Title

Mind over Matter: Food Addiction, Impulsivity, Glycemic Control, and Brain Tissue Injury in Type 2 Diabetes Mellitus

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Publication Date

2023

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

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A dissertation submitted in partial satisfaction of the

requirements for the degree

Doctor of Philosophy in Nursing

by

Jolene Tan Smeltzer

2023

ABSTRACT OF THE DISSERTATION

Mind over Matter: Food Addiction, Impulsivity, Glycemic Control, and Brain Tissue Injury in Type 2 Diabetes Mellitus

by

Jolene Tan Smeltzer

Doctor of Philosophy in Nursing

University of California, Los Angeles, 2023

Professor Sarah Eunkyung Choi, Chair

Type 2 Diabetes Mellitus (T2DM) is a significant public health concern with high morbidity and mortality burden. Maladaptive food behaviors contribute to poor glycemic outcomes for persons with Type 2 Diabetes Mellitus (T2DM). Factors which may contribute to poor T2DM dietary behaviors include food addiction (FA; overconsumption to the point where there are similar symptoms to substance use addiction) and impulsivity (lack of control in food consumption). FA and impulsivity behaviors can be reflected by differences in brain tissue integrity, but the relationships between FA, impulsivity, and brain tissue changes in persons with T2DM are unclear. To date, little is known about FA and impulsivity in association with A1c levels (indication of poor glycemic control) among T2DM patients. While studies indicate

associations between brain injury and A1c levels in T2DM patients, it is also unclear if FA and brain injury can independently predict glycemic control in T2DM. An examination of the brain associated with these behaviors has not been assessed in persons with T2DM.

The overarching purpose of this dissertation study is to offer valuable insights into the link between brain tissue integrity, food behaviors, and glycemic control in T2DM patients. Manuscript one compares the relationships between FA, impulsivity, and glycemic outcome (hemoglobin A1c) between 32 T2DM and 32 healthy patients between the ages 40-65 years. Participants completed the Yale Food Addiction Scale 2.0 (YFAS) and Barratt Impulsiveness Scale-11 (BIS) online questionnaires and A1c was measured with a fingerstick test. Between T2DM and healthy patients, there were no group differences in the prevalence of FA diagnosis, YFAS 2.0 scores, BIS-11 scores, or severity classification of FA diagnosis. There were positive correlations between two FA symptomatologies with higher A1c: food tolerance and food use in physically hazardous situations ($r= 0.254$, $r= 0.417$, $P <0.05$). There were no significant correlations between BIS-11 scores and A1c. In this study, two FA symptomatologies were linked to poor A1c suggesting that a subset of questions from YFAS 2.0 could provide clinicians insight into glycemic outcomes (A1c). This was the first study that investigated the associations between FA symptomatologies and A1c among T2DM patients and healthy controls.

In manuscript two, using diffusion tensor imaging data, mean diffusivity (MD) values were calculated, and region-of-interest analyses were performed on various brain areas to examine correlations between brain tissue integrity (measured by MD values) and YFAS 2.0 and BIS scores (partial correlations; covariates, age, and sex). Twenty-one T2DM participants between the ages 40-65 years completed brain magnetic resonance imaging (MRI) scans. There were significant correlations between tissue integrity and YFAS 2.0 scores in brain regions

regulating executive decision-making (cortices, precuneus, temporal); memory -visual or auditory (occipital, supramarginal); motor function (putamen); and emotion (cingulum) functions in T2DM patients. While there were no associations between BIS-11 scores and brain tissue integrity, there is now neuroimaging evidence of specific impaired brain sites that mediate FA symptomatologies among T2DM patients in this sample. Manuscript three determined which of the following were independent predictors of A1c status: food tolerance and food use during physically hazardous situations FA symptomatologies (found in manuscript one), and areas of brain damage (that are linked to A1c) in the following regions: areas mediating cognition/executive decision-making (frontal middle-right, frontal medial orbital -right) and emotion (cingulate). Among 32 T2DM patients, only tissue changes in the right medial orbitofrontal cortices (OFC) were an independent predictor of glycemic status, and not the two FA symptomatologies or the other brain regions. Findings from manuscript two and three regarding injury to brain areas regulating cognition (frontal cortices) further corroborate past structural neuroimaging studies that T2DM patients have brain injury in the frontal cortices affecting their decision-making. The dissertation identifies several interventions with the potential to promote neurogenesis or neuroprotection in areas of brain injury (e.g., cognitive brain training, neurofeedback, stem cell therapies, and nutritional supplementation).

This dissertation contributes to T2DM research by shedding light on the crucial role of brain regions in regulating food behaviors and, subsequently, managing A1c. This understanding shifts the focus of interventions from solely addressing physiological or behavioral aspects of T2DM to incorporating brain-based interventions that can improve glycemic outcomes. By highlighting these potential interventions, the dissertation opens new avenues for research and development in T2DM management and ultimately, improved care for T2DM patients.

The dissertation of Jolene Tan Smeltzer is approved.

Mary A. Woo

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University of California, Los Angeles

2023

DEDICATION

To my husband, Daniel, thank you for your countless acts of love and selfless devotion to our family. Daniel, your sacrificial and joyful care for Judson, Keenan, and me, enables us to reach for our dreams and to be a blessing to others. Soli Deo Gloria.

To my Tan and Smeltzer family and Lighthouse Community Church family for their love, prayers, and unwavering support throughout this challenging and rewarding process.

Heartfelt thanks to UCLA School of Nursing for financial support via the Dean Sarna Doctoral Fellowship Award and Jonas Nurse Scholar Program.

To my mentors from the UCLA/Charles R. Drew University (CDU) Bridge Program: Dr. Janet Mentes, Dr. Linda R. Phillips, Dr. Ebere Ume, and Dr. Sharon Cobb, who inspired, supported, and created opportunities for minority researchers like me, through financial support from the National Institute of Health/Nursing Research UCLA/CDU Partnership for Enhancing Diversity of Nurses with Research Careers (Grant Number: 5R25GM102777-02).

To Dr. Sarah Choi, for taking on the role of my chair and advisor, committing to my success, and teaching and mentoring me to pursue excellence in every regard of life.

To my committee members: Dr. Rajesh Kumar, Dr. Wendie Robbins, Dr. Timothy Fong, and especially, Dr. Mary A. Woo, whom I am honored to learn from, and I am forever grateful for all your graciousness towards my mistakes, your dedication to our research, and your generosity towards time spent in encouraging, guiding, and challenging me throughout my journey.

and

To everyone affected by T2DM, may this study and future studies help to improve your future.

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CURRICULUM VITAE

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PUBLICATIONS:

1. Nyamathi, A., Shin, S. S., **Smeltzer, J.,** Salem, B., Yadav, K., Krogh, D., & Ekstrand, M. (2018). Effectiveness of dialectical behavioral therapy on reduction of recidivism among recently incarcerated homeless women: A pilot study. *International Journal of Offender Therapy and Comparative Criminology*, doi.org/10.1177/0306624X18785516.
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1. Van, C., **Smeltzer, J.** (2022-poster). Reducing CAUTIs with a novel catheter technology in the ICU. 51st Critical Care Congress, San Juan, Puerto Rico, February 2022.
2. **Smeltzer, J.** (2021-oral symposium). The impact of a revised bladder protocol and foley catheter policy in MSICU to reduce catheter associated urinary tract infections (CAUTIs). Torrance Memorial Medical Magnet Re-Designation Site Visit Nursing Research/EBP Conference, Torrance, CA, January 2021.
3. **Smeltzer, J.** (2021-poster). Mood and cognition in patients with Type 2 Diabetes. Western Institute of Nursing Virtual Conference, April 2021.
4. **Smeltzer, J.** (2020-poster). Neighborhoods matter: Geographic Risk assessment of Los Angeles County and the role of disadvantaged schools in public health. UCLA School of Nursing Research Days, Los Angeles, CA, May 2020.
5. **Smeltzer, J.** (2019-oral symposium). Mortality and the sequence of diagnosis of obstructive sleep apnea and hypertension. Western Institute of Nursing Conference, San Diego, CA, April 2019.
6. **Smeltzer, J.** (2018-oral symposium). Perspectives on the community reintegration health needs of older adult parolees. Western Institute of Nursing Conference, Spokane, WA, April 2018.
7. **Smeltzer, J.**, Williams, P., Ofori, V., Shaheen, M., Kermah, D., Evers-Manly, S. (2017-oral symposium). Prevalence and predictors of post-partum depression and the use of mental health services. Western Institute of Nursing Conference, Denver CO, April 2017.

CHAPTER ONE

Introduction

Chapter One: Introduction

Background

Globally and nationally, diabetes is a rising public health concern, affecting over 37 million which is approximately 11.3% of the US population (Centers for Disease Control Prevention, 2022). According to the American Diabetes Association (2018), 1.5 million Americans are diagnosed with diabetes every year, and since 2015, it remains the seventh leading cause of death in the United States. It is projected that as many as one in three US adults will have diabetes by 2050 ((Boyle et al., 2010). Approximately 90-95% of patients with diabetes have Type 2 Diabetes (T2DM), which results from a combination of insulin resistance and some deficiency in insulin secretion as a compensating response to hyperglycemia (Centers for Disease Control Prevention, 2022). Though modern Western societies perpetuate sedentary lifestyle and overconsumption through urbanization and the ubiquity of food, there are heterogenous factors leading to impaired glucose tolerance, such as irreversible risk factors of age, genetics, race, ethnicity, and other comorbid diseases, as well as reversible factors, such as diet, physical activity, medications, surgery, infections, and smoking (Cho et al., 2018; Shaw et al., 2010; Whiting et al., 2011).

Diabetes can reduce an individual's life expectancy up to 15 years (Davies et al., 2004; Leal et al., 2009). Many severe comorbidities are associated with poorly controlled T2DM, including hypertension, dyslipidemia, cardiovascular disease, neuropathy, non-congenital blindness and retinopathy, nephropathy and renal disease, foot ulcers, peripheral artery disease, and limb amputations (Long & Dagogo-Jack, 2011). Epidemiologic evidence from T2DM studies in older adults indicate that there are more comorbid conditions than previously associated with T2DM, such as cognitive impairment, depression, urinary incontinence, fracture

risk, and increased risk of cancer (Harper & Lynch, 2005; Karter et al., 2015; Phelan et al., 2009; Shikata et al., 2013; Stewart & Liolitsa, 1999; Vestergaard et al., 2005).

Food Behaviors Among T2DM Patients

To prevent and control the DM-associated comorbidities and expenditures, T2DM self-management activities, such as weight management, increasing physical activity, and making diet and lifestyle modifications, are all recommended as first-line T2DM treatments (Daley & Wallymahmed, 2014). Studies suggest that achieving optimal glycemic control will help minimize long term complications, such as cardiovascular and kidney diseases (Vijan et al., 2005). To optimize glycemic control, T2DM patients are advised to practice self-management activities that integrate multiple treatment strategies, such as adherence to medication, diet, and physical activity recommendations. Particularly, dietary modification is considered an important aspect of T2DM self-management where it is proposed as first-line therapy for metabolic control (Bantle et al., 2006; Krawagh et al., 2011; UK Prospective Diabetes Study Group, 1998). Of all the T2DM self-management activities, healthy dietary behaviors are essential to the overall well-being of a patient if managed over the life course of the health condition (Diabetes Control Complications Trial Research Group, 1993; Sami et al., 2017).

Besides the amount of food consumed, the quality of food, and the nutrient content of dietary regimens (which was not measured in this study), adherence to dietary recommendations have been found to be important in achieving glycemic control and thereby necessary in T2DM treatment to prevent or delay micro- and macrovascular complications (Brown et al., 2016; Metz et al., 2000). T2DM management, however, is behaviorally and psychologically demanding, because it requires diligent self-care and on-going lifestyle modifications, such as inconvenient dietary restrictions (Uchenna et al., 2010). In fact, only 57% of insured individuals with T2DM

reported to have glycemic control (Dall et al., 2016; Menke et al., 2015). In comparison to all aspects of diabetes self-care activities, dietary management has been perceived to be the greatest barrier and more cumbersome than medication therapy (Glasgow et al., 1997; Vijan et al., 2005). Furthermore, T2DM patients were found to be less compliant in following a prescribed diet compared to patients with other chronic conditions, like hypertension or heart failure (Groop & Tuomi, 1997; Kravitz et al., 1993).

Despite the importance of dietary adherence in T2DM, current approaches that focus on patient education to influence healthy dietary behaviors have not been effective, because they are difficult to adopt and maintained by persons with T2DM (American Diabetes Association, 2019b; Davies et al., 2018; Sami et al., 2017). Clinicians and researchers then face a complex challenge to uncover the reasons that contribute to T2DM patients having poor food behaviors. Several factors that can influence T2DM patients' food choice behaviors and self-care activities have been reported, including severity of T2DM symptoms, perceptions of barriers or risk involved (self-efficacy), amount of social support, emotional or psychological stress, cultural and religious practices, economic stability, and the patients' physical and social environments (Aljasem et al., 2001; Daly et al., 2009; Nagelkerk et al., 2006; Vijan et al., 2005). Unfortunately, the most effective approach to understanding dietary behaviors has not been clearly established nor the direct causation of poor food behaviors. This knowledge gap challenges clinician's efforts to improve T2DM dietary behaviors and highlights the need to consider new factors, such as food addiction (FA) and impulsivity, in the evaluation of T2DM glycemic outcomes.

Role of the Brain in Poor T2DM Food Behaviors

Though it is unclear as to why T2DM patients engage in unhealthy eating behaviors,

prior research has suggested poor dietary behaviors could be linked to regional brain activity showing a resemblance between food and substance addiction. Food addiction (FA) may occur if there is elevated activation in the brain reward circuitry in response to food cues, and reduced activation of inhibitory brain regions in response to food intake to the point that there is an inability to change (stop overeating) when there are negative consequences (Blumenthal & Gold, 2010; Gearhardt et al., 2009b; Volkow & Baler, 2015). A competing view is that these maladaptive eating behaviors are due to impulsivity, where persons are unable to control their desires for immediate gratification by unhealthy eating and they forego greater delayed rewards for smaller instant rewards (Jimura et al., 2013; Kalon et al., 2016a; Volkow & Baler, 2015).

While the poor glycemic outcomes in T2DM may be due to FA or impulsivity (or a combination of both), an examination of these potential factors has not been evaluated in persons with T2DM. Moreover, to investigate the underpinnings in poor glycemic management, it is important to understand how the brain is involved by exploring brain changes related to T2DM. Brain status in relationship to FA and impulsivity has not been reported in T2DM patients. Though impulsive behaviors overlap with addiction concepts, human neuroimaging data have shown distinct differences: there is abnormal functioning in association with the orbitofrontal cortices and amygdala among substance abusers/addiction (Blumenthal & Gold, 2010; Gearhardt, Yokum, et al., 2011), whereas in impulsive subjects, the dysfunction is in insular, frontal cortices and hypothalamus (Dambacher et al., 2015; Jimura et al., 2013; Kalon et al., 2016a). In any case, these addiction and impulsive behaviors should be reflected by differences in the brain (in which all behaviors originate).

There are limited methods to evaluate the brain in intact human beings. Magnetic resonance imaging (MRI) of the brain provides very high-resolution images, is non-invasive, and

does not require radiation or administered contrast agents. Highly-innovative MRI methods have been used to evaluate the brains of T2DM subjects, and significant tissue injury has been found in the following brain regions: hyperactivity in the amygdala; hypoactivity in prefrontal cortex (regions associated with addiction) and gray matter damage in insular lobes, frontal cortices, cingulate, hypothalamus, and thalamus (regions associated with impulsivity) (Choi, Roy, Freeby, Mullur, et al., 2020; Choi, Roy, Freeby, Woo, et al., 2020; Roy et al., 2020). To date, there are no studies that have investigated structural integrity of the brain as the basis of the maladaptive food behaviors among T2DM. There have been, however, established neural functional imaging studies with other medical conditions such as obesity, eating disorders, and addiction (Fahy & Eisler, 1993; Gearhardt et al., 2012; Murphy et al., 2014). An exploration of the changes in specific brain regions as mentioned above that are associated with FA and impulsivity has yet to be evaluated and serve as a novel approach to understanding poor T2DM food behaviors and glycemic outcomes.

Though addiction and impulsivity are seldom studied or reported in T2DM, these factors have been strongly linked to adverse behaviors in other conditions such as disordered eating, as a coping mechanism of stress, and with obesity (Fahy & Eisler, 1993; Gearhardt et al., 2012; Murphy et al., 2014)**.** There are numerous links between high impulsivity and excessive consumption of substances such as drugs, alcohol, nicotine, and caffeine (De Wit, 2009). The neurobiology of patients with substance use disorders have been well-studied where the explanations for the negative consequences have been attributed to much more than the neurochemistry of reward or a behavioral disorder (Davis & Carter, 2009; Smith & Robbins, 2013). Similar to people with substance use disorders, T2DM patients know that they should abstain from engaging in maladaptive behaviors, but it could be that their impaired ability to

control impulses prevents them from doing the right thing (e.g., following a recommended diet). In both populations, they have great difficulties in translating knowledge to behavior in which FA studies have attributed such behaviors to impaired control, where there are cognitive and emotional changes that lead to overconsumption (Gordon et al., 2018).

Individuals with T2DM must continuously monitor what they eat, and meticulously restrict or abstain from eating certain types of foods. In order to achieve glycemic control, studies have shown that T2DM patients have difficulty adhering to their dietary regimen because of the rigor and discipline it requires to continuously regulate impulses and manage their T2DM self-care activities daily (Vijan et al., 2005). Given the stressful nature of having to exert frequent self-control with dietary choices, lapses in dietary adherence has been considered as a liberating impulse or reaction to their diabetes distress (Franks et al., 2012). Thus, prior literature has established a connection between FA, impulsivity, and poor eating behaviors. However, the mechanisms underlying the relationships between FA, impulsivity, brain changes, and glycemic outcomes are not fully understood, especially among T2DM patients.

Significance of the Study

Since food behavior is an important aspect of T2DM glycemic management and outcomes, it is imperative to investigate the science behind the poor dietary behaviors. The underlying etiology for poor dietary behaviors in uncontrolled T2DM is unclear, but could be a result of FA, impulsivity, or a combination of both. Moreover, it is known that people with addiction or impulsiveness, such as those who are alcohol/cocaine dependent or obese, show brain changes. However, relationships between these behaviors and the brain have not been reported in T2DM patients (Ersche et al., 2011; Wang et al., 2016). The findings from this dissertation increase understanding of the relationships between FA, impulsivity, brain tissue

injury, and glycemic outcomes and can guide clinicians' efforts to improve glycemic management in patients with T2DM. Findings could help identify and test novel interventions to reverse the brain changes or improve interventions, such as cognitive behavioral therapy, brain exercises, or vitamin supplementation to provide neuroprotection for specific sites in the brain that are linked to FA and impulsivity that can trigger poor dietary behaviors. The results of this study will be beneficial for providers to understand potential reasons patients with T2DM have poor food behaviors and poor glycemic status. Additionally, this study provides foundational knowledge for the development of interventions that can modify dysfunctional eating behaviors to healthy eating behaviors. Ultimately, this dissertation has the potential to impact T2DM self-management, clinical practice, and health outcomes.

Statement of Purpose

While the poor dietary behaviors in T2DM may be due to FA or impulsivity (or a combination of both), an examination of these potential etiologies for poor T2DM glycemic outcomes has not been evaluated in the condition. Moreover, there are no published studies which have linked these FA and/or impulsivity to T2DM related brain tissues changes or to glycemic outcomes. Therefore, the purpose of this quantitative cross-sectional dissertation was to determine the relationships between FA, impulsivity, brain tissue injury and glycemic outcomes (A1c) in T2DM patients.

Specific Aims

This dissertation is comprised of seven chapters where chapters four, five, and six are original manuscripts that were prepared and formatted for publication in peer-reviewed journals. The specific aims of this study were:

Manuscript #1: To compare FA (measured by the Yale Food Addiction Scale 2.0 [YFAS]), impulsivity (measured by Barratt Impulsiveness Scale [BIS-11]), and associations with glycemic outcomes (measured by A1c) between T2DM patients and healthy controls.

Manuscript #2: Examine associations between FA (YFAS 2.0 scores) and impulsivity (BIS-11) scores in relation to brain tissue injury (measured by mean diffusivity values).

Manuscript #3: Examine FA, and brain tissue injury (frontal cortices, cingulate) in relationship to glycemic control status; poorly controlled (A1c $\geq$ 7) versus well-controlled (A1c $<$ 7) and determine between FA symptomatologies and specific sites of brain injury which are independent predictors of glycemic outcomes (A1c).

Chapter Summary

The exploration of FA, impulsivity, brain tissue injury, and glycemic outcomes is essential to advancing clinical knowledge and improving T2DM health outcomes. This dissertation provides the groundwork for the development of new interventions to improve T2DM self-management activities. By identifying the potential reasons for poor glycemic outcomes in T2DM patients, clinicians have a better idea of how to appropriately intervene. This dissertation adds to the growing body of research that addresses the role of biobehavioral health in T2DM self-management. Though there is concern surrounding FA, there is minimal interest in its assessment in T2DM, even though there is growing evidence that supports the link between poor cognitive behaviors to areas of brain tissue injury, and its relation to poor T2DM glycemic outcomes (A1c). By exploring unconventional concepts like FA and impulsivity and associated brain tissue changes that may account for or drive poor T2DM glycemic outcomes, there is a potential paradigm shift in T2DM research. At the time of this dissertation research, no other studies examined FA, impulsivity, brain tissue injury, and glycemic outcomes (A1c) among

T2DM patients.

This dissertation research addresses gaps in knowledge in relation to T2DM glycemic outcomes (A1c) and the relationship to the brain in seven chapters. Chapter One, Introduction, presents an overview of the state of the science of food behaviors in T2DM and of the background, significance, and specific aims of the dissertation. Chapter Two presents the Review of Literature and synthesis of findings from studies on the neuro-biobehavioral mechanisms that may lead to poor food behaviors and glycemic outcomes among T2DM patients. Chapter Three presents the Conceptual Framework as it relates to the design and development of the dissertation. In Chapter Four, manuscript one, FA and impulsivity are compared between T2DM and healthy control groups, and there is discussion of the measurement (tools): Yale Food Addiction Scale 2.0 (YFAS) the Barratt Impulsivity Scale-11 (BIS-11). In chapters Five and Six (manuscripts two and three), there are investigations and analyses involving magnetic resonance data among T2DM patients.

Note: In diabetes literature, “self-management” and “self-care” are used interchangeably. For the purposes of this study, the term “self-management” is used to describe the diabetes-related behaviors of patients with T2DM.

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CHAPTER TWO

Review of Literature

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Type 2 Diabetes Mellitus

T2DM is a metabolic condition that is characterized by elevated blood glucose concentrations due to insulin resistance in peripheral tissues and/or inadequate insulin secretion in the pancreas (Oh et al., 2018). Insulin is a hormone found in the β-cells of the islets of Langerhans in the pancreas and long-term defects in these cells can affect insulin levels resulting in severe glucotoxicity that may impair insulin secretion (Himanshu et al., 2020). To maintain blood glucose concentration within a normal range, there is a balanced yet dynamic process between insulin action and secretion such that when insulin stimulates glucose uptake into peripheral tissues there is then an inhibition of gluconeogenesis and glycogenolysis in the liver, or when there is a decrease insulin action, then there is an upregulation of insulin secretion by the pancreas (Stumvoll et al., 2005). During T2DM, insulin resistance occurs such that cells (e.g. muscle cells and adipose tissues) fail to react to insulin and are unable to uptake glucose and hepatic glucose production still continues, thereby blood glucose concentrations become elevated, also known as hyperglycemia (Himanshu et al., 2020).

Criteria for the diagnosis of T2DM as determined by the World Health Organization (2011) and the American Diabetes Association (2019a) is primarily determined by 2-hour-plasma glucose level of $\geq$ 11.1 mmol/L (200 mg/dL) during an 75 g oral glucose tolerance test (OGTT) with a glucose or fasting plasma glucose (FPG) $\geq$ 7.0 mmol/L (126 mg/dL), or random plasma glucose of $\geq$ 11.1 mmol/L (200 mg/dL) with class symptoms of hyperglycemia or hyperglycemia crisis, or lastly through a test of an important biomarker of blood glucose control: glycated hemoglobin A1c, a protein that is found in red blood cells. A1c levels reflect an individual's blood glucose concentration from the past 8 to 12 weeks as the glycosylation

process relates to the typical life span of red blood cells, which is approximately 120 days. Therefore, A1c is a percentage value of hemoglobin that has blood glucose attached (glycosylated) over the past 2-3 months. World Health Organization (2011) and American Diabetes Association (2019a) recommends the target A1c levels to be < 7% for well-controlled T2DM and ≥ 7% for poorly controlled T2DM. Therefore, A1c is a gold-standard marker for T2DM self-management and clinical care.

Glycemic control is a priority for T2DM treatment because there are links to poor health outcomes. For example, patients diagnosed with T2DM (A1c ≥ 6.5%) compared to those with A1c less than 6.5%, are associated with significant health complications such as 4 times more likely to have moderate retinopathy (AOR: 4.0; $p < 0.001$) and there is on average a higher prevalence of nephropathy (17.1%) for those with A1c levels ≥ 6.5% compared to patients with lower A1c levels of < 6.5% (9.6%) (Butler et al., 2020). While the short-term effects of T2DM include hyperglycemia which can cause polyuria, polydipsia, polyphagia, and blurred vision, prolonged hyperglycemia has been linked to multiple organ failure, micro- and macro- vascular complications, along with other metabolic syndromes such as obesity, which is now commonly referred as 'diabesity' (Pinchevsky et al., 2020). To prevent serious health complications associated with T2DM, major treatments for T2DM require lifestyle modifications that comprise of several types of self-management activities that will be discussed in the next section.

