Walsh (1998) developed standardized procedures to investigate the abuse liability of drugs in research settings, using subjective effect reports. Most notably, Preston and Walsh (1998) recommended measuring subjective experience in individuals who are experienced with the substance or consume it in a problematic manner, as it is essential to assess abuse liability in those prone to engaging with the drug. Additionally, it was suggested to collect subjective effect reports for varied doses of the drug administered in a randomized order (K. L. Preston & S. L. Walsh, 1998). This was thought to allow for the measurement of possible dosing effects, such as increased euphoria at elevated doses of a drug, with the randomization reducing participant reporting bias. These methods have been adapted to successfully evaluate the abuse liability of a variety of drugs of abuse, such as opioids, amphetamines, and nicotine (Jasinski & Krishnan, 2009; Vansickel, Weaver, & Eissenberg, 2012; Walsh, Nuzzo, Lofwall, & Holtman, 2008; West et al., 2000).

Subjective effect reports of drug reinforcement vary for substances with a high, relative to low, abuse liability. When opioids or stimulants (high abuse liability) have been given to persons with histories of problematic drug use, the experience of positive, euphoric feelings immediately following consumption has strongly predicted future self-administration (Henningfield & Nemeth-Coslett, 1988; Jaffe & Jaffe, 1989). Greater abuse liability has also been associated with elevated desires to consume more, higher satisfaction from consuming the substance, and fewer reported adverse effects from ingesting the substance (Hatsukami, Zhang, O'Connor, & Severson, 2013; Henningfield & Nemeth-Coslett, 1988; Jaffe & Jaffe, 1989). Additionally, for substances ingested through the mouth (e.g., oral tobacco), liking for the drug's taste has been measured, though subjective effect reports to questions about satisfaction and euphoria have remained most closely related to higher abuse liability (Hatsukami et al., 2013). In contrast, substances with low abuse liability have been associated with less pleasurable subjective effects. For example, prior work examining the abuse liability of Modafinil, a stimulant used to treat narcolepsy, has concluded that the drug has little addictive potential, as subjective effect reports (e.g., experience of euphoria, satisfaction) are low and comparable to a saline placebo (Myrick, Malcolm, Taylor, & LaRowe, 2004).

Among substances with a high abuse liability (e.g., cocaine, nicotine), two features have been manipulated to enhance or reduce the drugs' addictive potential. First, a dose-dependent effect has frequently been observed in subjective effect reports, with higher doses of the substance correlated with subjective experiences indicative of greater abuse liability (Comer et al., 2008; Institute of Medicine, 2012; Rush, Kelly, Hays, Baker, & Wooten, 2002). For example, Rush and colleagues (2002) observed a step-wise dosing effect of subjective effect reports for 100mg, 200mg, and 300mg of orally administered cocaine. The greatest abuse liability was associated with the 300mg dose, though all doses of the cocaine exhibited elevated subjective effect reports relative to placebo (Rush et al., 2002). In contrast, substances with little addictive potential (e.g., Modafinil) have not exhibited a dose-dependent elevated on measures of subjective experience that correlate with addictive potential (Rush et al., 2002). Second, the rate in which the drug of abuse is absorbed into the system may alter subjective effect reports of abuse liability (Farre & Cami, 1991; Henningfield & Keenan, 1993; Institute of Medicine, 2012; Sellers, Busto, & Kaplan, 1989). For example, immediate-release nicotine delivery systems (e.g., cigarettes) have been more closely associated with subjective effect reports predicting high abuse liability than delayed or sustained release nicotine products (e.g., nicotine patch) (Henningfield, Miyasato, & Jasinski, 1985; Institute of Medicine, 2012; Pickworth, Bunker, & Henningfield, 1994; West et al., 2000). Thus, drugs of abuse with an elevated dose of an addictive agent that is rapidly absorbed into the body seem to have the greatest addictive potential, as measured by subjective effect reports.

Evaluating the subjective experience associated with nutritionally diverse foods may be a useful method for assessing the addictive potential of various foods. A recent study by Schulte and colleagues (2017) recruited an online community sample to rate 30 nutritionally diverse food items on five subjective effect indicators of abuse liability (craving, liking, pleasure, averseness, and intensity). Akin to drugs of abuse (Hatsukami et al., 2013; Henningfield & Nemeth-Coslett, 1988; Jaffe & Jaffe, 1989), highly processed foods were most associated with a profile of elevated addictive potential, evidenced by greater craving, liking, and pleasure, relative to minimally processed foods. While this study provided evidence that foods may vary in their abuse liability, indicated by measures of subjective experience, the methodology was limited to self-report and did not evaluate subjective effect reports while consuming the food items, as recommended by Preston and Walsh (1998) when assessing the addictive potential of substances.

Thus, the present study implemented methodology from the addiction literature and measured seven aspects of subjective effect reports in a taste test paradigm. Participants consumed a standardized (seven grams) portion of 14 foods that differed across two dimensions important in prior drug abuse liability work (Farre & Cami, 1991; Henningfield & Keenan, 1993; Institute of Medicine, 2012; Rush et al., 2002; Sellers et al., 1989). First, the foods had a range of "doses" of food characteristics, such as calories, fat, sugar, salt, and protein. Second, foods varied by GL, which measures the rate in which refined carbohydrates are absorbed into the bloodstream. The 14 food items were presented in a randomized order. After the standardized (7 gram) portion of one food item was consumed, individuals reported seven facets of their subjective experience with that food. The subjective effect questions were directly adapted from the abuse liability literature, such as craving for the substance, pleasure, averseness, satisfaction, and palatability (see Appendix B for specific questions). After providing subjective effect ratings for one food, participants rinsed their mouth out with water before proceeding with the next food item.

Foods with a possible elevated addictive potential were expected to be associated with subjective effect reports similar to drugs of abuse (e.g., greater wanting, euphoria, and satisfaction, less averseness). For drugs of abuse, addictive potential has been heightened by increasing the dose and absorption rate (Farre & Cami, 1991; Henningfield & Keenan, 1993; Institute of Medicine, 2012; Rush et al., 2002; Sellers et al., 1989). Similarly, it was expected that highly processed foods, with added amounts ("doses") of rewarding ingredients (e.g., added fats, refined carbohydrates, and/or salt) that may be rapidly absorbed (e.g., high GL), would be positively related to a greater abuse liability, as measured by subjective experience. Finally, prior studies have assessed drug abuse liability in individuals that exhibit a problematic, addictive-like response to the substance (Institute of Medicine, 2012; K. L. Preston & S. L. Walsh, 1998). Thus, subjective effect reports to food were evaluated in individuals who exhibit a phenotype consistent with an addictive-like response to food, as measured by the YFAS (Gearhardt et al., 2009b, 2016b), relative those without addictive-like eating behavior. Highly processed foods were hypothesized to have a particularly increased abuse liability for individuals with addictive-like patterns of food consumption.

As an exploratory analysis, the present study also explored whether subjective effect reports informed the relationship between food wanting and liking. Reports of wanting and liking for drugs of abuse may both be initially elevated, though an individual's wanting for the addictive substance increases over the course of an addiction, while liking remains the same or decreases (Berridge, 2009; T. E. Robinson & Berridge, 1993, 2001). The current study included subjective experience measures of both wanting (e.g., craving) and liking (e.g., taste, pleasure during consumption). Thus, this study aim investigated the association between subjective effect reports of wanting versus liking with a food's reinforcing value and actual food consumption, and individual differences in these associations based on endorsement of YFAS indicators of food addiction.

1.5.3 Ad Libitum Consumption of Drugs and Food

Inclusion of measures of both subjective experience and self-administration in the assessment of abuse liability has been recommended (Comer et al., 2008; K. L. Preston & S. L. Walsh, 1998), as the predictive validity of subjective effect reports for actual drug consumption has been mixed. Several studies have suggested that drugs with an elevated abuse liability, as measured by subjective effect reports, may more likely to be self-administered in both laboratory and naturalistic contexts (Comer et al., 2008; Henningfield, Cohen, & Heishman, 1991; Henningfield, Miyasato, & Jasinski, 1983; Products, 2012). Features of subjective experience have also been associated clinically relevant outcomes like elevated risk of drug relapse, which consists of self-administration during efforts of abstinence. For example, Shiffman and Kirchner (2009) found that individuals who reported greater desire for a cigarette and satisfaction from smoking were most likely to relapse during a quit attempt. While subjective experience and drug consumption in laboratory settings have often been correlated indicators of a drug's reinforcing potential (Comer et al., 2008; Henningfield et al., 1991; Henningfield et al., 1983; Institute of Medicine, 2012), other studies have not detected an association (Comer & Collins, 2002; Lamb et al., 1991). For instance, numerous studies have observed an association between subjective reports of craving with greater drug-taking behavior (D. H. Epstein, Marrone, Heishman, Schmittner, & Preston, 2010; Ferguson & Shiffman, 2009; Oslin, Cary, Slaymaker, Colleran, & Blow, 2009; Paliwal, Hyman, & Sinha, 2008), whereas other work has not found a relationship between aspects of subjective experience (e.g., craving) and drug consumption (Abrams, Monti, Carey, Pinto, & Jacobus, 1988; Tiffany, Singleton, Haertzen, & Henningfield, 1993; Walton, Blow, Bingham, & Chermack, 2003).

In order to parallel recommendations from the drug abuse liability research (Comer et al., 2008; K. L. Preston & S. L. Walsh, 1998), the current study also measured ad libitum consumption of the 14 nutritionally diverse food items. In addition to the subjective effect reports that may correlate with addictive potential, the direct measurement of food consumption aimed to increase predictive validity for actual eating behavior. After participants consumed standardized portions of all 14 foods in the taste test task and rated seven aspects of subjective experience for each food, they were instructed to wait while the next portion of the study was set up. Participants were told that they could consume as much of the "leftover" food from the taste test task as they would like. In order to reduce the likelihood that individuals chose to consume food out of boredom, they were also given magazines of neutral content (e.g., National Geographic) as an alternate reinforcing activity. Ad libitum food consumption was measured after 15 minutes.

Foods hypothesized to have the highest abuse liability, measured by subjective effect reports, were expected to be consumed in greater quantities. Further, individual differences in ad libitum food consumption based on YFAS food addiction categorization were also evaluated. Individuals with YFAS food addiction were anticipated to consume greater quantities of foods that may have an addictive potential (e.g., highly processed foods), relative to controls, due to a greater propensity for addictive-like eating with these foods. Individuals with YFAS indicators of addictive-like eating were not expected to differ from controls in their consumption of foods hypothesized to have little addictive potential (e.g., minimally processed foods).

1.5.4 Conclusion

The third aim of this study applied methodology from the drug abuse liability literature to investigate whether certain foods or food characteristics (e.g., fat) exhibit an addictive potential. Based on recommendations for assessing the addictive nature of substances (Comer et al., 2008; K. L. Preston & S. L. Walsh, 1998), the present work measured both subjective effect reports and self-administration (ad libitum consumption) for fourteen, nutritionally diverse food items. With respect to drugs, substances with a high abuse liability have been associated with subjective effect reports indicative of greater reinforcement (e.g., elevated euphoria and satisfaction, little averseness) (Hatsukami et al., 2013; Henningfield & Nemeth-Coslett, 1988; Jaffe & Jaffe, 1989) and increased self-administration (Comer et al., 2008; Institute of Medicine, 2012). Similarly, highly processed foods, with added fats, refined carbohydrates, and/or salt, were hypothesized to be most related to subjective effect responses elicited by addictive drugs and greater quantities of consumption. Further, the current approach allowed for the evaluation of the relationship between reported subjective experience and actual food consumption, which may have increased predictive validity for real-world eating behavior. Subjective effect reports indexing wanting (e.g., desire to consume more) versus liking (e.g., taste, palatability) were also compared to determine which was more implicated a food’s reinforcing value and actual food consumption. Finally, between-group differences in subjective experience and consumption were evaluated for individuals who exhibit a phenotype consistent with an addictive response to food, relative to those who do not. If certain foods may have an elevated addictive potential (e.g., highly processed foods), then it was expected that individuals with addictive-like eating behavior would find these foods more reinforcing and consume them in greater quantities, relative to controls.

In summary, this work may further elucidate whether certain foods may be similarly reinforcing as drugs of abuse and drive forward addictive-like eating behavior in susceptible individuals. Notably, the addictive potential of drugs of abuse increases when the substance is easily accessible for low prices and has greater social acceptability (Jaffe & Jaffe, 1989). In the modern food environment, highly processed foods are widely available, affordable, and integrated into social norms (e.g., donuts for morning meetings). If highly processed foods have an elevated abuse liability, the lack of regulation for accessing them may exacerbate their addictive potential among individuals prone to addictive-like eating. Thus, the present study may provide insight for whether certain foods or food characteristics have an elevated abuse liability, which may inform the development of policy initiatives to regulate the food environment.

CHAPTER 2

METHODS

2.1 Participants

Women (*N*=43) who participated in the current study were 25-40 years old (M=30.81, *SD*=4.14) and self-reported racial identification was as follows: 51.2% (*n*=22) White/Caucasian, 27.9% (*n*=12) Black/African-American, 9.3% (*n*=4) Hispanic, 7.0% (*n*=3) Multiracial, 2.3% (*n*=1) Asian, and 2.3% (*n*=1) Arab. BMI ranged from 24.70-51.00 (M=33.61, *SD*=5.59). Approximately half of participants (*n*=21) met criteria for moderate-to-severe YFAS 2.0 food addiction diagnostic score. This YFAS 2.0 threshold was met by endorsing 4 to 11 of the DSM-5 criteria for substance-dependence (e.g., loss of control over consumption), when the substance is food, plus clinically significant impairment or distress. In the group with YFAS 2.0 food addiction, symptom scores ranged from 4 to 11 (M=7.76, *SD*=2.14). The control group (*n*=22) endorsed zero or one markers of addictive-like eating as measured by the YFAS 2.0 (M=.23, *SD*=.43). The participant groups did not differ by age, income, or BMI (all *p*s>.34).

Participants were recruited through the University of Michigan's clinical research listserv (umhealthresearch.org), flyers posted throughout Washtenaw County, and advertisements posted to Craigslist. In order to recruit individuals who exhibited an addictive-like eating phenotype, recruitment materials contained language such as, "Do you lose control over your food consumption?" Flyers targeting healthy controls invited adults to participate in a study examining brain responses to food.

Potential participants completed an online screener, including the YFAS 2.0, to determine their eligibility for inclusion as a participant exhibiting a phenotype consistent with addictive-like eating or in the control group. Individuals were also asked about the presence of 1) contraindication to fMRI (e.g., metal implants), 2) symptoms of major psychiatric disorders, 3) current or previous eating disorder diagnoses, 4) current or previous substance-use disorders, including nicotine-use, 5) diet-related disease (e.g., diabetes), 6) dietary restrictions that would limit food consumption (e.g., lactose intolerance), and 7) current participation in treatment for eating-related problems or enrollment in a weight loss program (e.g., Weight Watchers). Potential participants who endorsed any of these questions were excluded from participation.

2.2 Measures and Procedures

Participants arrived at the fMRI center and completed written informed consent procedures for both the neuroimaging and behavioral components of the study. Individuals then completed a urine pregnancy test and the fMRI safety screener form to ensure that no MRI contraindications were present. Following consent procedures, participants first engaged in the fMRI food cue reactivity paradigm where they viewed pictures of foods and familiar, neutral stimuli (household items). After the scan, participants reported wanting and liking for each item presented in the fMRI task, including the food items and household item control group. Next, participants completed a taste test for fourteen of the foods shown in the fMRI study and rated them on measures to assess wanting, liking, and subjective experience. After the taste test, participants had the opportunity to consume the leftover food "ad libitum" for fifteen minutes. Individuals also completed a 24-hour, self-administered dietary recall and additional questionnaires examining emotional eating, food craving, and food motivation. Participants then had their body composition (e.g., adiposity) measured using technology for bioelectrical impedance analysis. Finally, individuals were debriefed and had the opportunity to ask questions about the protocol.

fMRI Food Cue Reactivity Paradigm: The scan began either between 11:30am-1pm or 1:30-4pm as participants were expected to be moderately hungry between breakfast and lunch or lunch and dinner, respectively. Participants were asked to eat normally on the day of their appointment but refrain from eating or drinking anything besides water two hours prior to the appointment to reduce variation in hunger. As a check for this, participants rated their hunger before the scan on a scale of 0 (not hungry at all) to 100 (never been hungrier) and were, on average, moderately hungry (M=50.56, *SD*=24.82; scale ranged from 0-100) and hunger did not differ by YFAS 2.0 food addiction status (p=.43). Participants who rated their hunger >70 were offered a food item not pictured in the fMRI task (e.g., clementine) to neutralize their hunger.

Prior to entering the fMRI scanner, participants practiced the cue reactivity task on a desktop computer. Individuals were told to view the food and household item pictures while thinking about how much they want each item as if it were in front of them. In prior studies of drug cue reactivity in samples with substance-use disorders, reward-related neural responses seem to be elevated when the item is accessible (Carter & Tiffany, 2001; Jasinska et al., 2014). Thus, in the current study, participants were told they have would have access to some of the items immediately after the scan. Specifically, it was clear that the foods would be available for consumption and household items could be taken home. In order to motivate individuals to attend to the pictures, they were told they would complete a picture-recognition task to identify which items were presented during the MRI scan. This has been a successful approach in prior research (Gearhardt, Yokum, Stice, Harris, & Brownell, 2014). In the present study, all participants exhibited 100% accuracy on the recall test, indicating attention to the task.

The current study utilized an event-related design to examine cue reactivity. Thirty-four diverse foods (19 highly processed and 15 minimally processed) and seventeen household items were included in the task, and all items were presented on a white background to reduce variation in luminance. Stimuli were each presented for 4 seconds, and between stimuli, a jitter of varied length (average=4 seconds) was shown (see Figure 1 for an example trial sequence). The task lasted approximately 13.5 minutes and consisted of six runs, with 17 events in each run. Total scan duration was approximately 45 minutes including breaks and anatomical scans. After the scan, participants rated how much they wanted each food and household item on a scale from 0 (no wanting) to 100 (extreme wanting) and how much they liked each item on a scale from -100 (dislike extremely) to 100 (like extremely). For food items, participants were also asked how frequently they consume the food and how familiar they are with the food item.

Taste Test: Fourteen foods shown in the fMRI task, representing a variety of nutritional characteristics were included in this task. The food items were presented in a randomized order, one at a time, and individuals rinsed their mouth with water between each food. Participants first consumed a small, standardized portion (7 grams) of a food item. Then, they rated the following indicators of subjective experience on visual analog scales, presented in a random order for each food: craving, liking for the taste, pleasure experienced while eating it, averseness of the taste, guilt experienced while eating it, intensity of the taste, and satisfaction from eating it (see Appendix B for wording and rating scales)[3]. These questions were selected because they directly

[3] General labeled magnitude scales (gLMS) were also used alongside visual analog scales (VAS) to rate craving and liking for the taste of each food presented in the taste test task. However, the two approaches were highly correlated (craving for highly processed foods: r=.71, p<.001; craving for minimally processed foods: r=.60, p=<.01); liking for taste of highly processed foods: r=.54, p=.014; liking for taste of minimally processed foods: r=.81, p<.001).

parallel methodology utilized when evaluating the abuse liability of potentially addictive substances (Farre & Cami, 1991; Henningfield & Keenan, 1993; Institute of Medicine, 2012; Rush et al., 2002; Sellers et al., 1989) and may be important factors in determining the likelihood that a food is associated with eating-related problems. Further, the foods were selected because they represent a variance of nutritional characteristics, such as calories, fat, refined carbohydrates, sodium, protein, and fiber. The foods were: chocolate, potato chips, cheese, nuts, cookies, gummy candy, banana, carrots, pizza, brown rice, pretzels, cucumber, granola bar, and apple. Table 1 includes information on the specific nutritional characteristics of these foods.

