Neurobehavioral and Neurophysiological Correlates of Health Behaviors

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ABSTRACT

Modifiable health behaviors are a leading cause of mortality and chronic disease in the United States. Engagement in maladaptive health behaviors is linked to poor physical, psychological, and cognitive outcomes including increased risk of cardiovascular disease, Alzheimer's disease, anxiety, and depression. Using a neurobehavioral approach, I examined the hypothesis that neurobehaviors are impaired in clinical populations, and that exercise improves these neurobehaviors as well as the underlying mechanisms. In the first study, I found that a range of neurobehaviors are affected in individuals with obesity, indicating hyperactivity of the reward system and hypoactivity of the executive system. Using these neurobehaviors as predictors, I created a neurobehavioral model predicting obesity with an accuracy of 65%. In the second study, I examined neurobehaviors in a population of individuals in recovery from substance misuse. I found that neurobehaviors are altered in this population suggesting heightened activity of the executive system supports success in recovery. In the third study, I examined the effects of a long-term exercise program on a range of neurobehaviors and neurophysiology as measured through electroencephalography. I found that long-term exercise improved psychological state, memory, and attention. Additionally, I found that decreased cortical activity in response to exercise is associated with improvements in psychological state. Collectively, these findings suggest that there is a bi-directional relationship between the body and brain, with optimal physical health promoting optimal mental functioning. Additionally, these findings suggest that interventions that support improved neurobehaviors and neural circuitry are critical to promote engagement in positive health behaviors.

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GENERAL AUDIENCE ABSTRACT

Modifiable health behaviors are a leading cause of mortality and chronic disease in modern industrialized societies. Engagement in poor health behaviors is linked to increased risk of chronic disease affecting the body and brain including cardiovascular disease, Alzheimer's disease, anxiety, and depression. This dissertation explores the psychological and cognitive factors influencing engagement in healthy behaviors, and the ability of an exercise intervention to improve these factors as well as the underlying mechanisms. In the first study, I found that a range of neurobehavioral factors are impaired in individuals with obesity, and that these factors can be used to predict obesity. In the second study, I examined similar outcomes in a population of individuals in recovery from substance misuse, and found that neurobehaviors are altered in this population suggesting heightened activity of the executive system which supports successful recovery. In the third study I found that long-term exercise improved psychological and cognitive outcomes. Additionally, I found that changes in the electrical activity of the brain in response to exercise are associated with improvements in psychological state. Collectively, these findings suggest that there is a bi-directional relationship between the body and brain, with optimal physical health promoting optimal mental functioning. Additionally, these findings suggest that interventions that support improved neurobehaviors and neural circuitry are critical to promote engagement in positive health behaviors.

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ATTRIBUTION

A brief description of the contributions made by co-authors who contributed to the work presented in this dissertation.

Chapter 2: Julia C. Basso contributed to the study design, data collection and analysis, and writing of the manuscript. Anvitha R. Metpally contributed to data collection, and Alison N. Tegge contributed to data analysis. Warren K. Bickel provided oversight of this work. This chapter has been previously published in *Behavioral Neuroscience and* has been reproduced with permission. Full citation: Satyal, M. K., Basso, J.C., Tegge, A.N., Metpally, A. R., and Bickel, W.K. (2021). A novel model of obesity prediction: Neurobehaviors as targets for treatment. *Behavioral Neuroscience,* 135(3), 426-442. https://doi.org/10.1037/bne0000385

Chapter 3: Julia C. Basso contributed to the study design, data analysis, and writing of the manuscript. Liqa Athamneh assisted in the writing of the manuscript. Warren K. Bickel provided oversight of this work. This chapter is currently under review for publication.

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CHAPTER 1
INTRODUCTION

The mind-body connection has been an area of interest dating back to at least Greek civilization (Panegyres & Panegyres, 2016; Stefanou, 2020). Recent evolutionary findings suggest that human neurobiological adaptations occurred in tandem with physical adaptations to support high levels of physical activity that was required for the hunter-gatherer lifestyle (Raichlen & Polk, 2013). While the human brain, and the size of the brain in particular, is traditionally thought to have adapted due to pro-social selection pressures, new evidence suggests that increased aerobic activity contributed to this neurobiological adaptation. Physically, longer hindlimbs developed to support endurance activity by increasing speed and reducing the energetic cost of activity and a larger semicircular canal system developed to support bodily stability during activity. A dramatic increase in the size of the brain occurred at the time of these physical adaptations.

While the human body and brain remains evolutionarily adaptive for the active hunter-gatherer lifestyle, much of the need for physical activity for survival has been rapidly eliminated in modern industrialized societies. Since the onset of industrialization, physical activity levels have steadily decreased worldwide (Ng & Popkin, 2012). Further, technological advances used in occupational and recreational settings promote sedentary behavior. It is therefore unsurprising that in recent years, only 10-24% of Americans have met the Physical Activity Guidelines for Americans (PAGA) (Clarke et al., 2019; Tucker et al., 2011). Additional factors in the modern environment also promote engagement in unhealthy behaviors, such as the widespread availability of highly processed, calorie-dense foods which promotes consumption of diets that are low in nutritional content (Cutler et al., 2003).

Health neuroscience is an emerging field focused on the link between the brain and the health of the physical body (Erickson et al., 2014). This relationship is bi-directional; that is, behaviors that impact physical health arise from the brain and changes in physical health impact neural processes. Modifiable health behaviors, such as lack of physical activity and unhealthy dietary intake, are related to the development of poor physical health outcomes including obesity, cardiovascular disease, and type 2 diabetes as well as poor brain health outcomes including accelerated age-related cognitive decline, dementia, anxiety, and depression (André et al., 2014; Popkin, 2006; Teychenne et al., 2015). Considering that engagement in maladaptive

health behaviors is a significant public health concern, it is imperative that we build an understanding of the neurobehaviors and neural processes influencing health-related decision-making and strategies to improve them. Previous findings suggest that greater top-down inhibitory control, which is mediated by activity of the prefrontal cortex, predicts engagement in a variety of positive health behaviors (Erickson et al., 2014; Hare et al., 2011).

Exercise is one such health behavior that impacts the body and brain in a systemic fashion. Engagement in exercise, defined as "planned, structured, and repetitive bodily movement done to improve or maintain… fitness" (Bouchard et al., 2012), is a promising strategy to improve these deficits and to maintain healthy psychological and cognitive health. Research to date suggests that exercise may enhance psychological and cognitive functions in multiple domains. Exercise has an effect, in particular, on behaviors that arise from engagement of the prefrontal cortex and the hippocampus. Exercise improves affect and executive function, both of which have been mapped to activity of the prefrontal cortex (Funahashi & Andreau, 2013; Myers-Schulz & Koenigs, 2012) as well as learning and memory, which relies on the hippocampus. Exercise is thought to enhance top-down control from the prefrontal cortex to regulate the activity of lower brain regions (Hall et al., 2001).

Evidence from human and rodent studies suggests that exercise promotes structural changes in the brain through the release of key neurochemicals including brain-derived neurotrophic factor (BDNF) (Ferris et al., 2007), which promotes the growth and survival of new neurons, as well as vascular endothelial growth factor (VEGF), and insulin-like growth factor 1 (IGF1) (Hillman et al., 2008). Evidence from rodent studies suggests that exercise-induced increases in cell proliferation and survival in the hippocampus may be a mechanism by which exercise improves hippocampal-dependent functions (Eadie et al., 2005; van Praag et al., 2005). In fact, BDNF activity is necessary for exercise-induced improvements in memory (Vaynman et al., 2004). VEGF and IGF1 promote the creation of new blood vessels, which increases blood flow, and therefore delivery of resources, to various brain regions to support increased activity.

While early scientific investigations of the connection between exercise and cognitive function were conducted in ageing populations, subsequent investigations suggest that exercise has cognitive benefits throughout the lifespan (Álvarez-Bueno et al., 2017; Etnier et al., 1997; Sherwood & Selder, 1979). However, there is a limited body of literature examining exercise-

induced cognitive effects in young and middle-aged adults as a majority of these investigations continue to be focused on cognitive ageing (Erickson et al., 2019).

Considering that there are co-occurring impairments to the health of the body and mind resulting from maladaptive health behaviors, it is important to identify the potential effects of approaches, such as exercise, to prevent or reverse these impairments and understand the underlying (neuro)physiology. We take a neurobehavioral approach to assessing brain health outcomes. Neurobehavioral assessments, including neurocognitive tasks and self-report questionnaires, measure psychological and cognitive domains that are linked to particular brain regions or circuitry. Using such assessments allows for the evaluation of brain function through behavioral tasks that can be used in noninvasive, large-scale studies.

The overall goal of this dissertation is to examine the bi-directional relationship between the brain and body in relation to health behaviors. This was probed through a series of three studies conducted in clinical and non-clinical populations, outlined below. In Chapter 2, we examined neurobehavioral factors associated with the clinical condition of obesity. In Chapter 3, we examined neurobehavioral factors related to eating behaviors in a population of individuals in recovery from substance misuse. In Chapter 4, we examined exercise-induced neurobehavioral and neurophysiological changes in a population of previously sedentary, middle-aged individuals.

Chapter 2: A novel model of obesity prediction: Neurobehaviors as targets for treatment.

Hypothesis 1: Individuals who are obese will report poorer dietary habits and decreased physical activity compared to individuals who are not obese.

Hypothesis 2: Individuals who are obese will display neurobehaviors indicative of a hyperactive impulsive system and a hypoactive executive system including heightened delay discounting and hedonic hunger; impaired exercise motivation, executive function, and affective state; and poorer self-image compared to individuals who are not obese.

Chapter 3: Changes in temporal discounting, hedonic hunger, and food addiction during recovery from substance misuse.

Hypothesis 1: Individuals in recovery from substance misuse will have steeper temporal discounting than non-substance users.

Hypothesis 2: Individuals in recovery from substance misuse will have an increased drive for palatable foods and symptoms of food addiction than non-substance users.

Chapter 4: Long-term exercise-induced decreased cortical activation predicts improvements in psychological state.

Hypothesis 1: A long-term exercise intervention, compared to a sedentary control, will improve aerobic capacity.

Hypothesis 2: A long-term exercise intervention, compared to a sedentary control, will improve psychological state and cognitive functions.

Hypothesis 3: A long-term exercise intervention, compared to a sedentary control, will increase the relative power in resting-state brain activity.

Hypothesis 4: Changes in aerobic capacity and resting-state brain activity will be associated with changes in psychological state and cognitive function.

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CHAPTER 2

A NOVEL MODEL OF OBESITY PREDICTION: NEUROBEHAVIORS AS TARGETS FOR TREATMENT

 Satyal, M. K., Basso, J. C., Tegge, A. N., Metpally, A. R., & Bickel, W. K. (2021). A novel model of obesity prediction: Neurobehaviors as targets for treatment. *Behavioral Neuroscience, 135*(3), 426–442. https://doi.org/10.1037/bne0000385

Abstract

Obesity is a worldwide epidemic that is on the rise, with approximately 30% of the world population classified as either overweight or obese. The United States has some of the highest rates of obesity, and in most countries in the world, obesity now poses more of a serious health concern than malnutrition. Obesity is a chronic, relapsing disorder that is both preventable and treatable; however, traditional interventions that target eating less and exercising more have low success rates, especially in the long term. Therefore, identifying the neurobehaviors that predict obesity is important to help identify targets to decrease BMI and improve obesity outcomes. Using the Competing Neurobehavioral Decisions System (CNDS) Theory, we hypothesized that individuals with obesity compared to individuals without obesity would display neurobehaviors marked by a hyperactive impulsive system and a hypoactive executive system. To test this hypothesis, we collected data from a battery of self-reported measures and neurocognitive assessments through Amazon Mechanical Turk from n = 178 obese (BMI ≥ 30) and n = 198 nonobese controls who were weight stable for the past 3 months. We found that compared to the nonobese control group, individuals with obesity showed heightened delay discounting (a marker of CNDS imbalance), impaired motivation, poor self-image, decreased affective state, and impaired executive function. Using a Bayesian network approach, we established a neurobehavioral model that predicts obesity with 64.4% accuracy and indicates an imbalance between impulsive and executive neural systems. Results from our study suggest that interventions targeting neurobehaviors may be integral to help improve obesity outcomes.

Introduction

Obesity is defined as an abnormal or excessive fat accumulation, with the World Health Organization classifying individuals with obesity as those with a body mass index (BMI) of 30 or above. Obesity is a worldwide epidemic with rates increasing 300% since 1975. Currently, an

estimated 39% of adults aged 18 years and over are classified as overweight (BMI 25–30), and 13% are classified as obese. In the United States, a staggering 42% of adults are obese. In most countries in the world, obesity now poses more of a serious health concern than malnutrition (Murray et al., 2012). Additionally, obesity is placing individuals at greater risk for the development of multiple fatal serious health conditions including hypertension, heart disease, stroke, Type 2 diabetes, cancer, and premature death, a phenomenon known as multimorbidity (Ezzati, 2017). Because of this, obesity has profound implications for the healthcare system, with this epidemic leading to an estimated annual medical cost of $147 billion (Carlson et al., 2015). Obesity is a preventable disease that results from engagement in maladaptive health behaviors, namely overeating and lack of physical activity. That is, the outcome of obesity is driven by a series of maladaptive decision-making choices. Contrarily, achieving a healthy weight requires balanced decision-making abilities that are geared toward healthy eating and engagement in physical activity. Because we live in an environment that affords us the ability to easily obtain high caloric foods without being physically active, we need to establish tremendous self-control when making decisions about our eating and exercise behaviors. First, when presented with ample food choices, we need to inhibit the behavior of choosing high calorically dense foods. Second, when presented with the opportunity to remain sedentary, we need to make an effort to become physically active.

From the perspective of the field of health neuroscience, the brain "affects and is affected by" these health-related behaviors; that is, the body and brain are interdependent (Erickson et al., 2014). Stemming from this idea, previous studies have examined obesity from a cognitive neuroscience perspective using technologies such as functional magnetic resonance imaging, electroencephalography, and transcranial magnetic stimulation (Batterink et al., 2010; Camus et al., 2009; De Ridder et al., 2016; Ha et al., 2020; Imperatori et al., 2015; Kim et al., 2018; Makaronidis & Batterham, 2018; Martin et al., 2010; Nijs et al., 2010; Park et al., 2017; Schmidt et al., 2018; Stice et al., 2008, 2011; Uher et al., 2005; Wang et al., 2001). The expensive and lengthy procedures of these technical experiments prohibit the inclusion of large sample sizes that are needed for population-based studies. Therefore, others have taken the approach of neurobehavioral assessments to examine the multivariate associates and predictors of obesity. Here, the term neurobehavior refers to an expansive range of behaviors, including both state and trait personality measures as well as cognitive abilities, that are emergent from the brain.

Systematic reviews of these neurobehavioral studies have identified several areas of cognition that have been examined in relation to obesity including executive function, time judgment, motor behaviors, attention, visuospatial abilities, language, memory, and food motivation (Emery & Levine, 2017; Vainik et al., 2013; Yang et al., 2018). Of those, executive function and food motivation displayed the most robust relationship to BMI and eating behaviors. Additionally, systematic reviews have identified several areas of personality that have been examined in relation to obesity including neuroticism, extraversion, openness/intellect, agreeableness, and conscientiousness (i.e., the Five-Factor Model of Personality; Vainik et al., 2013). Of those, the most significant predictor of obesity was impulsiveness, a subdomain of neuroticism.

Several brain regions and circuits emerge as being critically involved in obesity. First, cortical structures such as the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex regulate executive functions such as future planning and self-control, which are needed to drive healthy eating behaviors (Gluck et al., 2017; Lowe et al., 2019). Second, subcortical structures such as the nucleus accumbens and amygdala regulate our motivation, reward, and emotional reactivity, which drive us to act on our immediate needs or desires (e.g., eating dessert in the absence of hunger; Berthoud et al., 2017; Mietus-Snyder & Lustig, 2008). These higher and lower brain centers have reciprocal connections with one another such that altered top–down and bottom–up processing may be a likely neurobiological mechanism of obesity (Kaisari et al., 2019; Naets et al., 2018; Scarpina et al., 2016). These higher and lower circuits are then regulated by hormones and neuromodulators, such as ghrelin and leptin, that are released from hypothalamic centers and mediate signals of hunger and satiety (Timper & Brüning, 2017).

In this context, we examined obesity from the perspective of the Competing Neurobehavioral Decisions System (CNDS) Theory, which is inspired by the field of Neuroeconomics and posits that decisions are governed by the higher and lower systems described above (Bickel et al., 2018). The higher executive system is mediated by prefrontal and temporal brain regions (e.g., DLPFC and hippocampus) and governs long-term, future-oriented choices; whereas the lower impulsive system is mediated by limbic (e.g., midbrain, amygdala, habenular commissure, and dorsal striatum) and paralimbic (e.g., insula and ventral striatum) brain regions and governs reward-based choices. When the two systems are in homeostatic balance, individuals exhibit flexible decision-making processes that result in healthy choices.

However, when the impulsive system is hyperactive and the executive system is hypoactive, a dysregulation in behavior occurs, resulting in maladaptive behaviors and pathological states such as addiction. Recent research has shown that obesity, which some conceptualize as a food addiction (though controversy exists with this theory and new data sheds doubt on this comparison) (Avena et al., 2012; Blumenthal & Gold, 2010; Fletcher & Kenny, 2018; Vainik et al., 2020; Volkow et al., 2017; Wieland, 2019), may be governed by a similar imbalance between the two systems (Bickel et al., 2014; Foxall, 2016; Volkow et al., 2017). Specifically, individuals with obesity show hyperactivity in the nucleus accumbens and hypoactivity in the prefrontal cortex (Lowe et al., 2019; Martin & Davidson, 2014; Rapuano et al., 2017).

Here, we used both neurocognitive assessments as well as self-reported questionnaires in a large, population study to assess the most significant predictive measures of obesity. Though systematic reviews have assessed this area of inquiry previously, the novelty and value of the present study are that all neurobehavioral measures were assessed in the same sample. Alongside these neurobehavioral measures, we simultaneously collected measures of eating and exercise behaviors, motivations, and attitudes, which is yet another novelty of the current data set as many previous studies have not taken this approach. To assess the CNDS balance, we primarily used the neuroeconomic task of delay discounting (DD), which measures the rate of decline in the present value of a monetary reward based on its delay to receipt (Bickel et al., 2018). Other measures of executive tone include executive function, affective state, and self-evaluation, all of which have been mapped to the executive system (e.g., prefrontal cortex; Beer et al., 2010; Funahashi & Andreau, 2013; Gray et al., 2002; Hare & Duman, 2020; Liu et al., 2017; Perlstein et al., 2002; Yang et al., 2016). Additional measures of impulsive tone include the motivations for eating and exercise behaviors, which have been mapped to the impulsive system (e.g., nucleus accumbens; Basso & Morrell, 2015; Castro et al., 2015; Clithero et al., 2011; Herrera et al., 2016; Ikemoto & Panksepp, 1999; Reynolds & Berridge, 2002; Salamone et al., 2016). As these neurobehaviors are multifaceted, we acknowledge that interactions between these brain structures as well as other brain structures are also involved in their regulation, and we discuss our findings in this context (Genon et al., 2018; Ito et al., 2020; Salzman & Fusi, 2010). We explored the hypothesis that compared to non-obese controls, individuals with obesity demonstrate neurobehaviors that are weighted toward impulsive over executive decisions. We then used Bayesian network modeling to determine the most prominent neurobehavioral factors

that drive obesity. Our results indicate that neurobehaviors related to CNDS functioning (e.g., DD) may be important factors affecting obesity outcomes and possible targets for future weight-loss programs.

Methods

Recruitment, Participants, and Data Collection

Data were collected through Amazon Mechanical Turk (mTurk). The study was available to mTurk workers in the United States with a 90% or greater Human Intelligence Task (HIT) approval rate, indicating they provided good quality data in at least 90% of previously completed HITs. Participants were screened to ensure they met the inclusion criteria. In order to complete the questionnaire, participants needed to be between the ages of 18 and 45, have English as their primary language, be weight-stable for at least 3 months, not be pregnant or experiencing menopause, and not be colorblind. After screening, a total of 727 records were collected. Participants were compensated for the completion of the questionnaire and received bonus compensation if the data passed quality checks. All methods were approved by the Virginia Tech Committee on Activities Involving Human Subjects and were performed in accordance with the relevant guidelines and regulations.

Using mTurk, self-report questionnaires and neurocognitive assessments were administered in a randomized order to assess health behaviors, DD, executive functioning, affective state, eating motivations and attitudes, exercise motivations and attitudes, and self-evaluation (i.e., body image). All self-reported questionnaires were adapted to be administered in an online format and presented through Qualtrics, whereas the neurocognitive assessment was administered through Inquisit Web.

Records that were incomplete (i.e., progress <100%) or provided an invalid BMI were excluded from the analysis. A BMI of less than 15 or greater than 57 was considered invalid. In the case of multiple submissions, one submission from each mTurk Worker ID was included in the analysis. Additionally, we used a food purchasing task to screen for nonsystematic data (Epstein et al., 2010; Stein et al., 2015; Sze et al., 2017). Data were deemed systematic if they met the criteria of (a) trend, meaning purchasing decreased as the price increased, (b) bounce, meaning few local increases in purchasing occurred with price increases, and (c) reversal from zero using an algorithm developed by Stein et al. (2015). Data that were deemed unsystematic were excluded from the analysis. After data cleaning, 376 records were included in the analysis.

The sample for analysis consisted of 198 participants without obesity (BMI < 30) and 178 participants with obesity (BMI ≥ 30). Though BMI is a continuous variable, the classification of obesity via BMI is an important clinical construct (Gutin, 2018; Samuel et al., 2004); as such, we utilized this clinical categorization to investigate neurobehavioral differences between body weight groups.

Health Behaviors

Health behaviors included eating and drinking behaviors as well as engagement in physical activities. Eating behaviors were assessed using the Fat Intake Screener, and Fruit and Vegetable Intake Screener (Block et al., 2000). These food screeners are brief questionnaires asking about the frequency of intake of fatty foods, and fruits and vegetables, that were validated against a longer 100-item food frequency questionnaire. The Fat Intake Screener consists of 17 items scored on a 5-point Likert scale and summed for a total score. The Fruit and Vegetable Intake Screener consists of seven items scored on a 6-point Likert scale and summed for a total score. Drinking behaviors were assessed using the Beverage Intake Questionnaire (BEVQ-15) to estimate habitual intake of beverages, which was validated through comparison with three 24-hr dietary recalls (Hedrick et al., 2012). The BEVQ-15 is a 15-item quantitative questionnaire providing an estimate of habitual beverage intake (grams and kcals).

Exercise behavior was assessed using the Global Physical Activity Questionnaire (GPAQ), a 16-item interview measure that assesses physical activity during work, travel, and recreation as well as sedentary time (World Health Organization [WHO], n.d.). Time spent in moderate and vigorous physical activities are assigned four and eight Metabolic Equivalents (METs), respectively, to estimate weekly energy expenditure (MET minutes). Data cleaning was done per the World Health Organization GPAQ analysis guidelines (WHO, n.d.); due to this additional data cleaning, the analysis of GPAQ had a reduced sample size (N = 373).

Behavioral Economics Measures to Assess Balance Between the Impulsive and Executive Systems

The five-trial adjusting DD task, which measures both impulsivity and future valuation, was used as our primary measure of the balance between the impulsive and executive systems (Koffarnus & Bickel, 2014). For this task, participants were asked if they would prefer an immediate $500 reward or a $1,000 reward at different time delays, increasing or decreasing the

time delay based on the previous response. The natural log-transformed rate of monetary discounting (lnk) is reported.

Probability discounting was used as a control measure for our DD task and therefore we hypothesized that we would not see a significant difference between body weight groups (Bickel et al., 2014). For this task, participants were asked to choose between a smaller reward or a larger but less probable reward.

Additional Measures to Assess Impulsive Tone

Eating Motivations and Attitudes

Eating motivations and attitudes were evaluated using three different scales; namely, the Power of Food Scale (PFS); the Three-Factor Eating Questionnaire (TFEQ-R18); and the Eating Attitudes Test (EAT). Hedonic hunger or appetite for palatable foods was assessed using the PFS, a questionnaire that assesses the psychological impact of living in a food-rich environment (Lowe et al., 2009). The PFS has been validated in a general population as well as in a population with obesity and has been found to be reliable (Cronbach's $\alpha = 0.81–0.91$) (Cappelleri et al., 2009; Lowe et al., 2009). The PFS consists of 15 items scored on a 5-point Likert scale and summed for a total score as well as three subscale scores including food available, food present, and food tasted. Eating behaviors were assessed using the TFEQ-R18, which is a validated and reliable questionnaire to assess one's cognitive and emotional relationship to eating (de Lauzon et al., 2004; Karlsson et al., 2000). The TFEQ-R18 was originally developed for use in a population with obesity and has been validated against a food frequency questionnaire in a general population (de Lauzon et al., 2004). The TFEQ-R18 consists of 18 items that are scored on a 4-point Likert scale and summed for three different factor scores including cognitive restraint, emotional eating, and uncontrolled eating. Disordered eating behaviors were assessed using the EAT-26, which is a valid and reliable screening questionnaire originally developed as a screening tool for eating disorders (Garner et al., 1982). The EAT has been previously used in a variety of populations including adults, adolescents, and different cultural populations (Garfinkel & Newman, 2001). The EAT consists of 26 items that are scored on a 6-point Likert scale and summed for a total score (EAT score), and three subscales including dieting, oral control, and bulimia food preoccupation.

Exercise Motivations and Attitudes

Exercise motivations and attitudes were evaluated using two scales, the Behavioral Regulation of Exercise Questionnaire (BREQ-3) and the Subjective Exercise Experiences Scale (SEES). Motivation to engage in the exercise was assessed using the BREQ-3, which is a valid and reliable questionnaire (Cid et al., 2018). The BREQ-3 consists of 24 items that are scored on a 5-point Likert scale and averaged for 6 subscale scores including amotivation, external regulation, introjected regulation, identified regulation, integrated regulation, and intrinsic regulation. The Relative Autonomy Index (RAI) is an index indicating the degree to which individuals are self-determined to exercise, and is calculated as a sum of weighted subscale scores (Ryan & Connell, 1989):

RAI = (Amotivation*-3) + (External Regulation*-2) + (Introjected Regulation*-1) + (Identified Regulation*1) + (Integrated Regulation*2) + (Intrinsic Regulation*3)

Psychological responses to exercise were assessed using the SEES, which is a valid and reliable (Cronbach's $\alpha = 0.84–0.92$) questionnaire (McAuley & Courneya, 1994). The SEES consists of 12 items that are scored on a 7-point Likert scale and summed for 3 different factor scores including positive well-being, psychological distress, and fatigue.

