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Individual differences in LPP amplitude and theta power predict cue-induced eating during a cued food delivery task

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A

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Houston, Texas

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ABSTRACT

Due to individual differences in the brain's reward system, some individuals are more vulnerable than others to maladaptive, reward-seeking behaviors, such as substance use or compulsive eating. A body of research has demonstrated that individuals who attribute higher levels of incentive salience to reward-associated cues than to pleasant images (termed "C>P group" throughout) are more vulnerable to compulsive eating than those who attribute higher incentive salience to pleasant images than reward-associated cues (P>C group). Meanwhile, a separate body of research has demonstrated that cognitive control also regulates eating by enabling top-down attentional control. This dissertation aims to identify how both cognitive control and incentive salience act in tandem to regulate cue-induced eating. A central question of this research is: do individuals in the C>P group also show attenuated cognitive control?

Because the animal literature indicates that individuals who attribute high incentive salience to reward-associated cues also show attenuated top-down attentional control, I hypothesized that C>P individuals would also show attenuated cognitive control relative to P>C individuals. To test this hypothesis, I analyzed electroencephalogram (EEG) data collected during a controlled cued food delivery task, in which participants viewed images and were dispensed food rewards (candy) that they could choose to eat or discard, and non-food objects (beads, control condition). From the EEG recordings, I calculated the amplitude of the late positive potential (LPP) and power (μV^2) in the theta (θ, 4-8 Hz) frequency band as metrics of affective and cognitive processing, respectively. To identify individual differences in both affective and cognitive processing, I then conducted two separate *K*-

means (k = 2) cluster analyses using LPP and theta power data.

The LPP-based cluster analysis replicated previous findings: C>P individuals ate significantly more candies during the experiment than P>C individuals. However, I found no significant differences in theta power between the P>C and C>P groups. Meanwhile, the theta-based cluster analysis found that some individuals show higher theta during the candy condition than the bead condition (θCA>θBE), while others show higher theta power during the bead condition than the candy condition (θBE>θCA). Furthermore, the θCA>θBE group ate significantly more during the experiment than the θBE>θCA group. Finally, I crossed group assignments from both the LPP- and theta-based cluster analyses to create four groups based on LPP- and theta-based risk factors: those with no risk factors (P>C & θBE>θCA group), those with only an LPP risk factor (C>P & θCA>θBE), those with only a theta risk factor (P>C & θCA>θBE), and finally those with both risk factors (C>P & θCA>θBE). I found that individuals with no risk factors ate the least of all four groups, and the other three groups showed significantly higher levels of eating behavior on average.

From these results, I can conclude that both cognitive and affective brain systems are involved in regulating cue-induced eating. However, the finding that P>C and C>P individuals do not show significant differences in theta power suggests that cognitive and affective mechanisms may act independently in humans. Because an individual with an affective vulnerability to cue-induced eating may not also have a cognitive vulnerability, this underscores the need for targeted, individualized treatments for maladaptive behaviors. For example, these research findings could be applied to the use of transcranial magnetic stimulation (TMS) to ameliorate addictive disorders: individuals with higher theta power during food-related decision-making may be selected for excitatory stimulation of brain regions associated with cognitive control, such as dorsolateral prefrontal cortex (dlPFC), whereas individuals who attribute high incentive salience to reward-related cues may benefit from inhibitory stimulation of reward-associated areas, such as medial prefrontal cortex (mPFC).

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ADHD: Attention Deficit Hyperactivity Disorder

ANOVA: analysis of variance

BIS: Barratt Impulsiveness Scale

BMI: body mass index

BOLD: blood oxygen level-dependent

CESD: Center for Epidemiologic Studies Depression Scale

CI: confidence interval

CIG: cigarette images

D2: dopamine type 2 receptors

dlPFC: dorsolateral prefrontal cortex

EEG: electroencephalogram

ERN: error-related negativity

ERO: erotic images

ERP: event-related potential

FCQ: Food Cravings Questionnaire

FOOD: food images

fMRI: functional magnetic resonance imaging

IAPS: International Affective Picture System

ITI: inter-trial interval

LPP: late positive potential

LRP: lateral readiness potential

mPFC: medial prefrontal cortex

MUT: mutilation images

NEU: neutral images

PANAS: Positive and Negative Affect Schedule

PFS: Power of Food Scale

PLF: phase-locking factor

POL: pollution images

ROI: region of interest

ROM: romantic images

SAD: sad images

SE: standard error

SHAPS: Snaith-Hamilton Pleasure Scale

SLIM: Satiety Labeled Intensity Magnitude

SNR: signal-to-noise ratio

TMS: transcranial magnetic stimulation

WREQ: weight-related eating questionnaire

C>P: individuals with larger LPP responses to food cues than to pleasant images

P>C: individuals with larger LPP responses to pleasant images than to food cues

θCA>θBE: individuals with higher theta (4-8 Hz) power (μV^2) during the candy condition than during the bead condition

θBE>θCA: individuals with higher theta (4-8 Hz) power (μV^2) during the bead condition than during the candy condition

CHAPTER 1: Introduction

1.1 Public health burden of overeating and excess body weight

Excess body weight exerts an enormous public health burden both in the United States and globally. Body weight in the overweight and obese range, defined as a body mass index (BMI) ≥ 25 and ≥ 30 kg/m^2 respectively (Prospective Studies Collaboration, 2009), are major risk factors for a multitude of preventable illnesses, including diabetes, heart disease, and several cancers (Bozkurt et al., 2016; Islami et al., 2018). Not only does excess body weight confer adverse health outcomes, but it also creates a tremendous financial burden: obesity costs the U.S. healthcare system an estimated $149.4 billion per year (Kim and Basu, 2016), and is projected to affect 1.35 billion individuals globally by 2030 (Kelly et al., 2008).

Considering the substantial hardship attributable to obesity, it is critical that clinical researchers develop effective treatments to mitigate the sequelae related to excess body weight. Although numerous weight-loss interventions have been developed, current treatment programs for obesity rarely yield substantial, long-lasting results (Jeffery et al., 2000; Turk et al., 2009). A body of evidence suggests that, despite the many genetic and metabolic factors related to weight, the ultimate cause of obesity is excessive eating (Sharma and Padwal, 2010). A study identifying candidate genes attributed to BMI found that the majority are expressed in the nervous system (The LifeLines Cohort Study et al., 2015), suggesting that the genetic vulnerabilities leading to obesity are primarily related to the brain mechanisms that regulate eating behavior. However, obesity interventions aimed at reducing eating have not been optimally successful (Dombrowski et al., 2014; Wing et al., 2006), suggesting that interventions focused on reducing eating behavior alone are missing some critical aspects of obesity vulnerability. Thus, to develop more effective strategies aimed at ameliorating the

obesity epidemic, it is necessary to characterize the underlying mechanisms that regulate eating behavior.

1.2 The dopamine motive system & reward-seeking behaviors

Eating behavior and substance use share common neurobiological mechanisms. These overlapping mechanisms originally evolved for survival: specifically, to promote eating behavior and reproduction (Robinson and Berridge, 2003). Therefore, the reward systems of the brain can act as a double-edged sword: they can promote survival by incentivizing adaptive behaviors such as homeostatic eating and reproduction or undermine survival by incentivizing maladaptive behaviors such as compulsive eating or substance use (Dill and Holton, 2014). In light of these shared mechanisms, studying the brain systems involved in eating behavior may also shed light on those that confer vulnerability to substance use disorders.

Both the consumption of hyper-palatable, high-calorie foods and the consumption of drugs of abuse are known to increase striatal dopamine levels (Filbey et al., 2008; Volkow et al., 2017): in fact, this dopaminergic response is responsible for the appetitive nature of both food and drugs (Avena et al., 2008). As environmental cues signaling food or drug availability become associated with the food or drug, the cues themselves become rewarding, leading to dopaminergic activity in the presence of these cues. In so doing, the brain attributes incentive salience to these cues, thereby allocating attention to them in an automatic fashion (Berridge, 2018).

Often these highly salient cues can trigger reward-seeking behaviors, such as eating in the presence of cues: a behavior known as cue-induced eating (**Figure 1.1**). This process by which cues become increasingly salient, known as incentive sensitization, relies on the sensitization of mesolimbic dopaminergic neurons in response to stimulation from drugs or hyper-palatable

foods (Stice and Yokum, 2016). These "wanting" pathways of the brain involved in incentive sensitization are hypothesized to be a key regulator of hedonic overeating and "food addiction" which often lead to obesity (Avena et al., 2009; Blumenthal and Gold, 2010; Davis et al., 2014; Finlayson, 2017; Fletcher and Kenny, 2018; Lee and Dixon, 2017).

Figure 1.1: A model of cue-induced behavior. In this model, an individual sees a sign for "Le Donut" while driving to work. This individual knows that Le Donut has fantastic cronuts (a hybrid of a donut and a croissant) and is motivated by the food when they see the sign. This then prompts them to eat while attending the talk. In this example of cue-induced behavior, the sign is the cue, the cronut is the reward, and the cue-induced behavior is getting cronuts on the way to work.

1.3 Opposing brain systems can maintain or undermine energy balance during eating

Many neurobiological models posit that reward-seeking behaviors are regulated by two opposing brain systems: a top-down cognitive system that allocates attention in a goal-oriented fashion, and a bottom-up affective system that imbues cues with incentive salience in an automatic fashion, driven by choline and dopamine, respectively (**Figure 1.2**; Pitchers et al., 2018). These opponent systems have been demonstrated as key regulators of reward-seeking

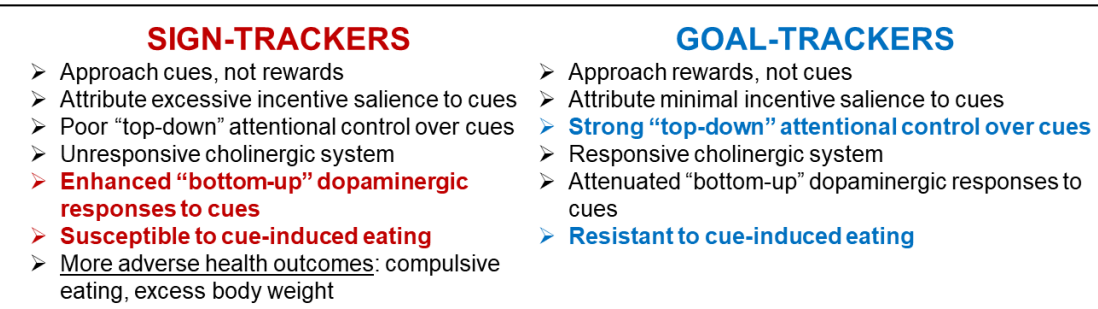

Figure 1.2: Theoretical models posit that reward-seeking behaviors are regulated by two opponent systems: a "hot" dopaminergic system that attributes excessive incentive salience to cues, and a "cold" cholinergic system that enables top-down attentional control. Sign-trackers show enhanced activity of their "hot" dopaminergic system, while goal trackers have a strong "cold" cognitive system. Figure adapted from Pitchers et al., 2018

behaviors such as eating (Appelhans, 2009; van den Bos and de Ridder, 2006) and substance use (Tanabe et al., 2019; Zilverstand, 2018). Thus, it is not only affective, reward-related systems of the brain but also cognitive control mechanisms that are involved in regulating eating.

Much like the "double-edged sword" described above, these opponent systems can promote or undermine survival. Feeding can be a homeostatic process when the brain's cholinergic control system and dopaminergic reward system are in balance, leading an individual to consume and expend energy at approximately equivalent rates. Meanwhile, the brain's bottom-up system can also override those top-down signals that maintain energy balance, thereby driving hedonic overeating. Substantial evidence from both human subjects' research and animal models has demonstrated that individuals will vary in their ability to engage these top-down cognitive systems and bottom-up affective systems, leading to these observed differences in eating behavior and excess body weight between individuals.

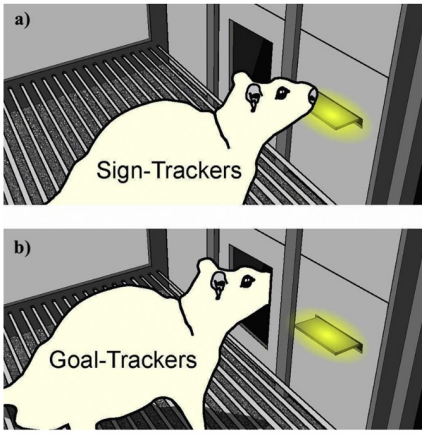

Figure 1.3: In the Pavlovian conditioned approach paradigm, a food pellet (reward) is dispensed in a magazine after a cue (lever) is illuminated, signaling the impending delivery of the reward. In this behavioral paradigm, some animals—termed "sign-trackers"—will approach the lever cue, while others ("goal-trackers") will approach the magazine containing a food reward. (Colaizzi et al., 2020) *Wiley has granted the author permission to republish this figure as a part of the author's dissertation. See **Appendix 3a** for full license information.*

1.4 Sign- and Goal- trackers show individual differences in the engagement of top-down and bottom-up brain systems

To investigate these individual differences in animal models, investigators use a Pavlovian conditioned approach paradigm, in which an environmental cue is presented before a reward, such as a food pellet, is dispensed (**Figure 1.3**; Colaizzi et

al, 2020). Some individuals, known as goal-trackers, will approach the reward; whereas others, called sign-trackers, will approach the cue that signals the availability of the reward. These two behavioral styles have meaningful consequences: sign-trackers are more vulnerable to maladaptive, reward-seeking behaviors. Studies have shown that sign-trackers tend to eat and self-administer drugs more than goal trackers (Kruzich et al., 2001; Tunstall and Kearns, 2015) and show other maladaptive, addiction-like behaviors (Colaizzi et al., 2020; Tomie et al., 2008).

These behavioral differences between sign-trackers and goal-trackers are driven by differences in their underlying neurobiology: for example, sign-trackers show attenuated cholinergic control and enhanced dopaminergic reward processing relative to goal trackers. When presented with reward-associated cues, goal-trackers show an increase in prefrontal cholinergic transmission, whereas sign-tackers show enhanced prefrontal dopaminergic transmission (Pitchers et al., 2017a). Sign-trackers also have a reduced choline transport and reuptake system (Koshy Cherian et al., 2017) and show lower levels of cholinergic transmission during a sustained attention task relative to goal-trackers (Paolone et al., 2013). Furthermore, sign-tracking behavior does not readily extinguish, even when sign-trackers are administered cognitive enhancing drugs (Fitzpatrick et al., 2019). Stimulation of the pathway between the prelimbic cortex and the paraventricular thalamus in sign-trackers decreases the incentive value of cues; meanwhile, inhibition of this same pathway in goal-trackers increases incentive value and dopamine levels in the nucleus accumbens shell (Campus et al., 2019). Evidence from optogenetics has shown that activity in the central amygdala appears to mediate many of the motivational aspects of cues in rodents (Warlow and Berridge, 2021).

Furthermore, some research groups have found that contextual cues signaling drug

availability reinstate drug-seeking behavior more effectively in goal-trackers than in sign-trackers. Notably, this reinstatement disappears when the basal forebrain is lesioned in goal-trackers, indicating that cholinergic transmission in the forebrain is necessary for goal-trackers to effectively respond to higher-order contextual cues (Pitchers et al., 2017b). In another study, obese rats showed downregulation of striatal dopamine D2 receptors and were predisposed to compulsive eating behavior (Johnson and Kenny, 2010). Based on these findings, it seems that both dopaminergic and cholinergic transmission are implicated in sign- and goal-tracking, and these behaviors likely rely on distinct neural pathways of the brain.

1.5 Humans show individual differences in the engagement of top-down and bottom-up brain systems

The interplay between these top-down and bottom-up systems described using preclinical models has also been demonstrated in humans. Sign-tracking and goal-tracking behaviors as defined in rodents do not currently have a direct analog in humans (Colaizzi et al., 2020; Stephens et al., 2011); rather, many studies look at upstream neural correlates and how these correlates contribute to downstream behavioral outcomes, such as substance use or eating behavior (Carbine et al., 2018; Smeets et al., 2019). From this work, there exists a similar dynamic to what has been shown in rodents: that humans will vary in the engagement of their executive control systems and incentive valuation of reward-related cues. Furthermore, these differences in underlying brain mechanisms also lead to differences in maladaptive, reward-seeking behaviors (Hofmann et al., 2009).

In humans, the top-down cognitive control system enables self-regulation of eating (Dohle et al., 2018; Hall, 2016), and activity in these cognitive control networks has been associated with long-term dietary treatment success (Weygandt et al., 2019). Inhibitory control, a specific executive function in which a prepotent response is inhibited, has been identified as a key

mechanism that enables individuals to resist overeating behaviors (Hofmann et al., 2009; Houben et al., 2014). Individuals with deficits in inhibitory control are more vulnerable to overeating behavior and often show higher rates of obesity (Stice and Yokum, 2016). Furthermore, individuals with attention deficit hyperactivity disorder (ADHD), a psychological disorder affecting executive functioning, are vulnerable to overeating and subsequent obesity (Davis et al., 2006; Dempsey et al., 2011).

Mechanistically, these differences in food-related inhibitory control are often associated with the cholinergic control mechanisms of the prefrontal cortex, as well as relay between prefrontal and reward & limbic areas. For example, overweight adolescents tend to show attenuated activity in frontal inhibitory brain regions in addition to enhanced activity in dopaminergic reward areas of the brain, such as the insula (Batterink et al., 2010). Furthermore, high BMI has been associated with increased activity among cognitive and limbic brain regions, such as the prefrontal cortex, insula, and striatum (He et al., 2019).

The role of the bottom-up dopaminergic incentive valuation system in humans has been demonstrated using a variety of paradigms, leveraging methodologies such as neuroimaging, eye-tracking, and behavioral assays. Many recent neuroimaging studies have found that a hyper-reactive dopamine response in the brain tends to result in compulsive reward-seeking behaviors, such as gambling, sex, and shopping (Olney et al., 2018). In one study, "sign-tracker" and "goal-tracker" analogs were identified in humans using eye-tracking, finding that human "sign-trackers" showed greater reward-prediction error-related blood oxygen level-dependent (BOLD) responses in dopaminergic reward and limbic areas, such as the nucleus accumbens, ventral tegmental area, ventromedial prefrontal cortex, caudate, putamen, and amygdala (Schad et al., 2019).

1.6 Individual differences in LPP responses to cues predict cue-induced eating

Our lab has previously used psychophysiology to demonstrate that humans will differ in their tendency to attribute incentive salience to cues. In these studies, participants are presented with emotional and neutral images while EEG is recorded from the scalp. From these EEG recordings, many have found that the amplitude of the late positive potential (LPP), an event-related potential (ERP) component which increases in amplitude for motivationally relevant images (Cuthbert et al., 2000), will vary between individuals. Some individuals will have higher LPP amplitudes in response to pleasant, high-arousing images than reward cues (referred to herein as the P>C group), whereas others will have higher LPP amplitudes in response to the reward cues than pleasant images (referred to herein as the C>P group). There are many downstream behavioral outcomes related to these individual differences in LPP responses: C>P individuals tend to eat more and are more likely to be obese (**Figure 1.4**; Versace et al., 2016, 2018).

