NEURAL RESPONSES OF YOUNG ADULT VAPERS TO FLAVORED VAPING PACKAGES AND THEIR SUBSEQUENT VAPING OUTCOMES

by

JOSHUA THOMAS MCMAINS

(Under the Direction of Lawrence Sweet)

ABSTRACT

Vaping is a growing threat to public health and there is much to learn regarding the factors that precede vaping initiation, maintenance, and potential escalation. Building upon prior research in the neuroscience of nicotine addiction, the current study utilized a novel functional magnetic resonance imaging (FMRI) approach to evaluate whether brain reactivity to vaping packaging predicts vaping frequency while also considering the potential moderating effect that trait food craving may have on this relationship. Overall, there were three core aims of the current study. First, we wanted to utilize a novel vaping packaging cue reactivity paradigm to functionally identify brain regions of interest (ROIs) that significantly respond to vaping packaging with either gray stimuli or colorful food stimuli. Second, we wanted to determine whether we could use the reactivity of these ROIs to both types of packaging to predict vaping outcomes (i.e., number of puffs on vaping devices reported in the four weeks following the initial study visit). Third, we wanted to assess whether the potential association between the ROIs reactivity to packaging and vaping outcomes was dependent upon an individual's self-reported level of trait food cravings. We identified 10 ROIs that exhibited the most robust significant reactivity to vaping packaging containing gray or colorful food stimuli. These ROIs are predominantly engaged in visual, language, and attentional processes. Analyses conducted from a sample of 59 young adult heavy vapers revealed that, in general, these ROIs were not predictive of vaping outcomes on their own. However, significant interactions between ROI reactivity to both types of vaping packaging and trait food craving were found to predict vaping outcomes. The interaction involving ROI reactivity to gray packaging was in the expected positive direction, but the interaction involving ROI reactivity to colorful food packaging was unexpectedly negative. The findings from this study contribute to our understanding of how the stimuli present on vaping packaging is processed, and how these neural responses can be used to predict vaping outcomes. Our findings may contribute to the development and guidance of evidence-based policies aimed at regulating the packages of vaping products.

INDEX WORDS: Vaping, Electronic Nicotine Delivery Systems, Packaging, Functional Magnetic Resonance Imaging, Young Adults, Food Cravings

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DEDICATION

This dissertation is dedicated to my wife, Rebecca, who has been a source of unwavering love, patience, encouragement, and support. I am truly thankful that you are my partner in life. I also dedicate this to my son, Thomas, for coming along during my final year of graduate school, brightening our lives daily, and providing the last bit of motivation I needed to complete this dissertation. I also dedicate this to my two dogs Oliver and Honey who were constant sources of unconditional love and support in the countless late nights working throughout graduate school.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

Problems stemming from substance use and misuse impact a sizable portion of the United States population, so understanding the factors that lead to the increased risk of substance use and its related problems is vital for prevention and treatment. Results from the 2022 National Survey on Drug Use and Health (NSDUH) found that an estimated 168.7 million people in the United States over the age of 12 used a substance (i.e., used tobacco products, vaped nicotine, drank alcohol, or used an illicit drug) in the month prior to being surveyed (Substance Abuse and Mental Health Services Administration [SAMHSA], 2023). In the United States, the fiscal impact of substance use and misuse is estimated to be over $740 billion annually – increasing each year – due to costs related to health care, lost productivity, and crime (National Institute on Drug Abuse, n.d.). Young adults (YA), defined as those between the ages of 18 and 25, are also at increased risk of substance use as they gain more independence (Arnett, 2007). This robust research finding has been recognized by the Annual National Survey on Drug Use and Health in publications also stating that substance use problems peak during this developmental period (SAMHSA, 2023). It has been concluded that increasing adult responsibilities and related stress can lead to increased substance use and begin patterns of negative health behaviors that extend into later adulthood (Rogers et al., 2021). Therefore, substance use prevention efforts have frequently focused on this critical period (Andsager et al., 2001; Arnett, 2007; Morgan et al. 2003; Rogers et al., 2021; Tan et al., 2018).

Cigarette smoking and nicotine vaping are two key contributors to overall substance use in the United States. Results from the 2022 NSDUH showed that an estimated 41.1 million people had smoked combustible cigarettes in the past month, while an estimated 23.5 million people had vaped nicotine with an e-cigarette or another type of vaping device (SAMHSA, 2023). The annual monetary impact on health care that cigarettes have are estimated to be over $225 billion, while vaping's impact is $15.1 billion and growing (Shrestha et al., 2022; Wang et al., 2023). It is noteworthy that cigarette smoking is declining overall (Schiller & Norris, 2023), yet vaping prevalence is rapidly increasing overall, with particularly accelerating increases among YAs (Farzal et al., 2019; Collins et al., 2019; Huang et al., 2019; Besaratinia & Tommasi, 2020).

Nicotine is a highly addictive chemical substance found in tobacco products like combustible cigarettes and vaping products (Grana et al., 2014; Perkins & Karelitz, 2013). Tobacco and nicotine routes of administration have significantly changed over the past century. Combustible cigarette use escalated in the first half of the 20th century and peaked in 1964 with approximately 42% of adults reporting that they were current smokers (Cummings and Proctor, 2014). From that point on, the number of cigarette smokers has steadily declined, and the number of adults who report being a current smoker fell to a historic low point in 2022 (11.2%; Schiller & Norris, 2023). A major contributor to this decline was an increase in the use of anti-tobacco advertisements and messaging beginning in 1967, and a ban on cigarette advertisements on television and radio by 1971 (Cummings and Proctor, 2014). With this increase in anti-tobacco messaging and the increasingly well-known known negative health outcomes associated with smoking cigarettes, including cancer, heart disease, stroke, and lung disease, public perception of cigarette smoking has become much less favorable (Mishra et al., 2015; Warren et al., 2014).

Despite increased public awareness of the negative health effects and declining numbers of cigarette smokers, it remains the leading cause of preventable death in the United States (U.S. Department of Health and Human Services, 2014). Prevalence differs by source, but it is clear that combustible cigarette smoking is decreasing while use of vaping products is rapidly increasing (Bandi et al., 2021; Pierce et al., 2023; Sanford et al., 2024), especially among the YA segment of the US population (Farzal et al., 2019; Collins et al., 2019; Huang et al., 2019; Besaratinia & Tommasi, 2020).

Electronic Nicotine Delivery Systems (ENDS)

E-cigarettes and other vaping devices are collectively known as electronic nicotine delivery systems (ENDS). ENDS may look like a combustible cigarette or a pen, but more commonly they resemble universal serial bus (USB) flash drives and come in both reusable and disposable configurations (Food and Drug Administration [FDA], 2023). These devices are typically battery-powered and hold a liquid containing nicotine known as “e-liquid” or colloquially as “vape juice” that is designed to be vaporized and inhaled (FDA, 2023; Raymond et al., 2018). The liquid in these devices varies widely among products, but the key psychoactive ingredient is usually cannabis or nicotine. Approximately half (54.2%) of adult vapers use products containing only nicotine, 7.4% use products that only contain cannabis, nearly a quarter (23.8%) use both cannabis and tobacco products, and 14.6% vape substances that contain neither (Mattingly et al., 2022). Among YA who vape, it is estimated that 37.3% vape nicotine only, 10.8% vape cannabis only, 30.5% vape both cannabis and nicotine, and 21.4% vape substances that contain neither (Mattingly et al., 2022). Non-cannabis vaping products nearly always include nicotine and often contain propylene glycol, vegetable glycerin, flavorings, and other additives (Glasser et al., 2017). Vitamin E acetate is an additive commonly found in aftermarket products that was tied to an increase in serious lung injuries in 2019 and highlights the often-unregulated side of developing and marketing of vaping products (Boudi et al., 2019; Soto et al., 2023). The amount of nicotine in these products varies as well, and labeling inaccuracies have shown that products may contain lower or higher levels of nicotine than advertised (Raymond et al. 2018). Some vaping products contain higher levels of nicotine than combustible cigarettes, which has amplified concerns about increasing the risk of nicotine addiction in vulnerable populations such as YAs (Grana et al., 2014).

Some consumers see ENDS as a safe tool for smoking cessation, but also as a replacement for combustible cigarettes. ENDS presents consumers with something that contains everything they may like about smoking while reducing many of the things they may not enjoy. These products have been marketed as a viable alternative to smoking because vapers would not smell like cigarette smoke or inhale the carcinogens that are well-known to be contained in combustible cigarettes (Ranjit et al., 2021; Shahab et al., 2017). ENDS vaping devices not only replace the method of nicotine delivery via cigarette, but they also maintain the ritualistic components of smoking (e.g., bringing one's hand to their mouth as part of the action of smoking) (Caponneto et al., 2012). In general, e-cigarettes are thought to be associated with fewer short-term negative health outcomes than combustible cigarettes; however, long-term effects are not as well known (NASEM, 2018). One known health concern associated with vaping is the fact that vapers are inhaling potentially toxic components contained in their e-liquid, including heavy metal particles (e.g., arsenic, chromium, nickel, and lead), formaldehyde, and acrolein (Glasser et al., 2017; Olmedo et al., 2018; Shahab et al. 2017).

E-cigarettes were introduced to the United States market in 2007 (Boudi et al, 2019). The popularity of e-cigarettes rose between 2014 and 2015, stabilized for a few years, and has increased every year since 2018 (Farzal et al., 2019). The e-cigarette company Juul Labs, Inc. was a major driver of this increased popularity in vaping by simplifying ENDS function and vape liquid production, in addition to unprecedented engagement in advertising, marketing, and promotions (Huang et al., 2019; Pennings et al, 2023). Their product could deliver almost twice the amount of nicotine compared to other vaping products at the time, which was comparable to a combustible cigarette (Rao et al., 2020). In fact, one Juul pod contains roughly the same amount of nicotine as a pack of cigarettes, but is easier to inhale (e.g., no coughing and wheezing) and thus easier to consume larger amounts of nicotine in a shorter period (Prochaska et al., 2022). While this new product was potent, the innovative social media marketing that took place was also thought to be a major contributor to the increased levels of vaping seen in adolescents and YAs (Collins et al., 2019; Huang et al., 2019).

Vaping has especially increased in popularity in both adolescent and YA populations over recent years and has become a common way for individuals to be introduced to nicotine products (Farzal et al., 2019; Jones & Salzman, 2020). Higher susceptibility for future vaping has been found in males and older youth (Bold et al., 2018). Vaping use in youth increased to a level in which it was labeled an epidemic in 2018 (Besaratinia & Tommasi, 2020). These vaping products are often flavored in appealing ways and marketed as safe alternatives to combustible cigarettes. While one in five high schoolers is thought to have tried vaping products at least once, elementary and middle school use has also been documented (Jones & Salzman, 2020). This is especially troubling as the long-term effects of vaping product use are not fully known and because nicotine use in adolescence can potentially lead to lifelong nicotine addiction (Birdsey et al., 2023). A significant portion of both adolescents and young adults who vape have been shown to be naïve to the level of nicotine in vaping products and the impact that it can have on their health (Golan et al., 2023; Morean et al., 2021). The 2023 National Youth Tobacco Survey has shown a small decline in use in high school students and an increase in middle school students, but this remains a public health concern because vaping products are the most used nicotine products by adolescents, and of those users approximately 1 in 4 use it daily (Birdsey et al., 2023). Additionally, use of vaping products with fruit and candy flavors in adolescents has been tied to long-term continued use (Leventhal et al., 2019). Therefore, vaping behaviors that begin in adolescence and increase long-term health risk are more likely to persist into young adulthood.

While the prevalence of vaping in adolescence is concerning, 24% of young adults are estimated to vape, and this is the highest percentage of any age group (SAMHSA, 2023). Vaping products are the most common tobacco product used by YAs, who frequently do not have a history of cigarette use (Cornelius et al., 2020). A known influence on increased vaping in YAs is marketing that specifically targets this age group on social media and other online advertising platforms (Huang et al., 2019; Kornfield et al., 2015). Over 70% of YAs endorse having been exposed to vaping marketing in the past month, which has been consistently found to be associated with increased experimentation and use (Chen-Sankey et al., 2019). Likely influenced by marketing, a boost in social status and group acceptance is often endorsed as a motive for vaping in YAs (Ranjit et al., 2021). The vast number of flavors is a motivator for initiation but can then serve as discussion points for these individuals and their peers as their use becomes more social in nature (Ranjit et al., 2021). Some YA vapers also report using flavored vapes to help curb their appetite and replace eating sweet foods, and limited evidence supports this notion that vaping flavored e-liquids lessens food cravings for sweet foods (Dyer et al, 2023). YAs have mixed perceptions of the overall safety of vaping and its efficacy as a smoking cessation tool, but those who are current users tend to endorse more positive perceptions (Kelsh et al., 2023).

E-cigarettes and other vaping products were initially advertised a healthier alternative to cigarettes and as a potential way to help with smoking cessation, yet there is still considerable debate about this relationship (Creamer et al., 2021; Glasser et al., 2017; Primack et al., 2018; Sanford et al., 2024). Evidence has been presented that vaping has the opposite gateway effect and facilitates the smoking of cigarettes even in never smoking individuals around 18 months after vaping initiation (Chapman et al., 2019; Primack et al., 2018). For instance, YAs who vape have five times as much increased risk of initiating cigarette smoking than those who do not vape (Primack et al., 2018). A model put forth by Soneji et al. (2018) estimated that 81 never-smoking adolescents and young adults who use vaping products would eventually become smokers for every one individual who quit smoking cigarettes with the assistance of e-cigarettes or other vaping devices.

Flavored ENDS

Flavors have become a key component to the marketing of e-cigarettes. The producers of these products not only want to make them satiating to consumers seeking nicotine, but also create a pleasant and enjoyable experience for any user (Leventhal et al., 2019). Towards this end, one way in which vaping differs from other nicotine products is with the vast number of flavors that exists with e-liquids including flavors that mimic high-calorie foods. There are over 14,000 estimated vape flavors available to consumers, with fruit and sweets (desserts and candy) flavors ranking among the most popular (Ma et al., 2022). Unlike cigarettes, flavored vaping products and advertisements feature salient and visually striking food cues that remain largely unregulated (Chadi et al., 2019).

Flavors, except mint/menthol have been long outlawed in cigarettes because they facilitate smoking initiation and increase addiction risk, especially children and young adults (Carpenter et al., 2005; Klein et al., 2008; Manning et al., 2009). Flavors in vape products are attractive and inherently rewarding to children and YA. Moreover, they are typically paired with nicotine in the vape solution, increase nicotine addiction risk, mask tobacco flavor, and influence appetite suppression effects of nicotine (Groom et al., 2020; Harrell et al, 2017; Kechter et al, 2022; Pepper et al., 2016; Romm et al, 2022).

Flavor attracts people while nicotine addicts them. Approximately 9 in 10 adolescent vapers are known to use flavored products, with fruit flavors being the most popular followed by flavors with candy, dessert, and other sweet themes, and mint/menthol (Birdsey et al., 2023). Flavor is often a primary reason for choosing to use a nicotine product in the first place, with 86% of YA vapers citing flavors as the reason for vaping initiation and escalation (Villanti et al., 2017). Vapers report higher levels of satisfaction when using flavored products (versus non-flavored), but also report higher self-perceived addiction to these products (Landry et al, 2019). Vapers who try and ultimately use a variety of flavors vape more and are more likely to smoke cigarettes (Lanza et al., 2020). Vaping advertisements with candy-like flavors have been shown to increase interest in purchasing and using vaping products in children (Vasiljevic et al., 2016). While not yet implemented on a larger scale, there is some evidence that standardized plain packaging can reduce the appeal that the colorful, flavor-themed packaging can have for youth, but this does not seem to have the same effect on adults (Simonavičius et al., 2023; Taylor et al., 2023).

Tobacco (and thus nicotine) have a historical relationship with weight management, and research has shown that some vapers may vape in or to help control their appetite and lose weight (Kechter et al., 2022). Some vapers report using food-related flavors of e-liquid as an alternative way to satisfy their food cravings because they may taste similar enough and are essentially calorie-free (Kechter et al., 2022). Women have been found to be more likely to use flavored vaping products to satisfy food cravings (Goldberg & Cataldo, 2018). With food cravings potentially satiated by flavors in addition to the known appetite-reducing effects of nicotine, there may be a decreased level of food consumption observed initially, but this may only serve to increase food and nicotine cravings long term (Dobbie et al., 2020; Kechter et al., 2022).

Like nicotine contained in e-liquid, flavors in vape products are also inherently rewarding and both result in craving, a construct often included in addiction research that refers to an intense urge and motivation to seek out and obtain a particular substance (Hormes & Rozin, 2010). High-caloric sweet foods and fruits are commonly craved foods (Meule, 2020a). Food cravings are commonly experienced by the general population, and not considered addictive behavior unless there is a loss of control over one's eating behavior (Meule & Kübler, 2012). Food craving is a multifaceted experience that can be separated out into two main types of craving. State food craving occurs when an experience of food craving is temporary whereas trait food craving represents a more stable experience of the frequency and intensity of general food cravings (Meule, 2020b). Current levels of hunger can affect the ratings of state food cravings, so trait food craving may be a better measure of stable food cravings where state-dependent variables cannot be controlled (Meule et al., 2014).