Executive Function

Response inhibition and attention were assessed using the Stroop Color-Word task (Stroop, 1935). Participants were presented with stimuli that were color words or rectangles written in colored font (e.g., the word "red" written in green font) and instructed to indicate the color of the word rather than its meaning using a keyboard press. Stimuli appeared on the screen in a randomized order and were displayed until the participant responded or for 400 ms with no response, which was followed by a 200-ms interval before the next stimulus was displayed. The task included stimuli of four different colors, and congruent (color and meaning the same), incongruent (color and meaning different), and control (colored rectangles) trials. Each color-congruency combination was repeated 7 times for a total of 84 trials presented in one test block. Percent correct and reaction time are reported. Stimuli were presented and responses were recorded using the Inquisit software (https://www.millisecond.com/). Participants were required to install the Inquisit software on their device to complete this task.

Affective State

Affective state measures were included to assess depression, anxiety, and positive and negative affect. Depression was assessed using the Beck Depression Inventory (BDI), which

is a valid and reliable (Cronbach's $\alpha = 0.81–0.86$) measure to assess symptoms of depression (Beck et al., 1988). The BDI consists of 21 items that are scored on a 4-point Likert scale and summed for a total score. Anxiety was assessed using the Beck Anxiety Inventory (BAI), which is a valid and reliable (Cronbach's $\alpha = 0.94$) questionnaire assessing symptoms of anxiety (Beck et al., 1988; Fydrich et al., 1992). The BAI consists of 21 items scored on a 4-point Likert scale and summed for a total score. Positive and negative affect were assessed using the Positive and Negative Affect Schedule (PANAS), which is a valid and reliable (Cronbach's $\alpha = 0.85–0.89$ in a nonclinical sample) questionnaire that assesses mood (Crawford & Henry, 2004; Watson et al., 1988). The PANAS includes 20 items that are scored on a 5-point Likert scale and summed for a positive affect score and a negative affect score.

Self-evaluation

Self-evaluation or perceived body image was assessed using the Body Attitudes Test (BAT), which is a valid and reliable (Cronbach's $\alpha = 0.93$) questionnaire that assesses body experience (Probst et al., 1995). The BAT includes 20 items that are scored on a 6-point Likert scale and summed for a total score (BAT score) as well as four subscales including negative appreciation, lack of familiarity, body dissatisfaction, and a rest factor.

Power Analysis and Statistics

To determine the sample size to sufficiently power our study, an a priori power analysis was conducted using G * Power 3.1 (Faul et al., 2009). The power analysis was based on a *t*-test difference between two independent means with a medium effect size ($d = 0.5$). In order to account for multiple testing as a result of several neurobehavioral measures, we used an alpha of 1 E-4 and 80% power, with results indicating a sample size of $n = 183$ per group. We compared demographic measures between groups using a χ^2 test of independence (household income, education, employment status, sex, race, and ethnicity) or an independent samples *t*-test (age). For χ^2 tests, all expected cell frequencies were greater than five. If reported personal income was greater than household income, the value for household income was replaced with the value for personal income. Household income was then stratified into low- (<$40,000 per year), middle- ($40,000–$125,000 per year), and high- (>$125,000 per year) income (Semega et al., 2017).

Between-group as well as continuous analyses were performed on all variables of interest. All self-report and cognitive task scores were compared between body weight groups using independent samples *t*-tests. For variables with unequal variances between groups, as

determined by Levene's test for homogeneity of variance, Welch's *t*-test was used. Additionally, the relationships among all self-report and cognitive task scores and BMI were examined using Pearson correlations. A supplementary correlation analysis was conducted in a subset of the data, excluding participants with a BMI in the underweight (BMI < 18.5) range. For comparisons that were considered part of a grouping (e.g., health behaviors; affective state), Bonferroni correction was applied and significance was determined based on the resulting alpha value. The Bonferroni-corrected alpha value is reported for each grouping in the results.

Finally, an exploratory analysis was performed using a Bayesian network approach to create a model that describes the relationship between BMI and five neurobehaviors (i.e., DD, affective state, eating attitudes, exercise attitudes, and self-evaluation). Bayesian network modeling was selected because this approach seeks to identify a directed acyclic graph that infers the conditional dependencies among the features. This directed acyclic graph consists of nodes representing variables of interest and paths between nodes representing probabilistic dependencies between them (Friedman et al., 1997; Pearl & Russell, 2003). Conditional probabilities represent the strength of the relationships between each cluster of nodes. Bayesian networks may be particularly useful in examining neurocognitive functions (Bielza & Larrañaga, 2014).

Here, we used Bayesian networks to examine the role of neurobehaviors in predicting obesity. Specifically, composite scores of five neurobehavioral measures were derived as follows:

1. affective state composite: mean of *z*-normalized BAI and *z*-normalized BDI;
2. eating attitudes and motivations composite: mean of *z*-normalized TFEQ Cognitive Restraint (reverse scored), *z*-normalized TFEQ Uncontrolled Eating, *z*-normalized TFEQ Emotional Eating, *z*-normalized PFS, and *z*-normalized EAT;
3. exercise attitudes and motivation: mean of *z*-normalized BREQ RAI (reverse scored), *z*-normalized SEES Positive Wellbeing (reverse scored), *z*-normalized SEES Fatigue, and *z*-normalized SEES Psychological Distress;
4. self-evaluation: BAT; and
5. DD: monetary discount rate (lnk).

Appropriate variables were reverse scored, as indicated above, to ensure higher scores reflected more negative outcomes. For analysis, these five composite measures were binned into ordinal categories of equal width and used as precipitants for predicting obesity. We estimated the Bayesian network using the tree augmented naive approach using 10-fold cross-validation (note that the Markov blanket and Markov blanket with feature selection methods did not achieve as high of a correct classification rate). The optimal network in each iteration was determined by minimizing the posterior classification error, that is, the number of incorrectly classified cases. Edge strengths in the Bayesian network are determined as the change in Bayesian Information Criterion (BIC) after removal of edge from the network. Analyses were completed using SPSS Statistics 26.0, GraphPad Prism, and R Version 4.0.2 (June 22, 2020) using the bnlearn package (Scutari, 2010).

Results

Participants completed the study in an average of 56.4 min (±1.6 min SEM); however, this time includes other self-reported measures not included in this study.

Participant Demographics

No significant differences were observed between body weight groups in age, $t(374) = -1.443$, $p = .150$, sex, $\chi^2(1) = 0.100$, $p = .752$, household income, $\chi^2(2) = .582$, $p = .747$, education, $\chi^2(3) = 4.477$, $p = .214$, employment status, $\chi^2(2) = 0.671$, $p = .715$, race, $\chi^2(3) = 5.405$, $p = .144$, or ethnicity, $\chi^2(1) = 0.113$, $p = .737$. Table 1 summarizes participant demographic information.

Health Behaviors

The Bonferroni-corrected critical alpha value for health behaviors measures is 0.0083. Individuals with obesity had a significantly higher fat intake $t(374) = -4.051$, $p < .001$, $N = 376$, than individuals without obesity. No significant differences were found between groups for fruit and vegetable intake, $t(374) = 0.290$, $p = .772$, $N = 376$, or beverage intake in kcal, $t(374) = -1.314$, $p = .190$, $N = 376$. Individuals with obesity reported significantly lower levels of weekly physical activity, $t(343.843) = 2.749$, $p = .006$, $N = 373$, than individuals without obesity, while no significant difference was found between groups for daily sedentary time $t(371) = 0.820$, $p = .413$, $N = 373$ (Figure 1, Supplemental Table 1). Additionally, continuous BMI was found to be positively correlated with fat intake ($r = .189$, $p < .001$, $N = 376$). No significant correlations

were found between BMI and fruit and vegetable intake, weekly physical activity, or daily sedentary time (Figure 2, Supplemental Table 8).

Behavioral Economics Measures to Assess Balance Between the Impulsive and Executive Systems

Discounting Measures

The Bonferroni-corrected critical alpha value for discounting measures is 0.025. Individuals with obesity had a significantly higher rate of monetary discounting, $t(374) = -2.909$, $p = .004$, $N = 376$, than individuals without obesity on the five-trial adjusting DD task (Figure 1, Supplemental Table 2). No significant difference was found between groups for probability discounting, $t(374) = 0.678$, $p = .498$, $N = 376$; (Figure 1, Supplemental Table 2). No significant correlation was found between continuous BMI and monetary discounting ($r = .112$, $p = .031$, $N = 376$) nor probability discounting ($r = -.045$, $p = .379$, $N = 376$) (Figure 2, Supplemental Table 8).

Additional Measures to Assess Impulsive Tone

Eating Motivations and Attitudes

The Bonferroni-corrected critical alpha value for eating motivation and attitude measures is 0.0045. Individuals with obesity reported significantly greater uncontrolled eating, $t(374) = -5.831$, $p < .001$, $N = 376$, and emotional eating, $t(374) = -4.684$, $p < .001$, $N = 376$, than individuals without obesity (Figure 1; Supplemental Table 3). No significant difference was found between groups for cognitive restraint ($t(374) = 0.541$, $p = .589$, $N = 376$). Individuals with obesity reported significantly higher appetites for palatable foods, $t(346.924) = -4.974$, $p < .001$, $N = 376$, including when food is available, $t(343.362) = -5.989$, $p < .001$, $N = 376$, and food is present, $t(374) = -5.004$, $p < .001$, $N = 376$, than individuals without obesity. No significant difference was found between groups when food is tasted, $t(374) = -2.096$, $p = .037$, $N = 376$. Individuals with obesity reported significantly greater bulimia food preoccupation, $t(348.149) = -4.528$, $p < .001$, $N = 376$, than individuals without obesity. No significant difference was found between groups for disordered eating (EAT total $t(364.451) = -2.534$, $p = .012$, $N = 376$), including dieting, $t(374) = -2.431$, $p = .016$, $N = 376$, and oral control, $t(374) = 0.218$, $p = .828$, $N = 376$. Neither group scored above the screening threshold for eating disorder evaluation. BMI was found to be positively correlated with uncontrolled eating ($r = .280$, $p < .001$, $N = 376$), emotional eating ($r = .223$, $p < .001$, $N = 376$), bulimia food

preoccupation ($r = .262$, $p < .001$, $N = 376$), and appetite for palatable foods ($r = .235$, $p < .001$, $N = 376$), including when food is available ($r = .270$, $p < .001$, $N = 376$) and when food is present ($r = .227$, $p < .001$, $N = 376$) (Figure 2, Supplemental Table 8).

Exercise Motivations and Attitudes

The Bonferroni-corrected critical alpha value for exercise motivation and attitude measures is 0.005. Individuals with obesity reported significantly lower positive well-being, $t(374) = 4.513$, $p < .001$, $N = 376$, and significantly greater psychological distress ($t(346.275) = -5.282$, $p < .001$, $N = 376$) and fatigue, $t(374) = -3.830$, $p < .001$, $N = 376$, in response to exercise compared to individuals without obesity (Figure 1; Supplemental Table 4). Additionally, individuals with obesity reported significantly lower self-determination for exercise, $t(370.578) = 8.198$, $p < .001$, $N = 376$, than individuals without obesity. Individuals with obesity reported higher amotivation, $t(361.150) = -4.735$, $p < .001$, $N = 376$, and external regulation, $t(374) = -3.085$, $p = .002$, $N = 376$, and lower identified regulation, $t(374) = 6.931$, $p < .001$, $N = 376$, integrated regulation, $t(374) = 5.572$, $p < .001$, $N = 376$, and intrinsic regulation, $t(374) = 5.074$, $p < .001$, $N = 376$, compared to individuals without obesity. No significant differences were found between groups for introjected regulation (Figure 1, Supplemental Table 4). BMI was found to be positively correlated with psychological distress ($r = .258$, $p < .001$, $N = 376$) and fatigue ($r = .165$, $p = .001$, $N = 376$) in response to exercise, and amotivation for exercise ($r = .223$, $p < .001$, $N = 376$). BMI was found to be negatively correlated with positive well-being in response to exercise ($r = -.206$, $p < .001$, $N = 376$), self-determination for exercise ($r = -0.307$, $p < .001$, $N = 376$), identified regulation ($r = -.287$, $p < .001$, $N = 376$), integrated regulation ($r = -.199$, $p < .001$, $N = 376$), and intrinsic regulation ($r = -.162$, $p = .002$, $N = 376$) (Figure 2, Supplemental Table 8).

Additional Measures to Assess Executive Tone

Executive Function

The Bonferroni-corrected critical alpha value for executive function measures is 0.00625. On the Stroop task, individuals with obesity had a significantly lower percent correct on congruent trials, $t(241.930) = 2.888$, $p = .004$, $N = 340$, compared to individuals without obesity (Figure 1, Supplemental Table 5). No significant differences were found between groups in overall percent correct, $t(250.335) = 2.726$, $p = .007$, $N = 340$, percent correct on incongruent trials, $t(269.392) = 2.402$, $p = .017$, $N = 340$, and control trials, $t(254.241) = 2.651$, $p = .009$, $N =$

340, or in overall, $t(338) = 0.827$, $p = .409$, $N = 340$, congruent, $t(338) = 1.312$, $p = .190$, $N = 340$, incongruent, $t(338) = 0.438$, $p = .661$, $N = 340$, or control, $t(338) = 0.739$, $p = .460$, $N = 340$, reaction times (Figure 1, Supplemental Table 5). No significant correlations were found between continuous BMI and executive function measures (Figure 2, Supplemental Table 8).

Affective State

The Bonferroni-corrected critical alpha value for affective state measures is 0.0125. Individuals with obesity reported significantly higher levels of anxiety, $t(356.127) = -3.623$, $p < .001$, $N = 376$, and depression, $t(374) = -2.693$, $p = .007$, $N = 376$, than individuals without obesity (Figure 1, Supplemental Table 5). The group without obesity reported mild anxiety while the group with obesity reported moderate anxiety. Additionally, the group without obesity reported minimal depression while those with obesity reported mild depression. No significant differences were found between groups for positive, $t(374) = 1.354$, $p = .177$, $N = 376$, or negative affect, $t(374) = -2.186$, $p = .029$, $N = 376$. BMI was found to be positively correlated with anxiety ($r = .197$, $p < .001$, $N = 376$) and depression ($r = .129$, $p = .012$, $N = 376$) (Figure 2, Supplemental Table 8).

Self-Evaluation

The Bonferroni-corrected critical alpha value for self-evaluation measures is 0.01. Individuals with obesity reported significantly more negative overall self-image (BAT total $t(341.750) = -7.899$, $p < .001$, $N = 376$) including greater negative appreciation ($t(342.615) = -9.809$, $p < .001$, $N = 376$), higher lack of familiarity, $t(341.436) = -6.315$, $p < .001$, $N = 376$, and greater body dissatisfaction, $t(374) = -6.859$, $p < .001$, $N = 376$, than individuals without obesity (Figure 1, Supplemental Table 7). BMI was found to be positively correlated with more negative self-image ($r = .401$, $p < .001$, $N = 376$), including negative appreciation ($r = .484$, $p < .001$, $N = 376$), lack of familiarity ($r = .323$, $p < .001$, $N = 376$), and body dissatisfaction ($r = .328$, $p < .001$, $N = 376$) (Figure 2, Supplemental Table 8).

Bayesian Network Modeling of the Relationship between BMI and Neurobehaviors

An exploratory analysis using a tree augmented naive Bayesian network with 10-fold cross-validation resulted in a model that accurately predicted obesity outcomes in 64.4% of cases (Figure 3). Testing of the model, with obesity defined as the “positive” condition, resulted in a sensitivity of 57.3%, and a specificity of 70.7%.

The network revealed that all five neurobehaviors (DD, exercise attitudes, eating attitudes, affective state, and self-evaluation) were direct predictors of the obesity outcome. The strongest direct relationship to obesity was from DD (arc strength = 46.36), followed by eating attitudes and motivations (arc strength = 41.44), exercise attitudes and motivations (arc strength = 31.53), self-evaluation (arc strength = 31.40), and affective state (arc strength = 4.62) (Table 2). Additionally, DD, exercise attitudes and motivations, and self-evaluation were predictors of affective state; and eating attitudes and motivations was a predictor of self-evaluation (Figure 3).

Discussion

Obesity is a chronic, relapsing, and progressive disease that is both preventable and treatable (Bray et al., 2017; De Lorenzo et al., 2020). Treatments for this disease include lifestyle change interventions, weight-loss medications and devices, and in extreme cases, bariatric surgery. However, treatment success rates, especially for programs implementing behavioral change, are low. This lack of success may be because obesity is not viewed from a holistic lens. New research indicates that obesity may be a more complex disorder stemming not from just eating too much or exercising too little, but actually a result of an imbalance in key brain circuits, namely the impulsive and executive systems. Using the framework of the CNDS theory and the statistical method of Bayesian network modeling, we have shown that obesity is predicted by a profile of neurobehaviors including enhanced impulsivity, impaired affective state, lower levels of motivation, and poor self-image. Several previous correlational and meta-analytic studies have established that overweight/obesity are related to impaired neurobehaviors including cognitive flexibility, short-term memory, fluid intelligence, impulsivity, and social functioning (Emery & Levine, 2017; Gray et al., 2020; Hovens et al., 2019; Mazza et al., 2020; Olivo et al., 2019; Vainik et al., 2013, 2018; Wood et al., 2019; Yang et al., 2018). The novelty of our data set is that we have provided a side-by-side comparison of a variety of neurobehaviors along with eating and exercise outcomes, establishing a model that predicts obesity with an accuracy of 64.4%. Our findings support the link between the body (e.g., BMI) and mind (e.g., neurobehavioral state) and suggest that neurobehaviors may be a target to enhance obesity treatment outcomes.

Impaired Neurobehavioral Profile in Obesity

Delay Discounting: A Task to Identify CNDS Balance

We have demonstrated that individuals with obesity have a significantly higher discount rate than individuals without obesity. Previous research has demonstrated mixed findings in this area; however, the most robust methodological study designs demonstrate a positive and significant association between DD and obesity (Tang et al., 2019), with BMI showing a significant positive correlation to discounting rate (Epstein et al., 2014). One recent study using data from the Human Connectome Project investigated cognitive dysfunction in obesity using a battery of 20 neurocognitive assessments and identified DD as the strongest predictor of obesity (Hovens et al., 2019), which our findings corroborate. DD is the behavioral tendency to undervalue rewards when the receipt of the reward is postponed in time. This behavior may have proven evolutionarily advantageous as the probability of actually receiving a reward often decreases as a temporal delay is introduced (Kagel et al., 1986). However, excessive discounting has been linked to impaired health behaviors and clinical issues such as addiction, and now, obesity (Bickel et al., 2019). We have previously proposed that DD is a candidate behavioral marker to establish the functioning of and balance between the executive and impulsive systems (Bickel et al., 2012, 2019). In this light, the present results demonstrate that individuals with obesity show a hyperactive impulsive system and a hypoactive executive system, indicating that DD may be a biomarker for obesity (Califf, 2018; Strimbu & Tavel, 2010).

Additional Findings that Indicate and Overactive Impulsive System in Obesity

Eating Motivations and Attitudes

We have shown that individuals with obesity report altered eating motivations compared to individuals without obesity. Namely, individuals with obesity report higher levels of uncontrolled and emotional eating, heightened appetite for palatable foods, and greater disordered eating including bulimia food preoccupation. Previous research using principal component analysis or meta-analytic techniques have indicated that various eating-related traits assessed through scales such as the PFS, TFEQ-R18, and EAT measure a similar construct, namely uncontrolled eating, and can be considered interchangeably (Price et al., 2015; Vainik et al., 2015, 2019). We, therefore, interpret our results as indicating that obesity is associated with uncontrolled eating, which is in line with previous findings showing that heightened motivation for consuming highly palatable foods is a hallmark of obesity (Campana et al., 2019; Ferrario, 2017; Lerma-Cabrera et al., 2016). Specifically, individuals with obesity compared to those without obesity display higher levels of hedonic hunger, or the motivational drive to eat in the

absence of hunger cues (Lowe & Butryn, 2007). Additionally, weight loss driven by either behavioral or surgical (i.e., gastric bypass surgery) interventions in individuals with obesity has been shown to decrease levels of hedonic hunger (Schulte et al., 2020; Schultes et al., 2010). Disordered eating, especially as it relates to undercontrolled eating such as binge eating disorder (BED), has also emerged as an issue in obesity (de Zwaan, 2001; McCuen-Wurst et al., 2018). The prevalence of BED in the adult U.S. population is approximately 5% but rises to 50% in adults with obesity seeking weight-loss treatment (Hudson et al., 2007). In line with our theoretical framework, these food-addiction-like behaviors in populations with obesity have been linked to pathological heightened activity of the impulsive system, namely the nucleus accumbens (Castro et al., 2015; Coccurello & Maccarrone, 2018; Yang et al., 2020).

Exercise Motivations and Attitudes

Surprisingly few studies have examined the motivation for physical activity in populations with obesity in a cross-sectional format such as this one. Using the framework of self-determination theory (Deci & Ryan, 2012), we have newly shown that individuals with obesity report lower levels of motivation for physical activity than individuals without obesity, specifically reporting higher levels of amotivation and lower levels of intrinsic regulation. Our results indicate that individuals with obesity rely on external pressure to exercise (external regulation) and find that exercise is less important (identified regulation) and contributes less to their sense of self (integrated regulation) than individuals without obesity. That is, on the spectrum of self-determination, individuals with obesity are non-self-determined to exercise compared to individuals without obesity. Additionally, we have newly shown that individuals with obesity report lower levels of positive well-being and greater levels of psychological distress and fatigue in response to exercise. This affective response to exercise may contribute to the lack of motivation to engage in exercise, especially considering that the level of exercise motivation positively correlates to the level of positive well-being and negatively correlates to the level of psychological distress and fatigue experienced with exercise (Supplemental Table 9; Supplemental Figure 1). Similarly, in individuals with obesity, acute exercise has little to no impact on improving mood states (Unick et al., 2012, 2015), and sedentary activity is more reinforcing than physical activity (Carr & Epstein, 2020; Epstein et al., 1991). Additionally, previous studies have shown that weight-loss interventions in individuals who are overweight and obese can increase the motivation to engage in physical activity (Silva et al., 2008, 2010;

Verloigne et al., 2011). We have previously demonstrated that regions integral to both the executive (i.e., medial prefrontal cortex) and impulsive (i.e., nucleus accumbens) systems are necessary for motivation to engage in physical activity (Basso & Morrell, 2015), suggesting that these regions may be involved in the amotivation to exercise in individuals with obesity.

Additional Findings that Indicate an Underactive Executive System in Obesity

Executive Functioning

We have shown that individuals with obesity, compared to individuals without obesity, demonstrate impaired executive function as measured by accuracy on the congruent trials of the Stroop Task. That is, individuals with obesity show a deficit in the ability to identify the color when the color and the meaning of the word match, a process referred to as the Stroop facilitation effect. Facilitation is a measure of attention and is a cognitive-behavioral process that relies on the anterior cingulate cortex, a region of the executive system (Carter et al., 1995; Lindsay & Jacoby, 1994). A meta-analysis that examined inhibitory control in obesity using several neurocognitive measures including the Stroop task, the stop-signal task, and the go/no-go task, found that individuals with obesity showed impairment in these prefrontal cortex-dependent behaviors compared to healthy weight controls (Lavagnino et al., 2016). Additionally, studies have shown that worsened executive functioning (i.e., working memory) is predictive of lower levels of weight loss in behavioral treatment programs for individuals with obesity (Dassen et al., 2018). Further, neuroimaging studies have identified that inhibitory control-related activity of the prefrontal cortex is negatively associated with both BMI and subsequent weight gain (Batterink et al., 2010; Hendrick et al., 2012; Kishinevsky et al., 2012; Weygandt et al., 2013). Our findings are in line with this body of work showing that impairment of the executive system is predictive of high BMI, continued weight gain, and obesity outcomes.

Affective State

Similar to what others have shown (Avila et al., 2015), we have demonstrated that individuals with obesity compared to individuals without obesity report higher levels of depression and anxiety. Research has found that obesity is a risk factor for serious mental health conditions including depression and anxiety (Avila et al., 2015). In fact, obesity is associated with an approximately 25% increase in odds of mood and anxiety disorders, with the strongest association between obesity and depression (Rajan & Menon, 2017; Simon et al., 2006). These mental health issues only exacerbate the impaired quality of life and levels of

disability, morbidity, and mortality that accompany obesity (Avila et al., 2015). Collectively, this research indicates that a bidirectional link exists between obesity and mental health disorders, and as such, the treatment of one can improve the course of the other (Amiri & Behnezhad, 2019; Jantaratnotai et al., 2017; Luppino et al., 2010; McElroy et al., 2004; Rao et al., 2020). Dysfunction in regions of the executive system, such as the ventromedial prefrontal cortex, has been linked to mental health issues such as depression and anxiety (Hare & Duman, 2020; Hiser & Koenigs, 2018), suggesting another area of the executive system that may be targeted in obesity.

Self-evaluation

We have shown that individuals with obesity report a more negative body image than individuals without obesity, including greater levels of negative appreciation, lack of familiarity, and body dissatisfaction. Previous research has shown that individuals with obesity report greater levels of impaired body image than individuals without obesity. This negative self-evaluation is an integral part of Body Dysmorphic Disorder (BDD), which is a clinical disorder characterized by excessive thoughts and repetitive behaviors regarding a preoccupation with physical appearance and is common in individuals with obesity (Sarwer et al., 2005, 1998). Body image disturbance is often a driving force for weight loss, and individuals who are overweight and obese are more motivated to lose weight to improve their physical appearance than to improve their health (Delgado et al., 2002; Latner & Wilson, 2011; Sarwer et al., 2005). Research shows that negative self-evaluation may persist even with weight loss because the individuals express dissatisfaction over some of the body shape changes that occur with weight loss (e.g., skin folds; Sarwer et al., 2005). Recent functional neuroimaging studies have implicated the executive system (medial PFC) in self-image, including self-referential and self-evaluative thought or the processing of information about the self (D'Argembeau et al., 2007; Mitchell et al., 2005; Owens et al., 2010).

Our Bayesian Network Model in Relation to the Competing Neurobehavioral Decisions System Theory

The CNDS Theory posits that our decisions are governed by two brain systems, namely the impulsive system and the executive system. As an example, in the case of eating, the impulsive system governs our approach to and consumption of palatable foods; whereas the executive system helps limit the overconsumption of said palatable foods. When the two systems

are in balance, we can engage in a variety of behavioral choices that result in healthy weight status (i.e., normal BMI). However, when the two systems are out of balance, our behavioral choices are more limited (e.g., eating only high-density caloric foods and/or limited participation in physical activity) and lead to overweight or obese outcomes. Specifically, the results of our model suggest that obesity manifests as a result of an imbalance between the impulsive and executive systems and namely, a hyperactive impulsive system and a hypoactive executive system.