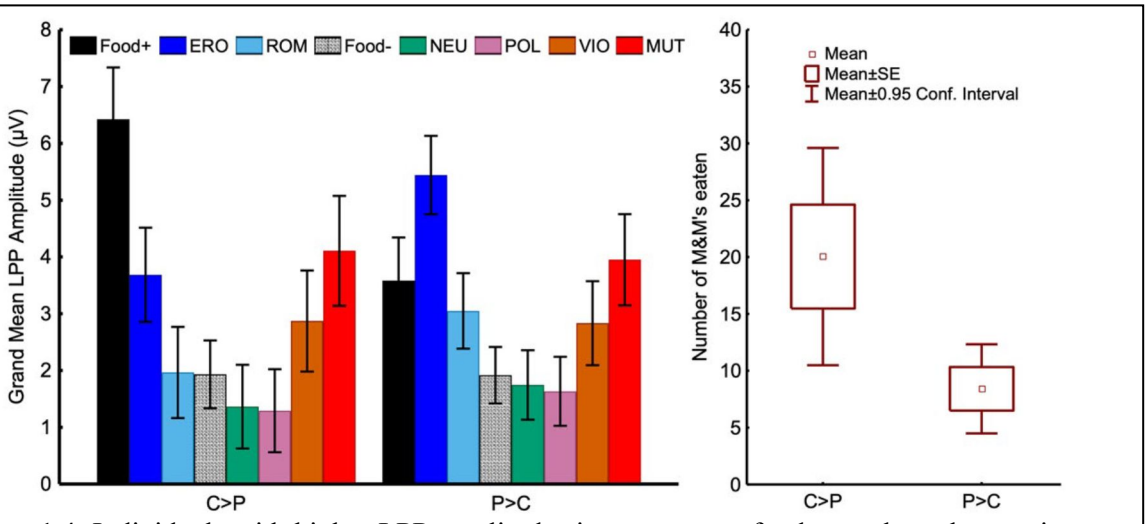

Figure 1.4: Individuals with higher LPP amplitudes in response to food cues than pleasant images (C>P group) eat significantly more than individuals with the opposite response pattern (P>C group). (Versace et al., 2018) *Wiley has granted the author permission to republish this figure as a part of the author's dissertation. See **Appendix 3b** for full license information.*

Because the LPP is a reliable index of the engagement of the brain's motivational systems (Bradley, 2009; Lang and Bradley, 2010), these previous findings using the LPP are consistent

with the literature demonstrating the role of the bottom-up motivational system in rodents. However, our lab has yet to characterize the role of the top-down cognitive control system in regulating eating behavior using the cue reactivity paradigm. Are some humans more vulnerable to maladaptive behaviors than others due simply to their affective responses to cues, or do these vulnerable individuals also show impaired cognitive control systems? And how do these processes act in tandem to simultaneously regulate eating? The cue reactivity paradigm presents an ideal means of probing the engagement of both the cognitive and affective brain systems involved in eating behavior.

1.7 The present study: overview, aims, and hypotheses

The present study is aimed at ascertaining how both cognitive and affective brain mechanisms act in tandem to regulate cue-induced eating in humans. A central question of this work is: are C>P individuals more vulnerable to maladaptive behaviors than others only due to their enhanced affective processing of cues, or is their cognitive control system impaired as well? Although findings from the animal literature show that sign-trackers show both enhanced dopaminergic responses to cues and attenuated cholinergic control, these mechanisms may act independently in humans.

To assess how cognitive control systems regulate cue-induced eating, I chose to monitor power in the theta frequency band. Theta power increases when there is a demand for cognitive control (Cavanagh and Frank, 2014): for example, when participants complete cognitively demanding tasks (Nigbur et al., 2011; Pinner and Cavanagh, 2017), or when they need to inhibit prepotent responses (Dippel et al., 2017). These findings suggest that theta can be used as a metric of cognitive processing. For this reason, I chose to monitor theta in an exploratory fashion as a metric of cognitive control.

In summary, my dissertation research aims to ascertain how both individual differences in the tendency to attribute incentive salience to cues and cognitive control act in tandem to regulate cue-induced eating behavior. To do so, I used a modified version of the cued food delivery task described in previous studies (Deweese et al., 2015). In this task, participants passively viewed emotional, neutral, and food-related images while EEG was recorded from the scalp. After the presentation of a food-related image, the participant was dispensed either a food (candy) or non-food (bead) object, which they could choose to eat (candy) or discard (**Figure 1.5**).

To ascertain individual differences in affective processing of cues, I measured the amplitude of the LPP in response to emotional and food-related images as described in previous studies (Versace et al., 2016, 2012, 2018). Meanwhile, to assess individual differences in the engagement of cognitive control, I monitored power in the theta frequency band after the candy or bead was dispensed to the participant. Finally, I compared these measures with the number of candies the participants ate during the task.

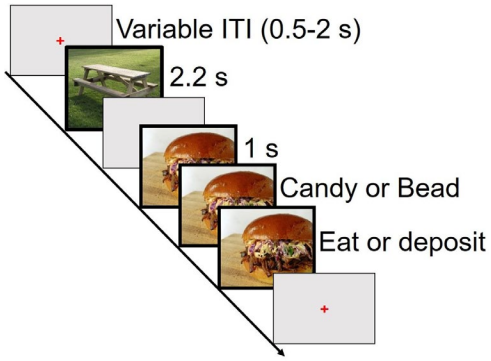

Figure 1.5: In the controlled cued food delivery task, participants view emotional, neutral, and food-related images while EEG is recorded from the scalp. After the presentation of a food-related image, either a candy or bead was dispensed to the participant. The participant could then choose to eat or discard the dispensed candies.

In **Chapter 2**, I summarized the theory, methodological concerns, and underlying physics related to the EEG signal. The information outlined in this chapter provides a theoretical and methodological framework for understanding the experimental content of subsequent chapters. I also outlined an experiment in which I used Monte Carlo simulations to calculate statistical

power for ERP studies investigating the LPP. This project aimed to ascertain the methodological specifications, such as the number of trials per condition or number of subjects per group, necessary to obtain sufficient statistical power at varying effect sizes. This project was not hypothesis-driven, but rather methods-based; however, I was able to successfully outline a useful reference material for the design of ERP experiments investigating the LPP.

In **Chapter 3**, I addressed how individual differences in both affective processing of cues and the engagement of cognitive control systems influence cue-induced eating using the controlled cued food delivery task described above (**Figure 1.5**). To ascertain individual differences in affective processing of cues, I calculated the amplitude of the LPP in response to cues and emotional images, much like our lab has in previous studies (Versace et al., 2012, 2016, 2018; see also **Figure 1.4**). This experiment included a control condition in which non-food objects were dispensed to the participant in addition to food rewards. This modification was intended to ascertain whether the observed effects in the LPP are related to food cues specifically, or if any cue signaling the delivery of a food- or non-food object is intrinsically motivationally relevant. I hypothesized that I would successfully reproduce previous findings from our lab: that even when including a control condition in the cued food delivery task, the C>P individuals will still eat more on average than individuals in the P>C group.

Meanwhile, to monitor the engagement of cognitive control systems during food-related decision-making, I measured theta power while the participant decides to eat or discard the candies dispensed during the task. My hypothesis was twofold: First, I hypothesized that theta power would increase when participants are deciding what to do with the objects dispensed during the task. Second, I hypothesized that individuals for whom theta power increases to high levels during the candy condition would eat less on average than the remaining

participants.

Next, I considered how both cognitive control and incentive salience simultaneously regulate cue-induced eating by comparing the LPP responses, theta power responses, and subsequent eating behavior of each participant. By crossing the results from both the LPP and theta, I aimed to determine the extent to which these two metrics predict cue-induced eating in tandem. I hypothesized that individuals in the P>C group who also had high levels of theta power during the candy condition would eat the least on average and that those in the C>P group who had low levels of theta power during the candy condition would eat the most.

Finally, in **Chapter 4** I discuss theoretical explanations for my findings and compare them against the existing literature, while also addressing the public health impact of these findings and how they may translate into weight-loss interventions in the clinic.

CHAPTER 2: Estimating statistical power for event-related potential studies using the late positive potential

This chapter is based upon the following original manuscript written by the author…

Gibney, K. D., Kypriotakis, G., Cinciripini, P. M., Robinson, J. D., Minnix, J. A., & Versace, F. (2020). Estimating statistical power for event-related potential studies using the late positive potential. *Psychophysiology*, 57(2). https://doi.org/10.1111/psyp.13482

2.1 BACKGROUND

Many research groups have leveraged psychophysiology, the use of physiological measures to study psychological processes, to characterize the mechanistic underpinnings of various psychological disorders, behaviors, or phenomena. EEG is a powerful physiological tool that measures the electrical activity of the brain by placing electrodes on the scalp, amplifying the signal recorded from those electrodes, then plotting the changes in voltage over time. Therefore, EEG provides a direct measure of brain activity, and its exquisite time resolution allows researchers to precisely pinpoint underlying brain activity associated with certain behaviors or modes of processing (Handy, 2005; S. Luck, 2014).

The EEG signal is generated by synchronized populations of cortical pyramidal neurons. When postsynaptic neurons are excited, this creates an extracellular voltage near the neuronal dendrites, which in turn creates a dipole, a region of positive charge that is separated over a distance from a region of negative charge. The electrodes used in EEG detect the sum of positive and negative charges in their vicinity; however, the dipole of a single neuron is too weak of a signal to be measured by an EEG electrode. Thus, it takes large populations of neurons acting as current dipoles to generate a detectable EEG signal. This phenomenon in

which the signal from many current dipoles in the brain sum to create a measurable EEG signal is known as volume conduction (Buzsáki et al., 2012; Jackson & Bolger, 2014; **Figure 2.1**)

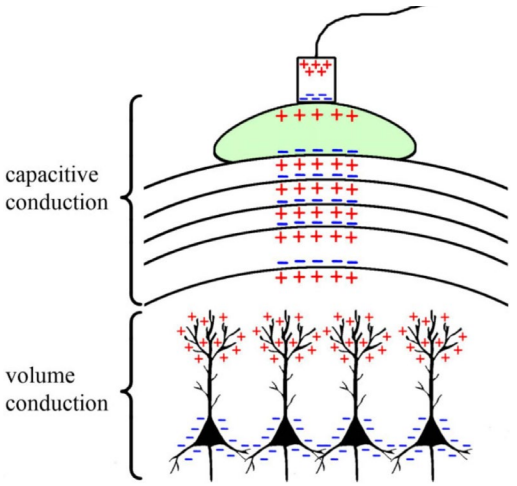

Figure 2.1 (above): The electrical potentials measured by the EEG signal are the result of large populations of pyramidal neurons acting as current dipoles (Jackson & Bolger, 2014). *Wiley has granted the author permission to republish this figure as a part of the author's dissertation. See* ***Appendix 3c*** *for full license information.*

EEG is a powerful tool for understanding the underlying neural activity related to a specific mode of processing. Psychophysiologists can extract several informative metrics of brain activity from EEG recordings, such as event-related potentials (ERPs). ERPs are calculated by time-locking a stimulus or event to a specific time point in the EEG recording, such as the presentation of a picture or the execution of a task. Then by averaging these time-locked segments of EEG together, researchers can create an averaged ERP waveform that characterizes brain activity associated with this event (Liu et al., 2012; S. Luck, 2014; **Figure 2.2**).

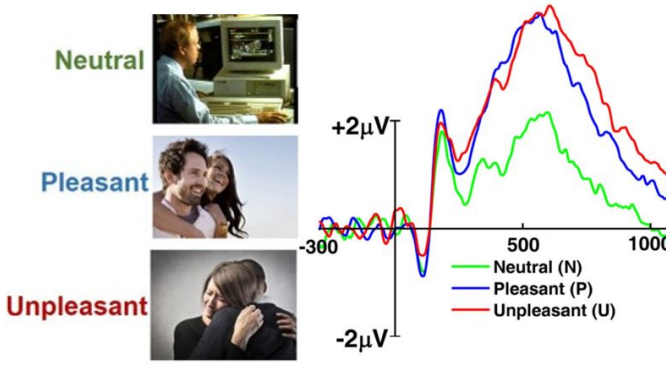

Figure 2.2 (above): In this example, human research participants look at images while an EEG is recorded from their scalp. Researchers may then time-lock the voltage deflections in their EEG associated with a particular image. These event-related voltage deflections in the EEG recording are known as event-related potentials (ERPs). This figure was adapted with permission from Liu et al., 2012. *Wiley has granted the author permission to republish this figure as a part of the author's dissertation. See* ***Appendix 3d*** *for full license information.*

The late positive potential, or LPP, is an ERP component with a positive deflection that takes place from 400-800 msec after the presentation of a stimulus (Keil et al., 2002; Weinberg and Hajcak, 2010). Emotional stimuli reliably elicit LPP responses, and more salient stimuli elicit LPP responses that are higher in amplitude than neutral or otherwise less emotionally arousing stimuli (Cuthbert et al., 2000; Schupp et al., 2004). For example, erotic scenes and mutilations commonly elicit larger LPPs than neutral pictures, such as household objects. It has also been found that drug-associated images, such as cigarette or cocaine pictures, can reliably elicit an LPP response in some individuals (Robinson et al., 2015; Webber et al., 2021). Thus, the LPP is a useful tool for the study of addiction, maladaptive behaviors, and other psychiatric disorders because it can be used to characterize the underlying affective processing associated with these pathologies (Culbreth et al., 2018; Fitzgerald et al., 2018).

Because images with higher levels of incentive salience evoke larger LPP responses, the LPP is a reliable metric of affective picture processing (De Cesarei and Codispoti, 2011; Olofsson et al., 2008). This incentive salience that is measured by the LPP is the result of dopaminergic activity in the brain's reward system that takes place in response to emotional contents (Bradley et al., 2001; Hickey and Peelen, 2015; Olney et al., 2018). Furthermore, concurrent EEG-fMRI studies have found that the BOLD activity associated with the LPP is comprised of re-entrant projections between the limbic system and visual association areas of the brain (Keil et al., 2009; Liu et al., 2012; Sabatinelli et al., 2013). Despite its utility in the study of brain activity, the EEG signal is plagued by a problem of signal-to-noise ratio (SNR). EEG data are often quite noisy, due to factors such as motion artifacts, blinks, or electrical noise. Furthermore, other factors such as the type of EEG net or the temperature of the recording environment can also contribute to the level of noise in the data (Kappenman and

Luck, 2010). Therefore, to obtain a reliable ERP signal, it is necessary to average together large numbers of trials among large participant samples. Accordingly, by averaging together many trials and subjects, researchers average out the noise and may characterize the true signal in these data (Handy, 2005; S. Luck, 2014). Such thoughtful experimental designs are critical in light of the finding that many published research findings are false (Ioannidis, 2005; Luck and Gaspelin, 2017), and there is a pervasive issue of reproducibility and reliability in research science, especially in the psychological domain (Munafò et al., 2017).

However, the more trials researchers include in an experiment, the longer the EEG recording session will take, which is often uncomfortable for the participant and expensive for the lab running such studies. Meanwhile, enrolling more research participants also has its downfalls: participants can be difficult to recruit, and labs may have limited funds for participant incentives. Considering this trade-off between the number of trials, number of subjects, and overall recording session time in addressing SNR issues, it is often difficult for researchers using ERPs to design sufficiently powered studies. However, because research findings using ERPs often direct translational applications for psychiatric disorders, it is critical to design reproducible, sufficiently powered ERP studies (Button et al., 2013; Munafò et al., 2017). How then, can research groups design reproducible experiments that reliably translate into effective, evidence-based treatments?

Previous work has used Monte Carlo simulations to calculate statistical power for within- and between-subjects experiments investigating ERPs components such as the error-related negativity (ERN) and lateral readiness potential (LRP; Boudewyn et al., 2018). However, these are only two ERP components that may differ substantially from

other ERP components in factors such as how they are calculated (stimulus-locked vs response-locked), the typical effect size of these components, or the SNR associated with a component. For those interested in the LPP specifically, it is necessary to conduct power analyses that better apply to LPP data.

To address this gap in knowledge, I followed a similar procedure as outlined by Boudewyn's group. Using Monte Carlo simulations, I simulated within- and between-subjects experiments investigating differences in the LPP at varying numbers of subjects per group, trials per condition, and effect sizes. This project was largely methods-based and exploratory, and as such, I had no a-priori hypothesis regarding these findings.

Table 2.1: Baseline Demographic Information

Variable	**%**	***N* = 314**
Sex		
Male	48.73	153
Female	50.32	158
No data	0.960	3
Race		
North American Indian/ Alaska Native	0.320	1
Asian	2.230	7
Black/ African American/ African Caribbean	61.15	192
Native Hawaiian/ Pacific Islander	0.640	2
White	30.57	96
Unknown/ prefer not to answer	2.870	9
Other/ more than one race	2.230	7
Ethnicity		
Hispanic	4.140	13
Not Hispanic	92.68	291
Unknown/ prefer not to answer	3.180	10
Smoking status		
Smoker	69.75	219
Never Smoker	30.25	95
	Mean	**SD**
Age	45.60	11.40

2.2 METHODS

2.2.1 Study participants

For the analyses presented here, I used data from 314 community participants whom our lab had previously recruited for clinical studies of smoking cessation (Stevens et al., 2019). The data included here were recorded at baseline, before the beginning of any treatment. All participants were recruited from the Houston metro area through newspaper and radio advertisements. Inclusion criteria for the studies were: age 18–65 years, fluent English speaker, not taking psychotropic medication, not diagnosed with a psychiatric disorder, and not having an uncontrolled medical illness. One

participant was later excluded from the analyses because of incomplete data, leaving 313 participants who were included in my analysis. Demographic information for the participants is provided in **Table 2.1**. Each participant provided informed consent, and the study was approved by The University of Texas MD Anderson Cancer Center's Institutional Review Board.

2.2.2 Picture-viewing task

The picture-viewing task used in this study included 192 images selected from the International Affective Picture System (IAPS; Lang et al., 2008) and other picture collections previously used by our lab (Carter et al., 2006; Versace et al., 2011). The set included four picture categories: pleasant, unpleasant, cigarette-related, and neutral. Each category included 48 images (pleasant: 16 erotic scenes, 16 romantic couples, and 16 food images; unpleasant: 16 mutilations, 16 sad contents, and 16 disgusting objects, pollution, and accidents; cigarette-related: 32 of people smoking and 16 of smoking paraphernalia; neutral: 32 of people engaged in mundane activities and 16 household objects; see the IAPS pictures used in this study[1]).

During the task, images were presented in pseudorandom order with no more than two pictures of the same category presented consecutively. Each picture was presented for 4 sec and was followed by an intertrial interval varying between 3-5 sec, during which the

[1] The IAPS pictures used in this study are: Neutral people: 2102, 2191, 2210, 2215, 2220, 2305, 2383, 2393, 2435, 2500, 2579, 2595, 2630, 2850, 7550, 2107, 2200, 2214, 2221, 2235, 2312, 2372, 2396, 2441, 2493, 2515, 2575, 2593, 2597, 9070; Neutral objects: 7000, 7002, 7004, 7006, 7009, 7010, 7030, 7034, 7040, 7041, 7052, 7053, 7054, 7055, 7056, 7059; Erotic scenes: 4611, 4658, 4659, 4669, 4677, 4680, 4687, 4690, 4691, 4693, 4695, 4696, 4698, 4783, 4800; Romantic couples: 4624, 4625, 4628, 4640, 4641, 4643, 4700; Food: 7330, 7340, 7350, 7410, 7430, 7460, 7470; Sad scenes: 2205, 2455, 2490, 2520, 2590, 2700, 2703, 2800, 2810, 2900, 3280, 9421, 9429, 9520, 9530, 9926; Unpleasant Objects: 6020, 6230, 6260, 9090, 9110, 9290, 9300, 9301, 9320, 9373, 9560, 9600, 9621, 9901, 9911, 9912; Mutilations: 3000, 3030, 3051, 3053, 3060, 3068, 3069, 3080, 3100, 3110, 3120, 3130, 3170, 3261, 9420, 9433. When less than 16 IAPS pictures were available in a category, we integrated the set using pictures with similar contents.

subjects saw a black background with a white fixation cross. The entire picture presentation and recording session lasted approximately 30 min. Sessions were divided into three 10 min blocks separated by a 30-sec break between blocks. Stimuli were presented using E-Prime 1 (PST Inc., Pittsburgh, PA) stimulus presentation software (Schneider et al., 2002) on a 42" plasma screen placed approximately 1.5 m from the participants' eyes. Images were subtended horizontally at a horizontal visual angle of approximately 24°.