Gaps in Literature

The causes of poor dietary behaviors are unclear, and T2DM self- management research focusing on dietary adherence is limited with varying results and recommendations. As there are many known factors that influence dietary self-management, this dissertation explored unconventional reasons for poor food behaviors. A few researchers have started to explore

addiction and impulsivity in nutrition fields but among obese and disordered eating populations. Emerging research in these fields have recently uncovered similarities in patterns of food intake and consumption of substance use drugs. These findings have led to the controversial theory that some foods, or things added to foods, may trigger an addictive process (Schulte et al., 2015). When applied to T2DM patient population, these unconventional concepts may help better understand the difficulty people experience in exhibiting healthier food choices.

Food Addiction

To address the root causes of poor dietary behaviors in T2DM patients, and thereby design interventions to improve T2DM glycemic outcomes, researchers need to understand the underlying mechanisms that sustain hedonistic eating behaviors. The argument that overeating is an addictive behavior or that food is addicting is a controversial perspective that must be first addressed by discussing the preludial considerations of the addiction concept. Addiction, as it relates to alcohol and opiates, is a relatively new concept as it was first referenced in the early 20th century (Berridge & Mars, 2004) and then referenced with other substances such as cocaine, amphetamine and nicotine after World War II (Berridge, 1997). Since then, there has been more findings to expand addiction science to include compulsive activities such as use of the internet, gaming, sexual behavior, and shopping (Grant et al., 2006; Holden, 2001; Orford, 2001). Historically, it has been noted between 1950 and 1970 there were about six publications written by founder of environmental medicine, Theron Randolph, that suggested food could be addictive and that overeating is an addictive behavior (Davis & Carter, 2009).

The concept of addiction has been characterized by the behavioral manifestations of a neuropsychiatric disorder, where there are four core behaviors: craving, impulsivity, compulsivity, and motivation (Belin-Rauscent et al., 2016; Vella & Pai, 2017). Addiction is a

chronic relapsing disorder that is further distinguished by two related neurobiological constructs, impulsivity and compulsivity, which are behaviors on opposing ends of the addiction process (Koob, 2008). According to addiction models, impulsivity is the initial process leading to addiction and compulsivity are the repetitive behaviors that continue despite the negative consequences (Vella & Pai, 2017; Voon, 2015). There are three stages to addiction: (a) the binge–intoxication stage, (b) the withdrawal–negative affect stage, and (c) the preoccupation–anticipation stage (Koob, 2008). A person with food addiction can be seen to go through these stages that are similar to substance addiction versus behavioral (e.g. pathological gambling) because there is a neurochemical effect in the brain (Ziauddeen & Fletcher, 2013).

Food is ubiquitous and it is challenging to determine its effect on consumption behaviors as well as definitively define and measure FA as the neuroscience evidence in humans is still nascent. Though there are several explanatory models for overeating and addictive foods, the prevailing and initial FA model was based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for substance addiction and the formalized tool that operationalizes the FA concept: Yale Food Addiction Scale (YFAS) (Ziauddeen & Fletcher, 2013). Created by Gearhardt et al. (2009a), the YFAS is the only validated tool that measures addictive-like eating behavior and there has since been an updated YFAS 2.0 based on DSM-V, to include changes to the substance-related and addictive disorders (SRAD, formerly substance use disorders) (American Psychiatric Association, 2013; Gearhardt et al., 2016). The substance dependence diagnostic criteria in YFAS is similar to the diagnosis of binge eating disorder (BED) or to the behaviors of obese individuals, which were: loss of control over consumption, especially unhealthy foods, and an inability to cut down to stop over consumption even when one has expressed a desire to stop or when presented with severe negative consequences like

diabetes, heart disease or stigma (Gold et al., 2003; Volkow & O'Brien, 2007). YFAS 2.0 is the most recently validated FA tool that was used for this dissertation and was further evaluated in Chapter Four: First Manuscript.

Biological Evidence for FA in Animal Models

Most of the evidence for food's addictive properties lies in the biological realm. The concept of FA began in 2001 when Wang et al. (2001) reported research findings connecting dopamine and obesity. Dopamine activation and inactivation modulates motivation and reward circuits in appetite regulation, and the genes controlling its availability also influence eating behavior (Fuemmeler et al., 2008; Need et al., 2006). On a neurochemistry level, genotypes such as OPRM1 mu-opioid receptor gene (A118G) (Miranda et al., 2010; Ramchandani et al., 2011) and DRD2 dopamine receptor (Taq1A A1) (Doehring et al., 2009; Munafò et al., 2007; Zuo et al., 2009) have been associated with addictions such as substance and cigarette abuse, along with health conditions like obesity (Comings et al., 1996; Noble et al., 1994; Spitz et al., 2000). However, the relationship between the DRD2 receptor and food consumption is complex, as evidence suggests that the A1 allele Taq1A polymorphism in DRD2 may indirectly trigger psychological traits leading to pathological and compulsive eating behaviors as there is an associated exaggerated reinforcing effect of food to compensate for the dopamine deficiency (Epstein et al., 2007; Nisoli et al., 2007). It has been hypothesized that overeating is a result of decreased activation of the dopamine circuits because it is a form of stimulus-seeking behavior, which can lead to weight gain and an increased risk of T2DM (Comings & Blum, 2000).

Studies have found that individuals with the Taq1A polymorphism of the DRD2 gene have reduced brain D2 receptor density and those who also have a substance abuse issue may be compensating with addictive behaviors for their insufficient dopamine activity (Comings &

Blum, 2000). In a randomized clinical dietary trial that explored the distribution of DRD2 genotypes among 93 adults for 74 weeks, the investigators determined whether T2DM individuals with the A1 allele Taq1A polymorphism would show differences in dietary habits and clinical outcomes or be less likely to adhere to either the low-fat, vegan or 2003 American Diabetes Association (ADA) recommended diets (Barnard et al., 2009). When compared to non-diabetes patients, the A1 allele (A1+) was significantly higher in T2DM whites, occurring in 47% of white participants (n = 49), versus 29% in a previous study (P = 0.01) (Noble, 2003). A1+ was found in 55% of black T2DM participants (n = 44) and when compared to A1 deficient (A1-) black subjects, they were significantly 11.2 kg heavier (P = 0.05), had greater fat intake (P = 0.002), saturated fat (P = 0.01) and cholesterol (P = 0.02).

Diet matters, especially as exploratory analyses indicated that the A1- T2DM whites in the vegan group significantly reduced their A1c levels (P = 0.01) when compared to the ADA diet. However, regression models did not find a significant predictor of A1c change in either blacks or whites for either diet group or DRD2 genotype status. The high prevalence of A1+ findings suggest that genetic and racial predispositions might be contributors to diabetes versus eating habits and weight gain. But the present study has limited evidence in discerning the effect of the therapeutic diets on glycemic control between A1+/A1- white and black T2DM patients and warrants further investigations in other diverse T2DM populations.

Further, lesions of the dopaminergic system or pharmacological blockade of dopamine receptors reduce the reward value of both sugar rich foods and drugs of abuse (Avena & Hoebel, 2003; Colantuoni et al., 2002; Colantuoni et al., 2001). Positron emission tomographic imaging studies have also shown that both obese individuals and drug dependent individuals have significantly lower dopamine receptor levels (Wang et al., 2001). This indicates that both

populations require more stimulation (either increased food or drug intake) to produce a significant release of dopamine to attain a perceived value of reward.

In addition to the dopamine system, there are more studies that now show that abuse of both food and drugs trigger the opiate pathways in the brain as well (Hoebel et al., 1999; Nieto et al., 2002). For example, studies have found that certain types of food intake, such as high fat sweets, can cause endogenous opiates to be released in the brain (Drewnowski et al., 1995). Specifically, in the brain, the nucleus accumbens (Bassareo & Di Chiara, 1999) is similarly activated by the consumption of either food or alcohol/drugs use because there is a greater release of extracellular dopamine causing the mesocorticolimbic dopaminergic reward pathways to trigger euphoric or pleasure reinforcing effects resulting from those consumptive behaviors (Hoebel, 1985; Volkow et al., 2002). In contrast, reinforcement value and craving behaviors in alcohol dependent subjects can be reduced with opiate blocker medications like naloxone (O'Malley et al., 2002). Interestingly, naloxone also works in both normal weight and obese binge eaters as it reduces their preference for sweet, high fat foods, as well as food consumption (Drewnowski et al., 1995).

Prior research based on basic animal neuroscience models have demonstrated that there are corresponding changes in the neurotransmitters of the brain like that of animals with substance-use addiction when there was bingeing or compulsive consumption of glucose, fructose, and junk food (Avena et al., 2009; Johnson & Kenny, 2010). For example, animal research has linked sugar consumption with behavioral indicators of dependence (Avena & Hoebel, 2003; Avena et al., 2005; Colantuoni et al., 2002; Gosnell, 2005; Hoebel et al., 1999; Rada et al., 2005). The types of dependence or addictive behaviors that developed from the variation in high-sugar high fat diets included: binge-eating, compulsive food-seeking and

withdrawal symptoms (Avena et al., 2008; Johnson & Kenny, 2010). Due to the intermittent variation in the diet of sucrose solution and chow, the rats started showing behavioral and neurochemical changes such as elevated self-stimulation thresholds, lower striatal D2 receptors, decreased accumbens, dopamine, and elevated acetylcholine, all of which are similar to the withdrawal state of drug dependency (Colantuoni et al., 2002; Colantuoni et al., 2001; Geiger et al., 2009; Hoebel et al., 1999; Johnson & Kenny, 2010). Other similarities with addiction symptomatology include somatic changes and anxiety and agitation, which occurred when dependent animals were not given sugar and as a result there was a drop in the body temperature and withdrawal behavioral changes (Colantuoni et al., 2001). Also, the rats were resistant to foot shocks as they were portraying compulsive food-seeking behaviors, which is a convincing indicator of a compulsive type of addictive behavior (Deroche-Gamonet et al., 2004; Johnson & Kenny, 2010).

Biological Evidence for FA in Humans

Since there is biological support for FA among animal models, there are few investigations of the FA indicators of dependence with humans. In humans, the neurobiological evidence from PET and MRI studies from the past decades have also shown that there are brain changes that occur with substance-use addiction (Blumenthal & Gold, 2010). Research has implicated parallels in neural functioning between addictive eating behaviors and substance use where there is an elevated activation in the reward circuitry in response to food cues and reduced activation of inhibitory regions in response to food intake (Gearhardt, Davis, et al., 2011). Initial evidence stemmed from studies of eating disorders such as binge-eating. For example, Gold et al. (2003) found that the majority of the substance dependence diagnostic criteria are similar to the criteria necessary to meet a diagnosis of binge eating disorder, such as a loss of control over

consumption and an inability to successfully stop or cut down on consumption despite an expressed desire to do so. Others note that, similar to individuals with substance dependence, some obese individuals continue to eat unhealthy foods even when there are severe negative health consequences, such as diabetes, heart disease, and stigmatization (Volkow & O'Brien, 2007).

There are limited studies on the concept of FA in the T2DM population, but recent results from a study with T2DM patients demonstrated that a substantial proportion of study subjects, over 70%, met the criteria for FA symptomatology (Raymond & Lovell, 2015). Raymond and Lovell (2015) demonstrated an association between FA symptomology and T2DM diagnosis where a majority of the sample reported unsuccessful behavioral attempts in reducing their intake of sweet, starchy, salty, and fatty foods/drinks. However, the study looked at the relationships between FA, impulsivity to the body mass index (BMI) of T2DM patients and not their glycemic outcomes such as A1c. Their cross-sectional design of 334 T2DM patients with a mean age of 41 and 66% females, indicated a statistical significance of an increased BMI ($P <$ .001) among T2DM who were classified as FA. Additionally, FA and impulsivity (non-planning) were significant predictors that explained 38% variance in BMI (Raymond & Lovell, 2015). The findings are novel for the T2DM patient population, because other studies investigating FA reported that there were significantly less subjects in the general population that met FA criteria such as 11.4% (Gearhardt et al., 2009a) and 19.9% (K. M. Pursey et al., 2014).

Among the many biopsychosocial factors along with the environmental, economic, and public health factors that are implicated in the development and progression of T2DM, obesity is considered the most modifiable risk factor (Alberti et al., 2007). The complex interaction between other psychological factors such as depression, stress, and anxiety has contributed to

increased cortisol levels (Vicennati et al., 2009), changes in appetite (Sinha & Jastreboff, 2013) and eating behaviors (Mouchacca et al., 2013) that have been associated with obesity (Blaine, 2008; Chen & Qian, 2012; Eyres et al., 2014; Stunkard et al., 2003) and increasing body mass index (Eyres et al., 2014; Kivimaki et al., 2009; Zhao et al., 2009). However, Raymond and Lovell (2015)'s study that explored the relationships between FA, mood, and impulsivity with BMI showed that depression, anxiety, stress, and other impulsivity types (motor and attentional) were not salient cross-sectional predictors of BMI in T2DM patients when compared to FA and impulsivity (non-planning).

Impulsivity

Impulsivity is a process of learned behavior by which individuals react toward rapid, unplanned events influenced by internal and external stimuli without thinking, planning, or consideration of the impact that the negative consequences have on self or to others (Moeller et al., 2001). Persons who are impulsive are unable to control thoughtless actions when triggered by an emotional stimulus (Spence, 1950). As of late, impulsivity has been recognized as more than just a singular personality trait but a multi-dimensional construct requiring multiple assessment tools in diet research (Adrian Meule, 2013).

Much of current dietary behavior literature focuses on stress-eating and eating disorders such as bulimia and binge eating, which are associated with impulsiveness (A. Meule, 2013; Racine et al., 2009; Steiger et al., 1999; Van Blyderveen et al., 2016). Impulse control has an important role in the self-regulation of certain dietary behaviors, such as moderation of food consumption (Hofmann et al., 2009). Poor impulse control can exacerbate the risk for T2DM and development of other related illnesses like obesity because the patients' ability to regulate the type and amount of food that they consume is impaired (Weygandt et al., 2013). The

implications of impulsive behavior may lead to compromised self-control, or the ability to abstain or engage in productive actions such as decision-making ability. Impulsivity can lead to poor self-control or rash decisions that can threaten health outcomes. For example, impulsiveness can lead to risk-taking driving behaviors precipitating to sudden deaths like suicide (Bourgeois, 1991; Cheah et al., 2008), substance abuse behaviors leading to addiction (Cservenka & Ray, 2017; Moeller et al., 2002; Perry & Carroll, 2008), and risky sexual behaviors leading to increased chances of contracting sexually transmitted diseases (Birthrong & Latzman, 2014; Deckman & DeWall, 2011; Derefinko et al., 2014).

In contrast to the negative outcomes of poor impulse control, an individual's ability to regulate his or her thoughts and behaviors such that he or she is able to engage in healthy behaviors and avoid unhealthy behaviors are positive examples of impulsivity. Studies have shown that greater impulse-control promoted better exercise regimen adherence (Hagger et al., 2010; Tedesqui & Young, 2017), reduced alcohol consumption (Jones & Field, 2013; Muraven et al., 2002), and less risky sexual behavior (Hernandez & Diclemente, 1992). Overall, impulsive patients tend to gravitate towards short-term rewards and are less likely to endure the discomfort associated with adherence to self-care behaviors even if it leads to long-term health benefits. Therefore, the impulsivity of an individual may influence health outcomes. For T2DM patients, impulse control requires regulation of health behaviors such as adherence to a diabetes diet on a daily basis.

Since there different types of impulsivity, A. Meule (2013) advocates the use of multiple subscales like the Barratt Impulsivity Scale-11 (BIS-11), to analyze the different aspects of impulsivity and their relationship to eating behaviors. BIS-11 distinguishes between the four dimensions of impulsivity: general impulsivity, attentional impulsivity, motor impulsivity, and

non-planning impulsivity (Patton et al., 1995). A. Meule (2013) literature review concluded that only attentional impulsivity (inability to focus) was consistently related to overeating, and only a weak relationship was reported between impulsivity (non-planning, e.g., lack of future orientation or forethought) and overeating. In a follow-up study by Meule et al. (2017) found that among the four types of impulsivity, non-planning impulsivity was once again shown to have no effect, and attentional and motor impulsivity predicted FA status among obese bariatric surgery candidates ($P = 0.013$). Besides FA status, other outcomes linked to impulsivity include findings from a study by Murphy et al. (2014), where they linked impulsivity and FA to increases in BMI. Due to its indirect positive association with BMI, impulsivity influences addictive food consumption, which is consistent with emerging findings and conceptualizations of FA. However, there is a dearth in the literature about impulsivity and FA in relation to poor glycemic outcomes (A1c).

In addition, brain tissue changes associated with FA and impulsivity among T2DM patients and their impact on glycemic outcomes (A1c) have not been examined. Therefore, this dissertation examined whether FA and/or impulsive behaviors are related to poor glycemic outcomes (A1c). The findings from the dissertation can help clinicians pinpoint the neurobiological characteristics of FA and/or impulsive eating behaviors among T2DM patients and by incorporating considerations of these neurobiological factors into current interventions there may be opportunities to improve T2DM dietary self-management and glycemic outcomes. There is the potential to help T2DM patients improve their glycemic outcomes through a treatment approach that addresses neurobiological impairments such cognitive brain therapies that can help with control of situations that can trigger addictive-eating behaviors, or training that devalues and desensitizes the perception of food stimuli (Adams et al., 2019; Schulte et al.,

2017).

Brain Connection to Food Addiction and Impulsivity in T2DM

Though T2DM can potentially impact the brain structure as well as result from brain changes, aspects of T2DM disease progression such as chronic hyperglycemia and insulin resistance, increase levels of proinflammatory cytokines, which can cause inflammation and deleterious vascular changes at certain sites in the brain (Heber & Carpenter, 2011; Roy et al., 2020). In the next section, there will be a presentation of findings from past magnetic resonance imaging (MRI) studies which shows there are brain changes in certain sites corresponding to addiction and impulsivity behaviors in substance users, obese, and disordered eating individuals. The new aspect of this dissertation research was to determine if there is a connection between T2DM-related brain tissue changes at certain sites that are correlated with either FA, impulsivity, or both.

Other complications of T2DM include regional brain changes due to impaired glucose metabolism in the brain that can alter the homeostatic cerebral environment that is normally conducive for neuronal vitality (Roy et al., 2020; Srikanth et al., 2011). However, with chronic hyperglycemia due to insulin resistance or decline in insulin action across the blood brain barrier as is characteristic in T2DM, the insulin receptors that are specifically concentrated in certain areas of the brain to help process cerebral glucose metabolism become impaired and contribute to reduced endothelial dependent vasodilation and decreased cerebral vascular reactivity to CO2 (Cholerton et al., 2011; Last et al., 2007; Novak et al., 2006). This change in the cerebral vasoreactivity along with T2DM metabolic and endocrinologic interplay promotes oxidative stress as there are increases in the formation and interaction of advanced glycation end products (AGEs) with AGEs receptors through non-enzymatic glycation, and thereafter inflammatory

processes that ultimately lead to vascular damage such as gray matter changes in the brain (Last et al., 2007; Roy et al., 2020; Srikanth et al., 2011). Specifically, Roy and colleagues (2020) found that there are decreased gray matter volumes in several brain regions in T2DM patients that control cognition (such as the prefrontal cortex, hippocampus, and cerebellum), anxiety (hippocampus, amygdala, insula, and cingulate), and depression (hippocampus, para-hippocampus, cingulate, insula, and thalamus ($P < 0.01$).

The findings expose the complications that can result from the development and progression of T2DM-related structural changes to specific sites in the brain as they are associated with functional changes like in cognition and mood. This suggests that it is crucial to consider and investigate the cerebral structural changes in the evaluation of poor food behaviors among T2DM patients, because there may be neural basis as to why patients have difficulty in dietary behaviors and have poor glycemic outcomes.

Impact of A1c on Brain Changes in T2DM

Researchers have proposed several contributing factors of T2DM progression such as inflammation, vascular damage, genetic predisposition, insulin resistance, and amyloid disposition but chronic hyperglycemia and oxidative stress, as measured by high levels of glycosylated end-product A1c, has been shown to be the primary underlying factor leading to functional and structural brain damage (Biessels et al., 2002; Kodl & Seaquist, 2008; Strachan, 2011). As the pathogenesis is still uncertain, brain imaging studies can help uncover the dysfunction in T2DM dietary self-management. In studies with T2DM patients, brain imaging uncovered another factor that could result from the vascular (e.g. ischemia or arteriosclerosis) or inflammatory processes known as white matter lesions (WMLS), which have also been linked to impaired cognition (Imamine et al., 2011; Jongen et al., 2007; Manschot et al., 2006; van Harten

et al., 2007).

Studies with A1c levels, however, provide convincing evidence of its relationship to cerebral atrophy. In a study by Gold et al. (2007), A1c levels was negatively correlated with hippocampus volume indicating that glycemic control impacts brain structure. In another large MRI data study that investigated diabetes status and duration, for patients with longer duration of diabetes there were significantly lower gray matter volumes, but after intensive treatment to decrease A1c, the progression of gray matter volume loss decreased (Erus et al., 2015). Within the same study, brain MRI studies also showed that A1c levels affect brain volume where for T2DM patients with well-controlled A1c levels (< 6%), the overall brain volume was significantly greater than those with poorly controlled A1c levels of 7-7.9%.

Another important marker of white matter integrity is apparent diffusion coefficient (ADC) or now known as mean diffusivity (MD), which is a measure of water diffusivity (van Bussel et al., 2017). In certain brain areas of T2DM patients, such as the hippocampus (Falvey et al., 2013) and multiple gray matter regions (Yau et al., 2010), studies have shown increase in ADC where there is reduced neuronal cell packing and increased extracellular space, typically indicative of cell loss of decreased neurogenesis. Damage to specific areas of the brain is critical as it is known that behaviors are controlled by the brain and past studies have found there are strong connections between T2DM self-management behaviors that are controlled at certain sites such as having brain changes in the prefrontal cortices and hippocampus (Falvey et al., 2013; Hempel et al., 2012; Kumar et al., 2008). Based on this line of thought, this study determined if there were any relationships between FA, impulsivity, and brain tissue injury via MD values, where higher MD values indicated greater brain tissue damage.

FA, Brain Structural Changes, and T2DM Glycemic Outcomes

As the previous section highlighted T2DM studies showing associations between A1c and alterations in brain structure, there are recent efforts that further underscore the role of the brain in assessing the value of hedonic food and regulating addictive-like eating behaviors ("food addiction") by investigating alterations in brain activity and connectivity. Research to support the 'Addictive Potential of Certain Foods' in the FA model by Schulte et al. (2017) (Figure 3.1) was initially supported by animal studies that modeled aspects of FA through rodents. There is evidence that rats that daily binge (12-hr access) on high sugar solutions (e.g., 25% glucose or 10% sucrose) and chow alternated with 12-hr food deprivation, created a behavioral and neurochemical state of opioid withdrawal (Avena et al., 2008, 2009). The results suggest the emergence of substance dependence as seen through somatic signs associated with opiate withdrawal when challenged with high-doses of the opioid antagonist naloxone (3 mg/kg) such as teeth chattering, forepaw tremor, and head shakes (Colantuoni et al., 2002).

To further elucidate on the evidence for 'Addictive Potential of Certain Foods,' there are animal studies with rats that do not overeat if nutritionally balance chow is readily available versus overeating chow that are high in fat and sugar or overconsumption is triggered in certain environments that they had previously eaten high-fat, high sugar foods (Boggiano et al., 2007; Hagan et al., 2003). In human studies, despite negative consequences, subjects overconsumed certain foods that contained added fat and refined carbohydrates (e.g. pizza, chocolate, cake, cookies) versus less refined foods (e.g. nuts, fruit, lean meat) (Curtis & Davis, 2014; Schulte et al., 2015). These types of palatable foods were more consumed during binge episodes (Vanderlinden et al., 2001), and craved more when compared to fruits and vegetables (Gilhooly et al., 2007; Ifland et al., 2009). This suggests biological and behavioral similarities between

food cues promoting addictive-like eating behaviors and drug cues triggering relapse in traditional addictive disorders (Boggiano et al., 2009).

On a cellular and molecular level among mice exposed to either a high-fat or high-carbohydrate diet for 4 weeks and then abruptly changed to a less palatable house chow, there were decreased levels of cyclic adenosine monophosphate response element binding protein (pCREB; a downstream signaling molecule in the dopamine reward pathway) in the striatum 24 hours after the change in both high-fat and high-carbohydrate diet group ($P < 0.01$) and still significantly decreased levels 1 week after the change for the high-fat group ($P < 0.01$ (Teegarden & Bale, 2007). The study also demonstrated a strong dietary preference as the mice were willing to endure aversive situations to obtain their preferred chow. Results from Teegarden and Bale (2007) supported past studies among mice with decreased pCREB levels, where they increased their response to aversive stimuli (e.g. portrayed avoidance behaviors during anxiety-inducing situations with bright lights) and increased preference towards appetitive stimuli like sucrose and drugs of abuse like morphine (Lutter & Nestler, 2009). Teegarden and Bale (2007) also showed a significant elevation in deltaFosB in the NAc, which is a transcription factor that accumulates after chronic exposure to drugs of abuse (McClung et al., 2004; Nestler et al., 2001) or natural rewards and in turn drives responses to obtain more rewards such as cocaine, opiates, sucrose or wheel-running (Nestler, 2005). As it is not merely the cues to eat, studies have demonstrated that palatable foods coupled with the individual's similar neuroadaptations to food as to drug exposure, serve as the basis of the FA conceptual model for this study (Figure 3.1).