Limitations and Future Directions

The main limitation of this study exists in the fact that we have collected data from a sample of individuals on Amazon mTurk. Therefore, our participants could be distinctly different from that of the general population and so the results might not directly translate. Additionally, participant inattention may affect the quality of data collected through mTurk (Goodman et al., 2013). However, we used several techniques including the inclusion of mTurk workers with a 90% or greater HIT approval rate, open answered questions, and both automatic and visual inspection of our data for systematic and reasonable data entry. Despite these limitations, data collections through mTurk afforded us the ability to collect a large enough sample size to sufficiently power our study for analysis of the differences of 46 variables between populations with and without obesity. Another limitation of this study is the cross-sectional study design, which does not allow for causal determination. However, this type of study is needed to first identify the neurobehavioral factors that predict obesity. Previous findings from longitudinal studies suggest that the relationship between body weight and neurobehaviors is bidirectional. That is, certain neurobehaviors (e.g., impaired executive function) can predict future body weight outcomes (Guxens et al., 2009; Hartanto et al., 2019; Hofmann et al., 2014), and likewise changes in body weight can lead to changes in neurobehavioral outcomes (Alosco, Galioto, et al., 2014; Alosco, Spitznagel, et al., 2014; Hartanto et al., 2019). Additionally, while the current study investigates a comprehensive range of neurobehaviors related to obesity, it does not account for additional factors, such as genetic susceptibility (Loos, 2012; Loos & Janssens, 2017) or environmental influences (Garfinkel-Castro et al., 2017; Popkin, 2006), that contribute to the development of obesity. The lack of these additional measures may limit the predictive power of the current model, which has a 64.4% accuracy. Given this level of accuracy, this model is limited in its usefulness for individual prediction or diagnosis. Nonetheless, the results

of this investigation provide evidence for the direct and indirect relationships of neurobehaviors to the development of obesity and suggest that improving neurobehaviors may aid in the prevention and/or treatment of obesity. Future studies should now focus on interventional strategies to support weight loss by targeting some of the factors identified in the present study.

At the individual level, combating obesity means significant weight loss brought about by decreasing food consumption and/or increasing physical activity. Altering and accurately tracking these health behaviors (i.e., eating and exercise) has proven challenging in the past, especially for individuals with clinical issues such as those with obesity, diabetes, or heart disease (Vanstone et al., 2013). A benefit of measures such as the ones utilized in the present study is that they can be quickly and easily collected in an office setting, much unlike the tracking of eating and exercise behaviors (Grandjean, 2012; Shim et al., 2014), and repeatedly measured over the course of time. For example, the self-reported measures assessed in the model would take approximately 30 min to complete and could be easily collected via phone or iPad in the waiting room. Our findings regarding the interconnected nature of neurobehaviors and obesity suggest that a strategy that directly targets the neurobehaviors behind overeating and lack of exercises such as cognition, mood, motivation, or impulsivity, might be an effective strategy for combating obesity. Previous literature on interventional strategies supports this idea. One recent meta-analysis and systematic review examined 66 studies that utilized cognitive training to affect eating behaviors and weight loss, finding that inhibition training, attention bias modification training, and episodic future thinking training were the most effective interventions (Yang et al., 2019). Our lab has successfully utilized episodic future thinking, which directly targets DD through the vivid imagining of positive future events, to decrease the demand for food in a hypothetical food purchasing task (Sze et al., 2017), and we are currently using this strategy to improve health behaviors in individuals with type 2 diabetes. Additionally, cognitive-behavioral therapy, which targets mood regulation and self-evaluation, has been recommended as a treatment for obesity and has been shown effective for improving eating behaviors, sustained weight loss, and psychological improvement in individuals with obesity (Braet et al., 2004; Cheroutre et al., 2020; Cooper et al., 2003; Kang & Kwack, 2020; Pekkarinen et al., 1996). We hypothesize that an interventional approach combining episodic future thinking with cognitive-behavioral therapy or other strategies known to improve mood and self-image may be excellent strategies for tackling obesity.

At a societal level, we exist in an environment where engaging in overconsumption of highly palatable, calorically dense foods and remaining sedentary is the easy choice. Contrarily, engaging in healthy eating and exercise behaviors requires both energetic and financial resources. The choice to make the healthy decision in this food-rich environment may be even more challenging for individuals with obesity compared to healthy weight controls. Our Bayesian Network Model suggests that individuals with obesity have an imbalance of key neural circuitry; namely, a hyperactive impulsive decision system and a hypoactive executive decision system. That is, the brains of individuals with obesity respond to the obesogenic environment in a fundamentally different way marked by a heightened response to the available highly palatable foods and a decreased ability to inhibit the response to consume the food. Our data additionally suggest that targeting neurobehavioral factors such as DD, mood, or cognition may help individuals with obesity to make healthy food and exercise choices and decrease their BMI.

Conclusions

Using the framework of the CNDS theory, we hypothesized that individuals with obesity compared to non-obese controls would display neurobehaviors marked by a hyperactive impulsive system and a hypoactive executive system. Results from our Bayesian Network Model supported this hypothesis, showing that obesity is predicted by a distinct neurobehavioral profile that includes heightened DD, impaired motivation, decreased affective state, and poor self-image. Considering that treatment success rates for obesity are low, understanding the neurobehavioral profile that predicts obesity is important to help identify targets to decrease BMI and improve outcomes for this chronic, relapsing, progressive disease. Our results suggest that targeting neurobehaviors such as mood, motivation, impulsivity, and executive function may help to improve obesity outcomes. In order to tackle obesity, which affects approximately 30% of the world population, we must look at this disease from a holistic perspective. Treatments must not simply be about eating less and exercising more. For example, future studies targeting neuromodulation of the prefrontal cortex might be helpful to initiate and sustain weight loss in populations with obesity. In fact, studies have shown promise with techniques such as repetitive transcranial magnetic stimulation (rTMS) or repetitive direct current stimulation (rDCS) of the DLPFC causing a decrease in food craving and calorie consumption and an increase in weight loss, especially long-term protocols (e.g., eight treatments over a course of 4 weeks; Higuera-Hernández et al., 2018; Jáuregui-Lobera & Martínez-Quiñones, 2018; Kim, Chung, et al.,

2019; Kim et al., 2018; Kim, Park, et al., 2019; Lee et al., 2018; Song et al., 2019). Experimental studies using single sessions of neuromodulation on executive control networks have even proven effective at decreasing food craving and consumption in individuals with eating disorders (e.g., BED, overweight, and obesity), suggesting that these techniques could serve as targeted treatments, and complementary treatments to traditional psychotropic medications, to enhance executive functioning in service of optimizing healthy behavioral choices (Fregni et al., 2008; Kekic et al., 2014, 2017; Lowe et al., 2017). Additionally, behavioral treatment interventions that include cognitive-behavioral therapy, episodic future thinking, meditation, cognitive training, or other alternative therapies that have been shown to enhance the functioning of the executive network may be the way of the future for tackling obesity.

Tables

Table 1. Demographic comparison between participants without obesity (n=178) and participants with obesity (n=198)

A) Frequency Table	Non-Obese	Obese	X2/t	p	B) Contingency Table	Non-Obese	Obese	Total n
Mean age	30.89 (0.45)	31.84 (0.48)	-1.443	0.150	n	198	178	376
Household income			0.582	0.747	Household income			
% Low income	25.8	27.5			Low income	51 (52.66) [0.05]	49 (47.34) [0.06]	100
% Middle income	66.2	66.3			Middle income	131 (131.12) [0.00]	118 (117.88) [0.00]	249
% High income	8.1	6.2			High income	16 (14.22) [0.22]	11 (12.78) [0.25]	27
Education			4.477	0.214	Education			
% High school/GED or lower	8.1	8.4			High school/GED or lower	16 (16.32) [0.01]	15 (14.68) [0.01]	31
% Some college	27.8	21.9			Some college	55 (49.50) [0.61]	39 (44.50) [0.68]	94
% College degree	53.5	52.2			College degree	106 (104.79) [0.01]	93 (94.21) [0.02]	199
% Advanced degree	10.6	17.4			Advanced degree	21 (27.38) [1.49]	31 (24.62) [1.66]	52
Employment Status			0.671	0.715	Employment Status			
% Working full time	75.3	78.1			Working full time	149 (151.66) [0.05]	139 (136.34) [0.05]	288
% Working part time	14.6	11.8			Working part time	29 (26.33) [0.27]	21 (23.67) [0.30]	50
% Not working	10.1	10.1			Not working	20 (20.01) [0.00]	18 (17.99) [0.00]	38
Sex			0.100	0.752	Sex			
% Female	44.4	46.1			Female	88 (89.52) [0.03]	82 (80.48) [0.03]	170
% Male	55.6	53.9			Male	110 (108.48) [0.02]	96 (97.52) [0.02]	206
Race			5.405	0.144	Race			
% White/Caucasian	73.7	69.1			White/Caucasian	146 (141.65) [0.13]	123 (127.35) [0.15]	169
% Black/African American	17.7	15.7			Black/African American	35 (33.18) [0.10]	28 (29.82) [0.11]	63
% Asian	6.1	7.9			Asian	12 (13.69) [0.21]	14 (12.31) [0.23]	26
% Other	2.5	7.3			Other	5 (9.48) [2.12]	13 (8.52) [2.35]	18
Ethnicity			0.113	0.737	Ethnicity			
% Hispanic	9.1	10.1			Hispanic	18 (18.96) [0.05]	18 (17.04) [0.05]	36
% Non-hispanic	90.9	89.9			Non-hispanic	180 (179.04) [0.01]	160 (160.96) [0.01]	340

A) Demographic information is reported as the percentage of individuals belonging to each group. B) Demographic information reported as the observed cell totals, (the expected cell totals), and [the χ^2 statistic for each cell]. "Other" race includes those who answered American Indian/Alaskan Native, Pacific Islander, or other. "Not working" includes those who answered not working, laid off, or homemaker.

Table 2. Bayesian Network Model arc strength.

Arc		
From (Predictor)	**To (Outcome)**	**Strength**
Delay Discounting	Affect	58.616361
Delay Discounting	Obesity	46.361231
Eating Attitudes and Motivations	Obesity	41.437493
Exercise Attitudes and Motivations	Affect	31.668234
Exercise Attitudes and Motivations	Obesity	31.527408
Self evaluation	Obesity	31.403465
Eating Attitudes and Motivations	Self evaluation	14.399477
Self evaluation	Affect	8.959232
Affect	Obesity	4.616077

Arc strength represents the change in Bayesian Information Criterion (BIC) after removal of the arc in the Bayesian Network.

Supplementary Table 1. Comparisons between body weight groups on measures of health behaviors.

	Non-Obese	Obese	df	t	p
Eating					
Fat Intake*	24.44 (0.80)	29.12 (0.83)	374	-4.051	<0.001
FV Intake	12.57 (0.44)	12.38 (0.48)	374	0.290	0.772
BEVQ- Total Daily kcal	838.85 (230.32)	1456.47 (424.25)	374	-1.314	0.190
BEVQ- Total Daily grams	3806.39 (385.67)	4958.71 (944.92)	374	-1.171	0.242
Exercise (GPAQ)					
Weekly MET Minutes*	4604.99 (561.03)	2718.84 (394.99)	343.843	2.749	0.006
Sedentary Time (Minutes/Day)	337.16 (13.77)	320.52 (14.95)	371	0.820	0.413

Data reported as Mean (SEM). *p<0.0083

Supplementary Table 2. Comparisons between body weight groups on discounting measures.

	Non-Obese	Obese	df	t	p
Delay Discounting					
Monetary Discounting*	-4.92 (0.18)	-4.12 (0.20)	374	-2.909	0.004
Probability Discounting	1.20 (0.12)	1.08 (0.14)	374	0.678	0.498

Data reported as Mean (SEM). *p<0.025

Supplementary Table 3. Comparisons between body weight groups on eating attitude and motivation measures.

	Non-Obese	Obese	df	t	p
Three-Factor Eating Questionnaire					
Uncontrolled Eating*	18.18 (0.41)	21.74 (0.46)	374	-5.831	<0.001
Emotional Eating*	6.04 (0.19)	7.33 (0.20)	374	-4.684	<0.001
Cognitive Restraint	12.72 (0.26)	12.52 (0.26)	374	0.541	0.589
Power of Food Scale*	35.20 (0.89)	42.30 (1.12)	346.924	-4.974	<0.001
Food Available*	11.88 (0.39)	15.66 (0.50)	343.362	-5.989	<0.001
Food Present*	9.76 (0.30)	12.02 (0.34)	374	-5.004	<0.001
Food Tasted	13.56 (0.33)	14.62 (0.39)	374	-2.096	0.037
Eating Attitudes Test	9.71 (0.85)	12.94 (0.95)	364.451	-2.534	0.012
Dieting	5.39 (0.46)	7.07 (0.51)	374	-2.431	0.016
Bulimia Food Preoccupation*	1.51 (0.23)	3.15 (0.28)	348.149	-4.528	<0.001
Oral Control	2.81 (0.27)	2.72 (0.27)	374	0.218	0.828

Data reported as Mean (SEM). *p<0.0045

Supplementary Table 4. Comparisons between body weight groups on exercise attitude and motivation measures.

	Non-Obese	Obese	df	t	p
Subjective Exercise Experiences Scale					
Positive Wellbeing*	19.28 (0.41)	16.47 (0.47)	374	4.513	<0.001
Psychological Distress*	8.40 (0.41)	11.87 (0.51)	346.275	-5.282	<0.001
Fatigue*	14.64 (0.47)	17.21 (0.48)	374	-3.830	<0.001
Behavioral Regulation of Exercise Questionnaire					
Relative Autonomy Index (RAI)*	7.29 (0.59)	0.96 (0.50)	370.578	8.198	<0.001
Amotivation*	0.79 (0.07)	1.33 (0.09)	361.150	-4.735	<0.001
External Regulation*	0.96 (0.08)	1.31 (0.09)	374	-3.085	0.002
Introjected Regulation	1.58 (0.08)	1.60 (0.09)	374	-0.195	0.845
Identified Regulation*	2.53 (0.07)	1.80 (0.08)	374	6.931	<0.001
Integrated Regulation*	2.10 (0.09)	1.41 (0.09)	374	5.572	<0.001
Intrinsic Regulation*	2.14 (0.09)	1.52 (0.09)	374	5.074	<0.001

Data reported as Mean (SEM). *p<0.005

Supplementary Table 5. Comparisons between body weight groups on executive function measures of the Stroop Task.

	Non-Obese	Obese	df	t	p
Percent Correct	0.91 (0.01)	0.86 (0.02)	250.335	2.726	0.007
Conguent*	0.93 (0.01)	0.87 (0.02)	241.930	2.888	0.004
Incongruent	0.88 (0.01)	0.83 (0.02)	269.392	2.402	0.017
Control	0.93 (0.01)	0.87 (0.02)	254.241	2.651	0.009
Reaction Time	1021.34 (27.47)	982.60 (39.31)	338	0.827	0.409
Congruent	965.80 (26.85)	908.02 (35.88)	338	1.312	0.190
Incongruent	1132.80 (35.03)	1106.94 (49.04)	338	0.438	0.661
Control	974.13 (27.74)	938.66 (40.66)	338	0.739	0.460

Data reported as Mean (SEM). *p<0.00625

Supplementary Table 6. Comparisons between body weight groups on affective state measures.

	Non-Obese	Obese	df	t	p
Anxiety*	10.96 (0.92)	16.13 (1.09)	356.127	-3.623	<0.001
Depression*	10.69 (0.91)	14.35 (1.02)	374	-2.693	0.007
Positive and Negative Affect Schedule					
Positive Affect	31.21 (0.66)	29.93 (0.68)	374	1.354	0.177
Negative Affect	18.12 (0.62)	20.16 (0.70)	374	-2.186	0.029

Data reported as Mean (SEM). *p<0.0125

Supplementary Table 7. Comparisons between body weight groups on self-evaluation measures.

	Non-Obese	Obese	df	t	p
Body Attitudes Test*	26.37 (1.16)	41.35 (1.50)	341.750	-7.899	<0.001
Negative Appreciation*	6.50 (0.48)	14.20 (0.62)	342.615	-9.809	<0.001
Lack Familiarity*	8.23 (0.43)	12.68 (0.56)	341.436	-6.315	<0.001
Body Dissatisfaction*	6.08 (0.30)	9.25 (0.36)	374	-6.859	<0.001
Rest Factor*	5.63 (0.18)	4.92 (0.17)	373.541	2.846	0.005

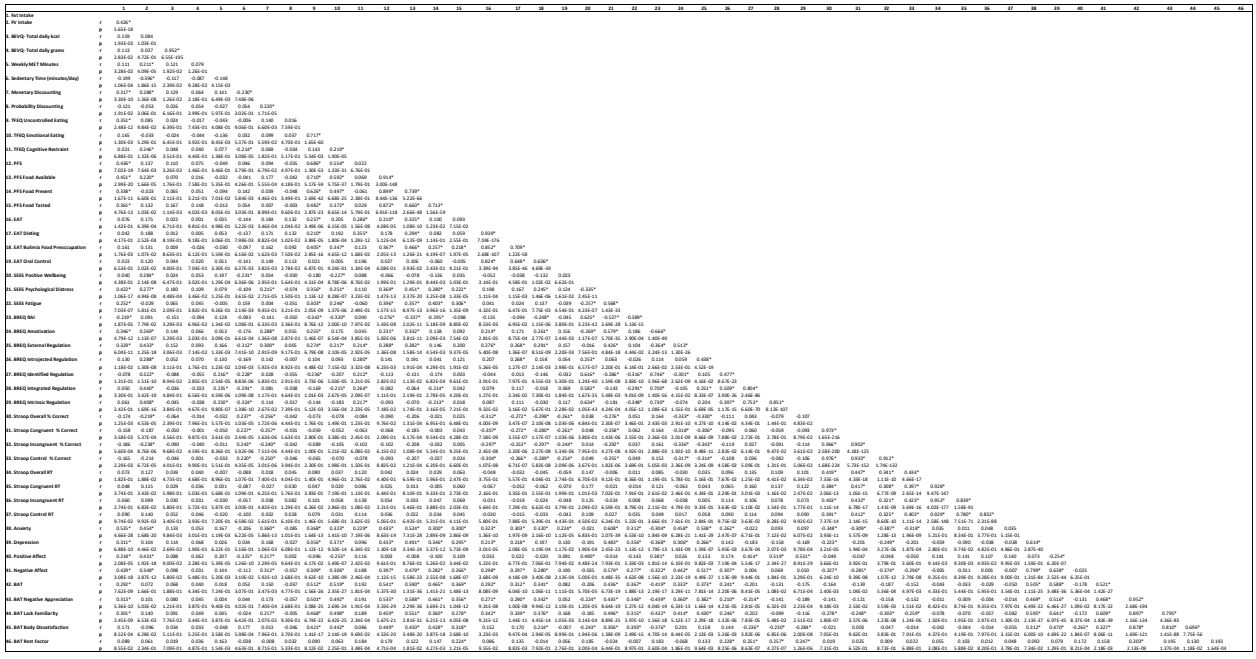
Data reported as Mean (SEM). *p<0.01

Supplementary Table 8. Correlations between BMI and all self-reported measures and cognitive tasks.

Measure	Full Dataset (BMI 15-57)			Excluding BMI<18.5 (BMI 18.5-57)		
	Correlation with BMI	p	Significant?	Correlation with BMI	p	Significant?
Health Behaviors						
Fat Intake	0.189	<0.001	Y	0.206	<0.001	Y
FV Intake	0.007	0.896	N	0.026	0.621	N
BEVQ- Daily kcal	0.065	0.212	N	0.064	0.215	N
BEVQ- Daily grams	0.057	0.271	N	0.055	0.297	N
Weekly MET Minutes	-0.102	0.049	N	-0.117	0.027	N
Sedentary minutes/day	0.030	0.560	N	0.027	0.611	N
Discounting						
Monetary Discounting	0.112	0.031	N	0.136	0.009	Y
Probability Discounting	-0.045	0.379	N	-0.035	0.504	N
Eating Motivations and Attitudes						
TFEQ Uncontrolled Eating	0.280	<0.001	Y	0.326	<0.001	Y
TFEQ Emotional Eating	0.223	<0.001	Y	0.273	<0.001	Y
TFEQ Cognitive Restraint	0.012	0.882	N	0.008	0.876	N
PFS	0.235	<0.001	Y	0.288	<0.001	Y
PFS Food Available	0.270	<0.001	Y	0.315	<0.001	Y
PFS Food Present	0.227	<0.001	Y	0.276	<0.001	Y
PFS Food Tasted	0.120	0.020	N	0.169	0.001	Y
EAT	0.142	0.006	N	0.151	0.004	Y
EAT Dieting	0.131	0.011	N	0.130	0.013	N
EAT Bulimia Food Preoccupation	0.262	<0.001	Y	0.281	<0.001	Y
EAT Oral Control	-0.013	0.808	N	-0.001	0.98	N
Exercise Motivations and Attitudes						
SEES Positive Wellbeing	-0.206	<0.001	Y	-0.21	<0.001	Y
SEES Psychological Distress	0.258	<0.001	Y	0.303	<0.001	Y
SEES Fatigue	0.165	0.001	Y	0.191	<0.001	Y
BREQ RAI	-0.307	<0.001	Y	-0.334	<0.001	Y
BREQ Amotivation	0.223	<0.001	Y	0.266	<0.001	Y
BREQ External Regulation	0.136	0.008	N	0.153	0.003	Y
BREQ Introjected Regulation	0.046	0.378	N	0.042	0.427	N
BREQ Identified Regulation	-0.287	<0.001	Y	-0.298	<0.001	Y
BREQ Integrated Regulation	-0.199	<0.001	Y	-0.210	<0.001	Y
BREQ Intrinsic Regulation	-0.162	0.002	Y	-0.167	0.001	Y
Executive Function (Stroop Task)						
Overall % Correct	-0.101	0.063	N	-0.095	0.085	N
Conguent % Correct	-0.094	0.084	N	-0.087	0.114	N
Incongruent % Correct	-0.100	0.067	N	-0.096	0.08	N
Control % Correct	-0.101	0.063	N	-0.092	0.093	N
Overall Reaction Time (RT)	-0.013	0.806	N	-0.013	0.813	N
Congruent RT	-0.053	0.329	N	-0.054	0.329	N
Incongruent RT	0.013	0.808	N	0.015	0.781	N
Control RT	-0.003	0.957	N	-0.004	0.947	N
Affective State						
Anxiety	0.197	<0.001	Y	0.220	<0.001	Y
Depression	0.129	0.012	Y	0.171	<0.001	Y
Positive Affect	-0.042	0.419	N	-0.036	0.488	N
Negative Affect	0.121	0.019	N	0.150	0.004	Y
Self Evaluation						
BAT	0.401	<0.001	Y	0.428	<0.001	Y
BAT Negative Appreciation	0.484	<0.001	Y	0.508	<0.001	Y
BAT Lack Familiarity	0.323	<0.001	Y	0.355	<0.001	Y
BAT Body Dissatisfaction	0.328	<0.001	Y	0.355	<0.001	Y
BAT Rest Factor	-0.131	0.011	N	-0.12	0.022	N

Bonferroni-corrected significance values: $p<0.0083$ (Health Behaviors); $p<0.025$ (Discounting); $p<0.0045$ (Eating Motivations and Attitudes); $p<0.005$ (Exercise Motivations and Attitudes); $p<0.00625$ (Executive Function); $p<0.0125$ (Affective State); $p<0.01$ (Self Evaluation).

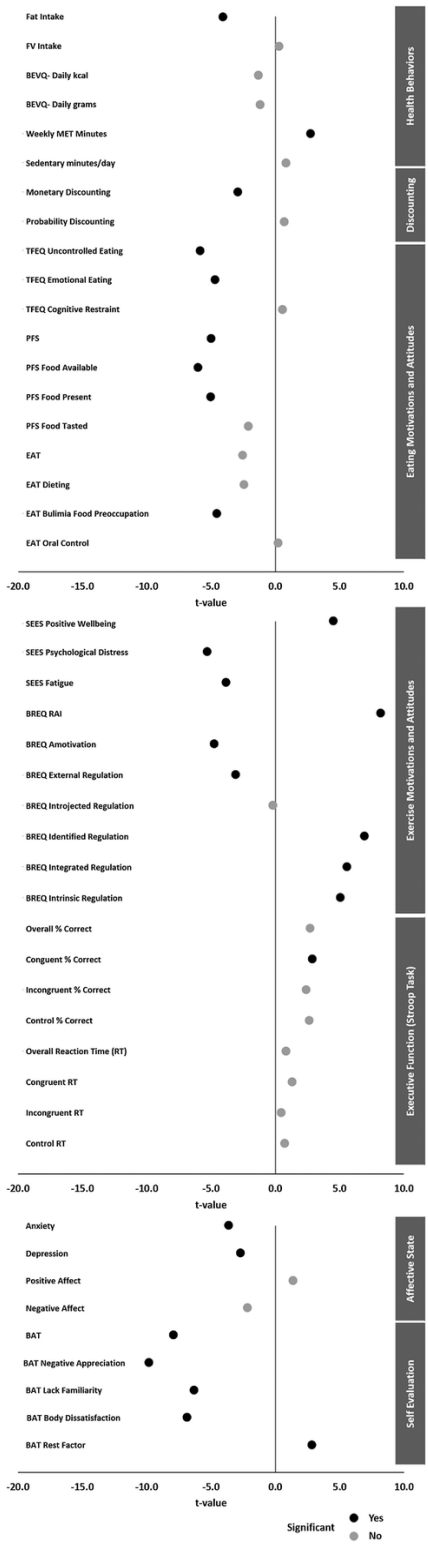
Supplementary Table 9. Correlation matrix of all self-reported measures and cognitive tasks.



*p<4.83E-05 (Bonferroni corrected critical alpha value)

Figures

Figure 1. Plot of t-Statistic for Differences Between Body Weight Groups on All Measures Note. Bonferroni-corrected significance values: $p < .0083$ (health behaviors); $p < .025$ (discounting); $p < .0045$ (eating motivations and attitudes); $p < .005$ (exercise motivations and attitudes); $p < .00625$ (executive function); $p < .0125$ (affective state); $p < .01$ (self-evaluation).