2.2.3 Data collection procedures

During the picture presentation, ERPs were recorded using a 129-channel geodesic sensor net amplified with an AC-coupled 200-MΩ impedance amplifier (EGI Geodesic EEG System 200; Electrical Geodesics, Inc., Eugene, OR) and referenced to Cz. Data were sampled at a rate of 250 Hz and were filtered online using a 0.1-Hz high-pass filter and a 100-Hz low-pass filter. As per the manufacturer's instructions, scalp impedance was below 50 KΩ at the beginning of the recording.

2.2.4 Data reduction procedures

Even though I used only data from neutral trials in the Monte Carlo simulations of experiments with synthetic effect sizes (see **Section 2.2.6**), I reduced the data and plotted the results of all picture categories to ensure that the data used in these analyses belonged to a standard LPP experiment. First, I corrected eyeblink artifacts using a spatial filtering method as implemented in BESA software (BESA GmbH, Gräfelfing, Germany) and transformed the data to the average reference. Then, I imported the data into BrainVision Analyzer 2.1 (Brain Products GmbH, Gilching, Germany) and filtered them with a high-pass filter of 0.1 Hz (12 dB/ octave), a low-pass filter of 30 Hz (12 dB/octave), and a notch filter of 60 Hz. The data were then segmented into 900-msec segments, starting 100 msec before stimulus presentation.

The 100-msec interval before stimulus presentation was defined as the baseline and subtracted from every data point in the segments.

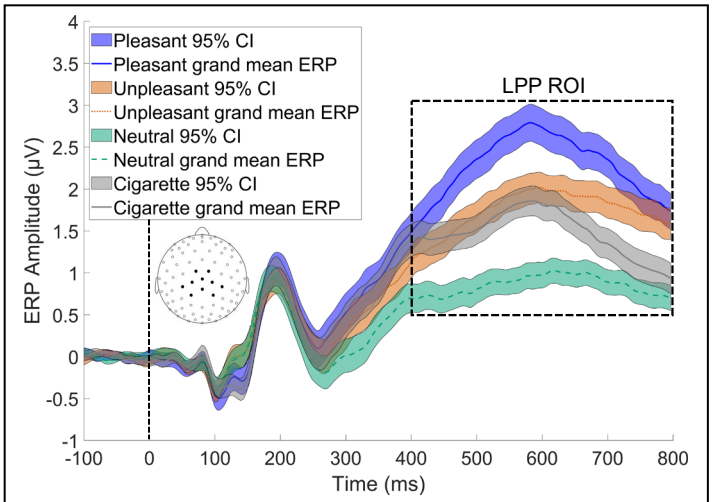

Figure 2.3: Grand mean ERPs (colored lines) and 95% confidence intervals (shaded) by picture category. ERPs evoked by each category are consistent with previous studies: more emotionally relevant picture categories evoke larger LPPs. ERP: event-related potential; CI: confidence interval; LPP, late positive potential; ROI, region of interest

Artifacts were identified in the segmented data and were defined by (a) an amplitude of above 100 μV or below −100 μV, (b) an absolute difference of greater than 100 μV between any two data points in a segment, and (c) a maximum gradient of 25 μV/msec voltage step between two contiguous data points in a segment. Channels contaminated by artifacts in more than 40% of the segments were interpolated using six neighboring channels. We averaged the voltage from 10 centroparietal sensors (EGI electrodes 7, 31, 37, 54, 55, 79, 80, 87, 106, 129; **Figure 2.3** inset shows their topographic location) because, in previous studies, these channels had shown the highest LPP differences between experimental conditions (Versace et al., 2011). I checked for the presence of artifacts in the averaged data using the same criteria mentioned above and discarded the segments contaminated by artifacts.

Then, data from subjects with fewer than 40 artifact-free neutral trials were removed, leaving data from 313 subjects with no artifacts. For each of the 313 subjects, I calculated a mean ERP for each picture category that I subsequently averaged into grand means and

95% confidence intervals shown in **Figure 2.3**. For each subject, I calculated the LPP as the average voltages between 400 and 800 msec after stimulus onset for each picture subcategory within the pooled sensors. As expected, images with high motivational relevance, such as erotic or mutilation images, prompted higher LPPs than images with low motivational relevance, such as neutral images (**Figure 2.4**).

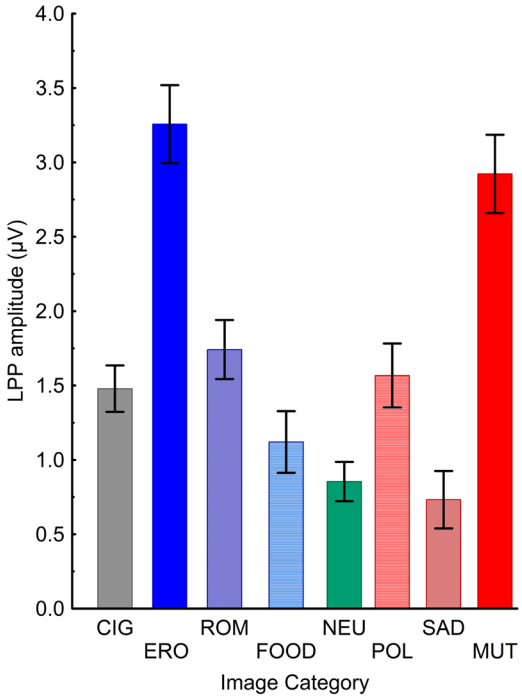

Figure 2.4: Bar charts depicting average LPPs and 95% confidence intervals by picture category. The LPPs evoked by our stimuli were consistent with previous findings regarding the LPP: Emotionally relevant images evoke greater LPPs than less salient images. LPP: late positive potential; CIG: cigarettes; ERO: erotica; ROM: romance; FOOD: food images; NEU: neutral; POL: pollution; SAD: sad images; MUT: mutilations

2.2.5 Noise visualization

Before proceeding with the Monte Carlo simulations, I assessed the level of noise in the neutral trials that I used in the Monte Carlo simulations of experiments with synthetic effect sizes. To visualize the noise in the segmented data, I followed the plus-minus averaging procedure outlined by Boudewyn and colleagues (2018; Schimmel, 1967). The goal of the procedure is to cancel the ERP signal and leave only the noise in the data.

First, for each subject, I separated the time series data from all odd and even neutral trials into unique vectors and averaged them individually. Then, for each subject, I subtracted the

mean of the odd trials from each even trial and vice versa. I tested the success of the procedure by averaging the time series data for all the trials (N = 12,520; 313 subjects * 40 neutral pictures) after the subtraction. The average (shown in **Figure 2.5**) ranged from 1.5×10^{-15} to -1.5×10^{-15} μV and thus remained at approximately zero, indicating that all the signal had been subtracted from the data, leaving only noise in the traces. To provide a more readable quantitative estimation of the variability around the mean, I calculated the percentage of trials at each time point that fell into each of four voltage bins: ±1 μV, ±5 μV, ±10 μV, and ±20 μV (**Figure 2.6**). At any given point, approximately 98% of the trials fell into the ±20 μV range, leaving 2% beyond that range. I decided to keep these outliers in the analysis to model the degree of noise typical in data collected in a clinical setting.

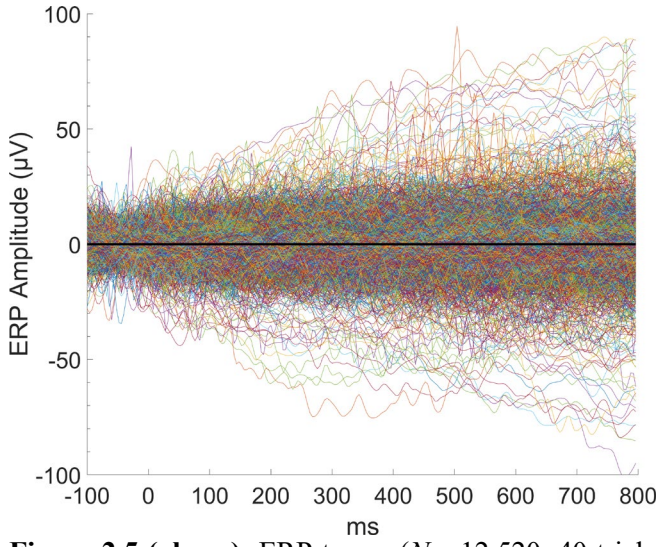

Figure 2.5 (above): ERP traces (N = 12,520, 40 trials per neutral category * 313 subjects) after plus-minus averaging reflect noise (colors). A black line reflecting average noise is overlaid. The average of the noise was approximately zero, indicating that the plus-minus averaging procedure subtracted out the signal and that only noise remained in the data.

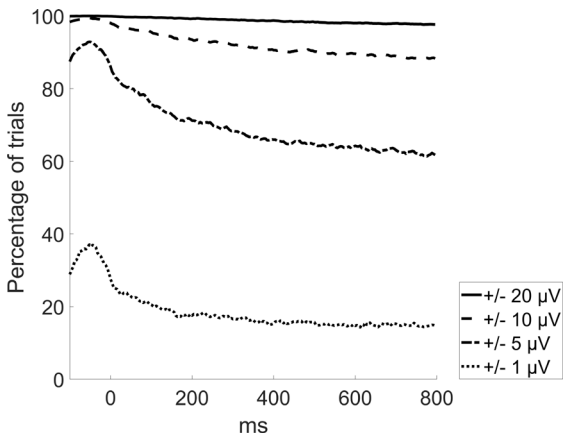

Figure 2.6 (above): Line plot showing the percentage of experimental trials within the voltage bins of ±20 μV, ±10 μV, ±5 μV, and ±1 μV. Approximately only 2% of trials exceeded the ±20 μV threshold at any given point.

2.2.6 Monte Carlo simulation of experiments with synthetic effects of known magnitude

To simulate ERP experiments using either within-subject or between-subjects designs, I randomly sampled subsets of subjects from the larger data set described above. For each subject, I randomly sampled subsets of neutral trials to which I added known effects to simulate LPP responses to different conditions, such as neutral and emotional stimuli. Each simulated experiment included a specific effect size, number of trials, and number of subjects. For within-subject designs, I selected twice the number of trials from each randomly sampled subject to simulate two experimental conditions.

For the between-subjects simulations, I sampled twice the number of subjects to simulate two experimental groups. For the within-subject analysis, I modeled each effect size by adding one-half of the simulated effect size to the LPP of one condition and subtracting one-half of the simulated effect size from the other. Similarly, between-subjects effect sizes were modeled by adding one-half the simulated effect size to the LPP of one group and subtracting one-half the simulated effect size from the LPP of the second group. The size of the synthetic effects that I added to the data ranged from 0 to 3 μV in increments of 0.1 μV, the number of trials ranged from 5 to 40 trials per condition in increments of five trials, and the number of subjects in each experiment ranged from 10 to 100 in 10-subject increments from 10 to 50 and a further increment of 50 to reach 100. Combining all parameters led to a total of 1,488 simulated experiments. Each simulated experiment was repeated 1,000 times. All Monte Carlo simulations were performed using MATLAB R2018b (The MathWorks, Inc., Natick, MA).

Table 2.2: Average LPP responses by picture category and differences from neutral

Picture Category	Average LPP (μV)	Average LPP difference from NEU (μV)
NEU	0.854131	0
SAD	0.731923	-0.12221
FOOD	1.120279	0.266148
CIG	1.478345	0.624214
POL	1.567271	0.71314
ROM	1.741594	0.887464
MUT	2.922355	2.068224
ERO	3.256931	2.4028

2.2.7 Monte Carlo simulation of experiments with real effects of estimated magnitude

In addition to simulating ERP experiments with synthetic effects of known magnitude, I also conducted simulations that are modeled on real experiments; that is, I simulated experiments aimed at testing a difference between conditions by selecting emotional and neutral trials without adding any effect. I estimated the magnitude of the effects that I was testing based on the differences observed between conditions in the grand averages computed across the 313 participants (see **Figure 2.4** and **Table 2.2**). For example, if the 2.1 μV difference observed between mutilations and neutral conditions reflects a real difference, how many times would I have obtained a statistically significant difference in an experiment that included, for instance, 10 participants and 15 trials per condition?

For the within-subject simulations, I randomly sampled subsets of subjects from the main data set as described for the within-subjects simulations described above. Then, from each subject, I randomly sampled subsets of trials from one emotional picture subcategory and the neutral picture category. Because the emotional picture subcategories contained only 16 pictures each, my real data simulations included only trials taken in sets of 5, 10, and 15 per category. Thus, a within-subject simulation, in this case, would include a specific number of subjects (10–100), a specific number of trials per condition (5–15), and a contrast between two specific conditions (e.g., erotica vs. neutral).

For the between-subjects simulations, I randomly sampled subjects as described for the between-subjects simulations described above. Then, within each subject I sampled two times the number of trials (5–15) from the neutral category and one times the number of trials (5–15) from each emotional picture subcategory. To model between-subjects differences, I computed the difference between the two sets of neutral trials for the subjects

in one group and the difference between neutral and emotional trials for subjects in the other group. Then I computed a between-subjects analysis of variance (ANOVA) on the two difference scores, effectively testing the interaction Group × Picture category. Thus, a between-subjects experiment modeled on a real experiment would include a specific number of subjects per group (10–100), a specific number of trials per emotional picture category (5–15), and a contrast between two specific conditions (e.g., erotica vs. neutral). All possible combinations of parameters led to 144 total experiments for both the within- and between-subjects analysis. Each experiment was repeated 1,000 times.

2.2.8 Statistical analysis

For each simulated experiment, I tested for statistically significant effects ($p < .05$) using one-way repeated measures ANOVAs for experiments simulating within-subject effects and one-way ANOVAs for experiments simulating between-subjects effects. It is important to note that these between-subjects ANOVAs essentially model the interaction effect of Group × Condition with two groups and two conditions. The synthetic effects added to the trials of the participants in each group can be thought of as the voltage difference between images belonging to two different categories. Similarly, in the simulations of experiments using real data, a contrast between two conditions was compared between two groups, effectively testing for the interaction Group × Picture category. This procedure allowed us to estimate the probability of obtaining a statistically significant outcome ($\alpha = .05$) for each combination of parameters. All ANOVAs were performed in R 3.5.0 (R Core Team, 2018). For each experimental condition, the percentage of *F*-values at or above the critical *F*-value was calculated to represent statistical power.

2.3 RESULTS

2.3.1 Monte Carlo simulation of experiments with synthetic effects of known magnitude

2.3.1.1 Within-subject analyses

As shown in **Figure 2.7**, within-subject analyses of synthetic effect sizes revealed that, when only 10 subjects were included in the experiment, 80% power was achieved only for differences in effect sizes larger than 1 μV, even when a large number of trials (40) was included for each experimental condition. With smaller numbers of trials and smaller differences in effect sizes, sufficient statistical power to detect the differences could not be

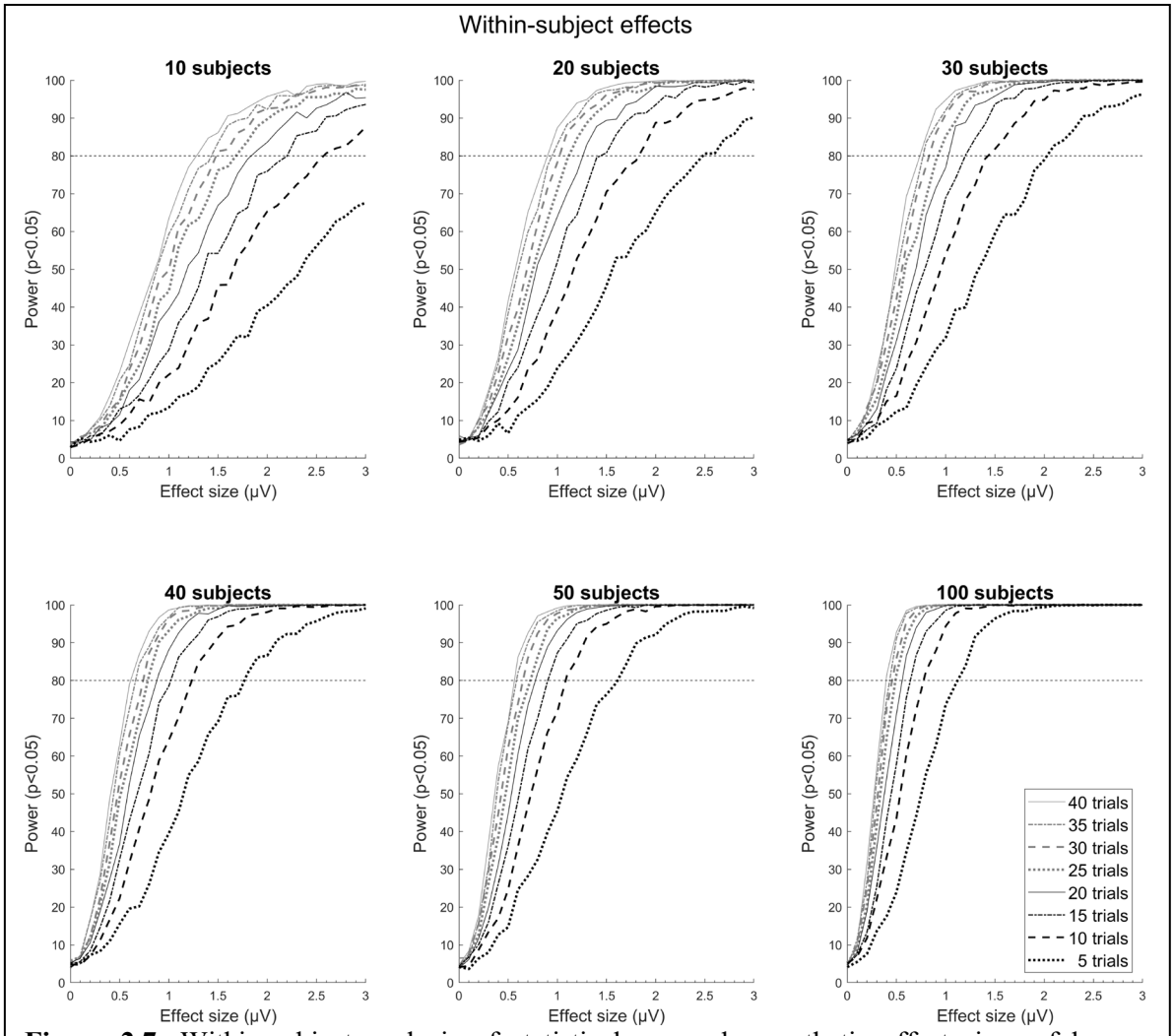

Figure 2.7: Within-subject analysis of statistical power by synthetic effect sizes of known magnitude at 5–40 trials per condition and for 10–100 subjects.

achieved. I found that, as the number of subjects increased, statistical power reached an asymptote at 100% at 1.5 μV for the experiments with a higher number of trials. This asymptote became apparent for experiments with smaller numbers of trials as the number of subjects increased and became evident for effect sizes as small as 1 μV with greater numbers of trials.