Ad-libitum Food Consumption: Following the taste test, participants were told that the next part of the research study would begin soon, and they were welcome to consume the leftover food from the taste test while they are waiting. Magazines without eating-related subject matter (e.g., National Geographic) were provided as an alternate reinforcing activity to engage in during this time. The researcher left the room for 15 minutes. Following the ad libitum consumption period, the researchers weighed the remaining food to determine the quantity consumed for each item. During the 15 minutes, water was freely available. This allowed for the examination of actual food consumption as an informative variable in predicting if a food item has an elevated addictive potential.

Subjective Experience Indicators: After the ad libitum consumption period, several additional indicators of abuse liability were asked. These questions were not asked during the taste test task, alongside the other subjective experience questions, as they may have influenced eating behavior during the ad libitum consumption task. For each of the 14 foods included in the taste test and ad libitum tasks, the following indexes were assessed: how out of control

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Further, due to adding the gLMS approach later than the VAS and thus having gLMS data for just 20 participants, only VAS ratings from the taste test task are presented.

participants felt while eating the food, likelihood of consuming the food in the next week, likelihood of purchasing the food in the future, likelihood of consuming the food if it were offered for free (see Appendix B for wording and rating scales).

2.3 Screening Measures

MINI: As part of the recruitment screening process, potential participants were asked the screening questions on the Mini International Neuropsychiatric Interview (MINI) for Mood Disorders (e.g., depression), Anxiety Disorders (e.g., generalized anxiety disorder), Trauma Disorders (e.g., post-traumatic stress disorder), Thought Disorders (e.g., schizophrenia), Eating Disorders (e.g., BED), and lifetime Substance-Use Disorders (e.g., alcohol dependence, nicotine-use disorder). If a screening question was endorsed, the rest of the relevant module was administered, and the person was excluded from participation if she met criteria for the disorder.

YFAS 2.0: All participants completed the YFAS 2.0, a questionnaire that applies the DSM-5 criteria of substance disorder to food (Gearhardt et al., 2016b) (see Appendix A). This questionnaire is an updated version of the original YFAS, which was based on the DSM-IV criteria for substance dependence(Gearhardt et al., 2009b). This measure exhibits good internal consistency (Kuder–Richardson α = .92), excellent convergent validity with measures of problematic eating behavior (e.g., BMI), evidence of discriminant validity with other constructs of eating disorders (e.g., BED), and good incremental validity in predicting BMI beyond binge eating frequency (Gearhardt et al., 2016b). Individuals who endorsed four or more behavioral indicators of addictive-like eating plus clinically significant impairment or distress on the YFAS 2.0 were categorized as exhibiting a phenotype consistent with addictive-like responses to food. Persons who endorsed zero or one marker of addictive-like eating on the YFAS 2.0 and did not report clinically significant impairment or distress were included in the control group.

2.4 Covariates

Hunger: Since hunger has been related to neural responses to food cues (Siep et al., 2009), individuals rated their current hunger at several time points during the appointment, including prior to the fMRI task, after the fMRI task, after the taste test, and after ad libitum consumption. Ratings were measured on a 100-point visual analog scale from 0 (not hungry at all) to 100 (never been hungrier). This allowed for the inclusion of hunger as a covariate in fMRI and behavioral analyses.

Body Composition: Elevated BMI has been associated with greater reward-related neural activation to food cues (Smith & Robbins, 2013; Tryon et al., 2015; Volkow et al., 2008; Volkow et al., 2012; Volkow & Wise, 2005; G. J. Wang, Volkow, Thanos, & Fowler, 2004). In order to measure for BMI and additional variables related to body composition, bioelectrical impedance analysis was used via an InBody scanner, a scale that has participants stand on footplates and hold handles for less than a minute, producing a medical-grade report on muscle, fat, water, BMI, basal metabolic rate, and percent body fat. In the current study, BMI was included in analyses as appropriate.

CHAPTER 3

RESULTS

3.1 Aim 1

3.1.1 Data Analytic Plan

fMRI Scanner and Data Acquisition: MRI images were acquired using a 3T GE Signa scanner with an 8 channel head coil located at the University of Michigan fMRI Laboratory. Visual stimuli were displayed using an LCD screen by Nordic Neuro Labs (Bergen, Norway). Mirrored glasses with the capacity for vision correction allowed participants to view the screen. Participants completed scanning in one 45-minute session. Echo planar imaging was used to measure blood-oxygen-level dependent (BOLD) signal as an indication of cerebral brain activation. Two structural image sets were acquired: 1) 2D T1 Axial Overlay (TR = 3170, TE = 24, flip angle = 111°, FOV = 22cm, slice thickness = 3.0mm, 43 slices, matrix = 256*192. 3D SPGR was acquired Axially (flip angle = 15°, FOV = 25.6cm, slick thickness = 1mm, 156 slices, matrix = 256*256). Functional T2*-weighted BOLD images will be acquired using a reverse spiral sequence of 40 contiguous axial 3 mm slices (TR = 2000ms, TE = 30ms, flip angle = 90°, FOV = 22cm). Slices were prescribed parallel to the AC-PC line, and images were reconstructed into a 64x64 matrix.

fMRI Data Analysis: Two participants were excluded from analyses due to movement greater than 5mm, resulting in 41 participants in this analyses (20 individuals with YFAS 2.0

food addiction and 21 control participants). Images were first skullstripped with a threshold of 0.5 then manually reoriented using the AC-PC plane as a reference point. fMRI data were preprocessed and analyzed using SPM12 (Wellcome Department of Imaging Neuroscience; Institute of Neurology, University College of London, London UK). Functional images were time-acquisition corrected to the slice obtained at 50% of the TR, realigned to the scan immediately preceding the anatomical T1 image, and smoothed with a 6mm FWHM isotropic Gaussian kernel. For time series analysis, a high-pass filter (128s) removed low frequency noise and signal drifts. The artifact detection tools (ART) toolbox in SPM12 was used for identifying motion spikes. Movements greater than 2mm in any direction were considered excessive and entered as regressors in first-level analyses. Additionally, vector files were created to indicate the onset timing for each condition of the event-related fMRI cue reactivity task. These first-level data were then evaluated across participants in second-level group analyses, using a fixed effects model.

Whole-brain analyses were conducted after the binarized DARTEL-derived sample-specific gray matter mask was applied. An overall significance level of $p<0.05$ corrected for multiple comparisons across the gray matter-masked whole brain was calculated. This was accomplished by first estimating the inherent smoothness of the masked functional data with the three-dimensional full-width-at-half-maximum module in AFNI ((R. W. Cox, 1996); AFNI version_17.0.03). This smoothness was then used in 10,000 Monte Carlo simulations of random noise at 3 mm3 through the gray matter masked data with the 3DClustSim module of AFNI (R. W. Cox, 1996).

Second-level analyses using one-sample t-tests were utilized to evaluate whole-brain activation to the contrasts of interest. Eight contrasts were specified: 1) Highly Processed Foods

> Minimally Processed Foods, 2) Minimally Processed Foods > Highly Processed Foods, 3) Highly Processed Foods > Household Items, 4) Household Items > Highly Processed Foods, 5) Minimally Processed Foods > Household Items, 6) Household Items > Minimally Processed Foods, 7) All Foods > Household Items, and 8) Household Items > All Foods. Preliminary findings suggested that the household items were highly rewarding across all participants, so akin to prior fMRI research using food pictures (Batterink, Yokum, & Stice, 2010; Brooks, Cedernaes, & Schioth, 2013), a fixation control condition was also included, which added six additional contrasts: 1) Highly Processed Foods > Fixation, 2) Fixation > Highly Processed Foods, 3) Minimally Processed Foods > Fixation, 4) Fixation > Minimally Processed Foods, 5) All Foods > Fixation, and 6) Fixation > All Foods. For all 14 contrasts, effects were considered significant at $p < .001$ with at least 44 voxels in the cluster (k). Effect sizes (*r*) were calculated from the Z-value using the formula: $Z/\sqrt{n}$.

In order to assess brain regions where fat or GL modulated neural activation to the food pictures, a separate set of vector timing files were created with fat and GL included as parametric modulators. Four contrasts were defined from these timing files: 1) Fat (positive), 2) Fat (negative), 3) GL (positive), 4) GL (negative). Second-level analyses compared main effects across participants, and effects were again considered significant at $p < .001$ with at least 44 voxels in the cluster (k). These four contrasts were added to the 14 defined above to total 18 contrasts for the main effect analyses in Aim 1.

Behavioral Wanting and Liking Ratings: For the wanting and liking ratings acquired after the fMRI scan, paired-sample t-tests were used to compare for highly processed foods with reported wanting and liking for minimally processed foods, respectively. Wanting and liking ratings for household items were also compared to that of both highly and minimally processed foods.

Associations of fMRI Cue Reactivity with Behavioral Wanting and Liking: Each participants' neural activation for significant peaks from the one-sample t-tests were extracted using SPM12. These data were then exported to SPSS 22.0 (SPSS for Windows, version 22.0, IBM-SPSS, Chicago, IL). Correlational analyses were used to explore associations between neural activity and wanting and liking ratings for highly processed foods, minimally processed foods, and household items.

3.1.2. Results

fMRI Cue Reactivity Task

Table 2 details the main effects observed across all contrasts.

Highly Processed versus Minimally Processed Foods

Highly processed, relative to minimally processed, foods exhibited decreased activation in the calcarine cortex (k=877 r=.82 (Figure 2); k=49, r=.55), fusiform gyrus (k=965, r=.79), and inferior temporal gyrus (k=76, r=.68). There were no regions where activation was significantly greater for highly processed, relative to minimally processed foods.

Highly Processed and Minimally Processed Foods versus Household Items

Highly processed foods showed decreased activation in the calcarine cortex, relative to household items (k=3969, r>1.0) (Figure 3). No regions demonstrated increased activation for highly processed foods, relative to the household items. Minimally processed foods, relative to household items, had higher activation in the middle temporal gyrus (k=112, r=.69) and less activation in the calcarine cortex (bilateral) (k>564 rs>-.98) putamen (k=453, r=-.73), and inferior (k=146, r=-.65) and middle (k=179, r=-.59) frontal gyri. Considering both highly processed and minimally processed foods together, food exhibited increased activation relative to household items in the middle temporal gyrus (k=163, *r*=-.66) and less activation in the calcarine cortex (k=3016, *r*>-1.0), insula (k>83 *r*s>-.60) (Figure 4), inferior frontal gyrus (k>108, *r*s>-.57) and inferior parietal lobe (k=49, *r*=-.57).

Highly Processed and Minimally Processed Foods versus Fixation

Highly processed foods vs fixation resulted in higher activation in the putamen (k=67, *r*=.64) (Figure 5) and precentral gyrus (k=319, *r*=.73) and less activation in the calcarine cortex (bilateral) (k>720, *r*>1.0). Minimally processed foods relative to fixation exhibited higher activation in the precentral gyrus (k=276, *r*=.63). When considering both highly processed and minimally processed foods together, food demonstrated elevated activation in the precentral gyrus (k=390 *r*=.72) relative to fixation and less activation in the occipital cortex (k=266, *r*=-.91), calcarine cortex (k=401, *r*=-.88), and lingual gyrus (k=70, *r*=-.67) compared to food.

Fat and GL

Table 3 illustrates the regions where fat and GL modulated neural activation to food pictures. Fat positively modulated activation to food pictures in the middle frontal gyrus (ks>52, *r*s>.55) and middle temporal gyrus (k=44, *r*=.51), and negatively modulated activation in the superior frontal gyrus (k=54, *r*=.57), occipital cortex (k=144, *r*=.55), middle cingulate (k=112, *r*=.53), and fusiform gyrus (k=78, *r*=.53). GL did not positively modulate activation to food pictures in any regions but negatively modulated activity in the middle cingulate (k=407, *r*=.68), calcarine cortex (k=584, *r*=.62), inferior frontal gyrus (k=1707, *r*=.61), middle temporal gyrus (ks>49, *r*s>.58), putamen (k=69, *r*=.59), OFC (k=44, *r*=.57), precuneus (ks>64, *r*s>.54), and inferior parietal lobe (k=271, *r*=.54).

<u>Behavioral Wanting and Liking Reports</u>

Highly processed foods were associated with significantly greater wanting ($t(42)=2.37$, $p=.02$) but not liking ($p=.07$) compared to minimally processed foods. Consistent with the expectation of using household items as a control group, wanting was higher for both highly processed ($t(42)=9.72$, $p<.001$) and minimally processed ($t(42)=9.39$, $p<.001$) foods relative to household items. Liking was also higher for both highly processed ($t(42)=7.90$, $p<.001$) and minimally processed ($t(42)=5.75$, $p<.001$) foods compared to household items.

Associations of fMRI Cue Reactivity with Behavioral Wanting and Liking

Food, Household Items, and Fixation

Self-reported wanting for highly processed foods was associated with less activation in the inferior frontal gyrus for all foods relative to household items ($r= -.33$, $p=.03$) and less activation in the calcarine cortex for highly processed food compared to fixation ($r=-.34$, $p=.03$). No significant associations were observed with liking for highly processed foods (*p*s>.06[4]), wanting for minimally processed foods (*p*s>.15), liking for minimally processed foods (*p*s>.08[5]), wanting for household items (*p*s>.13), or liking for household items (*p*s>.17).

Fat and GL

Self-reported wanting for minimally processed foods was negatively associated with activation in the parietal lobe peak where GL negatively moderated activation to food ($r=.34$, $p=.03$). In other words, individuals with more activation in the parietal lobe for high GL foods reported decreased wanting for minimally processed foods. There were no significant associations between peaks derived from the parametric modulator analyses with wanting for

[4] Trend-level associations were observed with greater activation in the fusiform gyrus for minimally processed compared to highly processed foods ($r=.29$, $p=.06$) and decreased activation in the calcarine cortex for household items compared to minimally processed foods ($r=-.28$, $p=.07$).
[5] Trend-level association was observed with greater activation in the middle temporal gyrus for minimally processed foods compared to household items ($r=.28$, $p=.08$).

highly processed foods (*p*s>.35), liking for highly processed foods (*p*s>.16), liking for minimally processed foods (*p*s>.13), or wanting for household items (*p*s>.27).

3.2 Aim 2

3.2.1. Data Analytic Plan

fMRI Data Analysis: For Aim 2, Analysis of variance (ANOVA) tests were utilized to examine whether individual differences emerged based on YFAS 2.0 food addiction categorization across all 18 contrasts defined for Aim 1. Both hunger and BMI were entered as covariates in the ANOVA models, and effects were considered significant at $p < .001$ with at least 48 voxels in the cluster (k).

Behavioral Wanting and Liking Reports*:* For Aim 2, one-way ANOVA tests were used to evaluate if the reported wanting and liking ratings, acquired after the fMRI task, for highly processed foods, minimally processed foods, and household items differed based on an individual's YFAS 2.0 food addiction categorization.

Associations of fMRI Cue Reactivity with Behavioral Wanting and Liking: Each participants' neural activation for significant peaks from the ANOVA analyses were again extracted using SPM12 and exported to SPSS 22.0. Given that these extracted peaks were differentially associated with neural activity based on YFAS 2.0 food addiction categorization, hierarchical linear regression modeling was used to assess not only the associations of each neural peak but also the interaction between neural activity and YFAS 2.0 food addiction categorization on wanting and liking ratings.

3.2.2. Results

fMRI Cue Reactivity Task

Table 4 details the differential associations for all contrasts of neural activity by food addiction categorization.

Highly Processed Versus Minimally Processed Foods

Individuals with YFAS 2.0 food addiction exhibited greater activation in the precuneus (k=50, η_p^2=.03) for highly processed, relative to minimally processed foods, whereas participants in the control group showed the opposite pattern of activation in this region (Figure 6). There were no regions where persons with YFAS 2.0 food addiction showed greater activation to minimally processed foods than controls, and no regions that control participants showed higher activation to highly processed foods than those with YFAS 2.0 food addiction.

Highly Processed and Minimally Processed Foods Versus Household Items

Control participants showed greater activation in the inferior frontal gyrus (k=112, η_p^2=.03) for minimally processed foods compared to household items. This region was also activated more for control participants when looking at both highly processed and minimally processed foods together, relative to household items (k=60, η_p^2=.03), likely driven by the association with minimally processed foods. There were no regions where persons with YFAS 2.0 food addiction exhibited greater activation to food (highly processed, minimally processed, or both) relative to household items, compared to controls. Additionally, control participants did not show elevated activation to household items compared to food (highly processed, minimally processed, or both), suggesting that the household item condition was particularly activating for individuals with YFAS 2.0 food addiction.

Highly Processed and Minimally Processed Foods Versus Fixation

No differences in neural activation by food addiction categorization emerged for any of the food versus fixation contrasts, providing support that the fixation condition may have been more equally neutral for those with and without YFAS 2.0 food addiction.

Fat and GL

For individuals with YFAS 2.0 food addiction, fat negatively modulated activation in the lingual gyrus (*x*=22, *y*=-62, *z*=-10; k=101, $p<.001$, $\eta_p^2=.03$) and for control participants, fat positively modulated activation in this region. There were no regions where GL differentially modulated neural activation for individuals with YFAS 2.0 food addiction versus control participants.

Behavioral Wanting and Liking Reports

Individuals with YFAS 2.0 food addiction reported greater liking for minimally processed foods (M=54.19, *SD*=22.56) compared to control participants (M=37.89, *SD*=21.83) ($F(1,41)=5.80$, $p=.02$). No significant differences by food addiction categorization were observed for wanting of minimally processed foods, or wanting and liking of highly processed foods or household items (all *p*s>.10). When looking only at persons with YFAS 2.0 food addiction, there was no significant difference between wanting ($p=.31$) or liking ($p=.67$) for highly processed versus minimally processed foods. In contrast, control participants exhibited significantly greater wanting ($t(21)=2.53$, $p=.02$) and liking ($t(21)=2.48$, $p=.02$) for highly processed foods compared to minimally processed foods. Both groups had higher wanting and liking ratings for highly and minimally processed foods compared to the household items (*p*s<.001).

Associations of fMRI Cue Reactivity with Behavioral Wanting and Liking

Hierarchical linear regressions were utilized to evaluate the associations between fMRI peaks and self-reported wanting and liking ratings. Separate hierarchical regression models specified the dependent variables of 1) highly processed food wanting, 2) highly processed food liking, 3) minimally processed food wanting, 4) minimally processed food liking, 5) household item wanting, and 6) household item liking. Step one of each model included YFAS 2.0 food addiction status and either the precuneus or inferior frontal gyrus peak extracted from the ANOVA. These variables were included in step two, along with an interaction term for the neural activity in the specified peak and YFAS 2.0 food addiction categorization, given that these fMRI peaks differ by YFAS 2.0 food addiction status. Neither the precuneus nor inferior frontal gyrus was significantly associated with any wanting or liking ratings (*p*s>.13), nor were the interaction terms with YFAS 2.0 food addiction status (*p*s>.08).