Though not always supported in research studies, there is strong evidence for the involvement of common neural pathways underlying craving for both addictive substances and food (Pelchat, 2002). It is widely accepted that nicotine acts on the dopamine pleasure and reward circuits in the brain and can alter the normal development of the brain (Castro et al., 2023; De Biasi & Dani, 2011). Long-term nicotine intake can also lead to mood changes, anxiety, social withdrawal, and make adolescents lose interest in school and extracurricular activities (Iniguez et al., 2009; Kutlu & Gould, 2015; Martin & Sayette, 2018; Wiener et al., 2020). Understanding how flavors in vape products play a role in craving these products is important to minimize initiation and escalation and the negative impacts of nicotine in vulnerable populations.

Functional MRI to Study Substance Use and Addiction

Functional MRI (FMRI) is a valuable tool for studying substance use and addiction due to the known impacts that both have on brain development and functioning (Courtney et al., 2024; Suckling & Nestor, 2017). FMRI is an indirect measure of neural activity that relies on changes in blood flow and relative oxygenation that follows changes in neural demands associated with neuron activation. Neurons require oxygen and glucose to sustain their functioning, so when brain regions are engaged in cognitive tasks, they require more blood flow (i.e., increased hemodynamic response) and exhibit increased blood oxygen level dependent (BOLD) signal that is detected using specialized magnetic resonance (MR) scanner sequences (Fowler et al., 2007; Logothetis, 2003).

As neural demand increases, oxygen-rich blood flow is increased to promote cognitive processes in certain brain regions. The BOLD FMRI technique is based on a measurement of the ratio between oxygen-rich and oxygen-poor blood. Hemoglobin is the protein that is responsible for transporting oxygen in the blood, and oxygen-rich blood (containing oxygenated hemoglobin) has a stronger MR signal compared to oxygen-poor blood (containing deoxyhemoglobin), which is weakly magnetic (Hillman, 2014). The ratio between these two states of hemoglobin underlies the BOLD signal. Increased BOLD signal helps to localize the relative changes in activity of brain regions because the relationship between changes in BOLD signal and changes in neural activity is linear (Logothetis, 2003).

FMRI is frequently utilized to identify consistent patterns of brain activity that serve to help us further understand craving and addiction. Patterns of brain response to FMRI paradigms (i.e., experimental challenges) have yielded neuromarkers that serve as objective measures of various components of addiction (e.g., craving), which are commonly paired together with subjective self-reports to improve assessment these constructs and understanding of neurobehavioral mechanisms (Koban et al., 2023). This complementary combination of subjective and objective measures is especially useful because self-reports are known to be confounded by social desirability and other biases, while FMRI allows objective assessments of underlying neural mechanisms outside of conscious awareness that drive addiction (Khalili et al., 2021).

A vast amount of research has utilized FMRI to understand brain structures and networks related to addiction to nicotine, but much of this work has focused on combustible cigarettes. As the prevalence and addictive potential of vaping is further understood, FMRI research related to vaping has increased (Vollstadt-Klein et al, 2021; Wall et al., 2017). A prominent goal of this research is understanding how brain function changes from initiation of substance use to addiction to development effective preventative and intervention strategies (Volkow & Morales, 2015). Using these complementary objective and subjective assessments, researchers have been able to predict addiction outcomes more accurately. Furthermore, the incremental predictive validity of FMRI has been demonstrated in studies that have evaluated the effect that cue-reactivity paradigms have on substance use outcomes (Owens et al., 2018; Ekhtiari et al., 2016; Lin et al., 2020).

Cue Reactivity and Package Paradigms to Study Addiction

Cue reactivity paradigms involve exposing an individual to substance-related stimuli that are intended to induce craving and increase psychophysiological activity (Carter & Tiffany, 1999). Understanding how cues for substance use transition from being neutral to being a meaningful signal of reward associated with a substance is important because these cues can then trigger a user to seek out a substance (Payne et al., 1991). FMRI cue-reactivity paradigms have been shown to be effective at predicting various substance use outcomes such as cessation and relapse, but more cue reactivity research with vaping is needed (Courtney et al., 2016; Owens et al., 2018; Versace et al., 2014).

Much of the FMRI cue reactivity research has been done with combustible cigarettes. There are both cortical regions and subcortical structures that have been shown to exhibit increased BOLD signal response specifically to smoking cues, including the precuneus, extended visual system (areas involved in visual sensation and perception), anterior cingulate gyrus, posterior cingulate gyrus, dorsal prefrontal cortex, medial prefrontal cortex, dorsal striatum, and the insula (Brody et al., 2007; Engelmann et al., 2012; Janes et al., 2009; Lin et al., 2020; Pennartz et al., 2023). In addition, studies using resting state functional connectivity to examine network synchrony in the absence of experimental stimulation or task demands have shown that synchronous fluctuations in baseline activity in the salience network, default mode network, and executive control network are associated with nicotine addiction involving cigarettes (Fedota & Stein, 2015). While these networks and network nodes are reactive to smoking cues, a meta-analysis of FMRI studies found that overlapping brain regions that have been long associated with craving (e.g., insula and striatum) also exhibit activation responses to food cues (Tang et al., 2012). Therefore, functional neuroimaging evidence suggests that food cues trigger hunger and food cravings via similar neural mechanisms as smoking cues among cigarette smokers. Whether the same relationship exists between food cues and vaping cues among vapers remains to be seen, but there are some similarities between vapers and smokers that suggest these conditions incentives may activate comparable brain networks.

Although there are fewer studies that assess cue reactivity related to vaping, studies that used these paradigms have found that reactivity to vaping device cues is positively associated with craving for vaping products (Keijsers et al., 2022). This is a result that mirrors what has been reported in the combustible cigarette research literature. Dual users of cigarettes and vaping products are common, and these users have shown higher cue reactivity to vaping products in addition to cigarettes (King et al., 2021). The reactivity to both types of nicotine products highlights a potential difficulty for individuals who use both products to reduce their use. These findings also highlight the potential overlap that exists in the neurobiological mechanisms of addiction across nicotine products and the need for more FMRI vaping cue reactivity studies to investigate whether these mechanisms differ from smoking cue reactivity. While much of the cue reactivity work is focused on the objects or devices used to intake nicotine, understanding how the reactivity to the packaging these products are sold in is also important.

Even though there are much fewer flavor choices with cigarettes compared to vaping products, menthol cigarettes sold in different packaging are a popular, and a more addictive product than non-menthol cigarettes (Wickham, 2020). Menthol cigarettes tend to have a distinct green hue to their packaging. Menthol smokers have shown increased activity in frontostriatal and occipital areas of the brain while undergoing a cue reactivity paradigm involving menthol cigarette packaging (Shi et al., 2023). The packaging seems to play a role in the behavior of seeking out cigarettes as well. Hogarth et al. (2015) found branded cigarette packaging was predictive of higher levels of tobacco-seeking, while plain packaging was predictive of a reduction in this behavior. Because there is a wider variety of flavors and packaging available for vaping products, understanding how these intentionally bright, colorful, and visually appealing packages may affect vaping behavior is crucial to investigate.

Though research specifically focused on the contents displayed on vaping packaging is lacking, Garrison et al. (2018) used FMRI to help understand the impact that advertising for flavored vaping products (included packaging) has on young adults. Their work showed that individuals prefer sweet and fruit flavored vaping products compared to plain tobacco flavor. In addition, they found that advertisements focused on these flavors took viewing time away from warning labels that are also commonly on vaping packaging. The nucleus accumbens was specifically shown to exhibit relatively greater activity when viewing vaping advertisements that contained images of various sweets and fruits. The nucleus accumbens is a well-known structure involved in cue reactivity to substances and is thus implicated in addiction (Chase et al., 2011; Koob and Volkow, 2010). Stronger activation in areas of the brain related to reward, including the middle portion of the anterior cingulate cortex, have been found in response to sweet flavors (compared to savory flavors) as well (Hellmich et al., 2024). Understanding more about the way food cues on vaping packaging influence vaping behaviors is important to inform potential regulation of these products.

Current Study, Aims, and Hypotheses

Vaping continues to be a growing threat to public health with numerous questions surrounding claims of its benefits compared to combustible cigarettes and unknown long-term health effects due to nicotine addiction and untested chemical additives. Therefore, it is imperative that research focus on the factors preceding vaping initiation, maintenance, and potential escalation, particularly among those most vulnerable to these risks. FMRI serves as a unique tool for helping to uncover the underlying brain mechanisms that lead to increased levels of vaping and risk of the negative consequences associated with vaping. By building on prior research that has investigated the link between food cravings and substance use using complementary subjective self-report and more objective behavioral and neuroimaging approaches, we hope to contribute to the understanding of vaping behavior and aid in the prevention and intervention for vaping among those vulnerable to its risks. The current study takes a novel approach to understanding the implications of the design of vaping packaging, how it draws on existing food cravings, and potentially leads to escalated vaping behavior.

The proposed study will examine neural responses to a FMRI cue reactivity to packages paradigm among 59 YAs who vape regularly. We will then determine whether these neural responses predict vaping frequency and evaluate how packaging stimuli and food cravings may affect this relationship. This approach will allow us to address the following aims and hypotheses:

Aim 1: Qualitatively evaluate the validity of the vape product packaging cue reactivity FMRI paradigm:

Benchmark. The benchmark of success for this aim is identification of the 10 most robust functional disjunction regions of interest (ROIs) for qualitative comparisons to prior cue reactivity research on vaping and cigarette smoking, and to quantitatively identify 10 functionally defined ROIs to address the hypotheses of aims two through three.

Hypothesis 1.1. Based on prior literature, we expect increases in brain activity in the bilateral visual system, anterior and posterior sections of the cingulate gyrus, dorsal and medial sections of the prefrontal cortex, striatum, and the insula to be among these clusters of significant task-related response, and therefore, the set of 10 functionally defined ROIs.

Aim 2: Determine whether brain response predicts vaping outcomes:

Hypothesis 2.1. There will be a significant main effect of FMRI response to gray packaging cues on vaping outcomes (total puffs across 4 weeks). Specifically, greater brain activation response to the cue reactivity across the 10 ROIs will be associated with a higher vaping frequency during the subsequent four weeks. The main effects of each ROI on four-week vaping frequency will also be assessed in follow-up linear multiple regression analyses to determine whether expected effects are driven by specific ROIs.

Hypothesis 2.2. There will be a significant main effect of FMRI response to food packaging cues on vaping outcomes (total puffs across 4 weeks). Specifically, greater brain activation response to the cue reactivity across the 10 ROIs will be associated with a higher vaping frequency during the subsequent four weeks. The main effects of each ROI on four-week vaping frequency will also be assessed in follow-up linear multiple regression analyses to determine whether expected effects are driven by specific ROIs.

Hypothesis 2.3. FMRI response to gray packaging cues will predict higher vaping frequency, but FMRI response to food packaging cues will increase the model's predictive utility. Additional variance will be explained by FMRI response to food packaging cues above and beyond the FMRI response to gray packaging cues alone. The main effects of each ROI on four-week vaping frequency will also be assessed in follow up linear multiple regression analyses to determine whether expected effects are driven by specific ROIs.

Aim 3: If the main effect of FMRI response to packaging cues on vaping outcomes is significant, we will determine whether this effect depends on self-reported trait food craving. If the main effect of FMRI response to packaging cues on vaping outcomes is not significant, we will, nevertheless, determine whether expected main effect for the whole network, or for each ROI, could be obscured by an interaction with packaging type or trait food craving. Follow-up analyses will be conducted for each of the 10 ROIs.

Hypothesis 3.1. It is predicted that the brain response across 10 ROIs and within each of the 10 ROIs from both packaging paradigms will interact with trait food craving (G-FCQ-T) to predict vaping outcomes (total puffs across 4 weeks), such that positive associations between ROI response to package cues will be stronger when participants report higher trait food craving (Figure 1.1).

Hypothesis 3.2. It is predicted that the brain response across 10 ROIs and within each of the 10 ROIs will statistically interact with responses specific to vape packaging with food stimuli and trait food craving (G-FCQ-T) to predict vaping outcomes (total puffs across 4 weeks), such that positive associations between ROI response to package cues will be stronger when participants have higher responses to flavored vape packaging and report higher trait food craving (Figure 1.2).

CHAPTER 2

METHOD

Participants

A sample of 67 YA (*M* = 20.03 years, *SD* = 1.47, Range = 18 - 24) heavy vapers without a history of smoking cigarettes were enrolled. However, three participants were excluded from data analysis for incomplete data and five were excluded due to artifacts (e.g., excessive head movement during MRI) that precluded FMRI data analysis. Therefore, the final sample included 59 YA vapers (*M* = 20.10 years, *SD* = 1.48, Range = 18 - 24) composed of 41 female (69.49%) and 18 male participants (30.51%). 43 participants identified as White (72.88%), 4 as Asian Indian (6.78%), 3 as Black or African American (5.08%), 3 as Korean (5.08%), 2 as Multiracial (3.39%), 1 as Vietnamese (1.69%), and 3 did not report their race (5.08%). Analyses involving the G-FCQ-T scores will have a sample of 46 YA vapers (*M* = 19.98 years, *SD* = 1.48, Range = 18 - 24) composed of 34 female (73.91%) and 12 male participants (26.09%). Study participants were recruited from local and university communities using internet and paper flier advertisements seeking YA vapers for participation in an FMRI study focusing on vaping product use. Participants received $45 for their participation. Examples of internet and paper flier advertisements are presented in Figure 2.1.

Participants were also recruited through undergraduate research pools at the university, and these students were compensated with the same amount of money as the other participants, but they also received course credit for fulfilling a requirement to participate in research. 31 participants were recruited from the Department of Communication Studies' research pool, 22 participants were recruited from non-research pool methods (i.e., internet and paper flier advertisements), 4 participants were recruited via word-of-mouth referrals, and 2 participants were from the Psychology Department's research pool.

Phone eligibility screenings were used to assess whether potential participants met inclusion criteria. To be eligible for the present study, potential participants met the study classification of "heavy vaper" which was defined as using a vaping device in 15 or more of the past 30 days. On average, participants used a vaping device in 25 of the past 30 days. Potential participants were excluded if they had any current or prior major medical, psychiatric, or neurological conditions. They were also excluded if they were disqualified for MRI due to safety (e.g., metal implants or other metal in their bodies, claustrophobia, pregnancy).

Procedures

Eligible participants were invited to participate in a lab-based data collection session that lasted three hours. During this time, written informed consent was obtained, followed by administration of a battery of surveys compiled onto a Qualtrics survey. This pre-scan survey included assessments of demographic information, vaping behavior, and trait food craving. Upon completing this survey, participants were trained to perform the FMRI paradigms, which included the vape packaging cue reactivity (CR) paradigm used in this study. During each neuroimaging run of this paradigm, participants were queried three times about how much they wanted to vape. After the 60-minute scanning session, participants completed a post-scan Qualtrics survey. This post-scan survey included questions about current nicotine cravings and the stimuli shown during the FMRI scan. These included queries about desire to eat, vape, and smoke and questions about their willingness to pay for the vape products shown, how realistic the product packaging was. Participants were sent links to weekly surveys through email or text message during the subsequent four weeks to gather information about their vaping frequency using the Timeline Followback method described in the measures section. Therefore, in order to reliably receive these survey links and the payment from the study, contact information and their preferred means of communication was verified during the lab visit. The surveys are designed to take less than 10 minutes to complete, and participants were compensated $2.50 for each survey they completed for a total of $10. The $45 for the study visit, and the potential extra $10 was emailed to participants after the four weeks of follow-ups were done.

Self-Report Measures

Timeline Followback (TLFB). TLFB is a structured self-reported retrospective quantitative estimate of substance use over a given period (Brown et al., 1998; Sobell and Sobell, 1992). In the present study, participants were asked each week in the weekly post-scan surveys about their use of ENDS over the previous seven-day period, including the number of puffs taken each day. The TLFB method is a validated and reliable measure of substance use behavior and provides information about the frequency and intensity of vaping (Brown et al., 1998; Sobell and Sobell, 1992). In addition, the TLFB method has been used previously with young adult vapers to assess their vaping frequency (Correa et al., 2019; Cassidy et al., 2020). Total number of reported puffs per day were summed across four weeks to serve as the vaping outcome variable. Yingst et al., (2020) used a similar method using puffs to report vaping frequency.