2.3.1.2 Between-subjects analyses

Overall, statistical significance is harder to achieve in between-subjects experimental designs than within-subject designs, and this was reflected in my results. **Figure 2.8** shows

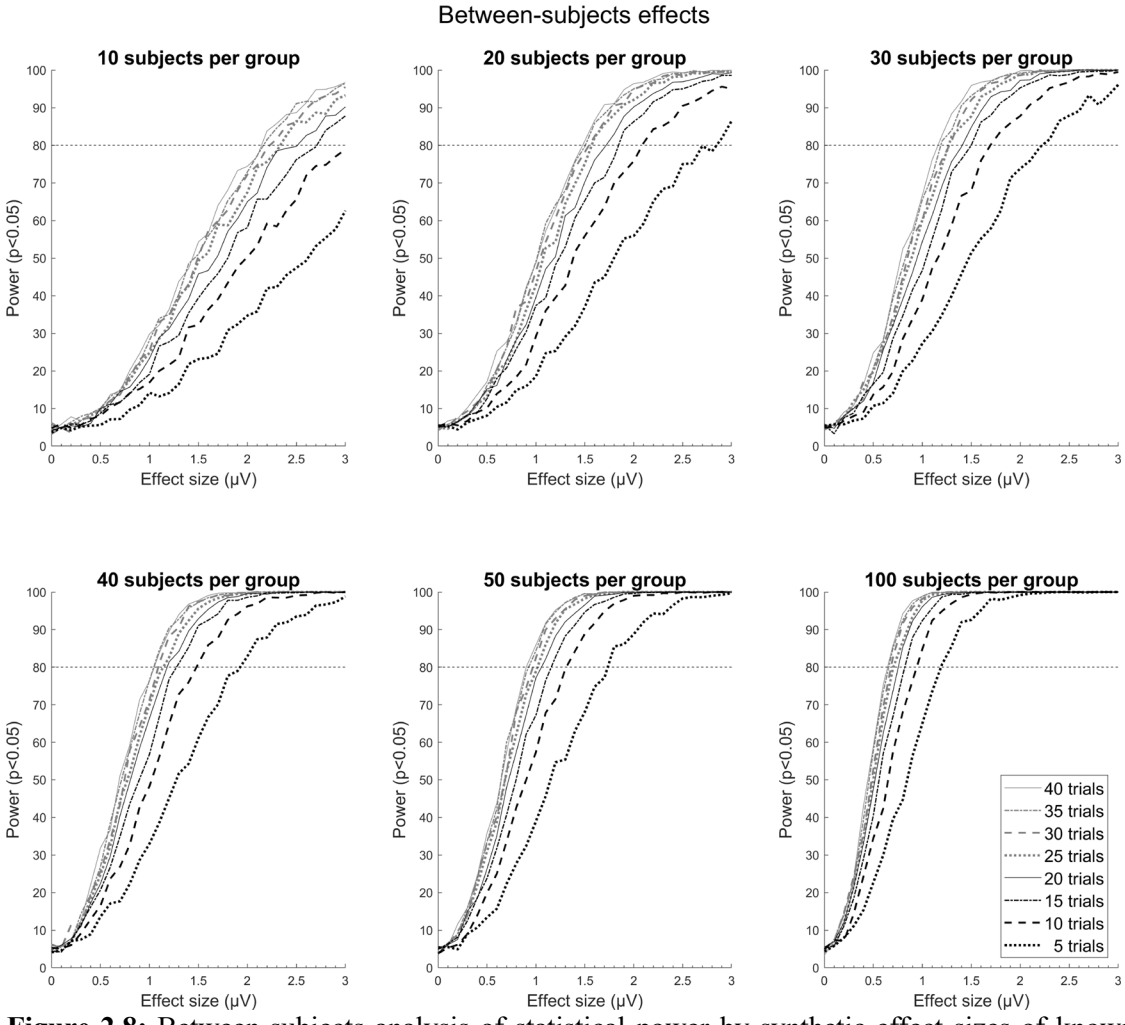

Figure 2.8: Between-subjects analysis of statistical power by synthetic effect sizes of known magnitude size at 5–40 trials and 10–100 subjects per group.

that statistical power was achieved only at higher effect sizes, greater numbers of trials, and relatively large sample sizes compared with what was observed in my within-subject analyses.

The slopes shown in **Figure 2.8** were generally less steep than the slopes shown in **Figure 2.7**, indicating that an increase in the size of the difference between conditions did not affect statistical power as dramatically in between-subjects designs as it did in within-subject designs. However, the overall trend of slopes increasing with increasing sample sizes was conserved.

At lower numbers of subjects per group, 80% statistical power was much harder to achieve between subjects than within subjects and was achieved only with greater numbers of trials. Starting at 40 subjects per group, statistical power reached an asymptote of 100% at 20 or more trials for effect sizes greater than 1.5 μV. This asymptote shifted to include smaller effect sizes and lower numbers of trials as subjects were added to the experiment, with 100 subjects per group reaching an asymptote at effect sizes as low as 1 μV. At 100 subjects per group, slopes were steepest, with 80% power achieved at effect sizes as low as 0.5 μV for experiments with 40 trials per condition.

2.3.2 Monte Carlo simulation of experiments with real effects of estimated magnitude

2.3.2.1 Within-subject analyses

Within-subject analyses of experiments with real effects of estimated magnitude closely replicated the results observed in the simulations using synthetic effects (**Figure 2.9)**: at lower effect sizes (<1 μV), the power is quite low, and it reached levels greater than 80% only at the highest numbers of subjects (>50) and number of trials (10 or more per condition). When larger differences (>2 μV) were tested, I observed levels of power greater than 80% even with lower

number of trials or subjects. Similar to the results from within-subject simulations of synthetic effects, an asymptote was visible in the within-subject simulations of contrasting picture categories but only at the highest effect sizes (>2 μV), trials per condition (10 or more), and

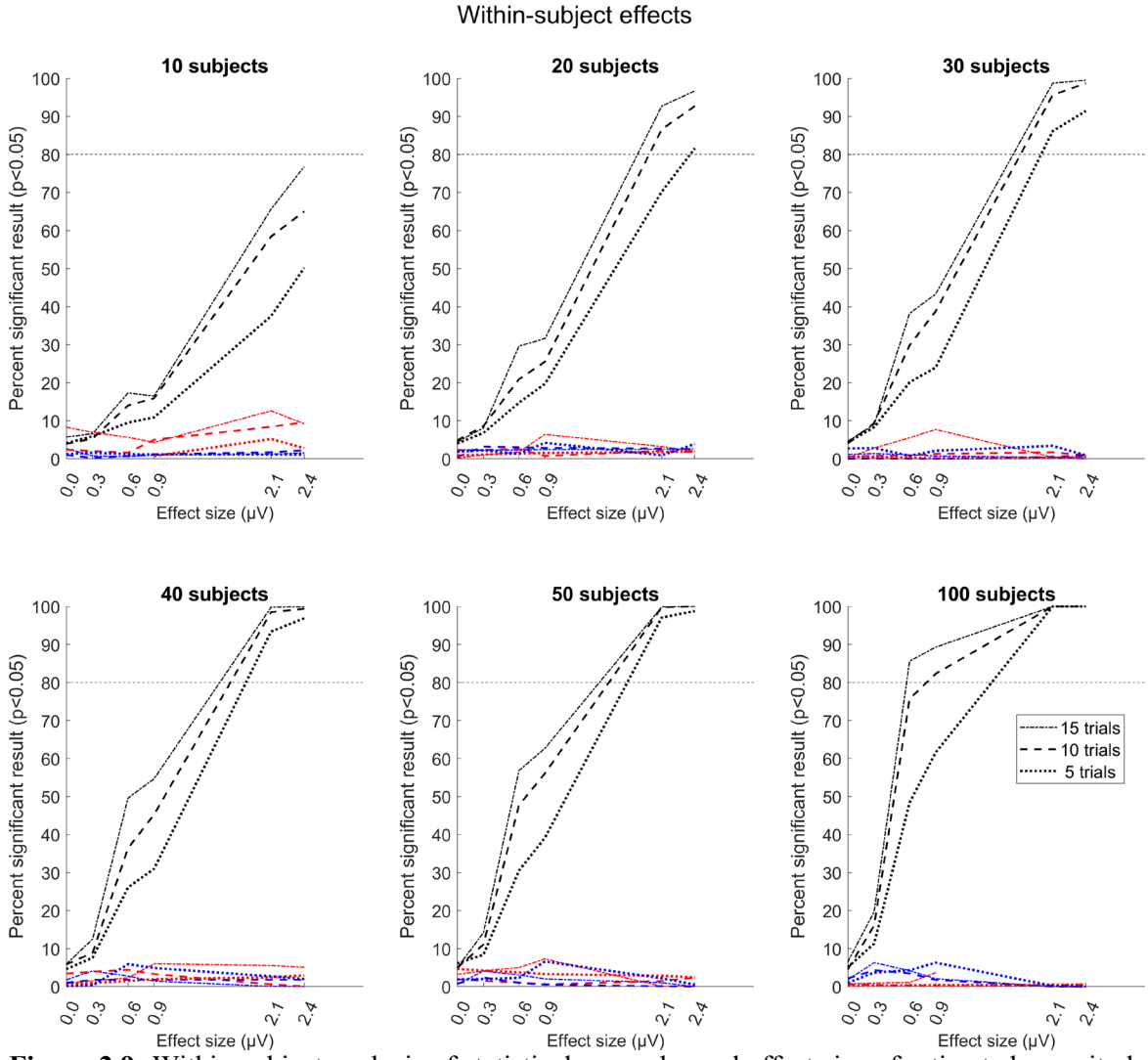

Figure 2.9: Within-subject analysis of statistical power by real effect size of estimated magnitude at 5–15 trials per condition (dotted, dashed, dash-dot; gray) and for 10–100 subjects. The difference between power calculations resulting from simulations of synthetic effect sizes of known magnitude and simulations of real effect sizes of estimated magnitude are depicted in colors, with positive differences (overestimations) depicted in red and negative differences (underestimations) depicted in blue for 5–15 trials per condition (dotted, dashed, dash-dot; colors). Included in these figures are effect sizes resulting from contrasting neutral vs. neutral (0 μV), neutral vs. food (0.2 μV), neutral vs. cigarettes (0.6 μV), neutral vs. romance (0.9 μV), neutral vs. mutilations (2.1 μV), neutral vs. erotica (2.4 μV)

numbers of subjects (40 or more).

2.3.2.2 Between-subjects analyses

Consistent with my findings from between-subjects analyses using synthetic effect sizes, **Figure 2.10** shows that, at the same numbers of subjects, trials, and effect sizes, the statistical power between subjects was lower than it was within subjects. Also, the asymptotic relationship between power and effect size in these analyses was apparent only

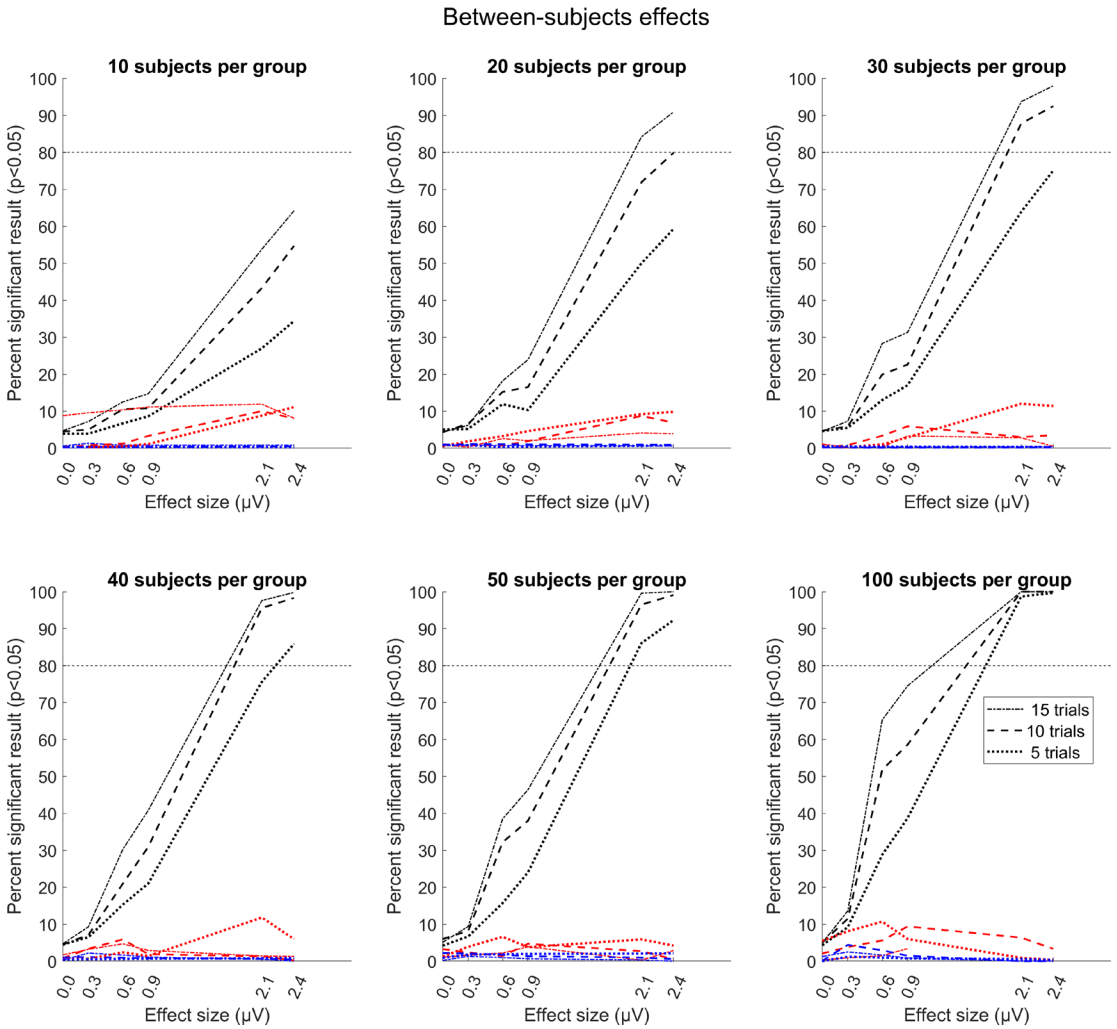

Figure 2.10: Between-subjects analysis of statistical power by real effect size of estimated magnitude at 5–15 trials per condition (dotted, dashed, dash-dot; gray) and for 10–100 subjects per group. The difference between power calculations resulting from simulations of synthetic effect sizes of known magnitude and simulations of real effect sizes of estimated magnitude are depicted in colors, with positive differences (overestimations) depicted in red and negative differences (underestimations) depicted in blue for 5–15 trials per condition (dotted, dashed, dash-dot; colors). Included in these figures are effect sizes resulting from contrasting neutral vs. neutral (0 μV), neutral vs. food (0.2 μV), neutral vs. cigarettes (0.6 μV), neutral vs. romance (0.9 μV), neutral vs. mutilations (2.1 μV), neutral vs. erotica (2.4 μV).

at the highest effect sizes (>2 μV) and subjects per group (50 or more).

2.3.3 Summary

Predictably, my results showed that increasing the number of trials and subjects increased statistical power and that statistical power was greater for larger effect sizes. Also, as expected, statistical power of at least 80% could be achieved at lower effect sizes, sample sizes, and trial numbers in within-subject as compared with between-subjects experiments. Furthermore, I found that, in both within-subject and between-subjects experiments of synthetic effect sizes, an increase in subjects more rapidly increased the statistical power at the lower range of effect sizes (<1 μV) until the power later reached an asymptote at the higher range of effect sizes (>1.5 μV). This asymptotic effect was visible in the simulations with effect sizes resulting from a difference between conditions, but only at effect sizes greater than 2 μV and at the highest numbers of subjects and trials. The results from the simulations of experiments using real data closely reflected those obtained using synthetic data for similar effect sizes.

2.4.1 DISCUSSION

The present study was concerned with how best to optimize the parameters that affect statistical power in ERP experiments that use the amplitude of the LPP to assess affective processes in within- and between-subjects designs. I adopted the simulation approach used by Boudewyn and colleagues (2018), but, I investigated the LPP, an ERP component that is heavily studied in the domain of affective neuroscience and has more modest effect sizes when compared with the ERN. Detecting differences in the amplitude of the LPP evoked by emotional versus neutral stimuli between groups often means investigating modest differences; accordingly, achieving sufficient statistical power under such conditions requires increasing the number of subjects and/or including a greater number of trials in the experiment. Here, I

provide a useful tool that researchers can use to evaluate the trade-offs and achieve their research objectives.

2.4.2 Different ERP components have different dynamics with respect to power

In a previous study that investigated statistical power for the ERN and LRP components (Boudewyn et al., 2018), the slope of the relationship between the statistical power and the number of trials was steepest at the middle range of the effect sizes (3–5 μV) and numbers of trials (10–12) investigated. In contrast, the present study found steeper slopes at the higher range of the numbers of subjects (50+) and trials (20+) but at lower effect sizes (0.4–1 μV). Therefore, the dynamics of study parameters as they relate to statistical power are different among ERP components. These dynamics are likely related to the properties of the ERP components themselves and the noise present in the data. As such, experiments that assess the LPP may benefit more from increasing numbers of trials and subjects than would experiments that focus on larger amplitude components such as the ERN. Thus, the SNR for the LPP may increase more with increased numbers of trials and subjects, as the variability between individuals and the noise within the component itself is averaged out.

2.4.3 Comparison of simulations based on experiments with synthetic effects of known magnitude and experiments with real effects of estimated magnitude

In addition to conducting simulations of experiments with known synthetic effects added to the data, I also conducted simulations of experiments aimed at detecting real effects for which I estimated the magnitude on a large sample of participants ($N = 313$). Even though the simulations based on real data allowed me to test only a smaller range of effects than those based on synthetic data, the results from the two sets of simulations were remarkably similar (**Figures 2.7** and **2.8**). The small differences between simulation results may relate to the uncertainty of the "true" effect size that exists within each simulated

experiment that uses real data when the magnitude of the effect can be only statistically estimated and is not actually known. The high similarity observed in the two sets of simulations also indicates that the noise in the EEG data is independent of the response evoked by the pictures: higher LPPs are not associated with higher levels of noise.

2.4.4 Impact on affective neuroscience

My results provide guidelines that neuroscientists can employ when designing experiments that use the LPP to investigate affective processes or when evaluating the results of these experiments. My findings indicate that between-subjects comparisons that include, for example, 10 subjects per group are extremely unlikely to produce meaningful results. As pointed out by Ioannidis and colleagues (Ioannidis, 2005), when experiments are grossly underpowered, a statistically significant result is likely to be artifactual. Even with 20 or 30 subjects per group, sufficient statistical power can be achieved only for effect sizes larger than 1 μV, which is larger than the LPP difference I found when comparing low arousing and neutral stimuli (**Table 2.2**). For investigators studying more modest differences, such as those often observed in interaction effects in both within- and between-subjects designs, my results indicate that, at a minimum, 40 trials and 50 subjects per group are needed to achieve sufficient statistical power.

These findings related to the SNR of the LPP signal also inform the field of affective neuroscience regarding the trade-off between adding subjects versus adding trials to an experiment. As shown in **Figure 2.8**, five trials per condition and 10 subjects per group achieves a statistical power of approximately 20% at an effect size of 1.5 μV. However, an experiment with the same parameters that includes 20 subjects per group achieves nearly 40% statistical power: by doubling the subjects per group, the power increases approximately

twofold in this example. Meanwhile, if the number of trials per condition is doubled to 10 trials per condition while still using 10 subjects per group and looking at a 1.5 μV effect size, statistical power is approximately 30%. Thus, my results indicate that adding subjects to an experiment has a greater effect on the statistical power than increasing the number of trials would.

However, due to the difficulties that come with the recruitment of human subjects, doubling the sample size may not be feasible, and some labs may favor adding trials to their experiments instead. Conversely, depending on the number of conditions used in the experiment, adding trials may not be feasible, as this could excessively increase the duration of the experiment. The results that I presented here offer researchers the opportunity to more precisely estimate the impact that decisions about important parameters in an experiment have on statistical power.