Regarding brain changes, there are a few studies that have utilized brain imaging to identify the brain structural integrity of T2DM patients in relation to FA and/or impulsivity. As initial human neuroscience evidence for FA was borrowed from drug dependence models,

seminal brain models that explain the neurological processes of the behavioral transition from drug taking to drug dependence were seen as a loss of executive control predominantly in the dorsal striatum (Everitt et al., 2008). Prior imaging studies relied mostly on functional MRI (fMRI) and positron emission tomography (PET) scans to explore the functional responses in human reward circuitry when stimulated with food cues predicting food or with pictorial representations of food (Ziauddeen & Fletcher, 2013). For example, the earliest PET scanning evidence that explored the neural basis of FA, correlated brain regions, such as reduced striatal D2 receptors, to obesity (Wang et al., 2001). The seminal study triggered succeeding studies to further explore the dopaminergic function related to eating and obesity, and there have also been replicated findings showing large overlap in receptor levels among obese (BMI>40) when compared to healthy controls (de Weijer et al., 2011; Wang et al., 2001).

As there have been limited studies involving structural integrity versus functionality of the brain, neural evidence from studies have shown that the brain structures corresponding to activation in conjunction with drug and alcohol craving include: amygdala (Childress et al., 1999; Grant et al., 1996a), anterior cingulate (Childress et al., 1999; Garavan et al., 2000; Maas et al., 1998), orbital frontal cortex (Wang et al., 1999), insula (Bonson et al., 2002; Breiter et al., 1997; Garavan et al., 2000; Hommer, 1999; Wang et al., 1999), hippocampus (Breiter et al., 1997; Garcia-Perez et al., 2013), caudate (Breiter et al., 1997; Garcia-Perez et al., 2013), and dorsolateral prefrontal cortex (Grant et al., 1996b; Maas et al., 1998). As it pertains to FA, fMRI studies in humans demonstrate that food and drug cues activate these same regions of the brain (only the brains of drug addicts respond to drug cues) (Blumenthal & Gold, 2010; Dagher, 2009; Pelchat, 2009). Furthermore, the basolateral amygdala's (BLA) glutamatergic projections into the nucleus accumbens (NAc), in conjunction with dopamine signaling in the NAc, is an

important neural circuit that controls reward-seeking behaviors in substance addiction disorders (Lintas et al., 2012) and in addictive eating disorders among humans and animal models (Berridge et al., 2010; Stuber et al., 2011).

Among humans, the nutritional state of fasting versus being fed increased brain activation to pictures of high-calorie over low-calorie foods in the ventral striatum, amygdala, anterior insula, and medial and lateral orbitofrontal cortex (OFC) (Goldstone et al., 2009). Though hunger makes all food appealing, Goldstone et al. (2009) further demonstrated the hedonic value of certain types of food through the brain reward system bias towards high-calorie versus low-calorie foods as there was a positive correlation with medial and lateral OFC activation during fasting. With time, exploration of the human neuroscience evidence for FA led to a few more studies that investigated the neural correlates to similar behaviors such as stress, since there have been links between stress and the development of addiction and the consumption of highly palatable foods (Sinha & Jastreboff, 2013).

Through studies involving food-cues to induce food craving, there was an increase in limbic and striatal reactivity to stress and food cues among obese subjects versus lean subjects (Jastreboff et al., 2013). Specifically, there was a correlation between higher activity in the insula and dorsal striatum with higher insulin levels, insulin resistance, and with food craving behaviors when exposed to favorite foods. Another study that investigated role of food during stress showed that corticotropin-releasing factors (CRF) injections into the medial shell of the NAc (a brain mechanism that indirectly increases intake of highly palatable foods to reduce the stressful state and also enhances desire by also inducing dopamine release), multiplied the attractiveness of food cues unlike past studies on CRF (Berridge et al., 2010). Past studies postulated that CRF release would produce a constant aversive drive among rodents to engage in pleasurable or

compulsive activities (increase intake of sucrose, fat, and drugs, or wheel-running) (Dallman, 2010; Dallman et al., 2003) or drug dependence among humans to reduce stress levels (Koob, 2007). However, the study conducted by Berridge et al. (2010) showed that CRF-induced elevations triggered a phasic peak of desire to obtain sugary treats when the sugar was physically present and a decreased desire when the sugar was not present. This novel explanation that stress overeating is conditional under certain types of food cue-triggered situations supports emerging evidence that certain characteristics of foods possess drug-like motivating potency.

Given that most of the neurological evidence for FA is among non-T2DM patients, there might be limitations in the current dissertation research because it is difficult to extend and apply the findings from substance addiction models of FA to T2DM patients. Another important limitation to consider is the fundamental difference between food and drugs in that unlike drugs, food do not have a direct nor simple pharmacological effect and can be consumed at any time or place (Everitt et al., 2008). There are also individual differences in the response to food cues, especially when hungry and satiated states are not explored in this study. Knowing the integral role of the brain in regulating responses to hedonic food, it has been predicted that different responses to food cues are associated with impaired inhibitory control or compulsivity in the prefrontal, dorsolateral, and inferior frontal cortex areas of the brain (Ziauddeen & Fletcher, 2013).

Impulsivity, Brain Structural Changes, and T2DM Glycemic Outcomes

Brain tissue changes to regions that are involved with impulsivity can impact an individual's ability to control desires for immediate gratification, which can result in unhealthy overeating and an inability to forego greater delayed rewards in exchange for instant smaller rewards (Jimura et al., 2013; Kalon et al., 2016b; Volkow & Baler, 2015). While impulsivity has

not been well-studied among T2DM, a majority of T2DM patients are obese and impulsivity has been well-studied and associated with obesity, disordered eating, drug addiction, and alcoholism (Alhassoon et al., 2015; Goldstein & Volkow, 2011; Nederkoorn et al., 2006; Pelchat, 2009). Deficient executive control in brain regions such as the frontal cortices, have been correlated with increased impulsivity and inhibitory functions in obese subjects (Kalon et al., 2016b; Kishinevsky et al., 2012; Nederkoorn et al., 2006). As a result, there is a loss of control over feeding behavior leading to weight gain and the deficits in executive function areas such as prefrontal cortex contributes to the progression of obesity (Kishinevsky et al., 2012).

There are limited brain T2DM studies that explore impulsivity, but there is consistent evidence that the distortion in insulin signaling (central insulin resistance) modulates activity in the central nervous system by depressing striatal dopamine tone in neural circuits that are responsible for behaviors including reward learning, cognition, impulsivity and regulation of consumption behaviors towards obesogenic/diabetogenic foods (Benedict et al., 2006; Guthoff et al., 2011; Heni et al., 2012; Heni et al., 2015; Kroemer et al., 2013; Kullmann et al., 2016; Kullmann et al., 2012; Schilling et al., 2014; Tschritter et al., 2006). To identify the neural correlates with impulsivity, the go-no-go task or stop signal task (SST) is a popular method that has been utilized under functional magnetic resonance imaging to determine areas of brain activation as well as the response and speed of the brain circuits in executing tasks to “go” and/or “stop” stimulus (Li et al., 2006). These tests allow researchers to determine if response inhibition is impaired for persons with certain predispositions or if one can meet the task demands under varying situations.

A study that distinguished the differences in the relationship between impulsivity, through go-no-go tasks, and markers of insulin resistance, showed that among T2DM patients

who were only receiving oral antidiabetic medications, their choice reaction times were shorter and A1c levels were higher (Lasselin et al., 2012). In that same study, for T2DM patients receiving insulin, their choice reaction times were similar to matched healthy controls, which indicates they were not as impulsive as T2DM patients without insulin therapy. Therefore, type of T2DM medication treatment (oral antidiabetics versus insulin) affects A1c levels, which in turn impacts choice reaction times. In another study, Hawkins et al. (2016) found that obese subjects with higher fasting plasma, such as in the pre-diabetic range (>100 mg/dL), had more commission errors (unable to stop their response to a stimulus; indicating inability to inhibit responses) and faster reaction times when performing a go–no-go task when compared to normal weight adults. Regardless of weight, prediabetic individuals made almost twice as many errors as healthy individuals, which indicates that the impaired glucose regulation in the brain, not BMI, was a predictor of impulsivity. The negative implication of glucose dysregulation (characteristic of T2DM patients) contributes to greater impulsivity, which then diminishes his or her inhibitory control from overconsuming highly palatable foods, thus perpetuating the unhealthy cycle of poor T2DM glycemic outcomes as detailed in the dissertation conceptual framework diagram (Figure 3.1).

Along with SST, there are other methods to measure impulsivity, such as delay-discounting (DD) -which is a tool that measures the act of pursuing a more immediate award versus waiting for a long-term reward (Madden & Bickel, 2010). Impulsive individuals with lower insulin sensitivity have been associated with discounting delayed rewards at higher rates (low DD scores) (Eisenstein et al., 2015). With regard to microstructural brain changes linked to impulsivity, patients with alcohol dependence have been well-studied where Wang et al. (2016) demonstrated that there were negative correlations between various types of impulsivity indices

(e.g. DD, SST, and BIS-11) and grey matter volumes (GMV) in the left medial prefrontal cortex of alcohol dependent patients. Other findings on the relationship between impulsivity deficits and microstructural alterations include negative associations between abnormal white matter integrity among the mesocorticolimbic system (e.g. decrease fractional anisotropy in the cingulum, anterior corpus callosum, anterior corona radiata) with impulsivity scores for alcohol dependent patients (Wang et al., 2016).

Another validated and widely used impulsivity measurement tool, Barratt Impulsivity Scale-11 (BIS) (Barratt, 1965), has been used in few studies with FA and T2DM, but not yet with investigations of T2DM-related brain changes and A1c outcomes (Raymond & Lovell, 2015). Though there is yet to be a structural neuroimaging study that explores the relationship of impulsivity with T2DM, there is evidence that BIS is a valuable tool in exploring the brain microstructures among three subject groups of non-drug users, and current and past methamphetamine users (Andres et al., 2016). Of the three groups, Andres et al. (2016) found that current users had the highest BIS scores, indicating higher impulsivity, correlating with higher fractional anisotropy in the putamen, and higher axial diffusivity in the white matter tracts assessed from diffusion tensor imaging (DTI), which could be due to meth-induced neuroinflammation from axonal swelling where there was greater water diffusion along axons. The findings demonstrate that microstructural alterations (high fractional anisotropy and lower mean diffusivity correlated with larger striatal volumes among both current and past methamphetamine users) contributes to greater impulsivity, which also supports a prior study that similarly showed higher gray matter density among methamphetamine users was associated with greater impulsivity (Schwartz et al., 2010).

The location of the increased axial diffusivity in the sagittal stratum and genu of the

corpus callosum (Andres et al., 2016) could be important brain sites in exploring impulsivity as the fiber tracts project to the orbitofrontal and prefrontal cortices, which are known to control inhibition (McClure et al., 2004). In a previously mentioned microstructural brain study with alcohol dependent patients (Wang et al., 2016), after Bonferroni corrections for multiple comparisons between the various impulsivity measures and brain tissue abnormalities, the gray matter volumes (GMV) was still negatively correlated with the total BIS-11 score ($r = -0.56$, $P < .05$) and average adjusted pumps of the balloon analogue risk task ($r = -0.61$, $P < .05$; BART; measures impulsivity where patients through a virtual program click a button on the computer as much as they would like to earn more money to inflate a balloon where $0.05 was given for each successful pump before the balloon burst and all money earned would be lost).

Corticospinal tract abnormalities have also associated with internet gambling disorders among adolescents, suggesting motor hyperactivity associated with greater impulsivity (Du et al., 2017). There was also reduced area and volume in the OFC among impulsive subjects, which supports past studies indicating the important of the OFC in regulating impulsive behavior (Bjork et al., 2009; Jiang et al., 2015; Mohammadi et al., 2016; Wang et al., 2017). Since there is a dearth in neuroimaging studies that explore impulsivity among T2DM patients, it may be crucial to understanding poor T2DM food behaviors and glycemic outcomes.

Chapter Summary

In summary, there have been limitations in T2DM research involving food behaviors and diabetes researchers have started to explore the evocative findings from the addiction and nutrition fields. Recent literature proposed new factors such as FA and impulsivity among obese and disordered eating individuals as potential contributors to poor dietary adherence. Since FA and impulsivity are associated with brain changes and T2DM patients are prone to brain changes,

this study investigated whether FA and impulsivity are linked to brain changes among the T2DM population and whether they impact glycemic outcomes. To explore the link between FA, impulsivity, and T2DM, brain areas of interest that have been found to have significant tissue injury in T2DM subjects include hyperactivity in the amygdala; hypoactivity in prefrontal cortex (regions associated with addiction) and gray matter damage in insular lobes, frontal cortices, cingulate, hypothalamus, and thalamus (regions associated with impulsivity) (Choi, Roy, Freeby, Mullur, et al., 2020; Choi, Roy, Freeby, Woo, et al., 2020; Roy et al., 2020). Addressing these critical gaps in knowledge will help researchers and clinicians better understand T2DM patients having difficulty in managing/adhering to their dietary behaviors.

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CHAPTER THREE

Conceptual Framework

Chapter Three: Conceptual Framework

Maladaptive food behaviors among T2DM are a prevailing issue, especially since T2DM patients consider self-management, particularly dietary management, more difficult to handle than the diagnosis of diabetes itself (Anderson, 1985; Rubin & Peyrot, 2001). Many even believe that T2DM is an unmodifiable condition that is not associated with their lifestyle habits such as dietary self-management (Stack et al., 2008). Numerous theories have been proposed to explain problematic eating behaviors of T2DM patients, including the Social Cognitive Learning theory (SCLT) and its Self-Efficacy construct (Bandura, 1971; Bandura, 1977). Self-efficacy influences T2DM self-management and has been linked to predicting outcomes such as glycemic control (D'Souza et al., 2017; Gao et al., 2013; Lee et al., 2016; Nakahara et al., 2006; Shen et al., 2019). To date, however, there are no theoretical frameworks that were specifically designed to explain the relationships between the constructs that were explored in this study: FA, impulsivity, T2DM-related brain changes, and T2DM glycemic outcomes.

Prevailing T2DM Theoretical Model

The Self-Efficacy component in SCLT has been a prevailing theoretical explanation that identifies key behavioral reasons why T2DM patients have poor eating behaviors. However, the theory by itself does not account for other factors that may contribute to poor food behaviors such as FA and the effect that foods with addictive substances have on the brain structure or reward circuitry. While there are studies that show reliable links between self-efficacy and T2DM self-management outcomes, the Self-Efficacy Model does not explore the neural basis as to why T2DM patients are unable to practice healthy dietary self-management behaviors. In addition, the Self-Efficacy theory does not account for the high-fat, high sugar foods that tend to

trigger compulsive food consumption which also contribute to T2DM disease progression. Considering that food may play an important role in eliciting addictive patterns of eating, it was necessary to identify another theoretical model like the FA Phenotype Model (Schulte et al., 2017), to explore how the addictive substances in food along with T2DM-related brain changes affects food behaviors and glycemic outcomes.

Food Addiction Phenotype Model

Since there are many factors that can influence food behaviors of T2DM patients, another emerging theoretical model is the FA Phenotype Model designed by Gearhardt and colleagues (Schulte et al., 2017). Scientific evidence for the FA Phenotype Model has been proposed in Chapter 2: Review of Literature, to account for the poor dietary behaviors among T2DM patients. FA was identified as a factor that could contribute to brain structural change. Established theoretical frameworks like the FA Phenotype Model laid a foundation to understanding the research problem as elements from this theoretical framework on health behavior served as a reference and guide to the design of this dissertation. In Figure 3.1 there are three overlapping concepts to explain FA: Behavioral Patterns of Engagement', 'Addictive Potential of Certain Foods' (e.g., high sugar foods) and the 'Individual's Risk Factors.' However, this model has been utilized in other patient populations such as in substance users and obese populations to explain health behavior and food decision-making behaviors but lack information on the potential neurobiological processes that may influence patients' dietary choices.

The FA Phenotype Model (Figure 3.1) by Schulte et al. (2017) posits that intake of certain foods have an 'Addictive Potential.' Foods with additives like refined carbohydrates (white flour or sugar), along with other palatable foods with added fat, could trigger the cycle of three phases of addictive-like eating behaviors parallel to behaviors of traditional addictive

disorders: a binge intoxication phase driven and characterized by the rewarding properties of the drug, a withdrawal phase accompanied by a negative emotional state as the acute rewarding drug properties wear off, and a preoccupation and anticipation phase that precedes renewed drug intake (Gearhardt et al., 2009a; Gearhardt, Davis, et al., 2011; Parylak et al., 2011; Schulte et al., 2015). 'Behavioral Patterns of Engagement' involves eating behaviors varying from bingeing to intermittent use and to eating to cope with aversive events. But the role of certain foods are important in the consideration of poor T2DM dietary behaviors because for behaviors like binge drinking, which elevates the addictiveness of alcohol as more concentrated doses are consumed, the act of bingeing is not as rewarding if the beverage was of lesser addictive potential like water (Herz, 1997; Schulte et al., 2017). Through the FA Phenotype model, it purports that eating behaviors would not advance to addictive-like or compulsive consumption without the interaction of both the 'Addictive Potential of Certain Foods' (e.g., high sugar foods) and the 'Individual's Risk Factors' (e.g., T2DM or impulsivity) (Figure 3.2). Since the original FA Phenotype Model (Figure 3.1) by Schulte et al. (2017) included 'Individual Risk Factors' as a general contributing factor to FA such as one's genetic vulnerability, it lacks specificity, resulting in the dissertation conceptual framework (Figure 3.2), which incorporates evidence from brain-related T2DM studies to delineate how T2DM contributes to brain changes in sites that control FA and impulsivity.

Dissertation Conceptual Framework

Since the causal pathway of FA, impulsivity, and brain structural changes in T2DM has not been completely established, the conceptual framework described in Figure 3.2 was proposed for this dissertation to highlight the underlying pathophysiological mechanisms and adverse effects of T2DM on brain physiology and in brain regions that control behavior such as FA,

impulsivity and ultimately, T2DM glycemic outcomes. The conceptual framework for this dissertation incorporated the pathophysiological and neurobiological processes of T2DM (as indicated by A1c) to address the specific ideas that are unique to this study. Altogether, Figure 3.2 displays elements of the behavioral and addictive food components of the substance-based theoretical framework of the FA Phenotype Model (Figure 3.1) and the neurobiological processes of the T2DM disease progression and associated brain changes. The interacting relationships between the proposed contributors gives insight into the etiology of poor food behaviors among T2DM patients.

The dissertation conceptual framework (Figure 3.2) incorporated T2DM disease progression and T2DM-related brain changes, which illustrates the interrelationships between an individual's T2DM status with his or her vulnerability for foods that are highly palatable, that leads to increased reward sensitivity, increased impulsivity, diminished inhibitory control, cognitive flexibility, and eventually compulsiveness/bingeing, tolerance/withdrawal, and craving/preoccupation behaviors which are characteristics of substance-related and addictive disorders and FA (Adams et al., 2019; Bandura, 1977; Schulte et al., 2017). Though there may be an overlap between FA and impulsivity concepts in non-T2DM populations, changes in brain regions have been largely supported by human functional neuroimaging data showing distinct differences between FA and impulsivity: there is abnormal functioning in association with the orbitofrontal cortices and amygdala among substance abusers/addiction (Blumenthal & Gold, 2010; Gearhardt, Yokum, et al., 2011), whereas in impulsive subjects, the dysfunction is in insular, frontal cortices and hypothalamus (Dambacher et al., 2015; Jimura et al., 2013; Kalon et al., 2016b; Reijmer et al., 2013). Given that A1c is a validated and reliable measure of glycemia which is reflective of T2DM self-management behaviors such as dietary adherence (Saudek &

Brick, 2009), and since A1c has been consistently linked to structural brain tissue injury (Erus et al., 2015; Kodl et al., 2008; Reijmer et al., 2013; Strachan, 2011), this study examined the relationship between structural brain tissue changes, FA, impulsivity, and T2DM outcomes via A1c levels.

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Figure 3.1 Contributors to a Food Addiction Phenotype (Schulte et al., 2017)

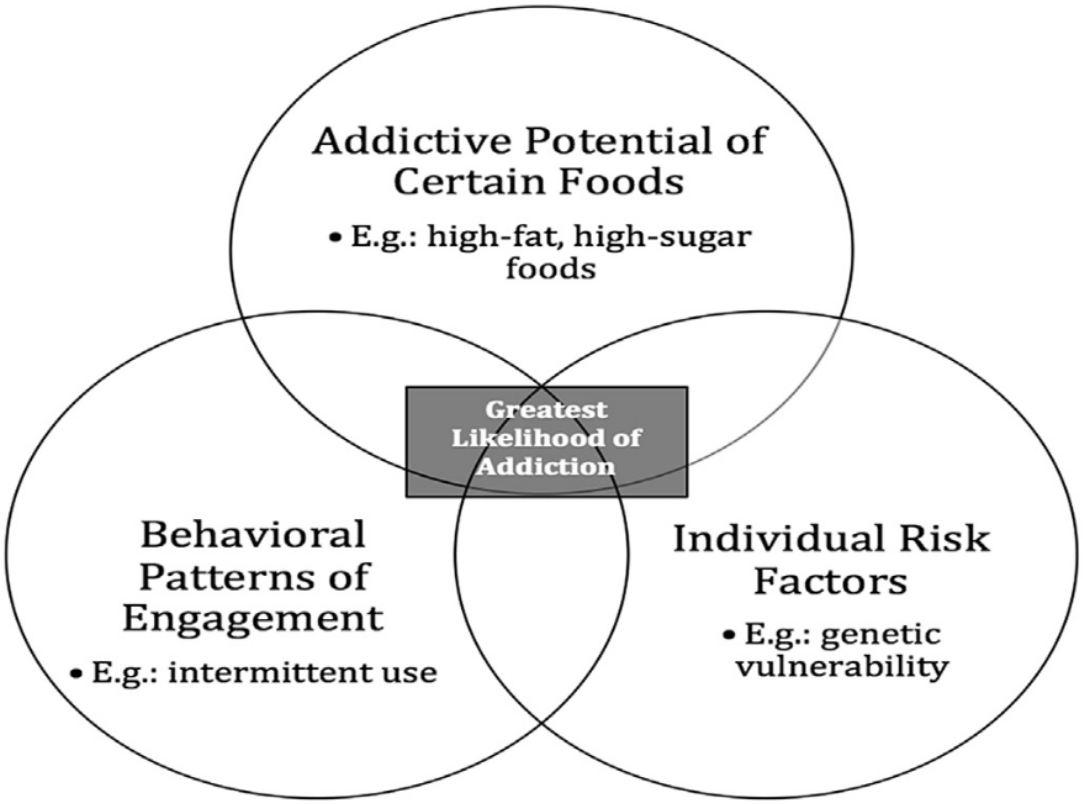
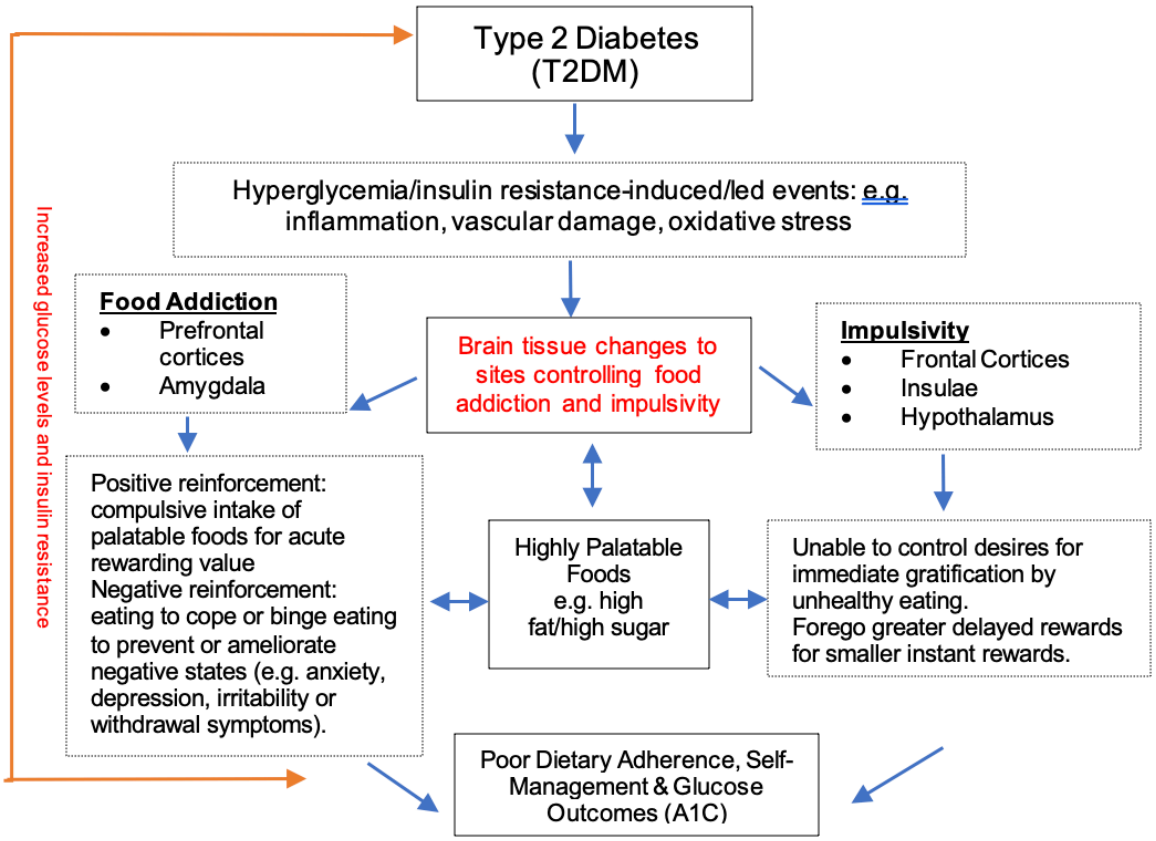


Figure 3.2 Dissertation Conceptual Framework for FA, Impulsivity, Glycemic Outcomes, Brain Tissue Changes, and T2DM Self-Management



CHAPTER FOUR: FIRST MANUSCRIPT

Relationships Among Food Addiction, Impulsivity, and Glycemic Control in Persons with Type 2 Diabetes Mellitus and Healthy Controls

Chapter Four: Relationships Among Food Addiction, Impulsivity, and Glucose Control in Persons with Type 2 Diabetes Mellitus and Healthy Controls

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Funding Support:

Ms. Smeltzer received financial support from the Jonas Nurse Scholar Program 2018-2020 and the UCLA School of Nursing Dean Sarna Doctoral Fellowship Award. All co-authors have no conflicts of interest to disclose related to this manuscript.