Fat Intake
FV Intake
BEVQ- Daily kcal
BEVQ- Daily grams
Weekly MET Minutes
Sedentary minutes/day
Monetary Discounting
Probability Discounting
TFEQ Uncontrolled Eating
TFEQ Emotional Eating
TFEQ Cognitive Restraint
PFS
PFS Food Available
PFS Food Present
PFS Food Tasted
EAT
EAT Dieting
EAT Bulimia Food Preoccupation
EAT Oral Control
Health Behaviors
Discounting
Eating Motivations and Attitudes
-20.0
-15.0
-10.0
-5.0
0.0
5.0
10.0
t-value
SEES Positive Wellbeing
SEES Psychological Distress
SEES Fatigue
BREQ RAI
BREQ Amotivation
BREQ External Regulation
BREQ Introjected Regulation
BREQ Identified Regulation
BREQ Integrated Regulation
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Overall % Correct
Conguent % Correct
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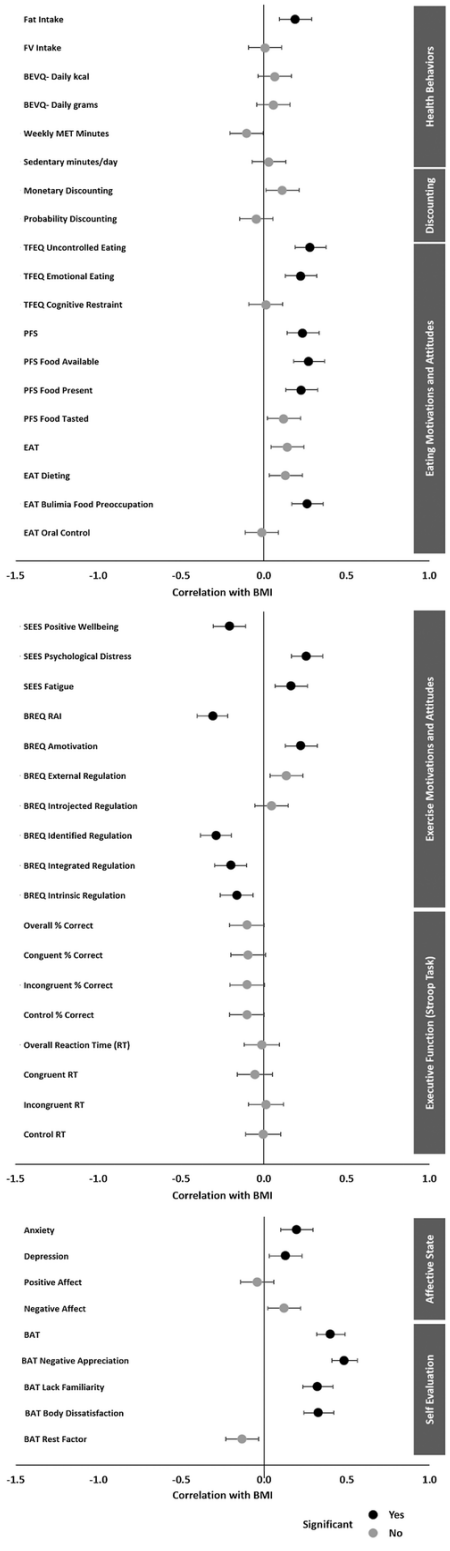
Overall Reaction Time (RT)
Congruent RT
Incongruent RT
Control RT
Exercise Motivations and Attitudes
Executive Function (Stroop Task)
-20.0
-15.0
-10.0
-5.0
0.0
5.0
10.0
t-value
Anxiety
Depression
Positive Affect
Negative Affect
BAT
BAT Negative Appreciation
BAT Lack Familiarity
BAT Body Dissatisfaction
BAT Rest Factor
Affective State
Self Evaluation
-20.0
-15.0
-10.0
-5.0
0.0
5.0
10.0
t-value
Significant
Yes
No

Figure 2. Plot of Correlations Between BMI and All Measures. Error Bars Represent 95% Confidence Intervals Note. Bonferroni-corrected significance values: $p < .0083$ (health behaviors); $p < .025$ (discounting); $p < .0045$ (eating motivations and attitudes); $p < .005$ (exercise motivations and attitudes); $p < .00625$ (executive function); $p < .0125$ (affective state); $p < .01$ (self-evaluation).


Fat Intake
FV Intake
BEVQ- Daily kcal
BEVQ- Daily grams
Weekly MET Minutes
Sedentary minutes/day
Monetary Discounting
Probability Discounting
TFEQ Uncontrolled Eating
TFEQ Emotional Eating
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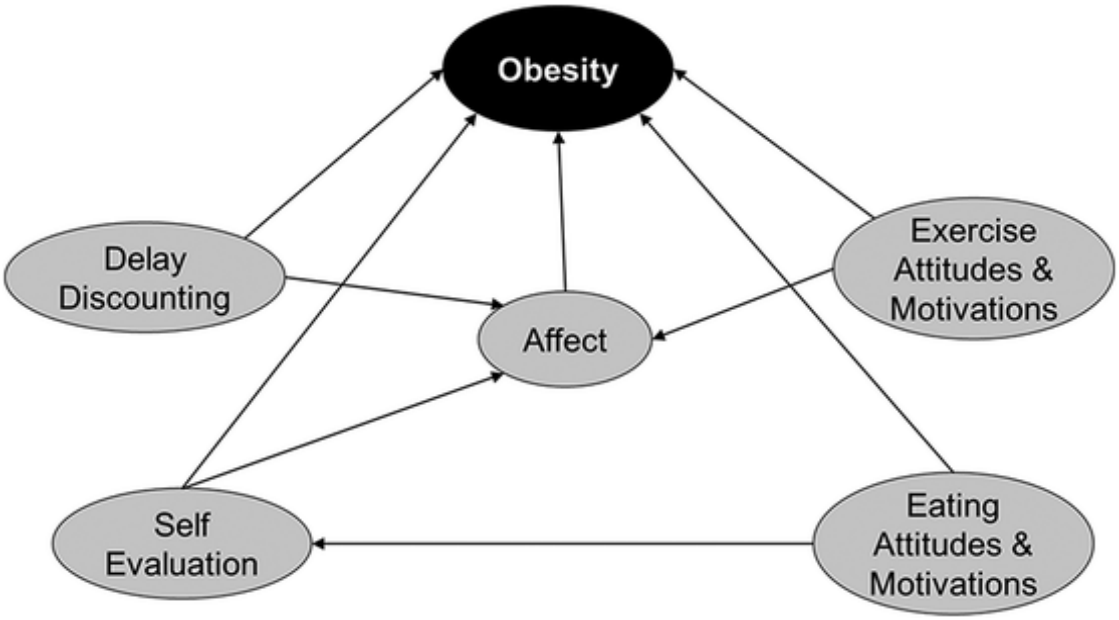
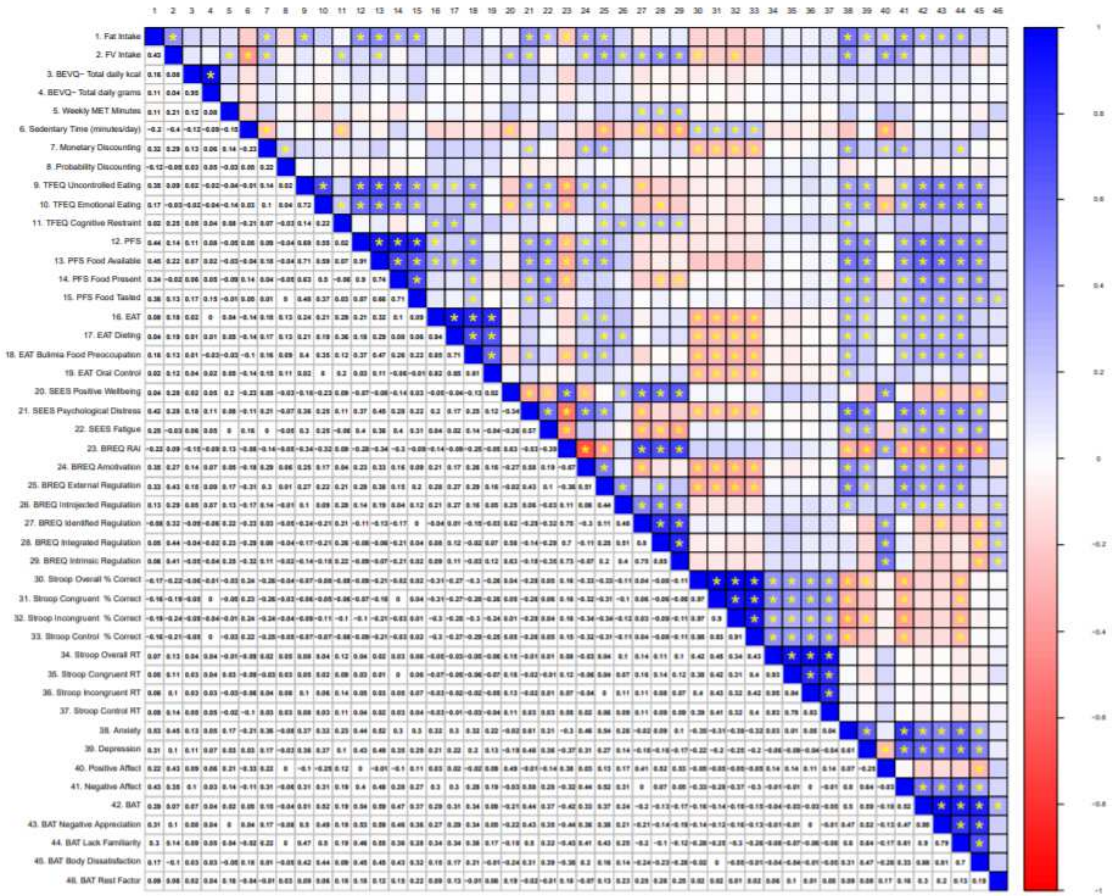
PFS
PFS Food Available
PFS Food Present
PFS Food Tasted
EAT
EAT Dieting
EAT Bulimia Food Preoccupation
EAT Oral Control
Health Behaviors
Discounting
Eating Motivations and Attitudes
-1.5
-1.0
-0.5
0.0
0.5
1.0
Correlation with BMI
SEES Positive Wellbeing
SEES Psychological Distress
SEES Fatigue
BREQ RAI
BREQ Amotivation
BREQ External Regulation
BREQ Introjected Regulation
BREQ Identified Regulation
BREQ Integrated Regulation
BREQ Intrinsic Regulation
Overall % Correct
Conguent % Correct
Incongruent % Correct
Control % Correct
Overall Reaction Time (RT)
Congruent RT
Incongruent RT
Control RT
Exercise Motivations and Attitudes
Executive Function (Stroop Task)
-1.5
-1.0
-0.5
0.0
0.5
1.0
Correlation with BMI
Anxiety
Depression
Positive Affect
Negative Affect
BAT
BAT Negative Appreciation
BAT Lack Familiarity
BAT Body Dissatisfaction
BAT Rest Factor
Affective State
Self Evaluation
-1.5
-1.0
-0.5
0.0
0.5
1.0
Correlation with BMI
Significant
Yes
No

Figure 3. Tree Augmented Naïve Bayesian Network Model of Neurobehaviors Accurately Predicting 64.4% Cases of Obesity



Supplementary Figure 1. Heat map correlation matrix of all self-reported measures and cognitive tasks.



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CHAPTER 3
CHANGES IN TEMPORAL DISCOUNTING, HEDONIC HUNGER, AND FOOD ADDICTION DURING RECOVERY FROM SUBSTANCE MISUSE

Abstract

Substance use disorders (SUDs) and obesity are both chronic, relapsing, remitting disorders that arise from a heightened preference for immediate-focused rewards (i.e., steep temporal discounting). During recovery from SUDs, overweight and obese outcomes are common as individuals may replace drug rewards for food rewards. However, little has been done to investigate the neuropsychological processes underlying food reward and addiction in individuals recovering from SUDs. Using data collected from the International Quit and Recovery Registry and Amazon Mechanical Turk, we aimed to elucidate the factors that influence the attraction to palatable foods in a population in recovery from substance misuse (n=114) as well as a population with no history of substance misuse (n=97). We hypothesized that individuals in recovery from substance misuse would have steeper temporal discounting, an increased drive for palatable foods (i.e., hedonic hunger), and greater food addiction symptoms than non-substance users. Contrary to our hypotheses, we found that individuals in recovery from SUDs show improved outcomes in temporal discounting, hedonic hunger, and food addiction symptoms. Moreover, recovery status and temporal discounting significantly predicted these outcomes. Our findings suggest that the enhanced executive control processes needed for successful SUD recovery may transfer to other reward-related processes such as food reward and consumption. Interventions targeted at improving executive function including episodic future thinking, meditation, or exercise, may be excellent ways to support a successful recovery and improve other reward-related processes, including food consumption, to decrease the risk of overweight or obese outcomes during recovery.

Introduction

Body weight gain and quality of food intake are significant concerns amongst individuals in recovery from substance use disorders (SUDs). Research has shown that during recovery from SUDs, individuals may engage in unhealthy eating behaviors, replacing their drug of choice or responding to drug or alcohol craving by consuming highly palatable foods, especially those high in fat and sugar (Hodgkins et al., 2003; Jackson & Grilo, 2002). Additionally, dysfunctional eating patterns and disordered eating, such as bulimia nervosa and binge eating disorder, are often seen

early in recovery (Cowan & Devine, 2008; Hodgkins et al., 2004; Jackson & Grilo, 2002; Orsini et al., 2014; Williamson et al., 1991). Stress and anxiety, commonly experienced during withdrawal and early recovery, are additional factors that contribute to uncontrolled eating behaviors (Koob & Volkow, 2016). The unhealthy eating behaviors experienced early in recovery can lead to weight gain and overweight or obese outcomes, which can in turn lead to other serious health conditions such as Type 2 diabetes or cardiovascular disease (Cowan & Devine, 2008). Therefore, determining the neuropsychological factors that contribute to increased food consumption is imperative.

SUDs and overeating, which can lead to obesity, involve overlapping behavioral- and endophenotypes, with some hypothesizing that obesity is a form of food addiction (Campana et al., 2019; Ferrario, 2017; Lerma-Cabrera et al., 2016). However, this hypothesis is not without controversy and recent research suggests that limited behavioral overlap exists between obesity and SUDs (Bickel et al., in press.; Vainik et al., 2020). Several convincing pieces of evidence exist to support the food addiction hypothesis. First, drugs of abuse and palatable foods are both strong positive reinforcers that activate the brain's reward system, including the nucleus accumbens and prefrontal cortex (Volkow, Wang, Fowler, et al., 2008; Volkow & Wise, 2005). Second, research shows that individuals with both SUDs and overeating display increased impulsivity, altered affective and cognitive states, and heightened reward salience and consummatory behavior of their substance of choice (Michaud et al., 2017). Third, overlapping alterations in neural structure and function exist between these two disorders. For example, microdialysis studies in rodents have shown that both drugs of abuse and highly palatable foods stimulate extracellular dopamine release in the nucleus accumbens (Di Chiara, 2002; Roitman et al., 2004). Neuroimaging studies in humans have also revealed that both individuals with SUDs and individuals with obesity display a reduction of dopaminergic D2 receptors in the striatum (Trifilieff & Martinez, 2014; Volkow et al., 2009; Volkow, Wang, Telang, et al., 2008; Wang et al., 2001) as well as reduced neural activity in prefrontal regions including the dorsolateral prefrontal cortex, orbitofrontal cortex, and cingulate gyrus (Volkow et al., 2009; Volkow, Wang, Telang, et al., 2008). Considering this interesting interrelationship, the examination of food salience and food addiction during recovery from SUDs is a relevant area of inquiry.

The Competing Neurobehavioral Decision Systems (CNDS) theory posits that the reward-driven impulsive system and the future-oriented executive system work in conjunction to govern

behavior (Bickel et al., 2018). The impulsive system consists of limbic and paralimbic brain regions (e.g., nucleus accumbens, amygdala), and the executive system consists of prefrontal and temporal regions (e.g., prefrontal cortex, hippocampus). Dysregulation of these systems, namely a hyperactive reward system and hypoactive executive system, leads to maladaptive health behaviors including both substance use and overeating (Bickel et al., 2021; Kekic et al., 2019; Levitt et al., 2020). Behaviorally, the balance between the two systems can be measured using a temporal discounting task termed delay discounting, which assesses an individual's preference for smaller, immediate rewards compared to larger, delayed rewards (McClure et al., 2004). Here, we use the framework of the CNDS theory to examine the hypothesis that heightened temporal discounting may underlie the heightened response to highly palatable foods during recovery and increased body weight.

Using data collected from the International Quit and Recovery Registry (IQRR; www.quitandrecovery.org) and Amazon Mechanical Turk (mTurk), we aimed to elucidate the neuropsychological factors that influence the attraction to palatable foods in a population in recovery from substance misuse as well as a population with no history of substance misuse. Specifically, we examined hedonic hunger and food addiction as metrics of food reward. Hedonic hunger refers to the preoccupation with and desire to consume foods for pleasure in the absence of hunger (Espel-Huynh et al., 2018), whereas food addiction (as measured by the Yale Food Addiction Scale) examines the DSM-IV criteria of substance dependence in relation to high-fat, high-sugar foods. We hypothesized that individuals in recovery from substance misuse would have an increased drive for palatable foods (i.e., hedonic hunger), greater symptoms of food addiction, and greater temporal discounting compared to non-substance users. We expected that temporal discounting and recovery status would predict food addiction symptoms, hedonic hunger, and body mass index (BMI).

Methods

Data were collected through the IQRR, an online community and registry for individuals in self-reported recovery from substance misuse or behavioral addictions. The initial assessment, completed upon registration, includes contact information, demographic information, and history of substance use and behavioral addictions. After registering, members may complete assessments that aim to advance the understanding of phenotypes of recovery. Participants earn a predefined number of points for completion of each assessment, which are redeemable for $1.00 per 100

points. The current investigation includes data from the initial assessment, which was completed upon registration, and 3 monthly assessments, all of which were programmed and administered through LimeSurvey.

Data for the non-SUD control group were collected through Amazon Mechanical Turk (mTurk), an online crowdsourcing platform that allows members to complete Human Intelligence Tasks (HITs) for compensation. The task was available to mTurk workers with a high (>90%) HIT approval rate, indicating that they provided high-quality data on at least 90% of previously completely HITs. Participants were screened to ensure they met inclusion criteria. To be included in the study, participants needed to be non-smokers, and have no self-reported history of substance abuse or over-consumption. History of substance abuse and overconsumption was assessed using three questions: 1) "Are you currently, or have you in the past been abusing alcohol or drugs?"; 2) "Do you now think, or have you in the past thought you may be over-consuming drugs or alcohol?"; and 3) "Are you currently in recovery from substance use or addiction?". Participants who responded "No" to all three questions qualified for the study. Participants were compensated for completion of the questionnaire and awarded bonus compensation if their data passed attention checks. All questions were programmed and administered through Qualtrics.

This study was approved by the Institutional Review Board at Virginia Polytechnic Institute and State University and was performed in accordance with relevant guidelines and regulations.

Measures

Demographics: Demographics were collected in the IQRR initial assessment, and collected after screening questions on mTurk as demographics have been previously associated with temporal discounting (Bickel et al., 2014; Stanger et al., 2012) and BMI (Berry et al., 2010; Claassen et al., 2019). Demographic information collected includes age, gender, race, ethnicity, education, and income. Age in the IQRR sample was calculated by subtracting the participant's year of birth from the year the assessment was completed.

Abstinence duration: Self-reported quit date was collected in the IQRR initial assessment. In the current assessment, participants were asked whether they have engaged in their primary substance since registering in the IQRR. Those who answered yes were subsequently asked if their use was ongoing. Those who answered "No" were asked to report an updated quit date. The most recent quit date was subtracted from the assessment completion date to calculate the number of

days in abstinence. Participants who reported a quit date that was the same day that they completed the assessment were considered ongoing users.

Body mass index (BMI): BMI was calculated from self-reported height in inches and weight in pounds as: BMI = weight / [height]^2 x 703.

Food addiction: The Yale Food Addiction Scale is a valid and reliable (Kuder-Richardson alpha=0.86) self-report questionnaire to assess symptoms and diagnosis of food addiction (Gearhardt et al., 2009). The questionnaire consists of 25 items that probe the DSM-IV criteria of substance dependence in relation to the consumption of high-fat, high-sugar foods. Items are scored for a symptom count ranging from 0-7. A diagnosis of food addiction occurs when clinical significance is indicated, and the symptom count is at least 3.

Hedonic hunger: The Power of Food Scale is a valid and reliable (Cronbach's alpha=0.91; test-retest reliability r=0.77) self-report questionnaire to assess hedonic hunger in food-rich environments (Cappelleri et al., 2009; Lowe et al., 2009). The questionnaire consists of 15 items scored from 1 (*don't agree at all*) to 5 (*strongly agree*). Items are summed for a total score, ranging from 15-75, and three subscale scores including food available (range 6-30), food present (range 4-20), and food tasted (range 5-25). The full text of the questionnaire is available in Cappelleri et al. (2009).

Temporal Discounting: The five-trial adjusting delay discounting task was used to assess future valuation and impulsivity (Koffarnus & Bickel, 2014). In this task, participants were asked if they would rather receive $500 now or $1000 in three weeks. The time delay in the subsequent trial is increased or decreased based on the participant's response. The delays continue to adjust in this manner for a total of five trials. The delay at which the reward loses 50% of its value compared to the immediate reward (ED_{50}) is provided by the indifference point. The inverse of the ED_{50} ($1/ED_{50}$) was calculated to provide an estimate of the discount rate (k). The natural log transformed discount rate [ln(k)] was used for analysis.

Data cleaning and statistics

Participants who did not complete all questionnaires, provided an invalid BMI, reported a primary behavioral addiction in the IQRR, were ongoing substance users, or who did not pass attention checks were excluded from all analyses. In the case of multiple submissions, only one record from each participant was included in the analyses.

Chi-square tests of independence were performed to compare the distributions of gender, race, ethnicity, household income, and education between individuals in recovery and the non-SUD control group. Independent samples t-tests were conducted to compare continuous variables including age, BMI, food addiction symptoms, hedonic hunger, and temporal discounting between groups. If a variable had unequal variance between groups, as determined by Levene's test for homogeneity of variance, Welch's t-test was used. ANCOVA was used to compare food addiction symptoms, hedonic hunger, and temporal discounting between groups after controlling for significant demographic variables. Multiple linear regression analyses were conducted to assess the association of recovery status and temporal discounting to food addiction symptoms, hedonic hunger, and BMI. Additionally, demographics (i.e., age, gender, race, household income, education) were included in multiple linear regressions to assess the association of recovery status and temporal discounting to food addiction symptoms, hedonic hunger, and BMI after adjusting for these demographic variables. Relationships among all neuropsychological variables, BMI, and time in abstinence were probed using Pearson correlations. All analyses were conducted in SPSS Statistics 26.0 with statistical significance determined at an alpha level of 0.05.

Results

Demographics

The final analysis included 211 participants (97 non-SUD controls, 114 in recovery). Participant characteristics are displayed in Table 1. Age ($t(187.9)=-6.770$, $p<0.001$), gender ($X^2(2)=17.780$, $p<0.001$), race ($X^2(3)=16.446$, $p<0.001$), household income ($X^2(5)=22.872$, $p<0.001$), and education ($X^2(3)=43.821$, $p<0.001$) were significantly different between groups.

Between groups comparisons

Independent samples t-tests showed that individuals in recovery have significantly fewer food addiction symptoms ($t(189.5)=3.396$, $p<0.001$), and lower hedonic hunger ($t(209)=5.489$, $p<0.001$), including when food is available ($t(209)=3.608$, $p<0.001$), present ($t(209)=4.597$, $p<0.001$), and tasted ($t(209)=7.640$, $p<0.001$) compared to the control group (Figure 1, Table 2). Additionally individuals in recovery have significantly lower rates of temporal discounting ($t(209)=3.038$, $p=0.003$) (Figure 1, Table 2).

After controlling for significant demographic characteristics, between groups comparisons revealed that individuals in recovery have significantly lower hedonic hunger ($F(1, 204)=12.160$, $p<0.001$) including when food is present ($F(1, 204)=10.531$, $p=0.001$) and food is tasted ($F(1,$

204)=31.723, p<0.001) (Table 3). No significant differences were observed between groups in food addiction symptoms (F(1, 204)=1.077, p=0.301) or temporal discounting (F(1, 204)=0.309, p=0.579) (Table 3).

Correlations

Pearson correlation analysis revealed that food addiction symptoms were significantly correlated with hedonic hunger (r=0.640, p<0.001) and temporal discounting (r=0.216, p=0.002), and hedonic hunger was significantly correlated with temporal discounting (r=0.222, p=0.001). Additionally, abstinence duration was positively correlated with BMI (r=0.220, p=0.019) and negatively correlated with temporal discounting (r=-0.282, p=0.002) (Table 4).

Regression models

The unadjusted regression model of temporal discounting and recovery status predicting food addiction symptoms was significant (F(2, 208)=9.459, p<0.001) and explained 7.5% of the variance in the outcome. The model indicated that temporal discounting (t=2.599, p=0.010) and recovery status (t=-2.879, p=0.004) were significant predictors of food addiction symptoms (Table 3). After adjusting for demographic variables, the overall model was significant (F(7, 203)=4.873, p<0.001) and explained 11.4% of the variance in the outcome. Temporal discounting (t=1.293, p=0.197) and recovery status (t=-0.989, p=0.324) did not significantly predict food addiction symptoms in the adjusted model (Table 5).

The unadjusted regression model of temporal discounting and recovery status predicting hedonic hunger was significant (F(2, 208)=18.214, p<0.001), and explained 14.1% of the variance in the outcome. The model indicated that temporal discounting (t=2.373, p=0.019) and recovery status (t=-4.943, p<0.001) were significant predictors of hedonic hunger (Table 4). After adjusting for demographic variables the overall model was significant (F(7,203)=7.805, p<0.001) and explained 18.5% of the variance in the outcome. Recovery status (t=-3.449, p=0.001), but not temporal discounting (t=0.871, p=0.385), was significantly associated with hedonic hunger in the adjusted model (Table 6).

The unadjusted (F(2, 208)=0.660, p=0.518) and adjusted (F(7, 203)=1.510, p=0.166) regression models of temporal discounting and recovery status predicting BMI were not statistically significant (Table 7).

Discussion

Recent work has identified that drugs of abuse and food, especially high calorically dense foods, activate similar reward circuitry of the brain, with some even conceptualizing obesity as a food addiction. During recovery from SUDs, overweight and obese outcomes are common as individuals may replace drug reward for food reward. However, little has been done to investigate hedonic hunger and food addiction symptoms in individuals recovering from SUDs. Considering that our work and others have shown that steep temporal discounting is a trans-disease process that underlies both SUD and obesity (Bickel et al., 2019, 2021), we were interested in investigating the relationship between temporal discounting, hedonic hunger, and food addiction symptoms in a group of individuals abstinent from substance misuse and non-substance users. Therefore, in this cross-sectional investigation, we utilized regression analyses to examine the predictive validity of recovery status and temporal discounting on hedonic hunger and food addiction symptomatology. We found that individuals in recovery from SUDs show improved outcomes in temporal discounting, hedonic hunger, and food addiction symptoms and that both recovery status and temporal discounting significantly predicted these outcome measures, which we hypothesize are due to the enhanced executive abilities needed to sustain abstinence. We also show that these effects are significantly affected by demographic variables. We discuss how our findings relate to the current literature as well as the clinical implication of these findings.

Recovery status predicts decreased hedonic hunger and food addiction symptoms

Our results revealed that recovery status predicts both hedonic hunger and food addiction symptoms. Specifically, compared to non-SUD controls, individuals in SUD recovery display lower levels of hedonic hunger as well as lower levels of food addiction, though the latter effect dissipated after controlling for demographic variables. This is the first time that hedonic hunger and food addiction have been examined in a group of individuals in recovery from SUDs. These findings suggest that somewhere in the process of active SUD or SUD recovery, changes in the reward-related response to food may occur, though future longitudinal, controlled studies will be needed to investigate this relationship.