One objective of this study was to simulate data with a higher degree of noise and with modest effect sizes, as many investigators may be interested in how to sufficiently power studies investigating small LPP amplitude differences or may work with noisy data. Hence, my results might be less informative when very robust effects (e.g., those greater than 3 μV) are under investigation or when the noise in the data is minimal. Furthermore, different ERP components might show different dynamics with respect to power, and as such future studies should specifically investigate statistical power for more components.

2.4.5 Conclusions

By sufficiently powering clinical affective neuroscience studies, investigators will collect more reliable results, thereby improving the reproducibility of their research findings. My findings may help researchers to plan and evaluate the results of experiments

that use the LPP as an index of motivational relevance and may ultimately foster the translation of results from basic science experiments to evidence-based treatments of disorders characterized by altered affective processing. Careful consideration of statistical power furthers the ultimate goal of translational affective neuroscience research: to bolster innovation in the psychiatric domain.

CHAPTER 3: Individual differences in late positive potential amplitude and theta power predict cue-induced eating

This chapter is based upon the following preprint written by the author…

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3.1 BACKGROUND

Overweight and obesity, characterized by a BMI of at least 25 kg/m^2 and at least 30 kg/m^2, respectively, increase the risk of cardiovascular disease, diabetes, and several types of cancer (Prospective Studies Collaboration, 2009). Losing even a modest amount of weight can have substantial health benefits, but most weight-loss interventions yield short-lived, suboptimal results (Jeffery et al., 2000; Turk et al., 2009). Identifying the neurobiological mechanisms underlying excessive eating—the ultimate cause of weight gain (Davis et al., 2014; de Lauzon-Guillain et al., 2017)—can help clinicians target the root causes of overeating, personalize interventions for weight loss, and improve weight loss treatment outcomes.

Neurobiological models of obesity have demonstrated that the brain's reward and cognitive control systems both play a major role in regulating food intake (Appelhans, 2009; van den Bos and de Ridder, 2006). The reward system guides eating behavior with bottom-up signals that dynamically assign motivational salience to food rewards and the cues associated with them (Pitchers et al., 2017a, 2017b). In contrast, cognitive control systems exert top-down control over eating behavior by enabling the implementation of intentional, goal-directed behavior (Hall, 2016). Failure of either mechanism can lead to maladaptive eating patterns, overeating of hyper-palatable foods, and weight gain (Stice and Yokum, 2016).

Preclinical findings demonstrated that animals differ in their tendency to engage bottom-up versus top-down driven behaviors in the presence of cues signaling the impending delivery of food rewards (i.e., food-related cues) (Sarter and Phillips, 2018). Individuals who attribute high motivational salience to food-related cues are prone to cue-induced compulsive reward-seeking behaviors (Flagel et al., 2011). On the other hand, those who do not attribute high levels of motivational salience to reward-related cues are less prone to cue-induced compulsive behaviors and are likely to implement goal-directed behaviors when faced with these cues (Pitchers et al., 2018).

Our lab has previously demonstrated that humans are also characterized by individual differences in the tendency to attribute motivational salience to food-related cues (Versace et al., 2016) and that these differences underlie vulnerability to cue-induced eating (Versace et al., 2018). In these experiments, we recorded event-related potentials (ERPs), a direct measure of brain activity (Hajcak et al., 2019), during a cued food delivery task. In this task, participants viewed emotional, neutral, and food-related images while we recorded electroencephalogram (EEG) from the scalp. After the presentation of some food-related images, we dispensed chocolate candies to the participants, which they could eat or discard (Deweese et al., 2015). To estimate the motivational salience of these images, we measured the amplitude of the late positive potential (LPP) in response to each image. The LPP is an ERP component that is reliably modulated by motivational salience: highly salient images such as erotica and mutilations prompt larger LPP responses than do images with lower salience, such as romantic or sad images (Cuthbert et al., 2000; Minnix et al., 2013; Weinberg and Hajcak, 2010). We found that individuals with larger LPP responses to food-related cues than to pleasant images (C>P group) ate significantly more during the experiment than did those with larger LPP

responses to pleasant images than to food-related cues (P>C group) (Versace et al., 2018).

These findings support the hypothesis that attributing higher motivational salience to food-related cues than to pleasant non-food-related stimuli increases vulnerability to cue-induced eating, but they are silent about the role of individual differences in the engagement of cognitive control systems in regulating cue-induced eating. Because results from animal models suggest that individuals who attribute high levels of motivational salience to food-related cues might also have poor top-down control over cue-induced behaviors (Pitchers et al., 2018; Robinson and Berridge, 2003; Sarter and Phillips, 2018; Tunstall and Kearns, 2015), the present study aimed to elucidate how both cognitive and affective mechanisms act in tandem to regulate cue-induced eating.

Activity in the theta frequency band has been proposed as a reliable correlate of the engagement of higher cognitive functions (Cavanagh et al., 2012; Cavanagh and Frank, 2014). Theta (θ; 4-8 Hz) power (μV^2) over midfrontal scalp sites increases when participants engage cognitive control mechanisms to inhibit prepotent responses (Haciahmet et al., 2021; Nigbur et al., 2011) or perform difficult tasks (Wang et al., 2018). In light of these findings, I used theta power in an exploratory fashion to approximate the engagement of cognitive control systems in food-related decision-making during a cued food delivery task.

This research is aimed at investigating the role that individual differences in both the attribution of motivational salience to food-related cues and the engagement of cognitive control systems have in regulating cue-induced eating during the cued food delivery task. I expected to replicate our lab's previous findings: namely, that individual differences in affective processing of cues predict cue-induced eating. I also aimed to elucidate whether the engagement of cognitive control systems, as indexed by theta power, differs between P>C and

C>P individuals, or if cognitive control mechanisms contribute to cue-induced eating behavior irrespective of C>P and P>C status. Results demonstrating that midfrontal theta power differs between the C>P and P>C groups would suggest that individuals attributing higher motivational salience to food-related cues might also have difficulty engaging cognitive control mechanisms when making food-related decisions, in a manner similar to what has been observed in animal models. Meanwhile, results demonstrating that individual differences in midfrontal theta power predict eating behavior regardless of C>P vs and P>C status would suggest that the engagement of cognitive control systems regulates cue-induced eating independently from the tendency to attribute motivational salience to food-related cues. By elucidating whether motivational salience and cognitive control mechanisms converge to regulate cue-induced eating or do so independently, I hope to inform clinical researchers of effective mechanistic targets for weight loss and other clinical interventions aimed at reducing maladaptive, reward-seeking behaviors.

3.2 METHODS

3.2.1 Participants

Our lab recruited sixty research participants from the Houston, Texas, metro area using flyers and magazine and newspaper advertisements. Participants were eligible if they were 18 to 65 years of age, were neither pregnant nor breastfeeding, and did not have a history of psychiatric disorders, seizures, head injuries with loss of consciousness, uncorrected visual impairments, eating disorders, or allergies, or any other illnesses that would prevent them from eating chocolate candy. Participants received monetary compensation for their time and travel totaling up to $60 each. One participant was excluded from the final analysis due to incomplete data. **Tables 3.1 and 3.2** show the demographic information for the participant sample.

Table 3.1: Demographic, biometric, and self-reported data for all subjects and for the LPP and theta-based participant groups							
	Mean (SD)						
Characteristic	**All subjects (*n* = 59)**	**C>P (*n* = 28)**	**P>C (*n* = 31)**	***p* (C>P vs. P>C)**	**θCA>θBE (*n* = 22)**	**θBE>θCA (*n* = 37)**	***p* (θCA>θBE vs. θBE>θCA)**
Age, years	45 (11.67)	43 (14.09)	48 (8.52)	0.10	43 (11.61)	47 (11.62)	0.21
Women, %	46	39	52	0.34	82	24	0.56
Race, %							
Black/African American	64	75	55		73	59	
White/Caucasian	24	14	32		18	27	
Asian	7	11	3		5	14	
More than one race	3	0	6		5	3	
I prefer not to say	2	0	3		0	3	
BMI, kg/m^2	31 (7.75)	30 (8.19)	31 (7.43)	0.69	31 (0.92)	31 (7.42)	0.85
Hispanic or Latino ethnicity, %	12	18	6		14	11	
BIS attention	15.57 (3.63)	15.52 (4.10)	15.61 (3.23)	0.92	15.62 (2.40)	15.54 (4.20)	0.94
BIS motor	21.26 (3.96)	21.33 (4.27)	21.19 (3.74)	0.89	21.62 (4.20)	21.05 (3.86)	0.61
BIS Non-planning	13.22 (2.63)	13.04 (2.68)	13.39 (2.62)	0.62	12.57 (2.20)	13.59 (2.80)	0.16
CESD	8.53 (4.76)	8.85 (5.44)	8.26 (4.15)	0.64	7.81 (3.76)	8.95 (5.24)	0.39
SHAPS	1.14 (2.54)	1.33 (2.99)	0.97 (2.12)	0.59	1.05 (3.04)	1.19 (2.26)	0.84
PANAS (+)	33.28 (9.59)	31.15 (10.08)	35.13 (8.89)	0.12	33.90 (8.74)	32.92 (10.14)	0.71
PANAS (-)	17.62 (7.64)	18.19 (7.24)	17.13 (8.05)	0.60	16.95 (8.37)	18.00 (7.28)	0.62
PFS	51.88 (19.22)	48.70 (19.88)	54.65 (18.50)	0.24	50.00 (21.7)	52.95 (17.87)	0.58
FCQ	101.69 (36.56)	99.07 (37.65)	103.97 (36.05)	0.62	96.62 (37.19)	104.57 (36.40)	0.43
WREQ routine restraint	1.64 (0.87)	1.43 (0.58)	1.83 (1.04)	0.08	1.46 (0.69)	1.75 (0.95)	0.23
WREQ compensatory restraint	2.17 (0.84)	2.05 (0.81)	2.27 (0.85)	0.32	2.17 (0.92)	2.16 (0.80)	0.96
WREQ susceptibility to external cues	2.30 (1.00)	2.21 (1.06)	2.37 (0.96)	0.57	2.41 (1.15)	2.23 (0.92)	0.52
WREQ emotional eating	2.09 (1.02)	1.95 (1.18)	2.21 (0.86)	0.34	2.13 (1.15)	2.06 (0.95)	0.79
SLIM	0.72 (39.15)	-3.24 (33.45)	4.30 (43.92)	0.46	-11.70 (36.43)	8.11 (39.31)	0.06
Number of candies eaten	11 (17.19)	14 (20.02)	8 (13.94)	0.21	14 (19.66)	9 (15.42)	0.22

3.2.2 Study procedures

The study included an eligibility screening of potential participants via telephone followed by an in-person laboratory visit. A research assistant met with the participant at each laboratory visit to explain the study and obtain informed consent. The research assistant then collected the participant's biometric information, including height and weight, and then administered a series of computerized questionnaires. After completing the questionnaires, the research assistant placed an EEG net on the participant's head and instructed the participant on how to complete the cued food delivery task. The research assistant then left the room and began both the EEG recording and the cued food delivery task. After completion of the EEG session and task, the participant was debriefed and given financial compensation. All study procedures were approved by The University of Texas MD Anderson Cancer Center Institutional Review Board.

3.2.3 Questionnaires

The computerized questionnaires used in this experiment consisted of those assessing hunger and satiety, eating habits, impulsivity, mood, affect, and hedonic tone. To assess hunger and satiety, we administered the Satiety Labeled Intensity Magnitude (SLIM) scale (Cardello et al., 2005) to each participant before and after completion of the cued food delivery task. To ascertain eating habits, we used the weight-related eating questionnaire (WREQ) (Schembre et al., 2009; Schembre and Geller, 2011), the Power of Food Scale (Lowe et al., 2009), and the Food Cravings Questionnaire (Nijs et al., 2007), which measure variables such as susceptibility to external cues, the influence of a food-abundant environment on eating, and food cravings, respectively. To measure impulsivity, we administered the Barratt Impulsiveness Scale (BIS) (Patton et al., 1995; Stanford et al., 2009). Finally, to identify variables relating to affect, mood,

and hedonic tone, we administered the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988), the Center for Epidemiologic Studies Depression Scale (Radloff, 1977), and the Snaith-Hamilton Pleasure Scale (Nakonezny et al., 2010; Snaith et al., 1995), respectively.

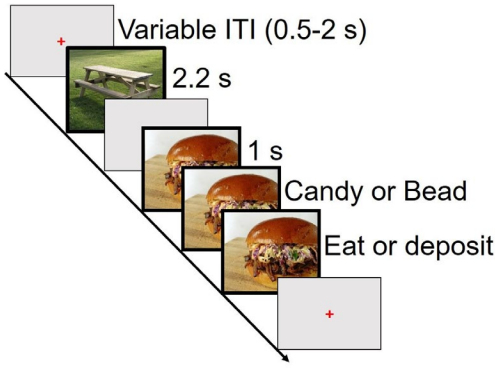

Figure 3.1: In the controlled cued food delivery task, participants view emotional, neutral, and food-related images while EEG is recorded from the scalp. After the presentation of a food-related image, either a candy or bead was dispensed to the participant. The participant could then choose to eat or discard the dispensed candies. ITI: inter-trial interval

3.2.4 Controlled cued food delivery task

Participants completed the cued food delivery task depicted in **Figure 3.1** (Deweese et al., 2015) with the addition of a control condition in which they were also dispensed plastic beads. During the task, participants viewed emotional, neutral, and food-related images presented on a 17-inch computer screen using E-Prime software (version 2.0.8.74; Psychology Software Tools, Inc., Pittsburgh, PA) while EEG was recorded from the scalp. After viewing a food-related image, each participant was dispensed either a chocolate candy, which they had the option to eat or discard, or a bead. Food-related images consisted salty or sweet contents (for example: pizza [salty], cake [sweet]). One of these two categories of food images (counterbalanced across participants) preceded the delivery of the candy, whereas the other preceded the delivery of the bead. Each participant was told at the beginning of the EEG session which category of food image would precede the candies and which would precede the beads. The pictures used in this task were selected from the International Affective Picture System (IAPS; Lang et al., 2008) and a set of pictures used in our previous studies (Versace et al., 2016, 2018)[2].

[2] The IAPS pictures used in this study are the following IAPS codes: 4604, 4611, 4647, 4650, 4653, 4658, 4659, 4660, 4666, 4668, 4669, 4677, 4680, 4687, 4690, 4691, 4693, 4694, 4695, 4696, 4698,

The cued food delivery task consisted of six experimental blocks that lasted about 5 min each. In each block, 55 images were presented pseudorandomly (no more than two images belonging to the same picture category were presented consecutively): 10 neutral (people and objects), 10 pleasant (erotica and romance), 15 unpleasant (mutilations, violence, and pollution), and 20 food-related (savory or sweet) images.

No images were repeated during the task. For the food images, the candy or bead was dispensed 1000 msec after the food cue appeared on the screen through a tube into a receptacle. The participant then could either pick up and eat the candy or discard it in a box. Each food image remained visible until the participant either deposited the candy or bead into the box or pressed a button indicating that they had finished eating the candy. All non-food images were presented for 2.2 sec, and a random intertrial interval (ITI) of 3-5 sec separated each trial. To familiarize the participants with the task, we ran 11 practice trials, two of which were followed by a candy or bead.

3.2.5 EEG recording procedures

We continuously recorded EEG during the task using a 129-channel Geodesic Sensor Net that was amplified with an AC-coupled high-input-impedance (200 MΩ) amplifier (Geodesic EEG System 200; EGI, Eugene, OR) and referenced to electrode Cz. EEG data were collected at a sampling rate of 250 Hz and filtered online using a 0.1-Hz high-pass and 100-Hz low-pass

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4800, 2501, 2550, 4597, 4600, 4612, 4616, 4619, 2208, 4599, 4610, 4624, 4625, 4640, 4641, 4643, 4700, 2037, 2039, 2102, 2107, 2190, 2191, 2210, 2273, 2305, 2359, 2374, 2377, 2383, 2393, 2396, 2397, 2411, 2435, 2441, 2500, 2511, 2512, 2575, 2594, 2595, 2620, 2630, 2635, 7550, 9070, 5390, 7000, 7001, 7002, 7006, 7009, 7010, 7011, 7012, 7018, 7020, 7021, 7026, 7030, 7034, 7040, 7041, 7050, 7052, 7053, 7054, 7055, 7056, 7059, 7061, 7062, 7081, 7090, 7150, 7233, 9322, 9902, 9941, 6020, 7079, 7521, 9010, 9090, 9110, 9290, 9291, 9295, 9300, 9301, 9320, 9373, 9560, 9600, 9621, 9911, 9912, 2703, 6211, 6312, 9429, 9520, 9530, 2811, 3500, 3530, 6210, 6230, 6231, 6242, 6260, 6313, 6315, 6350, 6360, 6510, 6540, 6550, 6560, 6571, 6832, 9414, 3000, 3030, 3051, 3053, 3060, 3064, 3068, 3069, 3071, 3080, 3100, 3103, 3110, 3120, 3130, 3140, 3150, 3170, 3180, 3181, 3211, 3213, 3225, 3261, 3400, 6021, 9253, 9265

filter. The scalp impedance was kept under 50 KΩ as per the manufacturer's instructions.

3.2.6 Data reduction

After collecting the EEG, the EEG data were filtered using a 30-Hz low-pass filter and visually inspected to identify broken channels, which were defined as any channels contaminated by artifacts in more than 50% of the recording. Any broken channels were interpolated using spherical splines. Next, the EEG recordings were corrected for blinks and horizontal eye movements using a spatial filtering method implemented in the BESA software program (version 5.1.8.10; MEGIS Software GmbH, Gräfelfing, Germany). The data were then transformed to the average reference and segmented as outlined below.

For the analysis of ERPs, each segment of EEG was time-locked to the onset of each picture in segments that started 1500 msec before the onset of the picture and lasted until 1500 msec afterward. For the time-frequency analyses, each segment of EEG was time-locked to the delivery of a candy or bead in segments that started 1500 msec before the dispensation of the candy or bead and lasted until 1500 msec afterward. The data were baseline-corrected using a 100-msec time bin before the onset of the pictures (ERPs) or the onset of the candy or bead dispensation (time-frequency) as the baseline. Artifacts in the -1000 to +1000-msec time window for each segment were then detected based on the following criteria: EEG amplitude above 100 or below -100 μV, an absolute voltage difference between any two points in a segment no greater than 100 μV, maximum voltage step between two contiguous data points of 20 μV, and less than 0.5 μV of variation in activity for more than 100 msec. Channels that were marked bad in more than 40% of the segments were interpolated, and any segment that included more than 12 bad channels after interpolation was discarded.

3.2.7 LPP

I used the amplitude of the LPP as a measure of cues' motivational salience. To calculate the LPP for each subject and picture category, I averaged the EEG responses that were time-locked to the onset of each picture during the 400- to 800-msec time window using a pooled set of centroparietal sensors (EGI HydroCel Geodesic Sensor Net sensors 7, 31, 37, 54, 55, 79, 80, 87, 106, 129; see **Figure 3.2** inset for a depiction of the sensors). This is the same spatiotemporal region of interest (ROI) used in our previous studies investigating the LPP (Versace et al., 2016, 2012, 2017).