Abstract

Background: Type 2 Diabetes Mellitus (T2DM) is a significant public health concern where unhealthy food behaviors are commonly associated with poor T2DM glycemic control and diminished health outcomes. Prior research has suggested that poor glycemic control in people with T2DM may be due to unhealthy behaviors related to food addiction (FA) or food impulsivity. To date, little is known about FA and impulsivity in association with glycemic outcomes among T2DM patients. **Purpose:** To compare the relationships between FA, impulsivity, and glycemic outcome (hemoglobin A1c) between T2DM and healthy patients. **Methods:** Using a comparative-correlational, cross-sectional design, 64 participants (32 T2DM, 32 healthy controls) between the ages 40-65 years completed the Yale Food Addiction Scale 2.0 (YFAS) and Barratt Impulsiveness Scale-11 (BIS) online questionnaires. A1c was measured with a fingerstick test. **Results:** Between T2DM and healthy patients, there were no group differences in the prevalence of FA diagnosis, YFAS 2.0 total scores, BIS-11 scores, or severity classification of FA diagnosis. There were positive correlations between two FA symptomatologies with higher A1c: food tolerance and food use in physically hazardous situations ($r= 0.254$, $r= 0.417$, $P <0.05$). There were no significant correlations between BIS-11 scores and A1c. There were positive correlations between two BIS-11 subscale scores (attention and non-planning) and YFAS 2.0 total scores ($r =0.312$, $r= 0.248$ respectively, $P <0.05$). **Conclusion:** In this study, a subset of questions within the YFAS 2.0 tool were linked to high A1c levels showing that persons with food tolerance and/or consumed foods during hazardous situations had poorer glycemic outcomes. Since FA may negatively impact glycemic control, routine screening with a subset of questions from YFAS 2.0 could identify FA behaviors that may impact glycemic management, thereby optimizing health outcomes among T2DM patients.

Introduction

Diabetes is a rising problem affecting more than 37 million people in the US and 90-95% of them have Type 2 Diabetes Mellitus (T2DM) (Centers for Disease Control Prevention, 2022). Diabetes is a significant public health concern with a 60% higher risk of early death (Centers for Disease Control Prevention, 2022). Adherence to dietary recommendations is critical for T2DM management to achieve optimal glycemic control and to help prevent or delay micro- and macrovascular complications (Brown et al., 2016; Metz et al., 2000), such as cardiovascular and kidney diseases (Jeffcoate, 2004; Skyler, 2000; White, 2012). However, many people with T2DM have difficulty adhering to recommended diets and they identify this as the most challenging part of their diabetes self-care (Glasgow et al., 1997; Vijan et al., 2005).

Unfortunately, it is unclear as to why a significant number of T2DM patients engage in unhealthy eating habits. Prior research has suggested a resemblance between food and substance use disorder, where a person with food addiction (FA) cannot rationally control food consumption to the point he/she may go through tolerance, withdrawal, and craving stages that are similar to substance addiction (Shriner & Gold, 2014; Ziauddeen & Fletcher, 2013). Since T2DM individuals may have unsuccessful behavioral attempts to follow recommended dietary intake, FA may be an area of exploration to understanding unhealthy food behaviors and glycemic outcomes and to identify potential interventions in T2DM patients.

There are three stages to addiction: (a) the binge–intoxication stage, (b) the withdrawal–negative affect stage, and (c) the preoccupation– anticipation stage (Koob, 2008). A person with FA can be seen to go through these stages that are similar to substance addiction versus behavioral (e.g. pathological gambling) because there is a neurochemical effect in the brain (Ziauddeen & Fletcher, 2013). Research has implicated parallels in neural functioning between

addictive eating behaviors and substance use where there is an elevated activation in the reward circuitry in response to food cues and reduced activation of inhibitory regions in response to food intake (Gearhardt, Davis, et al., 2011). Initial FA evidence stemmed from studies of eating disorders such as binge-eating. For example, Gold et al. (2003) found that the majority of the substance dependence diagnostic criteria are similar to the criteria necessary to meet a diagnosis of binge eating disorder, such as a loss of control over consumption and an inability to successfully stop or cut down on consumption despite an expressed desire to do so and when there are severe negative health consequences, such as diabetes, heart disease, and stigmatization (Volkow & O'Brien, 2007). Raymond and Lovell (2015) demonstrated an association between FA symptomatology and T2DM diagnosis where a majority of the sample reported unsuccessful behavioral attempts in reducing their intake of sweet, starchy, salty, and fatty foods/drinks. T2DM individuals diagnosed with FA had statistically significant higher body mass index (BMI) values, and FA and impulsivity (non-planning) were significant predictors that explained 38% variance in BMI (Raymond & Lovell, 2015).

An additional view to explain unhealthy eating behaviors among many T2DM patients is impulsivity. Impulsivity is a process of learned behavior by which individuals react toward rapid, unplanned events influenced by internal and external stimuli without thinking, planning, or consideration of the impact that the negative consequences have on self or to others (Moeller et al., 2001). Different aspects of impulsivity include sensation seeking (trying and enjoying exciting or dangerous activities), lack of perseverance or attentional impulsivity (inability to concentrate or stay focused on a task), urgency or motor impulsivity (acting rashly without thinking), and lack of pre-meditation or non-planning impulsivity (lack of forethought or future orientation) (Patton et al., 1995; Whiteside & Lynam, 2001). Impulse control has an important

role in the self-regulation of certain dietary behaviors, such as moderation of food consumption (Hofmann et al., 2009).

Poor impulse control (or high levels of impulsivity) can exacerbate the risk for T2DM because the individual's ability to regulate the type and amount of food that he or she consumes is impaired (Weygandt et al., 2013). Regarding dietary behaviors, impulsive T2DM individuals have an inability to control their desires for immediate gratification by eating poorly as they forego greater delayed rewards (e.g. glycemic control) for smaller instant rewards (Jimura et al., 2013; Kalon et al., 2016a; Volkow & Baler, 2015). The implications of impulsive behavior may lead to compromised self-control, or the ability to abstain, or engage in productive decision-making actions such as meal-planning. Impulsivity can lead to poor self-control or rash decisions that can threaten health outcomes. While the poor dietary behavior may be due to FA or impulsivity (or a combination of both), there are few studies of their relationships with A1c in persons with T2DM.

There are limited FA and impulsivity studies in T2DM, and these studies focus on psychological or metabolic factors such as depression and body mass index (BMI) (Raymond & Lovell, 2015; Yang et al., 2017). One study (Nicolau et al., 2020) examined FA in T2DM, and reported a 29.3% prevalence of FA in their sample, determined FA individuals had significantly higher A1c levels versus non-FA individuals, and discovered a greater proportion of FA versus non-FA individuals had diabetic retinopathy, neuropathy, nephropathy, and depression. Regarding impulsivity, only one study found positive associations between impulsivity scores and increases in A1c ($r= 0.4$, $P<0.001$) (Hadj-Abo et al., 2020). However, these standalone studies on FA and impulsivity expose the dearth in literature on FA, impulsivity and A1c and highlight the need for further exploration of their relationships.

Food Addiction (FA) Measure

The initial and prevailing tool that operationalizes the FA concept is the Yale Food Addiction Scale (YFAS) (Ziauddeen & Fletcher, 2013). The YFAS is a self-report instrument and the only validated tool in non-T2DM subjects that measures addictive-like eating behavior (Gearhardt, et al 2009a, Gearhardt et al., 2009b). Though YFAS has been utilized in studies with glycemic outcomes (Nicolau et al., 2020) and has exhibited strong convergent validity in FA severity classification with the World Health Organization BMI obesity classifications among T2DM patients, YFAS has yet to be correlated with A1c levels among T2DM patients. Therefore, this study explored associations between YFAS 2.0 symptomatologies and A1c levels. In a study in persons with eating behaviors, YFAS exhibited good internal ($\alpha = 0.86$), as well as convergent and divergent reliability (Gearhardt et al., 2009b). In another study, YFAS has shown strong internal consistency ($\alpha = 0.92$), had high convergent and incremental validity when compared to other measures relevant to eating behaviors [Three Factor Eating Questionnaire (TFEQ) disinhibition, TFEQ hunger, current BMI, highest lifetime BMI, and frequency of binge eating episodes, ranging from 0.24-0.63] (Gearhardt et al., 2016). In this study, the prevalence of the diagnosis of FA, the total score of YFAS 2.0, and the proportion of each symptom of FA were compared between T2DM patients and healthy controls. The associations between YFAS 2.0 symptomatologies and A1c and with impulsivity scores were also explored.

Impulsivity Measure

One of the most widely used impulsivity tool is the Barratt Impulsiveness Scale (BIS-11; (Barratt, 1959; Patton et al., 1995). This self-report instrument consists of 30 questions and three subscales of impulsivity: Motor Impulsiveness (acting without thinking), Non-planning

Impulsiveness (more interested in the present than the future) and Attentional Impulsiveness (lack of focus) (Patton et al., 1995; Stanford et al., 2009). The BIS-11 has been utilized in T2DM populations (Hadj-Abo et al., 2020; Raymond & Lovell, 2015; Wainwright et al., 2022) and reported validation and good reliability (0.62-0.83; Stanford et al., 2009; Vasconcelos et al., 2012) in non-T2DM samples and has been tested and reliably used among T2DM patients with a Cronbach's alpha = 0.95 (Hadj-Abo et al., 2020). On average it takes less than 15 minutes to complete.

While it is known that poor dietary choices significantly contribute to poor A1c and increased morbidity and mortality in T2DM, little is known about FA and impulsivity (as separate and overlapping concepts) among T2DM patients and of their relationships to glycemic outcomes (A1c). This study examined the relationships among FA, impulsivity, and glycemic control (A1c) among persons with T2DM and healthy controls. Specifically, associations between YFAS 2.0 and BIS-11 scores and A1c levels were explored.

Methods

Study Design

The study used a comparative-correlational, cross-sectional design, in a sample of 64 adult subjects (32 T2DM and 32 healthy controls/non-T2DM), who participated in the study between January to October 2022.

Sample and Setting

Subjects were recruited from a sample pool who completed participation in an on-going R01 study (Choi and Kumar: "Relationships Between Brain Tissue Integrity and Self-Care Abilities in Adults with Type 2 Diabetes; 1R01 NR017190-01). Subjects were recruited from the

University of California at Los Angeles (UCLA) clinics, campus, and surrounding communities. Inclusion criteria for the T2DM sample were subjects with outpatient status and on stable T2DM medication therapy (no changes in medications or dosages in previous 6 weeks). Then, age and gender match healthy controls were recruited where the inclusion criteria were normal blood pressure values (systolic <130 and diastolic < 80 mm Hg, not on antihypertensive medication therapy), and without Type 1 or T2DM. All participants were between 40-65 years of age; had no known neurological, psychiatric, cardiovascular, or past diagnoses of substance abuse and drug dependency, e.g., tobacco, cannabis, or cocaine use. This age group was chosen due to high prevalence of T2DM (Centers for Disease Control and Prevention, 2020) and to minimize differences in brain changes related to normal aging (Kumar et al., 2013; Kumar et al., 2011; Kumar, Delshad, et al., 2012). All participants were able to read and understand English.

Measures

Demographics and Hemoglobin A1c

Demographic data including race/ethnicity, age, and gender were obtained from the completed online questionnaires on Qualtrics (Qualtrics, Provo, UT, 2022). A1c data was obtained from the R01 study record within 12 months of YFAS and BIS questionnaires. The A1c test was conducted within 12 months prior to the YFAS and BIS questionnaires via a fingerstick sample of approximately 5μL of blood and were obtained via point-of-care A1CNow® (Polymer Technology Systems, Inc., Indiana) and available within 5 minutes. This device has demonstrated accuracy (on average 99% accuracy compared to certified reference lab) for the assessment of whole blood A1c and is certified by the National Glycohemoglobin Standardization Program (Mattewal et al., 2007; National Glycohemoglobin Standardization Program, 2010).

Yale Food Addiction Scale 2.0 (YFAS)

YFAS 2.0 is a 35-item self-report questionnaire (Table 4.7) that takes approximately 30 minutes to complete. It is a tool used to explore FA among various populations where there it explores concepts ranging from: tolerance, withdrawal symptoms, consuming larger amounts than intended, persistent desire or unsuccessful attempts to cut down, much time spent using or recovering from substance, continual use despite knowledge of consequences, activities given up due to use of substance (American Psychiatric Association, 2013). YFAS uses two scoring methods (see Appendix A): 1) continuous scoring method summarizing how many of the 11 Substance Use Disorders criteria (YFAS scores range from 0-11 symptoms) an individual reports he/she over-consumes highly palatable foods despite multiple attempts to limit overconsumption and, 2) there is a "diagnostic" threshold scoring or classification where the subject is considered FA if he/she endorses two or more FA symptoms (e.g. eating behaviors interfere with social and professional activities or withdrawal symptoms occur from abstaining from highly palatable foods) in addition to clinical significance of impairment or distress (e.g. significant life problems due to food and eating or eating behavior causes distress) within the past year (Gearhardt et al., 2016; Parylak et al., 2011). Questions on the YFAS 2.0 have eight frequency response options that range from "Never" to "Every Day," and depending on the frequency choice, there are different thresholds for each of the 35 questions for any of the 11-symptom criterion to be met. Those diagnosed with FA, there are specified severity thresholds for patients' FA symptoms where a participant can be characterized with mild (YFAS score of two or three symptoms and clinical significance), moderate (four or five symptoms and clinical significance), or severe food addiction (six or more symptoms and clinical significance) (Gearhardt et al., 2016).

Barratt Impulsiveness Scale 11

The BIS-11 is a 30-item self-report instrument (Table 4.8) that assesses the personality dimension of impulsivity by focusing on impulsive action, thought process, and personal attitudes (Patton et al., 1995). Subjects who score higher on the BIS-11 showed greater participation in a number of sensation-seeking or risk- taking behaviors like substance use (Reynolds et al., 2006). There are four possible Likert scale choices for each item: from a score of 1 (rarely/never), 2 (occasionally), 3 (often), and 4 (almost always/always) (Childress et al., 1999). The sum of the scores is the raw impulsiveness measure and the three second order factors are broken down to measure specific aspects of impulsivity. Possible scores for the entire scale range from 30-120 (see Appendix B), where a higher score reflects a higher level of impulsivity (Patton et al., 1995).

There are three BIS-11 subscales: Motor Impulsiveness (acting without thinking; factors motor and perseverance, e.g., "I do things without thinking"), Non-planning Impulsiveness (guidance for the present and not the future; self-control and cognitive complexity, e.g., "I am more interested in the present than the future") and Attentional Impulsiveness (lack of focus; factors attention and cognitive instability, e.g., "I don't pay attention") (Patton et al., 1995; Stanford et al., 2009).

Procedures

This study was approved by the UCLA Institutional Review Board (IRB). Subjects in the R01 study, who indicated a willingness to be contacted for future research investigations, were recruited for this study using an IRB-approved script and advertisements to contact subjects electronically over email and/or phone for follow-up. Interested subjects completed online questionnaires (YFAS 2.0 and BIS-11) via Qualtrics, a HIPAA and FERPA-compliant online

survey platform. The information sheet indicated that lab values (such as A1c), biophysical values (height, weight, waist circumference, blood pressure), and diabetes history collected in the R01 study they completed will be utilized for the current study. Participants received electronic gift card compensation ($25) for participation.

Data Analyses

Study data were entered and analyzed using Statistical Software for Social Sciences (SPSS v.28, Somers, NY). Descriptive statistics were used to obtain frequencies, percentages, means, and standard deviations. As much of the data were non-normally distributed, Mann-Whitney *U* test was used to compare group differences for continuous data and Chi-square analysis (or Fisher's exact test for cells with an expected count less than 5) were used for categorical variables. Spearman's rho correlation analyses were conducted for non-normal variables such as A1c, YFAS 2.0, and BIS-11 scores. Values with $P < 0.05$ on a two-tailed test were considered statistically significant for all analyses.

Results

Sample Characteristics

A total of 64 subjects (32 T2DM and 32 healthy controls) were enrolled and completed all study data collection. Demographic characteristics of T2DM patients and healthy controls are summarized in Table 4.1. Utilizing G*Power (version 3.1), Pearson correlation analyses (computationally identical to Spearman's correlation analyses) was used with an alpha of 0.05 and power of 0.80 (Faul et al., 2009) to determine a total sample size of 29 subjects (15 T2DM and 15 controls) would be needed to detect a large effect size (Cohen's r, 0.5) (2013).

Differences in Demographics and A1c Between Type 2 Diabetes Mellitus (T2DM) Patients and Healthy Controls (N=64)

Equal numbers of men and women with T2DM participated and more healthy women than healthy men (20 versus 12) participated in the study. There were no statistically significant differences in age, gender, YFAS total scores, BIS total scores and subgroup scores, and racial/ethnic background between the two groups. On average, T2DM patients were older (57.77±7.77 versus 56.02±7.25) and a majority of T2DM patients identified as Hispanic (14.1%), while a majority of healthy controls identified as White (18.8%; all of these variables had $p > 0.05$). A1c levels were statistically significantly different between groups, where T2DM subjects had higher A1c levels at 6.73±1.40 and healthy controls at 5.29±0.39 ($P < 0.001$).

Comparison of FA between Patients with T2DM and Healthy Patients

The percentage incidence of FA, symptom count, and severity levels of FA between T2DM patients (n=32) and healthy controls (n=32) are summarized in Table 4.1. The comparisons of YFAS symptomatology between T2DM patients and healthy controls are summarized in Table 4.2. The factor, "use in physically hazardous situations (e.g., driving/operating machinery)," was the only significantly different symptomatology between T2DM patients and healthy controls ($P < 0.05$) and the most common FA symptom among T2DM patients (43.8%). T2DM patients had higher YFAS total symptom count scores (2.09±3.38 versus 0.81±1.38, $P=0.241$). Though all FA-diagnosed participants had T2DM and only T2DM subjects were classified as having severe (more than 6 symptoms) FA, there were no significant differences between groups regarding severity classification of FA. While the prevalence of FA diagnosis was 12.5% among T2DM patients and 3.125% among healthy controls, 31.25% of T2DM patients and 18.75% of healthy controls had more than 2 FA

symptoms (minimum number of symptoms needed to be diagnosed with FA without clinical impairment). There were no significant group differences in the diagnosis of FA (having two or more FA symptoms AND positive clinical impairment) or having more than two symptoms.

Relationships between YFAS 2.0 Scores and A1c

Table 4.3 shows the summary of correlation analyses for each YFAS 2.0 symptomatology with A1c. For the correlation analyses, there were two significant FA symptomatologies in the sample (all subjects, both T2DM and controls) that were positively correlated with A1c: "tolerance" (increased food amounts for decreased effects) and "use in physically hazardous situations" (such as being distracted by thinking about food or by eating food while driving a car, crossing the street, or operating machinery; r= 0.254, P <0.05; r= 0.417, P < 0.001 respectively). The effect sizes of these significant findings were large: 0.504 and 0.646, respectively.

Relationships between BIS-11 Scores and A1c

The comparison of BIS-11 total and subscale scores between T2DM patients and healthy controls are summarized in Table 4.4. There were no significant differences in any of the BIS-11 scores between groups, but T2DM patients had lower BIS scores compared to healthy controls (64.94±5.95 versus 67.34±6.38). Correlation analyses between BIS-11 scores and A1c are summarized in Table 4.5. There were no statistically significant associations between BIS-11 total and subscale scores with A1c. The effect sizes ranged from 0.195 to 0.432 for the findings listed in Table 4.5.

Correlation between BIS-11 Scores and YFAS 2.0 Scores

The associations between BIS-11 total and subscale scores with the YFAS 2.0 total score

are summarized in Table 4.6. While there were no significant associations between the BIS-11 total scores and YFAS 2.0 total scores, there were positive associations between BIS-11 attention and non-planning subscale scores with the YFAS 2.0 total symptom score (r =0.312, r= 0.248 respectively, P <0.05). The effect sizes for the significant findings were large: 0.559 and 0.498 respectively.

Discussion

This is the first report that showed positive associations between FA symptomatology and glycemic outcomes (A1c), while impulsivity was not associated with A1c in this study. These findings indicate that there are specific questions within the YFAS 2.0 that can provide insight into the glycemic outcomes (A1c) (Table 4.3). Since tolerance (marked increase in amount; marked decrease in effect) in YFAS 2.0 was associated with poorer glycemic outcomes (higher A1c values), a closer investigation of the subset of questions from the YFAS 2.0 can be useful for clinicians to determine how the tolerance aspect of FA behavior affects T2DM glycemic outcomes (A1c levels). The two questions (Table 4.7) that were asked where patients had positively responded that at least one of these questions affected them at least two to three times a week were: 1) Eating the same amount of food did not give me as much enjoyment as it used to; and 2) I needed to eat more and more to get the feelings I wanted from eating (this included reducing negative emotions like sadness or increasing pleasure).

Prior FA findings show that T2DM patients with FA are known to have greater significant depressive symptoms as measured by the Beck Depression Inventory scores (36.4%) compared to T2DM without FA (18.5%) (P = 0.002) (Nicolau et al., 2020). In this study, T2DM patients with high A1c levels and food tolerance (decreased enjoyment while eating and an increased need to eat more) can be explained by the intake of palatable foods that used to prevent

or ameliorate negative states such as depression or stress but now the value of foods are acutely less rewarding or at the neurobiological level, due to a shift in the brain processing (Parylak et al., 2011). However, there is paucity of longitudinal FA research that further investigates the relationships of FA, psychological, and glycemic outcomes between T2DM patients and the general population without T2DM. Such comparisons would be beneficial to inform investigators and clinicians on how to design FA interventions or tailor care for people to optimize T2DM glycemic outcomes.

Along with tolerance, the next significant FA symptom that was associated with poor glycemic outcomes (higher A1c values), was the most common among T2DM patients: "use in physically hazardous situations." To be considered positive for this FA symptom, patients were asked if at least one of the three questions affected them by a certain frequency: 1) If they kept eating sweets even though the individual had diabetes or kept eating fatty foods despite having heart disease (affected them at least once a week or more); 2) If they were distracted by *thinking* about food even if they could have been hurt (e.g., when driving a car, crossing the street, operating machinery) (affected them at least once a month or more); and 3) If they were distracted by *eating* that they could have been hurt (e.g., when driving a car, crossing the street, operating machinery) (affected them at least 2-3 times a week or more). The significant associations between the aforementioned FA symptoms and A1c creates an opportunity for future studies that investigates potential interventions to decrease willful eating during harmful/stressful/dangerous circumstances or empower clinicians to employ behavioral, psychological, and/or family process therapies that can reduce diabetes related stress eating and thereby improve glycemic outcomes (Hilliard et al., 2016).