Some have conceptualized that SUDs and obesity share many overlapping behavioral phenotypes and that obesity may be a food addiction (Blanco-Gandía et al., 2020; Ifland et al., 2009; Takgbajouah & Buscemi, 2021). Specifically, both drugs of abuse and food activate similar brain circuitry (i.e., the mesocortical pathway). The motivational drive that supports drug/food seeking and consumption is regulated by these dopaminergic pathways. Repeated consumption of

drugs or food (especially high-calorically dense foods) alter the dopaminergic circuitry and response, causing habitual and inflexible responses that lead to SUD or obesity, respectively (Alonso-Alonso et al., 2015; Volkow et al., 2011, 2017). To this point, animal studies have shown that cross-sensitization occurs between drugs of abuse and food (Le Merrer & Stephens, 2006), additionally suggesting that the brain changes induced by substances may cause behavioral alterations to food reward and responsivity. In addition, SUDs are associated with a variety of physical changes that affect food consumption and absorption. For example, SUDs are associated with altered levels of hunger, impaired taste, malnutrition, constipation, damaged stomach lining, and altered metabolism and hormonal regulation. These physical changes in turn affect food-related brain processes, contributing to the interaction between drugs and food. During recovery from SUDs, these physical aspects may begin to improve as the maladaptive behavior of drug use is replaced by healthier behaviors such as improved eating, which again in turn cause changes to the brain (Mahboub et al., 2020; Neale et al., 2012).

In the present study, we investigated two aspects of food reward: hedonic hunger and food addiction. Food addiction is associated with increased BMI, obesity, and binge eating disorder (Burrows et al., 2017; Davis et al., 2011; Gearhardt et al., 2014; Ivezaj et al., 2016). Similarly, hedonic hunger is affected by food consumption and is known to be heightened in individuals with obesity (Rabiei et al., 2019; Ribeiro et al., 2018). Additionally, weight loss during weight loss interventions results in decreased hedonic hunger (O'Neil et al., 2012; Theim et al., 2013), indicating that hedonic hunger may be a flexible process that is associated with improved outcomes during recovery from obesity. Here, we newly show that in the process of recovery from SUDs, hedonic hunger and food addiction may show similar decreases as during recovery from obesity.

Others have investigated food preference, choice, and consumption in individuals in SUD recovery. For example, several studies have shown that individuals in SUD recovery show preference for and heightened consumption of sweet and high-calorically dense foods, especially in the early stages of recovery (Gambera & Clarke, 1976; Janowsky et al., 2003; Kampov-Polevoy et al., 2001; Nolan & Scagnelli, 2007). Additionally, a recent study found that individuals in treatment for SUD, compared to the general population, showed significantly higher food cravings and positive emotional eating as well as theoretical energy consumption in an online food choice task (i.e., all-you-can-eat buffet task) (Nolan, 2019). Though our findings seem contrary to this work, our population of individuals in recovery include those individuals who have from 1 day to

43.2 years of abstinence with an average of 8.4 (±1.01) years. This other work examined individuals who were early in recovery, when brain function is impaired by recent drug use, and decision-making processes are geared towards immediate gratification. Therefore, our work suggests that distinct changes in food reward and addiction may occur over the course of recovery.

Steep temporal discounting predicts heightened hedonic hunger and food addiction symptoms

As hypothesized, temporal discounting predicted hedonic hunger and food addiction symptomatology, although these effects dissipated after adjusting for demographics. Specifically, steep temporal discounting was associated with heightened levels of hedonic hunger and food addiction. Our group and others have previously found that temporal discounting, a behavioral indicator of the balance between the executive and reward systems, is associated with heightened hedonic hunger and food addiction (Satyal, Basso et al., 2021; VanderBroek-Stice et al., 2017), though this is the first time this relationship has been investigated in individuals recovering from substance misuse.

We additionally found that abstinent individuals with a history of substance misuse discount the future less than non-substance users. Further, we found that as time in recovery progresses, the discounting rate decreases. This is in line with previous findings indicating that individuals who discount less may be more likely to succeed in abstaining from substances (Sheffer et al., 2014; Stanger et al., 2012; Washio et al., 2011). This finding is akin to one of our recent cross-sectional studies comparing individuals who maintained substantial weight loss to weight-matched controls, showing that the weight loss maintenance group discounted the future less (Bickel et al., 2018). These findings suggest that individuals in recovery (either from drugs or overeating) show heightened executive control processes. As individuals with SUDs are hypersensitive to drug rewards (Kalivas & Volkow, 2005; Lawn et al., 2015), this enhanced level of executive control is needed to successfully resist the urge to consume drug rewards and maintain abstinence. If steep temporal discounting is a driver of hedonic hunger and food addiction, and temporal discounting is heightened during the early stages of recovery, then interventions that target temporal discounting, such as episodic future thinking, may help to improve food salience and eating behaviors in early recovery.

No association between BMI and temporal discounting or recovery status

Contrary to our initial hypothesis, there was no association between temporal discounting or recovery status and BMI. A recent meta-analysis found that about half of existing studies found

a positive association between temporal discounting and body weight while the other half found no association (Tang et al., 2019). The current study adds a sample of individuals in SUD recovery to this body of literature. Although some have reported weight gain during recovery (Nolan, 2013), no difference in BMI has been reported in other samples of individuals in SUD recovery compared to the general population (Nolan, 2019). In the current study, both the recovery and control groups have an average BMI that is considered overweight and is slightly lower than the average BMI of the general U.S. population (Fryar et al., 2018).

Demographic variables influenced our outcomes of interest

Our findings indicate that our outcomes were significantly affected by demographic variables. Specifically, our regression models revealed that age was significantly associated with food addiction symptoms and BMI, education was significantly associated with food addiction symptoms, and race was significantly associated with hedonic hunger in this dataset. Despite these associations between demographic variables and outcomes, some demographic variables may not be determinants of the independent and/or dependent variables and therefore may not truly be sources of confounding bias (Bartram, 2021). For instance, socioeconomic measures such as education have been previously associated with temporal discounting (Bickel et al., 2014). However, it is unclear whether education determines, per se, temporal discounting or the dependent variables in our models (e.g., food addiction, hedonic hunger, BMI). Therefore, we have provided results from all analyses both with and without controlling for demographic variables.

Limitations and future directions

While this study provides new insights into the relationships among recovery status, temporal discounting, and psychological responses to food, several limitations are worth noting. Participants recruited from the IQRR may not accurately represent the general SUD recovery population. As many IQRR members join the registry as a source of accountability and/or inspiration, the results of this study may reflect individuals in recovery who are prone to seek support. Similarly participants recruited from mTurk may not accurately represent the general population. Although mTurk produces reliable data, some characteristics of mTurk participants may differ from traditional samples (Behrend et al., 2011; Goodman et al., 2013). Additionally, characteristics of both traditional and mTurk sample characteristics may differ from characteristics of the general population. For example, the control group in this study, which was collected on

mTurk, is 32% female and 10.3% Hispanic whereas the general U.S. population is 50.8% female and 18.5% Hispanic (United States Census Bureau, n.d.).

The cross-sectional design of our study limits the ability to examine these relationships over time and to establish causality or temporal relationships among outcomes. Future longitudinal investigations are warranted to examine food addiction symptomatology, hedonic hunger, temporal discounting, and BMI in a repeated-measures design to clarify the trajectory of these outcomes throughout SUD recovery and abstinence. Future research may also investigate these outcomes specifically in users of different substances (e.g., alcohol, stimulants).

Conclusions

In this cross-section study, we found that both recovery status and temporal discounting predicted hedonic hunger and food addiction symptoms, though these predictive relationships were significantly affected by demographic characteristics. Our results support the idea that drugs of abuse and food engage similar brain circuitry and that individuals in recovery from SUDs may experience changes in not only drug-related reward processes but food-related reward processes as well. Our findings suggest that individuals in recovery from SUD actually show improved outcomes in temporal discounting as well as hedonic hunger and food addiction. This may be due to the fact that our dataset included individuals who were abstinent with a range of times in recovery up to 43.2 years (mean 8.4 years), rather than including individuals only early in recovery. Our findings suggest that the enhanced executive control processes needed for successful SUD recovery may transfer to other reward-related processes such as food reward and consumption. Indeed, previous research has shown that executive function improves over the course of recovery from SUDs, and our data support the idea that this executive recovery may support other reward-related processes as well. Additionally, considering that steep temporal discounting was associated with food addiction symptoms, our results support the idea that interventions targeted at improving executive function including episodic future thinking, meditation, or exercise may be excellent ways to support a successful recovery and improve in other reward-related processes including food consumption in support of decreasing the risk of overweight or obese outcomes during recovery.

Tables

Table 1. Participant Characteristics.

	Non-SUD	Recovery	t/X2	p
N	97	114		
Age[1]	32.6 (0.95)	44.5 (1.48)	-6.770	<0.001
BMI[1]	26.6 (0.58)	27.3 (0.57)	-0.816	0.416
Days Abstinent[1,2]	-	3071.9 (369.77)	-	-
Gender			17.780	<0.001
% Female	31 (32.0%)	64 (56.1%)		
% Male	66 (68.0%)	46 (40.4%)		
% Other/Prefer not to answer	0 (0.0%)	4 (3.5%)		
Race			16.446	<0.001
% Asian	32 (33.0%)	13 (11.4%)		
% Black/African American	8 (8.2%)	7 (6.1%)		
% White/Caucasian	51 (52.6%)	80 (70.2%)		
% Other[3]	6 (6.2%)	14 (12.3%)		
Ethnicity			1.904	0.168
% Hispanic	10 (10.3%)	6 (5.3%)		
% Non-Hispanic	87 (89.7%)	108 (94.7%)		
Household income			22.872	<0.001
% <$30,000	24 (24.7%)	45 (39.5%)		
% $30,000-$49,999	25 (25.8%)	16 (14.0%)		
% $50,000-$69,999	12 (12.4%)	8 (7.0%)		
% $70,000-$89,999	16 (16.5%)	11 (9.6%)		
% $90,000+	20 (20.6%)	20 (17.5%)		
% Prefer not to answer	0 (0.0%)	14 (12.3%)		
Education			43.821	<0.001
% High school/GED or lower	7 (7.2%)	32 (28.1%)		
% Some college	14 (14.4%)	34 (29.8%)		
% Bachelor's degree	64 (66.0%)	25 (21.9%)		
% Advanced degree	12 (12.4%)	23 (20.2%)		

[1]All variables are reported as frequencies and percentages with the exception of age, BMI, and days since last use which are reported as the mean and standard error.

[2]No statistical tests reported for days since last use as it is only collected in the recovery group.

[3]Other race includes those who identified as American Indian/Alaskan Native, Native Hawaiian/Pacific Islander, more than one race, and Other.

Table 2. Between-groups (non-SUD vs recovery) comparisons of neuropsychological measures.

	Non-SUD	Recovery	df	t	p
Food Addiction Symptoms**	2.73 (0.192)	1.90 (0.151)	189.5	3.396	<0.001
Hedonic Hunger**	44.59 (1.423)	33.93 (1.317)	209	5.489	<0.001
Food Available**	15.92 (0.685)	12.68 (0.589)	209	3.608	<0.001
Food Present**	12.37 (0.422)	9.65 (0.411)	209	4.597	<0.001
Food Tasted**	16.30 (0.429)	11.57 (0.439)	209	7.640	<0.001
Temporal Discounting**	-3.92 (0.292)	-5.07 (0.252)	209	3.038	0.003

Data is presented as Mean (SEM). **p<0.01

Table 3. Between-groups (non-SUD vs recovery) comparisons of neuropsychological measures controlling for age, gender, education, income, and race.

	Non-SUD	Recovery	F	p
Food Addiction Symptoms	2.73 (0.192)	1.90 (0.151)	1.077	0.301
Hedonic Hunger**	44.59 (1.423)	33.93 (1.317)	12.160	<0.001
Food Available	15.92 (0.685)	12.68 (0.589)	2.130	0.146
Food Present**	12.37 (0.422)	9.65 (0.411)	10.531	0.001
Food Tasted**	16.30 (0.429)	11.57 (0.439)	31.723	<0.001
Temporal Discounting	-3.92 (0.292)	-5.07 (0.252)	0.309	0.579

Data is presented as Mean (SEM). **p<0.01

Table 4. Pearson correlations.

	1	2	3	4	5[1]
1. Food Addiction Symptoms		0.640**	0.073	0.216**	-0.149
2. Hedonic Hunger			0.118	0.222**	-0.088
3. BMI				-0.066	0.220**
4. Temporal Discounting [ln(k)]					-0.282**
5. Days abstinent[1]					

[1]Days abstinent collected only in the recovery group (n=114). *p<0.05, **p<0.01

Table 5. Multiple linear regression models predicting food addiction symptoms.

	R	R^2	Adjusted R^2	F	β	t	p
Dependent variable: Food Addiction Symptoms							
Unadjusted**	0.289	0.083	0.075	9.459			<0.001
Temporal Discounting*					0.176	2.599	0.010
Recovery Status**					-0.195	-2.879	0.004
Adjusted**	0.379	0.114	0.114	4.873			<0.001
Temporal Discounting					0.094	1.293	0.197
Recovery Status					-0.076	-0.989	0.324
Age**					-0.231	-2.783	0.006
Gender					-0.065	-0.964	0.336
Education*					0.188	2.545	0.012
Income					-0.079	-1.105	0.270
Race					0.041	0.562	0.575

*p<0.05, **p<0.01

Table 6. Multiple linear regression models predicting hedonic hunger.

	R	R^2	Adjusted R^2	F	β	t	p
Dependent variable: Hedonic Hunger							
Unadjusted**	0.386	0.149	0.141	18.214			<0.001
Temporal Discounting*					0.155	2.373	0.019
Recovery Status**					-0.323	-4.943	<0.001
Adjusted**	0.460	0.212	0.185	7.805			<0.001
Temporal Discounting					0.060	0.871	0.385
Recovery Status**					-0.253	-3.449	<0.001
Age					-0.152	-1.904	0.058
Gender					-0.097	-1.506	0.134
Education					0.100	1.406	0.161
Income					-0.082	-1.190	0.236
Race*					0.152	2.147	0.033

*p<0.05, **p<0.01

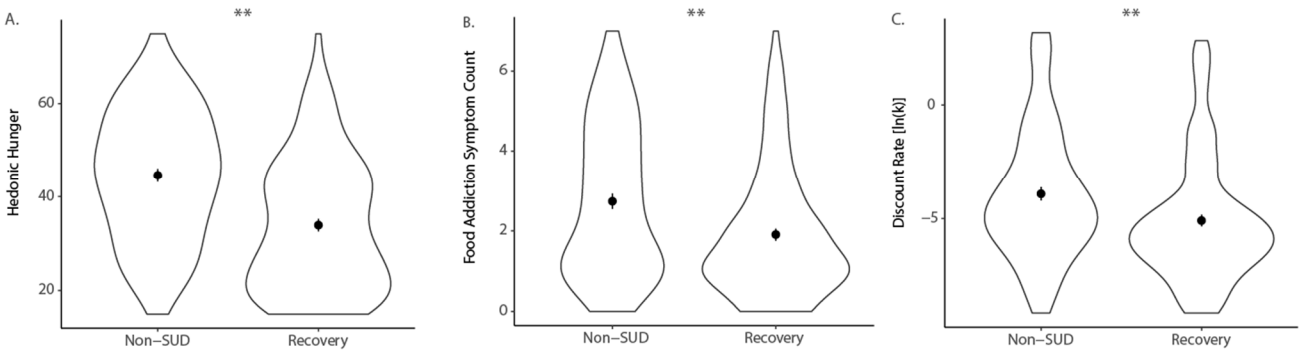
Table 7. Multiple linear regression models predicting BMI.

	R	R^2	Adjusted R^2	F	β	t	p
Dependent variable: BMI							
Unadjusted	0.079	0.006	-0.003	0.660			0.518
Temporal Discounting					-0.057	-0.810	0.419
Recovery Status					0.045	0.631	0.529
Adjusted	0.222	0.049	0.017	1.510			0.166
Temporal Discounting					0.016	0.208	0.835
Recovery Status					-0.062	-0.763	0.446
Age**					0.236	2.701	0.008
Gender					-0.015	-0.219	0.827
Education					-0.075	-0.955	0.341
Income					-0.067	-0.891	0.374
Race					-0.028	-0.360	0.719

*p<0.05, **p<0.01

Figures

Figure 1. Between groups comparisons of A) hedonic hunger, B) food addiction symptoms, and C) temporal discounting. Plotted as distributions, means (black dots), and SEM. **p<0.01



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CHAPTER 4
LONG-TERM EXERCISE-INDUCED DECREASED CORTICAL ACTIVATION PREDICTS IMPROVEMENTS IN PSYCHOLOGICAL STATE

Abstract

Exercise has a long history of improving fitness and physical health through adaptations of the cardiovascular, muscular, and skeletal system. However, it is still unknown how long-term exercise changes the brain, resulting in improved behavioral outcomes. In this study, we examined changes in fitness, psychological state, cognitive functions, and baseline brain activity as measured by electroencephalography (EEG) in response to a 3-month aerobic exercise intervention (n=27), compared to a sedentary control (n=17), in a population of previously sedentary, middle-aged adults. We found that although the exercise intervention did not improve cardiopulmonary fitness, individuals who exercised had improved positive affect, exercise motivation, body image, attention, and recognition memory. In terms of resting-state brain activity, long—term exercise increased relative power in lower frequency bands (i.e., delta, theta, alpha) and decreased relative power in beta activity. These exercise-induced changes in resting-state brain activity were correlated with improvements in positive affect, exercise motivation, and body image, providing novel evidence that exercise-induced decreases in cortical activity may be a mechanism by which exercise induces neurobehavioral improvements. A regular fitness regimen in middle-age is recommended to maintain and promote brain health during aging.

Introduction

The mind-body connection has been an area of scientific intrigue for many centuries (Panegyres & Panegyres, 2016), and one of the major philosophical neuroscientific questions that remains is how the body affects the mind. What is the connection between body health and brain health? How does physical movement create healthy and functional brain networks that promote mental wellbeing? Extant evidence exists showing that exercise is a panacea, improving health and functionality in perhaps every bodily system. Recent research has also shown that exercise benefits the brain in numerous ways. At the structural level, physical activity increases neurogenesis, synaptogenesis, gliogenesis, angiogenesis, and vasculogenesis (Voss et al., 2013). In addition, the neurons generated as a result of exercise have more intricate dendritic morphology, have a lower threshold of excitation for long-term potentiation, and

become functionally integrated into the existing brain circuitry (Farmer et al., 2004; H. van Praag et al., 1999; Vivar et al., 2016). At the behavioral level, physical activity improves sleep, decreases stress, enhances mood, and is beneficial for executive functions dependent on the prefrontal cortex (Gomez-Pinilla & Hillman, 2013; Hillman et al., 2008). Though a clear relationship exists between cardiorespiratory fitness and brain function (Tari et al., 2019), little is known about the underlying neural mechanisms.

Electroencephalograpy (EEG) data recorded from scalp electrodes provides a marker of synchrony at the neuronal network level, specifically at the level of the cortex. The spectral power in distinct brain oscillations (e.g., delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), and beta (12-35 Hz)) gives a measure of neural efficiency or the communication flow both within and between areas of the brain. Research over the past several decades has focused on the link between power in different frequency ranges and specific neurocognitive states (Wang, 2010). Delta activity is seen primarily during deep or slow wave sleep, but has more recently been shown to occur during awake states using intracranial recordings in humans (Sachdev et al., 2015) and has been associated with concentration during performance of cognitive tasks (Harmony, 2013). Theta activity is associated with the sleep to wake transition, is commonly seen during meditative states (D. J. Lee et al., 2018), and has been linked to memory encoding and formation (Düzel et al., 2010; Klimesch, 1999). Alpha activity is commonly associated with an awake but relaxed and restful state; however, this frequency range has more recently been linked to a range of sensory-cognitive processes (Başar, 2012; Başar & Güntekin, 2012). Beta activity is thought to underlie information processing and emotional cognition and increases with heightened arousal, attention, or stress (Jabbi et al., 2015).

Previous research has shown that both during and immediately after a single bout of exercise, power increases across a range of frequency bands including delta, theta, alpha, and beta (Crabbe & Dishman, 2004). This effect occurs with a moderate to large effect size across the brain, with no differences seen between electrode sites (Crabbe & Dishman, 2004). In addition, cross-sectional evidence points towards a relationship between engagement in physical activity or cardiorespiratory fitness level and neural synchrony. Compared to a control group who did not participate in high level sports activity, exercisers showed significantly higher levels of theta, alpha, and beta activity, with this effect seen from frontal to parietal electrode sites (Lardon & Polich, 1996). In addition, Ludyga et al. (2016) revealed that individuals with high

levels of cardiorespiratory fitness (VO_2 max) show a heightened alpha to beta ratio during rest. These results indicate that exercise, and in turn physical fitness, promote neural synchronization across a range of brain regions. However, a recent systematic review on studies examining the effects of exercise interventions on resting state EEG concluded that future studies should use sound biologically-based hypotheses with standardized EEG methods to enhance replicability of future studies (Gramkow et al., 2020). This collection of research indicates that the pattern of the EEG rhythm, and particularly the amplitude or power of these signals, makes this measure a good marker of conscious state. We predict that information within this neural signal may predict the mood and/or cognitive changes seen with prolonged exercise.

Other studies have taken the approach of examining exercise-induced changes in EEG-associated event-related potentials (ERP), which are aspects of the EEG recording (e.g., N100, P300) that occur on a millisecond time scale and correspond to a behavioral event or cognitive process (Sur & Sinha, 2009). Specifically, both acute and chronic exercise as well as cardiopulmonary fitness level have been linked to enhanced attentional arousal as evidenced by an increased amplitude and decreased latency in the P300 component, an ERP generated by a network of cortical structures including the frontal lobe, the anterior cingulate cortex, the infero-temporal lobe, and the parietal cortex (Hillman et al., 2008; Kumar et al., 2012; Lardon & Polich, 1996; Sharma et al., 2019). Exercise and fitness-induced changes in other ERPs including the CNV (contingent negative variation), ERN (error-related negativity), and N200 also indicate enhanced task preparation, error monitoring, and executive control processing, respectively, indicating that exercise may have an especially prominent effect on regions of the prefrontal cortex that regulate executive functions such as attention, working memory, cognitive flexibility, and future planning (Stroth et al., 2009; Jason R. Themanson et al., 2006; J. R. Themanson & Hillman, 2006; Wu et al., 2019).

Collectively, this work suggests that exercise-induced brain changes may be seen during both resting states as well as during cognitive challenge; however, little has been done to connect the three pieces of the puzzle: fitness, brain function, and neurophysiology. Here, we sought to determine an experimentally-deduced model that connects the body to the brain and suggests how exercise-induced changes in fitness relate to the changes in brain function and physiology. Therefore, we tested the hypothesis that exercise-induced increases in fitness would predict an increase in relative power of resting state brain activity and an increase in amplitude and

decrease in latency of ERPs associated with certain cognitive processes, especially those dependent on the prefrontal cortex. Furthermore, we hypothesized that these neural changes would underlie exercise-induced improvements in mood and/or cognition. To test these hypotheses, we randomly assigned previously sedentary, middle-aged adults to engage in moderate- to vigorous-intensity exercise at a cycling studio or play video games in the laboratory 3 times per week for 3 months. We utilized this population for several reasons. First, the majority of studies assessing the effects of exercise on mood and/or cognition have utilized young or elderly populations; middle-aged individuals are rarely studied in this context. In fact, the 2018 Physical Activity Guidelines for Americans Advisory Committee called for more research to be conducted in this population (United States. Department of Health and Human Services. Physical Activity Guidelines Advisory Committee, 2018). For our purpose, middle-aged individuals were ideal because they still 1) have the capability to engage in high-intensity exercise, and 2) have high levels of brain plasticity. Second, we hypothesized that individuals who were previously sedentary would have the largest room for fitness, mood/cognition, and brain improvements. Previous studies have shown that the lowest fit individuals often show the largest physical and mental benefits with exercise interventions (Arem et al., 2015). Before and after the intervention, participants completed cardiopulmonary fitness testing, a battery of mood and neuropsychological assessments, and had their brain activity recorded via EEG during an open-eyes, rest period as well as during cognitive challenge.

Methods

Participants

Participants (n=122) were recruited from New York, NY through online and flyer advertisements. All participants were healthy males and females between the ages of 30 to 59 years of age with English as their primary language. All participants were sedentary and low-fit, defined as engaging in 2 or fewer aerobic exercise sessions per week in the past 3 months, with aerobic exercise sessions lasting 20 minutes or less. Participants were excluded if they currently smoked, had back, hip or knee issues or other preexisting health conditions that made exercise difficult or unsafe. Participants were also excluded if they were diagnosed with and/or took medication for psychiatric or neurological conditions including anxiety, depression, bipolar disorder, schizophrenia, or epilepsy. Prior to participation, all participants gave their informed

consent. All study documentation and data collection methods were approved by and in compliance with the New York University Committee on Activities Involving Human Subjects.

Procedure

Figure 1 depicts the experimental timeline. Participants were randomly assigned to engage in either 3 months of a physically active (n=70) or a sedentary control (n=52) experience. Demographic information (i.e., age, gender, race, ethnicity, education) was collected for all participants at the pre-intervention testing session. Additionally, the Wechsler Test of Adult Reading (WTAR) was used to assess general IQ at the pre-intervention testing session (Wechsler, 2001). A total of 17 individuals completed the 3-month experimental intervention, and 27 individuals completed the control intervention. Before and after the 3-month period, participants completed 1) a cardiopulmonary fitness test; 2) a series of self-reported questionnaires; and 3) a battery of neuropsychological assessments. All self-reported questionnaires and neuropsychological tasks were administered on a computer. During all neuropsychological tasks, EEG data were recorded. In addition, EEG data were recorded during a 10-minute open eyes session where participants were instructed to fixate on a cross-hair in the middle of the computer screen and relax.

Experimental, exercise group: Participants engaged in competitive, indoor cycling classes 3 times per week, with each session lasting 45 minutes. All exercise sessions took place at Swerve Fitness in New York, NY (https://www.swervefitness.com). Heart rate was measured during the entirety of the exercise session using the Scosche Rhythm+ bluetooth/ANT+ armband heart rate monitor, which paired with the bicycles at Swerve.

Control, sedentary group: Participants engaged in competitive, non-physically active video games 3 times per week, with each session lasting 45 minutes. All video game sessions were conducted in the Suzuki laboratory at New York University and displayed on a television with a Nintendo Wii video game console. Video games included 2-dimensional board/show games (e.g., Monopoly, Wheel of Fortune, The Price is Right, Mario Party, Mario Kart, Rubik's World, or Trivial Pursuit); none were first-person shooter games or games that involved navigating around a 3-dimensional virtual environment, as these games have been shown to impact affective state and cognitive function (Clemenson et al., 2020; Kühn et al., 2019). Several video games were available so that participants did not become too familiar with or skilled at these games. Heart rate was measured during the entirety of the video game session using the

Polar H10 bluetooth heart rate sensor chest strap paired with the Polar FT7 watch, and average heart rate was captured for each video game session. Research participants or research staff from the Suzuki laboratory played video games with the participants, as this control group was designed to be a competitive, sedentary experience.