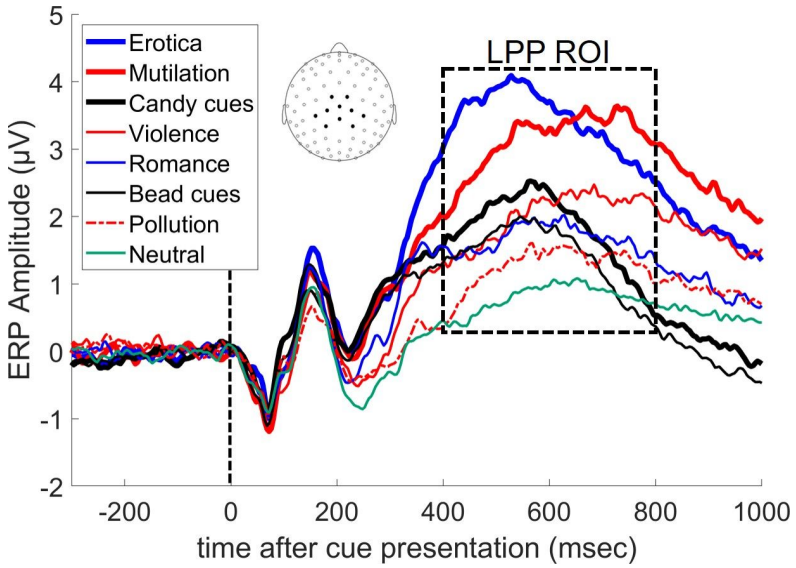

Figure 3.2: ERPs for centroparietal scalp sites (see inset for EEG electrode locations) showing that, on average, the LPP amplitude was higher for motivationally relevant pictures, such as mutilations or erotic images, than for other types of pictures. The box outlines the temporal ROI used to calculate the LPP for each picture category. Each picture was presented on the screen at 0 msec.

3.2.8 Theta power

To calculate theta power, the EEG data time-locked to the delivery of the candy or bead was transformed into the time-frequency domain using a continuous wavelet transform. The wavelet transform was based on a complex Morlet wavelet function with a Morlet parameter of 5 using 40 linear frequency steps from 1 to 40 Hz. The data were normalized using Gabor normalization and were baseline-corrected using a reference interval from -875 to -625 msec. To calculate theta power, the 4- to 8-Hz frequency bands were averaged.

3.2.9 Classification of participants

To classify the participants based on their LPP responses to cues, I followed a procedure used in our previous studies (Versace et al., 2016, 2018). Specifically, I *z*-transformed each participant's LPP data for each picture category, then I applied a *k*-means ($k = 2$) clustering algorithm to these *z*-transformed LPP values for each participant. The number of clusters ($k = 2$) was decided a priori based on previous findings (Versace et al., 2012, 2018).

To classify the participants based on their theta power amplitudes, I followed a similar strategy. Specifically, each participant's theta power values were *z*-transformed for the candy, bead, and neutral conditions during a 0- to 200-msec time bin using a pooled set of mid-frontal sensors. I then applied a *k*-means ($k = 2$) clustering algorithm to these *z*-transformed theta power values, with the a priori hypothesis that two distinct patterns of theta activity would be observed, much like our previous findings using the LPP.

3.2.10 Eating behavior

Because the number of candies the participants ate during the experiment is a count variable, I tested differences in eating behavior between groups using Poisson regression analysis. First, I compared the number of candies eaten during the experiment between the two LPP-derived groups. Second, I conducted another Poisson analysis to compare the number of candies eaten between the two theta power-derived groups. Third, I compared the number of candies eaten by the four groups formed by crossing the LPP and theta power-based groups using Poisson regression.

3.2.11 Demographics & questionnaires

To identify whether any demographic or psychological factors had confounding effects on the trends in eating behavior observed in the participant groups, I conducted Poisson regression

modeling the effect of group assignment on eating behavior. The demographic, biometric, and self-reported data outlined in **Table 3.1** were included in the model as covariates.

3.3 RESULTS

3.3.1 Event-related potentials

Figure 3.2 shows the grand averaged ERPs for each picture category. As expected, the amplitude of the LPP increased as a function of motivational salience irrespective of hedonic content. I formally tested this effect using LPP amplitude as a dependent variable in a repeated-measures analysis of variance (ANOVA) with the picture category as an eight-level factor (candy cues, bead cues, erotica, romance, neutral, pollution, violence, and mutilations; $F[7, 399] = 22.1$, $p < 0.001$). I also tested the quadratic trend of increasing LPP as a function of motivational salience under both pleasant and unpleasant conditions ($F[5, 290] = 46.3$, $p < 0.001$). Furthermore, I found that on average, food images preceding dispensation of the candy elicited larger LPPs than did food images preceding dispensation of the bead ($F[1, 58] = 5.02$, $p = 0.029$).

3.3.2 Classification of participants: LPP

Cluster analysis of the LPP responses identified the two hypothesized reactivity profiles: one group (C>P) had larger LPP responses to food cues than to pleasant images, and the other group (P>C) had larger LPP responses to pleasant images than to food cues. Both groups exhibited the canonical pattern of progressively larger LPP responses for both pleasant and unpleasant images as a function of their motivational salience (C>P group: $F = 87.5$, $p < 0.001$; P>C group: $F = 77$, $p < 0.001$) (**Figure 3.3A**). The P>C group had significantly larger LPP responses to pleasant images than to food cues ($F = 6.51$, $p = 0.013$), whereas the C>P group had significantly larger LPP responses to food cues than to pleasant images ($F = 59$, $p < 0.001$).

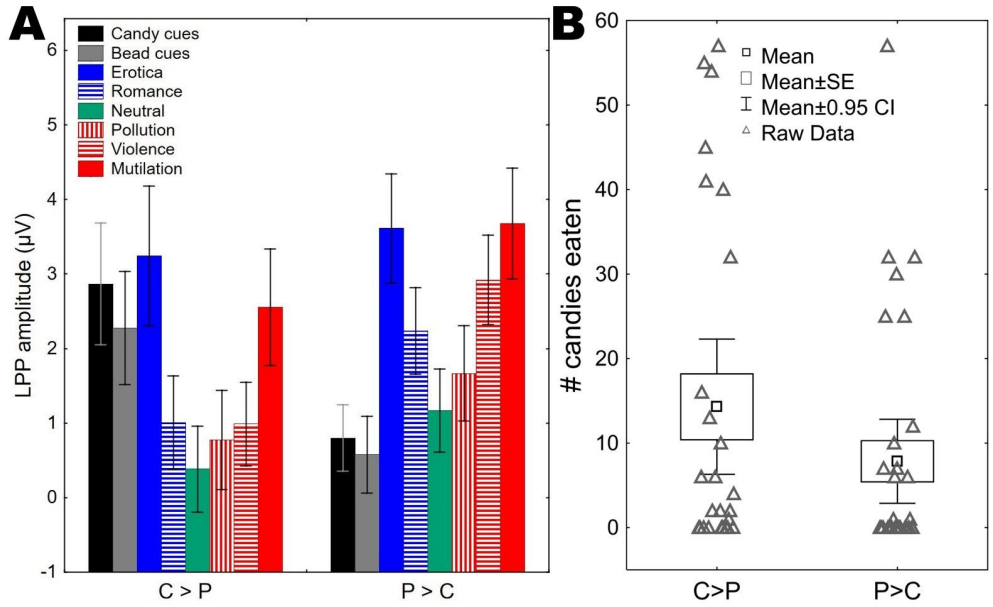

Figure 3.3 (above): I replicated the finding that individual differences in LPP responses to food cues & non-food-related pleasant images are predictive of cue-induced eating. (**A**) *K*-means clustering of the LPP responses identified two groups: one with higher LPP amplitudes for food cues than for pleasant images and one with higher LPP amplitudes for pleasant images than for food cues. Error bars: 95% CI. (**B**) The C>P group ate significantly more candies during the cued food delivery task than did the P>C group (Wald $X^2[1] = 43.1$, $p<0.001$). SE: standard error. Error bars: 95% CIs.

See **Figure 3.4** for the averaged LPP amplitudes across all pleasant picture contents by group assignment. After determining the group assignment for each participant, I then compared the number of candies eaten by the C>P and P>C groups (**Figure 3.3B**). Poisson regression analysis demonstrated that individuals in the C>P group ate significantly more during the experiment than did individuals in the P>C group

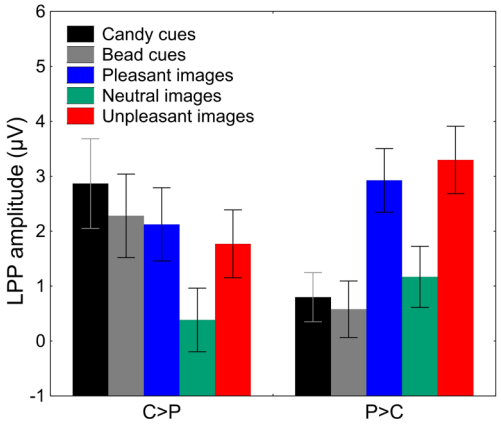

Figure 3.4 (above): Average LPP responses for each parent picture category (Pleasant, Unpleasant, etc.) by LPP group. After averaging LPP amplitudes for the emotional image subcategories (pleasant: erotica and romance; unpleasant: mutilations, violence, and pollution) together, I found that the C>P group had higher LPP amplitudes for food cues than for pleasant images, whereas the P>C group had higher LPP amplitudes for pleasant images than for food cues. Error bars: 95% CIs.

(Wald $X^2[1] = 43.1$, $p<0.001$). Demographic, biometric, and self-reported questionnaire data for the C>P and P>C groups are reported in **Table 3.1.**

3.3.3 Time-frequency power

To identify a set of EEG sensors to pool together in my analysis of theta power, I used the following procedure: using theta power as a dependent variable, I performed a repeated-measures ANOVA with condition (candy, bead, and neutral) as a factor for each time point and each EEG sensor. To identify the sensors and time points at which theta power exhibited statistically significant differences across conditions, I determined thresholds for the *F*-values resulting from these ANOVAs using Bonferroni correction. I then selected the sensors that showed statistically significant differences between conditions (candy, bead & neutral) during the 0- to 200-msec time bin (see **Figure 3.5** inset for this set of sensors), during which cognitive control-related effects in theta power are typically greatest (Cavanagh and Frank, 2014). See **Figure A1** of the Appendix for the topography of these *F*-values during this time bin.

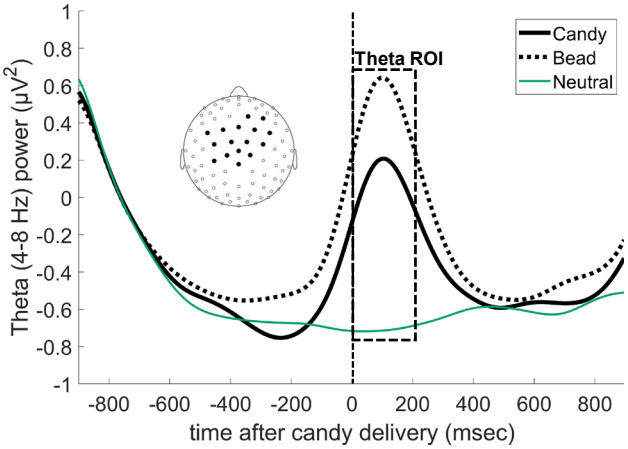

Figure 3.5: Time series data showing average theta power over mid-frontal scalp sites during the candy, bead & neutral experimental conditions. Theta power over midfrontal scalp sites (see inset for EEG electrode locations) increased during the candy and bead conditions but not when the participant was passively viewing neutral pictures. The box indicates the temporal ROI used to calculate theta power. The candies and beads were delivered at 0 msec. ROI: region of interest

I then averaged theta power in the 0- to 200-msec time bin from this pooled set of sensors to obtain a single theta power value for each participant under the candy, bead, and neutral conditions. **Figure 3.5** shows the time course of

theta power in the Candy, Bead & Neutral conditions. I found that, on average, power increased when either candies or beads were dispensed to the participant, but not when they passively viewed neutral pictures.

Next, to determine whether theta power differed between the C>P and P>C groups, I averaged the pooled and binned theta power values for these two groups. I found that the groups had similar dynamics in theta power under the candy, bead, and neutral conditions. A repeated-measures ANOVA demonstrated no significant interaction effect of group assignment (C>P and P>C) and condition (candy, bead, and neutral) (F[2, 114] = 0.667, p = 0.515) on theta power. These data are shown in **Figure 3.6.**

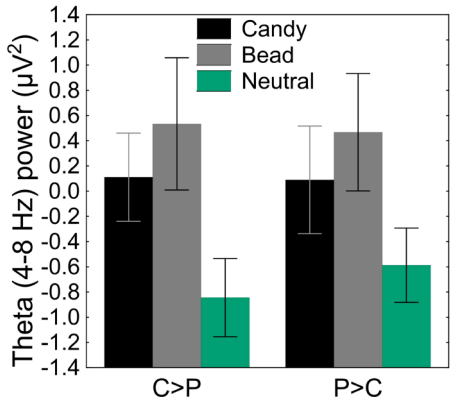

Figure 3.6 (above): Average theta power from the pooled midfrontal sensors in the 0-200 msec time bin under the candy, bead, and neutral conditions by C>P and P>C groups. I compared theta power for the candy, bead, and neutral conditions in the participant groups formed using *k*-means clustering with LPP data. A repeated measured ANOVA found no significant difference between groups. (F[2, 114] = 0.667, p = 0.515)

3.3.4 Classification of participants: theta power

Cluster analysis of theta power identified two participant groups (**Figure 3.7A**): one with higher theta power for the candy condition than for the bead condition than for the bead

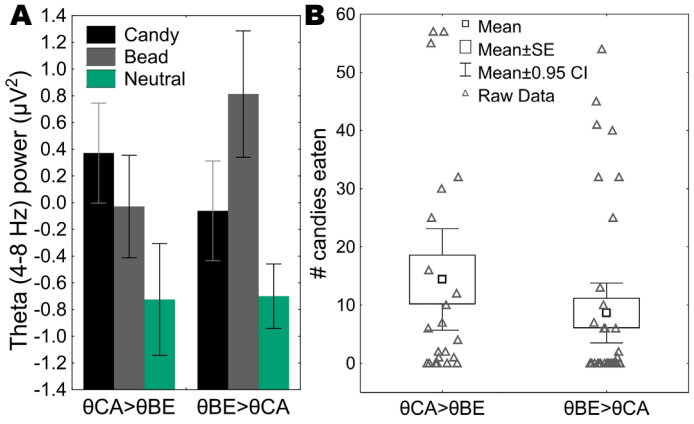

Figure 3.7 (above): I found that individual differences in theta power during food-related decision-making were predictive of cue-induced eating. (**A**) *K*-means clustering of theta power data identified two groups: one with higher theta power for the candy condition than for the bead condition (θCA>θBE group) and one with higher theta power for the bead condition than for the candy condition (θBE>θCA group). Error bars: 95% CIs. (**B**) The θCA>θBE group ate significantly more candies during the cued food delivery task than did the θBE>θCA group (Wald X^2[1] = 41.5, p < 0.001). SE: standard error. Error bars: 95% CI.

condition (θCA>θBE group) and the other with higher theta power for the bead condition than for the candy condition (θBE>θCA group). I then compared the number of candies eaten by these two groups during the experiment (**Fig. 3.7B**). Poisson regression analysis demonstrated that the θCA>θBE group ate significantly more candies than did the θBE>θCA group (Wald $X^2[1] = 41.5$, $p < 0.001$). Demographic, biometric, and self-reported questionnaire data for the θCA>θBE and θBE>θCA groups are reported in **Table 3.1.**

3.3.5. Classification of participants: LPP and theta power

Next, to determine how both individual differences in the attribution of motivational salience to food cues and the engagement of cognitive control confer vulnerability to cue-induced eating, I created four participant groups by crossing the results of the LPP and theta power classification procedures. I labeled these four groups 00 (the P>C and θBE>θCA groups), 01 (the P>C and θCA>θBE groups), 10 (the C>P and θBE>θCA groups), and 11 (the C>P and θCA>θBE groups). Demographic, biometric, and self-reported questionnaire data for these four crossed groups are reported in **Table 3.2**.

After crossing the group assignments for both the LPP and theta power cluster analyses, Poisson regression analysis demonstrated a significant effect of group assignment on the number of candies eaten during the experiment (Wald $X^2[3] = 106.2$, $p < 0.001$). Notably, although the individuals in group 00 ate the least, those in the three remaining groups had similar levels of eating behavior on average (Wald $X^2[2] = 0.825$, $p = 0.662$) (**Figure 3.8**).

Table 3.2: Demographic, biometric, and self-reported data for crossed participant groups							
	Mean (SD)						
Characteristic	**Group 00 (*n* = 20)**	**Group 01 (*n* = 11)**	***p* (00 vs. 01)**	**Group 10 (*n* = 17)**	***p* (00 vs. 10)**	**Group 11 (*n* = 11)**	***p* (00 vs. 11)**
Age, years	47 (9.15)	48 (7.62)	0.77	46 (14.26)	0.76	37 (12.63)	0.02
Women, %	50	55	0.81	47	0.86	27	0.22
Race, %							
Black/African American	50	64		71		82	
White/Caucasian	35	27		18		9	
Asian	5	0		12		9	
More than one race	5	9		0		0	
I prefer not to say	5	0		0		0%	
BMI, kg/m^2	30 (5.73)	33 (9.83)	0.28	32 (9.11)	0.46	28 (6.15)	0.34
Hispanic or Latino ethnicity, %	10	27		12		0	
BIS attention	15.20 (3.38)	16.36 (2.94)	0.35	15.94 (5.08)	0.60	14.80 (1.32)	0.72
BIS motor	21.20 (3.07)	21.18 (4.90)	0.99	20.88 (4.72)	0.81	22.10 (3.48)	0.47
BIS Non-planning	13.65 (2.85)	12.91 (2.17)	0.46	13.53 (2.83)	0.90	12.20 (2.30)	0.17
CESD	8.05 (4.02)	8.64 (4.54)	0.71	10.00 (6.36)	0.27	6.90 (2.60)	0.42
SHAPS	1.45 (2.52)	0.09 (0.30)	0.09	0.88 (1.93)	0.45	2.10 (4.25)	0.60
PANAS (+)	34.95 (9.60)	35.45 (7.85)	0.88	30.53 (10.52)	0.19	32.20 (9.75)	0.47
PANAS (-)	16.25 (6.26)	18.73 (10.75)	0.42	20.06 (8.02)	0.11	15.00 (4.37)	0.58
PFS	54.45 (17.61)	55.00 (20.90)	0.94	51.18 (18.56)	0.59	44.50 (22.32)	0.19
FCQ	105.05 (37.51)	102.00 (34.93)	0.83	104.00 (36.19)	0.93	90.70 (40.54)	0.34
WREQ routine restraint	1.98 (1.13)	1.55 (0.82)	0.27	1.47 (0.61)	0.10	1.37 (0.53)	0.12
WREQ compensatory restraint	2.28 (0.81)	2.24 (0.97)	0.90	2.02 (0.79)	0.32	2.10 (0.90)	0.58
WREQ susceptibility to external cues	2.25 (0.83)	2.58 (1.18)	0.37	2.21 (1.05)	0.90	2.22 (1.14)	0.94
WREQ emotional eating	2.12 (0.73)	2.36 (1.07)	0.46	1.99 (1.18)	0.68	1.88 (1.24)	0.51
SLIM	17.95 (39.16)	-20.50 (42.70)	0.02	-3.45 (37.31)	0.10	-2.91 (28.17)	0.13
Number of candies eaten	4 (8.89)	15 (18.76)	0.04	14 (19.74)	0.06	14 (21.42)	0.09

3.3.6 Demographics & covariates

I conducted Poisson regression analysis modeling the effect of crossed group assignment on eating behavior which included the demographic, biometric, and questionnaire data outlined in **Table 3.2** as covariates. I found a significant main effect of group assignment on eating behavior for all groups except for those with both LPP and theta risk factors (group 01 AKA the P>C and θCA>θBE group) after controlling for factors such as hunger and satiety (Cardello et al., 2005), eating behavior (Lowe et al., 2009; Nijs et al., 2007), sensitivity to reward and punishment (Torrubia et al., 2001), mood (Watson et al., 1988), and impulsivity (Stanford et al., 2009).