Considering that patients with higher A1c levels in this sample struggle with food

tolerance and use in physically hazardous situations, the current findings match past findings that patients with FA exhibit eating behaviors varying from bingeing (due to rewarding properties of foods), to intermittent use (due to acute rewarding food properties wearing off as seen in tolerance), and to eating to cope with aversive events (especially in hazardous situations) (Schulte et al., 2017). This study, however, is the first that linked FA symptomatologies to A1c. As mentioned earlier, only one study (Nicolau et al., 2020) examined FA with A1c levels but determined individuals diagnosed with FA had significantly higher A1c levels versus non-FA individuals. So the findings from this study builds upon Nicolau et al. (2020) study to inform clinicians that of the eleven FA symptomatologies, there are only two that are significantly associated to higher A1c values. Unlike the current study, the two prior studies on FA and T2DM focused on the relationships between psychological or metabolic factors such as depression and body mass index (BMI) to FA (Raymond & Lovell, 2015; Yang et al., 2017). Raymond and Lovell (2015) found that both YFAS scores and BIS-11 impulsivity (non-planning) scores accounted for 38% variance in BMI and is a significant predictor of worsening BMI and Yang et al. (2017) also found that higher YFAS scores are a significant predictor of higher BMI values but no associations with depression. Given that between 2015-2018, 89.9% of US adults 18 or older with diabetes were overweight or obese with BMI 25 kg/m^2 or higher, the findings from this study highlights the need to specifically address tolerance and use in physically hazardous situations to improve management of A1c which will also improve metabolic outcomes (BMI) among T2DM individuals with FA (Centers for Disease Control Prevention, 2022). While the short-term effects of T2DM include hyperglycemia which can cause polyuria, polydipsia, polyphagia, and blurred vision, prolonged hyperglycemia has been linked to multiple organ failure, micro- and macro- vascular complications, along with other metabolic syndromes such as

obesity, which is now commonly referred as ‘diabesity’ (Pinchevsky et al., 2020). While it is known that FA individuals are at higher risk for obesity and have higher A1c outcomes, to prevent serious health complications associated with T2DM such as obesity, major treatments for T2DM require attention to FA eating behaviors such as tolerance and use in physically hazardous situations.

While there is limited understanding in the etiology of these FA behaviors, findings in this study showed the correlation between FA symptomatologies and A1c. It suggests the need for clinicians to routinely utilize a subset of questions from the YFAS 2.0 tool to help identify people with T2DM who may need additional teaching on eating behaviors that can negatively impact A1c outcomes. There is also an opportunity for future studies to investigate how interventions can reduce tolerance and use in physically hazardous situations so that patients will be equipped to eat better and achieve better glycemic outcomes.

To reduce tolerance and use in physically hazardous situations, the study findings indicate the need for clinicians consider different treatment approaches that could address these adverse FA symptoms, such as neurofeedback (electroencephalography [EEG] biofeedback in real-time) to help patients regulate and change cognitive processes related to eating, or cognitive training to help individuals remove addictive-like foods, devalue and desensitize the perception of food stimuli, and control situations that can trigger addictive-eating behaviors (Adams et al., 2019; Hammond, 2011; Schmidt & Martin, 2016; Schulte et al., 2017). The use of EEG neurofeedback training is still novel but has been helpful in reducing cravings, overeating, opiate/cocaine substance use, and is a type of biofeedback tool that helps participants receive feedback of their brain wave activity in response to certain cues as well as real-time training to increase or decrease responses to improve control (Adams et al., 2019). The most promising

well-studied types of EEG training involve reducing EEG high beta activity (> 22 to 30 hertz), in which high frequency ranges are indicative of arousal, or multiple sessions of alpha-theta brain wave training where patients are encouraged to close their eyes to increase theta amplitude waves over alpha waves whereby simulating relaxation and such EEG trainings have enhanced participants' ability to significantly reduce stress or anxiety-induced food craving, consumption, and binge eating in non-T2DM populations (Imperatori et al., 2017; Schmidt et al., 2017; Schmidt & Martin, 2016). On the other hand, examples of cognitive training that can reduce attentional, affective, and motivational biases leading to overeating include response inhibition training where individuals have training tasks (e.g. repeated training sessions of sorting through pictures of healthy versus unhealthy foods) to improve their abilities to interrupt or override unhealthy eating behaviors resulting in some cases significant weight loss (Lawrence et al., 2015). Though neurofeedback and cognitive training such as response inhibition have reduced craving and food consumption behaviors in non-clinical populations as well as binge eating females, overweight/obese subjects and gambling behaviors and alcohol consumption in other populations, there is a need for further testing of the longevity of the effects and an understanding of the neurological mechanisms that impact food behaviors is warranted to improve future interventions (Adams et al., 2019; Imperatori et al., 2017; Schmidt et al., 2017; Schmidt & Martin, 2016; Schulte et al., 2017).

There may be other factors that contribute to impulsivity among the T2DM population that were either not present in the study sample or could have impacted the BIS-11 results. For example, the self-report nature or subjective interpretation of the frequency choices of the BIS-11 tool could account for the insignificant relationship between impulsivity and glycemic outcomes (A1c) among T2DM populations and in group comparison to the controls. Impulsivity

could have been underreported due to the social desirability aspect of self-report but since the questionnaires were online and were anonymous, this would likely be a minor factor (Joinson, 1999). It should be noted that the small sample size of patients could be a restrictive factor where type II error occurred and there could have been significant findings for impulsivity. The study was set up to detect large effect size 0.5 with a power of 0.8, but the actual effect sizes of the BIS-11 and A1c findings were low to moderate (Table 4.5). Another possible reason that BIS-11 scores were not associated with A1c in this study could be that, while BIS-11 is widely used and is the prevailing impulsivity tool, there are limited studies that have reported validity and reliability findings when used to investigate the relationships with glycemic outcomes such as A1c. To address reliability concerns, manual calculation of all BIS-11 scores were compared to the computer-generated scores resulting in 100% inter-rater reliability.

Only three prior studies that have utilized BIS-11 among T2DM patients (Hadj-Abo et al., 2020; Raymond & Lovell, 2015; Wainwright et al., 2022), only one investigated and found associations between BIS-11 scores and increases in A1c levels (r= 0.4, P<0.001) (Hadj-Abo et al., 2020). But generalization of their results is limited to German T2DM patients. In this study, while the total BIS-11 scores were not associated with total YFAS 2.0 scores, there were positive associations between specific types of impulsive behaviors and total YFAS 2.0 scores (attention and non-planning subscale scores: r =0.312, r= 0.248 respectively, P <0.05). Therefore, T2DM patients with attention difficulties such as intrusive or racing thoughts that impact their task/focus (e.g., 'I often have extraneous thoughts when thinking') had higher YFAS 2.0 scores. Also, T2DM patients with non-planning impulsiveness such as difficulties assessing, careful thinking, planning, and enjoying mental tasks that are challenging (e.g., 'I do things without thinking") had higher YFAS 2.0 scores as well. Interestingly, Wainwright et al. (2022) also

found statistical significance with BIS-11 attention and non-planning subscales among T2DM patients, like with this current study, but with different outcomes. Wainwright et al. (2022) discovered T2DM patients with high BIS-11 attention and non-planning scores were negatively associated to fewer days adhering to a diet per the Summary of Diabetes Self-Care Activities (SDSCA) diet subscale (r=-0.306, r=-0.393 respectively, $P<0.05$). Raymond and Lovell (2015) investigated BIS-11 among T2DM patients but with regards to BMI outcomes where BIS-11 non-planning scores significantly account for 38% of BMI variance ($P<0.05$). While there is still a dearth in the literature about impulsivity in relation to A1c, the current and past findings show that attention and non-planning are aspects of impulsivity that are problematic for T2DM patients.

Limitations

A limitation of this study includes the one-time (cross sectional), non-experimental design, as it is not possible to determine any causal relationships between food addiction, impulsivity, and A1c. Since the enrolled subjects of this study were recruited from an on-going NIH-funded R01 study where subjects were only eligible if he or she completed the R01 study, there was a limited pool of candidates and concern about achieving adequate power to detect an effect. However, as noted in Table 4.3 and Table 4.6, the sample size of this study was adequately powered to be able to detect large effect sizes for associations between FA symptomatology and A1c and attention/non-planning characteristics of impulsivity with FA symptomatology. While it is possible that the online administration of these instruments could have been confusing for the study participants, efforts were made to reduce variability of their answers and increase question clarity through provision of examples for each question to improve understanding, and the responses were anonymous to enhance objectivity in scoring.

Another limitation from recruiting subjects from an existing study conducted at a single institution is that generalizability to T2DM patients from other settings is limited. Despite the strict inclusion criteria with recruitment, this study included racially and ethnically diverse subjects where most of the sample identified as Hispanic/Latino and Asian/Pacific Islander. To the author's knowledge, no other FA studies among T2DM patients have included these racial/ethnic subgroups of the T2DM population. However, the limited subjects' pool led to a disproportionate number of females in the healthy control group versus an equal number of female and male participants among T2DM patients.

The A1c data capture is another limitation due to study recruitment and timeline constraints because the lab results were obtained up to 12 months prior to the YFAS 2.0 and BIS-11 measures. However, the YFAS 2.0 questionnaire was validated to assess an individual's eating behavior in the prior 12 months. Also, the recruitment of T2DM patients for this study led to a sample of patients who had an average A1c that was well-controlled (< 7%) per the recommended A1c target levels set by the World Health Organization (2011) and American Diabetes Association (2019a). Though A1c tests were obtained up to 12 months prior to the YFAS and BIS measures, A1c trends were being monitored and glycemic management was already stable at the time even though there was possible concern whether the A1c levels obtained reflect current glycemic outcomes. Perhaps the greater concern would be if the A1c levels could have led to less detection of FA and/or impulsivity as the sample of patients in this study were able to control their consumption behaviors to stabilize glycemic control within the last 2-3 months as reflected by their well-controlled A1c levels.

In addition, selection bias against those who are not technologically literate cannot be ruled out as only patients who responded to emails or were able to complete online

questionnaires were recruited. Those lost to follow-up and ineligible patients may have worse A1c, FA, and/or impulsivity. Future multi-institutional publicly accessible studies could be conducted to increase generalizability of findings to racially, ethnically, and gender-equitably diverse T2DM populations.

Another limitation to this study is that there may be indeterminant statistical implications with the occurrence of the COVID-19 pandemic in the year leading up to the administration of the online questionnaires. Study subjects were to answer the questions based off dietary behaviors that occurred within the prior 12 months, which included periods of peak COVID-19 rates from 2021 to 2022. There may not be normative representation of subjects reflective of the pre-pandemic times and this is the first reported study utilizing YFAS 2.0 and BIS-11 questionnaires since the COVID-19 pandemic. The effects of the pandemic on FA, impulsivity, and glycemic outcomes (A1c) on T2DM patients and healthy controls are unknown. These unaccounted mental health, psycho-social circumstances resulting from the pandemic could reflect the lack of statistical significance with BIS-11 scores and the possible underreport of clinical impairment/distress that is required to be diagnosed with FA.

Conclusion

The findings of this study show that a subset of questions within the YFAS 2.0 tool are linked to poor A1c outcomes. Persons who have a higher food tolerance and greater consumption of foods during hazardous situations have poorer glycemic outcomes (higher A1c values). However, there are questions surrounding the directionality of the relationship: whether FA causes poor attention and planning or do poor glycemic outcomes (high A1c) cause T2DM patients to have high tolerance and greater consumption of foods during hazardous situations. These findings could aid in the identification and testing of innovative solutions to treat elevated

A1c. Unfortunately, the most effective approach to understanding dietary behaviors has not been clearly established nor the direct causation of poor dietary adherence and glycemic outcomes (A1c). This knowledge gap challenges clinician's efforts to improve T2DM dietary behaviors and highlights the need to consider the brain (in which all behaviors originate) to investigate the underlying etiology for poor dietary behaviors, which could be a result of FA, impulsivity, or a combination of both. Moreover, it is known that people with addiction or impulsiveness, such as those who are alcohol/cocaine dependent or obese, show brain changes. However, relationships between these behaviors and the brain have not been reported in T2DM patients and could be the impetus for future T2DM studies (Ersche et al., 2011; Wang et al., 2016). In the meantime, it appears that FA may negatively impact glycemic control and suggest the need for routine screening of FA with a subset of questions from YFAS 2.0 to modify FA behaviors and promote optimal glycemic management that can ultimately improve health outcomes among T2DM patients.

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Table 4.1 Differences in Demographics and A1c Between Type 2 Diabetes Mellitus (T2DM) Patients and Healthy Controls (N=64)

	T2DM N=32 (Mean±SD)	**Healthy Control N=32 (Mean±SD)**	***P*-value**
Gender (men/women)	(16/16)	(12/20)	0.321
Age (years)	57.77±7.77	56.02±7.25	0.356
A1c	6.73±1.40	5.29±0.39	<0.001**
Racial Background White Asian Hispanic Other	**Number (Prevalence)** n=8(12.5%) n=8(12.5%) n=9(14.1%) n=7(10.9%)	**Number (Prevalence)** n=12(18.8%) n=11(17.2%) n=6(9.4%) n=3(4.7%)	0.324

SD, Standard Deviation
***P* <0.001

Table 4.2 Comparison of Food Addiction (FA) Between Patients with T2DM and Healthy Controls (N=64)

	T2DM N=32	**Healthy Control N=32**	***P*-value**
YFAS Total (Symptom Count 0-11)	2.09±3.38	0.81±1.38	0.241
Diagnosis of FA (more than 2 FA symptoms + clinical impairment/distress)	4(12.5%)	1(3.125%)	0.355
More than 2 FA symptoms	10(31.25%)	6(18.75%)	0.248
Severity Classification of FA Diagnosis: • Severe (6+ symptoms and clinical impairment/distress) • Moderate (4-5 symptoms and clinical impairment/distress) • Mild (2-3 symptoms and clinical impairment/distress)	 4(100%) - -	 - 1(100%) -	0.200
YFAS 2.0 Symptom Criterion and Clinical Impairment/Distress			
1. Substance taken in larger amount and for longer period than intended.	6(18.8%)	4(12.5%)	0.732
2. Persistent desire or repeated unsuccessful attempts to quit.	7(21.9%)	4(12.5%)	0.509
3. Much time/activity to obtain use, recover.	6(18.8%)	2(6.3%)	0.257
4. Important social, occupational, or recreational activities given up or reduced.	5(15.6%)	2(6.3%)	0.426
5. Use continues despite knowledge of adverse consequences (e.g., emotional problems, physical problems).	4(12.5%)	1(3.1%)	0.355
6. Tolerance (marked increase in amount; marked decrease in effect).	4(12.5%)	0	0.113
7. Characteristic withdrawal symptoms; substance† taken to relieve withdrawal.	7(21.9%)	2(6.3%)	0.148
8. Continued use despite social or interpersonal problems.	6(18.8%)	1(3.1%)	0.104
9. Failure to fulfill major role obligation (e.g., work, school, home).	3(9.4%)	0	0.238
10. Use in physically hazardous situations (e.g., driving/operating machinery).	14(43.8%)	3(9.4%)	0.004*
11. Craving, or a strong desire or urge to use.	5(15.6%)	1(3.1%)	0.196
12. Use causes clinically significant impairment or distress.	4(12.5%)	2(6.3%)	0.672

FA, Food Addiction; YFAS, Yale Food Addiction Scale
*$P < 0.05$

Table 4.3 YFAS 2.0: Correlations Between FA Symptom Criterion and Clinical Impairment/Distress and A1c (N=64)

YFAS 2.0 Symptom Criterion and Clinical Impairment/Distress	Correlation (r)	*P*-value
1. Substance† taken in larger amount and for longer period than intended.	0.162	0.200
2. Persistent desire or repeated unsuccessful attempts to quit.	0.051	0.692
3. Much time/activity to obtain use, recover.	0.143	0.258
4. Important social, occupational, or recreational activities given up or reduced.	0.079	0.536
5. Use continues despite knowledge of adverse consequences (e.g., emotional problems, physical problems).	0.155	0.222
6. Tolerance (marked increase in amount; marked decrease in effect).	0.254[a]	0.043*
7. Characteristic withdrawal symptoms; substance† taken to relieve withdrawal.	0.157	0.215
8. Continued use despite social or interpersonal problems.	0.145	0.252
9. Failure to fulfill major role obligation (e.g., work, school, home).	0.178	0.158
10. Use in physically hazardous situations (e.g., driving/operating machinery).	0.417[b]	0.001*
11. Craving, or a strong desire or urge to use.	0.209	0.907
12. Use causes clinically significant impairment or distress.	0.016	0.900

FA, Food Addiction; YFAS, Yale Food Addiction Scale

‡YFAS 2.0 questionnaire wording based on Diagnostic and Statistical Manual of Mental Disorders V and patients were to answer with any foods or beverages they had difficulty with in the past 12 months

[a]Effect size: 0.504

[b]Effect size: 0.646

*$P < 0.05$

Table 4.4 Comparison of BIS-11 Scores Between T2DM patients and Healthy Controls

	T2DM N=32 (Mean±SD)	**Healthy Control N=32 (Mean±SD)**	***P*-value**
BIS Total Score	64.94±5.95	67.34±6.38	0.236
BIS-Attention Subscale	13.34±3.32	13.31±3.91	0.819
BIS-Motor Subscale	19.16±3.22	19.47±3.28	0.756
BIS-Non-Planning Subscale	21.44±5.4	20.19±4.45	0.278

BIS, Barratt Impulsivity Scale; SD, Standard Deviation

Table 4.5 Correlation Between BIS-11 Scores and A1c (N=64)

	Correlation Coefficient (r)	***P*-value**	**Effect Size**
BIS Total Score	-0.052	0.682	0.228
BIS-Attention Subscale	0.121	0.340	0.348
BIS-Motor Subscale	0.038	0.764	0.195
BIS-Non-Planning Subscale	0.187	0.139	0.432

BIS, Barratt Impulsivity Scale
*$P < 0.05$

Table 4.6 Correlations Between YFAS 2.0 Total Score and BIS-11 Scores (N=64)

	Correlation coefficient (r)	***P*-value**
BIS Total Score	0.097	0.446
BIS-Attention Subscale	0.312[a]	0.012*
BIS-Motor Subscale	0.216	0.086
BIS-Non-Planning Subscale	0.248[b]	0.048*

BIS, Barratt Impulsivity Scale
[a]Effect size: 0.559
[b]Effect size: 0.498
*$P < 0.05$

Table 4.7 Full Yale Food Addiction Scale Version 2.0

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

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

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

IN THE PAST 12 MONTHS:	Never	Less than monthly	Once a month	2-3 times a month	Once a week	2-3 times a week	4-6 times a week	Every Day
1. When I started to eat certain foods, I ate much more than planned.	0	1	2	3	4	5	6	7
2. I continued to eat certain foods even though I was no longer hungry.	0	1	2	3	4	5	6	7
3. I ate to the point where I felt physically ill	0	1	2	3	4	5	6	7
4. I worried a lot about cutting down on certain types of food, but I ate them anyways.	0	1	2	3	4	5	6	7
5. I spent a lot of time feeling sluggish or tired from overeating.	0	1	2	3	4	5	6	7
6. I spent a lot of time eating certain foods throughout the day.	0	1	2	3	4	5	6	7
7. When certain foods were not available, I went out of my way to get them. For example, I went to the store to get certain foods even though I had other things to eat at home.	0	1	2	3	4	5	6	7
8. I ate certain foods so often or in such large amounts that I stopped doing other important things. These things may have been working or spending time with family or friends.	0	1	2	3	4	5	6	7
9. I had problems with my family or friends because of how much I overate.	0	1	2	3	4	5	6	7
10. I avoided work, school, or social activities because I was afraid, I would overeat there.	0	1	2	3	4	5	6	7

11. When I cut down on or stopped eating certain foods, I felt irritable, nervous, or sad.	0	1	2	3	4	5	6	7
12. If I had physical symptoms because I hadn't eaten certain foods, I would eat those foods to feel better.	0	1	2	3	4	5	6	7
13. If I had emotional problems because I hadn't eaten certain foods, I would eat those foods to feel better.	0	1	2	3	4	5	6	7
14. When I cut down on or stopped eating certain foods, I had physical symptoms. For example, I had headaches or fatigue.	0	1	2	3	4	5	6	7
15. When I cut down or stopped eating certain foods, I had strong cravings for them.	0	1	2	3	4	5	6	7
16. My eating behavior caused me a lot of distress.	0	1	2	3	4	5	6	7
17. I had significant problems in my life because of food and eating. These may have been problems with my daily routine, work, school, friends, family, or health.	0	1	2	3	4	5	6	7
18. I felt so bad about overeating that I didn't do other important things. These things may have been working or spending time with family or friends.	0	1	2	3	4	5	6	7
19. My overeating got in the way of me taking care of my family or doing household chores.	0	1	2	3	4	5	6	7
20. I avoided work, school, or social functions because I could not eat certain foods there.	0	1	2	3	4	5	6	7
21. I avoided social situations because people wouldn't approve of how much I ate.	0	1	2	3	4	5	6	7
22. I kept eating in the same way even though my eating caused emotional problems.	0	1	2	3	4	5	6	7
23. I kept eating the same way even though my eating caused physical problems.	0	1	2	3	4	5	6	7
24. Eating the same amount of food did not give me as much enjoyment as it used to.	0	1	2	3	4	5	6	7
25. I really wanted to cut down on or stop eating certain kinds of foods, but I just couldn't.	0	1	2	3	4	5	6	7
26. I needed to eat more and more to get the feelings I wanted from eating. This included reducing negative emotions like sadness or increasing pleasure.	0	1	2	3	4	5	6	7
27. I didn't do well at work or school because I was eating too much.	0	1	2	3	4	5	6	7
28. I kept eating certain foods even though I knew it was physically dangerous. For example, I kept eating sweets even though I had diabetes. Or I kept eating fatty foods despite having heart disease.	0	1	2	3	4	5	6	7

29. I had such strong urges to eat certain foods that I couldn't think of anything else.	0	1	2	3	4	5	6	7
30. I had such intense cravings for certain foods that I felt like I had to eat them right away.	0	1	2	3	4	5	6	7
31. I tried to cut down on or not eat certain kinds of food, but I wasn't successful.	0	1	2	3	4	5	6	7
32. I tried and failed to cut down on or stop eating certain foods.	0	1	2	3	4	5	6	7
33. I was so distracted by eating that I could have been hurt (e.g., when driving a car, crossing the street, operating machinery).	0	1	2	3	4	5	6	7
34. I was so distracted by thinking about food that I could have been hurt (e.g., when driving a car, crossing the street, operating machinery)	0	1	2	3	4	5	6	7
35. My friends or family were worried about how much I overate.	0	1	2	3	4	5	6	7

Note. Retrieved from https://sites.lsa.umich.edu/fastlab/yale-food-addiction-scale/ (Gearhardt et al., 2016)

Gearhardt, A. N., Corbin, W. R., & Brownell, K. D. (2016). Development of the Yale Food Addiction Scale version 2.0. *Psychology of Addictive Behaviors, 30*(1), 113-121. https://doi.org/10.1037/adb0000136

Table 4.8 Barratt Impulsiveness Scale 11.0

DIRECTIONS: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate circle on the right side of this page. Do not spend too much time on any statement. Answer quickly and honestly.						
	① Rarely/Never	② Occasionally	③ Often	④ Almost Always/Always		
1 I plan tasks carefully.	①	②	③	④		
2 I do things without thinking.	①	②	③	④		
3 I make-up my mind quickly.	①	②	③	④		
4 I am happy-go-lucky.	①	②	③	④		
5 I don't "pay attention."	①	②	③	④		
6 I have "racing" thoughts.	①	②	③	④		
7 I plan trips well ahead of time.	①	②	③	④		
8 I am self controlled.	①	②	③	④		
9 I concentrate easily.	①	②	③	④		
10 I save regularly.	①	②	③	④		
11 I "squirm" at plays or lectures.	①	②	③	④		
12 I am a careful thinker.	①	②	③	④		
13 I plan for job security.	①	②	③	④		
14 I say things without thinking.	①	②	③	④		
15 I like to think about complex problems.	①	②	③	④		
16 I change jobs.	①	②	③	④		
17 I act "on impulse."	①	②	③	④		
18 I get easily bored when solving thought problems.	①	②	③	④		
19 I act on the spur of the moment.	①	②	③	④		
20 I am a steady thinker.	①	②	③	④		
21 I change residences.	①	②	③	④		
22 I buy things on impulse.	①	②	③	④		
23 I can only think about one thing at a time.	①	②	③	④		
24 I change hobbies.	①	②	③	④		
25 I spend or charge more than I earn.	①	②	③	④		
26 I often have extraneous thoughts when thinking.	①	②	③	④		
27 I am more interested in the present than the future.	①	②	③	④		
28 I am restless at the theater or lectures.	①	②	③	④		
29 I like puzzles.	①	②	③	④		
30 I am future oriented.	①	②	③	④		

Note. Retrieved from (Patton et al., 1995)

CHAPTER FIVE: SECOND MANUSCRIPT

Food Addiction and Impulsivity Associations with Brain Tissue Injury in Persons with Type 2 Diabetes Mellitus

Chapter Five: Food Addiction and Impulsivity Associations with Brain Tissue Injury in Persons with Type 2 Diabetes Mellitus

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Funding Support:

Ms. Smeltzer received financial support from the Jonas Nurse Scholar Program 2018-2020 and the UCLA School of Nursing Dean Sarna Doctoral Fellowship Award. All co-authors have no conflicts of interest to disclose related to this manuscript.