General Food Craving Questionnaire - Trait (G-FCQ-T). The G-FCQ-T is a validated and reliable questionnaire that measures the intensity and frequency of general experiences of food craving (Nijs et al., 2007). It is comprised of 21 items that query responses that include 1 (never), 2 (rarely), 3 (sometimes), 4 (often), 5 (usually), and 6 (always). The G-FCQ-T has a four-factor structure that includes preoccupation with food (e.g., “I feel like I have food on my mind all the time.”), loss of control (e.g., “Once I start eating, I have trouble stopping.”), positive outcome expectancy (e.g., “When I eat what I crave, I feel great.”), and emotional craving (e.g., “My emotions often make me want to eat.”). The responses to all items are summed together for a total score. Higher scores indicate more intense and frequent food cravings. Variations of the Food Craving Questionnaire have been used to assess cravings in young adults, and in vapers (Ljubisavljevic et al., 2016; Maldonado et al., 2024). In addition, higher scores on the trait version of the FCQ have been shown to be positively correlated with activity in the striatum and orbitofrontal cortex (Ulrich et al., 2016). This questionnaire was administered via the pre-scan Qualtrics survey.

Penn State Electronic Cigarette Dependence Index (PS-ECDI). The PS-ECDI is a validated 10-item scale that is used to measure e-cigarette dependence (Foulds et al., 2015). The scale includes questions to evaluate various constructs of dependence like the time of the first e-cigarette for the day (e.g.,“ On days that you can use your electronic cigarette freely, how soon after you wake up do you first use your electronic cigarette?”), number of times used per day (e.g.,“ How many times per day do you usually use electronic cigarette?”), cravings (e.g.,“ Do you ever have strong cravings to use an electronic cigarette?”), irritability (e.g.,“ When you haven’t used an electronic cigarette for a while or when you tried to stop using it, did you feel more irritable because you couldn’t use an electronic cigarette?”), and waking up at night to use e-cigarettes (e.g.,“ Do you sometimes awaken at night to use your electronic cigarette?”). The potential response differs by question, but the responses to all items are summed together, and scores can range from 0 to 20. Scores from 0 to 3 indicate no dependence, scores from 4 to 8 indicate low dependence, scores from 9 to 12 indicate medium dependence, and scores of 13 or more indicate high dependence on e-cigarettes.

Neuroimaging

MRI Acquisition. Blood Oxygen Level Dependent (BOLD) FMRI data were acquired during a visual vape packaging CR task using a GE 3.0T MRI (Discovery MR750) scanner with a 32-channel head coil. A whole-brain high-resolution T1-weighted structural scan (FOV=256^2mm, matrix=256^2, slice thickness=1mm) was acquired before whole-brain T2* echoplanar data acquisitions for anatomical reference. Echoplanar data was acquired using the following parameters: TR = 2000ms, TE = 25ms, FOV = 208x180 mm, matrix = 104x90, MB factor = 3, slice thickness = 3.5mm. The full scanning protocol was approximately one hour in duration and included the vape packaging CR paradigm.

The vape packaging CR paradigm was presented in two 318s imaging runs that were counterbalanced across participants. Participants were presented with blocks of images of vaping packaging with flavors representing various fruits, mint, and other sweets, and a scrambled image control condition. Stimuli were displayed on an LCD screen located behind the scanner that the participant could view through an MRI-safe mirror system. The packaging stimuli consisted of two types of colored images and a grayscale visual control condition. *Food packaging* contained images of the food-based flavor (e.g., an image of a mango) in addition to a color associated with the flavor (e.g., a mango shade of orange for mango) and the verbal label for the flavor (e.g., “Mango”). *Color packaging* contained only the color and name of the flavor (e.g., the color green and the word “Mint”). *Gray packaging* exhibited only the name of the flavor on a grayscale package. Examples of the flavor, color, gray, and scrambled control vaping packaging are presented in Figure 2.2.

During each imaging run, scrambled and gray image control conditions were shown three times for 20s each, and flavor and color image experimental conditions were shown three times each for 30s each. Therefore, all blocks consisted of 6 stimulus image presentations. Each imaging run also included three queries about how much participants wanted to vape on a 7-point Likert scale (“1 - very little” to “7 - very much”) after viewing the flavor, color, and gray image stimulus blocks for the first time. Responses were recorded with two handheld two-button boxes. Participants selected their rating (1-7) using their right hand and submitted their response using their left hand.

FMRI Quantification. Analysis of Functional Neuroimages (AFNI; Cox, 1996) software was used to quantify individual brain responses during the vape packaging CR paradigm based on example script 6b of the afni_proc.py program (Script retrieved in April 2022; Taylor et al., 2018). This python script facilitates an overall processing pipeline that calls upon several AFNI subprograms to accomplish slice-time correction, registration, outlier/motion censoring, removal of linear drift, application of a 5mm blur, and stereotaxic standardization. Effects per voxel were quantified for each experimental condition with general linear modeling (i.e., subprogram 3dDeconvolve) of observed BOLD signal using the presentation time course of three package types (i.e., flavor, color, gray) convolved with a gamma function and covariates (e.g., observed movement, linear drift) as regressors. This yielded individual 3-dimensional brain maps of beta coefficients per voxel for each task condition that represent the strength of association between the condition and observed BOLD signal relative to the scrambled control condition.

Regions of interest (ROIs) were functionally defined based on significant response to only two of the package conditions (i.e., food and gray) compared to the scrambled control image baseline. To accomplish this, voxel-wise one-sample t-tests were calculated versus a hypothetical mean of zero (i.e., no difference between each of the two package conditions and the scramble control condition). Results were thresholded at an FDR corrected $p < .001$

significance and a >10 voxel cluster size. Two thresholded group summary maps reflecting food and gray were created and then combined by using “or” logic, such that voxels were averaged and included in the combined mask if they were included as significant in either of the two package condition maps. The averaged group summary map was then further thresholded to identify the center of mass coordinates of the 10 largest (by voxel size) and most intense (by level of response) clusters. Large clusters >1000 voxels were separated into sub-clusters by decreasing the p-threshold until peak coordinates could be identified to resolve separate clusters. A final set of 10 functionally defined ROIs were defined by 5mm radius spheres surrounding center of mass coordinates of clusters or the peak of clusters that had been separated due to large size (i.e., >1000 voxels). Effects were averaged per condition per ROI per person for use in hypothesis testing.

Statistical Analysis

For aim one, identified 10 brain regions with significant neural response to food and gray stimuli on vaping packaging compared to the baseline control condition (scrambled images). The procedure for this analysis is further discussed above in the section “FMRI Quantification.” Because this is the first study of its kind, these clusters were compared qualitatively to relevant prior literature on vaping and cigarette smoking to evaluate the validity of the paradigm and to aid in interpretation of subsequent hypothesis testing results. Based on prior research, we hypothesized that bilateral regions of the visual system, the anterior cingulate gyrus, the posterior cingulate gyrus, the dorsal prefrontal cortex, the medial prefrontal cortex, the striatum, and the insula will be among these functionally defined ROIs.

Prior to hypothesis testing, the weighted averages for each ROI were calculated per condition per person for use in statistical analysis. To begin the process of calculating these averages, the means and standard deviations of the effects were calculated to check for outliers (i.e., values that were three or more standard deviations above or below the mean). Once identified, outliers were then Winsorized by finding the next closest value and changing the outlier to be one decimal unit above (if positive) or below (if negative) the next closest value (Dixon & Yuen, 1974). Once outliers were Winsorized, the voxel size of each ROI was divided by the total number of voxels (545), and that ROI-specific weight was multiplied by their raw effect scores to produce their weighted average. The averages of each of the 10 ROIs were then summed together to create the weighted average for all ROIs combined.

The remaining hypotheses were analyzed in R Studio using relevant functions within the 'tidyverse,' 'psych,' 'readxl,' 'lm.beta,' 'interactions,' 'ggpubr,' 'moments,' 'Hmisc,' 'correlation,' 'rempsyc,' 'openxlsx2,' and 'stargazer.' These packages allowed us to assess normality, skewness, and kurtosis in addition to calculating zero-order correlations, linear regression models, and extracting data for use in tables and figures.

For Aim 2, Hypothesis 2.1., to determine if there was a main effect of the activation to packaging with gray stimuli (i.e., weighted average of gray condition across all ROIs) of the FMRI markers (i.e., independent variable) on four-week vaping frequency (i.e., dependent variable), a simple linear multiple regression analysis was conducted. Sex was entered as a covariate for this analysis due to the known potential confounding effects on the IV and DV. In addition, we assessed the individual ROIs and their relationship with vaping frequency using the same linear multiple regression model. Hypothesis H.2.1. will be supported if there is a significant positive main effect of ROI response to the gray packaging predicting 4-week vaping frequency. One-tailed significance levels of $p<.05$ were used due to the predicted directions of effects.

For Aim 2, Hypothesis 2.2., to determine if there was a main effect of the activation to packaging with food stimuli (i.e., weighted average of food condition across all ROIs) of the FMRI markers (i.e., independent variable) on four-week vaping frequency (i.e., dependent variable), a simple linear multiple regression analysis was conducted. Sex was entered as a covariate for this analysis due to the known potential confounding effects on the IV and DV. In addition, we assessed the individual ROIs and their relationship with vaping frequency using the same linear multiple regression model. Hypothesis H.2.2. will be supported if there is a significant positive main effect of ROI response to the food packaging predicting 4-week vaping frequency. One-tailed significance levels of $p<.05$ were used due to the predicted directions of effects.

For Aim 2, Hypothesis 2.3., to determine if there was a main effect of both the activation to packaging with food stimuli (i.e., weighted average of the food condition across all ROIs) of the FMRI markers and of the activation to packaging with gray stimuli (i.e., weighted average of the gray condition across all ROIs) on four-week vaping frequency (i.e., dependent variable), a simple linear multiple regression analysis was conducted with both predictors entered into the model. Sex was again entered as a covariate for this analysis. To determine if there was a significant R^2 change between the regression model assessing the main effect of the activation to packaging with gray stimuli alone (from Hypothesis 2.1) and the regression model assessing the main effects of both the activation to packaging with food stimuli and to gray stimuli (model from the beginning of Hypothesis 2.3), an ANOVA was conducted with the two models entered as arguments. In addition, as follow-up analyses, we assessed the individual ROIs and their relationship with vaping frequency using the same linear multiple regression models and conducted ANOVAs for each ROI as well. Hypothesis H.2.3. will be supported if the regression model assessing the main effects of the activation to both packaging types is significantly better at predicting (i.e., R^2 change significantly improves when activation to packaging with food stimuli was added into the model) vaping outcomes compared to the regression model assessing the main effects of the activation to packaging with gray stimuli alone. One-tailed significance levels of $p<.05$ were used due to the predicted directions of effects.

Aim 3 is planned to examine predicted moderation effects on the expected main effect of brain response to both types of vape product packages on four-week vaping frequency.

For Hypothesis 3.1., to evaluate the potential moderator role of trait food craving, a moderation analysis was conducted using RStudio. The ‘lmtest,’ ‘car,’ ‘jtools,’ ‘interactions,’ and ‘ggplot2’ packages were be utilized for this specific analysis. These packages allowed us to calculate a moderated multiple regression model, interpret the moderation effect (i.e., trait food craving x ROI response to gray/food packaging interaction), visualize the interaction effect, and assess model assumptions. Sex was entered as a covariate due to the known potential confounding effects on primary IVs and DVs. Hypothesis H.3.1. will be supported if the interaction effect of trait food craving (G-FCQ-T) x brain response to both package types across the 10 ROIs exhibit statistical significance predicting 4-week vaping frequency. It is predicted that the brain response to vape product packaging with colorful food stimuli will exhibit significantly stronger positive association with four-week vaping frequency than responses to the gray packaging without images to indicate flavor. One-tailed significance levels of $p<.05$ will be used due to the predicted directions of effects. Follow-up regressions were conducted per ROI to determine whether expected effects were driven by specific ROIs.

For hypothesis H.3.2, to further evaluate the potential moderator role of trait food craving, a moderation analysis was conducted using RStudio with the same packages used to complete the previous analysis for hypothesis H.3.1. Sex was entered as a covariate for this analysis as well.

Hypothesis H.3.2. will be supported if the interaction effect of trait food craving (G-FCQ-T) x brain response to only food packaging across the 10 ROIs exhibit statistical significance predicting 4-week vaping frequency. It is predicted that the brain response to vape product packaging with colorful food stimuli will exhibit a strong positive association with four-week vaping frequency on its own. One-tailed significance levels of $p<.05$ will be used due to the predicted directions of effects. Follow-up regressions were conducted per ROI to determine whether expected effects were driven by specific ROIs.

Power Analysis

Power analyses were conducted using the G*Power 3 software (Version 3.1.9.7; Faul et al., 2007). Because the data for the current research was collected before analysis, a sensitivity power analysis was used to compute an effect size the proposed analyses would be able to detect based on a given alpha error probability, desired level of power, sample size, and number of predictors. f^2 represents the effect size an analysis would be able to detect. An $f^2 \geq 0.02$, an $f^2 \geq 0.15$, and an $f^2 \geq 0.35$ represents small, medium, and large effects sizes, respectively (Cohen, 1988). Both analyses utilized the linear multiple regression: Fixed model, R^2 deviation for zero statistical test under the F tests family. Prior literature in cue reactivity to vaping packaging with food cues is limited, but one study found a large effect ($\eta_p^2 = 0.27, p = .02$) of condition (viewing sweet, tobacco, or control images) on activity in nucleus accumbens (Garrison et al., 2018). However, extant research is lacking information about predicting vaping frequency based on neural responses to vaping packaging with or without flavor cues such as food stimuli. To compare to work in the combustible cigarette literature, neural reactivity during cue reactivity paradigms (including, but not limited to packaging) has been shown to predict the initiation of smoking and medium to large effect sizes have been produced (Conklin et al., 2015; Lin et al., 2020).

Aim 1, Hypothesis.1.1: Prior CR studies reliably elicit brain significant responses in the visual system structures, anterior and posterior sections of the cingulate gyrus, dorsal and medial sections of the prefrontal cortex, striatum, and the insula (Brody et al., 2007; Engelmann et al., 2012; Janes et al., 2009; Lin et al., 2020; Pennartz et al., 2023). These effects are very large due to the way they are thresholded and the use of multiple comparison correction and they have obtained significant effects in sample sizes smaller than the present proposal.

Aim 2, Hypothesis.2.1 and Hypothesis 2.2: A power analysis was conducted using a one tailed alpha error probability of 0.05 (given the directional hypotheses), power of 0.80, a sample size of 59, and 2 predictors. This study will be adequately powered to detect an f^2 of 0.136, which is a medium effect size. Relevant research literature has reported medium effect sizes in similar studies, which suggest that the present study has sufficient statistical power (Garrison et al., 2018).

Aim 2, Hypothesis 2.3: A power analysis was conducted using a one tailed alpha error probability of 0.05 (given the directional hypotheses), power of 0.80, a sample size of 59, and 3 predictors. This study will be adequately powered to detect an f^2 of 0.158, which is a medium effect size. Relevant research literature has reported medium effect sizes in similar studies, which suggest that the present study has sufficient statistical power (Garrison et al., 2018).

Aim 3, Hypothesis.3.1: A power analysis was conducted using a one tailed alpha error probability of 0.05 (given the directional hypotheses), power of 0.80, a sample size of 46, and 6 predictors. This study will be adequately powered to detect an f^2 of 0.276, which is a medium effect size. Given the medium effects reported in similar smoking literature, we conclude that the design may be sufficient to detect expected effects in H.3.1 with this sample size (Conklin et al., 2015; Lin et al., 2020). Relevant research literature assessing vaping and trait craving together has not been found to provide us with the size of expected effects.

Aim three, Hypothesis 3.2: A power analysis was conducted using a one tailed alpha error probability of 0.05 (given the directional hypothesis), power of 0.80, a sample size of 46, and 4 predictors. This study will be adequately powered to detect an f^2 of 0.231 which is a medium effect size.

CHAPTER 3

RESULTS

The primary study variables were assessed for normality using the Shapiro-Wilk test for normality (Shapiro & Wilk, 1965). The scores on the G-FCQ-T were normally distributed ($p >$ .05) across the study sample and had a mean of 48.89 (*SD* = 16.93, range = 21 - 91) out of a maximum score possible of 126. The scores on the PS-ECDI were normally distributed ($p > .05$) across the study sample and had a mean of 8.46 (*SD* = 5.03, range = 0 - 20) out of a maximum score possible of 20 which indicated that the sample exhibited low to medium dependence on e-cigarettes. The mean total number of puffs on a vaping device was 777.78 (*SD* = 893.96, range = 0 - 3600) and they were not normally distributed (W = 0.79, $p < .001$). Log-10, square root, and cube root transformations were completed, and the cube root transformation provided the best approximation to a normal distribution (W = 0.99, $p = 0.68$). The weighted average of responses across all functionally defined ROIs to each, the gray and the food packaging, were normally distributed (*p*s > .05). Average beta coefficient response was 0.18 (*SD* = 0.16) to gray packages and 0.33 (*SD* = 0.21) to food packages, indicating that these conditions elicited greater responses than the control condition and that the mean response to packages with food stimuli was nearly twice as intense and the response to gray packages.