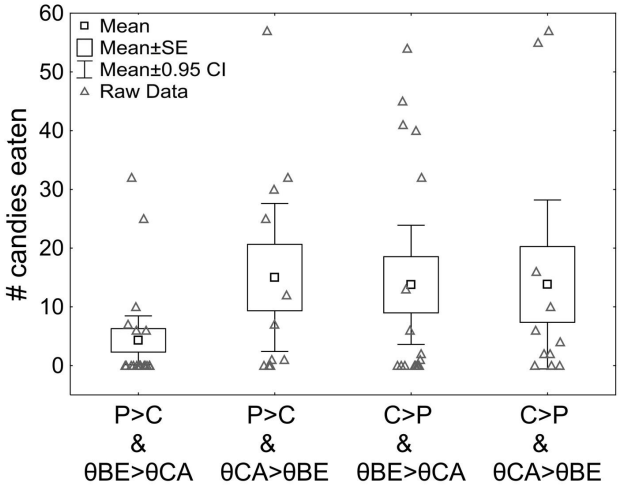

Figure 3.8: I found that individuals with neither LPP nor theta-based "risk factors" (P>C & θBE>θCA [group 00]) ate the least of all four groups, but the three remaining groups exhibited similar levels of eating behavior on average. Poisson regression found a significant effect of group on eating behavior (Wald $X^2[3] = 106.2$, $p < 0.001$) when comparing all four groups; however when group 00 was left out of the model, the difference between the three remaining groups was non-significant (Wald $X^2[2] = 0.825$, $p = 0.662$). SE: standard error. CI: confidence interval. Error bars: 95% CIs.

3.4 DISCUSSION

This study was aimed at determining the role that individual differences in affective and cognitive brain systems have in regulating cue-induced eating. This work is informed by results from animal models demonstrating that individual differences in top-down attentional control and bottom-up attribution of motivational salience to food-related cues influence reward-seeking behaviors. By investigating both food-related decision-making and the motivational

salience of cues, I aimed to elucidate how these mechanisms contribute to cue-induced eating behavior in humans. Because I found that both LPP and theta power-based groups showed statistically significant differences in eating behavior, it is likely that these mechanisms act independently to regulate eating behavior during the cued food delivery task.

By applying cluster analysis to the LPP responses evoked by food-related and non-food-related motivationally salient images, I identified two reactivity profiles associated with vulnerability to cue-induced eating: individuals with larger LPP responses to food-related cues than to pleasant images (C>P group) ate significantly more than did individuals with larger LPP responses to pleasant stimuli than to food-related cues (P>C group). These results replicate those from previous studies (Versace et al., 2016, 2018) and support the hypothesis that individual differences in the tendency to attribute motivational salience to food-related cues compared to other pleasant stimuli underlie vulnerability to cue-induced eating (Colaizzi et al., 2020; Flagel et al., 2011; Sarter and Phillips, 2018; Versace et al., 2017).

Furthermore, I found that midfrontal theta power increased after the delivery of candies and beads, and individual differences in midfrontal theta power were associated with vulnerability to cue-induced eating. Specifically, individuals with higher phasic theta power following the delivery of candies than of beads (θCA>θBE) ate more during the cued food delivery task than did individuals with the opposite theta response pattern (θBE>θCA). Authors have proposed that changes in theta power over midfrontal scalp sites represent an index of the engagement of cognitive control mechanisms (Cavanagh and Frank, 2014) because midfrontal theta tends to increase when an individual is executing a task that requires increased attentional demands, such as inhibiting prepotent responses (Haciahmet et al., 2021; Nigbur et al., 2011) and performing otherwise cognitively demanding tasks (Wang et al.,

2018). In light of these findings, the results of the present study suggest that some individuals struggle with food-related decision-making and that these individuals are more likely to engage in cue-induced eating when a palatable food option is available (Hall, 2016; Stice et al., 2019).

In addition, I found that the LPP-based and θ-based reactivity profiles likely reflect affective and cognitive mechanisms that independently contribute to cue-induced eating. This is evidenced by the finding that the C>P and P>C groups had similar theta power dynamics during food-related decision-making. Furthermore, after crossing the group assignments for the LPP and theta-based cluster analyses, I found that the group with neither the LPP nor the theta risk factor (P>C and θBE>θCA group) ate the least of all four groups, and that the three remaining groups exhibited similar levels of eating behavior on average. These results imply that individuals at risk for cue-induced behaviors due to the presence of both LPP and theta-based risk factors are no more vulnerable to cue-induced behaviors than are those who have only one of these two risk factors. Further studies are needed to determine if this finding is consistent across populations and paradigms.

Whereas the validity of the LPP in predicting cue-induced behavior has been well replicated (Versace et al., 2012, 2018; Versace and Kypriotakis, 2022) and is consistent with theoretical models concerning the motivational salience of cues (Pitchers et al., 2018; Sarter and Phillips, 2018), the predictive validity of a theta-based correlate described in the present study is novel and should be considered preliminary until replicated.

Although in previous studies researchers have used theta power to index the engagement of higher cognitive functions during the execution of cognitively demanding tasks (Cavanagh and Frank, 2014), in the present study, I did not explicitly manipulate cognitive load during food-related decision-making. Because I did not explicitly manipulate cognitive control via a

cognitively demanding task, inferring from these results that the observed dynamics in theta power are in fact due to the engagement of higher cognitive functions remains speculative.

Also, although my results suggest that individual differences in the ability to exert cognitive control are independent from the tendency to attribute motivational salience to cues, studies using preclinical models suggested that these two cognitive-motivational styles are coupled: animals with high motivational salience attributed to food-related cues are also more impulsive and less able to implement top-down attentional control in the presence of cues than are those who do not attribute high motivational silence to food-related cues (Koshy Cherian et al., 2017; Paolone et al., 2013; Pitchers et al., 2017c; Sarter and Phillips, 2018).

Considering these incongruous findings, theta power analysis as implemented in the present study may not capture the same aspects of cognitive control that are captured using animal models, which may be more related to impulsivity specifically than to top-down attentional control in general (see Chapter 4, section 4, pages 60-62 for a further discussion of impulsivity and top-down attentional control). The self-reported data did not demonstrate significant differences in impulsivity scores between groups, which may explain the divergent findings of the present study and those in the animal literature.

Meanwhile, results from human and animal studies of cue-induced behavior may be inconsistent because of the inherent differences between humans and animal models (Colaizzi et al., 2020): complex human behaviors result from a more evolved cognitive control system (Hall, 2016) than that of animal models and thus might not be probed as effectively using animal behavioral approaches. Further studies leveraging the paradigm that we used here will facilitate the bidirectional translation and improvement of both animal models and human subjects research investigating cue-induced behavior.

My findings are consistent with those for neurobiological models suggesting that both high reactivity to food-related cues and deficits in cognitive control can lead to excessive eating (Stice and Yokum, 2016). Moreover, because my results suggest that cognitive control and reward networks independently contribute to cue-induced eating, these findings further emphasize the need for individualized treatments of maladaptive, reward-seeking behaviors.

These findings have worthwhile clinical implications: by separating the roles of both affective and cognitive psychophysiological correlates in predicting cue-included eating, it is possible to identify potential biomarkers of vulnerability to overeating and obesity that could guide treatment decisions. For example, using repetitive transcranial magnetic stimulation (rTMS), a non-invasive neuromodulation technique (Klomjai et al., 2015), a clinician can upregulate brain activity in cognitive control networks (George et al., 2010) or downregulate brain activity in reward networks (Hanlon et al., 2018).

Thus, a patient identified to have high affective vulnerability may be selected for inhibitory rTMS of the ventromedial prefrontal cortex, which is commonly implicated in reward processing (Kearney-Ramos et al., 2018). Also, a patient with cognitive vulnerability may be more effectively treated with excitatory rTMS of the dorsolateral prefrontal cortex, which is commonly implicated in executive control (Niendam et al., 2012).

In conclusion, my results demonstrated that both the amplitude of the LPP and theta power are predictive of cue-induced eating behavior, suggesting that both affective and cognitive mechanisms are implicated in the regulation of cue-induced eating. By simultaneously measuring both the amplitude of the LPP and theta power while participants were in the presence of food-related cues and actual food rewards, I clarified the mechanisms underlying cue-induced eating behaviors. Continuing this line of investigation may inform clinicians of

mechanisms underlying maladaptive eating and may foster the development of personalized clinical interventions for excessive eating.

CHAPTER 4: Discussion

4.1 Overview

Previous work has investigated the role of individual differences in affective processing of cues, finding that individuals who attribute high levels of incentive salience to food cues are more likely to engage in maladaptive behaviors such as cue-induced eating (Versace et al., 2018). Furthermore, there is a body of research demonstrating that cognitive control enables top-down attentional control over cues (Campus et al., 2019), thereby allowing an individual to resist maladaptive behaviors in a goal-oriented fashion (Pitchers et al., 2018, 2017a). Although substantial evidence implicates both cognitive and affective mechanisms independently, there is a need for research characterizing how both cognitive control and incentive salience act in tandem to regulate cue-induced eating.

In light of this gap in knowledge, my dissertation is aimed at answering the following question: are individuals with heightened incentive responses to cues also impaired in their top-down attentional control, or do they possess an otherwise typical cognitive control system? I hypothesized that individuals with heightened incentive responses to cues would also show impaired top-down attentional control over cues, which is in line with the animal literature concerning sign- and goal-trackers (Koshy Cherian et al., 2017; Paolone et al., 2013). To test this hypothesis, I monitored psychophysiological measures of affective processing of cues (LPP amplitude) and cognitive control (theta power) during a controlled cued food delivery task (see **Figure 3.1**). I then used *k*-means clustering to identify individual differences in both metrics.

Although I did find the expected LPP groups (P>C and C>P; see also **Figure 3.2**), I did not find significant differences in theta between these two groups (**Figure 3.5**). I did, however,

find that there are individual differences in theta power during food-related decision-making and that these differences are predictive of cue-induced eating (see **Figure 3.6**). I then crossed group assignment from both cluster analyses, creating four groups with varying "risk factors" (neither LPP nor theta, LPP only, theta only, both risk) based on their LPP and theta responses. I found that individuals with neither risk factor at the least of all four groups, but the remaining three groups showed similar levels of eating behavior on average (see **Figure 3.7**).

4.2 Controlling for the incentive salience of cues preceding non-food objects

In this experiment, participants completed a controlled version of the cued food delivery task used in previous studies (Deweese et al., 2015), in which participants are dispensed candies after one category of food cue (sweet or savory, counterbalanced across participants) and beads after the other (see **Figure 3.1**). The bead condition was added to the experiment to determine whether the observed effects are related to the incentive salience of cues preceding food rewards, or if rather the receipt of any non-food object may also elicit the same effects. I found that, despite the addition of the candy condition, I was still able to reproduce previous findings: the P>C and C>P groups persisted in my data, and the addition of the bead condition did not appear to substantially change the overall pattern of LPP responses (**Figure 3.2**). From these findings, I can conclude that the patterns of LPP responses observed during a cued food delivery task are related to the incentive salience of food cues, rather than the receipt of any non-food object.

4.3 Stimulus-locked ERPs and time-frequency power

I elected to use time-frequency analysis rather than event-related potentials to characterize cognitive control during the cued food delivery task to compensate for uncertainty in the timing of the decision-making process. To calculate an ERP, it is necessary to precisely time-lock to

the exact event of interest and then average together many time-locked segments from multiple different trials (Handy, 2005; S. Luck, 2014). Because I am interested in the engagement of cognitive control during food-related decision-making, I would need to time-lock to the exact moment that the participant decides to eat or discard the candies to calculate an ERP. However, because the participant makes a spontaneous choice in this experiment, it is uncertain exactly what time each participant makes this decision (Cosme et al., 2020). In the case of ERPs, out-of-phase signals will cancel out when averaged together (S. J. Luck, 2014a), making it difficult to determine if any observed ERP effects are truly related to cognitive processing or rather due to out-of-phase signals nullifying any true brain activity (**Figure 4.1**). I addressed these concerns in two ways: first, by focusing on the analysis of time-frequency power, and second by time-locking to the delivery of the candy, rather than the presentation of the picture.

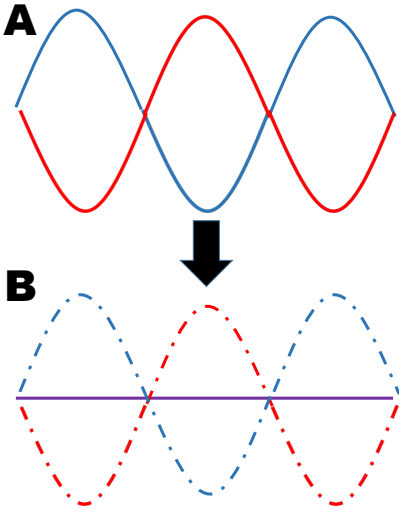

Figure 4.1: Out-of-phase ERP waveforms will cancel out during the averaging process. (**A**) Two out-of-phase waveforms (red and blue) overlaid on top of each other. (**B**) After averaging, these two out-of-phase waveforms (dash-dot, red and blue), will result in a null waveform (purple)

By analyzing time-frequency power, I may visualize brain activity without nullifying out-of-phase signals during the averaging process. When using wavelet-based techniques to conduct time-frequency analysis, power can be thought of as the coefficient of the wavelet transform. The output of a wavelet transform is always positive, and where there is higher power, there is higher activity in that frequency band (Hermann et al., 2005; Samar et al., 1999). Power does not cancel out when averaging together out-of-phase signals (S. J. Luck, 2014b), which allows me to visualize brain activity associated with an event that may take

place at a variety of latencies. In this case, by focusing on theta power, I may visualize brain activity likely associated with cognitive control that takes place during the uncertain period in which the participant is deciding to eat or discard candies dispensed during the task.

However, despite the aforementioned concerns, a preliminary analysis of phase information from this experiment suggests that time-locking to the delivery of the candy or bead adequately addressed these uncertainties in latency. After analyzing phase information from EEG segments that were time-locked to the delivery of the candy or bead, I primarily found in-phase signals, suggesting that the brain activity visualized here is likely evoked (See **Figure A2**). A summary of these analyses is outlined in Section 2 of the Appendix.

4.4 Theta power does not differ between P>C and C>P groups

Based on the findings from the animal literature that sign-trackers show impaired top-down attentional control relative to goal-trackers, I hypothesized that C>P individuals, my analog to sign-trackers in humans, would show attenuated theta power during food-related decision-making relative to P>C individuals, my analog for goal-trackers in humans. However, I found no significant differences in theta power between groups (**Figure 3.5**). Because individuals in the C>P group did not also show attenuated theta relative to the P>C group, this suggests that humans with enhanced incentive responses to cues do not also possess an impaired cognitive control system. Furthermore, this finding suggests that affective and cognitive mechanisms as measured by the LPP and theta in this experiment independently contribute to cue-induced behaviors.

These findings are limited by some confounding factors. First, it is important to clarify that sign- and goal-tracking as described using animal models are behaviors (Brown and Jenkins, 1968; Sarter and Phillips, 2018); meanwhile, the present study outlines the underlying brain

mechanisms that lead to outcomes resembling sign- and goal-tracking in humans. Many studies investigating human analogs of sign-tracking have used other behavioral measures, such as eye-tracking, to model the sign- and goal-tracking styles seen in Pavlovian conditioned approach paradigms, while others may also focus on underlying neurobiology (Anselme and Robinson, 2020; Schad et al., 2019; Tomie et al., 2008). Because the present study investigates underlying brain activity related to these cognitive-motivational styles rather than the sign- and goal-tracking behaviors themselves, it may not be appropriate to make direct comparisons between my results and those from animal models (Stephens et al., 2011).

Moreover, this inconsistency between the animal literature and my results may relate to the inherent differences between animals and humans, especially in the cognitive domain. Humans have evolved much more sophisticated cognitive control systems than most animal models and as a consequence have a more developed prefrontal cortex than rodents (Laubach et al., 2018). These differences in underlying brain mechanisms lead to profound differences in cognitive faculties, thereby enabling much more complex behaviors and self-regulation abilities in humans (Hall, 2016). For these reasons, I hesitate to draw direct comparisons between human and rodent neurobiology based on the results of my dissertation research.

Finally, it may be that the observed differences in top-down attentional control that are commonly found in animal models may be more reflective of impulsivity than true cognitive control (Colaizzi et al., 2020; Spoelder et al., 2017). Cognitive control encompasses a family of various executive functions, each of which have separate roles and characteristics, and when exerting cognitive control, and individual is using one or more of these executive functions toward some goal or outcome (Hogarth et al., 2012; Niendam et al., 2012). One executive function included in cognitive control is response inhibition, or inhibitory control, which

allows an individual to inhibit a prepotent response. For example, if someone is predisposed to compulsive eating, inhibitory control enables that individual to stop themselves from eating (Kohl et al., 2018).

Although attenuated top-down cognitive control is often associated with impulsivity, these constructs are not identical. Impulsivity is a trait in which an individual tends to act prematurely without foresight (Leshem, 2016). Much like the various executive functions that are a part of cognitive control, there are various domains of impulsivity, including sensory or reflection impulsivity, motor impulsivity or impulsive action, reward sensitivity or impulsive choice impulsivity, and risky decision making. Thus, these are a set of behavioral characteristics that can vary between individuals. Also, these behaviors described by impulsivity are dependent on an individual's ability to engage executive function in various contexts, such as motor control, sensory gating, or decision-making (Dalley et al., 2011).

Of note, attenuated top-down cognitive control is associated with both impulsivity and compulsivity (Robbins et al., 2012). In rodent models, sign-trackers show enhanced affective processing of cues as well as attenuated cognitive control compared to goal-trackers (Pitchers et al., 2017a), which often manifests as impulsivity (Spoelder et al., 2017). Meanwhile, in our human analog of sign- and goal-tracking (P>C and θCA>θBE groups, etc), I found that our metrics of affective processing of cues and cognitive control were independent of one another. While many behavioral assays in animals are able to effectively probe response inhibition,

Because we did not explicitly instruct participants not to eat the candies dispensed during the task, the present study demonstrated brain activity associated with response selection rather than directly measuring response inhibition, which is commonly implicated in impulsivity. For the aforementioned reasons, it appears that the impulsivity that differs between sign- and goal-

trackers in animal models is not being directly manipulated in the present study. In this case, I would not be comparing analogous brain mechanisms. In fact, my self-report data for the participant groups show no significant differences in impulsivity as measured by the Barratt Impulsiveness Scale (Patton et al., 1995; Stanford et al., 2009; see **Tables 3.1** and **3.2**).

4.5 Increases in theta power predict cue-induced eating

I found that theta increases during the candy and bead conditions of the controlled cued food delivery task, but not during other conditions (**Figure 3.4**). This finding indicates that theta increases when the participant needs to make a behavioral response, which is consistent with the literature indicating that theta is involved in response monitoring and internal attention (Cavanagh et al., 2012; Cooper et al., 2015; Eschmann and Mecklinger, 2022; Janowich and Cavanagh, 2019; Kam et al., 2019; Sandre and Weinberg, 2019). I also found that individual differences in theta power responses to the Candy and Bead conditions were predictive of cue-induced eating.