Abstract

Background: Maladaptive dietary behaviors contribute to poor glycemic outcomes for persons with Type 2 Diabetes Mellitus (T2DM). Factors which may contribute to poor T2DM dietary behaviors include food addiction (FA; overconsumption to the point where there are similar symptoms to substance use addiction) and impulsivity (lack of control in food consumption). FA and impulsivity behaviors can be reflected by differences in brain tissue integrity, but the relationships between FA, impulsivity, and brain tissue changes in persons with T2DM are unclear. **Purpose:** To investigate the associations between FA, impulsivity, and brain tissue integrity in persons with T2DM. **Methods:** Using a cross-sectional, correlational study design, 21 T2DM participants between the ages 40-65 years who completed brain magnetic resonance imaging (MRI) scans, were recruited to complete the Yale Food Addiction Scale 2.0 (YFAS) and Barratt Impulsiveness Scale-11 (BIS) online questionnaires. Using diffusion tensor imaging data, mean diffusivity (MD) values were calculated, and region-of-interest analyses were performed on various brain areas to examine correlations with YFAS 2.0 and BIS scores (partial correlations; covariates, age, and sex). **Results:** Significant correlations between tissue integrity and YFAS 2.0 scores were found in brain regions regulating executive decision-making (cortices, precuneus, temporal); memory -visual or auditory (occipital, supramarginal); motor function (putamen); and emotion (cingulum) functions in T2DM patients. No associations emerged between BIS-11 scores and brain tissue integrity. **Conclusions:** Significant correlations appear between FA and brain tissue integrity in this population with T2DM and findings indicate that FA has a brain structural basis in T2DM adults. Further studies are needed to understand the impact of FA on these altered brain tissue areas and to identify interventions to protect or promote neurogenesis and determine if such interventions improve T2DM outcomes.

Introduction

It is projected that as many as one in three US adults will have diabetes by 2050 (Boyle et al., 2010) and approximately 90-95% of them will have Type 2 Diabetes (T2DM) (Centers for Disease Control Prevention, 2022). Studies have shown that T2DM patients have difficulty adhering to their dietary regimen and managing their daily T2DM self-care activities (Al-Salmi et al., 2022; Vijan et al., 2005) largely because individuals with T2DM must continuously monitor what they eat, and meticulously restrict or abstain from eating certain types of foods to achieve glycemic control (Daley & Wallymahmed, 2014). As much of behavior is regulated by the mind, it is important to understand the relationships of the brain, behaviors which could impact eating (such as food addiction and impulsivity), and diabetes status (glycosylated end-product A1c) in persons with T2DM. Uncontrolled T2DM (as measured by high levels of glycosylated end-product A1c) and/or stress, have been shown to be the primary underlying factors leading to functional and structural brain damage (Biessels et al., 2002; Kodl & Seaquist, 2008; Strachan, 2011).

Definitions of Food Addiction (FA) and Impulsivity

Though it is unclear as to why some T2DM patients engage in unhealthy eating habits, prior research has suggested poor dietary behaviors could be linked to regional brain activity showing a resemblance between maladaptive food and drug consumption (Blumenthal & Gold, 2010; Gearhardt, Davis, et al., 2011; Small et al., 2001; van Bloemendaal et al., 2014). Food addiction (FA) may occur if there is elevated activation in the brain reward circuitry in response to food cues, and reduced activation of inhibitory brain regions in response to food intake to the point that there is an inability to change (stop overeating) when there are negative consequences (Blumenthal & Gold, 2010; Gearhardt et al., 2009b; Volkow & Baler, 2015). Another possible

factor in poor dietary behaviors is impulsivity, which can impact an individual's ability to control desires for immediate gratification, and can result in unhealthy overeating and an inability to forego greater delayed rewards (like glycemic control) in exchange for instant smaller rewards (Jimura et al., 2013; Kalon et al., 2016b; Volkow & Baler, 2015).

Brain Areas Associated with FA/Impulsivity

Both FA and impulsivity (or a combination of both) are controlled by the brain. However, brain status in relationship to FA and impulsivity has not been reported in T2DM patients. Though there may be overlap in concepts between FA and impulsivity, these behaviors should be reflected by differences in the brain (in which all behaviors originate). Human neuroimaging in non-T2DM persons has shown that among substance users/FA there are brain changes in areas that control reward responses (insula, striatum, amygdala, and orbitofrontal cortices (OFC)), and more specifically addiction stages such as withdrawal/negative affect state (amygdala) and preoccupation/anticipation stage -craving (OFC and amygdala) (Blumenthal & Gold, 2010; Gearhardt, Yokum, et al., 2011; Koob & Volkow, 2010). In impulsive subjects, brain changes occur in areas that involve decision-making and self-control/regulation of psychological, physiological responses (insular, frontal cortices and hypothalamus) (Dambacher et al., 2015; Jimura et al., 2013; Kalon et al., 2016a).

Brain Status in T2DM

Magnetic resonance imaging (MRI) techniques, such as diffusion tensor imaging (DTI), have been used to detect significant acute and chronic microstructural axonal (white matter damage linking gray matter sites) and structural tissue injury (gray matter damage in areas receiving, processing, and releasing information) in the following brain regions in T2DM: regions associated with addiction (amygdala, prefrontal cortices) and regions associated with

impulsivity (insular lobes, frontal cortices, cingulate, hypothalamus, and thalamus (Choi, Roy, Freeby, Mullur, et al., 2020; Choi, Roy, Freeby, Woo, et al., 2020; Roy et al., 2023; Roy et al., 2020). These structural imaging studies paired with neuropsychological assessments revealed that the structure changes in brain regions that regulate executive control and mood, such as the prefrontal cortices, frontal cortices, cingulate, para-hippocampal, hippocampus, cerebellum, insula, lingual gyrus, basal-forebrain, and temporal cortices, have been associated with decreased cognitive functioning and higher depression in uncontrolled T2DM patients (Choi, Roy, Freeby, Mullur, et al., 2020; Choi, Roy, Freeby, Woo, et al., 2020; Roy et al., 2023; Roy et al., 2020).

In addition to DTI visualization of the brain, mean diffusivity (MD) can provide additional valuable information of brain status. Mean diffusivity is a measure of the magnitude of water molecular motion tissue abnormalities, where greater tissue injury or cellular loss is indicated by higher MD values (Woo et al., 2015). An exploration of the alterations in specific brain regions (measured by MD values) that are associated with FA and impulsivity have yet to be evaluated and serve as a novel approach to understanding underlying causes of poor T2DM dietary self-management and glycemic outcomes (as measured by glycosylated hemoglobin A1c).

Food Addiction (FA) Measure

The Yale Food Addiction (YFAS) is the most widely used self-report tool among obese and individuals with eating disorders that was specifically designed to assess and operationalize FA (Gearhardt, et al 2009a, Gearhardt et al., 2009b). Though prior validation and reliability studies focused on psychological or metabolic outcomes, YFAS has been utilized in recent T2DM research as FA is considered an important factor in poor glycemic outcomes, especially since T2DM is a common comorbidity with obesity (Nicolau et al., 2020; Raymond & Lovell,

2015; Yang et al., 2017). The current version (YFAS 2.0) is based on DSM-V and include changes to the substance-related and addictive disorders (SRAD, formerly substance use disorders) (American Psychiatric Association, 2013; Gearhardt et al., 2016). Though there has been limited use and findings on reliability among T2DM patients, in a study with eating behaviors, YFAS exhibited good internal ($\alpha = 0.86$), as well as convergent and divergent reliability (Gearhardt et al., 2009b). In another study, YFAS has shown strong internal consistency ($\alpha = 0.92$), had high convergent and incremental validity when compared to other measures relevant to eating behavior [Three Factor Eating Questionnaire (TFEQ) disinhibition, TFEQ hunger, current BMI, highest lifetime BMI, and frequency of binge eating episodes, ranging from 0.24-0.63] (Gearhardt et al., 2016). In this study, the total score of YFAS (ranging from 0-11) was used to determine the associations between FA and the brain tissue integrity of regional brain sites. Despite the self-report nature of the tool, which may lead to underreports of FA behaviors, this study may provide clinicians insight into the relationship between the YFAS 2.0 tool and brain tissue integrity for T2DM patients, which has not been reported before.

Impulsivity Measure

While impulsivity has not been well-studied among T2DM, a majority of T2DM patients are obese and impulsivity has been well-studied and associated in persons with obesity, disordered eating, drug addiction, and/or alcoholism (Alhassoon et al., 2015; Goldstein & Volkow, 2011; Nederkoorn et al., 2006; Pelchat, 2009). The most widely used and longstanding tool to measure a person's level of impulsiveness was developed in 1959 by Ernest Barratt known as the Barratt Impulsiveness Scale and the most recent version BIS-11 was updated in 1995 (Barratt, 1959; Patton et al., 1995). Very few studies have utilized BIS-11 among T2DM populations (Hadj-Abo et al., 2020; Raymond & Lovell, 2015) but it has been tested and reliably

used among T2DM patients with a Cronbach's alpha = 0.95 (Hadj-Abo et al., 2020). In studies with other clinical populations such as substance abuse/dependence, depression, bipolar, attention-deficit/hyperactivity disorder, suicidal ideation, and criminal offense, the internal consistencies ranged from moderate to strong with Cronbach's alpha values 0.62 to 0.83, test–retest stability 0.66 to 0.83, and criterion-related validity was established (Stanford et al., 2009; Vasconcelos et al., 2012). With the general population, BIS-11 has exhibited good internal consistency for the entire scale ($\alpha = 0.83$), as have the second order factors: attentional impulsiveness, $\alpha = 0.74$, motor impulsiveness, $\alpha = 0.69$, and non-planning impulsiveness, $\alpha = 0.72$ (Patton et al., 1995). In this study, associations between BIS-11 scores from three subcategories of impulsivity: attention, motor, and non-planning and the brain tissue integrity of regional brain sites were investigated.

While it is known that the brain is abnormal in non-T2DM individuals with FA or impulsivity, brain status in relationship to these behaviors has not been reported in T2DM. Since there is a dearth in neuroimaging studies that explore FA or impulsivity among T2DM patients, it may be crucial to understanding poor T2DM dietary adherence and potential interventions through greater understanding of the neurological links with these behaviors, especially since FA and impulsivity have been found to be important characteristics of problematic eating behaviors (Jentsch et al., 2014).This study was designed to investigate the relationships between FA, impulsivity, and brain status of individuals with T2DM.

Methods

Study Design

The study used a correlational, cross-sectional design, with 21 T2DM patients enrolled in

the study between January to October 2022.

Sample and Setting

The T2DM patients were recruited from a pool of subjects who had completed MRI and study visits (to eliminate the possibility of any neural changes that may occur with time, medication, or T2DM self-care changes) from an on-going R01 study conducted by Choi and Kumar: "Relationships Between Brain Tissue Integrity and Self-Care Abilities in Adults with Type 2 Diabetes" (1R01 NR017190-01A1). The racially and ethnically diverse subjects from the RO1 study were recruited from the University of California at Los Angeles (UCLA) Gonda Diabetes Center, UCLA campus, and the surrounding communities. The T2DM inclusion criteria for the R01 study were subjects between 40-65 years of age, either gender, outpatient status, on stable T2DM medication therapy (no changes in medications or dosages in previous 6 weeks), able to lay flat, and understood/read English. Exclusion criteria included: claustrophobia, metallic-based tattoos, metallic implants or devices (such as implantable cardioverter-defibrillators [ICD], pacemaker, embolic coils, aneurysm clips), or any other material which could be hazardous in the MRI scanner environment, body weight > 300 pounds (weight and size restrictions of MRI scanner device), pregnancy (if subject is female), history of stroke, seizure disorder, head trauma, diagnosed with psychiatric disease (clinical depression, schizophrenia, manic-depressive), and airway or chest deformities that would interfere with breathing, mechanical ventilatory support, and renal failure (requiring dialysis). Also, subjects must be without any neurological or cardiovascular conditions that would induce brain injury, diagnosed with dementia, or sleep disordered breathing, chronic obstructive pulmonary disease, cystic fibrosis, presence of brain mass lesions, or a current or past diagnosis of substance abuse or drug dependency (e.g., tobacco, cannabis, or cocaine use) that would modify brain tissue.

Measures

Demographic and Clinical Data

Demographic data such as race/ethnicity, age, and gender were obtained from the completed online questionnaires on Qualtrics (Qualtrics, Provo, UT, 2022). A1c data was obtained on the day of the MRI scans which were from the R01 study record and within 12 months of YFAS and BIS questionnaires. A fingerstick sample of approximately 5μL of blood was obtained and results obtained via point-of-care A1CNow® (Polymer Technology Systems, Inc., Indiana) were available within five minutes. The A1C Now has demonstrated accuracy (on average 99% accuracy compared to certified reference lab) for the assessment of whole blood A1c and is certified by the National Glycohemoglobin Standardization Program (Mattewal et al., 2007; National Glycohemoglobin Standardization Program, 2010).

Magnetic Resonance Imaging (MRI)

MRI methodology is a non-invasive approach to examine the living human brain, without the need of radiation or contrast agents. MRI methods provide an avenue to quantitatively assess the structural integrity of the brain, as well as structural changes in the tissue. Brain MRI studies were performed on a 3.0-Tesla MRI scanner (Siemens, Magnetom, Prisma Fit) in the UCLA Department of Radiology, and high-resolution T1-, Proton Density-, and T2-weighted images were obtained for assessment of any visible gross brain pathologies such as infarcts, tumors, cysts, mass lesions.

High-resolution T1-weighted imaging. High-resolution T1-weighted images were collected using the magnetization prepared rapid acquisition gradient echo pulse sequence (MPRAGE) [repetition time (TR) = 2200 ms, echo time (TE) = 2.34 ms, inversion time=900 ms, flip angle (FA) = 9º], with 320x320 matrix size, 230x230 mm field of view (FOV), 0.9 mm slice thickness, and 192

sagittal slices. The scanning time was ~ 7 min.

Diffusion tensor imaging (DTI). DTI was performed using an echo-planar-imaging with twice-refocused spin-echo pulse sequence (TR = 12000 ms; TE = 87 ms; FA = 90°; bandwidth = 1346 Hz/pixel; matrix size = 128×128; FOV = 230×230 mm^2; slice thickness = 1.7 mm; 92 slices; no interslice-gap; diffusion directions = 30; b = 0, 800 s/mm^2) in the axial plane, and two separate scans were collected. Scanning time was approximately ~14 min.

Proton-density (PD) and T2-weighted imaging. PD and T2-weighted images were collected (TR = 10,000 ms, TE1,2 = 17, 134 ms, FA = 130°) using a dual-echo turbo spin-echo pulse sequence in the axial plane, with 256x256 matrix size, 230x230 mm FOV, 3.0 mm slice thickness, and 56 slices. Scanning time was ~ 5 min.

Questionnaires

Yale Food Addiction Scale 2.0

YFAS 2.0 is a 35-item self-report questionnaire that operationalizes behavioral indicators of "food addiction" based on DSM-V diagnostic criteria for substance-related and addictive disorders (SRADs) where there are 11 symptom criterion (Gearhardt et al., 2016). YFAS uses two scoring methods: 1) continuous scoring method summarizing how many of the eleven SRAD criteria (scores range from 0-11) an individual reports he/she over-consumes highly palatable foods despite multiple attempts to limit overconsumption and, 2) there is a "diagnostic" threshold scoring or classification where the subject is considered FA if he/she endorses two or more FA symptoms (e.g. eating behaviors interfere with social and professional activities or withdrawal symptoms occur from abstaining from highly palatable foods) in addition to clinical significance of impairment or distress (e.g. significant life problems due to food and eating or eating behavior causes distress) within the past year (Gearhardt et al., 2016; Parylak et al., 2011).

Questions on the YFAS 2.0 have eight frequency response options that range from "Never" to "Every Day," and depending on the frequency choice, there are different thresholds for each of the 35 questions for any of the 11-symptom criterion to be met. For those diagnosed with FA, there are specified severity thresholds for patients' FA symptoms where a participant can be characterized with mild (YFAS score of two or three symptoms and clinical significance), moderate (4 or 5 symptoms and clinical significance), or severe food addiction (6 or more symptoms and clinical significance) (Gearhardt et al., 2016). YFAS takes approximately 30 minutes to complete and has been used among obese, T2DM, and patients with eating disorders (Nederkoorn et al., 2006; Nicolau et al., 2020; Kirrilly M. Pursey et al., 2014; Raymond & Lovell, 2015; Yang et al., 2017).

Barratt Impulsiveness Scale-11

The BIS-11 is a 30-item self-report instrument that assesses the personality dimension of impulsivity by focusing on impulsive action, thought process, and personal attitudes (Patton et al., 1995). Subjects who score higher on the BIS-11 showed greater participation in a number of sensation-seeking or risk- taking behaviors like substance use (Reynolds et al., 2006). There are four possible Likert scale choices for each item: from a score of 1 (rarely/never), 2 (occasionally), 3 (often), and 4 (almost always/always) (Childress et al., 1999). The sum of the scores is the raw impulsiveness measure and the three second order factors are broken down to measure specific aspects of impulsivity. Possible scores for the entire scale range from 0-120, where a higher score reflects a higher level of impulsivity (Patton et al., 1995). On average it takes approximately less than 15 minutes to complete BIS-11.

Originally, the questionnaire was designed to assess impulsivity as a single construct but advances in research on impulsivity has led to its emergence as a multi-dimensional construct

consisting of six factors: attention, motor, self-control, cognitive complexity, perseverance, and cognitive instability. These factors can be grouped into three major categories: Motor Impulsiveness (acting without thinking; factors motor and perseverance, e.g., “I do things without thinking”), Non-planning Impulsiveness (guidance for the present and not the future; self-control and cognitive complexity, e.g., “I am more interested in the present than the future”) and Attentional Impulsiveness (lack of focus; factors attention and cognitive instability, e.g., “I don’t pay attention”) (Patton et al., 1995; Stanford et al., 2009).

Data Collection Procedures

This study was approved by the UCLA Institutional Review Board (IRB# 20-001188). The R01 research coordinator under the direction of Dr. Choi screened and identified subjects for the parent R01 study and had subjects indicate whether they would allow contact for future research opportunities. The research coordinator utilized an IRB-approved script and advertisements to contact the R01 subjects electronically over email and by phone for potential participation in this study (on relationships between FA, impulsivity, and brain status). Interested subjects responded back by email, the research coordinator forwarded subjects’ contact information to the PI of the present study (Smeltzer), explanation of the study was conducted by Smeltzer over email and phone if necessary. The PI emailed the IRB-approved information sheet for the potential participants to review and for record-keeping and the web address where participants electronically consented to participate in the study and online questionnaires (YFAS 2.0 and BIS-11) via Qualtrics (Qualtrics, Provo, UT, 2022), a HIPAA and FERPA-compliant online survey platform. The information sheet indicated that the current study would collect lab values (such as A1c), MRI scans, and diabetes history collected from the parent R01 study. Participants received electronic gift card compensation ($25) for participation. Time to complete

all study questionnaires ranged from 10 to 30 minutes.

Data Analyses

Clinical, demographic, and biophysical data were entered and analyzed using Statistical Software for Social Sciences (SPSS v.28, Somers, NY). Descriptive (frequencies, percentages, means, and standard deviations) and bivariate statistics (chi-square, t-tests) were used for demographic and clinical variables. Partial correlations were utilized to analyze associations between areas of brain tissue integrity (average MD values) and FA (YFAS 2.0 scores) and impulsivity (BIS-11 attention and non-planning subscale scores). Effect sizes were calculated with SPSS v.28 for the partial correlations statistical analyses that were used for the MRI and questionnaire relationship evaluations.

MRI Diffusion Tensor Imaging Data Analyses

Brain imaging analyses used several software for evaluation of images, data processing, and analyses: statistical parametric mapping package SPM 12 (http://www.fil.ion.ucl.ac.uk/spm/), DTI-Toolkit (v0.6.4.1) (Wang et al., 2017), MRIcroN (Rorden et al., 2007), and MATLAB (http://www.mathworks.com/). These MRI imaging analyses were completed by the Kumar Neuroimaging Research Lab at UCLA.

To calculate mean diffusivity (MD) values, the average background noise level from outside the brain parenchyma was calculated using non-diffusion and diffusion-weighted images, and this noise threshold was used in all T2DM subjects to suppress non-brain regions (only those regions outside the brain parenchyma) during MD calculations. The diffusion ($b = 800$ s/mm^2)-weighted images, collected from 30 diffusion directions, and non-diffusion ($b = 0$ s/mm^2) images was used to calculate diffusion tensor matrices (Le Bihan et al., 1991) from each series using the

DTI-Studio software (Jiang et al., 2006). The diffusion tensor matrices were diagonalized, and principal eigenvalues (λ1, λ2, and λ3) was calculated at each voxel (Basser & Pierpaoli, 1998; Pierpaoli et al., 1996). Mean diffusivity [MD = λ1+λ2+λ3)/3] values were determined at each voxel using principal eigenvalues (Alexander et al., 2007; Le Bihan et al., 2001; Pierpaoli et al., 1996), and whole brain MD maps were generated with voxel intensities on the MD representing the corresponding MD values.

Next steps were to realign, average, normalize and smooth MD maps. First, we realigned and averaged the four MD maps and b0 images, derived from each DTI series, to remove any potential differences in alignment due to head-motion, and to create one MD map per subject. The averaged MD maps were normalized to a Montreal Neurological Institute (MNI) common space (Ashburner & Friston, 2005) based on *a priori*-defined distributions of gray, white, and cerebrospinal fluid types, as described for other DTI-based measures (Choi et al., 2019; Kumar, Chavez, et al., 2012; Kumar et al., 2011; Kumar et al., 2006; Kumar et al., 2010). The resulting normalization parameters were applied to corresponding MD maps and non-diffusion weighted images. The normalized MD maps were smoothed using an isotropic Gaussian filter (10 mm kernel), and smoothed MD maps were used for further analyses. High-resolution T1-weighted images of T2DM subjects were also normalized to MNI space. T1-weighted images were partitioned into gray, white, and cerebrospinal fluid tissue types, based on unified segmentation approach (Ashburner & Friston, 2005), and normalization parameters were applied to corresponding T1-weighted images. The normalized b0 images from all T2DM subjects were averaged to create whole brain mean background images, which was used for structural identification.

We compared the normalized and smoothed MD maps voxel-by-voxel with YFAS 2.0

scores and BIS 11.0 (attention, motor, and non-planning) subscale scores using partial correlations (SPM12; covariates, age, and gender; uncorrected threshold, $P < 0.005$). Brain clusters with significant relationships with YFAS 2.0 and BIS-11 subscale scores were overlaid onto a background image for structural identification. Brain areas showing significant associations in the T2DM sample population were extracted from all the subjects and region-of-interest (ROI) analyses were used to determine average MD values in those areas based on whole-brain voxel-by-voxel comparisons. Region-of-interest masks were outlined for various brain areas using clusters determined by voxel-by-voxel analysis procedures. The ROI masks were also used to calculate average MD values of those specific brain sites from T2DM patients with normalized and smoothed MD maps. The average MD values of those areas were correlated with YFAS 2.0, and BIS-11 subscale scores (attention and non-planning) using partial correlation analyses in SPSS to examine correlation effect sizes (covariates, age, and gender, $P< 0.05$).

Results

Twenty-one subjects (of the 32 T2DM subjects in the parent R01 grant) were eligible for this study, where participants needed to have completed MRI scans from the R01 study within 12 months of participation in this study (Figure 5.1). A sample size of 21 subjects can detect large effect sizes (0.811 to 0.901) for the partial correlations analyses between YFAS 2.0 scores and MD values, as well as detection of small to moderate effect sizes (0.387 to 0.522) for the partial correlation analyses between BIS-11 subscale scores (attention and non-planning) and MD values (see Table 5.2 and Table 5.3).

Sample Characteristics

Demographic and clinical characteristics of T2DM patients are summarized in Table 5.1.

Correlations between Brain Damage and YFAS 2.0 Scores

Summary of MD values at specific brain regions that showed significant positive correlations with YFAS 2.0 scores along with large effect sizes are listed in Table 5.2. To visualize the specific locations in the brain that are positively correlated with YFAS 2.0 scores, the images can be found in Figure 5.2 and Figure 5.3. The following damaged brain regions were significantly positively correlated with total YFAS 2.0 scores: visual memory (occipital inferior -left (Figure 5.2a)); executive decision-making and motor function (frontal superior medial -right (Figure 5.2b); precuneus -left (Figure 5.3e)); putamen -right (Figure 5.2c); frontal mid -Right (Figure 5.2d); supramarginal -left (Figure 5.3a); auditory memory (supramarginal -right (Figure 5.3b); temporal superior -right (Figure 5.3c); and emotion (cingulum posterior -left (Figure 5.3d).

Correlations between Brain Damage and BIS-11 Scores

The summary found in Table 5.3 shows no significant relationships between MD values at the aforementioned brain sites and BIS-11 subscale scores (attention and non-planning), and small to moderate effect sizes for each coefficient correlation between BIS-11 subscale scores (attention and non-planning) to MD values.

Discussion

This study shows among 21 T2DM patients shows there is neurological basis for FA through altered brain tissue integrity impacting the following general functions: executive decision-making (frontal cortices, precuneus, temporal); memory, visual or auditory (occipital,

supramarginal); motor function (putamen); and emotion (cingulum). There were, however, no correlations between impulsivity scores and brain tissue damage. Understanding FA behaviors is an important factor to consider in maintaining brain integrity related to achieving optimal T2DM outcomes. There is now neuroimaging evidence of specific impaired brain sites that mediate FA behaviors among T2DM patients.