3.3 Aim 3

3.3.1. Data Analytic Plan

<u>Subjective Effect Reports:</u> HLM with robust standard errors was used to model the association of food characteristics (processing, and fat per gram/GL) with each subjective effect question at level one, and the influence of participants' presentation of an addictive-like phenotype and BMI on this association at level two.[6] The data informed three decisions related to the subjective effect report outcome measures. First, the subjective effect reports of liking, pleasure, and satisfaction were highly correlated (*r*s>.75, *p*s<.001). Given that these constructs are theoretically similar, a composite score, referenced moving forward as enjoyment, was developed by summing across these three variables. Second, the subjective effect questions of likelihood to purchase in the future and consume in the next week were also highly correlated (*r*=.87, *p*<.001) and conceptually related and were also summed into a composite score, referenced as intentions to consume in the future. Third, recent research using a similarly diverse

[6] Hunger was also included as a level-two variable in all models but was not a significant predictor for any level-one variable and did not alter the associations between YFAS 2.0 food addiction and BMI for any level-one variable. Thus, hunger was removed from all models to aid in ease of interpretation.

range of foods and food attributes (Schulte, Smeal, et al., 2017) demonstrated that the subjective effect reports of averseness and intensity were not differentially associated with highly processed versus minimally processed foods, with few foods reported as very aversive or not intense. As the current data also followed this pattern, these questions were excluded from further analyses.

Thus, the six outcome variables used in the HLM models were 1) craving, 2) enjoyment, 3) guilt, 4) loss of control, 5) intentions to consume in the future, and 6) likelihood to consume if offered for free. For each of the six outcome variables, HLM models were examined separately with 1) a dummy-coded variable of processed (highly processed or minimally processed) then 2) total fat grams per gram of food (grand centered) and GL for the presented serving size (grand centered) as level two variables[7]. For each model, the level one equation was examined first to evaluate whether significant variance existed among participants for the intercept and partial slopes. In each model, chi-square tests indicated significant variability for both the intercept and partial slope parameters (all $ps<.001$). However, in some models, fat and GL did not account for sufficient variance in the outcome measure at level one (e.g., guilt) and thus could not be treated as random effects. This may be due to a smaller sample size and may be improved through continued recruitment. In the current study, since the food items included represent only a sample of all foods, it was beneficial to treat fat and GL as random effects when possible, as this approach increases generalizability for the sample (included foods) on the population (all foods). However, since one of the study's theoretical questions is to examine individual differences in the influence of these food attributes on the outcome variable, the HLM approach was retained and fat or GL were treated as fixed effects when necessary and noted in the results section accordingly.

[7] Akin to the two other aims, fat and GL were retained as the food characteristics of interest, and unique associations with salt were not explored due to multicollinearity issues between salt and fat (r=.50, p=.002).

For each model, the intercept (β_0) reflects the model-predicted subjective effect rating for an minimally processed food (or a food with average fat content and GL). This is predicted for the average participant, defined as someone without YFAS 2.0 food addiction and of average BMI. The partial slopes ($\text{e.g.}, \beta_1$) reveal impact of processing (or fat and GL) on subjective effect ratings for the average participant[8]. Level two analyses were conducted with YFAS 2.0 food addiction (dichotomized) and BMI (grand centered). Effect sizes (Cohen's *d*) were calculated using the following formula ($2t/\sqrt{\eta}$). The HLM model equations were as follows:

Processing

Level-One Equation for Processing as a Predictor of Each Subjective Effect Report:

$$[SUBJECTIVE\ EFFECT] = \beta_0 + \beta_1 * (PROCESSING) + r$$

Level-Two Equations for Participant-Specific Predictors of Processing

$$\beta_0 = \gamma_{00} + \gamma_{01} * (YFAS2) + \gamma_{02} * (BMI) + \mu_0$$

$$\beta_1 = \gamma_{10} + \gamma_{11} * (YFAS2) + \gamma_{12} * (BMI) + \mu_1$$

Fat and GL

Level-One Equation for Fat and GL as a Predictor of Each Subjective Effect Report:

$$[SUBJECTIVE\ EFFECT] = \beta_0 + \beta_1 * (FAT) + \beta_2 * (GL) + r$$

Level-Two Equations for Participant-Specific Predictors of Fat and GL[9]

$$\beta_0 = \gamma_{00} + \gamma_{01} * (YFAS2) + \gamma_{02} * (BMI) + \mu_0$$

$$\beta_1 = \gamma_{10} + \gamma_{11} * (YFAS2) + \gamma_{12} * (BMI) + \mu_1$$

$$\beta_2 = \gamma_{20} + \gamma_{21} * (YFAS2) + \gamma_{22} * (BMI) + \mu_2$$

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[8] The magnitude of the partial slopes is dependent on the range of the variable. Given that fat grams per gram of each food had a smaller range than GL for the presented serving size, the magnitudes of the partial slopes for GL were larger. Rather, the *p* values and *d* values provide more translatable measures of effect size.

[9] For models where fat and/or GL were treated as fixed effects, the random error term for the β_1 and/or β_2 equations, respectively, (e.g., μ_2) was not included.

Ad Libitum Food Consumption: It was intended to utilize HLM to evaluate how a food's nutritional attributes influenced caloric consumption in the ad libitum task at level one and whether individual differences (e.g., YFAS 2.0 food addiction) altered the associations at level two, chi-squared tests revealed insignificant variance in the intercept and parameters to warrant HLM (all *p*s>.07). This may be attributed to many participants not consuming all, or even a majority of, the foods offered in the ad libitum task, which led to many empty cells in the dataset. In order to address this, summary scores were created for the amount of calories consumed from highly processed and minimally processed foods. Then, the following analyses were utilized: 1) paired-samples t-tests to investigate whether caloric consumption differed for highly processed and minimally processed foods, 2) one-way ANOVA to assess whether caloric consumption varied based on an individuals' YFAS 2.0 food addiction status and BMI, and 3) correlational analyses to evaluate whether caloric consumption of highly processed foods and minimally processed foods was associated with subjective effect reports (examining the average subjective effect rating (e.g., craving) for highly processed foods and minimally processed foods accordingly) for the overall sample. With respect to the third analysis, hierarchical regressions investigating the interaction between YFAS 2.0 food addiction status and subjective effect reports on the association with caloric consumption did not reach statistical significance, perhaps due to power issues. However, exploratory correlational analyses were conducted to examine descriptive differences in the associations between subjective experiences and caloric consumption those who met for YFAS 2.0 food addiction and then, separately, controls.

3.3.2. Results

Subjective Effect Reports

Table 5 summarizes the HLM findings for processing with all subjective effect reports, and Table 6 details the HLM findings for fat and GL with all subjective effect reports.

Craving

Processing: The model-predicted craving rating of an minimally processed food by the average participant (γ_{00}) was 28.98 on a scale from 0-100, although individuals with elevated BMI reported a significantly lower craving rating for minimally processed foods (γ_{02}=-1.09, *d*=-.70, *p*<.05). Highly processed foods were reported as being significantly more craved than minimally processed foods by the average participant (γ_{10}=11.58, *d*=1.03, *p*<.001), meaning that there was an average 11.58 point increase in craving ratings for highly processed foods compared to minimally processed foods. This association was particularly strong for individuals with elevated BMI when controlling for YFAS 2.0 food addiction (γ_{12}=2.06, *d*=1.34, *p*<.001), such that a one unit increase in BMI from the sample average was related to a 2.06 increase in a highly processed food's craving rating. YFAS 2.0 food addiction status did not significantly alter the positive association between craving ratings and highly processed food (*p*=.55).

Fat and GL: The craving rating for a food with average fat and GL by the average participant (γ_{00}) was 35.60. The average participant reported elevated craving for foods higher in fat (γ_{20}=27.72, *d*=.72, *p*=.04) but not GL (*p*=.41). BMI, when controlling for YFAS 2.0 food addiction, was associated with greater craving for foods with higher GL (γ_{12}=06, *d*=.74, *p*=.04) and trend-level for foods higher in fat (γ_{22}=4.14, *d*=.63, *p*=.07) No significant relationships emerged between fat content and GL with craving at level one or with YFAS 2.0 food addiction at level two.

Enjoyment Composite Score

Processing: For the average participant, the model-predicted rating (γ_{00}) was 91.83 on a scale from -100 to 300. Ratings were significantly higher for highly processed, relative to minimally processed foods, for the average participant (γ_{10}=69.82, *d*=1.78, *p*<.001), with highly processed foods being rated as 69.82 points greater than minimally processed foods. YFAS 2.0 food addiction was a positively associated with enjoyment ratings for minimally processed foods (γ_{01}=68.46, *d*=1.15, *p*<.01) but negatively associated with these ratings for highly processed foods (γ_{11}=-60.91, *d*=-.85, *p*=.02). In contrast, BMI was positively associated with enjoyment for highly processed foods (γ_{12}=7.98, *d*=1.26, *p*<.001)

Fat and GL: In this model, fat was treated as a fixed effect due to lack of variance on enjoyment ratings at level one. The model-predicted enjoyment rating for a food with average fat grams and GL by the average participant was 131.73, although this was significantly higher for individuals with YFAS 2.0 food addiction (γ_{01}=33.65, *d*=.86 *p*=.02). Fat was positively associated with increased ratings by the average participant (γ_{20}=143.60, *d*=.30, *p*<.001), although GL was not (*p*=.24). The positive association between fat and enjoyment ratings was particularly strong for individuals with elevated BMI (γ_{22}=.17.84, *d*=.27, *p*<.01). YFAS 2.0 food addiction was not a significant predictor at level two.

Guilt

Processing: The guilt rating of a minimally processed food by the average participant (γ_{00}) was predicted to be 4.78 on a scale from 0-100. The average participant reported significantly more guilt for highly processed foods than minimally processed foods (γ_{10}=13.02, *d*=1.03, *p*<.01), with an average 13.02 increase in guilt ratings for highly processed foods. This association was particularly strong for individuals with YFAS 2.0 food addiction when controlling for BMI (γ_{11}=31.13, *d*=1.46, *p*<.001), with persons exhibiting food addiction reporting an average guilt rating 18.11 points higher than a control participant (γ_{11}-γ_{10}=18.11). BMI did not significantly alter the positive association between guilt ratings and highly processed food (*p*=.24).

Fat and GL: In this model, both fat and GL were treated as fixed effects due to lack of variation with guilt at level one. The model-predicted guilt rating for a food with average fat grams and GL by the average participant was 12.22, though this was significantly higher for individuals with YFAS 2.0 food addiction (γ_{01}=19.49, *d*=1.10, *p*<.01). Fat (γ_{20}=1.05, *d*=.29, *p*<.01) and GL (γ_{10}=.43, *d*=.25, *p*<.01) were both positively associated with increased ratings by the average participant, but significantly more related for individuals with YFAS 2.0 food addiction (fat: γ_{21}=.1.95, *d*=.36, *p*<.001) and GL: γ_{11}=.99, *d*=.31, *p*<.001), when controlling for BMI. BMI was a non-significant level two predictor for fat or GL in this model (*p*>.06).

Loss of Control

Processing: The model-predicted loss of control rating for a minimally processed food by the average participant (γ_{00}) was 8.86 on a scale from 0-100. While the average participant did not report significantly higher loss of control for highly processed foods than minimally processed foods (*p*=.32), this association was trending towards significant for individuals with YFAS 2.0 food addiction (γ_{11}=15.65, *d*=.65, *p*=.07) when controlling for BMI. In other words the average loss of control rating for a highly processed food was 15.65 points higher for a person with YFAS 2.0 food addiction, relative to a control participant. BMI was not a significant level two predictor in this model (*p*=.72).

Fat and GL: In this model, fat was treated as a fixed effect due to lack of variance on loss of control ratings at level one. For the average participant, the model-predicted loss of control rating for a food with average fat grams and GL was 12.18, though this was higher for individuals with elevated BMI (γ_{02}=.99, *d*=1.35, *p*<.001). Fat was positively associated with increased ratings by the average participant (γ_{20}=.79, *d*=.24 *p*=.02) but GL was not (*p*=.94). YFAS 2.0 food addiction and BMI were not significant level two predictors for fat and GL in this model (*p*s>.06).

Intention to Consume Composite Score

Processing: The intention to consume rating for an minimally processed food by the average participant (γ_{00}) was 27.21 on a scale from -200-200, though this was significantly higher for individuals with YFAS 2.0 food addiction (γ_{01}=71.96, *d*=1.01, *p*<.01). While the average participant did not report significantly different intention to consume for highly processed foods than minimally processed foods (*p*=.45), individuals with YFAS 2.0 food addiction reported a significant negative association (γ_{11}=-109.86, *d*=-1.24, *p*=.001) when controlling for BMI. In contrast, participants with elevated BMI exhibited a significant positive relationship between intention to consume with highly processed foods (γ_{12}=10.51, *d*=1.26, *p*<.001) when controlling for YFAS 2.0 food addiction. Thus, participants with food addiction uniquely reported negative intentions to consume highly processed foods, whereas persons with elevated BMI endorsed positive intentions to consume highly processed foods.

Fat and GL: In this model, fat was treated as a fixed effect due to lack of variance on intention to consume ratings at level one. The model-predicted intention to consume rating for a food with average fat grams and GL was 36.11 for the average participant, although this was significantly higher for individuals with elevated BMI (γ_{02}=4.82, *d*=1.00, *p*=.01). GL (γ_{10}=-2.44, *d*=-.80, *p*=.03) but not fat (*p*=.22) was associated with decreased ratings by the average participant. For individuals with elevated BMI when controlling for YFAS 2.0 food addiction, intention to consume ratings increased with elevated fat (γ_{22}=.73, *d*=.38, *p*<.001) and GL (γ_{12}=.34, *d*=.76, *p*=.04).

Consume in the Future if Free

Processing: The model-predicted consume if free rating of an minimally processed food by the average participant (γ_{00}) was 32.63 on a scale from -100-100, though this was significantly higher for individuals with YFAS 2.0 food addiction (γ_{01}=44.23, *d*=1.40, *p*<.001) when controlling for BMI. The average participant reported greater consume if free ratings for highly processed foods than minimally processed foods (γ_{10}=26.07, *d*=1.38, *p*<.001). This association was particularly strong but negative for individuals with YFAS 2.0 food addiction when controlling for BMI (γ_{11}=-50.97, *d*=-2.04, *p*<.001). In contrast, participants with elevated BMI had a strong, positive association between consume if free ratings for highly processed foods (γ_{12}=3.61, *d*=1.45, *p*<.001).

Fat and GL: In this model, both fat and GL were treated as fixed effects due to lack of variation with likelihood to consume if free ratings at level one. For the average participant, the model-predicted consume if free rating for a food with average fat grams and GL was 47.52. Fat (γ_{20}=1.56, *d*=.27, *p*<.01) but not GL (*p*=.62) was associated with increased ratings for the average participant. However, individuals with YFAS 2.0 food addiction exhibited significant, negative associations between consume if free ratings with both fat (γ_{21}=-1.88, *d*=-.25, *p*<.01) and GL (γ_{11}=-1.27, *d*=-.22, *p*=.02), when controlling for BMI. The opposite association between fat and consume if free ratings was observed for individuals with elevated BMI (γ_{22}=.28, *d*=.40, *p*<.001) when controlling for YFAS 2.0 food addiction. BMI was not a significant level two predictor for GL in this model (*p*=.31).

Ad Libitum Food Consumption Task

Overall

On average, participants ate 256.86 calories (SD = 227.57; range = 0-934.66) during the ad libitum consumption task. Across all participants, the largest number of calories came from pizza (M=72.41, *SD*=115.20), cheese (M=49.78, *SD*=75.81), and chocolate (M=45.47, *SD*=112.68) (see Table 7 for an overview of calories consumed from specific foods, highly processed foods and minimally processed foods). As may be expected given the greater caloric density of highly processed foods, participants consumed more calories from highly processed foods (M=218.94, *SD*=213.10) than minimally processed foods (M=42.61, *SD*=42.26) (t (37)=5.41, *p*<.001).[10]

Individuals Differences

One-way ANOVA tests revealed no significant differences between the number of calories consumed from highly processed foods or minimally processed foods for individuals with YFAS 2.0 food addiction, relative to controls (ps > .44). ANOVA also revealed that participants with YFAS 2.0 food addiction consumed significantly more calories from bananas compared to controls (M=10.38, *SD*=13.36 and M=2.75, *SD*=7.43, respectively) (F (1,41)=5.43, *p*=.03). No other differences in caloric consumption emerged for specific food items. BMI was positively associated with calories consumed from highly processed foods (*r*=.36, *p*=.03) but not minimally processed foods (*p*=.52). Hunger was not significantly correlated with caloric consumption (*p*s > 53).

<u>Ad Libitum Consumption and Subjective Effect Reports</u>

[10] There was not a significant difference by weight for the amount of highly processed food versus minimally processed food consumed (p=.77). However, this may not be a clinically meaningful difference, as it is hypothesized that the added amounts of fat and refined carbohydrates that give highly processed foods a greater caloric density are rewarding and may drive overconsumption. Throughout the rest of the results pertaining to ad libitum consumption, nearly identical findings were observed by calories and weight, and thus only calories are presented.

Across all participants, caloric consumption from highly processed foods was significantly associated with the following average subjective effect report ratings for highly processed food: craving (r=.37, p=.02), enjoyment composite score (r=.33, p<.05), intention to consume composite score (r=.49, p<.01), and consume if free (r=.40, p=.02). Caloric consumption of minimally processed foods was not significantly associated with any average subjective effect report ratings for minimally processed foods (all ps >.14).

When looking only at individuals with YFAS 2.0 food addiction, caloric consumption from highly processed foods was significantly associated with the following average subjective effect report ratings for highly processed food: craving (r=.68, p<.01), enjoyment composite score (r=.61, p=.01), and intention to consume composite score (r=.63, p=.01). Additionally, caloric consumption from minimally processed foods was significantly associated with the following average subjective effect report ratings for minimally processed food: intention to consume composite score (r=.58, p=.02) and consume if free (r=.60, p=.02).

For control participants, there are no significant associations between caloric consumption from highly processed foods with any average subjective effect report ratings for highly processed foods (all ps > .09). Caloric intake from minimally processed foods was significantly associated with average consume if free ratings for minimally processed foods (r=.47, p=.03).

CHAPTER 4

DISCUSSION

4.1 Aim 1: Ambivalence as a Possible Moderator of Reward Responses for Food

4.1.1 Review of Findings

The fMRI cue reactivity data contrasted hypotheses predicting greater reward-related neural activation for highly processed food cues, relative to cues for minimally processed foods and household items. Rather, highly processed food cues yielded significant deactivation compared to minimally processed food cues in regions associated with visual attention (calcarine cortex) (Klein, Paradis, Poline, Kosslyn, & Le Bihan, 2000) and visual processing (inferior temporal gyrus) (Buckner, Koutstaal, Schacter, & Rosen, 2000). Considering both highly and minimally processed foods together, food cues showed deactivation relative to household items in areas implicated in reward (putamen, insula) (Kirsch et al., 2003), executive control (middle frontal gyrus) (Talati & Hirsch, 2005), semantic processing (left inferior frontal gyrus) (Poldrack et al., 1999) and visual attention (calcarine cortex). Further, fat and GL negatively modulated neural responses to food cues in reward-related regions, such as the middle cingulate, putamen, and medial OFC (Berridge & Kringelbach, 2015; Kirsch et al., 2003).