Because cognitive control enables self-regulation of eating, I expected that individuals with higher theta, my exploratory metric of cognitive control, during the candy condition would eat less than those with lower theta power during the candy condition. However, I found the opposite result: the θCA>θBE group ate significantly more than the θBE>θCA group (**Figure 3.6**). This counterintuitive finding may mean that individuals in the θCA>θBE group must engage cognitive control mechanisms to higher levels than θBE>θCA individuals to resist eating. These individuals may struggle with food-related decision-making, making them more likely to engage in cue-induced eating when a palatable food reward is available (Berthoud, 2012; Hall, 2016; Stice et al., 2019).

4.6 Theta power as a metric of cognitive control during food-related decision making

Based on the literature indicating that power in the theta frequency band increases when participants complete cognitively demanding tasks (Cavanagh and Frank, 2014; Haciahmet et al., 2021; Janowich and Cavanagh, 2019; Sandre and Weinberg, 2019), I aimed to use theta power in an exploratory fashion as a metric of the engagement of cognitive brain systems during food-related decision making. However, most studies investigating theta as a metric of cognitive control use canonically cognitive tasks such as the Go/No-Go or Stroop tasks (Eschmann and Mecklinger, 2022; McDermott et al., 2017; Nigbur et al., 2011).

Because the cued food delivery task is not a validated task for the study of cognitive control, it is speculative to conclude that the brain activity seen during the candy and bead conditions is reflective of cognitive processing. It is possible that my findings concerning theta power during the cued food delivery task are not reflective of the engagement of cognitive control, but perhaps another mechanism that remains to be identified.

4.7 Individuals with only one risk factor are just as vulnerable as those with both

After obtaining the groups from both cluster analyses (LPP and theta), I crossed group assignments to create a total of four groups: those who are not at risk of cue-induced eating based on their LPP or theta responses (P>C & θBE>θCA group), those who are at risk based on their LPP responses only (C>P & θBE<θCA group), those who are at risk based on their theta responses only (P>C & θCA>θBE group), and finally those who are at risk based on both measures (C>P & θCA>θBE group). I found that individuals with neither risk factor (LPP or theta) ate the least of all four groups, but the three remaining groups show similar levels of eating on average (**Figure 3.7**).

Although my findings confirm my prediction that individuals with no risk factors would

eat the least of all four groups, I did not expect to find that individuals with both risk factors eat similarly to those with only one risk factor. If each risk factor contributes equally to an individual's propensity for cue-induced eating, then why would individuals with both risk factors eat as many candies as those with only one? This finding suggests that having only one risk factor is just as deleterious as having two, which further supports the hypothesis that cognitive and affective mechanisms as indexed in the present study independently contribute to reward-seeking behaviors.

4.8 Future directions

Because the cued food delivery task is not yet a validated probe of cognitive control, future studies may build upon this research by employing validated tasks for the study of cognitive control in addition to the cued food delivery task. By collecting data using both a validated cognitive task, such as a Stroop, Flanker, or Go/No-Go tasks (Imburgio et al., 2020; Raud et al., 2020; Reyes et al., 2015), and a cued food delivery task, it is possible to compare one subject's brain activity during a canonically cognitive task against their activity during the cued food delivery task, thereby corroborating whether cognitive control is indeed manipulated during the cued food delivery task.

For example, should researchers observe increases in theta power during a canonically cognitive task that are comparable to those theta power increases found during a cued food delivery task in the same individual, it would support the conclusion that increases in theta during the cued food delivery task are in fact related to cognitive control.

Additionally, because we did not explicitly instruct the participants not to eat the candies dispensed during the cued food delivery task, I can't decisively conclude that the brain activity recorded during the present study is related to response inhibition specifically, but rather to

response selection in general. The next version of this study should include a condition in which the participant is explicitly instructed not to eat, so that food-related inhibitory control can be directly manipulated and measured.

Furthermore, it may be worthwhile for future studies to employ imaging modalities beyond merely EEG in order to further elucidate the underlying brain mechanisms involved in the cued food delivery task. EEG alone lacks the spatial resolution to infer which underlying neuroanatomical structures are implicated in a given experiment; however, modalities leveraging magnetic resonance can effectively address such limitations. Thus, an experiment employing concurrent EEG-fMRI could identify the specific neuroanatomical locus associated with the cognitive and affective processing probec in the present study.

In addition to collecting EEG, future studies could also collect diffusion imaging data from those same participants, which would allow investigators to compare structural connectivity between the P>C, θBE>θCA, etc groups identified using EEG. A similar approach could be implemented using resting state fMRI to identify if there are differences in functional connectivity between groups as well. Finally, magnetic resonance spectroscopy (MRS) approaches could allow future investigators to identify neurotransmitter systems implicated in these individual differences in LPP and theta power found in the present study.

It may also be worthwhile to manipulate the cued food delivery task itself, such that the participant must directly engage top-down cognitive systems. For example, if experimenters explicitly instruct the participant not to eat the candies dispensed during the task, they may visualize the brain activity associated with a top-down control aimed at resisting eating. Thus, we may more concretely observe the brain activity involved in food-related response inhibition (Houben et al., 2014), rather than the brain activity responsible for general food-related action

planning (Cavanagh et al., 2012; Houben et al., 2014; Wang et al., 2018; Zilverstand, 2018).

Finally, future studies should attempt to replicate these findings using a different participant sample to determine if these results are consistent across populations. It is possible that many extraneous factors not directly manipulated or measured in the present study could influence our findings: for example, various personality traits could lead to differences in executive functioning, and cultural factors could influence an individual's eating behavior (Sharma and Padwal, 2010; Simon et al., 2010). Furthermore, because individuals with psychiatric or other disorders were excluded from the present study, the effects observed in the present study may not generalize well to patient populations.

4.9 Clinical applications

My dissertation research demonstrates that both incentive salience and top-down attentional control mechanisms contribute to cue-induced behaviors. Furthermore, my results also suggest that these mechanisms act independently. Because these individual differences in incentive salience and top-down cognitive control independently contribute to reward-seeking behaviors, treatments directed at reducing emotional responses may not ameliorate maladaptive behaviors in individuals with cognitive vulnerabilities and vice versa. This in turn emphasizes the need for individualized treatments aimed at reducing maladaptive, reward-seeking behaviors (Frank et al., 2019).

By characterizing the underlying brain activity associated with cue-induced eating, this research may inform the development of future treatments aimed at reducing maladaptive, cue-induced behaviors such as compulsive eating or substance use. The underlying neural correlates associated with these vulnerabilities, namely, incentive salience and top-down attentional control, could become targets for the development of treatments aimed at reducing

maladaptive behaviors.

For example, if an individual is identified via EEG to have heightened LPP responses to food cues, clinical researchers may identify that individual as having affective vulnerabilities to cue-induced eating. This person could then be selected to receive inhibitory repetitive transcranial magnetic stimulation (rTMS) treatment stimulating reward-related areas of the brain, such as the medial prefrontal cortex (mPFC) (Hanlon et al., 2018; Kearney-Ramos et al., 2018). In so doing, this may reduce the attribution of incentive salience to food cues, thereby limiting cue-induced eating.

Similarly, an individual with theta power responses that are greater during the candy condition may be selected for excitatory rTMS stimulation of the dorsolateral prefrontal cortex (dlPFC). Hypothetically, this would enable top-down control or reduce the activity of the brain's reward system (Li et al., 2017; Notzon et al., 2018). Furthermore, including an rTMS component to such work would further help to elucidate the underlying brain mechanism of interest. For example, if we were to find that rTMS stimulation of dlPFC increases theta responses, we may conclude that theta as measured in this experiment is indeed reflective of cognitive processing.

In addition to brain stimulation treatment modalities, this work could also be used to determine which patients to allocate to various treatments. For example, by using the P>C and C>P group assignments, collaborators from the Versace lab were able to develop an algorithm for determining which individuals are at risk for smoking relapse (Frank et al., 2019) . Similar work using the LPP has also identified who was a better candidate for particular medications: one study found that the C>P group responded better to varenicline than to bupropion as a smoking cessation treatment (Cinciripini et al., 2017). Future research integrating theta into

these predictions may be better able to identify ideal candidates for particular medications, or who to monitor for relapse risk.

4.10 Conclusions

My dissertation provides multiple impactful contributions to both the fields of psychophysiology and the translational neuroscience of addiction. Specifically, this research addresses multiple important gaps in the literature: statistical methods for psychophysiology experiments investigating the LPP, theta power as an exploratory metric of cognitive control during food-related decision making, and the interaction between emotion & cognition in regulating cue-induced eating, to name a few. By characterizing brain activity during affective processing of cues and food-related decision-making, this work may identify how both mechanisms act in concert to regulate cue-induced eating. Ultimately, this allows clinical investigators to elucidate not only the affective mechanisms that make some individuals vulnerable to cue-induced eating, but also the cognitive mechanisms that make others resilient.

In **Chapter 2**, I reported the results from statistical power calculations of ERP studies investigating the LPP, thereby providing a key resource allowing psychophysiologists to design sufficiently powered ERP experiments. This work outlines the estimated statistical power of both within-subject and between-subjects experiments investigating the LPP at varying combinations of numbers of subjects, numbers of trials, and effect sizes. By making this reference material available, this work enables other researchers to design sufficiently-powered ERP studies investigating the LPP, which therefor ensures more reliable and reproducible results. This bolstered reproducibility may in turn foster the development of more effective treatments for psychological disorders.

Next, in **Chapter 3**, I outlined how psychophysiological metrics of cognitive control

(theta) and incentive salience (LPP) are predictive of subsequent cue-induced eating behavior. Because theta power has not yet been employed as a metric of cognitive control during a cued food delivery task, I was able to identify in an exploratory fashion whether the theta power dynamics as observed in this experiment were consistent with the literature. I found that theta power increased during conditions that required the participant to make a decision or response, meanwhile there were no changes in theta when the participant was passively viewing images. This is consistent with previous findings demonstrating that power in the theta frequency band increases when the participant must engage higher cognitive functions. Thus, in this research I demonstrated a novel use of time-frequency analysis in monitoring higher cognitive functions during food-related decision making.

The experiment outlined in **Chapter 3** is also novel: as compared to previous versions of the cued food delivery task, this task includes a control condition, during which the participant is dispensed a bead rather than a candy reward. By analyzing data collected during the controlled version of the cued food delivery task, I was able to identify how, if at all, the brain reacts to the receipt of any non-food object during this task. Thus, this experimental manipulation allowed me to address the following question: are the observed effects due only to the incentive salience of receiving any object, or are these findings specific to food rewards?

I found that including the bead condition did not change the overall pattern of LPP responses observed previously: some individuals were more reactive to food cues than pleasant images, and vice versa. From these findings I can conclude that the individual differences in LPP responses and the differences in eating behavior between groups are likely due to the brain's reactivity to cues predicting food rewards, and not to any non-food object.

Finally, as a part of the research outlined in **Chapter 3**, I used both theta power and the

LPP to successfully predict cue-induced eating behavior. Previous studies using the cued food delivery task have focused primarily on the LPP, and as such the use of theta power in this way provides novel information regarding the role of higher cognitive functions during a cued food delivery task. I found that by leveraging *k*-means clustering, I was able to identify groups with two distinct patterns of both LPP and theta power responses, and these groups identified using k-means showed significant differences in eating behavior as well.

Next, by crossing group assignment for both of the two cluster analyses, I found that individuals with neither the LPP or theta-based "risk factor" ate the least of all four groups, but the three remaining groups showed similar levels of eating behavior on average. While our findings for the "no risk" group were consistent with my expectations, the finding that individuals with both risk factors ate as much as those individuals with only one risk factor was not in keeping with my predictions. These findings suggest that, while both metrics are predictive of cue-induced eating, they likely are related to underlying cognitive and affective mechanisms that confer risk for cue-induced eating independently of one another.

From these findings, I can conclude that while both cognitive control and incentive salience are responsible for regulating cue-induced eating, they likely do so independently. Ultimately, this work allows us to identify not only the mechanisms that make some individuals vulnerable to maladaptive behaviors, but also the mechanisms that make others resilient. This research is likely to translate into more effective evidence-based treatments for mitigating maladaptive behaviors, thereby furthering the development of precision medicine approaches for ameliorating addictive disorders.

APPENDIX

1. Choosing the set of sensors for the analysis of mid-frontal theta power

To analyze theta power information depicted in **Figures 3.5-3.7**, I pooled power (μV^2) in the theta (4-8 Hz) frequency band from the set of sensors depicted in **Figure 3.5**. This choice of sensors was based both on the literature and on my exploratory findings. Previous work has found that changes in theta related to cognitive control are highest at mid-frontal scalp sites during the 0-200msec time bin. To determine exactly which mid-frontal sensors to use in this analysis, I conducted a repeated measures ANOVA comparing theta power for the candy, bead, and neutral conditions for each timepoint and sensor. After conducting Bonferroni correction for multiple comparisons, I then visualized the topography of these *F*-values on the scalp surface, focusing on statistically significant sensors during the 0-200 msec time bin (**Figure A1**). The analysis of theta power presented in Chapter 3 was conducted using the sensors depicted in **Figure A1**.

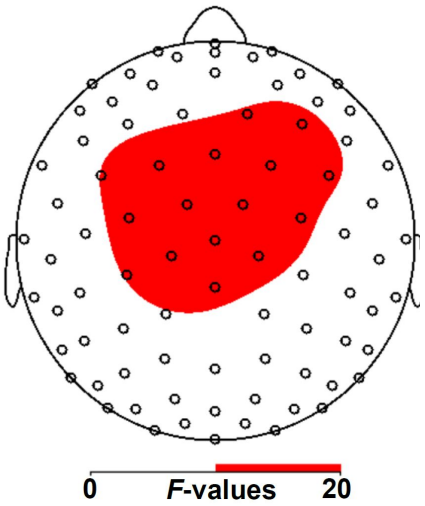

Figure A1: EEG sensors showing statistically significant differences between Candy, Bead, and Neutral conditions during the 0-200msec time bin after Bonferroni correction. Critical $F \approx 9.6$ ($\alpha = 0.05$)

2. Phase information from Candy & Bead trials suggest that brain responses are primarily evoked

As mentioned in **Section 4.3**, I focused on the analysis of time-frequency power rather than ERPs to ascertain brain activity related to the decision-making process. This was intended to accommodate the fact that, because I do not know exactly when the participant decides to eat or discard the candies dispensed during the task, it is possible that out-of-phase signals would cancel out when averaged together (**Figure 4.1**). Furthermore, unlike the analysis of the LPP,

I also time-locked my EEG segments for this analysis to the delivery of the candy rather than the presentation of the picture.

Although the analysis of time-frequency power was fruitful in allowing me to predict cue-induced eating behavior, it appears that time-locking to the delivery of the candy was sufficient to accommodate the confounds mentioned above. To ascertain if the time-frequency data shown in Chapter 3 were related to a true brain oscillation, I conducted a preliminary analysis of phase information from EEG segments that were time-locked to the delivery of the candy. I then conducted a continuous wavelet transform based on a Morlet complex wavelet function with linear frequency steps from 1 to 40 Hz. These data were normalized using a Gabor normalization and were calculated with a Morlet parameter of 5. The phase data were output as complex values, and I then averaged these complex values to calculate phase-locking factor.

Spectrograms visualizing phase information for the Candy, Bead, and Neutral conditions are depicted in **Figure A2**. I found phase locking at 0 msec (candy/bead delivery) for the candy and bead conditions, but not for the neutral condition during which no reward was dispensed. Because we see phase-locking at 0 msec during trials in which the participant needs to make a decision, but not during trials in which the participant is passively viewing neutral pictures, it is likely that the brain responses to the candy and bead are evoked, rather than induced.

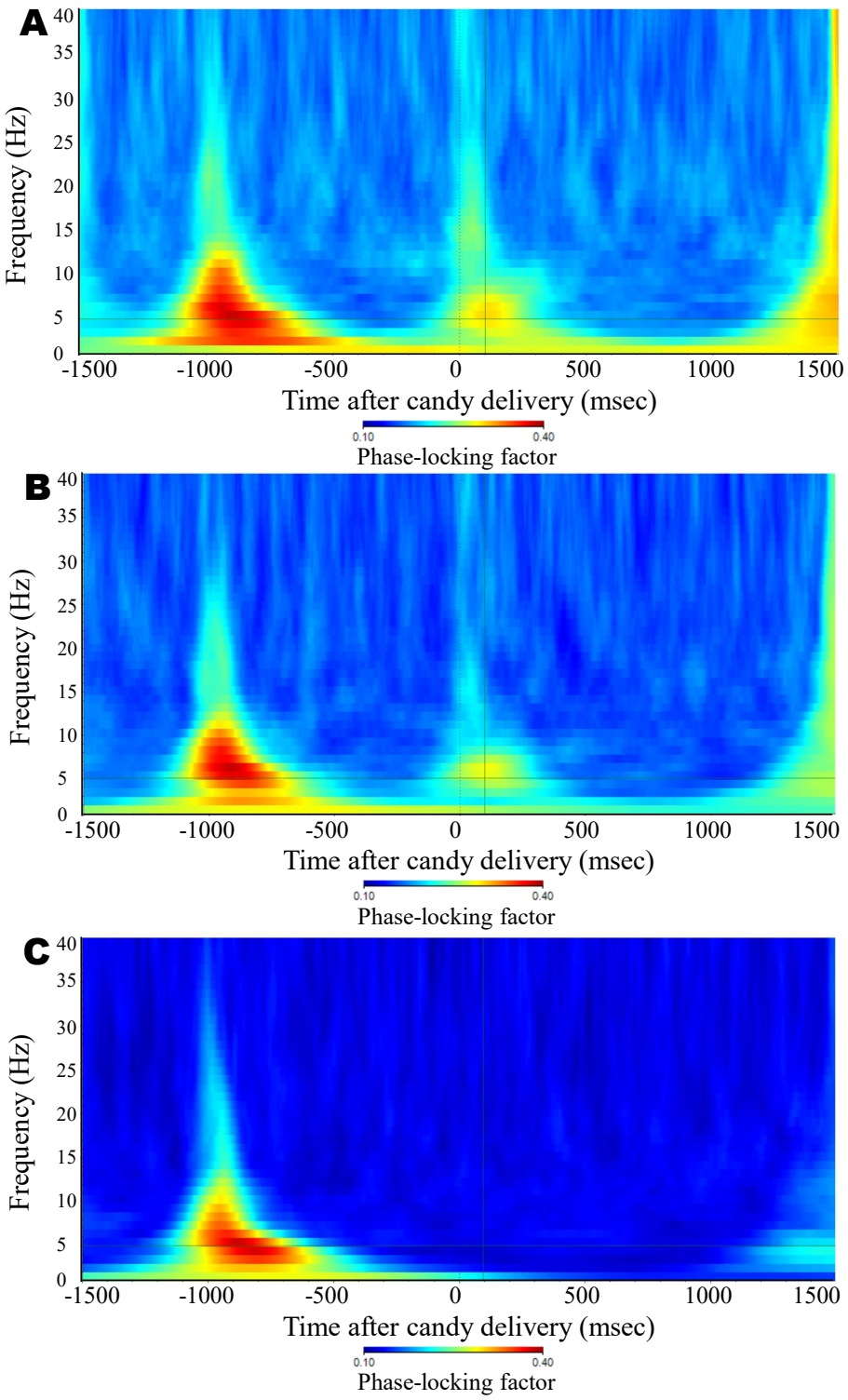

Figure A2: Spectrograms from 1-40 Hz depicting phase information for the Candy (**A**), Bead (**B**), and Neutral (**C**) conditions of the cued food delivery task. The candy or bead was dispensed at 0 msec. I found phase-locking at 0 msec in the candy and bead conditions, but no phase-locking at 0 msec in the neutral condition. This suggests that brain activity associated with the decision-making process during this task is evoked, rather than induced.

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c. Jackson & Bolger, 2014

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d. Liu et al 2012

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