FA is a multi-dimensional, complex conceptualization to explain overeating, but this study suggests there is a neurobiological abnormality as the basis of the breakdown in eating behavioral control systems that is measured and assessed through YFAS 2.0. YFAS 2.0 reflects the 11 eating-related symptomatologies of DSM-V SRADs, such as substance taken in larger amount and for longer period than intended; persistent desire or repeated unsuccessful attempts to quit; much time/activity to obtain, use, recover; important social, occupational, or recreational activities given up or reduced; use continues despite knowledge of adverse consequences (e.g., emotional problems, physical problems); tolerance (marked increase in amount; marked decrease in effect); characteristic withdrawal symptoms, substance taken to relieve withdrawal; continued use despite social or interpersonal problems; failure to fulfill major role obligation (e.g., work, school, home); use in physically hazardous situations; or a strong desire or urge to use; in addition to clinical significance of impairment or distress (e.g. significant life problems due to food and eating or eating behavior causes distress). While YFAS 2.0 may be an incomplete tool to assess poor dietary behaviors, the complexities in the relationship between food consumption behaviors and T2DM should not be undermined as there are personal, clinical, and now neurological realities that impact the individual's T2DM condition.

This study adds to the growing evidence of structural neuroimaging studies among T2DM patients, especially regarding damage to brain areas of significance in this study:

cognition (frontal cortices) and mood (cingulate). Specifically, Roy and colleagues (2020) found that there are decreased gray matter volumes in several brain regions in T2DM patients that control cognition (such as the prefrontal cortex, hippocampus, and cerebellum), anxiety (hippocampus, amygdala, insula, and cingulate), and depression (hippocampus, para-hippocampus, cingulate, insula, and thalamus) ($P < 0.01$). Recently, Roy et al. (2023) published newer findings on the acute and chronic microstructural damage in areas mediating cognition and mood (cerebellum, insula, frontal and prefrontal cortices, cingulate, and lingual gyrus) among T2DM patients. Their findings suggest that T2DM may account for the impaired connectivity mechanisms underlying the large-scale brain cognitive and mood regulatory networks, as reflected by the significantly associated poor cognition and mood scores resulting from the neuropsychological assessments (Roy et al., 2023). Altogether, the current study and past structural T2DM MRI findings expose the complications that can result from the development and progression of T2DM-related structural changes to specific sites in the brain as they are associated with functional changes like in cognition, mood, and FA. This suggests that it is crucial to consider and investigate the cerebral structural changes in the evaluation of poor dietary adherence among T2DM patients, because there may be neural basis as to why patients have difficulty in adhering to a diabetes diet.

Treatments

In consideration of the findings that injury to brain structures among T2DM patients are linked to various cognitive behaviors related to FA, there is opportunity to improve T2DM outcomes through treatments that can restore the connectivity damage in the axons, nerve fibers, or myelin sheets or preserve the tissue structure. Methods such as mesenchymal stem cell (MSC) therapies (known for regenerative medicine due to trophic factors that can influence the cellular

environment around damaged tissues to self-renew or enhance tissue repair) and electroacupuncture have been tested among animal models for successful neuronal regeneration, immunomodulation, and angiogenesis for ischemic stroke and intracerebral hemorrhage (Grochowski et al., 2018; Li et al., 2021). However, there are limited publications, and many studies are still in early phases for MSC therapies among humans and in treating neurodegenerative disorders like Parkinson's disease, Alzheimer's disease, and Multiple Sclerosis (Grochowski et al., 2018; Jovic et al., 2022). While application of stem cell therapy in the clinical setting and human trials are still nascent with sourcing challenges and safety concerns such as cell overgrowth/tumor growth, there is potential to improve the quality of life for patients with chronic conditions and enable some promising cellular-based therapies.

Upon implementing neuroprotective or neurogenerative treatments, it is unknown if treating the significant areas of brain damage impacts FA behaviors, thereby improving A1c levels and outcomes. While it is known that certain areas of the brain among T2DM patients are impaired, this study highlights that there is an overlap in brain areas associated with FA and to previous findings of cognition and mood among T2DM patients as mentioned above (frontal cortices and cingulate). Unlike past behavioral, dietary, and educational interventions that have been difficult for T2DM patients to adhere to resulting in high recidivism, attrition, and stigma, there is opportunity to implement tailored education and therapies in consideration of functional deficits of cognitive impairment and mood disorders as a way to further address maladaptive eating behaviors that are characteristic of FA.

Impulsivity

This study did not show a neurological link for impulsivity, which could be due to the complexity of the impulsivity concept and the BIS-11 tool could just be a modest measurement

tool on its own among T2DM patients. There are a variety of methods to measure impulsivity and typically each technique focuses on either of the following three categories: self-report, psychophysiological/biological, or laboratory behavioral measures (Dougherty et al., 2003). Also, since both YFAS 2.0 and BIS-11 fall into the self-report category, therein lies an inherent problem of the utility of the tool as impulsive patients are asked to assess their own abilities in situations where they may lack more than one dimension of control, which among T2DM patients can result in underreporting of FA or impulsivity related to eating behaviors.

Given the limitations of BIS-11, another behavioral measurement tool that can also be utilized is known as delay-discounting (DD), which is an approach that addresses the "impulsive choice" domain. DD involves a series of choices that measures the act of pursuing a smaller but more immediate award versus waiting for a larger, long-term reward (Madden & Bickel, 2010; Madden & Johnson, 2010). Studies that utilized DD among T2DM patients have shown significant findings. For example, there were positive associations between high DD scores (more impulsive) and higher A1c values ($r = 0.242$, $P = 0.023$) (Lebeau et al., 2016), higher risk of observing A1c $\geq$ 7% with greater monetary impatience (DD measured through fictive monetary choice) (OR = 5.1, CI 1.7–15.4, $P = 0.004$) (Reach et al., 2011), and impulsive individuals with lower insulin sensitivity have been associated with discounting delayed rewards at higher rates (high DD scores) (Eisenstein et al., 2015). The DD tool can be another useful for future studies, however, its use among T2DM patients in relation to glycemic outcomes (A1c) are still limited. Given that BIS-11 has been beneficial in measuring "impulsive personality traits," it will be beneficial to utilize DD tools as well to measure the "impulsive choice" behaviors, to thoroughly account for other nuances of impulsivity in future T2DM studies involving A1c glycemic outcomes.

Limitations

Since this study sample had more patients with controlled T2DM status (71.4%) versus uncontrolled, it could be that impulsivity was difficult to be detected within this study sample as the well-controlled A1c values reflect their self-control in eating behaviors over the past three months. Also, to address the time gap (4-12 months) between A1c data capture and YFAS 2.0 and BIS-11 measures, given the majority of the T2DM patients had controlled A1c levels, the glycemic management was already stable at the time and the A1c trends were being monitored. In addition, the YFAS 2.0 questionnaire was validated to assess an individual's eating behavior in the prior 12 months.

Another limitation of this study includes the cross-sectional, correlational design since it is not possible to determine causal relationships between food addiction, impulsivity, and areas of brain tissue injury among T2DM patients. Since the enrolled subjects of this study were recruited from an on-going NIH-funded R01 study where subjects were only eligible if completed the R01 study, there was a limited pool of candidates. This recruitment bias presents another limitation where the characteristics of this T2DM sample (majority of patients have controlled glucose status, higher income, and completed at least a 4-year degree program) may not reflect the demographics of the majority of T2DM patients in the US. Therefore, generalizability of findings to T2DM patients from other settings are limited. A strength of the study is a racially and ethnically diverse study population where most of the sample identified as "Hispanic/Latino" and/or "Other" which included Black and mixed ethnic groups. To the author's knowledge, no other FA studies involving MRI procedures among T2DM patients have largely included these subgroups of the T2DM population.

Although the sample size was small, there were significant large positive correlations

between FA scores and MD values and large effect sizes as well, but there may be other important factors (that past studies have investigated) not accounted for in this study that may contribute to FA, impulsivity, and brain tissue injury among the T2DM population such as medications, anxiety, depression, sleep quality, or T2DM self-care management activities (Cabrera-Mino et al., 2021; Choi, Roy, Freeby, Mullur, et al., 2020; Roy et al., 2020). Given the limitations of this study, a longitudinal study with a large sample size is warranted, especially to evaluate the findings from this present study in consideration of a clinical variable that is important for glycemic outcomes among T2DM patients: A1c.

Since most of the neurological evidence for FA is among non-T2DM patients, there may be limitations in the current study because it is difficult to extend and apply the findings from substance addiction models to FA. Several important limitations to consider are the fundamental differences between food and drugs in that unlike drugs, food do not have a direct nor simple pharmacological effect and because food is ubiquitous, it is not restricted and can be consumed at any time or place (Everitt et al., 2008; Volkow & Wise, 2005). Despite the biological similarities between food and drug consumption, the food intake process differs in that it increases glucose in the brain as the pleasurable activity activates the brain through fast sensory signals and through slow ingestion processes (Gearhardt et al., 2009b). And though dopamine release due to FA does not equate to addictive properties, the increase in dopamine release has been associated with greater perceptions of reward of both food and psychoactive substances (Volkow et al., 2002). Finally, there are also individual differences in the response to food cues, especially when hungry or satiated, which are appetite states that are not explored in this study.

Conclusion

This study sheds light on the additional impact that FA has on brain integrity and on dietary behaviors of T2DM patients. Findings from this study, thus far, suggest that FA behaviors in T2DM patients have a neurological basis, thereby impacting T2DM self-care behaviors, and highlight the need to further investigate the clinical implications of brain injury on FA to improve T2DM glycemic outcomes. Brain DTI studies such as this one provide compelling evidence of the relationships between structural brain damage and FA among T2DM patients. This neuroimaging study further contributes to the knowledge surrounding the structural alterations that link FA to T2DM patients. Interestingly, the findings showed that a majority of the sample were not diagnosed with FA (only two were diagnosed with FA in this study) and did not have poor glucose control, but there were positive associations between brain tissue injury and higher FA scores. While there was a significant discovery that FA is associated with greater tissue injury in areas that control one's ability to make decisions (frontal cortices) or regulate emotions (cingulum), it is important to consider therapies that address brain tissue damage associated with FA behaviors, in hopes that T2DM patients can improve dietary adherence and glycemic control. Brain tissue damage in critical areas that regulate executive function and emotions negatively impacts eating behavior associated with FA, thereby possibly contributing to poor dietary adherence and glycemic outcomes. Future use of routine FA screening tools like YFAS 2.0 along with multiple impulsivity tools, will be helpful for clinicians to identify high-risk patients in need of cognitive and mood deficit tailored treatments that addresses FA and impulsivity, which may lead to optimal metabolic or glycemic management that can ultimately maintain brain tissue integrity. Furthermore, findings suggest clinicians should identify and test novel interventions to reverse the structural brain changes such as stem cell therapies, cognitive

behavioral therapy, or vitamin supplementation to provide neuroprotection and neurogenesis for specific sites in the brain that are linked to FA and impulsivity and to ultimately promote healthy eating behaviors and better health outcomes.

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Figure 5.1 Flow Diagram of Recruitment Process of T2DM Participants

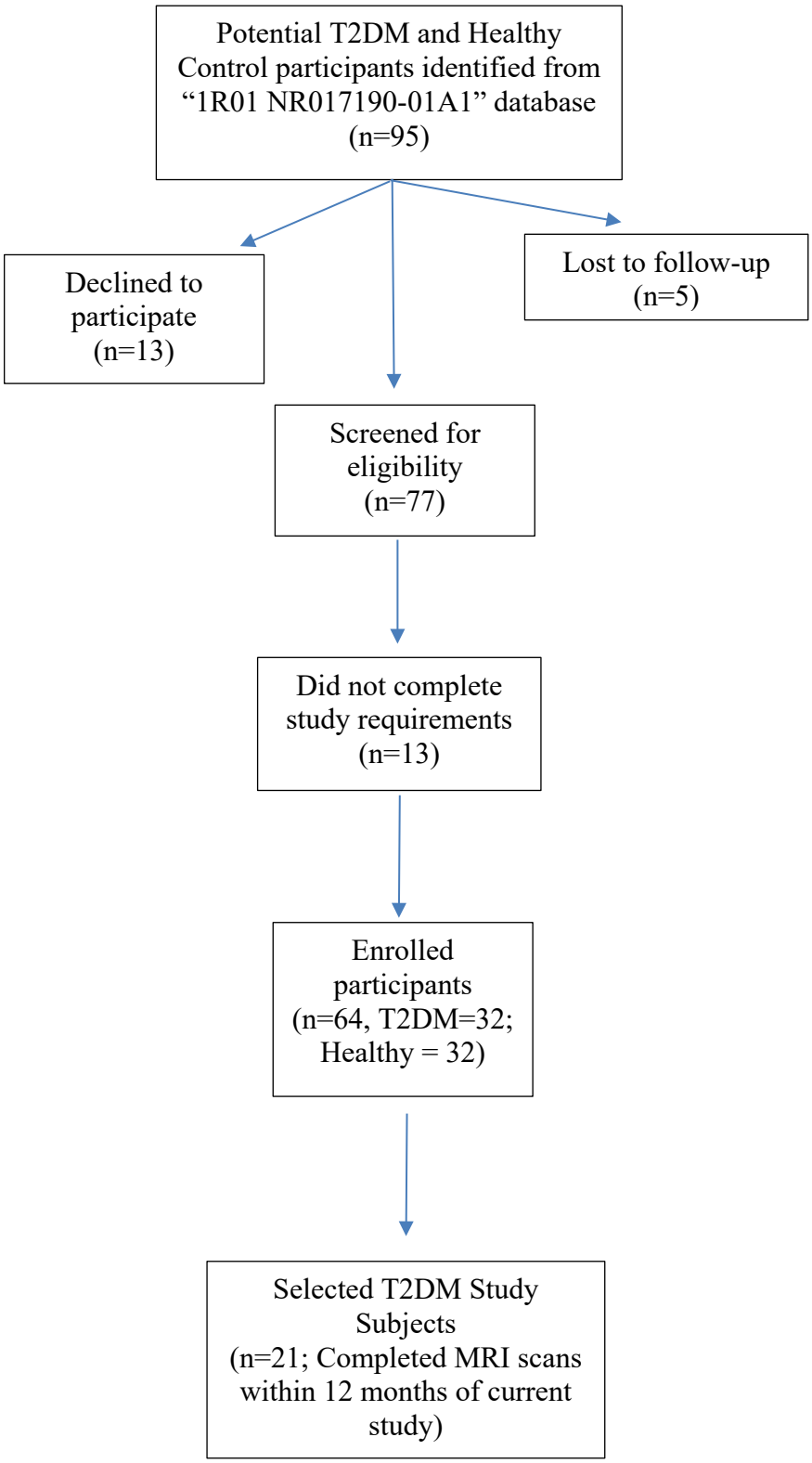
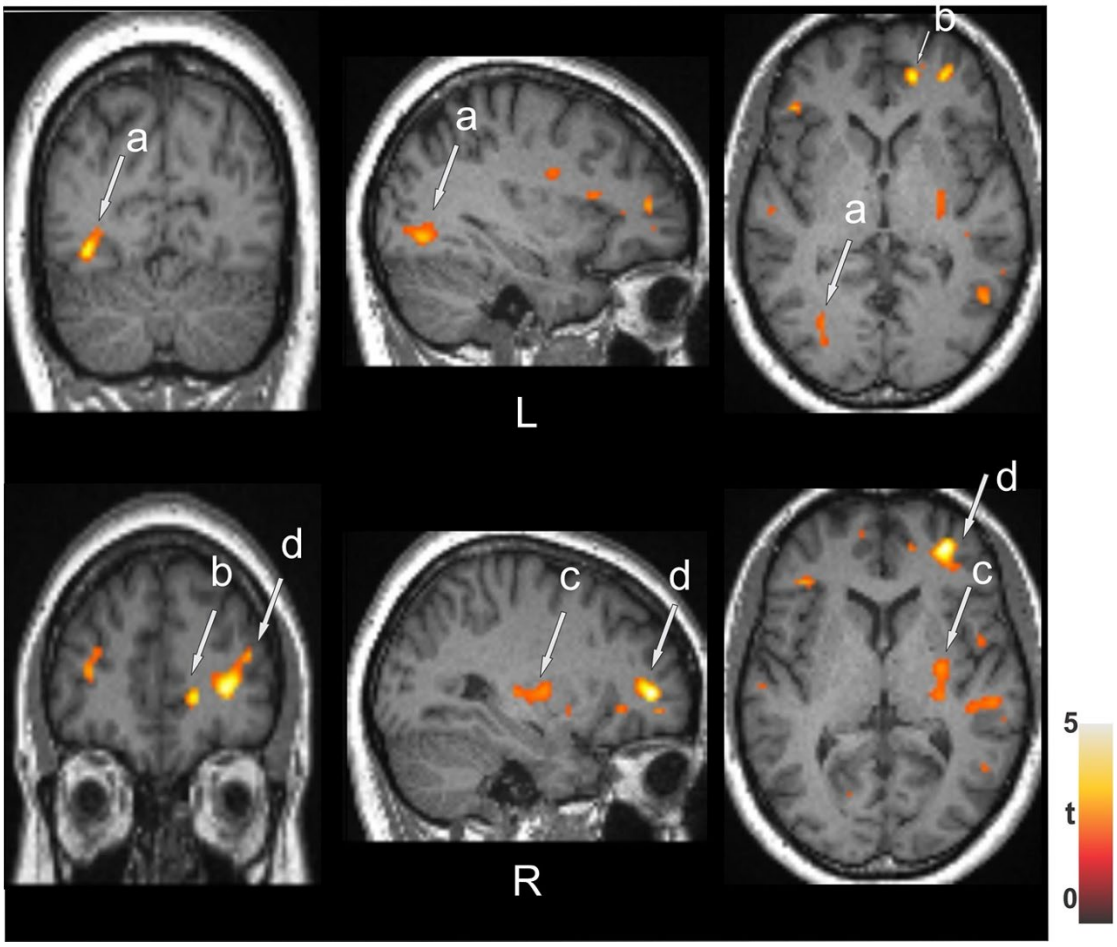
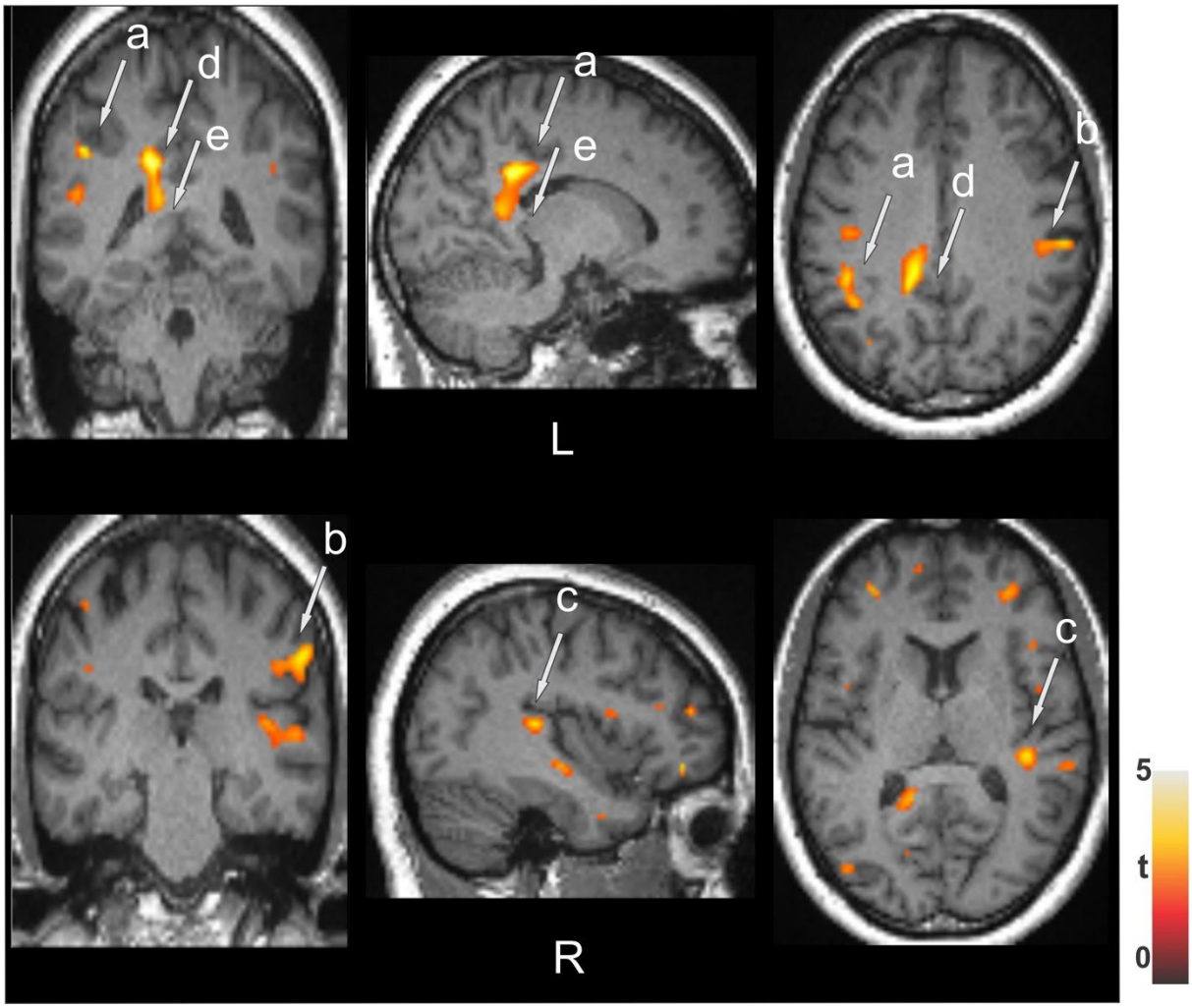


Figure 5.2 Brain Regions Showing Significant Correlations Between Mean Diffusivity with YFAS 2.0 Total Scores in Patients with T2DM



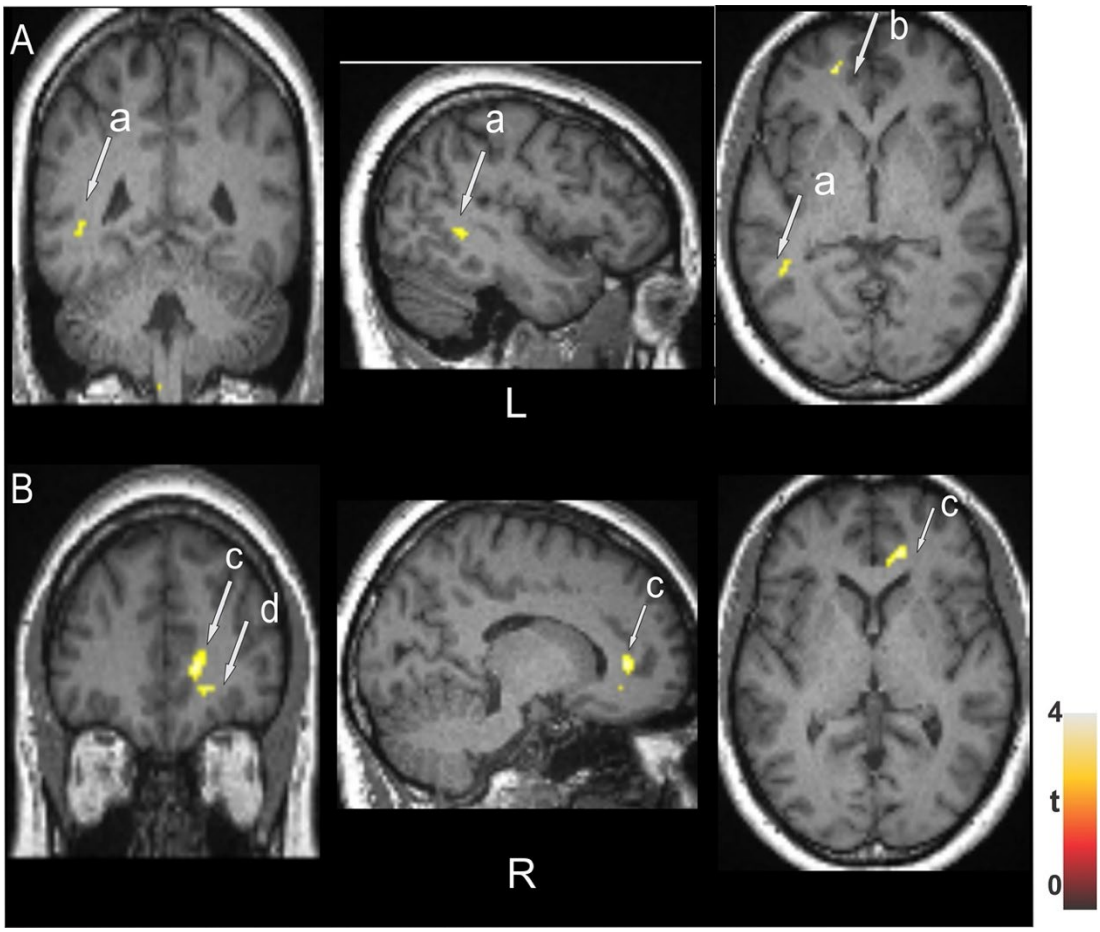
Significant positive relationships between YFAS 2.0 total scores and MD values in the following brain regions of T2DM patients: occipital inferior -Left (a), frontal superior medial -right (b), putamen -right (c), frontal mid -Right (d). All images are in neurological convention (L = Left; R = right). Color bar indicates t-statistic values.

Figure 5.3 Brain Regions Showing Significant Correlations Between Mean Diffusivity with YFAS 2.0 Total Scores in Patients with T2DM Continued...