When the fixation cross was used as the control condition, highly processed food cues, relative to fixation, showed increased activation in the putamen, a reward region, and the precentral gyrus, a motor area (Stippich, Ochmann, & Sartor, 2002). Minimally processed food cues yielded greater activation in the precentral gyrus compared to fixation, and this was also observed considering all foods together. Lastly, all food cues, relative to fixation, exhibited deactivation in visual processing areas (occipital cortex, calcarine cortex, and lingual gyrus) (Zeki et al., 1991).

Consistent with hypotheses, the pattern of the behavioral wanting and liking ratings paralleled the incentive sensitization framework (Berridge & Robinson, 1995a). Participants endorsed greater wanting, but not liking, for highly processed foods, relative to minimally processed foods. With respect to drugs of abuse, wanting has been a greater predictor than liking for compulsive consumption (Berridge & Robinson, 1995a). Thus, the separation of wanting and liking observed only with highly processed foods parallels the incentive sensitization process for addictive substances.

In contrast to hypotheses, greater reported wanting for highly processed foods was associated with increased activation in visual attention regions (inferior frontal gyrus, calcarine cortex) for the control conditions (household items, fixation). Further, elevated reports of liking for the household items were related to increased activation in reward areas (e.g., middle cingulate) for high-fat or high-GL foods. These opposite associations contrast a multitude of literature in substance-use disorders that have demonstrated a close correlation between self-reported craving (wanting) and reward-related activation to drug-relevant cues (for a review, see (Chase, Eickhoff, Laird, & Hogarth, 2011)).

4.1.2 Possible Moderators: Ambivalence, Availability, and Motivation to Change Behavior

When compared to neutral (household item) cues, neural responses to food cues, particularly highly processed food cues, were associated with deactivation in regions that have been typically related to increased reactivity to food and drug cues (Kuhn & Gallinat, 2011;

Noori, Cosa Linan, & Spanagel, 2016; D. W. Tang et al., 2012). These contrasting findings may have been driven by the sample of women all with overweight and obesity, half of whom met criteria for YFAS 2.0 food addiction. This group may be particularly subject to weight loss attempts (Williamson, Serdula, Anda, Levy, & Byers, 1992) and weight stigma and discrimination (Lieberman, Tybur, & Latner, 2012; Puhl, Andreyeva, & Brownell, 2008). As such, it is plausible to consider that some of the present participants may experience ambivalence about highly processed foods, desiring to eat them for hedonic pleasure while trying to limit consumption due to negative consequences on physical health and body shape/weight (Stroebe, Mensink, Aarts, Schut, & Kruglanski, 2008). Additionally, it is feasible that individuals with higher body weight may also experience ambivalence about minimally processed foods, desiring to consume them in accord with weight loss goals but also wanting to eat the palatable, highly processed foods available in the modern food environment. In the current study, the observed discrepancy between behavioral wanting/liking reports and neural responses may suggest the presence of ambivalence towards the foods, which may have influenced neural responses to food cues.

Notably, ambivalence has been identified as an important moderator of neural responses to drug cues among individuals with substance-use disorders. In a particularly relevant study, Wilson and colleagues (2013) observed that self-reported ambivalence in smokers was associated with decreased reactivity to cigarette cues in reward (e.g., striatum) and visual attention (e.g., cuneus) regions, but not related to elevated activity in cognitive control (e.g., dlPFC). Wilson and colleagues (2013) discussed that having the cigarette available following the fMRI cue reactivity task likely amplified the effects of ambivalence, such that persons with high ambivalence given an opportunity to smoke exhibited blunted reward responses due to conflict about the impending availability of the drug. In the present study, this pattern of deactivation in reward regions without increased activity in cognitive control regions was also observed. Further, emphasizing the availability of the foods following the fMRI task may have similarly amplified ambivalence towards the foods.

The current approach decided to clearly express that the food items (and household items) would be available to participants following the fMRI task, in parallel with prior studies of drug cue reactivity (Hayashi, Ko, Strafella, & Dagher, 2013; McBride et al., 2006). In previous protocols of substance use disorders, the anticipated availability of the substance enhanced neural responses in regions related to reward and motivation (McBride et al., 2006) and increased behavioral reports for subjective craving (wanting) for the substance (Hayashi et al., 2013; McBride et al., 2006). While a recent review corroborated the utility of emphasizing drug availability among active users, the authors also suggested that active substance users that are ambivalent about their use may exhibit a blunted reward-related responses to drug cues (Jasinska et al., 2014). Thus, while it was expected that noting the foods' availability to participants in the present work would have amplified food cue reactivity and the cognitive process of interest, wanting, this may have had the reverse impact on individuals with greater ambivalence towards the foods.

In addition to ambivalence, motivation for behavior change may significantly alter neural responses to drug cues for individuals with substance-use disorders. For instance, individuals seeking treatment for substance-use have exhibited diminished reward-related neural responses compared to those who use freely (Brody et al., 2007; Grusser et al., 2004; S. J. Wilson, Sayette, & Fiez, 2004). Elevated reported motivation to decrease or quit substance use has also been associated with lower reward responses for drug cues (Prisciandaro, McRae-Clark, Myrick, Henderson, & Brady, 2014; S. J. Wilson, Sayette, & Fiez, 2012), particularly when the availability of the substance was emphasized (S. J. Wilson et al., 2012). While the current study excluded individuals who reported dieting or involvement in a formal weight loss program (e.g., Weight Watchers), there may have been individual differences in motivation to cut down on or abstain from certain foods that contributed to deactivation of reward responses to food cues for some participants.

This may speak to a unique consideration for problematic consumption of highly processed foods, such that motivation to change eating behavior may present more fluidly than substance use quit attempts. For substance-use disorders, “quit attempts” can be marked by distinct periods of abstinence, as it is logistically feasible to cut out all substance use. However, the central difference with problematic, addictive-like consumption of highly processed foods is the spectrum by which it can occur. While an individual could fairly reasonably abstain from the highly processed foods most associated with addictive-like eating (e.g., pizza, chocolate, ice cream) (Schulte et al., 2015), there is simply more gray area with respect to what constitutes a highly processed food. For instance, a turkey sandwich varies in being more closely categorized as a highly versus minimally processed food based on factors such as the type of bread (white versus whole wheat), toppings (cheese versus lettuce) and condiments (mayonnaise versus mustard) used. Thus, unlike existing substance-use disorders, complete abstinence from all highly processed foods may be less achievable. As such, for some individuals, most eating decisions may invoke ambivalence and a fluctuating level of motivation to satisfy their hedonic drive towards highly processed foods or eat more closely in accord with society’s value of thinness. If participants exhibited ambivalence in the present study, indicated by the opposite associations between neural cue reactivity and behavioral reports of wanting, then they may have been somewhat motivated to disengage reward-related responses to the food cues.

4.1.3 Putamen Activation for Highly Processed Foods, Relative to Fixation

In the present study, highly processed foods exhibited greater activation in the putamen, relative to fixation. The putamen is a component of the dorsal striatum, which is a region that has been closely implicated in habitual, compulsive reward responses in prior work of drug cue reactivity in active substance users (Engelmann et al., 2012; Vollstädt‐Klein et al., 2010) and food cue reactivity in individuals with obesity (Murdaugh, Cox, Cook, & Weller, 2012; Stoeckel et al., 2008). It may be that this association was only observed when comparing activation to fixation and not the household item control condition because the fixation was a more neutral stimulus. For instance, the household item cues may have been more salient to individuals with higher ambivalence to the food cues. In support, behavioral wanting reports for highly processed foods were associated with greater activation in visual attention regions for the household items. Nevertheless, the observed elevated putamen activation for highly processed foods does support the study hypothesis that these foods may be capable of triggering reward-related responses. However, in the majority of previous drug or food cue reactivity studies in individuals with substance-use disorders or obesity, respectively, have observed a wider network of reward-related activation than just one region (Engelmann et al., 2012; Murdaugh et al., 2012; Schacht et al., 2013; Stoeckel et al., 2008; D. Tang et al., 2012). The limited reward activation in this study may be due to the challenges of investigating only women with overweight or obesity.

For instance, in prior food cue reactivity studies in individuals with obesity, the control group of participants has frequently consisted of persons of normal weight (Jastreboff et al., 2013; Martin et al., 2010; Rothemund et al., 2007; Stice, Spoor, Bohon, Veldhuizen, & Small, 2008; Stoeckel et al., 2008). Inclusion of a normal weight control group may have increased the magnitude of main effects in reward regions for food, as half of the sample may have likely been less impacted by ambivalence towards the foods and desire to change their eating behavior. In contrast, these factors may have had varied influence on each of the present participants in a manner that increased individual differences and muddied the main effects. Notably, there may have been considerable individual variability in ambivalence, as the two items on the YFAS 2.0 that may index ambivalence ("I worried a lot about cutting down on certain types of food, but I ate them anyways" and "I really wanted to cue down on or stop eating certain kinds of foods, but I just couldn't") had a wide range of responses (M=5.05, *SD*=2.73, range=1-8 (full range) and M=4.44, *SD*=2.86, range =1-8 (full range), respectively). Since ambivalence and motivation to change behavior have been identified as moderators of neural reactivity to drug cues in substance-use disorders (Brody et al., 2007; Grusser et al., 2004; S. J. Wilson et al., 2013; S. J. Wilson et al., 2004), attempts to reduce variability of these factors in previous studies of drug cue reactivity may inform ways to improve upon the present approach.

4.1.4 Methodological Lessons Learned

Notably, prior work on substance-use disorders (Baumann & Sayette, 2006; Saladin, Brady, Graap, & Rothbaum, 2006) suggests that the neutral laboratory environment of the current study may have allowed for easier disengagement in participants motivated to do so. Not only were the stock-photo food cues in the present fMRI task minimally representative of environmental food cues (e.g., commercials, images with branding), but the experience of being in the MRI scanner is also novel. For instance, individuals are in a tightly enclosed space with a headcoil to view the food cues and inundated with sounds and pressures. Further, this tightly enclosed space may have triggered body image concerns among this sample of women with overweight or obesity. While reward responses in fMRI cue reactivity tasks have been associated with translatable outcomes (e.g., higher ACC response to cocaine cues predictive of time to relapse (Sinha & Li, 2007)), this approach may be susceptible to challenges of external validity. In the current study, the standardized visual cues and novel fMRI environment may have aided in blunting some individuals' reward responses to the highly processed food cues if they were ambivalent or motivated to cut down on their consumption.

As such, future studies may consider how to reduce ambivalence in a way that enhances, rather than deactivates, reward responses. Isolation of hedonic drive for highly processed foods may be achievable through approaches that more effectively override cognitive control and inhibitory efforts. One idea rooted in the incentive sensitization framework for substance-use disorders is the importance of presenting cues in context with drug use, including environment (e.g., in situations where use occurs), stimuli (e.g., consistent with preferred brand or delivery system), and/or mood (e.g., consistent with triggers for use like negative affect) (Berridge & Robinson, 2011). It follows that ways to enhance context to have more effectively triggered wanting in the current study may have been to use personalized food cues (e.g., guided imagery scripts for favorite food cues (Hommer et al., 2013)) and/or increase negative affect (e.g., stress) in participants. Indeed, stress induction has yielded high reward responses to drug cues and craving in persons with cocaine dependence (Duncan et al., 2007) and for food cues and elevated food cravings in adults with obesity (Jastreboff et al., 2013). In addition, similar to a priming dose, if participants consumed a standardized amount of a preferred highly processed food prior to the fMRI task, this may reduce their ambivalence by increasing hedonic drive for highly processed foods (Spencer & Fremouw, 1979). This approach may have be able to trigger an abstinence violation effect, akin to that seen in substance users (Collins & Lapp, 1991), in persons who had higher motivations to reduce consumption of these foods and perhaps subsequently elevated reward-related neural reactivity to these cues.

Another possible methodological approach to reduce ambivalence may have been to administer highly processed foods during the fMRI scan. This protocol was used in the only other neuroimaging study of a sample categorized based on YFAS food addiction (Gearhardt, Yokum, et al., 2011). While the present study decided to use visual cues in order to increase the breadth of foods included in the fMRI task, an advantage to consuming the food in the scanner is mandatory consumption, which likely reduces ambivalence and inhibition. The types of foods that can be delivered in the MRI scanner are limited to liquids (e.g., water, sugar-sweetened beverages) or semi-liquids (e.g., milkshake, smoothie) but could vary across food attributes (e.g., high or low in fat and GL). An approach that makes all participants consume the highly processed food(s) as part of the protocol may enhance reward reactivity by emphasizing the availability of the food, while minimizing individual differences in ambivalence and motivation to inhibit responses.

4.1.5 Limitations and Future Directions

The primary limitation of the present study is that ambivalence was not explicitly measured and thus the interpretations of the data are solely based on similarities with prior work where ambivalence was investigated. Given the speculation that ambivalence may significantly moderate the current findings, future studies exploring food cue reactivity in samples where ambivalence may be high (e.g., persons with obesity and/or YFAS food addiction) should consider evaluating this construct. Strobe and colleagues (2008) developed a 12-item questionnaire assessing ambivalence towards “palatable” foods (considered highly processed by the current definition). This measure could more concretely elucidate the contribution of ambivalence to food cue reactivity, wanting, and liking in future research. In addition, a state-based measure of motivation to change behavior (e.g., consume fewer highly processed foods) may be helpful to evaluate how this factor may influence neural and behavioral reward responses to food, akin to drugs of abuse. Another limitation is that the current approach prioritized internal validity (e.g., using a neutral environment/emotional state, stock photo food cues on white backgrounds) in a manner that may have compromised external validity. Thus, consistent with incentive sensitization perspectives of addiction, increasing contextual factors (e.g., personalized cues, negative affect) may more effectively override cognitive control and isolate hedonic drive for highly processed foods in future research.

4.1.6 Conclusions

Collectively, the present findings were largely inconsistent with hypotheses and prior research investigating fMRI cue reactivity in substance-use disorders. The observed deactivation towards highly processed food cues, as well as food cues generally, coupled with elevated reported wanting for these foods, suggests high levels of ambivalence in this sample of women with overweight or obesity. In support, the current data resemble previous studies in substance-use disorders where the sample exhibited greater ambivalence or motivation to decrease their drug use. The present work may speak to two central differences between drug use and highly processed food consumption. First, the vast availability of highly processed foods, coupled with the strong value of thinness in Western society, likely elevates ambivalence about food and eating behavior on a wider scope. Second, individuals may have more fluctuating motivations to change their eating behavior, as abstinence from all highly processed foods may be less feasible in the modern food environment. Thus, while ambivalence and motivation to reduce use are important moderators of neural and behavioral reward responses to drugs of abuse, these factors may have even greater influence with highly processed foods and warrant concrete evaluation in future research. In summary, the present findings do not necessarily provide evidence against the addictive potential of highly processed foods, but rather highlight the complex challenges of directly adapting empirical approaches of studying substance-use disorders to obesity and food addiction.

4.2 Aim 2: Food Addiction is Associated with Habitual, Compulsive Neural Responses to Highly Processed Foods

This study investigated whether YFAS 2.0 food addiction was differentially associated with neural and behavioral responses to food cues in a sample of overweight and obese women. In the fMRI cue reactivity task, individuals with YFAS 2.0 food addiction exhibited greater activation in the precuneus, a reward-related visual area (Engelmann et al., 2012), for highly processed, relative to minimally processed, food cues. There were no regions where control participants showed higher activation to highly processed food cues. Further, persons with YFAS 2.0 food addiction had significant deactivation in the left inferior frontal gyrus, a region implicated in semantic processing (Moss et al., 2005; Poldrack et al., 1999), for minimally processed food cues and all food cues, relative to household item cues. In contrast to hypotheses, those with YFAS 2.0 food addiction reported higher liking for minimally processed foods compared to control participants and no differences emerged for wanting or liking for highly processed foods. The behavioral reports of wanting and liking were not associated with neural activity in the precuneus or inferior frontal gyrus peaks.

4.2.1 Food Addiction Related to Precuneus Activation for Highly Processed Food Cues

The precuneus is a posterior visual region responsible for detecting stimuli salience and has been functionally connected to reward-related areas as the striatum and ACC (Engelmann et al., 2012; Hong et al., 2009). The function of the precuneus has generally been investigated as part of the default mode network, suggesting that increased engagement of this region may reflect episodic memory retrieval and self-perception (Cavanna & Trimble, 2006; Raichle et al., 2001). Thus, one possible explanation for elevated precuneus reactivity to highly processed food cues in individuals with YFAS 2.0 food addiction may be greater self-referential processing regarding the significance of these foods. For example, persons with YFAS 2.0 food addiction may have particularly salient memories and self-related judgments about highly processed foods.

While the precuneus has broadly been associated with the default mode network, recent research has specifically investigated the function of this region in the context of substance-use disorders, which may provide further insight for interpreting the present findings. Previous studies have observed strong precuneus activation to drug-specific cues in persons with alcohol-, tobacco-, and opioid-use disorder (Engelmann et al., 2012; Schacht et al., 2013; Yang et al., 2009), particularly when the drug has been available (McBride et al., 2006), interpreted to reflect an attention bias for drug-specific cues (Engelmann et al., 2012). In addition, it has been suggested that the precuneus may be functionally connected with reward regions through communication of the salience of visual stimuli in the environment (e.g., drug cues) to the striatum and ACC (Engelmann et al., 2012; Hong et al., 2009). Elevated activation in the precuneus to drug cues has been associated with clinical meaningful indexes, such as severity of tobacco- and alcohol-use disorders (Courtney, Ghahremani, London, & Ray, 2014). This association has piqued curiosity for whether the precuneus may be a region particularly susceptible to addiction-related neuroplastic changes (Courtney et al., 2014). Interestingly, precuneus responses to drug cues have not reliably correlated with reported drug craving (Courtney et al., 2014). As such, it has been suggested that precuneus activation may be triggered by a habitual cue response, prominent in individuals with more severe drug addiction, and may reflect a biological experience of craving (Courtney et al., 2014). This contrasts reward areas that have been associated with subjective craving reports, such as the insula, which relies on conscious, interoceptive information to increase craving (Naqvi & Bechara, 2010; Naqvi, Gaznick, Tranel, & Bechara, 2014).

In prior fMRI food cue paradigms, the precuneus has not been studied in as much detail as in drug cue reactivity tasks. The most notable findings relate to the precuneus deactivation for high-calorie (highly processed) food cues observed in individuals with obesity who have lost weight (Pursey et al., 2014) or undergone gastric bypass surgery (Ochner et al., 2011; Ochner et al., 2012). Akin to Courtney and colleagues' (2014) observations in substance-use disorders, this may similarly speak to the neuroplasticity of this region with respect to prolonged, possibly compulsive eating of highly processed foods. It may be that the precuneus response to highly processed food cues diminishes as excessive consumption of these foods decreases, which is required for weight loss or gastric bypass surgery.

In the current study, the elevated precuneus response to highly processed food cues was unique to individuals with YFAS 2.0 food addiction. Given previous work in samples of persons with substance-use disorders or obesity, this may suggest that, within the context of overweight and obesity, food addiction represents a severe phenotype of habitual craving for highly processed foods. Also consistent with Courtney and colleagues (2014), precuneus activation was not associated with behavioral wanting (craving) reports. Thus, akin to substance-use disorders, the elevated precuneus response in persons with YFAS 2.0 food addiction may reflect a greater biological craving response to highly processed, relative to minimally processed foods. Increased precuneus activation may represent fairly "raw" information about the rewarding salience of the highly processed food cues, before being subject to more conscious reward evaluation and cognitive control processes in functionally connected areas like the ACC. Notably, the precuneus may reveal the reward salience of highly processed foods before information about motivation is integrated and may thus be less influenced by ambivalence towards these foods or efforts to cut down on consumption.