<u>H.1.1</u>:

Significant responses to gray packaging, shown in figure 3.1, were found in the bilateral supplementary motor area (SMA), bilateral caudal dorsolateral prefrontal cortex (dlPFC), bilateral inferior parietal lobule, right superior occipital gyrus, bilateral precuneus, bilateral insula/inferior frontal gyrus, bilateral visual identification system (visuoidentification regions from the inferior occipital gyrus to the inferior temporal gyrus, and including the lingual and fusiform gyri), and the left cerebellum.

Significant responses to food packaging, shown in figure 3.2, were found in the bilateral SMA, bilateral caudal dlPFC, bilateral inferior parietal lobule, bilateral medial frontal gyrus/anterior cingulate, bilateral orbitofrontal cortex, bilateral precuneus/posterior cingulate, bilateral insula/inferior frontal gyrus, bilateral posterior thalamus, left entorhinal cortex, bilateral amygdala, bilateral visual identification system (visuoidentification regions from the inferior occipital gyrus to the inferior temporal gyrus, and including the lingual and fusiform gyri), and the left and medial cerebellum.

Once these two thresholded group summary maps reflecting responses to food and gray packages were created, they were then combined to identify the most robust brain regions that significantly responded (FDR-corrected $p < .001$) to either package type. Robustness was operationally defined by exhibiting higher levels of overall response intensity in addition to having the largest cluster of voxels. A total of 10 brain regions with significant neural response to vaping packaging with food or gray stimuli compared to the baseline control condition (scrambled images) were identified. These regions of interest (ROIs) are identified with their name, voxel size, and RAI Talairach coordinates in Table 3.1. These ROIs are shown in Figure 3.3.

The LCIFS, LEC, LIPL, LPT, RCIFS, RFG, RIOG, and RIPL exhibited mean activation responses during each package condition, while the RLG and RSOG exhibited mean deactivation responses. Responses of each ROI were assessed for normality using Shapiro-Wilk test (Shapiro & Wilk, 1965). ROI responses that were not normally distributed underwent transformation before inclusion in planned follow up inferential tests of individual ROIs. Individual ROI responses to gray packaging were normally distributed except the RIOG (W = 0.92, p = .001). Log-10, square root, and cube root transformation were completed, and the square root transformation provided the best approximation to a normal distribution (W = 0.97, p = 0.12). Most of the individual ROI responses to food packaging were normally distributed except LIPL (W = 0.96. p = .05), RFG (W = 0.96, p = .04), and RIOG (W = 0.92, p = .001). Log-10, square root, and cube root transformation were completed, and the square root transformation provided the best approximation to a normal distribution for the RIOG (W = 0.96, p = .045), RFG (W = .96, p = .06), and LIPL (W = .98. p = .32).

H.2.1:

A linear regression was used to assess if overall network brain response to gray packaging predicted number of puffs while controlling for sex. The overall regression result, shown in Table 3.2, was not statistically significant (R^2 = 0.01, F(2,56) = 1.29, p = 0.14). Follow-up analyses, shown in Table 3.3, also revealed that none of the individual ROIs were significant predictors of number of puffs.

H.2.2:

A linear regression was used to assess if overall brain response to food packaging across all ROI predicted number of puffs while controlling for sex. The overall regression result, shown in Table 3.4, revealed a strong effect in the predicted direction, but it was not statistically significant (R^2 = 0.03, F(2,56) = 1.89, p = 0.08). Follow up analyses of individual ROIs, listed in Table 3.5, revealed strong effects in the predicted direction in the LCIFS (p = .017), RFG (p = .038), and RCIFS (p = .038); however, they did not survive FDR correction using Hochberg's step-up procedure (Hochberg, 1988).

<u>H.2.3:</u>

Two linear regressions were used to determine whether brain responses would predict vaping puffs, and then an ANOVA was used to compare the fit of the two regression models. The first linear regression was used to assess if using brain response across all 10 ROIs during exposure to gray packaging, while controlling for sex, would predict vaping puffs at follow up. This model was not significant ($R^2 = 0.01$, $F(2,56) = 1.29$, $p = 0.14$). The second linear regression was used to assess if entering brain response across all 10 ROIs during exposure to food packaging as a predictor in addition to brain response to gray packaging, while controlling for sex, would predict vaping puffs at follow up. The second linear regression result, listed in Table 3.6, was also not statistically significant ($R^2 = 0.01$, $F(3,55) = 1.27$, $p = 0.15$). As planned, an ANOVA was used to compare the fits of the two models (i.e., one with all ROI gray effects and the other with both all ROI gray and food effects), and it was not statistically significant ($p = 0.14$). Full results of the ANOVA are shown in Table 3.8. Therefore, adding in the brain response to food packaging did not increase the predictive utility of brain response to gray packaging alone.

Follow up regression analyses, shown in Table 3.7, of individual ROIs responses to both gray and food packaging revealed that the overall models for LPT ($p < .01$) and LCIFS ($p = .04$) were significant predictors of puffs. The LCIFS did not survive FDR correction using Hochberg's step-up procedure, but the LPT remained significant after FDR correction.

Follow up analyses using ANOVAs to compare model fits of the two models for each individual ROI (i.e., one with ROI gray effects and the other with both ROI gray and food effects), listed in Table 3.9, revealed that the LPT ($p < .01$), and LCIFS ($p = .03$) were strong predictors of vaping puffs at follow up. Therefore, the individual ROI response to food packaging, when added in as a predictor, increased the predictive utility of the model compared to individual ROI response to gray packaging alone. The LCIFS did not survive FDR correction using Hochberg's step-up procedure, but the LPT remained significant after FDR correction.

In sum, brain responses to neither gray nor food packaging predicted vaping outcomes. Comparing the first model (ROI response to gray only) and the second model (ROI response to gray and food packaging) across the full set of ROIs did not reveal significant differences. However, models for the LPT and LCIFS showed predictive utility that increased when individual ROI response to food was added into their respective models.

H.3.1:

A linear regression was used to assess if overall network brain activation during exposure to gray and food packaging would interact with trait food craving to predict follow up vaping puffs while controlling for sex. The overall model result, shown in Table 3.10, was not significant ($R^2 = 0.01$, $F(6,39) = 1.10$, $p = 0.19$), but there was a significant interaction between response to food packaging and trait food craving ($p = .02$), and between response to gray packaging and trait food craving ($p = .04$). To facilitate interpretation of these two significant interactions, interaction plots are presented in Figure 3.4 and Figure 3.5.

The gray packaging and trait food craving interaction effects exhibited the predicted direction, such that among participants with higher brain responses to gray packaging, higher trait food craving led to more total vaping puffs than did lower trait food craving. The food packaging and trait food craving interaction effects did not exhibit the predicted direction, such that among participants with higher brain responses to food packaging, higher trait food craving led to fewer total vaping puffs than lower trait food craving.

To further investigate the interaction between ROI response to food packaging and trait food craving, we conducted follow-up analysis applying the Johnson-Neyman technique (Johnson & Neyman, 1936). This method identifies specific values of the trait food craving variable where the effect of the ROI response to food packaging is statistically significant, using actual data rather than arbitrary cutoff points to define significance. This approach ensures more data-driven and accurate conclusions. Our analysis using the Johnson-Neyman technique revealed that for individuals with trait food craving levels at or below approximately 34 on a 21 – 126 scale, an increased response from all ROIs combined to food packaging was significantly associated with increased levels of vaping puffs at follow-up. Additionally, for individuals with trait food craving levels at or above 103, an increased response from all ROIs combined to food packaging was significantly associated with decreased levels of vaping puffs at follow-up. Given that our observed data range for the trait food craving variable was 21-91, this latter finding, however, falls outside this range. This exploratory analysis thus helps empirically determine the regions of significance for the interaction result. To visually inspect these results, see the Johnson-Neyman plot in Figure 3.6.

These overall effects were further examined in follow up interaction analyses of each ROI that are listed in Table 3.11. Follow-up interaction analyses of individual ROIs revealed that the LCIFS regression model was significant (p = .03), and the interaction between LCIFS response to gray packaging and trait food craving (p = .03) and LCIFS response to food packaging and trait food craving (p = .04) were significant, but only the interaction between LCIFS response to gray packaging was in the predicted direction. Among participants with higher LCIFS response to gray packaging, higher trait food craving led to more total vaping puffs than lower trait food craving. The LCIFS response to food packaging and trait food craving interaction did not exhibit effects in the predicted direction, such that among participants with higher LCIFS response to food packaging, higher trait food craving led to fewer total vaping puffs than lower trait food craving.

While the LIPL regression model was not significant, there was a significant interaction between LIPL response to food packaging and trait food craving ($p = .05$), but it was not in the expected direction. Among participants with higher LIPL response to food packaging, higher trait food craving led to fewer total vaping puffs than lower trait food craving.

While the RCIFS regression model overall did not significantly predict the vaping outcome, there was a significant interaction between RCIFS response to gray packaging and trait food craving that did ($p = .03$), and a significant interaction between RCIFS response to food packaging and trait food craving ($p = .02$). Only the interaction between RCIFS response to gray packaging was in the predicted direction. Among participants with higher RCIFS response to gray packaging, higher trait food craving led to more total vaping puffs than participants with lower trait food craving. The RCIFS response to food packaging and trait food craving interaction did not exhibit effects in the predicted direction, such that among participants with higher RCIFS response to food packaging, higher trait food craving led to fewer total vaping puffs than lower trait food craving.

While the RFG regression model was not significant, there was a significant interaction between RFG response to food packaging and trait food craving that predicted vaping puffs at follow-up ($p = .01$), but not in the expected direction. Among participants with higher RFG response to food packaging, higher trait food craving led to fewer total vaping puffs than lower trait food craving.

While there were significant interactions between the four individual ROIs (i.e., LCIFS, LIPL, RCIFS, and RFG) and trait food craving, none of these interactions remained significant after FDR correction.

H.3.2:

Due to the expectation that food packaging would be a better predictor of vaping outcome, a linear regression was used to evaluate if overall brain response during exposure to food packaging alone would interact with trait food craving to predict vaping puffs while controlling for sex. The overall model result, shown in Table 3.12, was not significant (R^2 = -0.02, $F(4,41) = 0.77$, $p = 0.27$). Follow-up analyses, listed in Table 3.13, of individual ROIs revealed that the LCIFS overall model significantly predicted vaping puffs at follow up ($p = .04$), but the interaction between LCIFS and trait food craving did not. Conversely, the RFG model was not significant, but the interaction between RFG activation response to food packaging and trait food craving significantly ($p = .03$) predicted vaping puffs at follow up. Additionally, while the LPT model was not significant, the interaction between LPT response to food packaging and trait food craving ($p = .04$) significantly predicted vaping puffs at follow up. While significant, the interactions between both the RFG and LPT and trait food craving did not predict vaping puffs at follow up in the predicted direction. For both ROIs, among participants with higher response to food packaging, higher trait food craving led to fewer total vaping puffs than lower trait food craving. While there were significant interactions between both ROIs and trait food craving, neither of the interactions remained significant after FDR correction.

CHAPTER 4

DISCUSSION

The current study examined how neural responses to the stimuli present on simulated vaping packaging predicted vaping outcomes in a sample comprised of 59 YAs who vape heavily. Trait food cravings were also investigated to determine whether they affected the expected relationship between brain response to packaging stimuli and subsequent vaping. The main aims of the current study were to (1) identify functionally defined regions of interest (ROIs) that exhibit significant neural responses while viewing vaping packages with gray stimuli and with colorful food stimuli; (2) determine whether these neural responses to vaping packages predict vaping outcomes; and (3) test the potential moderator effect of trait food craving on the association between neural responses and vaping frequency four weeks later.

Overall, findings showed that brain regions that exhibited significant responses to vaping packages were not directly associated with vaping outcomes during the subsequent four weeks. However, vaping outcomes were significantly predicted by interactions between these neural responses and trait food craving. Additionally, during follow-up analyses it was revealed that vaping outcomes were strongly predicted by both direct and indirect effects in specific ROIs, including the LCIFS, LIPL, RCIFS, RFG, and LPT. While the study hypotheses received mixed support, findings provide evidence that FMRI is a tool with unique utility to facilitate understanding of vaping outcomes. While the current study is an extension of prior research, this novel approach to understanding the effects of the design of vaping packaging, how it draws on trait food cravings, and potentially leads to escalated vaping behavior, is expected to contribute significantly to the nicotine and vaping research literature.

Aim 1

Group summary maps were created to identify functionally defined ROIs for hypothesis testing and to qualitatively compare the areas of the brain that significantly responded to vape product packaging to areas that are often reported in prior cue reactivity research on vaping and cigarette smoking. The benchmark of success for the first aim of the study was to identify the 10 most robust functional disjunction regions of interest (ROIs). We conclude that this benchmark was met, as 10 ROIs were identified that displayed significant response to vaping packaging with either gray or food stimuli. These 10 ROIs were represented throughout the major lobes of the brain.

As has been reported by prior tobacco product cue reactivity research, portions of the precuneus, extended visual system, anterior and posterior cingulate gyri, dorsal and medial prefrontal cortex, and the insula exhibited significant response to either the gray packaging or food packaging (Brody et al., 2007; Engelmann et al., 2012; Janes et al., 2009; Lin et al., 2020; Pennartz et al., 2023). The striatum was the sole area of the brain, often implicated in the cue reactivity literature, in which we did not find expected significant response to either the gray or food packaging. Therefore, most of the areas of the brain that are consistently implicated in the combustible cigarette literature showed significant response to the vaping stimuli, so Hypothesis 1.1 was mostly supported.

While these brain regions exhibited significant response to either type of packaging, only the 10 most robust regions were included in hypothesis testing. This explains why, for example, the left hemisphere visual perception system is not represented in the 10 most robust ROIs even though it significantly responded to both types packaging. While both hemispheres exhibited significant responses in the visual system, the left hemisphere response was less robust. Inclusion of only the most robust clusters as ROIS was done to limit multiple comparisons and to optimize prediction of vaping outcomes.

Findings from Hypothesis 1.1 suggest the neural response to visually presented vape product packaging occurs in systems that mediate selective attention, language, and visual perception. These same brain systems have been implicated in cigarette cue reactivity research (Courtney et al., 2016; Owens et al., 2018; Versace et al., 2014). The lack of response found in reward areas of the brain – which are often implicated in the cigarette cue reactivity literature – may be due to the fact that the current study used novel vaping packaging stimuli. Thus, the participants may not find packaging that they have never seen before to be rewarding. Additionally, the level of addiction severity, as measured by the PS-ECDI, was potentially too low to produce activation in the striatum or other reward areas of the brain. In fact, other research with a comparable sample (displaying low to medium dependence on e-cigarettes) to ours did not observe significant activation in reward areas of the brain when viewing vaping cues either (Nichols et al., 2016). If a person's addiction level is lower, then their cravings will be lower and reward areas may not be as reactive. Additionally, novel stimuli may be more salient and this can lead to the increased reactivity in visual and attentional areas that we observed.

Much of the overlap was with brain structures that engage in visual processing. These include the right fusiform gyrus (RFG), right inferior occipital gyrus (RIOG), right lingual gyrus (RLG), and the right superior occipital gyrus (RSOG). These areas engage in the higher order processing of visual information involved in processing of faces, object recognition, and the reading of textual information (de Haas et al., 2021; Margalit et al., 2017; Mechelli et al., 2000;

Weiner & Zilles, 2016). Engagement of these regions is evidence of a heightened focus on the visual details of the stimuli contained on the packaging. The heightened response to the colorful food packaging is consistent with prior research on menthol cigarette packaging, where menthol cigarette smokers exhibited more intense activation responses in occipital lobe structures while viewing archetypal green-hued menthol packaging (Shi et al., 2023). One subcortical nucleus was included among the 10 most robust. The left posterior thalamus (LPT) is predominantly made up of the pulvinar and lateral geniculate nucleus of the thalamus. These areas are well known as nodes in visual processing pathways and suggest processing of the contralateral right visual field where vaping cartridges were present (Barron et al., 2015).

Two frontal ROIs were identified. The left and right caudal inferior frontal sulci (LCIFS and RCIFS) are in the lateral prefrontal cortex and have known involvement in phonological working memory processes (Papoutsi et al., 2009). The LCIFS and RCIFS are also components of the inferior frontal junction that engages in attention shifting (Ruland et al., 2022). Additionally, the LCIFS overlaps with Broca's area, suggesting that the language system may be engaged by the packaging, possibly due to reading, perceiving language syntax, and semantic processing functions associated with this area, as both types of packaging included written verbal information (Ford et al., 2010). The right inferior frontal cortex, which includes the RCIFS, is a known area tied to inhibitory control (Aron et al., 2014).

One of the temporal lobe ROIs outside of the visual system was the left entorhinal cortex (LEC). This region includes the primary input and output pathway between the hippocampus and association cortex of all lobes, implicating engagement of memory processes and visuoidentification, specifically the encoding and retrieval of the features of objects (Schultz et al., 2015).