Self-reported measurements: A series of self-reported questionnaires was administered to assess psychological state These questionnaires were completed at home. If at the time of laboratory assessment, participants had not completed the questionnaire, they were required to complete the questionnaires in the laboratory. In some instances, data is missing because the participant failed to complete either the pre- or post-intervention survey. Participants were asked to refrain from drinking alcohol or using other illicit substances during the assessment. These questionnaires included the Behavioral Regulation in Exercise Questionnaire (BREQ-2), Body Attitude Test, and Positive and Negative Affect Scale (PANAS).

Neuropsychological assessments

Mnemonic Similarity Task: This hippocampal-dependent task assesses both recognition memory and behavioral pattern separation (Stark et al., 2013). Participants viewed 128 images and were asked to classify them as indoor or outdoor items via button press. In an unexpected, subsequent trial, participants viewed another 192 images and were asked to identify whether they were old (33% targets), similar (33% lures), or new (33% foils) in comparison to the previously presented objects. All images were presented for 2000 ms followed by an inter-stimulus interval of 500 ms. Participants were given 30 s of rest after every 64 images, and 2 min of rest in between the first and second portions of the task. This task was adapted for the computer from (Lacy et al., 2011), and sets D and E were utilized from this repository of images. Non-responses were excluded from all calculations including percentage correct and reaction time. Recognition memory performance was calculated as “old” responses to targets minus “old” responses to foils; pattern separation performance (Lure Discrimination Index or LDI) was calculated as “similar” responses to lures minus “similar” responses to foils. As this test was particularly challenging, a cutoff was made to exclude participants who did not understand the task or did not comply with task instructions. To be included in analyses, participants needed to perform above chance (33%), have less than 25% no response, and have pressed each response button at least once. Lures were categorized into 5 bins based on level of similarity, with Bin 1 being most mnemonically similar and Bin 5 being least mnemonically similar. Lure bin performance was

calculated as 1 minus the percent "old" responses in each lure bin. Due to the differing levels of difficulty between Sets D and E, Set E scores were converted using the conversion tool. Proportion values that were not between 0 and 1 after the conversion calculation were clipped at 0 and 1.

Spatial Navigation Task: This hippocampal dependent task assessed spatial navigation ability and episodic memory. For the spatial navigation component, in an encoding phase, participants were instructed to explore a 3-dimensional virtual environment (city town) and find the location of 12 distinct store locations within this environment while learning the layout of the space. In a remembering phase, participants were instructed to deliver virtual items to the previously visited store locations. The time it took for the participant to find each of the locations was assessed, and the average seek duration was calculated for each of the encoding and remembering phases (Average Seek Duration). Average Rate was calculated by dividing the distance traveled by the seek duration. For the episodic memory component, participants were asked a series of questions regarding their experience. First, participants were presented with an image of either a storefront they visited or a lure storefront and asked whether or not they visited this particular location (Landmark Score, Part 1). Second, participants were presented with an image of a delivery site and a delivery item and asked to identify whether or not it was a correct pairing (Association Score). Third, participants were presented with an image of 2 delivery items and asked to identify which item was delivered first (Temporal Score). Percentage correct and reaction time were calculated for each of the Landmark (Part 1), Association, and Temporal Scores. In a free recall phase, participants were asked to recall both the objects they delivered (Object Score) as well as the locations they visited (Landmark Score, Part 2) by typing in this information in a series of 12 boxes. Percentage correct was calculated for this free recall phase. An Episodic Memory Score was calculated based on average percentage correct and average reaction time for each of the component scores. The Spatial Navigation Task was built using Unity game engine (www.unity3d.com), Quantum Theory's Urban Construction Pack (https://www.assetstore.unity3d.com/en/#!/content/8081), and custom code. The task design and spatial map utilized for the task was adapted from previous work showing task-activated place cell firing in the hippocampus (Miller et al., 2013). A distractor task (i.e., correctly identifying letters) was included as a control condition to determine if participants were paying attention to the task, and data were excluded if less than 80% average correct on the distractor task.

Stroop Task: The Stroop task tests prefrontal cortex functioning tests attention and response inhibition (Stroop, 1935). Participants were presented with the words "RED", "BLUE," "GREEN" or "YELLOW" in either their congruent (same) or incongruent (different) colors. Participants were then asked to indicate via button press the color rather than the meaning of the word. Three sets of 48 trials were presented. A fixation cross was presented for 500 ms, followed by the colored word for 1500 ms, followed by an intertrial interval of 850 to 1100 ms. 30 s of rest was provided after each set. Calculated values included the total count and percentage correct as well as the average reaction time (RT) for both congruent and incongruent trials. An interference score was calculated using the formula:

$$I = [(\text{Total Correct Congruent}) - (\text{Total Correct Incongruent})] / [(\text{Total Correct Congruent}) + (\text{Total Correct Incongruent})] * 100$$

adapted from the formula used by (Valgimigli et al., 2010). Data were excluded if greater than 25% no response or less than 80% accuracy on all completed trials.

N-Back Task: This prefrontal cortex-dependent task tests the capacity for short-term memory (Kirchner, 1958). Participants were presented with a series of letters and asked to determine whether each letter matched the letter presented n-items prior. Twelve sets of trials were presented; each set consisted of 0-, 1-, 2- and 3-back trials. Participants were shown a different set of 30+N random letters, each for 500 ms and had an additional 2500 ms to respond. 30 s of rest was provided in between each trial, with rest extending to 120 s after each set. Percent of correct responses to target trials, and reaction times were recorded. Data were excluded if greater than 50% incorrect in the 0-back trial.

Reading Span Task: This dual-processing test, dependent on the prefrontal cortex, assesses short-term memory (Daneman & Carpenter, 1980). Participants viewed a series of sentences followed by unrelated words. Three sets of trials were presented; each set consisted of 2-, 3-, 4-, 5-, and 6-sentence trials. After the presentation of each set, participants were asked to recall the words as well as respond to a comprehension question about a particular sentence. 30 s of rest was provided in between each set. Accuracy of recall, reaction time, and a comprehension score were recorded. Data were excluded if fewer than 20% of words were recalled regardless of order.

Probabilistic Learning Task: In this striatal-dependent probabilistic learning task, participants were shown a series of insects and two flowers. For each trial, participants were

instructed to guess which flower was associated with the insect displayed. For each insect, one of the flowers was randomly chosen to be correct for 80% of the trials and the other flower for 20% of the trials (Delgado et al., 2005). 201 trials were presented in seven blocks (six learning blocks, and one test block) of 30 trials. 30 s of rest was provided in between each set. Accuracy of trials and reaction times were recorded. The learning rate was calculated as: (Block 6 percent correct) - (Block 1 percent correct). Data were excluded if greater than 25% average no response across trials.

Pursuit Rotor Task: This striatal-dependent task assesses procedural learning (Adams, 1952; Fillmore & Vogel-Sprott, 1994). Participants were instructed to keep the computer cursor over a 1.5 cm red target dot rotating clockwise at 12 revolutions per minute (RPM) along a 1 cm circular track. Fifteen 60 s trials were presented, with 30 s of rest provided in between trials. Every 3 trials, rest was extended to 120 s. Time on target, distance from the target, and number of hits were recorded. Hits were defined as when the cursor moved from an off-target location to an on-target location. Data were excluded if less than 20% of total time was on target.

Submaximal Exercise Test: To estimate maximal aerobic capacity, participants performed a pre- and post-intervention submaximal cycle ergometry test following general procedures for submaximal testing (American College of Sports Medicine, 2017). Before beginning, participants were equipped with a heart rate (Polar H7; Polar, Bethpage, NY). The participants were allowed to sit and rest for several minutes to obtain a resting heart rate. The participants then warmed-up on the cycle ergometer for 2 minutes with no resistance and maintained a cycling cadence of 50 RPMs. After the 2-minute warm-up, the test began. Each stage of the test lasted 1 minute, and the participants' heart rates were recorded at the end of each stage. The first stage (following the warm-up) applied 0.5kg resistance (150 kgm/min) on the cycle. Each stage added an additional 0.5kg of resistance for 3 to 4 stages. The test continued until 2 heart rates > 110 BPM were observed or the participant could not maintain a cycling cadence of 50 RPMs. The heart rate values were used to predict maximal work rate via the following equation: ((slope of heart rates×(206.9-(0.67×age)))-workrate intercept). The VO_{2peak} was then estimated using the ACSM equation for leg cycling: (7+(((1.8×(predicted max 〖workrate)〗)/(body mass)))) (American College of Sports Medicine, 2017). Data are missing for 10 participants due to heart rate monitor malfunctions during the fitness test.

Body composition: To measure participants' body composition, a commercial bioelectrical impedance analysis scale was used (GW22025; GoWiseUSA, Phoenix, AZ). Participants were asked to maintain a normal level of hydration before the assessment was taken. The participant would remove their shoes and socks, standing with their bare feet on the electrodes of the scale to allow an assessment of densitometry. The scale converted body density to a percent body fat, muscle, and bone as well as total body water, after given information about age and sex.

EEG data collection, pre-processing, time-frequency and event-related potential analysis: EEG signals were obtained from each participant using an Electro-Cap International (ECI), Inc. electro-cap (Eaton, OH) consisting of 20 active electrodes arranged in an elastic spandex-type cap with recessed, pure tin electrodes, placed in accordance to the International 10–20 System (Fp1, Fp2, Fpz, F3, F4, F7, F8, Fz, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, O1, and O2). The A1 and A2 electrodes were connected to the right and left ear lobes. The electro-cap was connected to an Intan Technologies RHD2000-Series Recording System (Los Angeles, CA), controlled by the open source RHD2000 software. Before all recording sessions, head circumference was measured and participants were fit with the appropriate cap size. For the subject's comfort, disposable sponge disks were applied to Fp1, Fp2, F7 and F8. Nasion to inion distance was measured, and once the cap was in the correct positioning, electro-gel (ECI) was applied to all electrodes to reduce the system impedance. Data were sampled at 2500 Hz and referenced to the average ear lobe signal. At the beginning of each recording session, all impedances were <20 kΩ.

MATLAB (version 2015a, The MathWorks, Inc., Natick, MA) was used for offline processing of the EEG data, along with the RHD2000 Toolbox and the EEGLAB Toolbox (Delorme & Makeig, 2004). The continuous baseline data were first resampled at 500 Hz and then a band-pass filter was applied. Data were low-pass filtered at 45 Hz to remove high-frequency movement artifacts, and high-pass filtered at 1 Hz to remove slow fluctuations unrelated to our signals of interest. Channels were then rejected using the automatic channel rejection feature of EEGLAB; any electrode with a probability distribution exceeding 5 z-scores from the mean was excluded. Before rejection of an entire electrode, data were checked via visual inspection. In the instance where the majority of the data were clean, the electrode was kept and data were cleaned after epoching. Data were then epoched into 1 second segments, and

the baseline was removed. Automatic epoch rejection was then conducted; any epoch exceeding 1000 microvolts was excluded. Before rejection of an epoch, data were checked via visual inspection. If an epoch was indicative of an eye blink or eye movement, it was kept in the data set. Independent Component Analysis (ICA) using the algorithm runica was then run to reject eye blinks and eye movements. Appropriate ICAs were then rejected using visual inspection of both the components by map and the component activities.

Time-frequency analysis was performed using an in-house designed MATLAB program. Relative power was extracted for delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), and beta (12-35 Hz) frequencies. Relative power was calculated as the power in a given band divided by the power in the 1-21 Hz frequency range; this was done to normalize the signal across participants, as noise level in the EEG signal was variable from subject to subject. One subject was removed from the final analyses because relative power values were more than ±2 standard deviations from the mean.

MATLAB (version 2019a, The MathWorks, Inc., Natick, MA) was used for offline processing of the EEG data, along with the RHD2000 Toolbox and the EEGLAB and ERPLAB Toolboxes (Delorme & Makeig, 2004; Lopez-Calderon & Luck, 2014). The continuous baseline data were first resampled at 500 Hz and then a band-pass filter was applied. Data were low-pass filtered at 45 Hz to remove high-frequency movement artifacts, and high-pass filtered at 1 Hz to remove slow fluctuations unrelated to our signals of interest. Channels were then rejected using the automatic channel rejection feature of EEGLAB; any electrode with a flat signal for more than 5 seconds was removed. Before rejection of an entire electrode, data were checked via visual inspection. Independent Component Analysis (ICA) using the algorithm runica was then run to reject components arising from sources other than the brain. Components were labeled using the ICLabel classifier within EEGLab (Pion-Tonachini et al., 2019). Components identified as less than 50% brain were removed from the data. Data were epoched into task-related bins (e.g., congruent trials and incongruent trials in the Stroop task) beginning 500 ms before stimulus presentation to 1500 ms after stimulus presentation. Artifact detection using a moving window peak-to-peak threshold with a window width of 200 ms, 100 ms step, and a voltage threshold of 100 μV was conducted on the epoched data. Channels that were flagged as artifacts in a majority of epochs were removed from the data. ERPs for each bin for each participant were averaged; epochs that were marked as artifacts were excluded from the average

ERPs. Average ERPs from each participant in an experimental group were averaged to generate a Grand Average for the group. Due to excessive noise in the data requiring data from a majority of participants to be excluded, the ERP analysis was not completed. An example of a Grand Average using only clean data (n=2) is provided in Figure 2.

Statistical analyses: Independent samples t-tests and chi-square tests of independence were used to compare baseline demographic and anthropometric measures between groups. Two-way analysis of variance was utilized to determine the effect of time (i.e., pre- and post-intervention) and group (i.e., experimental exercise group and sedentary control group) on fitness, self-report, neuropsychological, and brain activity outcomes. Relationships among changes in brain activity measures and self-report and neuropsychological outcomes were probed using Pearson correlations.

Results

Participant characteristics: At baseline, there were no differences in age ($t(42)=0.709$, $p=0.428$), gender ($p=1.00$), race ($p=0.768$), ethnicity ($p=0.220$), education ($p=0.572$), or general IQ ($t(42)=-0.766$, $p=0.448$) between the exercise and control group (Table 1). Additionally, there were no significant differences between the exercise and control group in weight ($t(42)=-0.570$, $p=0.572$), BMI ($t(42)=-1.005$, $p=0.321$), total body water ($t(41)=1.537$, $p=0.132$), percent fat mass ($t(41)=-1.363$, $p=0.180$), percent muscle mass ($t(41)=0.565$, $p=0.575$), or percent bone mass ($t(41)=-0.792$, $p=0.433$) at baseline (Table 2).

Heart rate and fitness: Average heart rate across the entire study was significantly different between the exercise and control groups ($t(39)=-14.157$, $p<0.001$), with exercisers (145.70 beats per minute ±3.46 SEM) showing a significantly higher average heart rate than controls (78.79 beats per minute ±2.35 SEM) during the 36 sessions (Figure 3A). Maximal aerobic capacity showed no significant change over time or between groups (Figure 3B, time*group $F(1,38)=1.488$, $p=0.230$, partial $\eta^2=0.038$). No significant interaction effect was found for anthropometric measures including total body water (time*group ($F(1, 41)=2.353$, $p=0.133$, partial $\eta^2=0.054$), percent fat (time*group $F(1,41)=3.266$, $p=0.078$, partial $\eta^2=0.074$), percent muscle (time*group $F(1, 41)=1.323$, $p=0.257$, partial $\eta^2=0.031$), percent bone (time*group $F(1, 41)=0.450$, $p=0.506$, partial $\eta^2=0.011$), and BMI (time*group $F(1, 42)=3.354$, $p=0.074$, partial $\eta^2=0.074$).

Psychological state

Affective state: Mood state was measured via the Positive and Negative Affect Schedule (PANAS), which assess both general negative affect (composed of fear, sadness, guilt, hostility, shyness, and fatigue subscales) and general positive affect (composed of joviality, self-assurance, attentiveness, serenity, and surprise subscales). Higher scores on this 60-item scale equate to greater levels of positive or negative affect. A significant interaction effect was found for general positive affect (time*group $F(1,26)=5.268$, $p=0.030$, partial $\eta^2=0.168$) (Exercise 32.00±1.50 / 35.27±1.56; Control 32.77±2.96 / 31.54±2.85) (Figure 4A). Exercisers showed a significant increase in general positive affect over time ($F(1,14)=10.143$, $p=0.007$, partial $\eta^2=0.420$), whereas controls showed no change ($F(1,12)=0.498$, $p=0.494$, partial $\eta^2=0.040$). This effect was driven by attentiveness (time*group $F(1,26)=4.327$, $p=0.048$, partial $\eta^2=0.143$; Exercise 13.00±0.74 / 15.20±0.76; Control 14.00±1.07 / 13.69±1.10).

Exercise motivation: The motivation to participate in exercise was measured via the Behavioral Regulation in Exercise Questionnaire (BREQ-2), which assesses amotivation, external regulation (i.e., doing something for an external reward), introjected regulation (i.e., doing something to avoid negativity), identified regulation (i.e., doing something to obtain a goal), and intrinsic regulation (i.e., doing something for enjoyment), as well as the relative autonomy index (RAI) that gives a quantitative value for self-determination. Higher scores on this questionnaire equate to greater levels of motivation to exercise. A significant interaction effect was found for the RAI (time*group $F(1,26)=8.261$, $p=0.008$, partial $\eta^2=0.241$) (Exercise 7.76±1.66 / 10.04±1.36; Control 8.66±1.68 / 5.75±2.13) (Figure 4A). Exercisers showed a non-significant increase in exercise motivation over time ($F(1,14)=3.280$, $p=0.092$, partial $\eta^2=0.190$), whereas controls showed a significant decrease ($F(1,12)=5.124$, $p=0.043$, partial $\eta^2=0.299$). This effect was driven by intrinsic regulation (time*group $F(1,26)=9.402$, $p=0.005$, partial $\eta^2=0.266$; Exercise 2.05±0.33 / 2.70±0.33; Control 2.54±0.33 / 2.29±0.41).

Body attitudes: Attitudes towards the physical body was measured via the Body Attitudes Test (BAT), which assesses negative appreciation of body size, lack of familiarity with one's own body, general body dissatisfaction, and a rest factor, as well as an overall BAT score. Higher scores on this test equate to greater levels of body attitudes disturbance. A significant interaction effect was found for negative appreciation of body size (time*group $F(1,26)=4.456$, $p=0.045$, partial $\eta^2=0.146$) (Exercise 13.07±2.30 / 10.67±2.12; Control 12.77±2.24 / 13.31±2.49) (Figure 4A). Exercisers showed a significant decrease in negative appreciation over time

(F(1,14)=6.968, p=0.019, partial η^2=0.332), whereas controls showed no change (F(1,12)=0.255, p=0.623, partial η^2=0.021).

Cognitive functions

Recognition memory: Recognition memory and behavioral pattern separation were assessed via the Mnemonic Similarity Task. A significant interaction effect was found for recognition memory or the ability to correctly identify previously seen images (time*group F(1,31)=5.255, p=0.029, partial η^2=0.145) (Table 3). Exercisers showed a non-significant increase in recognition memory over time (F(1,20)=3.002, p=0.099, partial η^2=0.131), and controls showed a non-significant decrease in recognition memory over time (F(1,11)=2.693, p=0.129, partial η^2=0.197) (Figure 4B). Contrary to our initial hypothesis, no significant interaction effect in behavioral pattern separation or the ability to distinguish between two similar images was seen (time*group F(1,31)=0.001, p=0.975, partial η^2<0.001), indicating that exercise showed no additional improvement over our control group. Additional variables showed a significant time effect, indicating a learning effect over time (Table 3).

Response inhibition: Response inhibition and attention were assessed using the Stroop Task. A significant interaction effect was found for overall reaction time for correct responses (time*group F(1,26)=5.188, p=0.031, partial η^2=0.166) and reaction time on correct congruent trials (time*group F(1,26)=7.149, p=0.013, partial η^2=0.216). Exercisers showed a significant decrease in overall RT for correct responses (time F(1,16)=15.035, p=0.001, partial η^2=0.484) and RT on correct congruent trials (time F(1,16)=17.054, p=0.001, partial η^2=0.516) while controls showed no difference for overall RT (time F(1,10)=0.033, p=0.860, partial η^2=0.003) or correct congruent RT (time F(1,10)=0.086, p=0.775, partial η^2=0.009) (Figure 4C). There were significant time effects for the percent correct on incongruent trials, and reaction time on both congruent and incongruent trials (Table 4).

Working memory: Working memory was assessed using both the N-back Task and the Reading Span Task. There were no significant interaction effects in the N-back Task. Percent correct on N3 trials showed a significant time effect (Table 5). A significant interaction effect was seen for the Reading Span Task RT on four-sentence trials (time*group p=0.014, partial η^2=0.150) (Table 6). The exercise group showed no difference in RT over time (F(1,25)=2.737, p=0.111, partial η^2=0.099) while the controls showed a significant increase in RT (F(1,13)=4.853, p=0.046, partial η^2=0.272) (Table 5).

Probabilistic learning: No significant interaction effects were found for the Probabilistic Learning Task. Significant time effects were seen for percent correct in block 2 ($F(1,40)=6.851$, $p=0.012$, partial $\eta^2=0.146$) and block 4 ($F(1,40)=4.644$, $p=0.037$, partial $\eta^2=0.104$), reaction time in block 2 ($F(1,40)=4.940$, $p=0.012$, partial $\eta^2=0.110$) and block 4 ($F(1,40)=4.648$, $p=0.037$, partial $\eta^2=0.104$) (Table 7).

Procedural learning: Procedural learning was assessed using the Pursuit Rotor Task. No significant interaction effects were found in this task. Significant time effects were seen for percent time on target in block 1 ($F(1,38)=31.506$, $p<0.001$, partial $\eta^2=0.453$), block 2 ($F(1,38)=4.678$, $p=0.037$, partial $\eta^2=0.110$), block 3 ($F(1,38)=5.633$, $p=0.023$, partial $\eta^2=0.129$), and overall ($F(1,38)=11.590$, $p=0.002$, partial $\eta^2=0.234$); average time on target in block 2 ($F(1,38)=5.279$, $p=0.027$, partial $\eta^2=0.122$), block 3 ($F(1,38)=5.504$), $p=0.024$, partial $\eta^2=0.127$), and overall ($F(1,38)=4.393$, $p=0.043$, partial $\eta^2=0.104$); and number of hits in block 1 ($F(1,38)=16.284$, $p<0.001$, partial $\eta^2=0.300$), block 2 ($F(1,38)=8.426$, $p=0.006$, partial $\eta^2=0.181$), and block 3 ($F(1,38)=8.240$, $p=0.007$, partial $\eta^2=0.178$) (Table 8).

Spatial navigation: In the spatial navigation task, significant interaction effects were found for correct temporal reaction time ($F(1,35)=1.441$, $p=0.047$, partial $\eta^2=0.108$) and episodic memory reaction time ($F(1,36)=7.530$, $p=0.013$, partial $\eta^2=0.163$) (Table 9).

Baseline EEG changes

Relative delta power (1-4 Hz): Averaged across the entire brain, a significant interaction (Figure 5A, time*group $F(1,38)=7.068$, $p=0.011$, partial $\eta^2=0.157$) was seen for the change in relative delta power. Both exercise ($F(1,19)=6.727$, $p=0.018$, partial $\eta^2=0.261$) and control groups ($F(1,19)=19.673$, $p<0.001$, partial $\eta^2=0.509$) showed a significant increase in relative delta power; however, against our hypothesis, the control group showed a significantly greater increase in relative dela power over the exercise group. No between group effects were seen for the change in relative delta power in any single electrode (Figure 5B, C).

Relative theta power (4-8 Hz): Averaged across the entire brain, a significant time*group interaction (Figure 6A, $F(1,38)=8.519$, $p=0.006$, partial $\eta^2=0.183$) was seen for the change in relative theta power. The exercise group showed a significant increase ($F(1,19)=69.691$, $p<0.001$, partial $\eta^2=0.786$), whereas the control group showed no change in relative theta power ($F(1,19)=2.977$, $p=0.101$, partial $\eta^2=0.135$). No between group effects were seen for the change in relative theta power in any single electrode (Figure 6B, C).

Relative alpha power (8-12 Hz): Averaged across the entire brain, a significant time*group interaction (Figure 7A, $F(1,38)=94.320$, $p<0.001$, partial $\eta^2=0.713$) was seen for the change in relative alpha power. The exercise group showed a significant increase ($F(1,19)=321.664$, $p<0.001$, partial $\eta^2=0.944$), whereas the control group showed a significant decrease ($F(1,19)=18.074$, $p<0.001$, partial $\eta^2=0.488$) in relative alpha power. At the level of the individual electrodes, significant between group differences were seen at frontal (Fz $t(33)=-2.335$, $p=0.026$, Fpz $t(33)=-2.315$, $p=0.027$, F4 $t(33)=-2.522$, $p=0.017$), central (C3 $t(33)=-3.237$, $p=0.003$, C4 $t(33)=-2.976$, $p=0.005$), temporal (T5 $t(33)=-2.388$, $p=0.023$, T6 $t(33)=-2.654$, $p=0.012$), parietal (P3 $t(33)=-2.432$, $p=0.021$, P4 $t(33)=-2.709$, $p=0.011$), and occipital (O1 $t(33)=-2.030$, $p=0.050$, O2 $t(34)=-2.454$, $p=0.020$) sites (Figure 7B, C).

Relative beta power (12-35 Hz): Averaged across the entire brain, a significant time*group interaction (Figure 8A, $F(1,38)=10.098$, $p=0.003$, partial $\eta^2=0.210$) was seen for the change in relative beta power. The exercise group showed a significant decrease ($F(1,19)=52.999$, $p<0.001$, partial $\eta^2=0.736$), whereas the control group showed no change ($F(1,19)=0.176$, $p=0.680$, partial $\eta^2=0.009$) in relative beta power. No between group effects were seen for the change in relative beta power at the level of the individual electrodes (Figure 8B, C).