Evidence for the possible role of ambivalence in persons with YFAS 2.0 food addiction is insinuated by no significant differences for wanting and liking for highly processed foods, relative to controls, but increased liking for minimally processed foods. This suggests that persons with YFAS 2.0 food addiction may be simultaneously habitually craving highly processed foods, demonstrated by the greater precuneus responses to these cues, while not endorsing greater wanting and liking. Interestingly, on a self-report index of how frequently participants typically consume each food cued in the fMRI task, no differences emerged for highly processed food consumption by YFAS 2.0 food addiction status ($p=.76$). In other words, despite no greater reported wanting or liking for highly processed foods, relative to controls, persons with addictive-like eating behavior tended to consume similar quantities of these foods, perhaps in a more compulsive manner. The contrast between reported wanting/liking and consumption frequency also supports the inherent ambivalence within YFAS 2.0 food addiction, as the phenotype is marked by being drawn to the hedonic nature of highly processed foods yet experiencing persistent, unsuccessful attempts to cut down on their consumption (Gearhardt et al., 2016a).

Further, the present findings for individuals with YFAS 2.0 food addiction are mostly consistent with the incentive sensitization theory, positing that compulsive drug use is maintained through habitual wanting rather than liking for the drug (Berridge & Robinson, 1995a, 2011). However, it may have been expected that self-reported wanting for highly processed foods would have been elevated in those with YFAS 2.0 food addiction, in parallel with precuneus activation signaling greater biological wanting. This may importantly illustrate the differences between habitual, unconscious wanting and conscious hedonic evaluation, with the former being more associated with YFAS 2.0 food addiction in the current study and compulsive substance use in prior research (Berridge & Robinson, 1995a; T. E. Robinson & Berridge, 2001).

It follows that one extension of the current findings may be to assess the precuneus' association with highly processed food consumption for individuals with YFAS 2.0 food addiction to more concretely assess its possible role in driving compulsive consumption. Further, longitudinal approaches may be useful in elucidating if the precuneus may exhibit neuroplastic changes resulting from prolonged, addictive-like consumption of highly processed foods, as has been suggested with respect to chronic drug abuse (Courtney et al., 2014). In addition, the present findings may suggest that intervention approaches used to reduce habitual craving in substance-use disorders may also be effective for the treatment of addictive-like eating, such as attentional retraining, which involves practicing with approach/avoid tests to reduce biases towards drug cues (W. M. Cox, Fadardi, Intriligator, & Klinger, 2014; Kerst & Waters, 2014; Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011).

Overall, the uniquely increased precuneus reactivity to highly processed, relative to minimally processed, food cues in participants with YFAS 2.0 food addiction parallels prior work in substance-use disorders and supports the incentive sensitization framework emphasizing the importance of habitual wanting in driving compulsive consumption. However, it may have been expected that other regions implicated in habitual wanting, such as the dorsal striatum

(Volkow et al., 2006), would have also been significantly more activated for those with YFAS 2.0 food addiction compared to controls. It may be that individuals with YFAS 2.0 food addiction are most responsive in the precuneus, reflecting more biological craving and thus not being as influenced by goal directed information (e.g., desire to cut down on consumption). Yet, prior studies observing elevated precuneus activation to drug cues in substance users have noted a wider range of reward response (e.g., striatum, insula) (Engelmann et al., 2012; Goldstein et al., 2007). This has also been observed for individuals with obesity in response to high-calorie (highly processed) food cues (Stoeckel et al., 2008), which raises question about how the present approach differs from prior work in samples with obesity that observed a range of cue-induced reward activation.

4.2.2 Comparison of the Present Work with Prior Studies

The current study was the first to explore a behavioral phenotype of overweight and obesity by recruiting participants based on whether or not they met YFAS 2.0 food addiction criteria. Only one prior study has explored fMRI cue reactivity in individuals with elevated symptoms of YFAS food addiction, which observed the hypothesized increase in reward regions (e.g, caudate, dlPFC) when anticipating a highly processed food cue (Gearhardt, Yokum, et al., 2011). In contrast with the current study, Gearhardt and colleagues' (2011) sample included 28 women ranging from normal weight to obese and categorized participants based on having 0-1 versus 3+ YFAS food addiction symptoms. Further, only two participants in this sample met the YFAS food addiction diagnostic score threshold of 3 or more symptoms plus clinically significant impairment or distress. Thus, the current study's inclusion of only women with overweight and obesity, with half meeting the YFAS 2.0 food addiction diagnostic threshold, is an improvement over Gearhardt and colleagues' (2011) work, as it allowed for comparisons focused on food addiction with less variance in BMI.

However, administering the highly processed food in the MRI scanner may be one possible advantage of Gearhardt and colleagues' (2011) approach that may have contributed to observing the hypothesized increased reward responses. Administering food during the fMRI cue reactivity task may have reduced ambivalence for how much participants desired to consume the cued food items, as they did not have the option to refrain from eating them. Given that ambivalence seems particularly influential for women with overweight, obesity, and/or YFAS 2.0 food addiction (Havermans, Giesen, Houben, & Jansen, 2011; Meule & Kubler, 2012; Nijs & Franken, 2012), administering food during the fMRI task akin to Gearhardt and colleagues (2011) may have not only elevated the main effects of highly processed food cues in reward regions but also may have increased potential to assess individual differences based on YFAS 2.0 food addiction status.

There have also been several studies that have used neuroimaging techniques to explore possible phenotypes within obesity by recruiting participants with or without BED. Interestingly, the approaches have often investigated neural correlates of behavioral economics (Balodis, Kober, et al., 2013) or impulse control (Balodis, Molina, et al., 2013) tasks, which may speak to the complexity of phenotyping food-specific psychological processes in individuals with elevated BMI. However, there have been two studies that employed fMRI cue reactivity paradigms to investigate differential neural responses in individuals with overweight or obesity, with or without BED.

First, Schienle and colleagues (2009) observed that individuals with overweight and BED, relative to those with only overweight, exhibited increased activation in the medial OFC when viewing highly processed food cues. The highly processed food cues may have elevated reward activation in the group with overweight and BED due to a 12-14 hour fast preceding the fMRI task, which has been shown to amplify reward reactivity (Siep et al., 2009). Additionally, allowing participants to passively view the food cues rather than emphasizing the availability of the food following the MRI scan may have reduced ambivalence. Second, Weygandt and colleagues (2012) found that greater activation to highly processed food cues in the ventral striatum differentiated whether individuals with obesity had BED. This study also involved passive viewing of the food cues and utilized pattern recognition analyses, rather than ANOVA techniques, to reveal which brain regions were uniquely associated with BED (Weygandt et al., 2012).

While these studies did vary in their approach relative to the current work, both found just one brain region that appeared to differentiate food cue reactivity patterns for those with and without BED in the context of overweight or obesity. Similarly, the present study observed that the precuneus may be particularly implicated in highly processed food cue reactivity for persons with YFAS 2.0 food addiction. Thus, the differences in neural responses to food cues between behavioral phenotypes of obesity may be highly specialized. For instance, individuals with obesity and BED may exhibit higher reward evaluation for food cues, evidenced by greater medial OFC activation (Schienle et al., 2009), whereas the current study reveals that individuals with overweight/obesity and YFAS 2.0 food addiction may experience more compulsive, habitual highly processed food consumption based on elevated precuneus responses. Nevertheless, akin to prior work phenotyping obesity based on BED (Schienle et al., 2009; Weygandt et al., 2012), future studies investigating neural food cue responses for those with YFAS 2.0 food addiction may consider allowing for passive viewing of the food cues. This may have more allowed to greater engagement of a wider range of reward responses (e.g., striatum, OFC) relative to the current approach of emphasizing the food's availability in a way that may have amplified ambivalence.

Considering food cue reactivity tasks more broadly, another methodological difference of previous studies that have observed greater activation to high calorie foods in individuals with obesity is the use of persons of normal weight as a control group (Jastreboff et al., 2013; Martin et al., 2010; Rothemund et al., 2007; Stice, Spoor, Bohon, Veldhuizen, et al., 2008; Stoeckel et al., 2008) or on a BMI spectrum ranging from lean to obese (Stice, Spoor, Bohon, & Small, 2008; Yokum et al., 2011). While this approach has provided important evidence for the overlapping neural circuitry in obesity and addiction (Volkow et al., 2008; Volkow et al., 2012), the heterogeneous origins of obesity (Wright & Aronne, 2012) limit the utility of using obesity as a proxy for problematic eating behavior. Thus, prior studies (Gearhardt, Yokum, et al., 2011; Schienle et al., 2009; Weygandt et al., 2012) and the present methodology of phenotyping within overweight and obesity may contribute to a more comprehensive understanding of mechanisms implicated in elevated BMI, identification of who these processes may be most relevant to, and the development of novel, targeted interventions.

If future research aims to understand food-related psychological processes that may vary based on a food addiction phenotype within obesity, then methodological recommendations may be gleaned from the present work. As described, administration of the food during the scan or passive viewing of the food cues may warrant consideration given their success in previous work exploring obesity phenotypes (Gearhardt, Yokum, et al., 2011; Schienle et al., 2009; Weygandt et al., 2012). Further, studies may also consider using fMRI tasks that effectively differentiate between persons with a substance-use disorder versus those who use the substance recreationally. These participant groupings may parallel persons with obesity and YFAS 2.0 food addiction, who exhibit behavioral indicators of addiction to highly processed foods, versus individuals with only obesity who do not report problems related to their highly processed food consumption. One approach that has differentiated between persons with alcohol-use disorder versus social drinkers is including a preload of alcohol consumption prior to the fMRI alcohol cue reactivity task. The preload seems to increase reward-related activation (e.g., nucleus accumbens, ACC, OFC) for alcohol cues and self-reported wanting (craving) in persons with alcohol-use disorder but not social drinkers (George et al., 2001; Myrick, Anton, et al., 2004), perhaps through reducing ambivalence by triggering an abstinence violation effect (Collins & Lapp, 1991). Thus, inclusion of a highly processed food preload may effectively reduce ambivalence in the current study in a manner that enhances individual differences in neural responses and behavioral reports of wanting and liking for highly processed foods.

4.2.3 Limitations and Future Directions

While the present work was novel in exploring a food addiction phenotype within overweight and obesity, there were several limitations that should be considered in the future. First, while the elevated precuneus responses to highly processed foods uniquely in individuals with YFAS 2.0 food addiction may suggest that these persons exhibit a habitual, biological craving for these foods, there were no other measures of unconscious wanting. Thus, future studies may consider integrating implicit tasks (e.g., Implicit Attitudes Test) to assess associations with precuneus responses for highly processed food cues and conscious, self-reported wanting and liking for these foods. Second, there was no assessment of ambivalence, which may not only have moderated main effects but may have been particularly relevant to persons with YFAS 2.0 food addiction. Ambivalence towards highly processed foods emerges from the current work as an essential construct to measure in future studies with samples of individuals with elevated BMI and/or YFAS 2.0 food addiction. Third, emphasizing the availability of the cued food items may have increased ambivalence, particularly in those with YFAS 2.0 food addiction, in a manner that diminished individual differences in more classic reward regions (e.g., striatum). As such, future research may implement methodology that has been effective in enhancing reward reactivity for food (e.g., passive viewing of food cues) or drug (e.g., preloading with substance prior to cue reactivity task) cues.

4.2.4 Conclusions

The current findings suggest that food addiction seems to reflect a unique behavioral phenotype within overweight and obesity. Individuals with YFAS 2.0 food addiction, relative to control participants, exhibited greater activation in the precuneus to highly processed food cues compared to minimally processed food cues. Similar precuneus responses have been observed in active substance users with respect to drug cues and may reflect greater habitual wanting (craving) of the substance. Thus, food addiction may represent a subtype of overweight and obesity marked by severe, biological craving for highly processed foods which may contribute to addictive-like eating of these foods. Further, persons with YFAS 2.0 food addiction may exhibit increased ambivalence towards highly processed foods, given the contrast between high precuneus cue reactivity but minimal self-reported wanting or liking of these foods. It is possible that the current approach of highlighting the availability of the food items following the scan may have increased inhibitory processes during the fMRI cue reactivity task among ambivalent participants, reducing reward-related activity and the potential to assess individual differences in these regions. As such, future studies may utilize paradigms that have been found to be differentially triggering to persons with substance-use disorders versus recreational users (e.g., administering a preload of the substance before the fMRI task) in order to further understand differences between persons with high BMI and YFAS 2.0 food addiction versus those with only elevated BMI. Nevertheless, the present work provides preliminary evidence that the food addiction phenotype is differentially associated with neural cue reactivity and self-reported wanting and liking for highly processed foods. This novel study represents an important step in elucidating mechanisms that may drive an addictive-like process to highly processed foods for some individuals and how this may contribute to the understanding of obesity.

4.3 Aim 3: Highly Processed Foods Exhibit Elevated Abuse Liability, Particularly for Those with Food Addiction

4.3.1 Subjective Effect Reports

Differential Associations for Food Items

Overall, highly processed foods were associated with greater reported craving, enjoyment, guilt, and likelihood to consume if offered for free. This supports Schulte and colleagues' (2017) work in a large, online community sample, which observed that highly processed foods were more closely associated with subjective effect report indicators of abuse liability than minimally processed foods. In the current study, fat and GL were similarly associated with subjective effect report questions as highly processed foods (fat associated with higher reported enjoyment, guilt, and likelihood to consume if free; GL related to more reported guilt and intention to consume in the future), which provides support that the amount, or "dose", of these attributes, and the rate in which carbohydrates are absorbed by the system may be important. However, a food's processing categorization emerged as the most significant attribute in determining abuse liability, perhaps because several minimally processed foods exhibited elevated fat (e.g., nuts) or GL (e.g., banana). Given that the combination of added fat and high

GL only occurs in highly processed foods (e.g., chocolate, pizza) and appears to be particularly important to abuse liability, processing category is the focus of this discussion.

The primary finding that highly processed foods were more associated with facets of abuse liability than minimally processed foods provides support for recent research suggesting that highly processed foods are most implicated in addictive-like eating behavior (Pursey et al., 2015; Schulte et al., 2015). Akin to prior research evaluating the abuse liability of drugs of abuse (Hatsukami et al., 2013; Henningfield & Nemeth-Coslett, 1988; Jaffe & Jaffe, 1989), highly processed foods were associated with a reported drive to consume more of the food and greater enjoyment and satisfaction. These indicators have been strongly related to future self-administration of addictive substances (Henningfield & Nemeth-Coslett, 1988; Jaffe & Jaffe, 1989), and may similarly index that highly processed foods are more likely to be consumed in a compulsive manner. Notably, minimally processed foods (e.g., fruits, vegetables, meat/fish) were found to have very little relationship to features of addictive potential, supporting the idea that foods vary in their abuse liability.

Relatedly, a recent debate in the field has been whether addictive-like eating may be best conceptualized as a substance-based food addiction versus a behavioral eating addiction (Hebebrand et al., 2014; Schulte, Potenza, & Gearhardt, 2017). The present data provide support for a substance-based framework of food addiction, where highly processed foods exhibited features of abuse liability not observed with minimally processed foods. If the behavioral, eating addiction hypothesis were supported, all foods would have been fairly equally related to subjective effect report indicators of addictive potential. However, the term ‘food addiction,’ reflecting a substance-based perspective, has been criticized as a misnomer (Vella & Pai, 2017), as it does not reflect growing evidence that highly processed foods may be most likely to have an addictive potential (Pursey et al., 2015; Schulte et al., 2015; Schulte, Smeal, et al., 2017). Thus, one implication of the current findings may be to refine the term to 'highly processed food addiction' in order to more accurately represent the state of the literature. In addition, future research is warranted to investigate how rewarding attributes of highly processed foods (e.g., added fat, high GL) may interact to increase the addictive potential of these foods for some individuals.

Individuals Differences: YFAS 2.0

Participants with YFAS 2.0 food addiction had a particularly strong, positive association between highly processed foods with reported guilt and trended towards significance on loss of control. In contrast, these individuals reported negative associations between highly processed foods with reported enjoyment, intention to consume in the future, and likelihood to consume if offered for free. Similar findings were observed with fat and GL (for both: positive associations for highly processed foods with reported guilt but negative associations with likelihood to consume if free), again suggesting the importance of the amount of these attributes and how quickly carbohydrates are absorbed in the system in elevating a food's abuse liability. However, processing category was again the strongest differentiating attribute.

Guilt and Loss of Control

The current findings parallel Schulte and colleagues' (2017) and suggest that reported guilt and, at trend-level significance, loss of control may be important components in the addictive-like consumption of highly processed foods. Although the association between highly processed foods and loss of control was subthreshold, the difference of individuals with YFAS 2.0 food addiction endorsing ratings about 15 points higher, on average, than control participants is clinically meaningful. Further, the timing of this question being asked after the ad libitum consumption period may have influenced this state-based response, as most individuals did not consume large quantities of highly processed foods during the task. Yet, loss of control, or consuming foods in greater quantities or over a longer period of time than intended, is a diagnostic criterion for substance-use disorders and thus also a symptom of food addiction as conceptualized by the YFAS 2.0. As such, the majority of participants with YFAS 2.0 food addiction endorsed typically experiencing loss of control over highly processed foods, even if their state-based self report on this index in the present study was only trend-level significant. Broadly, the unique association of reported loss of control with highly processed foods for persons with YFAS 2.0 food addiction is consistent with theoretical perspectives of this addictive-like eating phenotype and likely an important feature of abuse liability for highly processed foods.

In substance-use disorders, loss of control over use has often been coupled with increased guilt (Marlatt & George, 1984), where guilt has been thought to be a consequence of losing control, directly triggered in susceptible individuals by an addictive substance. While guilt has also been related to loss of control eating (e.g., binge eating) (Gormally, Black, Daston, & Rardin, 1982), traditional eating disorder perspectives have posited that guilt and cognitive perceptions (e.g., unhealthiness) of highly processed foods may be causal for loss of control eating (Rogers & Smit, 2000). Thus, one important next step is to identify the temporal relationships between affective states (e.g., guilt) and addictive-like, loss of control eating of highly processed foods. Indeed, one extension of the current study is utilizing ecological momentary assessment (EMA) to investigate this. Applying theories of substance-use disorders to food addiction, it may be expected that the highly processed foods have a direct role in prompting loss of control eating in persons with YFAS 2.0 food addiction, which then elevates guilt.

Enjoyment

The uniquely negative association between highly processed foods and reported enjoyment among participants with YFAS 2.0 food addiction is somewhat inconsistent with prior work on subjective experience in substance-use disorders that has observed greater reported enjoyment for addictive substances. One possibility is that a tolerance effect may have contributed, such that the small, seven-gram portion of each highly processed food was not sufficient to trigger a reward response akin to what may be experienced when eating these foods in an addictive-like manner. Yet, this finding supports this study's hypothesis for the role of incentive sensitization for those with addictive-like eating. This theory suggests that liking is not as strong of a driver for prolonged, compulsive consumption in those with addictive disorders and may decrease or remain stable over time (Berridge, 2009; T. E. Robinson & Berridge, 1993, 2001). In parallel, the negative association between reported enjoyment (liking) and highly processed foods was only observed for individuals with YFAS 2.0 food addiction and not for controls. However, consistent with incentive sensitization theory for the importance of wanting in driving compulsive consumption (Berridge, 1996, 2009), it may have been expected that reported craving (wanting) would have had a strong, positive association with highly processed foods for those with YFAS 2.0 food addiction, but this was not observed.