The two parietal lobe ROIs were the right inferior parietal lobules (LIPL and RIPL). These regions are known for involvement in visuospatial attention, symbolic logic (e.g., language and arithmetic), and social cognition (Numssen et al., 2021). The LIPL and RIPL are collectively known for their involvement in visuospatial attention, and they are key structures of the frontoparietal attention network, with strong connectivity to frontal lobe areas, including the RCIFS (Malhotra et al., 2009; Singh-Curry & Husain, 2009; Uddin et al., 2019). The RIPL has also been shown to be activated by drug cues (Chase et al., 2011). Increased attention and reactivity to drug cues in this region has been shown to be predictive of the development of substance use disorders (Hill-Bowen et al., 2021). The LIPL has also been shown to be uniquely involved in language perception, reading, and mental arithmetic, further supporting our conclusions about engagement of the left hemisphere language system to read package information (Barbeau et al., 2017; Brownsett & Wise, 2010; Rivera et al, 2005).

Aim 2

The second aim of the current study has three hypotheses, all focused on whether brain reactivity predicts vaping outcomes.

Hypothesis 2.1 was not supported. It was expected that the combined brain response across the 10 ROIs to vaping packaging with grayscale stimuli would be associated with increased vaping in the four weeks following the initial study visit. However, combined ROI response to gray packaging, statistically controlling for sex, was not a significant predictor of total number of puffs over the subsequent four weeks. Additionally, follow-up analyses revealed that none of the individual ROIs, also statistically controlling for sex, were significant predictors of total number of subsequent puffs.

Findings from Hypothesis 2.1 suggest that exposure to the gray packaging is not predictive of vaping outcomes, and this is potentially due to the packaging being less salient and generally eliciting a low level of neural response. Research observing differences in brain activation to plain (though still with color) and branded packaging with health warning labels displayed on them, found that there was increased activity in the extended areas of the visual cortex when observing branded packages compared to plain package (Maynard et al., 2017). This follows other research showing a decreased cue-eliciting effect of plain packaging (Hogarth et al., 2015). In fact, numerous studies have shown that plain cigarette and vaping packaging, lacking typical design elements, are less appealing overall and rated as such by adolescents and adults (Gomes et al., 2024; White et al., 2015).

Findings from Hypothesis 2.1 suggest that responses to gray package stimuli are not effective predictors of outcome, perhaps due to low visual salience. It is also possible that this was confounded by interaction effects, and this may have masked the effect we were expecting.

Hypothesis 2.2 was partially supported. It was expected that the combined brain response from the 10 ROIs to vaping packaging with food stimuli would be associated with increased vaping in the four weeks following the initial study visit. However, combined response to food packaging across all ROIs, statistically controlling for sex, was only a marginally significant predictor of total number of puffs. Although the overall model was not significant, the effect was strong and in the expected positive direction. Planned follow-up analyses revealed that three of the 10 individual ROIs, the LCIFS, RCIFS, and RFG, were significant predictors of total number of puffs after statistically controlling the effects of sex. The effects of each of these ROIs were also in the predicted direction. However, none of these ROIs remained significant after multiple comparisons correction.

Findings from Hypothesis 2.2 suggest that the current study was not sufficiently powered to detect the direct effects of predicting vaping outcomes using brain responses to vape packaging. However, this warrants further investigation because effects were trending in the hypothesized direction and nominally significant in some cases (i.e., did not survive FDR correction). The overall ROI model may also have been non-significant because of the weighted averaging method by which the ROI responses were combined. This combined method may be masking the more robust effects of smaller individual ROIs.

Of the three ROIs that nominally predicted vaping outcome, the LCIFS and RCIFS are both associated with increased vigilance and shifting attention while the RFG is associated with visual processing and object recognition (Ruland et al., 2022; Weiner & Zilles, 2016). This increased activation in attentional and visual perception areas may reflect the higher level of salience that the stimuli present on food vaping packaging (i.e., the colorful packaging and the presence of salient food cue) may possess. Participants may have been shifting their attention to focus on the various stimuli present on the food vaping packaging that the gray packaging lacks.

Hypothesis 2.3 was partially supported. This hypothesis was designed to determine whether there was an incremental effect of food packaging compared to grayscale packaging. It was expected that combined brain responses to vaping packaging with grayscale and food stimuli would predict vaping outcome. It was further expected that when responses to food stimuli was added as a predictor into the model including only response to gray packaging as a predictor, the predictive utility of the model would increase (i.e., demonstrating the added predictive utility of the food stimuli). However, not only did the combined model not significantly predict vaping outcome, but the two separate models with only gray stimuli or food stimuli added were not significantly different from each other. Therefore, adding brain response to food packaging into the original model did not enhance the predictive utility of the model.

Planned follow-up analyses of the individual ROIs and their response to combined gray and food packaging showed that the LCIFS and LPT models were significant predictors of vaping puffs during the subsequent four weeks. The effects of the LCIFS and LPT model containing both types of responses were partially in the predicted direction. ROI response to gray packaging had a negative association with vaping puffs, while ROI response to food packaging had a positive association with vaping puffs in the model using both responses as predictors. Both the LCIFS and LPT models with both predictors were significantly different than the models with only ROI response to gray packaging. After multiple comparisons correction, only the LPT remained a significant predictor of vaping puffs.

Findings from Hypothesis 2.3 suggest that combined ROI response to food packaging may not predict vaping outcomes above and beyond the ROI response to gray packaging. However, these findings also suggest that the gray packaging is potentially less salient overall and this may be responsible for the non-significant, and overall weaker response. Given the fact that the main effects in Hypotheses 2.1 and 2.2 were not significant, it is not surprising that the model, with ROI response to gray packaging and ROI response to food packaging both entered as predictors, was not significant either. However, individual ROI did garner different results than the combined effects of our 10 ROIs. As previously stated, a known function the LCIFS is associated with shifting attention and having increased attention towards objects, so this may reflect that increased attention towards the more salient cues on the food packaging is predictive of vaping outcomes (Ruland et al., 2022). Additionally, The LPT engages in visual processing, so perhaps the predictive nature of this ROI is reflecting an increased level of attention and feature processing of the packaging with food cues (van der Laan et al., 2011). In fact, color sensitive neurons have been found in the pulvinar nucleus of the posterior thalamus, so the added color that the food packaging has may be driving this effect (Saalman & Kaster, 2011).

Aim 3

The third aim of the current study has two hypotheses that were both focused on brain reactivity predicting vaping outcomes with trait food craving moderating the relationship between reactivity and vaping.

Hypothesis 3.1 was partially supported. It was expected that, controlling for sex, increased ROI response to vaping packaging with gray and food stimuli would interact with trait food cravings to predict higher levels of vaping where higher trait food cravings were observed. Brain responses to both types of packaging significantly interacted with trait food craving to predict vaping outcomes. However, only the responses to gray packaging interaction with trait food craving was in the predicted direction. Therefore, higher response to gray packaging and higher levels of trait food craving were predictive of higher amounts of vaping. Additionally, higher response to gray packaging and lower levels of trait food craving were predictive of lower amounts of vaping. This portion of Hypothesis 3.1 was supported. Conversely, the ROI response to food packaging interaction with trait food craving, while significant, was not in the predicted direction. Therefore, higher ROI response to food packaging and higher levels of trait food craving were predictive of lower amounts of vaping, so this portion of Hypothesis 3.1 was not supported.

Follow-up analyses for Hypothesis 3.1 showed that the LCIFS, LIPL, RCIFS, and RFG significantly interacted with trait food craving to predict vaping outcomes. As was observed in the main analysis examining the combined response of 10 ROIS, our predicted effects were partially supported for the individual ROIs. The LCIFS and RCIFs showed the same pattern in which their response to gray packaging and its response to food packaging both interacted with trait food cravings. When the response in these two ROIs to gray packaging was higher, participants with higher levels of trait food cravings vaped more. The LIPL and RFG response to gray packaging did not interact with trait craving. When the response from the LCIFS, RCIFS, LIPL, and RFG to food packaging was higher, participants with higher levels of trait food cravings vaped less.

While the portion of Hypothesis 3.1 related to ROI response to gray packaging was supported, the portion related to ROI response to food packaging was not supported. Considering that the main effect of ROI response to gray packaging on vaping outcomes was positive, though not significant, the positive direction of the interaction with trait food craving seems logical. The main effect of ROI response to food packaging on vaping outcomes was also positive, but only marginally significant. Therefore, like the gray packaging interaction, we would expect a positive effect, but this was not the case for the combined ROI response to food packaging or the response of the individual ROIs.

Findings from Hypothesis 3.1 suggest that among individuals with higher levels of trait food craving, increased brain activation to gray packaging may be predictive of increased vaping behaviors. This result was expected, but it was expected to coincide with increased brain activation to food packaging being even more predictive of vaping outcomes. The gray packaging is likely the most novel packaging that the participants have seen, so perhaps there is a novelty effect that is affecting our results. In food and diet research, similar unexpected outcomes have been seen with household items compared to food items, where household items elicited stronger responses in visuospatial and attentional regions compared to food stimuli

(Schulte et al., 2019). Individuals who display addictive-like eating are known to have a heightened level of ambivalence (simultaneous positive and negative attitudes) towards food and this can be a barrier to adopting healthier eating behaviors. Schulte et al. (2019) suggest that perhaps a lack of ambivalence towards neutral stimuli is driving this unexpected outcome as they may be seeing these neutral items more positively than the food stimuli. Future research should consider the level of ambivalence a person may have towards food or vaping cues. In the current study, all images of vaping packaging still contain images of vaping cartridges. The gray packaging only has the color and food image associated with the flavor removed. The cartridges on the packaging remain. Vaping cues have been shown to reliably induce cravings for vaping products (Keijsers et al., 2022). This may provide support for vaping packaging to be stripped down in detail even further to remove any vaping device cues.

Increased brain activation to food packaging was expected to be associated with higher levels of vaping, but it was not. The LCIFS, RCIFS, LIPL, and RFG all exhibited activation to food packaging, but were associated with decreased vaping. A possible explanation for this unexpected result is that participants are trying to inhibit their own behavior, of wanting to vape, because they are experiencing craving from the colorful food stimuli on the packaging. The activation of the visual and attention-related ROIs suggests that the stimuli are salient. The LIPL is a structure that plays a role in visual attention and works with frontal lobe structures like the RCIFS through the frontoparietal attention network (Malhotra et al., 2009; Singh-Curry & Husain, 2009; Uddin et al., 2019). Additionally, the RCIFS plays a role in inhibitory control (Aron et al., 2014). It is possible that the LIPL is still guiding selective attention, but the RCIFS may be involved in inhibiting the person from looking at the craving-inducing colorful food cues on the packaging because it is making them crave. The RCIFS may be guiding the LIPL to shift the focus of their attention to a part of the packaging that is less craving inducing. To provide evidence for this possible explanation, the inclusion of eye tracking techniques during the vape package FMRI paradigm would be useful in interpreting the activation of these ROIs. In fact, this combination of methods has been used in cigarette smoking research and has allowed individual differences in attentional bias and neural responses during exposure to drug cues to be further understood (Kang et al., 2012). Further research is needed to understand, among those higher in trait food craving, the negative association between ROI response to food packaging and vaping.

Hypothesis 3.2 was partially supported. Before hypothesis testing, we expected that brain reactivity to vaping packaging with food stimuli would be a better predictor of increased vaping by itself than brain reactivity to vaping packaging with gray stimuli, but as the prior analyses have shown this has not been supported. Nonetheless, it was expected that increased ROI response to vaping packaging with food stimuli would interact with trait food cravings to predict higher levels of vaping where higher trait food cravings were seen. ROI response to vaping packaging with food stimuli did not significantly interact with trait food craving to predict vaping outcomes. Therefore, the main hypothesis was not supported.

Follow-up analyses for Hypothesis 3.2 showed that the RFG and LPT response to vaping packaging with food stimuli significantly interacted with trait food craving to predict vaping outcomes, but neither were in the expected direction. When both the RFG and LPT response to food packaging was higher, participants with higher levels of trait food cravings vaped less. We expected participants to vape more when RFG and LPT response was higher and when the participants had higher trait food cravings, but as with the analyses in Hypothesis 3.1, our predicted effects were in the opposite direction.

Findings from Hypothesis 3.2 suggest that, as the sole predictor, ROI response to food packaging does not interact with trait food craving to predict vaping outcomes. As previously stated, the sample with trait food craving data was smaller than the sample used to address the hypotheses in Aims 1 and 2. With the decreased sample size, we were likely not sufficiently powered to detect the effect of the ROI response to food packaging interacting with trait food craving to predict vaping outcomes. Additionally, among the participants in this sample, a relatively small group of individuals (n = 8) reported higher levels (+ 1 SD) trait food craving and this may be biasing our results (Meule, 2018). Among these individuals there is a higher level of variance with trait food craving and this is a challenge for this variable to serve as a valid and reliable estimate within our analyses. Thus, future studies with larger sample sizes would yield more reliable estimates of high levels of trait food craving. The trend of the negative association between ROI activation and vaping outcome, while not significant, did follow the same trend seen in Hypothesis 3.1. The attention-related structures did not exhibit significant interactions with trait food cravings to predict vaping outcomes in this analysis. Research coming from the food and diet literature has shown that individuals with higher levels of self-regulation have been found to have higher activation levels in visual areas of the brain (Smeets et al., 2013). This may help explain why areas involved in visual perception are exhibiting significant interactions in the opposite direction of what was expected. We did not include a self-regulation measure in this study, but future studies may consider this to determine if self-regulation is potentially responsible for the overall lower amount of vaping despite the increased levels of trait food craving. In addition, the inclusion of eye tracking and more qualitative assessments of packages may help untangle the complexity of these interactions.

General Conclusions

While we did not find significant responses in reward-related brain areas that are often implicated in the combustible cigarette literature, we did observe strong responses to our vaping package paradigm within known nodes of visual processing, selective attention, and language networks. The increased activation that we observed in these visual processing, language processing, and selective attention areas has been attributed to increased selective attention towards the more salient food and vaping cues, which is consistent with prior research (Hellmich et al., 2024; van der Laan et al., 2011). Like cigarette packaging, vaping packaging serves as a powerful cue for nicotine use, and these packages are designed with the intent of magnifying their cue effects (Shi et al., 2023; Wakefield et al., 2002). Because substance cues are often reported as a reason for relapse, the presence of salient cues on vaping packaging may maintain and potentially lead to escalation of vaping (Buczkowski et al., 2014). These packages, and the flavors that are often displayed with bright and colorful food cues, serve as an important advertising and marketing tool for vaping companies, thus there is a call for the investigation of their contributions to the initiation and escalation of vaping behaviors (Leventhal et al., 2019).

Due to the presence of some unexpected and marginally significant findings, further research is needed to determine how vaping packages affects young adults and their subsequent vaping outcomes. Future research should consider the strong and significant interaction effects that we have found with trait food craving and the salient food cues on packaging. While responses to grayscale packaging in those with higher levels of trait food craving predicted increased vaping, future research should determine whether the effect remains if all vaping cues are stripped from the packaging. Future research should focus on whether generic or plain packaging, devoid of any vaping cues, is associated with decreased neural responses compared to vaping packaging used in the current study which contained images of vaping cartridges on every package type. The implementation of plain packaging policies may reduce motivation to vape especially in vulnerable youth who find the bright and colorful packaging containing food cues appealing (Simonavičius et al., 2023). This appeal contributes to the introduction and initiation into nicotine use that can continue into adolescence, young adulthood, and beyond (Jones & Salzman, 2020). By minimizing the number of adolescents introduced to vaping, we can limit how many of those individuals go on to develop nicotine addiction through vaping and smoking cigarettes in adulthood. While reducing the appeal of these vaping products to youth is beneficial to not prompt the initiation of nicotine use, there is also evidence that adults who may be using vaping as a smoking cessation tool do not find generic packaging to be less appealing (Taylor et al., 2023). In addition to other regulatory strategies, the regulation of packaging in addition to the restriction of the use of flavors in both cartridge-based and disposable vaping products would theoretically reduce the desirability of these products in youth and reduce their risk of nicotine use overall (Reiter et al., 2024).

Increased brain responses in those with higher levels of trait food cravings to vaping packaging containing food and vaping cues (i.e., cartridges) warrant further research aimed at understanding how these stimuli influence vaping behaviors in samples that are more representative of vapers overall. Flavors are often cited as a reason to initiate nicotine vaping, and the appetitive food cues on packaging can further entice individuals with higher levels of food cravings (Villanti et al., 2017). Additionally, both cigarette and vaping users have been known to use nicotine to suppress their appetite and cravings, but evidence suggests that the effectiveness of this strategy is exaggerated (Chao et al., 2017; Kechter et al., 2022). Smokers who experience higher levels of nicotine dependence have been found to have higher levels of food cravings, but not after accounting for symptoms of stress and depression (Chao et al., 2017). In fact, the increased nicotine and food intake may be collectively associated with increased stress and depressive symptoms. Those who use vaping products with appetitive flavors often report doing so to satisfy their food cravings (Kechter et al., 2022). However, in the long term this does not decrease their food and nicotine consumption and instead increases it (Dobbie et al., 2020). The vaping flavors and nicotine both act on the reward systems of the brain, and it is no surprise that the high caloric sweet foods and fruits that individuals often crave are often the same flavors the vapers desire (Castro et al., 2023; De Biasi & Dani, 2011; Ma et al., 2022; Meule, 2020a). Overall, this study contributes to our understanding of vaping packaging by highlighting the interaction of the stimuli present on the packaging and existing trait food cravings in predicting vaping outcomes. These findings have implications for public health and stress the need for regulation of the allurement and enticement of vaping packaging containing appetitive food stimuli in addition to other vaping cues.