Exercise-induced changes in baseline brain activity are associated with changes in psychological state

For correlational investigations, we limited our exploration to behavioral and brain effects that showed response to the exercise intervention. In the case of delta, theta, and beta, we explored the relationship between changes in whole brain oscillatory activity and changes in our psychological and cognitive outcomes, as no individual electrode site displayed a significant between-groups effect. In the case of alpha, we explored these relationships at each brain region (i.e., frontal, central, parietal, temporal, and occipital) as 55% of electrodes displayed a significant between-groups effect (Table 10). No significant correlations were seen for whole brain delta. For whole brain theta, a significant correlation was seen for BAT ($r=-0.477$, $p=0.025$). For whole brain beta, a significant correlation was seen for BAT ($r=0.447$, $p=0.037$). In regard to frontal alpha activity, significant relationships were seen at Fpz for GPA ($r=0.436$, $p=0.042$); no significant relationship was seen for Fz or F4. In regard to central alpha activity, significant relationships were seen at C3 for GPA ($r=0.531$, $p=0.011$) and RAI ($r=0.490$,

p=0.021); no significant relationship was seen for C4. For temporal alpha activity, a significant relationship was seen at T6 for RAI (r=0.497, p=0.019); no significant relationships were seen at T5. In regard to parietal alpha activity, a significant relationship was seen at P4 for RAI (r=0.459, p=0.032); no significant relationships were seen at P3. In regard to occipital alpha activity, a significant relationship was seen at O2 with RAI (r=0.430, p=0.046); no significant relationship was seen for O1. There were no significant relationships between baseline brain activity and recognition memory on the MST nor reaction time on correct congruent trials on the Stroop task.

Discussion

The present study examined the relationship between changes in fitness, psychological state, cognitive functioning, and baseline brain activity that result from a long-term exercise regimen in previously sedentary, low fit, middle aged individuals. We found that compared to a sedentary control group, 3 months of aerobic exercise without changes in cardiopulmonary fitness improved general positive affect, exercise motivation, and body image as well as attention and recognition memory. Long-term exercise also increased relative power in delta, theta, and alpha activity and decreased relative power in beta activity during a resting state, suggesting that long-term exercise promotes decreased cortical activation during periods of rest. Further, decreased cortical activity induced by long-term aerobic exercise was significantly associated with improved psychological state as measured by increased general positive affect, improved body image, and enhanced exercise motivation. This is the first study to provide evidence that changes in baseline brain activity may serve as a mechanism for exercise-induced improvements in psychological state.

Long-term exercise improves psychological state and cognitive functioning

Beyond physical health and performance benefits, exercise leads to improvements in psychological state and cognitive functioning. In the present study, we found that long-term aerobic exercise enhanced general positive affect, exercise motivation, body image, recognition memory, and attention in a population of previously sedentary, middle-aged adults. The mood-enhancing effects of both acute and long-term exercise are well-documented in the scientific literature (Basso & Suzuki, 2017; Blumenthal et al., 1982; Edwards & Loprinzi, 2018; R. E. Lee et al., 2001; Reed & Ones, 2006). In fact, aerobic exercise training has been shown to be an effective treatment for mood disorders (Hearing et al., 2016; Martinsen et al., 1989). Further, the

opposite effect (i.e., sedentary behavior associated with more negative mood states) has been observed as well (DeMello et al., 2018). Similar to our current findings, others have demonstrated that engaging in a regular exercise regimen increases self-determination for exercise in clinical populations (Gerber et al., 2018; Pearson & Hall, 2013). Additionally, our findings regarding body attitudes are consistent with previous findings suggesting that exercise improves body image. A meta-analysis reported that regular exercisers have more positive body image than non-exercisers, and that body image is improved by exercise intervention (Hausenblas & Fallon, 2006).

While previous research has explored the relationship between exercise and cognition, this is one of the first studies to do so in a middle-aged population. In this study, we demonstrated that long-term exercise improved recognition memory, a hippocampal- and peripheral cortex-dependent function, and attention, a prefrontal cortex dependent function. In line with our findings, previous work has linked exercise to improvements in memory and increases in hippocampal volume and neurogenesis (Erickson et al., 2011; Henriette van Praag et al., 2005). Additionally, exercise has been shown to improve PFC functions as well as increase PFC activity to support these functions (Basso et al., 2015; Yanagisawa et al., 2010)

Long-term exercise alters baseline brain activity towards a state of decreased cortical activation

This is the first study to report that long-term exercise in healthy, previously sedentary adults alters cortical EEG activity patterns towards a state of decreased cortical activation. Here, we demonstrated that long-term exercise increases activation in the lower frequency bands (i.e., relative whole brain delta, theta, and alpha power) while decreasing activation in the higher frequency bands (i.e., relative beta power). The effects in the alpha frequency range were most significant, with effects seen at frontal, central, temporal, parietal, and occipital electrode sites. Early work by Bonvallet, Dell, and Hiebel in cats and dogs demonstrated a strong link between the cardiovascular and autonomic arousal that arises during exercise and cortical activation, finding that as heart rate and blood pressure increases due to the metabolic demands of exercise, cortical activation progressively decreases (Bonvallet et al., 1954). In line with this early finding, several reports in humans indicate that a single session of aerobic exercise increases power in the alpha frequency range (Fumoto et al., 2010), with effects lasting up to 30 minutes after exercise cessation (Crabbe & Dishman, 2004; Schneider et al., 2009). Acute aerobic exercise also increases individual alpha peak frequency (iAPF), with exhaustive exercise

proving more effective than steady state exercise (Gutmann et al., 2015, 2018). Specifically, alpha activity has been shown to have a reciprocal relationship with brain activation (Andreassi, 2010). Looking beyond alpha activity, in a quantitative synthesis that reviewed 18 studies with a total of 282 participants, Crabbe and Dishman concluded that acute exercise increases power in delta, theta, alpha 1, alpha 2, beta 1, beta 2, and beta c with similar effect sizes in a range of cortical brain areas including frontal, parietal, temporal, and occipital regions (Crabbe & Dishman, 2004). Chronic exercise paradigms have been less examined and studies have revealed mixed findings, showing significant increases in alpha-2 and beta-3 band activity and decreases in delta and beta-1 bands; however, these studies were primarily conducted in persons with disability or disease (Amjad et al., 2019; Deslandes et al., 2010; Dishman et al., 2010; Gramkow et al., 2020; Kubitz & Landers, 1993; Ludyga et al., 2017; Villafaina et al., 2019). Other cross-sectional work revealed that athletic individuals with high cardiopulmonary fitness levels, compared to those with low cardiopulmonary fitness levels, show a higher alpha/beta ratio both during rest and exercise, indicating that fitness confers neural efficiency - the brain can be less active when completing its tasks of daily living (Ludyga et al., 2016). Our findings fit in nicely with this collection of work, demonstrating that physical activity practices that enhance cardiovascular output can decrease cortical activation at rest, supporting a brain state associated with a calm and relaxed wellbeing.

Decreased cortical activation predicts exercise-induced improvements in psychological state

This is the first study to report that long-term exercise-induced changes in resting state brain state predict improvements in psychological state. Specifically, decreased cortical activation was associated with increased mood, improved body image, and heightened exercise motivation. Others have considered the cerebral lateralization hypothesis as underlying acute exercise induced improvements in mood state. That is, resting EEG asymmetry is a biological marker for both state and trait affect and predicts the affective response to emotion-eliciting stimuli (Tomarken et al., 1992). Specifically, frontal asymmetry in the alpha band measures the functional association between the frontal lobe and the amygdala and is a widely accepted biomarker of emotional reactivity and regulation, with left frontal asymmetry associated with positive emotions and approach behaviors and right asymmetry associated with negative emotions and avoidance behaviors. Studies have found that heightened baseline levels of left frontal alpha asymmetry predict the reduction in anxiety experienced after exercise (Petruzzello

& Landers, 1994; Petruzzello & Tate, 1997). We add to this literature by showing that long-term exercise can decrease cortical activation, which may underlie or lead to positive changes in psychological state including an overall positive attitude, feeling better about oneself, and having more motivation to engage in healthy behaviors. Further, these findings suggest that aerobic training may lead to enhanced parasympathetic nervous system activity and decreased central nervous system activity, which contribute to enhanced feelings of wellbeing. Future studies are warranted to investigate the effects of chronic exercise on both peripheral and central nervous system activity and their relationship to mood state changes.

Limitations and Future Directions

The present study had several limitations. First, this study had a high dropout rate due to the intensive nature and requirements of the study, with more participants dropping out of the control group than the experimental group. This high dropout rate was despite various strategies for retention including participant compensation, weekly newsletters, research personnel attendance at the exercise and video game sessions, and free beverages offered after the exercise sessions. Second, due to technical challenges, we were unable to test maximal aerobic exercise with a traditional VO_2max test. Instead, we utilized a submaximal exercise test to estimate maximal aerobic capacity. Third, based on this estimate and despite engaging in three aerobic exercise sessions per week where heart rate reached moderate to vigorous intensities, the estimated maximal aerobic capacity of our experimental participants did not change from baseline. Future studies should incorporate VO_2 testing to assess maximal aerobic capacity and utilize exercise protocols that ensure changes in fitness levels over time. Despite this lack of aerobic changes, we found a variety of mood and cognitive changes as well as resting brain state changes. Our findings indicate that long-term exercise influences brain physiology towards a state of heightened parasympathetic activity and that these changes underlie exercise-induced improvements in psychological state. Future studies are warranted to investigate the ways in which long-term exercise alters the autonomic nervous system as measured through electrocardiogram, skin conductance, or other measures that can be obtained at the level of the body and subsequently how these metrics are related to changes in central nervous system activity. Further, considering the exercise-induced changes in cognitive measures such as attention and recognition memory, future studies should investigate the EEG indices of such changes through techniques such as event-related potential analysis. Alternatively, researchers

could utilize magnetic resonance imaging to investigate the long-term changes in prefrontal cortical or hippocampal areas associated with attention and recognition memory, respectively.

Conclusions

Exercise has a long history of improving fitness and physical health through adaptations at the level of the cardiovascular, muscular, and skeletal system. Though the most recent recommendations from the Physical Activity Guidelines for Americans indicate that physical activity should be used to promote mental wellbeing (Piercy et al., 2018), it is unknown how long-term exercise changes the brain, resulting in improved functional outcomes. Here, we show for the first time that long-term exercise in healthy, sedentary, middle-aged adults promotes decreased cortical activity, an indicator of a balanced autonomic nervous system geared towards decreased sympathetic and increased parasympathetic functioning. We further show that this change in resting brain state activity underlies the change in psychological state experienced from long-term exercise, namely improvements in positive affect, body image, and exercise motivation. In addition, we newly found that long-term exercise improves both attention and recognition memory in healthy, sedentary, middle-aged adults, cognitive functions that depend on the prefrontal cortex and hippocampus, respectively. These new findings indicate that long-term exercise can help improve both brain function and physiology in middle-aged adults who were previously sedentary. We recommend that a regular fitness regimen should be incorporated into activities of daily living to promote brain health during aging.

Tables

Table 1. Baseline demographic measures.

	Control	Exercise	t	p
N	17	27		
Age	46.59 (2.06)	44.93 (1.34)	0.709	0.428
Gender				1
% Female	64.7	63		
% Male	35.3	37		
Race				0.768
% American Indian/Alaskan Native	0	3.7		
% Asian	29.4	22.2		
% Black/African American	29.4	18.5		
% White/Caucasian	41.2	48.1		
% Other	0	7.4		
Ethnicity				0.220
% Hispanic/Latino	5.9	22.2		
% Not Hispanic/Latino	94.1	77.8		
Education				0.572
% Elementary school	0	3.7		
% High school	5.9	0		
% Vocational/Technical school	0	3.7		
% Some college	11.8	18.5		
% Bachelors degree	41.2	44.4		
% Masters degree	41.2	22.2		
% Professional degree (e.g. MD, JD)	0	7.4		

Age presented as mean (SEM). All other data presented as percentages.

Table 2. Baseline anthropometric measures.

	Control	Exercise	t	p
Weight (lbs)	170.27 (9.14)	177.12 (7.60)	-0.570	0.572
BMI	27.24 (0.92)	32.88 (4.40)	-1.005	0.321
Body Composition				
Total Body Water	53.96 (1.53)	49.81 (1.86)	1.537	0.132
Fat	28.35 (1.90)	32.49 (2.04)	-1.363	0.180
Muscle	29.90 (1.17)	28.80 (1.33)	0.565	0.575
Bone	8.23 (0.31)	9.89 (1.60)	-0.792	0.433

All data presented as mean (SEM).

Table 3. Mnemonic similarity task.

	Control (n=12)		Exercise (n=21)		TIME	TIME*GROUP
	Before	After	Before	After	p value (effect size)	p value (effect size)
Percent Correct						
Overall	61.66 (2.37)	62.32 (2.56)	63.24 (1.86)	67.51 (1.91)	0.071 (0.102)	0.179 (0.057)
Targets/Old	85.08 (2.60)	78.78 (3.19)	80.58 (2.73)	82.91 (2.34)	0.461 (0.018)	0.115 (0.078)
Lures/Similar	30.95 (4.80)	39.59 (5.26)	35.67 (4.14)	44.81 (3.76)	0.008 (0.207)*	0.937 (0.000)
Foils/New	68.97 (5.29)	68.59 (5.68)	73.47 (3.83)	74.78 (2.42)	0.867 (0.001)	0.762 (0.003)
Reaction Time Correct Responses						
Overall	1174.82 (15.35)	1169.71 (27.80)	1186.41 (21.68)	1166.96 (25.42)	0.466 (0.017)	0.669 (0.006)
Targets/Old	1044.02 (28.63)	1064.00 (37.26)	1041.44 (28.81)	1072.89 (25.69)	0.242 (0.044)	0.792 (0.002)
Lures/Similar	1321.30 (27.44)	1279.86 (34.19)	1367.63(31.53)	1277.84 (31.22)	0.031 (0.146)*	0.411 (0.023)
Foils/New	1156.67 (34.18)	1185.99 (35.11)	1150.16 (34.96)	1150.15 (31.20)	0.566 (0.011)	0.566 (0.011)
Bin Score (1-p|old)						
Bin 1 (Most Similar)	0.24 (0.06)	0.24 (0.05)	0.28 (0.04)	0.31 (0.03)	0.700 (0.005)	0.815 (0.002)
Bin 2	0.28 (0.05)	0.38 (0.05)	0.34 (0.05)	0.40 (0.04)	0.080 (0.096)	0.603 (0.009)
Bin 3	0.39(0.07)	0.44 (0.05)	0.45 (0.06)	0.54 (0.05)	0.173 (0.059)	0.649 (0.007)
Bin 4	0.48 (0.05)	0.55 (0.08)	0.58 (0.05)	0.58 (0.04)	0.488 (0.016)	0.558 (0.011)
Bin 5 (Least Similar)	0.58 (0.05)	0.69 (0.08)	0.61 (0.05)	0.78 (0.04)	0.010 (0.195)*	0.547 (0.012)
Recognition Score						
	0.74 (0.04)	0.69 (0.03)	0.72 (0.03)	0.77 (0.02)	0.908 (0.000)	0.029 (0.145)*
Lure Discrimination Index						
	0.07 (0.05)	0.12 (0.06)	0.15 (0.05)	0.20 (0.05)	0.185 (0.056)	0.975 (0.000)

All data presented as mean (SEM). *p<0.05

Table 4. Stroop task.

	Control (n=11)		Exercise (n=17)		TIME	TIME*GROUP
	Before	After	Before	After	p value (effect size)	p value (effect size)
Percent Correct						
Overall	0.94 (0.02)	0.98 (0.005)	0.96 (0.01)	0.97 (0.01)	0.006 (0.256)*	0.079 (0.256)
Congruent	0.98 (0.01)	0.98 (0.01)	0.98 (0.01)	0.98 (0.004)	0.535 (0.015)	0.805 (0.002)
Incongruent	0.90 (0.03)	0.98 (0.01)	0.94 (0.01)	0.96 (0.01)	0.006 (0.260)*	0.069 (0.122)
Correct Reaction Time						
Overall	898.37 (26.54)	894.76 (22.93)	922.34 (23.18)	860.81 (23.22)	0.017 (0.202)*	0.031 (0.166)*
Congruent	837.55 (25.17)	843.83 (21.58)	861.38 (23.03)	800.72 (24.20)	0.039 (0.154)*	0.013 (0.216)*
Incongruent	959.18 (29.20)	945.69 (30.03)	983.31 (24.97)	920.90 (25.40)	0.025 (0.178)*	0.139 (0.082)
Interference Score	8.63 (2.74)	3.43 (1.24)	6.72 (1.56)	4.25 (1.20)	0.009 (0.235)*	0.322 (0.038)

All data presented as mean (SEM). *$p<0.05$

Table 5. N-back task.

	Control (n=11)		Exercise (n=16)		TIME	TIME * GROUP
	Before	After	Before	After	p value (effect size)	p value (effect size)
Target Percent Correct						
Overall	0.65 (0.05)	0.69 (0.06)	0.66 (0.04)	0.71 (0.04)	0.081 (0.117)	0.916 (<0.001)
N0	0.88 (0.04)	0.86 (0.03)	0.84 (0.03)	0.80 (0.05)	0.339 (0.037)	0.899 (0.001)
N1	0.73 (0.07)	0.75 (0.07)	0.80 (0.04)	0.84 (0.04)	0.273 (0.048)	0.738 (0.005)
N2	0.56 (0.09)	0.63 (0.09)	0.60 (0.06)	0.69 (0.07)	0.053 (0.142)	0.775 (0.003)
N3	0.44 (0.07)	0.53 (0.07)	0.42 (0.06)	0.49 (0.05)	0.036* (0.164)	0.811 (0.002)
Reaction Time Correct						
Overall	706.32 (43.60)	681.31 (49.47)	741.54 (29.70)	747.76 (42.67)	0.701 (0.007)	0.525 (0.018)
N0	591.36 (22.97)	584.27 (45.95)	605.78 (29.55)	601.43 (34.61)	0.816 (0.002)	0.955 (0.000)
N1	673.29 (52.76)	638.28 (34.88)	719.00 (34.52)	655.99 (29.60)	0.068 (0.127)	0.591 (0.012)
N2	833.33 (92.87)	764.69 (73.01)	819.28 (40.71)	863.88 (102.69)	0.852 (0.001)	0.382 (0.032)
N3	752.40 (51.94)	849.85 (101.02)	865.74 (56.59)	982.72 (91.82)	0.078 (0.124)	0.868 (0.001)

All data presented as mean (SEM). *p<0.05

Table 6. Reading span task.

	Control (n=14)		Exercise (n=26)		TIME	TIME * GROUP
	Before	After	Before	After	p value (effect size)	p value (effect size)
Percent Correct						
Overall	0.64 (0.05)	0.68 (0.04)	0.73 (0.03)	0.77 (0.03)	0.021 (0.132)*	0.977 (<0.001)
Two Sentence	0.82 (0.06)	0.86 (0.05)	0.90 (0.03)	0.92 (0.02)	0.342 (0.024)	0.865 (0.001)
Three Sentence	0.82 (0.05)	0.85 (0.04)	0.89 (0.03)	0.87 (0.03)	0.938 (<0.001)	0.309 (0.027)
Four Sentence	0.65 (0.06)	0.70 (0.05)	0.77 (0.04)	0.81 (0.04)	0.147 (0.054)	0.941 (<0.001)
Five Sentence	0.53 (0.07)	0.55 (0.05)	0.56 (0.04)	0.66 (0.05)	0.138 (0.057)	0.315 (0.027)
Six Sentence	0.39 (0.05)	0.46 (0.05)	0.51 (0.04)	0.58 (0.05)	0.028 (0.121)*	0.911 (<0.001)
Percent Correct Disregarding Order						
Overall	0.69 (0.05)	0.73 (0.04)	0.77 (0.03)	0.80 (0.03)	0.088 (0.075)	0.897 (<0.001)
Two Sentence	0.83 (0.06)	0.86 (0.05)	0.90 (0.03)	0.92 (0.02)	0.497 (0.012)	0.937 (<0.001)
Three Sentence	0.84 (0.04)	0.85 (0.04)	0.91 (0.02)	0.88 (0.03)	0.616 (0.007)	0.446 (0.015)
Four Sentence	0.69 (0.06)	0.77 (0.04)	0.80 (0.03)	0.82 (0.03)	0.049 (0.098)*	0.304 (0.028)
Five Sentence	0.59 (0.07)	0.62 (0.05)	0.64 (0.04)	0.72 (0.04)	0.138 (0.057)	0.525 (0.011)
Six Sentence	0.52 (0.06)	0.54 (0.05)	0.61 (0.03)	0.66 (0.04)	0.222 (0.039)	0.643 (0.006)
Reaction Time						
Overall	16660.00 (1260.32)	17599.52 (1512.69)	17268.05 (1204.19)	16786.87 (1541.94)	0.817 (0.001)	0.476 (0.013)
Two Sentence	10820.48 (1684.66)	10020.46 (1412.96)	9866.92 (581.53)	9727.95 (1397.68)	0.696 (0.004)	0.783 (0.002)
Three Sentence	12422.86 (1724.43)	12936.67 (1582.82)	11647.69 (727.54)	12752.31 (1645.73)	0.451 (0.015)	0.782 (0.002)
Four Sentence	16218.57 (1816.14)	19345.24 (2853.89)	17648.20 (1530.32)	15560.26 (1068.56)	0.609 (0.007)	0.014 (0.150)*
Five Sentence	20874.29 (1680.61)	19520.96 (1425.69)	23186.41 (2334.59)	21921.54 (2003.29)	0.454 (0.015)	0.980 (<0.001)
Six Sentence	22963.81 (2193.31)	26174.28 (3386.59)	23991.02 (1848.84)	23972.30 (2152.89)	0.318 (0.026)	0.313 (0.027)
Comprehension Percent Correct						
	0.71 (0.04)	0.68 (0.04)	0.68 (0.03)	0.76 (0.04)	0.451 (0.015)	0.147 (0.054)

All data presented as mean (SEM). *p<0.05

Table 7. Probabilistic learning task.

	Control (n=16)		Exercise (n=26)		TIME	TIME * GROUP
	Before	After	Before	After	p value (effect size)	p value (effect size)
Percent Correct (PC)						
Test phase (Block 7)	0.52 (0.03)	0.58 (0.04)	0.61 (0.02)	0.58 (0.02)	0.506 (0.011)	0.098 (0.067)
Block 1	0.45 (0.03)	0.49 (0.03)	0.49 (0.02)	0.47 (0.03)	0.707 (0.004)	0.239 (0.035)
Block 2	0.50 (0.03)	0.56 (0.02)	0.51 (0.02)	0.55 (0.02)	0.012 (0.146)*	0.520 (0.010)
Block 3	0.53 (0.03)	0.57 (0.03)	0.56 (0.02)	0.59 (0.02)	0.139 (0.054)	0.887 (0.001)
Block 4	0.53 (0.03)	0.60 (0.02)	0.56 (0.02)	0.58 (0.03)	0.037 (0.104)*	0.216 (0.038)
Block 5	0.56 (0.04)	0.58 (0.03)	0.58 (0.02)	0.56 (0.03)	0.962 (0.000)	0.368 (0.020)
Block 6	0.57 (0.03)	0.60 (0.03)	0.57 (0.02)	0.59 (0.02)	0.226 (0.036)	0.776 (0.002)
Reaction Time Correct						
Test phase (Block 7)	955.42 (63.30)	1029.94 (50.64)	999.42 (55.45)	975.16 (54.73)	0.647 (0.005)	0.370 (0.020)
Block 1	1440.00 (99.67)	1337.12 (128.17)	1523.44 (72.34)	1461.83 (80.17)	0.271 (0.030)	0.781 (0.002)
Block 2	1203.89 (66.34)	1133.54 (64.78)	1263.05 (67.53)	1092.44 (55.38)	0.032 (0.110)*	0.361 (0.021)
Block 3	1128.62 (66.47)	1040.56 (65.40)	1112.77 (60.14)	1040.34 (67.64)	0.151 (0.051)	0.888 (0.001)
Block 4	1154.48 (69.20)	977.42 (58.45)	1090.50 (71.03)	1015.91 (58.16)	0.037 (0.104)*	0.385 (0.019)
Block 5	1087.32 (73.99)	1013.66 (52.97)	1034.62 (51.90)	999.57 (63.00)	0.367 (0.020)	0.747 (0.003)
Block 6	942.25 (62.42)	994.91 (63.46)	982.49 (57.14)	952.48 (65.09)	0.837 (0.001)	0.455 (0.014)
Learning Rate (B6PC-B1PC)	0.11 (0.04)	0.11 (0.04)	0.08 (0.03)	0.12 (0.04)	0.596 (0.007)	0.403 (0.018)

All data presented as mean (SEM). *p<0.05

Table 8. Pursuit Rotor Task.

	Control (n=15)		Exercise (n=25)		TIME	TIME * GROUP
	Before	After	Before	After	p value (effect size)	p value (effect size)
Percent time on target						
Overall	56.27 (3.11)	60.78 (3.04)	55.36 (2.59)	61.28 (2.29)	0.002 (0.234)*	0.646 (0.006)
Block 1	50.36 (2.93)	58.47 (3.12)	49.87 (2.76)	59.42 (2.42)	0.000 (0.453)*	0.650 (0.005)
Block 2	58.07 (2.71)	60.64 (3.27)	54.87 (2.83)	60.23 (2.39)	0.037 (0.110)*	0.452 (0.015)
Block 3	58.32 (3.62)	61.66 (3.11)	56.85 (2.78)	62.48 (2.25)	0.023 (0.129)*	0.549 (0.010)
Block 4	58.35 (3.89)	62.34 (3.36)	59.83 (2.50)	63.00 (2.63)	0.069 (0.084)	0.829 (0.001)
Average time on target (ms)						
Overall	162.18 (19.23)	141.85 (9.16)	170.24 (17.18)	137.43 (6.09)	0.043 (0.104)*	0.626 (0.006)
Block 1	149.08 (18.95)	131.93 (8.74)	152.51 (13.74)	132.11 (6.00)	0.103 (0.068)	0.886 (0.001)
Block 2	167.75 (20.71)	140.32 (9.00)	169.81 (18.03)	134.43 (6.23)	0.027 (0.122)*	0.773 (0.002)
Block 3	169.11 (19.63)	142.96 (9.52)	174.73 (18.51)	141.63 (6.99)	0.024 (0.127)*	0.785 (0.002)
Block 4	162.79 (18.83)	152.19 (11.55)	183.92 (19.45)	141.57 (6.45)	0.077 (0.080)	0.283 (0.030)
Average distance away from target (cm)						
Overall	0.94 (0.05)	0.90 (0.06)	1.01 (0.06)	0.97 (0.05)	0.392 (0.019)	0.921 (0.000)
Block 1	1.00 (0.04)	0.95 (0.09)	1.17 (0.11)	0.95 (0.04)	0.064 (0.088)	0.190 (0.045)
Block 2	0.89 (0.04)	0.88 (0.05)	1.02 (0.07)	0.98 (0.07)	0.740 (0.003)	0.817 (0.001)
Block 3	0.92 (0.06)	0.89 (0.06)	0.95 (0.05)	0.94 (0.06)	0.636 (0.006)	0.815 (0.001)
Block 4	0.94 (0.08)	0.88 (0.07)	0.90 (0.04)	0.99 (0.10)	0.799 (0.002)	0.257 (0.034)
Number of Hits						
Block 1	233.64 (19.31)	279.33 (17.36)	219.50 (14.52)	275.37 (7.01)	0.000 (0.300)*	0.688 (0.004)
Block 2	242.31 (22.20)	270.16 (16.10)	224.71 (15.09)	274.03 (7.13)	0.006 (0.181)*	0.424 (0.017)
Block 3	241.96 (22.42)	273.04 (16.61)	224.88 (14.99)	274.00 (7.57)	0.007 (0.178)*	0.523 (0.011)
Block 4	250.04 (24.30)	259.76 (16.55)	234.88 (16.06)	272.36 (6.56)	0.099 (0.070)	0.326 (0.025)

All data presented as mean (SEM). *$p<0.05$

Table 9. Spatial navigation task.