One possible explanation may be that the current sample size was underpowered to detect a significant association. Yet, given the more robust findings across other indexes of subjective experience, the data may indicate a methodological limitation. It may be that self-report measures of craving do not adequately capture the intense wanting that contributes to compulsive use for individuals with YFAS 2.0 food addiction who report a great deal of guilt and loss of control for highly processed foods. For instance, asking “how much do you want more of this [highly processed] food right now” may be met with ambivalence by those with addictive-like eating behavior, as they may be trying to avoid or cut down on these foods to prevent experiencing loss of control. As detailed above, the extension using EMA in this population may also be useful for capturing important individual differences related to craving and wanting. In addition, future research may consider utilization of implicit measures of wanting and liking (e.g., response time tasks).

Intentions to Consume in the Future and Likelihood to Consume if Free

Participants with YFAS 2.0 food addiction uniquely exhibited a negative association between highly processed foods with reported intentions to consume these foods in the future and if offered for free. These data may speak to the ambivalence these individuals have for highly processed foods, as they endorse loss of control consumption but report not intending to eat these foods in the future. These findings first suggest that persons with addictive-like eating behavior are endorsing intending to cut down or abstain from highly processed foods, which is also observed for individuals with substance-use disorders with respect to drugs of abuse when attempting to quit (Best, Ghufran, Day, Ray, & Loaring, 2008; Fagan et al., 2007). Notably, this is inconsistent with the personal responsibility narrative of problematic overeating (Kent, 2009; United States Surgeon General & Richmond, 1979), instead suggesting that highly processed foods may directly contribute to the problem despite an individual’s best intentions. In further support, participants with YFAS 2.0 food addiction reported a significantly stronger, positive association for their intentions to consume minimally processed foods, relative to controls.

These observations also demonstrate that restraint seems to have an important role in addictive-like eating, perhaps in a similar manner as substance-use disorders where individuals have attempted to cut down or abstain, albeit often unsuccessfully (Best et al., 2008; Fagan et al., 2007). Similar to guilt, restraint has been viewed from an addiction perspective as a consequence of loss of control caused by an addictive substance (Marlatt, 1979), whereas eating disorder frameworks have suggested that dietary restraint causes loss of control eating (Fairburn, 1995, 2008). Consistent with the substance-use disorder theories, the food addiction perspective hypothesizes that highly processed foods may be capable of altering neural and behavioral reward responses in persons susceptible to an addictive-like eating phenotype, which may drive loss of control eating (Gearhardt, Davis, et al., 2011). These individuals may then engage in executive control techniques like dietary restraint with highly processed foods in order to protect themselves from the foods' hedonic effects. While the reported negative intentions to consume highly processed foods may insinuate restraint, the present work did not include a specific measurement of this construct. However, a brief food frequency measure was administered for each of the foods in this task, and no significant differences were observed for how often individuals with YFAS 2.0 food addiction endorsed consuming these highly processed foods, relative to controls (p=.76). Given significantly lower intentions to consume these foods among those with YFAS 2.0 food addiction, this may suggest alternating periods of restraint and compulsive consumption. However, future research is needed to explore the seemingly important roles of dietary restraint and attempts to cut down/abstain from highly processed foods in persons with food addiction, with emphasis on longitudinal research to elucidate temporal associations.

<u>Individual Differences: BMI</u>

BMI altered the associations between highly processed foods and subjective effect reports in opposite directions as YFAS 2.0 food addiction. Individuals with elevated BMI exhibited strong, positive relationships between highly processed food and reported craving, enjoyment, intention to consume in the future, and likelihood to consume if free. Opposite findings as YFAS 2.0 food addiction were also found for BMI for the roles of fat (positive associations with reported enjoyment and intentions to consume in the future) and GL (positive associations with reported intentions to consume in the future). The associations with fat demonstrated that the amount of fat (e.g., "dose") elevated the rewarding nature of food in this group, however, the GL was less influential for those with elevated BMI.

The present data strongly suggest that obesity is not a sufficient proxy for problematic eating behavior. As the current approach isolated the unique associations of BMI versus YFAS 2.0 food addiction by controlling for each variable in the same statistical model, some overlap did exist since all participants had overweight/obesity with half exhibiting YFAS 2.0 food addiction. However, the data support that BMI and YFAS 2.0 food addiction are differentially related to the subjective effect report indicators of abuse liability. Notably, the associations unique to elevated BMI present a group of individuals who seem to report craving and enjoying highly processed foods and intending to consume them in the future. Further, important characteristics of an addictive-like phenotype seem to be absent, such as reported loss of control eating and guilt, the separation of craving (wanting) and enjoyment (liking), and efforts to cut down on or abstain from these foods. Although YFAS 2.0 food addiction has been observed across weight classes, there may be an overrepresentation among individuals with obesity (Gearhardt et al., 2016b; Hauck, Weiss, Schulte, Meule, & Ellrott, 2017). Given that researchers have recently called for more precise subtyping within obesity (Blundell, Dulloo, Salvador, &

Fruhbeck, 2014; Field, Camargo, & Ogino, 2013), the current work supports the utility of food addiction as a clinically useful behavioral phenotype.

4.3.2 Ad Libitum Consumption Task

Overall

Considering all participants, more calories were consumed from highly processed foods, relative to minimally processed foods, which may be expected given the greater caloric density from highly processed foods. In contrast to the study hypothesis, no differences in caloric consumption for either highly processed or minimally processed foods were observed based on YFAS 2.0 food addiction status. It was expected that individuals with YFAS 2.0 food addiction, relative to controls, would have consumed greater quantities of highly processed foods due to these foods being implicated in addictive-like eating (Schulte et al., 2015). In light of the subjective effect report data, these persons' eating behavior may have been influenced by the ambivalence they endorsed for highly processed foods, reporting loss of control eating and guilt but negative enjoyment and intentions to consume them in the future or if offered for free. It may have been that participants with YFAS 2.0 food addiction were able to utilize restraint to cut down on or abstain from these foods during the 15-minute ad libitum consumption period, in order to protect against loss of control eating.

Another possible reason that persons with YFAS 2.0 food addiction did not differ in eating behavior from controls may be the environment where the eating task occurred. This study presented the 14 food items in a neutral, non-cued environment to minimize biasing participants' consumption towards a particular type of food (e.g., cues for fast food may have encouraged consumption of highly processed foods). However, this was likely at significant expense to external validity, as the neutral environment may have allowed for persons with YFAS 2.0 food addiction to successfully use executive control to reduce or abstain from consuming highly processed foods. For persons with substance-use disorders, contextual factors, such as drug cues and negative affect (e.g., stress), may be key for overriding executive functioning mechanisms (Li & Sinha, 2008; T. E. Robinson & Berridge, 2001; Sinha, Catapano, & O'Malley, 1999), whereas these factors seem to have less influence on persons without substance-use issues (Myrick, Anton, et al., 2004; Pomerleau, Fertig, Baker, & Cooney, 1983). In parallel, cues and negative affect have been thought to motivate compulsive, hedonic overeating in susceptible individuals (Berridge, 2009; Berridge, Ho, Richard, & DiFeliceantonio, 2010) and seem to be mechanisms contributing to food addiction (Gearhardt, Yokum, et al., 2011; Pivarunas & Conner, 2015). Thus, future studies aiming to directly measure in-lab eating behavior of individuals with YFAS 2.0 food addiction may consider using an environment with cues for highly processed foods or invoking stress prior to the eating task. Given that cues and/or strong emotional states seem to be particularly relevant for addiction-prone individuals, this design may be more effective at elucidating individual differences. For the current study participants, eating behavior data, including the eating environment and emotional state, will be collected through the EMA extension study in order to increase external validity.

Although no significant differences emerged in ad libitum food consumption based on YFAS 2.0 food addiction status, BMI was positively associated with increased consumption of highly processed, but not minimally processed foods. This is consistent with greater associations between BMI with the subjective effect reports of intentions to consume these foods in the future or if offered for free. Further, this reiterates key differences between elevated BMI and YFAS 2.0 food addiction. Most notably, those with higher BMI do not seem to exhibit the distress and restraint around highly processed foods as observed for those with YFAS 2.0 food addiction.

Further, the neutral environment used in the ad libitum task seemed to have less influence on eating behavior for those with higher BMI, perhaps because these participants were not engaging executive control to limit their consumption of highly processed foods akin to those with YFAS 2.0 food addiction. In summary, in a neutral environment, BMI was more associated with consumption of highly processed foods. However, an individual's YFAS 2.0 food addiction status may be a more useful phenotype to investigate processes contributing to addictive-like eating, which may be more effectively exacerbated in a more triggering eating environment.

Associations with Subjective Experience

Overall, only highly processed food consumption during the ad libitum task was correlated with subjective experience, with positive associations with reported craving, enjoyment, intention to consume in the future, and likelihood to consume for free. These observations are consistent with prior work that has assessed subjective experience indicators of abuse liability for drugs of abuse (Hatsukami et al., 2013; Henningfield & Nemeth-Coslett, 1988; Jaffe & Jaffe, 1989) and supports that highly processed foods may have a greater addictive potential than minimally processed foods. While the sample size may have been underpowered to detect statistically significant interactions between YFAS 2.0 food addiction status and subjective effect reports in predicting ad libitum food consumption, fascinating descriptive differences emerged when examining each group independently.

When looking only at participants with YFAS 2.0 food addiction, highly processed food consumption during the ad libitum task was positively associated with reported craving, enjoyment, and intentions to consume in the future. Again, these findings are consistent with subjective experience studies of substance-use disorders, where craving and enjoyment have been important predictors of future self-administration (Henningfield & Nemeth-Coslett, 1988;

Jaffe & Jaffe, 1989). Notably, it appears that individuals with YFAS 2.0 food addiction who reported less ambivalence around highly processed foods (e.g., endorsing positive enjoyment and intentions to consume) ate more of these foods than those with higher ambivalence, as was endorsed on average in this group. This may suggest some heterogeneity within this participant group based on whether a person was actively "using" highly processed foods or trying to cut down on or abstain from them. These two states have been commonly observed in individuals with addictive disorders and may alter neural reactivity to addictive substances and behavior (McBride et al., 2006). Additionally, these states seem to be relatively unstable and malleable within a person based on contextual factors (e.g., highly cued environment) (Conklin, 2006; Larabie, 2005). Thus, the present findings may be broadly moderated by whether an individual with YFAS 2.0 food addiction was in a state of actively consuming or cutting down on highly processed foods. Direct measurements of this may be important for understanding nuanced cognitive-behavioral mechanisms underlying addictive-like eating.

For participants with YFAS 2.0 food addiction, there was also a significant, positive relationship between minimally processed food consumption in the ad libitum task with reported intentions to consume these foods in the future and likelihood to consume these foods if offered for free. Given that there was a significant, negative association between reported intentions to consume highly processed versus minimally processed foods for this group ($t(14)=-2.68$, $p=.02$), individuals with YFAS 2.0 food addiction who had more ambivalence for highly processed foods may have consumed greater quantities of minimally processed foods during the ad libitum task. This would also support the heterogeneity within this group based on whether a person was actively consuming versus cutting down on highly processed foods.

When examining only control participants, reported likelihood to consume minimally processed foods was associated with ad libitum consumption of these foods. Notably, no subjective experience indicators of abuse liability were significantly associated with consumption of highly processed foods. In parallel, prior work examining subjective effect reports for addictive substances has observed that subjective effect reports like craving and enjoyment are unique predictors of self-administration for individuals who exhibit problematic use (K. Preston & S. Walsh, 1998). As such, the associations between subjective effect reports with highly processed food consumption only for those with YFAS 2.0 food addiction provide evidence that the YFAS 2.0 is a valid tool for identifying persons who exhibit a phenotype consistent with an addictive-like response to these foods. Further, these findings demonstrate strong similarities between subjective experiences for drugs of abuse among individuals with substance-use disorders and subjective experience for highly processed foods for persons with YFAS 2.0 food addiction.

4.3.3 Limitations and Future Directions

There were several limitations to the present work that may inform future research directions. First, and perhaps most significant, was that a direct measure of whether a person was attempting to cut down on or abstain from highly processed foods was not included. The data suggest that there may have been heterogeneity within the YFAS 2.0 food addiction participants on this variable, which should be evaluated in future research to understand its influence on subjective experience (e.g., craving) and eating behavior. Second, some of the subjective effect report questions were asked after the ad libitum consumption task to reduce influence on eating behavior (see Appendix B), including loss of control. This may have decreased the range of scores on this index, as few participants consumed large quantities of highly processed foods in the ad libitum task. It may be that a state-based index of loss of control does not generalize sufficiently to typical engagement with various foods. Third, as described above, the neutral environment used in the ad libitum consumption task seemed to be ineffective at provoking overeating and addictive-like eating. Thus, subsequent studies evaluating eating behavior in YFAS 2.0 food addiction may implement contextual factors that are relevant to addictive-like consumption, such as an environment rich with highly processed food cues or invoking a stressor in participants prior to the eating period. Fourth, while 14 foods were utilized in the ad libitum task in order to have a range of food attributes (e.g., calories, fat grams), all participants only selected a few foods to consume. This created numerous empty cells in the data, which prevented utilization of HLM to model multilevel associations. As such, future research may consider reducing the number of foods available in an ad libitum task or have participants order from a menu with a higher number of options.

4.3.4 Conclusions

This study evaluated subjective experience indicators of abuse liability for highly processed and minimally processed foods in a sample of women with or without YFAS 2.0 food addiction. Subjective effect reports revealed that highly processed foods may have an elevated addictive potential, whereas minimally processed foods were not significantly related to facets of abuse liability. Additionally, individuals with YFAS 2.0 food addiction uniquely reported elevated guilt and loss of control for highly processed foods and decreased enjoyment and intentions to consume these foods in the future. This ambivalence suggests that mechanisms contributing to substance-use disorders, such as loss of control, incentive sensitization, and desire to cut down/abstain, may also be relevant to addictive-like eating. Importantly, an individual's BMI had opposite associations with highly processed foods as YFAS 2.0 food addiction status, endorsing minimal loss of control and guilt and increased enjoyment and intentions to consume these foods in the future. Thus, elevated BMI seems to be an insufficient proxy for problematic eating behavior, and the current data instead support the YFAS 2.0 food addiction phenotype as more clinically useful. Lastly, consumption of highly processed foods in the ad libitum task was predicted by subjective effect reports, particularly for those with YFAS 2.0 food addiction, consistent with prior work in substance-use disorders. Collectively, the present findings support that highly processed foods may exhibit an addictive potential, and YFAS 2.0 food addiction status was differentially associated with subjective effect report indicators of abuse liability and their ability to predict eating behavior.

TABLES

Table 1. Nutritional Characteristics of Taste Test Food Items

Food Item	Calories	Fat (g)	Carbohydrates (g)	Sugar (g)	Sodium (mg)	Protein (g)	Fiber (g)
Apple	3.7	0.0	1.0	0.7	0.1	0.0	0.2
Banana	6.2	0.0	1.6	0.8	0.1	0.1	0.2
Brown Rice	9.5	0.2	2.0	0.0	0.8	0.3	0.2
Carrots	2.9	0.0	0.6	0.4	4.8	0.0	0.2
Cashews	39.7	3.3	2.1	0.5	0.0	1.2	0.2
Cheese	25.7	2.1	0.2	0.0	56.0	1.6	0.0
Chips	40.0	2.5	3.8	0.3	42.5	0.5	0.3
Chocolate	34.1	2.0	4.3	3.9	6.0	0.5	0.2
Cookie	33.8	1.4	5.1	2.9	27.8	0.2	0.0
Cucumber	1.1	0.0	0.3	0.1	0.1	0.1	0.1
Granola Bar	26.3	0.6	5.5	2.0	23.3	0.3	0.1
Gummy Bears	22.1	0.0	5.2	2.9	6.4	0.6	0.0
Pizza	18.1	0.7	2.1	0.2	33.8	0.6	0.1
Pretzels	27.5	0.3	5.8	0.3	112.5	0.5	0.3

Note: all nutritional information reflects the standardized 7g portion used in the taste test task

Table 2. Main Effects for fMRI Cue Reactivity Contrasts

	x	*y*	*z*	# voxels in cluster	Activation cluster *Z*	$p_{uncorrected}$	p_{FDR}	Effect Size Z-value (*r*)
Minimally processed>Highly processed: increased activation								
Calcarine cortex	18	-94	4	877	5.24	<.001**	.01*	.82
	4	-58	12	49	3.55	<.001**	.43	.55
Inferior temporal gyrus	44	-64	-8	76	4.34	<.001**	.11	.68
Fusiform gyrus	-22	-78	-12	965	5.04	<.001**	.01*	.79
Household>Highly processed: increased activation								
Calcarine cortex	16	-92	4	3969	>8	<.001**	<.001**	>1.25
Minimally processed>Household: increased activation								
Middle temporal gyrus	-54	-52	2	112	4.43	<.001**	.10	.69
Household>Minimally processed: increased activation								
Calcarine cortex	-10	-94	-10	797	6.89	<.001**	<.001**	1.08
	16	-92	2	564	6.27	<.001**	<.001**	.98
Putamen	-34	-6	-6	453	4.65	<.001**	<.05*	.73
Inferior frontal gyrus	-48	-40	10	146	4.14	<.001**	.21	.65
Middle frontal gyrus	44	44	2	179	3.77	<.001**	.50	.59
All Food>Household: increased activation								
Middle temporal gyrus	-58	-64	10	163	4.20	<.001**	.20	.66
Household>All Food: increased activation								
Calcarine cortex	-10	-92	-10	3016	7.51	<.001**	<.001**	1.17
Insula	-42	10	0	354	4.32	<.001**	.15	.67
	50	14	-6	83	3.85	<.001**	.32	.60
Inferior frontal gyrus	42	44	0	234	4.03	<.001**	.29	.63
	-44	44	6	108	3.68	<.001**	.41	.57
Inferior parietal lobe	-54	-34	46	49	3.65	<.001**	.43	.57
Highly processed>Fixation: increased activation								
Putamen	20	14	4	67	4.08	<.001**	.56	.64
Precentral gyrus	56	4	26	319	4.65	<.001**	.19	.73
Fixation>Highly processed: increased activation								
Calcarine cortex	16	-92	2	883	7.24	<.001**	<.001**	1.13
	-16	-94	0	720	6.57	<.001**	<.001**	1.03
Minimally processed>Fixation:								

increased activation Precentral gyrus	58	6	28	276	4.03	<.001**	.83	.63
All Food>Fixation: increased activation Precentral gyrus	56	6	26	390	4.63	<.001**	.16	.72
Fixation>All Food: increased activation								
Occipital cortex	-16	-94	0	266	5.85	<.001**	<.001**	.91
Calcarine cortex	16	-90	2	401	5.61	<.001**	<.001**	.88
Lingual gyrus	-26	-70	-2	70	4.28	<.001**	.05*	.67