Limitations

There are important limitations of the current study that should be considered when interpreting the study outcomes. First, the participants in this study were limited to young adults who were classified as heavy vapers without a history of combustible cigarette use. There are various definitions of heavy vapers, so these results should only be interpreted within the context of our definition of a heavy vaper and these results may not generalize to other samples of vapers. While the goal of this research was to assess outcomes in young adults, they are not the only age group who vapes. It is unknown whether these results would generalize to other age groups. Additionally, the participants in this study were predominantly white and female. While the prevalence of vaping is highest among White YAs and males, this study population does not accurately reflect the true diversity and range of individuals who vape (Kramarow & Elgaddal, 2023a). Additionally, it is quite common for individuals who vape to also smoke combustible cigarettes or have a history of smoking them. Among adult vapers, 29.4% also smoke combustible cigarettes while 40.3% have a history of smoking cigarettes (Kramarow & Elgaddal, 2023b). The sample of the current study is solely focused on individuals without a history of smoking cigarettes (30.3% of adults fall into this category) so these results may not generalize to this substantial portion of vapers who are dual users of these two methods of nicotine use or at least have a history of smoking cigarettes.

Second, After accounting for incomplete, missing, or invalid data, this study's sample size was below what would be considered acceptable for hypothesis testing despite finding strong effects in expected brain regions at the group level reliably (Turner et al., 2018). Specifically, the sample for the analyses including trait food cravings were even lower, so this affected the statistical power for hypothesis testing. With a larger sample that is more reflective of those who vape, there are important effects with smaller effect sizes that could be uncovered.

Third, the amount of prior FMRI research that has been done in relation to vaping is quite limited. Some of the rationale and many of the power estimates that we used for this study were based on similar research that was published in the combustible cigarette literature. It remains unclear whether results from combustible cigarette research literature will generalize to vaping. More research in this area is necessary to determine the nature of this relationship between the two types of nicotine use methods.

Fourth, FMRI is a useful tool to help understand the underlying mechanisms that drive substance use and addiction, but it has limitations. Small movements during scanning sessions can be a major hinderance to the quality of the data (Wylie et al., 2014). Exclusion due to excessive movement can threaten internal and external validity. Furthermore, given significant variability in brain organization and functioning, larger samples are important to obtain reliable group level effects and account for participants who are inevitably excluded due to excessive motion during FMRI data processing.

Fifth, self-report measures are known to have limitations in which a person, intentionally or unintentionally, does not report their behavior accurately. In the current study, this could certainly occur when individuals are reporting their levels of food cravings or amount of vaping that they could perceive as being unhealthy or abnormal. This will affect the ability to predict outcomes. Ultimately, this is why a combination of objective assessments alongside these subjective assessments is essential (Khalili et al., 2021).

Future Directions and Conclusions

We have provided evidence of the utility of this novel vaping cue reactivity paradigm using FMRI. Addiction to nicotine is signaled by increased neural responses to nicotine-related cues that individuals have been conditioned to over time. Drug cues elicit cravings which are responsible for the maintenance, escalation, and even relapse of substance use. Our FMRI results show that young adult vapers without a history of smoking cigarettes displayed significant neural responses to vaping cues associated with the packaging of vaping products. However, these are some of the first findings that are uncovering the neurocognitive mechanisms tied to the maintenance and potential escalation of vaping behaviors. Other researchers can expand on this work to explore the impact that other variables, such as mental health (i.e., depression) and stress, the use of other tobacco products and other substances, and the interpersonal and social factors have on the underlying mechanisms that lead to vaping initiation, maintenance, and escalation (McCausland et al., 2024). Additionally, we provide evidence that a person's trait food cravings can affect the connection between their perception of vaping specific cues and their own vaping behaviors. Therefore, further investigation into how food craving interact with neural responses to vaping to predict vaping outcomes is warranted. Finally, researchers should consider a multimethod approach in which FMRI data is collected alongside psychophysiological responding (e.g., eye tracking, galvanic skin response, heart rate variability).

Because understanding vaping outcomes using an FMRI vaping packaging cue reactivity paradigm is a novel approach, there are many aspects that future researchers can build upon and improve. While future sample sizes should be larger, it is also important that they be more representative of the population of people who vape. The current study provides insight into the potential impact of the design of vaping packaging. We identified brain regions, primarily involved in visual perception, selective attention, and language functioning, that significantly responded to vaping packaging with food and vaping cues (i.e., cartridges). We propose that the cues present on these packages elicit increased focus and attention on vaping packages, and this remains true even if color is removed. This increased attention is likely a product of the increased salience of the packaging stimuli. These, often intentional, design features are drawing the attention of individuals and eliciting significant neural responses that are interacting with their trait food cravings to predict vaping outcomes. Even though, unexpectedly, the grayscale packaging in the current study interacted with trait food craving to predict increased levels of vaping, there is evidence that the presence of vaping cues, like cartridges for vaping devices, are enough to elicit a significant response. The color and the food stimuli that are often present on vaping packaging may only serve to increase the overall salience of the packaging. Therefore, more research is needed to determine if packaging without any vaping cues may lead to less reactivity overall. By understanding how the stimuli present on vaping packaging influence these neural systems, we can inform policies that can be implemented to restrict the content allowed on vaping packaging.

Adapting what is observed in research into public health policies and initiatives is critical for reducing the impact that vaping has on vulnerable populations like adolescents and young adults. While the public health threat of vaping continues to grow, this research will add to the limited existing research findings to inform work towards preventing the initiation and escalation of vaping overall.

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TABLES

Table 3.1

Regions of Interest (ROIs) with Significant Response to Gray or Food Packaging

ROI	Size (In Voxels)	x	y	z
1. Right Inferior Occipital Gyrus (RIOG)	120	-28.3	+94.3	-10.9
2. Right Superior Occipital Gyrus (RSOG)	101	-16.2	+89.9	+14.3
3. Right Caudal Inferior Frontal Sulcus (RCIFS)	97	-45.7	-15.1	+29.8
4. Right Inferior Parietal Lobule (RIPL)	75	-30.7	+63.7	+39.9
5. Left Inferior Parietal Lobule (LIPL)	63	+28.1	+63.7	+34.9
6. Right Lingual Gyrus (RLG)	26	-12.5	+72.6	-6.0
7. Left Posterior Thalamus (LPT)	23	+21.4	+30.4	-0.8
8. Left Caudal Inferior Frontal Sulcus (LCIFS)	20	+42.5	-8.7	+28.6
9. Left Entorhinal Cortex (LEC)	10	+30.1	+8.3	-27.1
10. Right Fusiform Gyrus (RFG)	10	-38.5	+61.9	-13.8

Note: Center of mass RAI Talairach x, y, z coordinates are reported. Size = number of 3.5mm isometric voxels. Significance threshold is FDR-corrected $p < .001$ and at least 10 voxels.

Table 3.2:
Hypothesis 2.1 Linear Regression Results: All ROI Responses to Gray Packaging

	Unstandardized Coefficients		Standardized Coefficient		
	B	S.E.	β	*t*	*p*
1. All ROI Response to Gray	1.351	3.066	0.058	0.441	0.331
2. Sex	-1.632	1.026	-0.210	-1.591	0.059
Constant	8.046	0.763	-	10.542	0.000***
Residual standard error: 3.587 on 56 degrees of freedom Multiple R^2: 0.04397, Adjusted R^2: 0.009831 *F*-statistic: 1.288 on 2 and 56 *DF*, *p*-value: 0.142					

Note: ($n = 59$); Dependent Variable: total number of puffs (total puffs across 4 weeks); All ROI Response to Gray = weighted average of 10 functionally defined ROIs ; * = One-tailed $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

Table 3.3:

Follow-Up Analyses of Hypothesis 2.1 Linear Regression Results: Individual ROI Response to Gray Packaging

	1	2	3	4	5	6	7	8	9	10
LCIFS	64.43 (65.43)									
LEC		40.065 (163.77)								
LIPL			4.350 (23.439)							
RCIFS				6.553 (14.994)						
RFG					59.483 (75.632)					
RIOG						3.113 (5.727)				
RIPL							18.634 (17.624)			
RLG								-30.394 (28.141)		
LPT									-78.369 (66.911)	
RSOG										-2.411 (7.211)
Sex	-1.544 (1.008)	-1.574 (1.016)	-1.572 (1.016)	-1.590 (1.016)	-1.632 (1.014)	-1.715 (1.050)	-1.700* (1.014)	-1.616 (1.007)	-1.641 (1.006)	-1.612 (1.024)
Constant	7.726*** (0.787)	8.203*** (0.632)	8.153*** (0.862)	7.984*** (0.869)	7.895*** (0.738)	6.701** (2.948)	7.652*** (0.810)	7.712*** (0.762)	8.588*** (0.615)	8.037*** (0.906)
Observations	59	59	59	59	59	59	59	59	59	59
Multiple R^2	0.057	0.042	0.041	0.044	0.051	0.046	0.059	0.060	0.064	0.043
Adjusted R^2	0.023	0.007	0.007	0.010	0.017	0.012	0.026	0.027	0.030	0.008
Residual Std. Error ($df = 56$)	3.563	3.591	3.592	3.587	3.574	3.584	3.558	3.556	3.550	3.590
F Statistic ($df = 2; 56$)	1.692	1.218	1.205	1.286	1.509	1.341	1.769	1.795	1.902	1.245

Note: Unstandardized coefficient and standard error are reported for each ROI. * = One-tailed $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

Table 3.4:
Hypothesis 2.2 Linear Regression Results: All ROI Responses to Food Packaging

	Unstandardized Coefficients		Standardized Coefficient		
	B	S.E.	β	*t*	*p*
1. All ROI Response to Food	2.625	2.266	0.153	1.159	0.126
2. Sex	-1.788	1.022	-0.230	-1.749	0.043*
Constant	7.467	0.891	-	8.382	0.000***

Residual standard error: 3.551 on 56 degrees of freedom
Multiple R^2: 0.06312, Adjusted R^2: 0.02966
F-statistic: 1.886 on 2 and 56 *DF*, *p*-value: 0.081

Note: (n = 59); Dependent Variable: total number of puffs (total puffs across 4 weeks); All ROI Response to Food Packaging = weighted average of 10 functionally defined ROIs ; * = One-tailed $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

Table 3.5:

Hypothesis 2.2 Linear Regression Follow-Up Analyses: Individual ROI Responses to Food Packaging

	1	2	3	4	5	6	7	8	9	10
LCIFS	97.908* (45.272)									
LEC		184.090 (145.661)								
LIPL			16.964 (12.840)							
RCIFS				17.129* (10.052)						
RFG					64.779* (38.016)					
RIOG						3.166 (5.755)				
RIPL							18.030 (13.784)			
RLG								2.929 (31.005)		
LPT									85.954 (62.968)	
RSOG										-2.545 (8.201)
Sex	-1.601 (0.976)	-1.546 (1.002)	-1.579 (1.001)	-1.744* (0.996)	-1.904* (1.010)	-1.769 (1.079)	-1.661 (1.003)	-1.564 (1.016)	-1.599 (1.000)	-1.598 (1.021)
Constant	7.098*** (0.766)	7.498*** (0.827)	1.954 (4.816)	7.588*** (0.680)	-13.462 (12.768)	6.620** (3.060)	7.474*** (0.825)	8.297*** (0.607)	7.490*** (0.797)	8.210*** (0.598)
Observations	59	59	59	59	59	59	59	59	59	59
Multiple R^2	0.115	0.067	0.070	0.088	0.088	0.046	0.069	0.041	0.072	0.042
Adjusted R^2	0.083	0.034	0.036	0.055	0.055	0.012	0.036	0.007	0.038	0.008
Residual Std. Error (df = 56)	3.452	3.543	3.538	3.504	3.504	3.584	3.540	3.593	3.535	3.590
F Statistic (df = 2; 56)	3.624**	2.019	2.097	2.700*	2.700*	1.344	2.078	1.191	2.158	1.237

Note: Unstandardized coefficient and standard error are reported for each ROI. * = One-tailed p < 0.05, ** = p < 0.01, *** = p < 0.001.

Table 3.6:
Hypothesis 2.3 Linear Regression Results: All ROI Responses to Gray and Food Packaging

	Unstandardized Coefficients		Standardized Coefficient		
	B	S.E.	β	*t*	*P*
1. All ROI Response to Gray	-1.219	3.840	-0.053	-0.318	0.376
2. All ROI Response to Food	3.176	2.867	0.185	1.108	0.137
3. Sex	-1.788	1.032	-0.229	-1.720	0.046*
Constant	7.504	0.906	-	8.286	0.000***

Residual standard error: 3.58 on 55 degrees of freedom
Multiple R^2: 0.06483, Adjusted R^2: 0.01382
F-statistic: 1.271 on 3 and 55 *DF*, p-value: 0.147

Note: (n = 59); Dependent Variable: total number of puffs (total puffs across 4 weeks); All ROI Response to Gray = weighted average of 10 functionally defined ROIs; All ROI Response to Food Packaging = weighted average of 10 functionally defined ROIs ; * = One-tailed $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

Table 3.7:
Linear Regression Results, Hypothesis 2.3 Follow-Up Analyses, Individual ROI Response to Gray and Food Packaging

	1	2	3	4	5	6	7	8	9	10
LCIFS (Gray)	-10.985 (75.299)									
LCIFS (Food)	102.047* (53.768)									
LEC (Gray)		-55.175 (179.392)								
LEC (Food)		204.932 (161.734)								
LIPL (Gray)			-27.329 (30.597)							
LIPL (Food)			26.913 (17.015)							
RCIFS (Gray)				-8.149 (17.092)						
RCIFS (Food)				19.957* (11.732)						
RFG (Gray)					-51.608 (102.683)					
RFG (Food)					82.947 (52.644)					
RIOG (Gray)						1.780 (8.098)				
RIOG (Food)						1.913 (8.137)				
RIPL (Gray)							5.597 (24.179)			
RIPL (Food)							15.029 (19.009)			
RLG (Gray)								-51.580 (35.725)		
RLG (Food)								37.543 (38.959)		
LPT (Gray)									-190.674** (77.330)	
LPT (Food)									187.800** (73.084)	
RSOG (Gray)										-1.655 (10.053)
RSOG (Food)										-1.246 (11.432)
Sex	-1.606 (0.985)	-1.532 (1.011)	-1.542 (1.003)	-1.742* (1.003)	-1.942* (1.020)	-1.774 (1.088)	-1.686 (1.018)	-1.632 (1.007)	-1.824* (0.962)	-1.613 (1.034)
Constant	7.142*** (0.829)	7.508*** (0.834)	-0.990 (5.843)	7.835*** (0.859)	-19.229 (17.230)	6.375* (3.280)	7.420*** (0.864)	7.601*** (0.771)	7.321*** (0.766)	8.080*** (0.995)
Observations	59	59	59	59	59	59	59	59	59	59
Multiple R^2	0.115	0.069	0.083	0.092	0.092	0.047	0.070	0.076	0.164	0.043

Adjusted R^2	0.067	0.018	0.033	0.042	0.043	-0.005	0.019	0.025	0.118	-0.009
Residual Std. Error ($df = 55$)	3.483	3.572	3.545	3.528	3.527	3.614	3.570	3.559	3.385	3.622
F Statistic ($df = 3; 55$)	2.381*	1.356	1.659	1.851	1.860	0.897	1.380	1.505	3.596**	0.819

Note: Unstandardized coefficient and standard error are reported for each ROI. * = One-tailed $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

Table 3.8:
ANOVA Results, Hypothesis 2.3, Comparing All ROIs Regression Models

	Res. *DF*	RSS	*DF*	Sum of Sq	*F*	*p*
Model 1 (Gray)	56	720.53				
Model 2 (Gray + Food)	56	704.81	1	15.719	1.2267	0.136

Note: Model 1 = All ROI Response to Gray predicting total puffs; Model 2: All ROI Response to Gray and All ROI response to Food predicting total puffs; * = One-tailed $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

Table 3.9:

ANOVA Results, Hypothesis 2.3, Comparing Individual ROIs Regression Models

		Res. *DF*	RSS	*DF*	Sum of Sq	*F*	*p*
LCIFS	Model 1 (Gray)	56	710.72				
	Model 2 (Gray + Food)	55	667.03	1	43.686	3.6021	0.032*
LEC	Model 1 (Gray)	56	722.25				
	Model 2 (Gray + Food)	55	701.77	1	20.485	1.6055	0.105
LIPL	Model 1 (Gray)	56	722.58				
	Model 2 (Gray + Food)	55	691.14	1	31.437	2.5017	0.060
RCIFS	Model 1 (Gray)	56	720.57				
	Model 2 (Gray + Food)	55	684.55	1	36.016	2.8937	0.047
RFG	Model 1 (Gray)	56	715.13				
	Model 2 (Gray + Food)	55	684.24	1	30.885	2.4826	0.060
RIOG	Model 1 (Gray)	56	719.23				
	Model 2 (Gray + Food)	55	718.51	1	0.72167	0.0552	0.408
RIPL	Model 1 (Gray)	56	708.87				
	Model 2 (Gray + Food)	55	700.91	1	7.9659	0.6251	0.216
RLG	Model 1 (Gray)	56	708.27				
	Model 2 (Gray + Food)	55	696.51	1	11.76	0.9287	0.170
LPT	Model 1 (Gray)	56	705.74				
	Model 2 (Gray + Food)	55	630.09	1	75.646	6.603	0.006**
RSOG	Model 1 (Gray)	56	721.58				
	Model 2 (Gray + Food)	55	721.43	1	0.15573	0.0119	0.457

Note: Model 1 = Individual ROI Response to Gray predicting total puffs; Model 2: Individual ROI Response to Gray and All ROI response to Food predicting total puffs; * = One-tailed $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

Table 3.10:
Linear Regression Results, Hypothesis 3.1, All ROI Response to Gray and Food Packaging Interacting with Trait Food Craving

	Unstandardized Coefficients		Standardized Coefficient		
	B	S.E.	β	*t*	*p*
1. All ROI Response to Gray	-29.133	16.578	-1.287	-1.757	0.044*
2. All ROI Response to Food	27.313	11.455	1.729	2.384	0.011*
3. Trait Food Craving	0.072	0.040	0.354	1.797	0.040*
4. Sex	-0.098	1.231	-0.013	-0.080	0.468
5. All ROI Response to Gray x Trait Food Craving	0.665	0.360	1.817	1.846	0.036*
6. All ROI Response to Food x Trait Food Craving	-0.572	0.255	-2.193	-2.240	0.015*
Constant	4.227	2.192	-	1.928	0.061

Residual standard error: 3.405 on 39 degrees of freedom
Multiple R^2: 0.145, Adjusted R^2: 0.01341
F-statistic: 1.102 on 6 and 39 *DF*, *p*-value: 0.189

Note: (*n* = 59); Dependent Variable: total number of puffs (total puffs across 4 weeks); All ROI Response to Gray = weighted average of 10 functionally defined ROIs; All ROI Response to Food Packaging = weighted average of 10 functionally defined ROIs ; Trait Food Craving = scores on G-FCQ-T; All ROI Response to Gray x Trait Food Craving = interaction between weighted average of 10 functionally defined ROIs and scores on G-FCQ-T; All ROI Response to Food x Trait Food Craving = interaction between weighted average of 10 functionally defined ROIs and scores on G-FCQ-T; * = One-tailed $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

Table 3.11:
Linear Regression Results, Hypothesis 3.1 Follow-Up Analyses, Individual ROI Response to Gray and Food Packaging Interacting with Trait Food Craving

	1	2	3	4	5	6	7	8	9	10
LCIFS (Gray)	-440.092									
	(264.269)									
LCIFS (Food)	435.707**									
	(181.253)									
LEC (Gray)		-15.235								
		(591.846)								
LEC (Food)		1,157.415								
		(783.734)								
LIPL (Gray)			-133.923							
			(113.484)							
LIPL (Food)			120.832**							
			(53.455)							
RCIFS (Gray)				-119.874*						
				(60.348)						
RCIFS (Food)				91.017**						
				(36.407)						
RFG (Gray)					-593.477					
					(355.609)					
RFG (Food)					542.717***					
					(196.567)					
RIOG (Gray)						-35.598				
						(26.202)				
RIOG (Food)						27.293				
						(26.189)				
RIPL (Gray)							-82.389			
							(91.599)			
RIPL (Food)							120.239			
							(73.719)			
RLG (Gray)								-153.440		
								(174.546)		
RLG (Food)								223.997		
								(169.307)		
LPT (Gray)									-131.449	
									(340.377)	
LPT (Food)									385.499	
									(272.184)	
RSOG (Gray)										9.951
										(41.791)
RSOG (Food)										10.404
										(44.607)
Trait Food Craving	0.039	0.097*	0.657*	-0.031	3.333**	-0.048	0.043	0.024	0.055	-0.018
	(0.047)	(0.057)	(0.366)	(0.048)	(1.387)	(0.178)	(0.046)	(0.054)	(0.045)	(0.074)
Sex	-0.422	0.055	-0.350	-1.013	-0.426	0.209	-0.540	-0.301	-1.094	-0.221
	(1.084)	(1.268)	(1.158)	(1.161)	(1.165)	(1.343)	(1.181)	(1.206)	(1.155)	(1.234)
LCIFS (Gray) x Craving	9.384*									
	(5.007)									
LCIFS (Food) x Craving	-6.433*									
	(3.600)									

LEC (Gray) x Craving		-0.144 (11.932)								
LEC (Food) x Craving		-18.687 (13.706)								
LIPL (Gray) x Craving			2.064 (2.312)							
LIPL (Food) x Craving			-1.823* (1.078)							
RCIFS (Gray) x Craving				2.736* (1.397)						
RCIFS (Food) x Craving				-1.586* (0.783)						
RFG (Gray) x Craving					13.590 (8.336)					
RFG (Food) x Craving					-10.174* (4.298)					
RIOG (Gray) x Craving						0.868 (0.537)				
RIOG (Food) x Craving						-0.726 (0.518)				
RIPL (Gray) x Craving							1.808 (1.932)			
RIPL (Food) x Craving							-2.070 (1.499)			
RLG (Gray) x Craving								1.978 (3.483)		
RLG (Food) x Craving								-3.196 (3.062)		
LPT (Gray) x Craving									-1.008 (6.989)	
LPT (Food) x Craving									-3.783 (6.262)	
RSOG (Gray) x Craving										-0.204 (0.824)
RSOG (Food) x Craving										-0.296 (0.827)
Constant	4.924** (2.292)	2.423 (3.560)	-34.621* (18.222)	8.872*** (2.293)	-170.80** (64.086)	11.289 (11.221)	5.219** (2.234)	6.601** (2.870)	4.696** (2.141)	9.087** (3.731)
Observations	46	46	46	46	46	46	46	46	46	46
Multiple R^2	0.253	0.073	0.165	0.185	0.203	0.085	0.123	0.097	0.207	0.050
Adjusted R^2	0.138	-0.069	0.036	0.059	0.081	-0.056	-0.012	-0.042	0.085	-0.096
Residual Std. Error (*df* = 56)	3.184	3.544	3.365	3.325	3.287	3.522	3.449	3.499	3.279	3.588
F Statistic (*df* = 2; 56)	2.196*	0.516	1.283	1.474	1.657	0.605	0.910	0.698	1.697	0.344

Note: Unstandardized coefficient and standard error are reported for each ROI. * = One-tailed $p <$ 0.05, ** = $p < 0.01$, *** = $p < 0.001$.

Table 3.12:
Linear Regression Results, Hypothesis 3.2, All ROI Response to Food Packaging Interacting with Trait Food Craving

	Unstandardized Coefficients		Standardized Coefficient		
	B	S.E.	β	*t*	*p*
1. All ROI Response to Food	9.397	6.143	0.595	1.530	0.067
2. Trait Food Craving	0.057	0.040	0.282	1.434	0.080
3. Sex	-0.544	1.228	-0.070	-0.443	0.330
4. All ROI Response to Food x Trait Food Craving	-0.145	0.108	-0.556	-1.343	0.093
Constant	4.915	2.189	-	2.246	0.015*

Residual standard error: 3.463 on 41 degrees of freedom
Multiple R^2: 0.0702, Adjusted R^2: -0.02052
F-statistic: 0.7738 on 4 and 41 *DF*, *p*-value: 0.274

Note: ($n = 59$); Dependent Variable: total number of puffs (total puffs across 4 weeks); All ROI Response to Gray = weighted average of 10 functionally defined ROIs; All ROI Response to Food Packaging = weighted average of 10 functionally defined ROIs ; Trait Food Craving = scores on G-FCQ-T; All ROI Response to Food x Trait Food Craving = interaction between weighted average of 10 functionally defined ROIs and scores on G-FCQ-T; * = One-tailed $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

Table 3.13:
Linear Regression Results, Hypothesis 3.2 Follow-Up Analyses, Individual ROI Response to Food Packaging Interacting with Trait Food Craving

	1	2	3	4	5	6	7	8	9	10
LCIFS (Food)	238.754* (134.173)									
LEC (Food)		1,157.994 (734.322)								
LIPL (Food)			77.480* (38.042)							
RCIFS (Food)				41.992 (27.514)						
RFG (Food)					281.155* (120.263)					
RIOG (Food)						0.543 (19.986)				
RIPL (Food)							61.959* (35.220)			
RLG (Food)								106.950 (105.810)		
LPT (Food)									453.109* (206.982)	
RSOG (Food)										19.218 (23.887)
Trait Food Craving	0.053 (0.047)	0.096* (0.055)	0.466 (0.279)	0.036 (0.035)	1.474* (0.764)	0.048 (0.164)	0.056 (0.043)	-0.001 (0.042)	0.070* (0.041)	-0.003 (0.040)
Sex	-0.409 (1.105)	0.055 (1.192)	-0.288 (1.147)	-0.782 (1.183)	-0.649 (1.159)	-0.213 (1.324)	-0.495 (1.161)	-0.269 (1.210)	-0.665 (1.150)	-0.187 (1.187)
LCIFS (Food) x Craving	-2.448 (2.893)									
LEC (Food) x Craving		-18.927 (12.183)								
LIPL (Food) x Craving			-1.168 (0.742)							
RCIFS (Food) x Craving				-0.477 (0.550)						
RFG (Food) x Craving					-4.364* (2.307)					
RIOG (Food) x Craving						-0.047 (0.322)				
RIPL (Food) x Craving							-0.836 (0.702)			
RLG (Food) x Craving								-1.657 (1.860)		
LPT (Food) x Craving									-7.476* (4.116)	
RSOG (Food) x Craving										-0.467 (0.438)
Constant	4.387* (2.316)	2.467 (3.421)	-22.058 (14.433)	5.928*** (1.791)	-86.539** (40.023)	6.924 (10.191)	4.754** (2.146)	8.635*** (2.188)	4.310** (2.045)	8.353*** (2.085)

Observations	46	46	46	46	46	46	46	46	46	46
Multiple R^2	0.183	0.073	0.123	0.101	0.146	0.020	0.103	0.041	0.128	0.049
Adjusted R^2	0.103	-0.017	0.037	0.014	0.062	-0.076	0.016	-0.052	0.043	-0.044
Residual Std. Error (df = 56)	3.246	3.457	3.363	3.404	3.319	3.555	3.401	3.517	3.353	3.503
F Statistic (df = 2; 56)	2.296*	0.811	1.436	1.156	1.749	0.208	1.178	0.439	1.510	0.526

Note: Unstandardized coefficient and standard error are reported for each ROI. * = One-tailed $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

FIGURES

Figure 1.1.

Conceptual Model for Hypothesis 3.1.

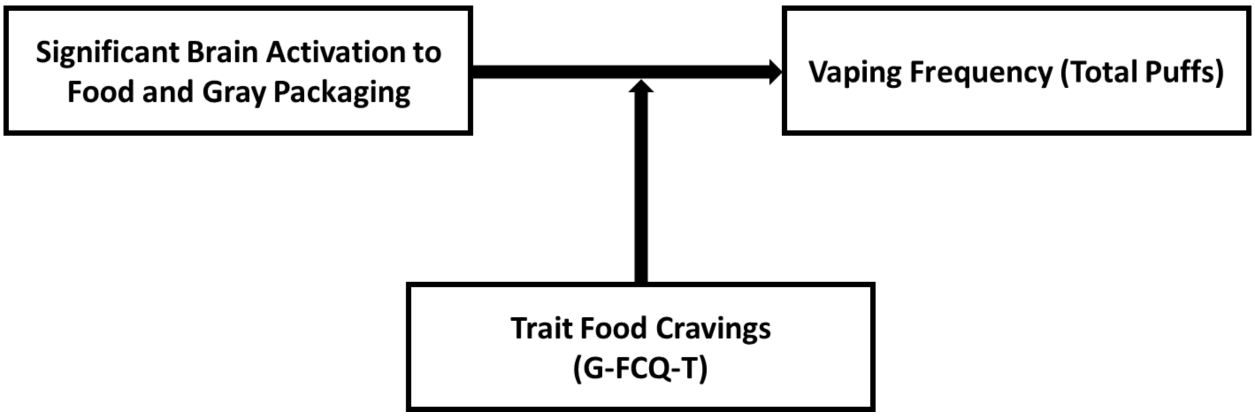


Figure 1.2.

Conceptual Model for Hypothesis 3.2.

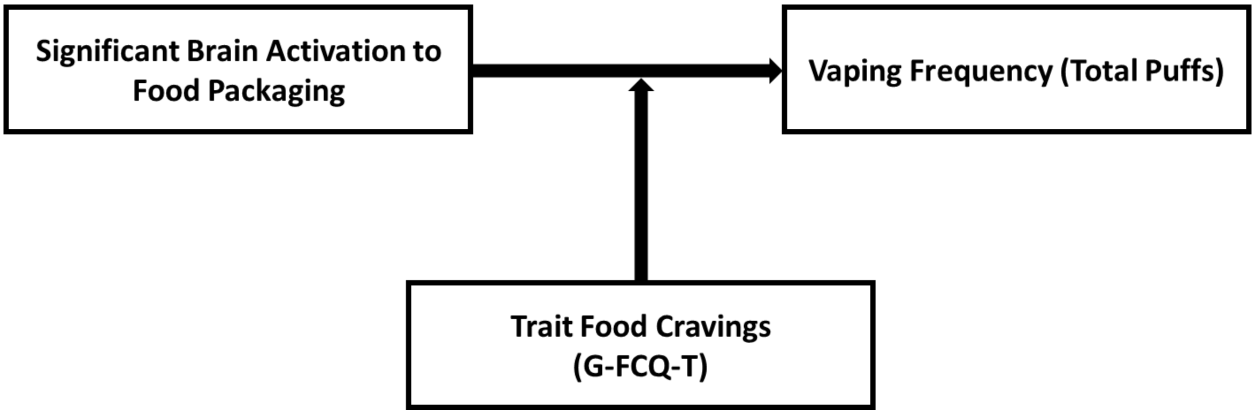


Figure 2.1

Example Internet/Paper Flier Advertisements

(A)

(B)

Figure 2.2

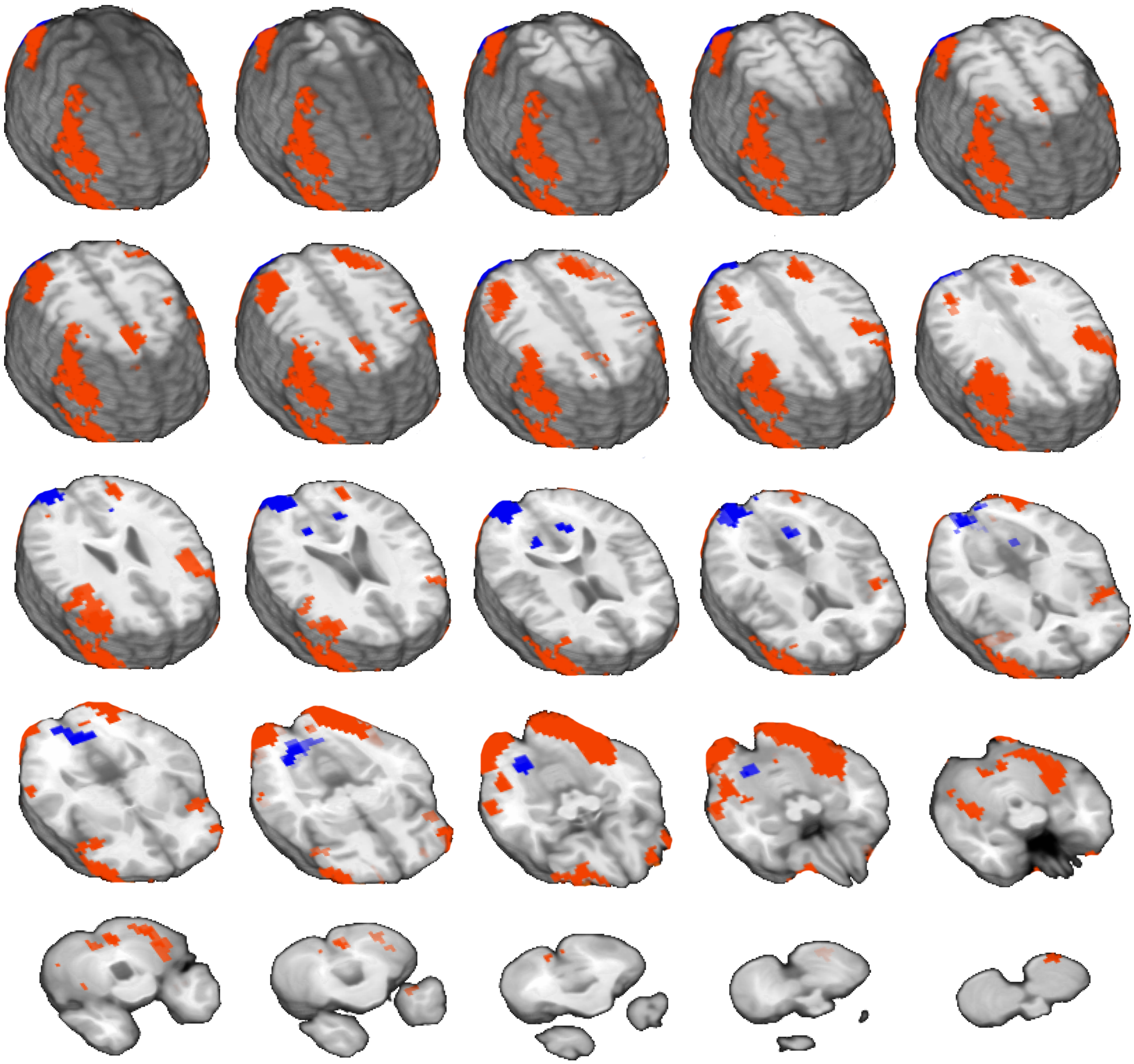
Example Packaging of Three Stimulus Types and Control

(A) (B) (C) (D)

Note. Figures 2.2A – 2.2C display three examples of vaping packaging with (A) food image, color, and name; (B) food color and name; (C) grayscale color scheme and food name, respectively. Figure 2.2D displays an example of a scrambled control image. Scrambled images were created by pixelating images of vaping packages and scrambling the pixels to serve as a control condition.