	Control (n=14)		Exercise (n=23)		TIME	TIME * GROUP
	Before	After	Before	After	p value (effect size)	p value (effect size)
Seek Duration						
Average Seek Duration (Phase 1)	91.79 (5.75)	89.28 (7.78)	91.51 (7.29)	81.49 (5.56)	0.292 (0.032)	0.526 (0.012)
Average Seek Duration (Phase 4)	103.86 (15.95)	119.39 (22.67)	98.46 (8.39)	85.11 (8.78)	0.912 (0.000)	0.149 (0.059)
Seek Rate						
Average Rate (Phase 1)	4.72 (0.26)	5.07 (0.51)	4.73 (0.25)	5.41 (0.30)	0.059 (0.098)	0.529 (0.011)
Percent of Optimal Rate (Phase 1)	0.31 (0.02)	0.34 (0.03)	0.32 (0.02)	0.36 (0.02)	0.059 (0.098)	0.529 (0.011)
Average Rate (Phase 4)	5.05 (0.34)	5.06 (0.36)	5.24 (0.32)	5.54 (0.33)	0.502 (0.013)	0.513 (0.012)
Percent of Optimal Rate (Phase 4)	0.34 (0.02)	0.34 (0.02)	0.35 (0.02)	0.37 (0.02)	0.502 (0.013)	0.513 (0.012)
Landmark						
Landmark Percent Correct (Phase 2)	84.23 (3.06)	80.36 (3.31)	86.05 (2.07)	88.04 (2.20)	0.654 (0.006)	0.167 (0.054)
Landmark Percent Correct (Phase 5)	64.67 (5.72)	67.26 (3.54)	61.66 (5.00)	69.38 (3.61)	0.129 (0.065)	0.444 (0.017)
Correct Landmark Reaction Time (Phase 2)	3.55 (0.16)	3.36 (0.13)	3.98 (0.21)	3.70 (0.24)	0.129 (0.065)	0.737 (0.003)
Object						
Object Percent Correct (Phase 5)	38.45 (6.13)	41.67 (5.52)	49.08 (5.63)	43.48 (5.76)	0.748 (0.003)	0.239 (0.039)
Association						
Association Percent Correct (Phase 6)	88.10 (2.13)	88.69 (3.16)	89.49 (1.90)	87.68 (1.49)	0.704 (0.004)	0.454 (0.016)
Correct Association Reaction Time (Phase 6)	2.89 (0.13)	2.95 (0.14)	2.97 (0.17)	3.01 (0.17)	0.703 (0.004)	0.918 (0.000)
Temporal						
Temporal Percent Correct (Phase 7)	66.07 (3.26)	71.43 (4.39)	70.29 (2.96)	67.21 (3.72)	0.757 (0.003)	0.255 (0.037)
Correct Temporal Reaction Time (Phase 7)	2.87 (0.16)	3.12 (0.26)	3.30 (0.21)	2.97 (0.17)	0.786 (0.002)	0.047 (0.108)*
Episodic Memory						
Episodic Memory Score	68.30 (2.54)	69.88 (3.08)	71.32 (2.96)	71.16 (2.18)	0.669 (0.005)	0.603 (0.008)
Episodic Memory Reaction Time	3.10 (0.12)	3.74 (0.20)	3.91 (0.20)	3.68 (0.25)	0.228 (0.041)	0.013 (0.163)*

All data presented as mean (SEM). *p<0.05

Table 10. Correlations between baseline brain activity and significant psychological and cognitive measures.

		Change in positive affect	Change in exercise motivation	Change in body attitudes	Change in recognition memory	Change in attention
Whole-brain	**Change in relative delta power**	-0.24	-0.20	-0.37	0.23	0.18
	Change in relative theta power	-0.14	-0.10	-0.48*	0.25	0.10
	Change in relative beta power	-0.06	-0.14	0.45*	-0.20	-0.19
	Change in relative alpha power	0.36	0.41	-0.06	-0.12	-0.24
Frontal	**Fz**	0.29	0.42	0.05	-0.07	-0.35
	Fpz	0.44*	0.42	0.16	0.10	-0.20
	F4	0.32	0.23	-0.29	-0.16	-0.26
Central	**C3**	0.53*	0.49*	0.10	-0.02	-0.15
	C4	0.39	0.38	-0.03	0.07	-0.25
Temporal	**T5**	0.34	0.36	0.11	-0.16	-0.20
	T6	0.41	0.50*	0.09	-0.22	-0.35
Parietal	**P3**	0.22	0.35	0.003	0.05	0.00
	P4	0.37	0.46*	0.03	-0.04	-0.19
Occipital	**O1**	0.18	0.27	0.08	-0.08	-0.17
	O2	0.26	0.43*	-0.09	-0.17	-0.06

*p<0.05 *p<0.01

Figures

Figure 1. Diagram of study procedure.

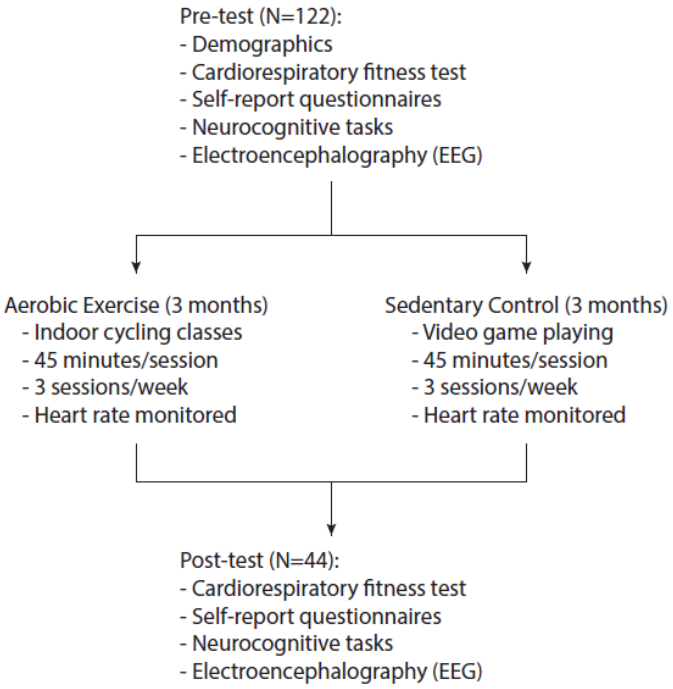


Figure 2. Example of ERP Grand Average.

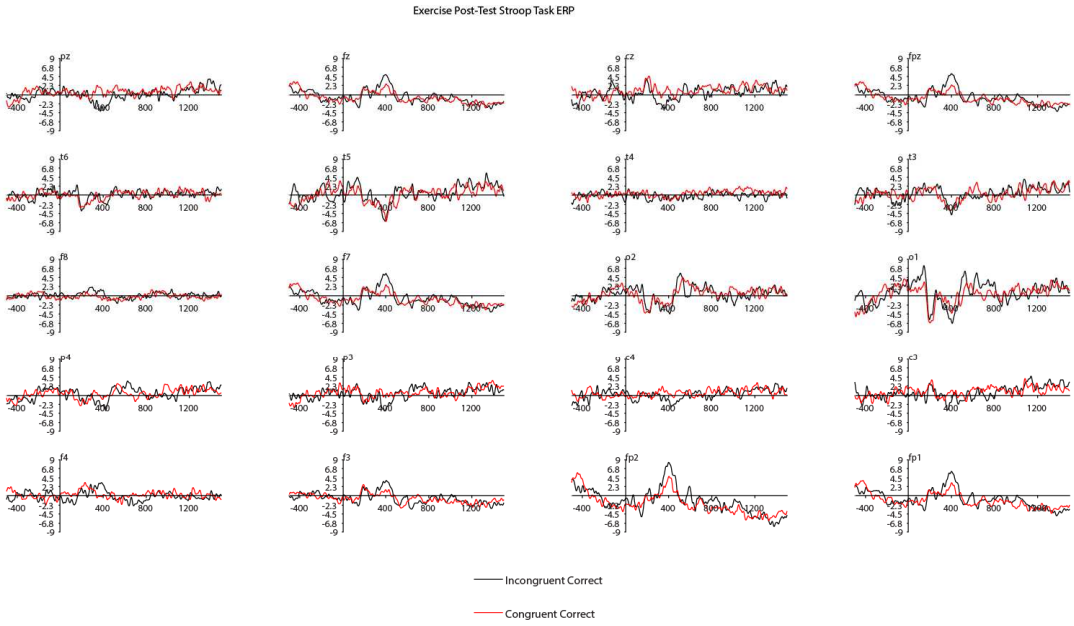


Figure 3. Fitness measure. A) The exercise group had an elevated heart rate compared to the control group during intervention sessions. B) There was no significant change in estimated maximal aerobic capacity over time or between groups.

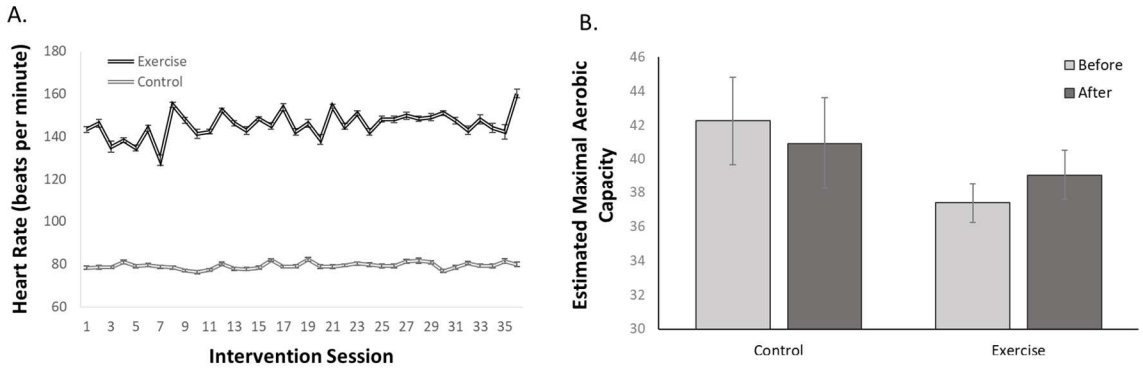


Figure 4. Significant time*group interaction effects were found for A) positive affect, exercise motivation, body attitudes, B) recognition memory, and C) attention. *p<0.05

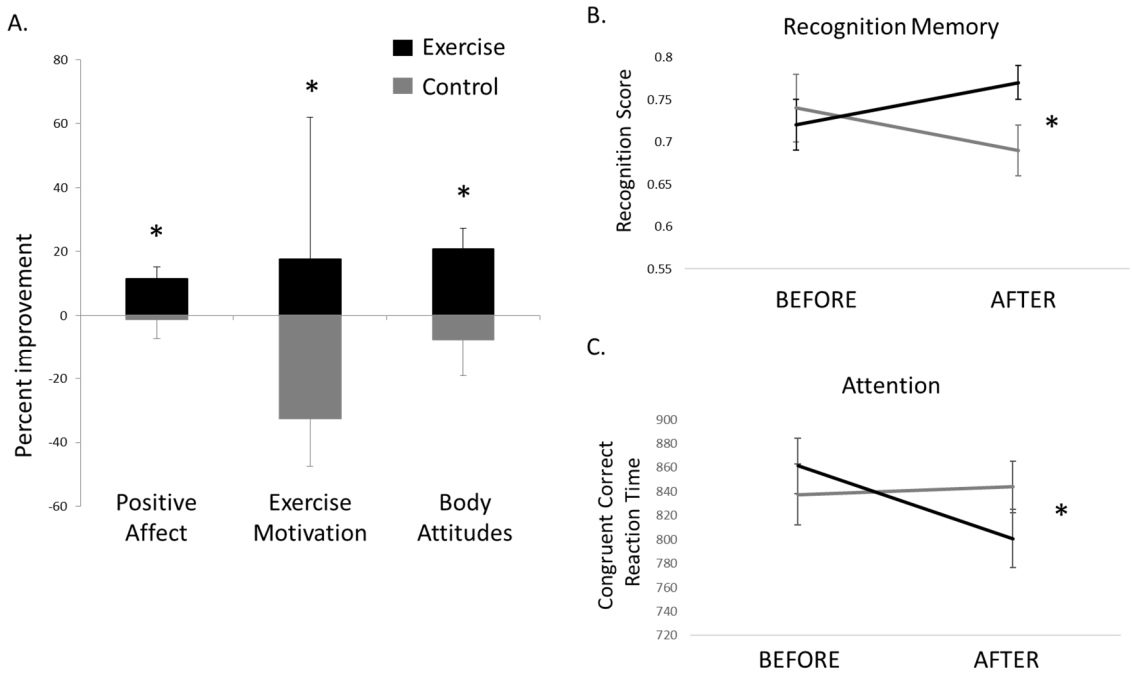


Figure 5. Changes in relative delta power. A) There was a significant time*group interaction effect in whole-brain relative delta power. B) There was no significant effect in any individual electrode. C) Plot of changes in relative delta power at individual electrode sites. *p<0.05

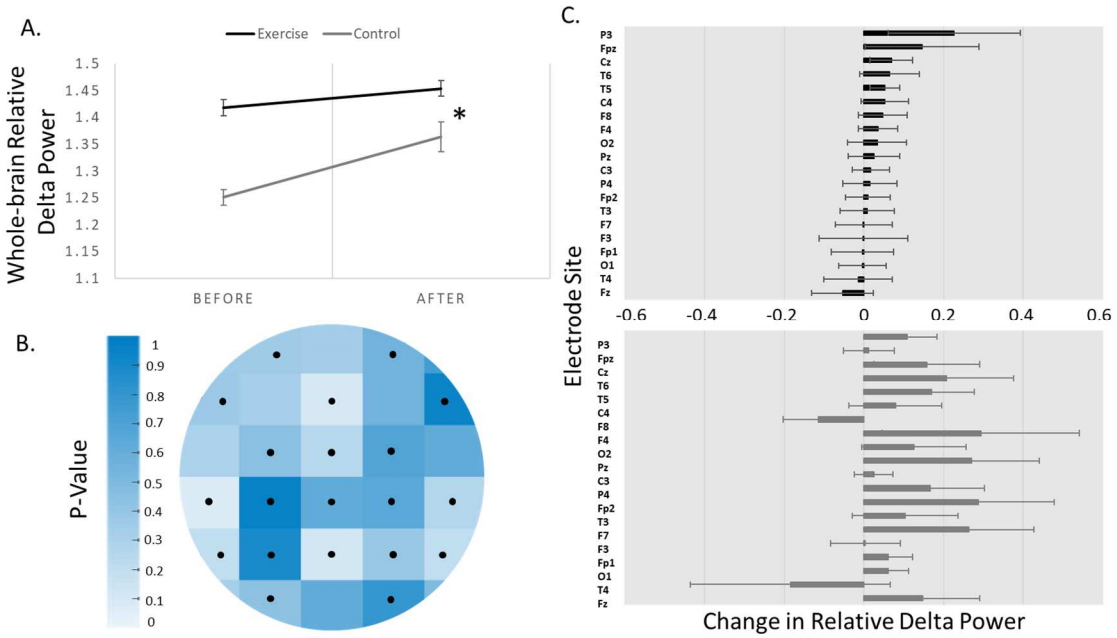


Figure 6. Changes in relative theta power. A) There was a significant time*group interaction effect in whole-brain relative theta power. B) There was no significant effect in any individual electrode. C) Plot of changes in relative theta power at individual electrode sites. *p<0.05

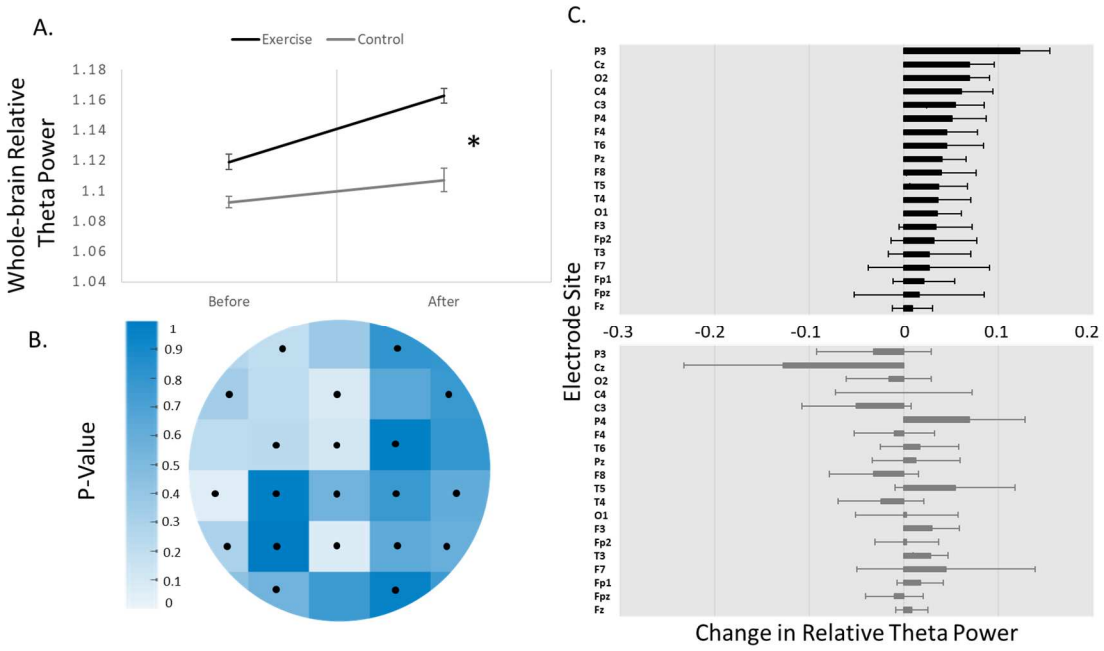


Figure 7. Changes in relative alpha power. A) There was a significant time*group interaction effect in whole-brain relative delta power. B, C) There was a significant effect at the Fz, Fpz, F4, C3, C4, T5, T6, P3, P4, O1, and O2 electrodes. *p<0.05

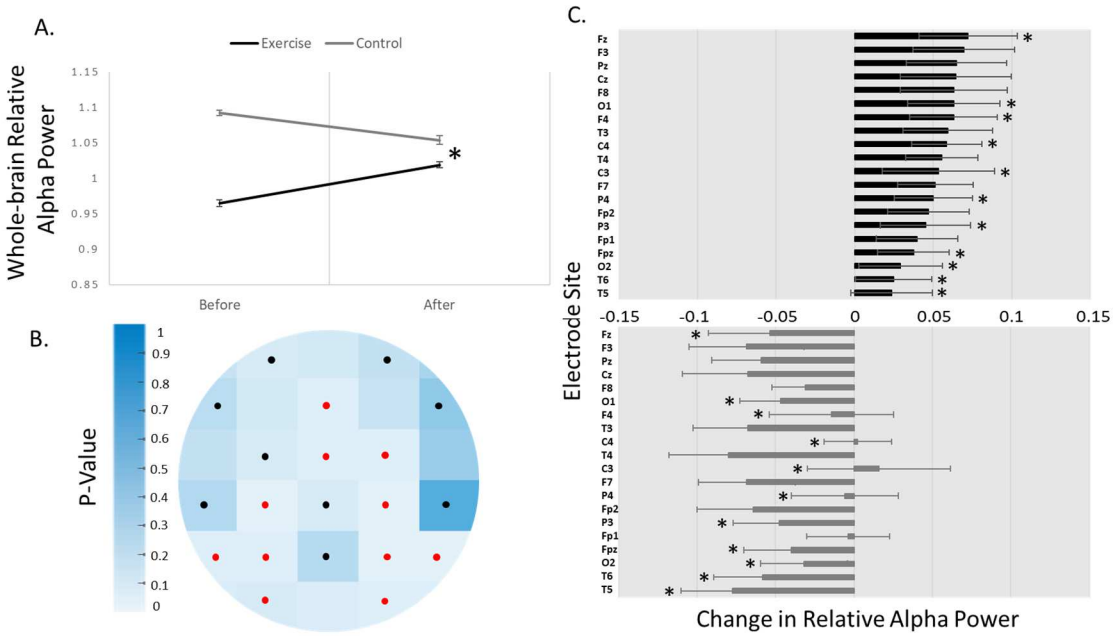
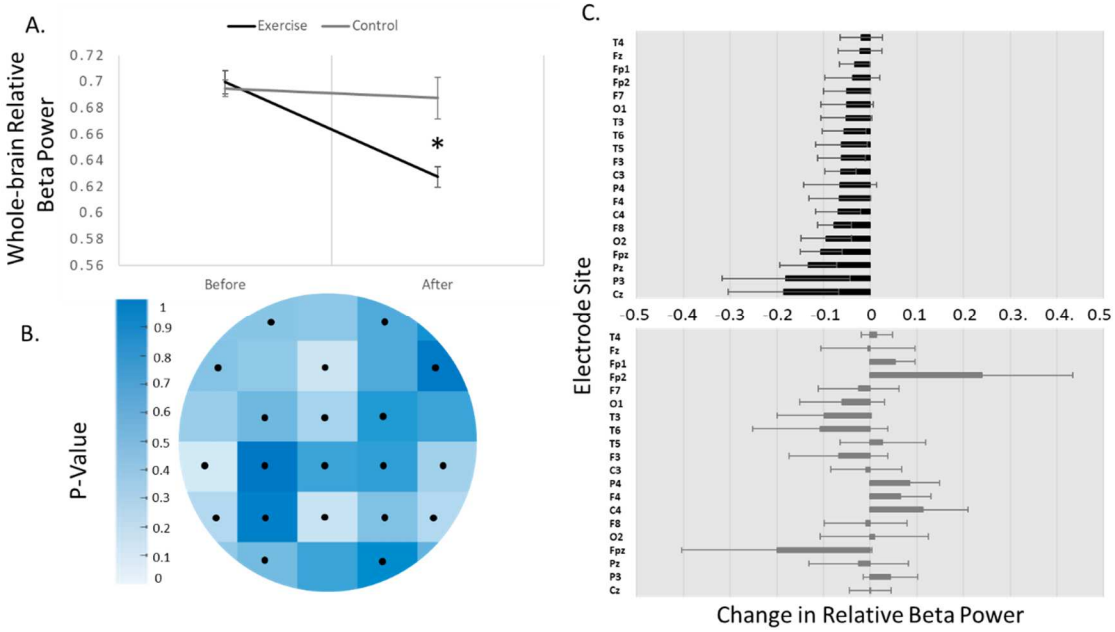


Figure 8. Changes in relative beta power. A) There was a significant time*group interaction effect in whole-brain relative beta power. B) There was no significant effect in any individual electrode. C) Plot of changes in relative beta power at individual electrode sites. *p<0.05



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CHAPTER 5
SUMMARY AND CONCLUSION

My dissertation set out to explore the neurobehavioral correlates of health behaviors, the effects of exercise on these neurobehaviors, and the associated neurophysiological mechanisms. This was investigated through 3 cross-sectional and interventional studies. In Chapters 2 and 3, I examined neurobehavioral balance through the lens of the Competing Neurobehavioral Decision Systems theory in 2 populations - individuals with obesity and individuals in recovery from substance misuse. In Chapter 4, I examined the ability of an exercise intervention to improve neurobehaviors and neurophysiological signals.

In Chapter 2, I explored the neurobehavioral correlates of obesity, a condition which develops in part through engagement in maladaptive health behaviors. Individuals in this clinical population showed heightened delay discounting, impaired motivation, poor body image, decreased affective state, and impaired executive function. These neurobehavioral alterations suggest that this population has heightened activity of the reward system and impaired activity of the impulsive system. Using these neurobehaviors as predictors, I created a Bayesian network model that accurately predicted approximately 65% of cases of obesity.

In Chapter 3, I examined neurobehavioral factors associated with eating behaviors in a population of individuals in recovery from substance misuse. Considering that substance use disorders may cause persistent impairments in the top-down executive system and that substantial weight gain is commonly reported during substance use recovery, I anticipated that individuals in recovery from substance misuse would show heightened delay discounting similarly to individuals with obesity and other clinical populations (Bickel et al., 2019). However, we found that these individuals showed lower delay discounting than a healthy control group, suggesting that individuals in recovery actually may have heightened executive control. As this was a population of individuals who are currently abstinent, this heightened executive control may be important in supporting their avoidance of substance use.

In Chapter 4, I examined the effects of a long-term aerobic exercise intervention on a range of neurobehaviors as well as cortical neurophysiological signals in a population of previously sedentary, middle-aged individuals. I found that long-term exercise improves a range of neurobehaviors in this population including recognition memory, attention, affect, body image, and motivation. Further, I found that improvements in affect, body image, and motivation

are related to decreased resting-state cortical activation, suggesting that this is a mechanism for the neurobehavioral improvements.

Considering that exercise improves several of the neurobehaviors that are shown to be impaired in clinical populations, it is a promising intervention not only to maintain physical health and prevent chronic disease but to enhance brain health and behaviors as well. Improvements in neurobehavioral function induced by exercise may, in turn, lead to improvements in other aspects of health. For example, exercise improves top-down executive function; this improvement, in turn, supports subsequent engagement in positive health behaviors and avoidance of risky health behaviors (Allan et al., 2016). Future investigations may explore the impacts of additional behavioral interventions that improve neurobiological systems and mechanisms of communication between the body and brain. Promising interventions for future study may include episodic future thinking, cognitive behavioral therapy (Felmingham et al., 2007), and mindfulness (Creswell et al., 2016).

My findings suggest that these behavioral improvements occur through enhanced communication between areas within the brain as evidenced through the oscillatory activity in the EEG signal. Multi-modal physical activity, such as dance, may induce further neurobehavioral improvements through the engagement of a wide variety of brain regions (Basso et al., 2020). Engagement of these widespread systems involved with sensory, motor, cognitive, social, emotional, rhythmic, and creative behaviors may enhance neural communication among these areas to support improved neurobehavioral functions. Future research may explore the impacts of multi-modal forms of physical activity compared to traditional aerobic exercise on brain health, neurobehaviors, and neurophysiology.

Although exercise is undoubtedly beneficial to the body and mind, maintenance of a regular exercise routine can be challenging for a variety of reasons (Schutzer & Graves, 2004; Tulloch et al., 2013). Enjoyment is a strong predictor of exercise adherence and maintenance. Although different forms of exercise may have some differential effects mechanistically (Cassilhas et al., 2012), any amount or form of regular physical activity has benefits over sedentary behaviors. As there are numerous ways to engage in exercise and physical activity, it is recommended that individuals engage in enjoyable physical activities to successfully maintain a regular physical activity regimen.

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