Note: *$p<.05$; **$p<.01$

Table 3. Fat and Glycemic Load (GL) as Modulators of fMRI Cue Reactivity

	x	*y*	*z*	# voxels in cluster	Activation cluster *Z*	$p_{uncorrected}$	p_{FDR}	Effect Size Z-value (*r*)
Fat: positively modulated activation to food in:								
Middle frontal gyrus	-32	56	14	52	3.62	<.001**	.84	.57
	-40	28	38	54	3.51	<.001**	.84	.55
Middle temporal gyrus	-56	-18	-14	44	3.24	<.001**	.84	.51
Fat: negatively modulated activation to food in:								
Superior frontal gyrus	22	-4	50	54	3.64	<.001**	.98	.57
Occipital cortex	40	-74	16	144	3.52	<.001**	.98	.55
Middle cingulate	4	26	34	112	3.39	<.001**	.98	.53
Fusiform gyrus	36	-54	-10	78	3.37	<.001**	.98	.53
GL: positively modulated activation to food in:								
No significant peaks	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
GL: negatively modulated activation to food in:								
Middle cingulate	10	-42	34	407	4.35	<.001**	.91	.68
Calcarine cortex	12	-80	12	584	3.94	<.001**	.91	.62
Inferior frontal gyrus	34	20	30	1707	3.93	<.001**	.91	.61
Middle temporal gyrus	56	-2	-22	49	3.93	<.001**	.91	.61
	60	-40	-4	370	3.73	<.001**	.91	.58
Putamen	-26	8	2	69	3.77	<.001**	.91	.59
Orbitofrontal cortex	12	44	-10	44	3.67	<.001**	.91	.57
Precuneus	-14	-66	58	64	3.59	<.001**	.91	.56
	-10	-44	68	76	3.55	<.001**	.91	.55
	6	-58	40	100	3.48	<.001**	.91	.54
Inferior parietal lobe	42	-48	54	271	3.43	<.001**	.91	.54

Note: *$p<.05$; **$p<.01$

Table 4. Differential Associations of Neural Activation by Food Addiction Categorization

	x	*y*	*z*	# voxels in cluster	Activation cluster *Z*	$p_{uncorrected}$	p_{FDR}	Effect Size (η_p^2)
FA>Control, Highly processed>Minimally processed: increased activation								
Precuneus	12	-52	62	50	3.90	<.001**	.71	.03
Control>FA, Minimally processed>Household: increased activation								
Inferior frontal gyrus	-38	36	16	112	4.03	<.001**	.79	.03
Control>FA, All Food> Household: increased activation								
Inferior frontal gyrus	-36	36	16	60	3.57	<.001**	.63	.03

Note: FA=YFAS 2.0 food addiction; *p<.05; **p<.01

Table 5. Hierarchical Linear Model Summary for Subjective Effect Reports by Processing Categorization

Parameter	Estimate	Std. Error	*t*-value	*d.f.*	*p*-value	*d*-value
Craving						
For Intercept, β_0						
Intercept, γ_{00}	28.98	3.83	7.57	35	<.001**	2.56
FA, γ_{01}	10.90	5.96	1.83	35	.08	.62
BMI, γ_{02}	-1.09	.52	-2.08	35	.05*	-.70
For Processing Slope, β_1						
Intercept, γ_{10}	11.58	3.79	3.06	35	<.01**	1.03
FA, γ_{11}	-3.56	5.89	-.60	35	.55	-.20
BMI, γ_{12}	2.06	.52	3.96	35	<.001**	1.34
Enjoyment Composite						
For Intercept, β_0						
Intercept, γ_{00}	91.83	14.59	6.29	35	<.001**	2.13
FA, γ_{01}	68.46	20.12	3.40	35	<.01**	1.15
BMI, γ_{02}	-3.23	2.07	-1.56	35	.13	-.53
For Processing Slope, β_1						
Intercept, γ_{10}	69.82	13.26	5.27	35	<.001**	1.78
FA, γ_{11}	-60.91	24.15	-2.52	35	.02*	-.85
BMI, γ_{12}	7.98	2.13	3.74	35	<.001**	1.26
Guilt						
For Intercept, β_0						
Intercept, γ_{00}	4.78	2.00	2.40	35	.02*	.81
FA, γ_{01}	1.70	3.51	0.48	35	.63	.16
BMI, γ_{02}	-.19	.31	-.61	35	.55	-.21
For Processing Slope, β_1						
Intercept, γ_{10}	13.02	4.26	3.05	35	<.01**	1.03
FA, γ_{11}	31.13	7.20	4.33	35	<.001**	1.46
BMI, γ_{12}	-.59	.48	-1.21	35	.24	-.41
Loss of Control						
For Intercept, β_0						
Intercept, γ_{00}	8.86	3.53	2.51	33	.02*	.87
FA, γ_{01}	-2.65	5.15	-.51	33	.61	-.18
BMI, γ_{02}	1.26	.83	1.51	33	.14	.53
For Processing Slope, β_1						
Intercept, γ_{10}	5.82	5.71	1.02	33	.32	.36
FA, γ_{11}	15.65	8.40	1.86	33	.07	.65
BMI, γ_{12}	-.47	1.32	-.36	33	.72	-.13

Intention to Consume Composite						
For Intercept, β_0						
Intercept, γ_{00}	27.21	18.92	1.44	33	.16	.50
FA, γ_{01}	71.96	24.71	2.91	33	<.01**	1.01
BMI, γ_{02}	-1.19	2.72	-.44	33	.67	-.15
For Processing Slope, β_1						
Intercept, γ_{10}	15.58	20.25	.77	33	.45	.27
FA, γ_{11}	-109.86	30.81	-3.57	33	<.01**	-1.24
BMI, γ_{12}	10.51	2.91	3.62	33	<.001**	1.26
Likelihood to Consume if Free						
For Intercept, β_0						
Intercept, γ_{00}	32.63	7.90	4.13	33	<.001**	1.44
FA, γ_{01}	44.23	11.00	4.02	33	<.001**	1.40
BMI, γ_{02}	-.85	1.09	-.78	33	.44	-.27
For Processing Slope, β_1						
Intercept, γ_{10}	26.07	6.59	3.96	33	<.001**	1.38
FA, γ_{11}	-50.97	8.69	-5.87	33	<.001**	-2.04
BMI, γ_{12}	3.61	.87	4.17	33	<.001**	1.45

Note: *p<.05; **p<.01

Table 6. Hierarchical Linear Model Summary for Subjective Effect Reports by Fat and Glycemic Load (GL)

Parameter	Estimate	Std. Error	*t*-value	*d.f.*	*p*-value	*d*-value
Craving						
For Intercept, β_0						
Intercept, γ_{00}	35.60	3.60	9.90	35	<.001**	3.35
FA, γ_{01}	8.86	5.07	1.75	35	.09	.59
BMI, γ_{02}	.08	.49	.17	35	.87	.06
For GL Slope, β_1						
Intercept, γ_{10}	.18	.22	.84	35	.41	.28
FA, γ_{11}	-.14	.31	-.46	35	.65	-.16
BMI, γ_{12}	.06	.03	2.19	35	.04*	.74
For Fat Slope, β_2						
Intercept, γ_{20}	27.72	12.99	2.14	35	.04*	.72
FA, γ_{21}	-1.61	20.98	-.08	35	.94	-.02
BMI, γ_{22}	4.14	2.24	1.85	35	.07	.63
Enjoyment Composite						
For Intercept, β_0						
Intercept, γ_{00}	131.73	9.79	13.46	35	<.001**	4.55
FA, γ_{01}	33.65	13.20	2.55	35	.02*	.86
BMI, γ_{02}	1.33	1.15	1.16	35	.26	.39
For GL Slope, β_1						
Intercept, γ_{10}	1.08	.90	1.19	35	.24	.40
FA, γ_{11}	-2.51	1.29	-1.95	35	.06	-.66
BMI, γ_{12}	.21	.12	1.72	35	.09	.58
For Fat Slope, β_2						
Intercept, γ_{20}	143.60	45.71	3.14	453	<.01**	.30
FA, γ_{21}	-77.01	64.39	-1.20	453	.23	-.11
BMI, γ_{22}	17.84	6.19	2.88	453	<.01**	.27
Guilt						
For Intercept, β_0						
Intercept, γ_{00}	12.22	3.75	3.26	35	<.01**	1.10
FA, γ_{01}	19.49	6.00	3.25	35	<.01**	1.10
BMI, γ_{02}	-.52	.50	-1.05	35	.30	-.35
For GL Slope, β_1						
Intercept, γ_{10}	.43	.15	2.77	488	<.01**	.25
FA, γ_{11}	.99	.28	3.47	488	<.001**	.31
BMI, γ_{12}	-.05	.03	-1.91	488	.06	-.17
For Fat Slope, β_2						
Intercept, γ_{20}	1.05	.33	3.16	488	<.01**	.29
FA, γ_{21}	1.95	.49	3.93	488	<.001**	.36
BMI, γ_{22}	-.01	.04	-.18	488	.86	-.02
Loss of Control						
For Intercept, β_0						

Intercept, γ_{00}	12.18	2.17	5.61	33	<.001**	1.95
FA, γ_{01}	6.29	3.94	1.60	33	.12	.56
BMI, γ_{02}	.99	.25	3.88	33	<.001**	1.35
For GL Slope, β_1						
Intercept, γ_{10}	.02	.23	.08	33	.94	.03
FA, γ_{11}	.44	.35	1.24	33	.23	.43
BMI, γ_{12}	-.04	.05	-.75	33	.46	-.26
For Fat Slope, β_2						
Intercept, γ_{20}	.79	.32	2.45	429	.02*	.24
FA, γ_{21}	1.07	.58	1.86	429	.06	.18
BMI, γ_{22}	.01	.09	.10	429	.92	.01
<u>Intention to Consume Composite</u>						
For Intercept, β_0						
Intercept, γ_{00}	36.11	12.02	3.00	33	<.01**	1.04
FA, γ_{01}	9.18	16.39	.56	33	.58	.19
BMI, γ_{02}	4.82	1.68	2.88	33	<.01**	1.00
For GL Slope, β_1						
Intercept, γ_{10}	-2.44	1.06	-2.31	33	.03*	-.80
FA, γ_{11}	-2.46	1.51	-1.63	33	.11	-.57
BMI, γ_{12}	.34	.15	2.17	33	.04*	.76
For Fat Slope, β_2						
Intercept, γ_{20}	1.54	1.58	.97	429	.22	.09
FA, γ_{21}	-3.93	2.09	-1.88	429	.06	-.18
BMI, γ_{22}	.73	.18	3.98	429	<.001**	.38
<u>Likelihood to Consume if Free</u>						
For Intercept, β_0						
Intercept, γ_{00}	47.52	5.33	8.92	33	<.001**	3.11
FA, γ_{01}	15.10	9.01	1.68	33	.10	.58
BMI, γ_{02}	1.21	.80	1.52	33	.14	.53
For GL Slope, β_1						
Intercept, γ_{10}	-.20	.40	-.50	462	.62	-.05
FA, γ_{11}	-1.27	.53	-2.39	462	.02*	-.22
BMI, γ_{12}	.07	.07	1.02	462	.31	.09
For Fat Slope, β_2						
Intercept, γ_{20}	1.56	.53	2.94	462	<.01**	.27
FA, γ_{21}	-1.88	.69	-2.73	462	<.01**	-.25
BMI, γ_{22}	.28	.06	4.28	462	<.001**	.40

Note: *p<.05; **p<.01

Table 7. Ad Libitum Caloric Consumption by Food Items and Food Groups

Food	Mean (Standard Deviation)	Range
Pizza	72.41 (115.20)	0-446.52
Cheese	49.78 (75.81)	0-335.38
Chocolate	45.47 (112.68)	0-553.96
Gummy Candy	26.14 (42.76)	0-157.93
Chips	16.86 (47.60)	0-293.66
Nuts	14.94 (34.76)	0-150.74
Cookie	11.95 (27.90)	0-110.74
Granola Bar	11.70 (24.26)	0-90.09
Apple	11.32 (21.12)	0-88.92
Banana	6.48 (11.29)	0-40.58
Brown Rice	4.24 (18.76)	0-121.77
Cucumber	3.09 (5.50)	0-24.09
Carrot	2.55 (5.95)	0-33.50
Pretzels	1.13 (4.41)	0-23.55
Total Highly Processed Foods	218.94 (213.10)	0-869.23
Total Minimally Processed Foods	42.61 (42.26)	0-157.30
Total All Foods	256.86 (227.57)	0-934.66

FIGURES

Figure 1. Example of Event-Related fMRI Cue Reactivity Trials

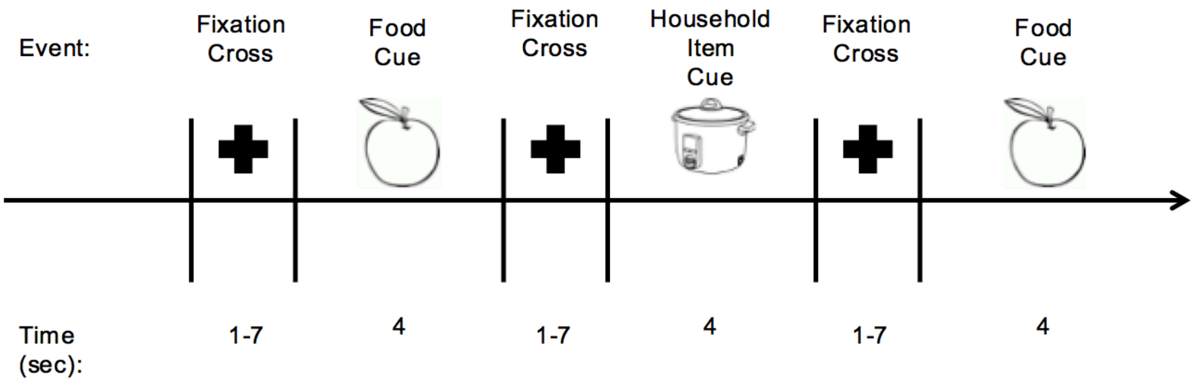


Figure 2. Axial section of deactivation in the calcarine cortex (18, -94, 4; *Z*=5.24; $p_{uncorrected}$<.001; $p_{FDR=}$.01) for highly processed (HP) versus minimally processed (MP) foods, with the bar graphs of parameter estimates from that peak.

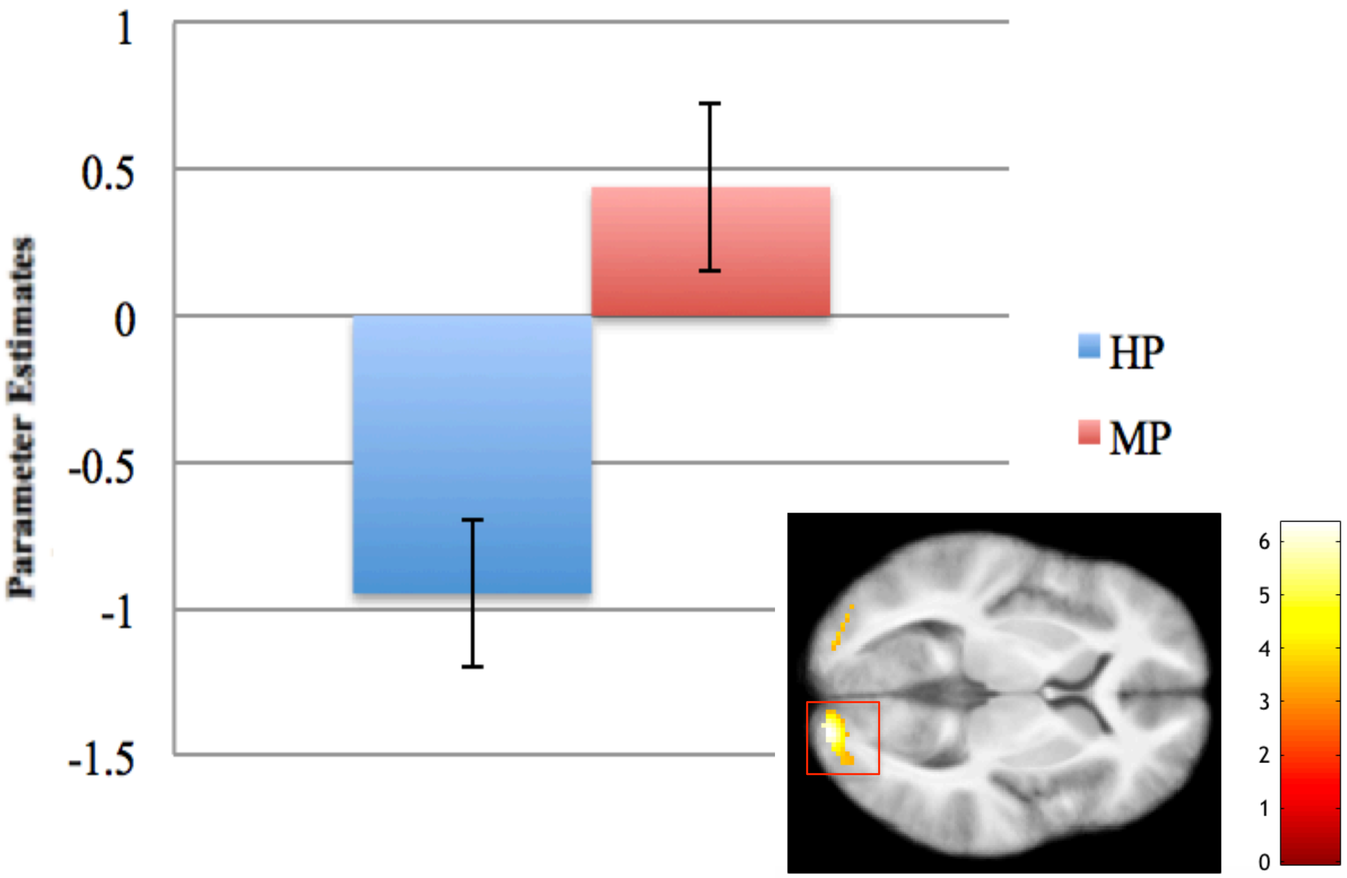


Figure 3. Axial section showing deactivation in the calcarine cortex (16, -92, 4; *Z*>8; $p_{uncorrected}$<.001; p_{FDR}<.001) for highly processed foods (HP) versus household items (HI), with the bar graphs of parameter estimates from that peak.