Figure 3.1

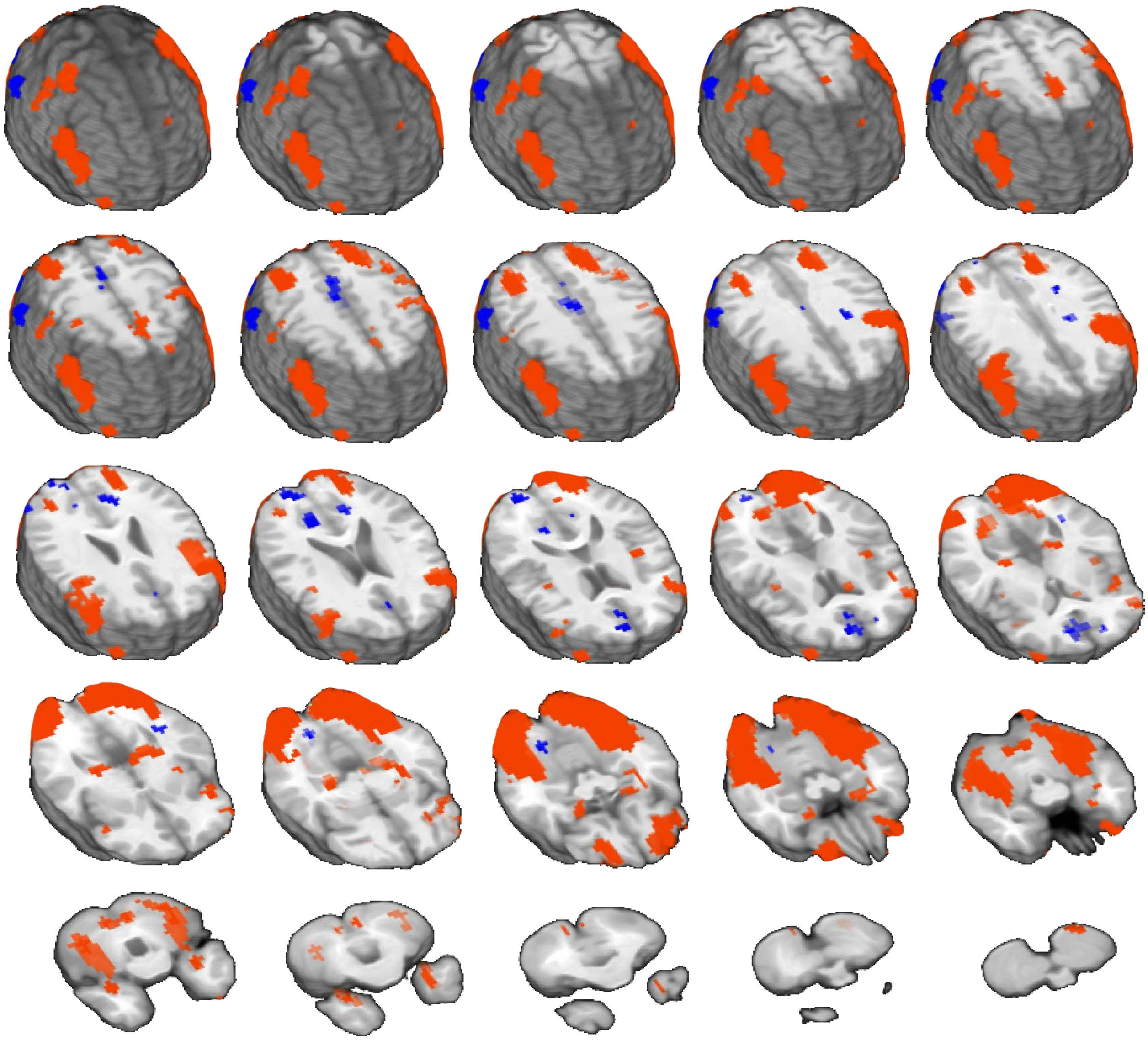
Significant Brain Responses to Gray Packaging



Note: Brain activation (red) and deactivation (blue) to grayscale vaping packaging with no food stimuli. Map is thresholded to FDR-corrected $p < .001$. Slices are from z-plane = 75 to z-plane = -45 in 5-millimeter increments.

Figure 3.2

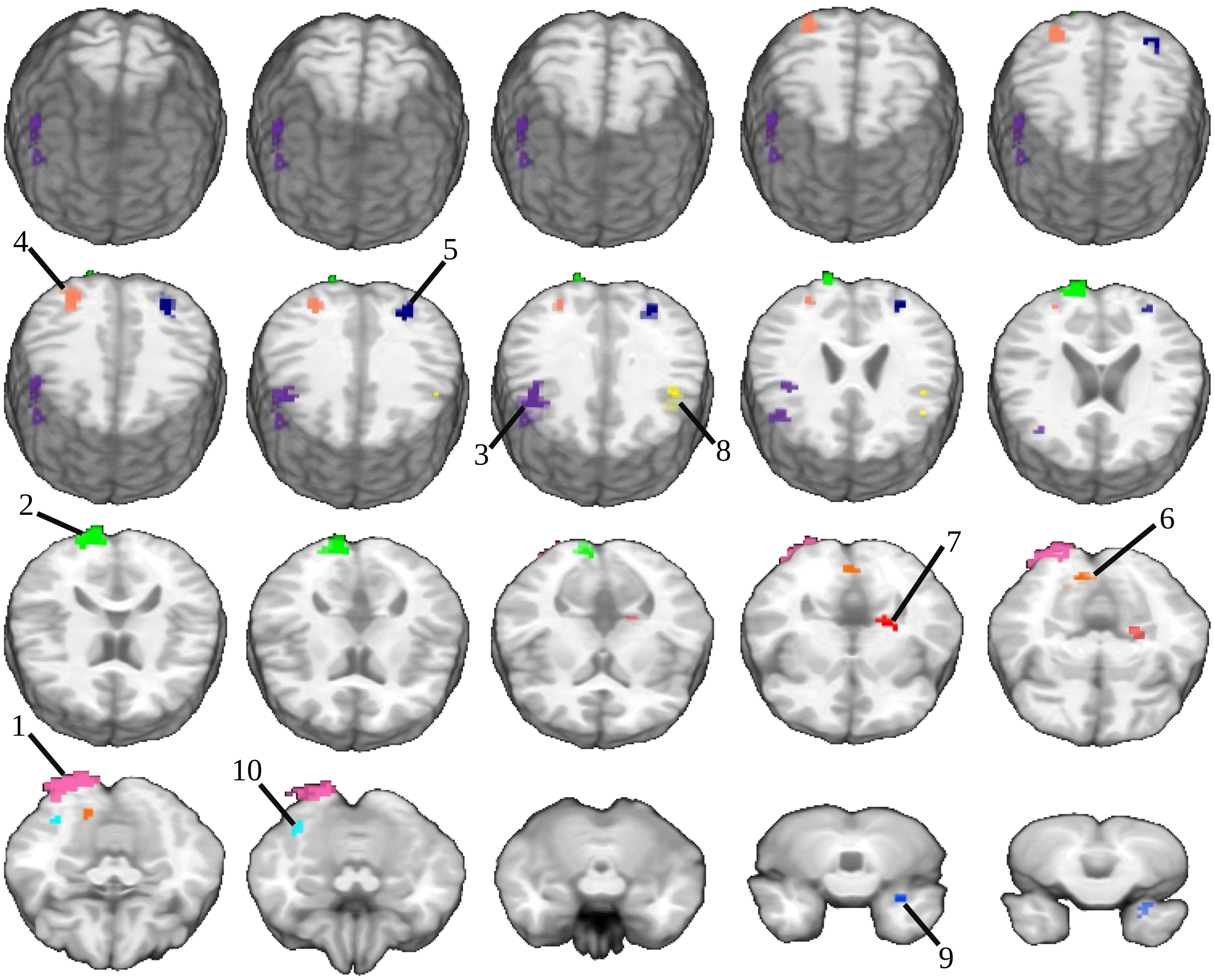
Significant Brain Responses to Food Packaging



Note: Brain activation (red) and deactivation (blue) to colorful vaping packaging with food stimuli. Map is thresholded to FDR-corrected $p < .001$. Slices are from z-plane = 75 to z-plane = -45 in 5-millimeter increments.

Figure 3.3

Regions of Interest (ROIs) with Significant Response to Gray or Food Packaging



Note: Regions of interest (ROIs) with significant response to gray or food packaging. Numbers correspond to each ROI listed in Table 3.1. ROI Colors: 1 = Pink, 2 = Green, 3 = Purple, 4 = Salmon, 5 = Navy Blue, 6 = Orange, 7 = Red, 8 = Yellow, 9 = Blue, and 10 = Cyan. Slices are from z-plane = 65 to z-plane = -30 in 5-millimeter increments.

Figure 3.4

Interaction Plot, Hypothesis 3.1, All ROI Response to Gray Packaging and Trait Food Craving

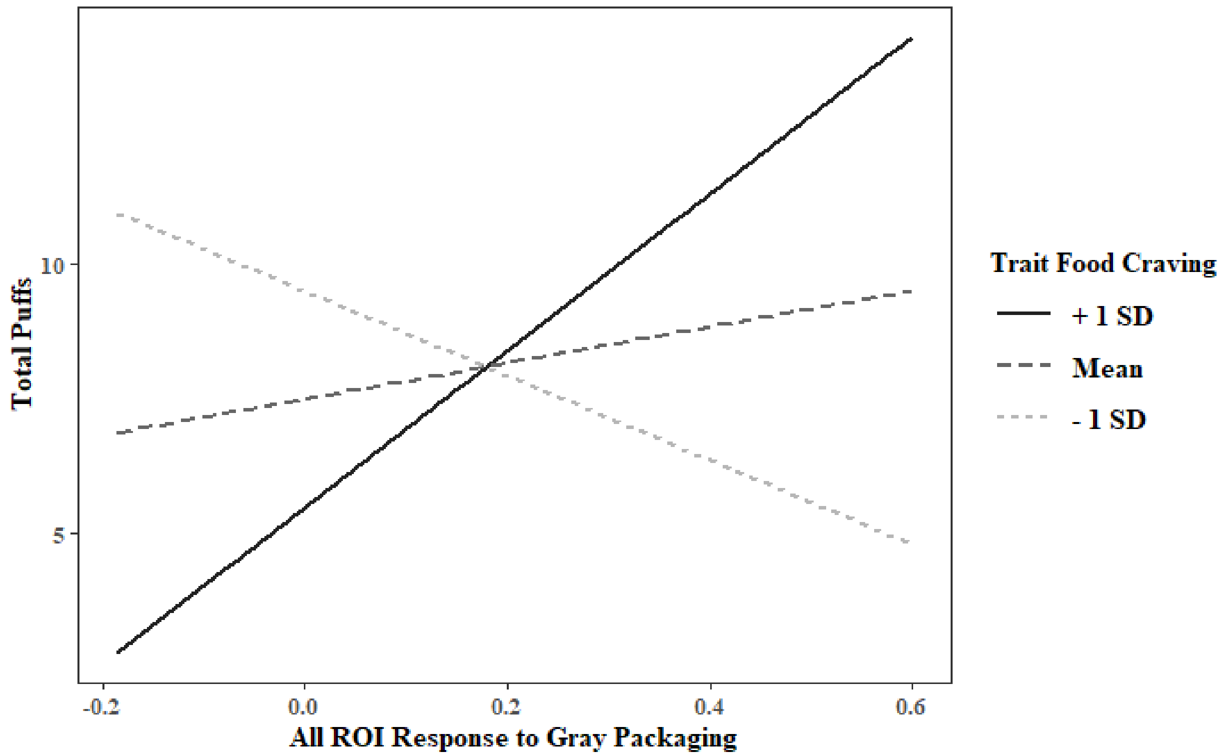


Figure 3.5

Interaction Plot, Hypothesis 3.1, All ROI Response to Food Packaging and Trait Food Craving

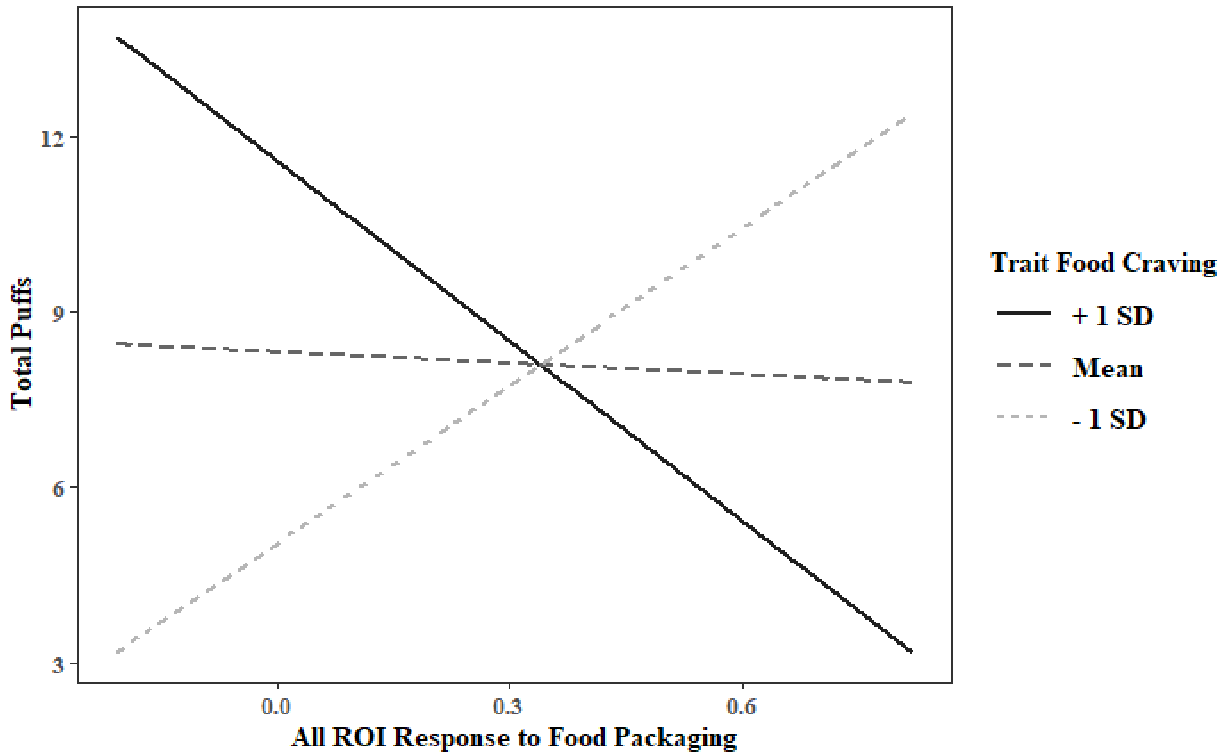


Figure 3.6

The Johnson-Neyman Plot on Moderating Effect of Trait Food Craving on the Associations between All ROI Response to Food Packaging and Vaping Puffs