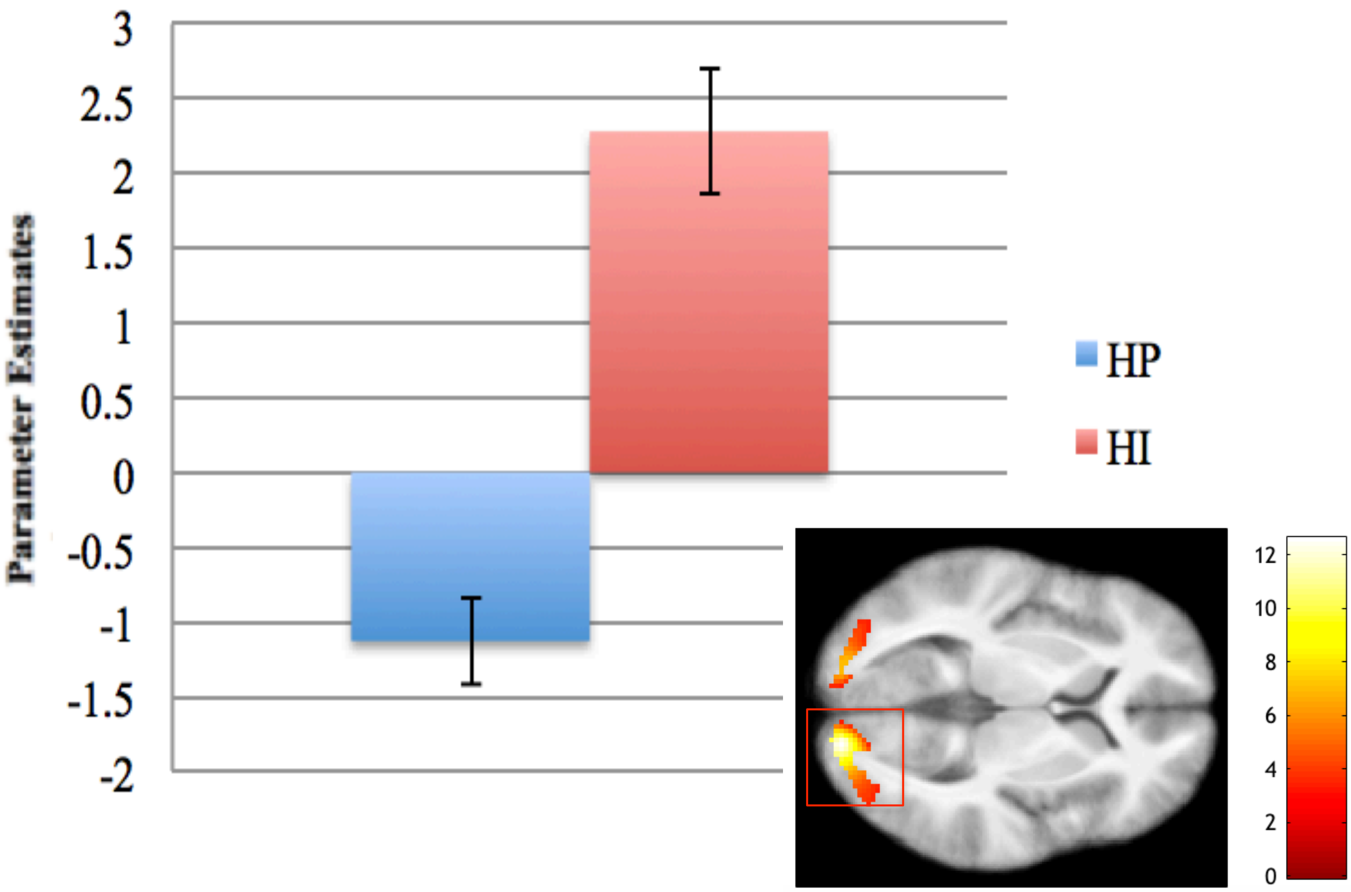


Figure 4. Coronal section of the insula (-42, 10, 0; Z=4.32; $p_{uncorrected}$<.001; $p_{FDR=}$.15) showing less activation for all foods (AF) versus household items (HI), with the bar graphs of parameter estimates from that peak.

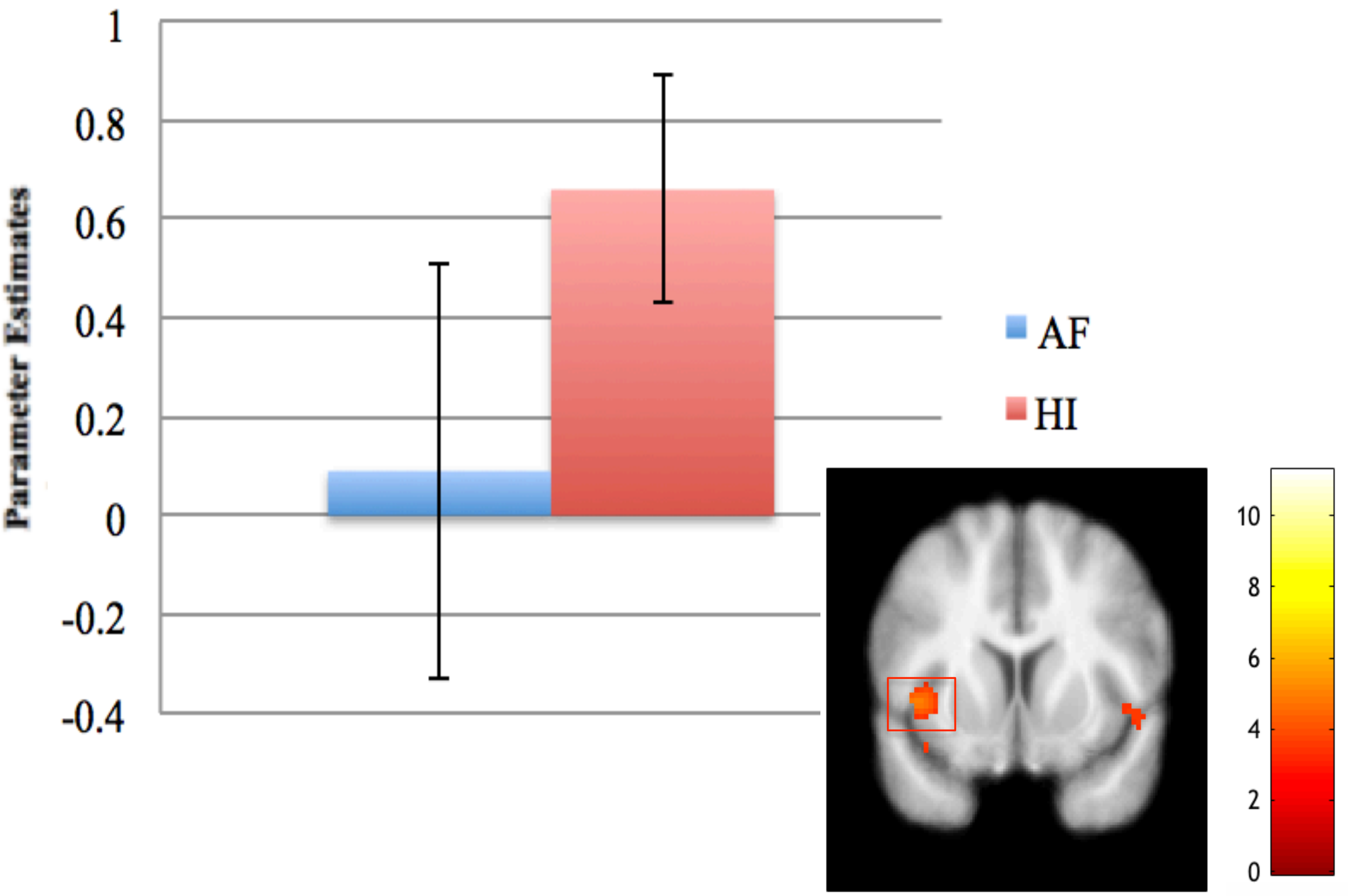


Figure 5. Coronal section of the putamen (20, 14, 4; Z=4.08; $p_{uncorrected}$<.001; $p_{FDR=}$.56) showing increased activation for highly processed foods (HP) versus fixation (FX), with the bar graphs of parameter estimates from that peak.

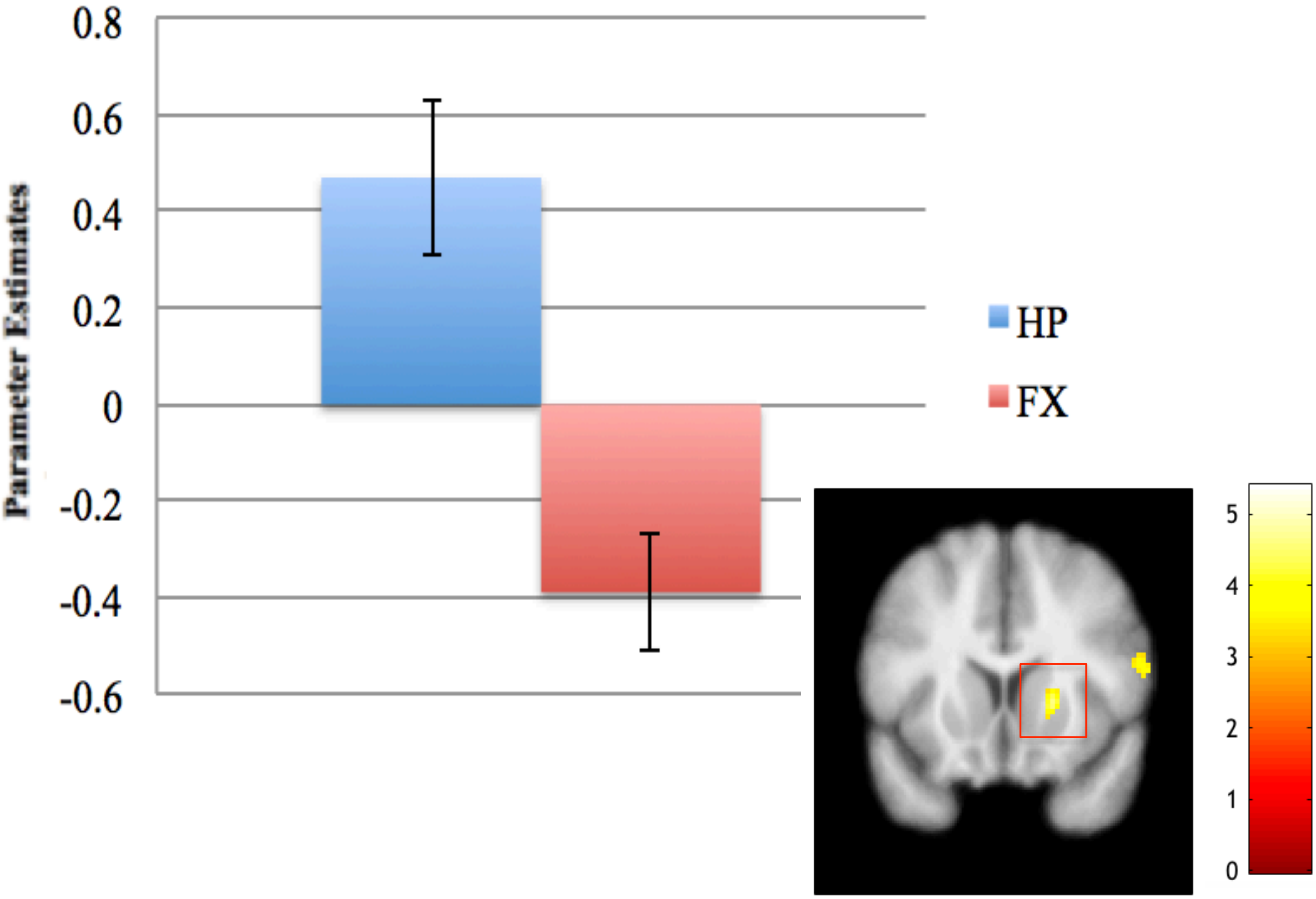
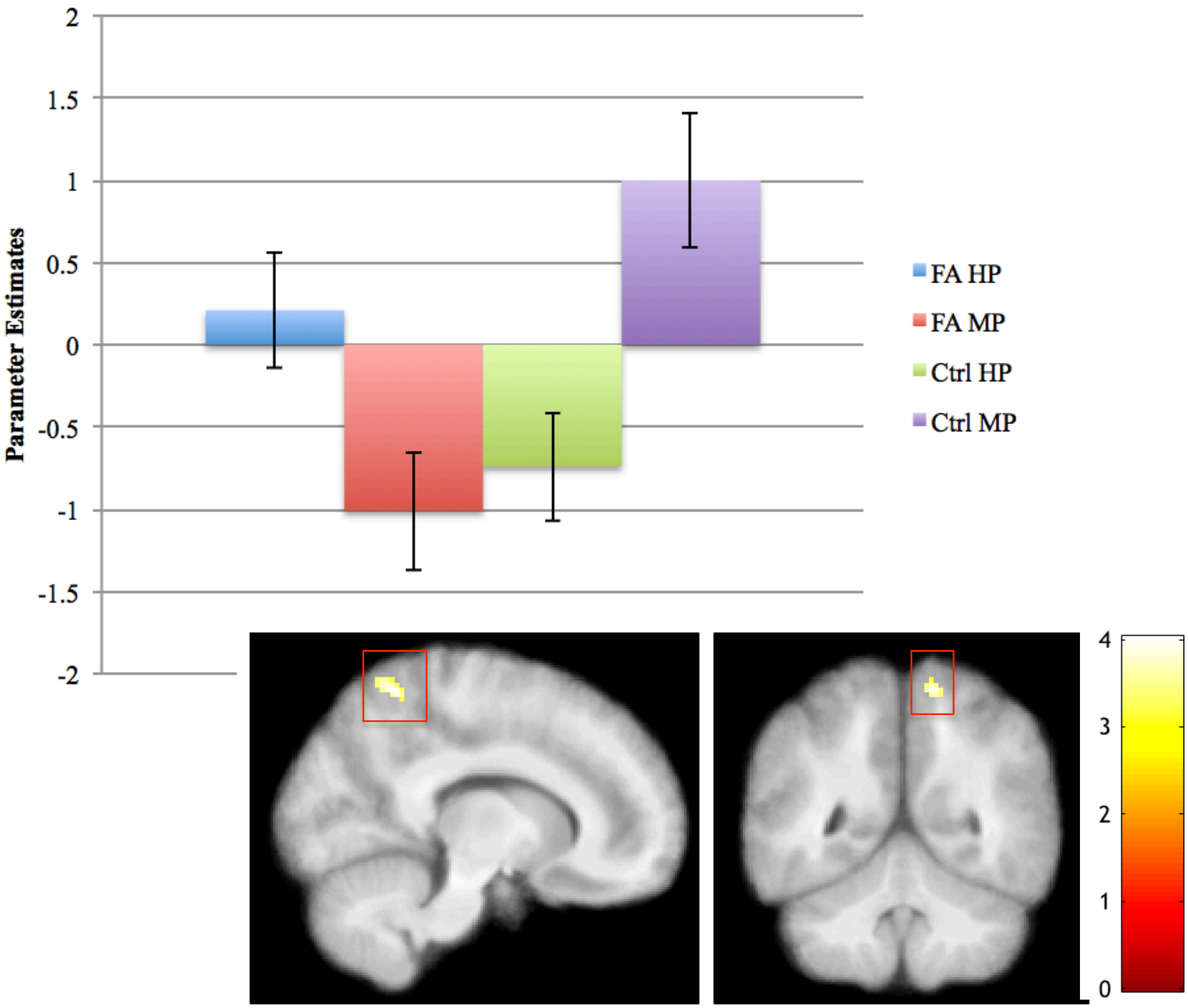


Figure 6. Sagittal and coronal sections of the precuneus (12, -52, 62; *Z*=3.90; $p_{uncorrected}$<.001; p_{FDR}=.71) during the fMRI food cue reactivity task (highly processed (HP) versus minimally processed (MP) foods) with greater activation in participants with YFAS 2.0 food addiction versus controls, with the bar graphs of parameter estimates from that peak.



APPENDIX A

The Yale Food Addiction Scale Version 2.0

This survey asks about your eating habits in the past year. People sometimes have difficulty controlling how much they eat of certain foods such as:

- Sweets like ice cream, chocolate, doughnuts, cookies, cake, candy
- Starches like white bread, rolls, pasta, and rice
- Salty snacks like chips, pretzels, and crackers
- Fatty foods like steak, bacon, hamburgers, cheeseburgers, pizza, and French fries
- Sugary drinks like soda pop, lemonade, sports drinks, and energy drinks

When the following questions ask about "CERTAIN FOODS" please think of ANY foods or beverages similar to those listed in the food or beverage groups above or ANY OTHER foods you have had difficulty with in the past year

All items are rated on the following scale:
0 = Never
1 = Less than monthly
2 = Once a month
3 = 2-3 times a month
4 = Once a week
5 = 2-3 times a week
6 = 4-6 times a week
7 = Every day

IN THE PAST 12 MONTHS:

1. When I started to eat certain foods, I ate much more than planned.
2. I continued to eat certain foods even though I was no longer hungry.
3. I ate to the point where I felt physically ill.
4. I worried a lot about cutting down on certain types of food, but I ate them anyways.
5. I spent a lot of time feeling sluggish or tired from overeating.
6. I spent a lot of time eating certain foods throughout the day.
7. When certain foods were not available, I went out of my way to get them. For example, I went to the store to get certain foods even though I had other things to eat at home.
8. I ate certain foods so often or in such large amounts that I stopped doing other important things. These things may have been working or spending time with family or friends.
9. I had problems with my family or friends because of how much I overate.
10. I avoided work, school, or social activities because I was afraid I would overeat there.
11. When I cut down on or stopped eating certain foods, I felt irritable, nervous or sad.

12. If I had physical symptoms because I hadn’t eaten certain foods, I would eat those foods to feel better.
13. If I had emotional problems because I hadn’t eaten certain foods, I would eat those foods to feel better.
14. When I cut down on or stopped eating certain foods, I had physical symptoms. For example, I had headaches or fatigue.
15. When I cut down or stopped eating certain foods, I had strong cravings for them.
16. My eating behavior caused me a lot of distress.
17. I had significant problems in my life because of food and eating. These may have been problems with my daily routine, work, school, friends, family, or health.
18. I felt so bad about overeating that I didn’t do other important things. These things may have been working or spending time with family or friends.
19. My overeating got in the way of me taking care of my family or doing household chores.
20. I avoided work, school or social functions because I could not eat certain foods there.
21. I avoided social situations because people wouldn’t approve of how much I ate.
22. I kept eating in the same way even though my eating caused emotional problems.
23. I kept eating the same way even though my eating caused physical problems.
24. Eating the same amount of food did not give me as much enjoyment as it used to.
25. I really wanted to cut down on or stop eating certain kinds of foods, but I just couldn’t.
26. I needed to eat more and more to get the feelings I wanted from eating. This included reducing negative emotions like sadness or increasing pleasure.
27. I didn’t do well at work or school because I was eating too much.
28. I kept eating certain foods even though I knew it was physically dangerous. For example, I kept eating sweets even though I had diabetes. Or I kept eating fatty foods despite having heart disease.
29. I had such strong urges to eat certain foods that I couldn’t think of anything else.
30. I had such intense cravings for certain foods that I felt like I had to eat them right away.
31. I tried to cut down on or not eat certain kinds of food, but I wasn’t successful.
32. I tried and failed to cut down on or stop eating certain foods.
33. I was so distracted by eating that I could have been hurt (e.g., when driving a car, crossing the street, operating machinery).
34. I was so distracted by thinking about food that I could have been hurt (e.g., when driving a car, crossing the street, operating machinery).
35. My friends or family were worried about how much I overate.

APPENDIX B

Subjective Effect Report Questions

Asked during the taste test protocol:
1. "How much do you crave this food right now?" a. 0 = no craving b. 100= extreme craving
2. "How much did you like the taste of this food?" a. -100 = dislike extremely b. 100 = like extremely
3. "How much pleasure did you experience while consuming this food?" a. 0 = no pleasure b. 100 = extreme pleasure
4. "How aversive did you find the taste of this food?" a. 0 = not at all aversive b. 100 = extremely aversive
5. "How guilty did you feel while consuming this food?" a. 0 = no guilt b. 100 = extremely guilty
6. "How intense was the taste of this food" a. 0 = not at all intense b. 100 = extremely intense
7. "Was this food satisfying?" a. 0 = not at all satisfying b. 100 = extremely satisfying
Asked after the ad libitum consumption task:

1. How out of control did you feel when consuming this food? a. 0 = not out of control at all b. 100 = extremely out of control
2. How likely are you to consume this food again in the next week? a. -100 = definitely will not consume again in the next week b. 100 = definitely will consume again in the next week
3. How likely are you to intentionally purchase this food in the future? a. -100 = definitely will not purchase this food b. 100 = definitely will purchase this food
4. How likely would you be to consume this food again in the future if it were offered to you for free? a. -100 = definitely would not consume this food b. 100 = definitely would consume this food

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