Significant positive relationships between YFAS 2.0 total scores and MD values in following brain regions of T2DM patients: supramarginal -left (a), supramarginal -right (b), temporal superior -right (c), cingulum posterior -left (d), and precuneus -left (e). All images are in neurological convention (L = Left; R = right). Color bar indicates t-statistic values.

Figure 5.4 Brain Regions Showing Significant Correlations Between Mean Diffusivity with BIS-11 Scores in Patients with T2DM



Significant positive relationships between BIS-11 Attention subscale scores and MD values in following brain regions of T2DM patients from SPM12 MRI analyses: temporal mid -left (a), and frontal superior -left (b). Significant positive relationships between BIS-11 Non-planning subscale scores and MD values in following brain regions of T2DM patients from SPM12 MRI analyses: cingulum anterior -right (a), and frontal -right (b). All images are in neurological convention (L = Left; R = right). Color bar indicates t-statistic values.

Table 5.1 Demographic and Clinical Characteristics of Type 2 Diabetes Mellitus (T2DM) (N=21)

	T2DM
Gender (men/women)	N=21(10/11)
Age (years)	57.433±8.320
A1c	6.314±0.938
A1c Status	
Controlled (<7%)	15(71.4%)
Uncontrolled (≥ 7%)	6(28.6%)
Duration of Diabetes History	10.26±7.088
Diagnosed with FA	2(9.5%)
YFAS Total Score	1.90±3.129
BIS Total Score	63.86±5.893
BIS-Attention	12.95±2.376
BIS-Motor	18.86±2.886
BIS-Non-Planning	21.24±5.309
Racial Background	
White	n=5(23.8%)
Asian	n=4(19%)
Hispanic	n=6(28.6%)
Other	n=6(26.8%)

BMI, body mass index; YFAS, Yale Food Addiction Scale; BIS, Barratt Impulsivity Scale

Table 5.2 Association between Regional Brain Mean Diffusivity (MD) values with YFAS 2.0 Scores While Corrected for Age and Gender (N=21) -Partial Correlations

Brain Regions	**MD** $\times 10^{-3}\ mm^2/s$ **(Mean±SD)**	**YFAS 2.0 (0-11) (Mean±SD)**	**Correlation Coefficient r**	***P*-value**	**Effect Size**
Occipital -Left	0.811±0.046	1.905±3.129	0.693	0.001*	0.832
Frontal Superior Medial -Right	0.806±0.042	1.905±3.129	0.722	<0.001*	0.849
Frontal Mid -Right	0.836±0.041	1.905±3.129	0.821	<0.001*	0.901
Putamen -Right	0.717±0.034	1.905±3.129	0.658	0.002*	0.811
Supramarginal -Left	0.855±0.056	1.905±3.129	0.764	<0.001*	0.874
Supramarginal -Right	0.971±0.099	1.905±3.129	0.7	0.001*	0.837
Temporal Superior -Right	0.882±0.068	1.905±3.129	0.665	0.002*	0.815
Cingulum Posterior -Left	0.903±0.064	1.905±3.129	0.7	0.001*	0.837
Precuneus -Left	0.888±0.061	1.905±3.129	0.711	0.001*	0.843

MD, Mean Diffusivity; YFAS, Yale Food Addiction Scale
*$P < 0.05$

Table 5.3 Association between Regional Brain Mean Diffusivity (MD) values with BIS-11 Scores While Corrected for Age and Gender (N=21) -Partial Correlations

Brain Regions	**MD** $\times 10^{-3}$ mm^2/s **(Mean±SD)**	**BIS-11 (Mean±SD)**	**Correlation Coefficient r**	***P*-value**	**Effect Size**
Temporal Mid	0.786±0.031	12.95±2.376[a]	0.15	0.539	0.387
Frontal Superior -Left	0.758±0.035	12.95±2.376[a]	0.216	0.374	0.464
Frontal Right	0.763±0.033	21.24±5.309[b]	0.273	0.258	0.522
Cingulum Anterior	0.804±0.038	21.24±5.309[b]	0.230	0.343	0.480

MD, Mean Diffusivity; BIS, Barratt Impulsivity Scale

[a]BIS-11 Attention subscale scores used.

[b]BIS-11 Non-planning subscale scores used.

*$P < 0.05$

CHAPTER SIX: THIRD MANUSCRIPT

Can Food Addiction or Brain Injury Predict Glycemic Control Status (A1c) in Type 2 Diabetes Mellitus?

Chapter Six: Can Food Addiction or Brain Injury Predict Glycemic Control Status (A1c) in Type 2 Diabetes Mellitus?

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Funding Support:

Ms. Smeltzer received financial support from the Jonas Nurse Scholar Program 2018-2020 and the UCLA School of Nursing Dean Sarna Doctoral Fellowship Award. All co-authors have no conflicts of interest to disclose related to this manuscript.

Abstract

Background: Our recent research has shown that of the eleven food addiction (FA) symptomatologies, only two (food tolerance and eating during physically hazardous situations) are significantly associated with higher A1c levels (indication of poorer glycemic control) in T2DM adults. In addition, studies indicate associations between brain injury and A1c levels and FA in T2DM patients. However, it is unclear if FA and brain injury can independently predict glycemic control in T2DM. **Purpose:** To evaluate the relationships of FA and brain injury to glycemic control (A1c) in T2DM adults. **Methods:** 32 T2DM participants completed the Yale Food Addiction Scale 2.0 (YFAS) questionnaire and brain magnetic resonance imaging (MRI). Bivariate statistical analyses and stepwise logistic regression were conducted (dependent variable: A1c glycemic status; covariates: two FA symptomatologies and two major brain regions linked to A1c status in T2DM (frontal cortices and cingulate). **Results:** Among T2DM participants, 12.5% were positive for FA symptom #6 (food tolerance) and 43.8% were positive for FA symptom #10 (food use during physically hazardous situations). These FA symptomatologies were not predictive for A1c glycemic groups. Brain damage in the following regions were linked with A1c: areas mediating cognition/executive decision-making (frontal middle-right, frontal medial orbital -right) and emotion (cingulate). Only tissue changes in the right frontal medial orbital brain region were an independent predictor of glycemic status, and not the two FA symptomatologies or the other brain regions. **Conclusions:** Brain injury at the right frontal medial orbital region (associated with executive thinking) independently predicts glycemic status. Thus, potential interventions which may promote neurogenesis and/or protect this brain area may help T2DM patients improve their dietary self-management, glycemic control, and health status.

Introduction

Type 2 Diabetes Mellitus (T2DM) is a metabolic condition that is characterized by elevated blood glucose concentrations due to insulin resistance in peripheral tissues and/or inadequate insulin secretion in the pancreas (Oh et al., 2018). Glycemic control (as assessed by glycosylated hemoglobin [A1c]) is a priority for T2DM treatment because it is linked to poor health outcomes. For example, patients diagnosed with T2DM (A1c $\geq$ 6.5%) compared to those with A1c less than 6.5%, are associated with significant health complications (four times more likely to have moderate retinopathy (AOR: 4.0; $P < 0.001$) and a higher prevalence of nephropathy (17.1%).(Butler et al., 2020). Prolonged hyperglycemia has been linked to multiple organ failure, micro- and macro- vascular complications, and other metabolic syndromes, such as obesity, which is now commonly referred as 'diabesity' (Pinchevsky et al., 2020).

Though there are heterogenous factors leading to impaired glucose tolerance, such as irreversible risk factors of age, genetics, race, and ethnicity, there are also reversible factors, such as other comorbid diseases, diet, physical activity, medications, surgery, infections, and smoking (Cho et al., 2018; Shaw et al., 2010; Whiting et al., 2011). Other considerations impacting glycemic control, that account for hedonistic eating in the presence of highly palatable foods, is a concept commonly related to substance-related use and addiction disorders (SRAD) known as food addiction (FA). FA may occur if there is elevated activation in the brain reward circuitry in response to food cues, and reduced activation of inhibitory brain regions in response to food intake (indicating brain dysfunction/injury) to the point that there is an inability to change (stop overeating) when there are negative consequences (Blumenthal & Gold, 2010; Gearhardt et al., 2009b; Volkow & Baler, 2015).

The underlying etiology for poor dietary behaviors in uncontrolled T2DM is unclear, but

could be a result of FA, brain tissue injury, or a combination of both. Moreover, it is known that non-T2DM people with addiction or impulsiveness, such as those who are alcohol/cocaine dependent or obese, show regional brain activity linking maladaptive food and drug consumption behaviors (Blumenthal & Gold, 2010; Fletcher & Kenny, 2018; Gearhardt, Davis, et al., 2011; Small et al., 2001; van Bloemendaal et al., 2014). However, the predictive association of FA and brain tissue injury on glycemic control have not been reported in persons with T2DM (Ersche et al., 2011; Wang et al., 2016).

Food Addiction

Interrelationships between an individual's T2DM glycemic control status with his or her vulnerability for foods that are highly palatable, can lead to increased reward sensitivity, greater impulsivity, diminished inhibitory control, less cognitive flexibility, and eventually higher compulsiveness/bingeing, more tolerance/withdrawal, and more craving/preoccupation behaviors which are characteristics of maladaptive food and drug consumption (Adams et al., 2019; Bandura, 1977; Schulte et al., 2017). FA has been studied among obese and disordered eating populations (Clark & Saules, 2013; Eichen et al., 2013; Meule et al., 2017; K. M. Pursey et al., 2014; Volkow & O'Brien, 2007), and most recently there are reports of some studies among T2DM populations (Hadj-Abo et al., 2020; Nicolau et al., 2020; Raymond & Lovell, 2015; Yang et al., 2017). The two prior studies on FA and T2DM focused on the relationships between psychological or metabolic factors such as depression and body mass index (BMI) to FA (Raymond & Lovell, 2015; Yang et al., 2017). Nicolau et al. (2020) examined FA with A1c levels and determined individuals diagnosed with FA had significantly higher A1c levels versus non-FA individuals. However, the above-mentioned studies focused on descriptive and correlational analyses of FA and T2DM and lacked investigation of the etiology of FA and

T2DM status through neuroimaging.

Relationship Between FA and A1c

Findings from a prior dissertation research study (manuscript one) has shown that two FA symptomatologies (#6 food tolerance and #10 food use in physically hazardous situations), as measured by the Yale Food Addiction Scale 2.0 (YFAS), are associated with higher A1c levels (r= 0.254, r= 0.417 respectively, P <0.05). In addition, through brain magnetic resonance imaging and diffusion tensor imaging (DTI) analyses of the T2DM subjects in another dissertation study (manuscript two), we found that there is a neural basis to FA as revealed through positive associations between YFAS scores to damaged brain regions regulating executive decision-making (cortices, precuneus, temporal); memory -visual or auditory (occipital, supramarginal); motor function (putamen); and emotion (cingulum) functions in our sample of T2DM patients. These recent FA studies provide additional evidence that FA is related to A1c levels and brain integrity and highlight the need to study the type of relationship between these two FA symptomatologies and glycemic status in T2DM.

Brain Status and Relationship to A1c in T2DM

Magnetic resonance imaging (MRI) techniques such as DTI, have been used to detect significant acute and chronic microstructural (white matter damage to connectivity, where axon signaling occurs) and structural tissue injury (gray matter damage in areas receiving, processing, and releasing information) in brain regions of persons with T2DM. It has been demonstrated that chronic hyperglycemia is an important factor in functional and structural brain injury (Biessels et al., 2002; Kodl & Seaquist, 2008; Strachan, 2011). Roy and colleagues (2020) found that there are structural injury/decreased gray matter volumes in several brain regions in persons with T2DM that control cognition (such as the prefrontal cortex, hippocampus, and cerebellum),

anxiety (hippocampus, amygdala, insula, and cingulate), and depression (hippocampus, para-hippocampus, cingulate, insula, and thalamus) ($P < 0.01$). Furthermore, Roy et al. (2023) recently published findings on the acute and chronic microstructural damage in areas mediating cognition and mood (cerebellum, insula, frontal and prefrontal cortices, cingulate, and lingual gyrus) among T2DM patients. Their findings suggest that T2DM may account for the impaired microstructures (through white matter damage to connectivity mechanisms) underlying the large-scale brain cognitive and mood regulatory networks, as reflected by the significantly associated poor cognition and mood scores resulting from the neuropsychological assessments (Roy et al., 2023). Investigators have identified that frontal cortices (executive decision-making) and cingulate (emotion) brain areas are significantly linked to A1c status (Cabrera-Mino et al., 2021; Choi, Roy, Freeby, Mullur, et al., 2020; Roy et al., 2023; Roy et al., 2020). However, it is unclear whether such brain injury, which occurs in brain regions that can adversely impact behaviors which can contribute to poor dietary habits, are linked to A1c outcomes.

Specific Aims

There are no published reports which explore the predictive abilities of FA and brain tissue injury for T2DM glycemic control (A1c) status. Therefore, the primary specific aim for this study was to determine whether FA and/or brain injury could be independent predictor(s) for A1c status. Such information could provide insights into chronic hyperglycemia etiologies in T2DM and identify potential innovative interventions to improve T2DM outcomes.

Methods

Study Design

The study used cross-sectional and correlational research designs to examine T2DM

adults (the sample included T2DM adults with controlled glycemic status < 7% A1c and uncontrolled glycemic status ≥ 7% A1c). Thirty-two subjects (21 T2DM with controlled glycemic status, 11 T2DM with uncontrolled glycemic status) participated in the study between January to October 2022.

Sample and Setting

The T2DM sample was recruited from the pool of subjects who had completed MRI data collection for an on-going R01 study within 12 months of contact with the PI (to minimize the possibility of any neural changes that may occur with time, medication, or T2DM self-care changes). The R01 study was conducted by Choi and Kumar: "Relationships Between Brain Tissue Integrity and Self-Care Abilities in Adults with Type 2 Diabetes" (1R01 NR017190-01A1). The racially and ethnically diverse subjects from the R01 study were recruited from University of California at Los Angeles (UCLA) Gonda Diabetes Center, UCLA campus, and the surrounding communities. The T2DM inclusion criteria for this study and the R01 investigation were between 40-65 years of age, either gender, outpatient status, on stable T2DM medication therapy (no changes in medications or dosages in previous 6 weeks), able to lay flat, and understood/read English. Exclusion criteria included: claustrophobia, metallic-based tattoos, metallic implants or devices (such as implantable cardioverter-defibrillator, pacemaker, embolic coils, aneurysm clips), or any other material which could be hazardous in the MRI scanner environment, body weight > 300 pounds (weight and size restrictions of MRI scanner device), pregnancy (if subject is female), history of stroke, seizure disorder, head trauma, diagnosed with psychiatric disease (clinical depression, schizophrenia, manic-depressive), and airway or chest deformities that would interfere with breathing, mechanical ventilatory support, and renal failure (requiring dialysis). Also, subjects had to be without any neurological or cardiovascular

conditions that would induce brain injury, diagnosed with dementia, or sleep disordered breathing, chronic obstructive pulmonary disease, cystic fibrosis, presence of brain mass lesions, or a current or past diagnosis of substance abuse or drug dependency (e.g., tobacco, cannabis, or cocaine use) that would modify brain tissue.

Measures

Demographic and Clinical Data

Demographic data such as race/ethnicity, age, gender, education, and annual gross income were obtained from the completed online questionnaires on Qualtrics (Qualtrics, Provo, UT, 2022). A1c data was obtained on the day of the MRI scans which were from the R01 study record and within 12 months of YFAS questionnaires (Choi, Roy, Freeby, Mullur, et al., 2020).

Questionnaires

Yale Food Addiction Scale 2.0

Of the 11 SRAD-related symptomatologies that YFAS measures, only two were used in this study per previous findings of significant associations with A1c levels: symptom #6 (food tolerance) and symptom #10 (food use during hazardous situations). There are 35 questions in the YFAS self-report questionnaire and for an individual to be considered positive for any of the 11 symptomatologies, scores for each symptom are 0 or 1, where 1 indicates yes. Symptom criterion #6 (food tolerance) comprised of two questions from YFAS, numbers 24 and 26 (e.g., "eating the same amount of food did not give me as much enjoyment as it used to"). Symptom criterion #10 (food use during hazardous situations) comprised of questions 28, 33, and 34 (e.g., "I was so distracted by thinking of eating/eating that I could have been hurt like when driving a car, crossing street, or operating machinery").

Magnetic Resonance Imaging (MRI)

Brain MRI studies were performed on a 3.0-Tesla MRI scanner (Siemens, Magnetom, Prisma Fit) in the UCLA Department of Radiology, and high-resolution T1-, Proton Density-, and T2-weighted images were obtained for assessment of any visible gross brain pathologies such as infarcts, tumors, cysts, mass lesions. There were no cases of severe or unexpected neurological injury, visible gross brain pathology, or head-motion/imaging artifacts detected in our sample.

High-resolution T1-weighted imaging. High-resolution T1-weighted images were collected using the magnetization prepared rapid acquisition gradient echo pulse sequence (MPRAGE) [repetition time (TR) = 2200 ms, echo time (TE) = 2.34 ms, inversion time=900 ms, flip angle (FA) = 9º], with 320x320 matrix size, 230x230 mm field of view (FOV), 0.9 mm slice thickness, and 192 sagittal slices. The scanning time was ~ 7 min. These images were assessed for gross brain pathology.

Diffusion tensor imaging (DTI). DTI were performed using an echo-planar-imaging with twice-refocused spin-echo pulse sequence (TR = 12000 ms; TE = 87 ms; FA = 90°; bandwidth = 1346 Hz/pixel; matrix size = 128×128; FOV = 230×230 mm^2; slice thickness = 1.7 mm; 92 slices; no interslice-gap; diffusion directions = 30; b = 0, 800 s/mm^2) in the axial plane, and two separate scans were collected. Scanning time was approximately ~14 min. These images were used to identify and to assess brain damage in specific brain regions.

Proton-density (PD) and T2-weighted imaging. PD and T2-weighted images were collected (TR = 10,000 ms, TE1,2 = 17, 134 ms, FA = 130°) using a dual-echo turbo spin-echo pulse sequence in the axial plane, with 256x256 matrix size, 230x230 mm FOV, 3.0 mm slice thickness, and 56 slices. Scanning time was ~ 5 min.

Data Collection Procedures

This study was approved by the UCLA Institutional Review Board (IRB# 20-001188). The R01 research coordinator under the direction of Dr. Choi screened and identified subjects for the parent R01 study and had subjects indicate whether they would allow contact for future research opportunities. The research coordinator utilized an IRB-approved script and advertisements to contact subjects electronically over email and by phone for potential participation in this study (on relationships of FA to brain status). Interested subjects responded back by email, the research coordinator forwarded subjects' contact information to the PI of the present study (Smeltzer), explanation of the study was conducted by Smeltzer over email and phone if necessary. The PI emailed the IRB-approved information sheet for their review and record-keeping and the web address where participants electronically consented to participate in the study and completed online questionnaires (YFAS) via Qualtrics (Qualtrics, Provo, UT, 2022), a HIPAA and FERPA-compliant online survey platform. The information sheet recorded lab values (such as A1c), MRI scans, and diabetes history collected in the parent R01 study. Participants received electronic gift card compensation ($25) for participation. Time to complete all study questionnaires ranged from 10 to 30 minutes.

Data Analyses

Clinical, demographic, and biophysical data were entered and analyzed using Statistical Software for Social Sciences (SPSS v.28, Somers, NY). Descriptive (frequencies, percentages, means, and standard deviations) and independent sample *t*-tests were used for continuous demographic and clinical variables with normal distribution. Chi-square analysis (or Fisher's exact test for cells with an expected count less than 5) were used for categorical variables. Brain

region continuous data were normally distributed per Shapiro-Wilk's test of normality. Logistic regression (forward stepwise option) analyses were used to identify if the following covariates: two YFAS symptomatologies and three brain areas (two frontal subregions and cingulate), were independent predictors of A1c status (dependent variable) in T2DM subjects.

MRI Diffusion Tensor Imaging Data Analyses to Measure Brain Injury

Brain imaging analyses required several software for evaluation of images, data processing, and analyses: statistical parametric mapping package SPM 12 (http://www.fil.ion.ucl.ac.uk/spm/), DTI-Toolkit (v0.6.4.1) (Wang et al., 2017), MRIcroN (Rorden et al., 2007), and MATLAB (http://www.mathworks.com/). These MRI imaging analyses were completed by the Kumar Neuroimaging Research Lab at UCLA. No subjects included in this study showed any major visible brain pathology, head-motion, or other imaging artifacts.

To calculate mean diffusivity (MD) values, the average background noise level from outside the brain parenchyma was calculated using non-diffusion and diffusion-weighted images, and this noise threshold was used in all T2DM subjects to suppress non-brain regions (only those regions outside the brain parenchyma) during MD calculations. The diffusion ($b = 800$ s/mm^2)-weighted images, collected from 30 diffusion directions, and non-diffusion ($b = 0$ s/mm^2) images was used to calculate diffusion tensor matrices (Le Bihan et al., 1991) from each series using the DTI-Studio software (Jiang et al., 2006). The diffusion tensor matrices were diagonalized, and principal eigenvalues ($\lambda1$, $\lambda2$, and $\lambda3$) was calculated at each voxel (Basser & Pierpaoli, 1998; Pierpaoli et al., 1996). Mean diffusivity [$MD = \lambda1+\lambda2+\lambda3)/3$] values were determined at each voxel using principal eigenvalues (Alexander et al., 2007; Le Bihan et al., 2001; Pierpaoli et al., 1996), and whole brain MD maps were generated with voxel intensities on the MD representing

the corresponding MD values.

Next steps were to realign, average, normalize and smooth MD maps. First, we realigned and averaged the four MD maps and b0 images, derived from each DTI series, to remove any potential differences in alignment due to head-motion, and to create one MD map per subject. The averaged MD maps were normalized to a Montreal Neurological Institute (MNI) common space (Ashburner & Friston, 2005) based on *a priori*-defined distributions of gray, white, and cerebrospinal fluid types, as described for other DTI-based measures (Choi et al., 2019; Kumar, Chavez, et al., 2012; Kumar et al., 2011; Kumar et al., 2006; Kumar et al., 2010). The resulting normalization parameters were applied to corresponding MD maps and non-diffusion weighted images. The normalized MD maps were smoothed using an isotropic Gaussian filter (10 mm kernel), and smoothed MD maps were used for further analyses. High-resolution T1-weighted images of T2DM subjects were also normalized to MNI space. T1-weighted images were partitioned into gray, white, and cerebrospinal fluid tissue types, based on unified segmentation approach (Ashburner & Friston, 2005) , and normalization parameters were applied to corresponding T1-weighted images. The normalized b0 images from all T2DM subjects were averaged to create whole-brain mean background images, which was used for structural identification.

Brain areas significantly linked to A1c status (frontal cortices and cingulate) were specifically measured. Region-of-interest (ROI) analyses was used to determine average MD values in those areas based on whole-brain voxel-by-voxel comparisons. Region-of-interest masks were outlined for various brain areas using clusters determined by voxel-by-voxel analysis procedures. The ROI masks were also used to calculate average MD values of those specific brain sites from T2DM subjects with normalized and smoothed MD maps.

Results

From the parent R01 sample, 32 T2DM subjects (21 controlled T2DM; 11 uncontrolled T2DM) were eligible for this study (Smeltzer: FA and brain region relationships to A1c).

Sample Characteristics

Demographic characteristics of T2DM patients with controlled and uncontrolled glycemic status are summarized in Table 6.1. There were no statistically significant differences in age, gender, BMI, duration of diabetes history, racial background, income, and educational status between the groups. A1c measurements were significantly different between the two glycemic control groups where uncontrolled T2DM patients had higher A1c values at 8.218±1.359 versus 5.952±0.523 for T2DM patients with controlled glycemic status (P <0.001). Twenty-one patients had controlled T2DM status (< 7% A1c) versus 11 has uncontrolled T2DM status (≥ 7% A1c).

FA

The FA results for symptomatologies #6: food tolerance, and #10: food use during hazardous situations, are summarized in Table 6.2. Among T2DM patients (N=32), 12.5% were positive for symptom #6: food tolerance, and 43.8% were positive for symptom #10: food use during hazardous situations. When comparing uncontrolled T2DM (n=11) to controlled T2DM (n=21), one (9.1%) of uncontrolled T2DM and three (14.3%) of the controlled T2DM were positive for symptom #6 and ten (42.9%) of the uncontrolled T2DM and five (45.5%) of controlled T2DM were positive for symptom #10. There were no A1c group differences in the proportion of symptomatologies.

Brain Region Injury

The results from the MD calculations from the DTI analyses (where increased MD indicates higher brain injury) were calculated for four brain areas (results summarized in Table 6.3). As one of these brain areas (Left [L] frontal superior region) was not statistically significant, it was not used for additional calculations nor included in the logistic regression model. Voxel-by-voxel MD changes in three brain areas which were statistically different between A1c status groups can be seen in Figure 6.1. The three brain areas that were used as covariates in a logistic regression analyses model were: areas mediating cognition/executive decision-making (right [R] middle frontal and right medial orbital frontal cortices [OFC]) and emotion (cingulate),

FA and Brain Regions as Predictors of A1c status

Utilizing forward stepwise logistic regression, the following covariates were entered into the model to predict A1c status (dependent variable): YFAS #6 (food tolerance) and #10 (food use during hazardous situations) symptom criterion scores (categorical) and the MD values of the three brain regions (R middle frontal, R medial OFC, and cingulate) linked in the literature and our own analyses to A1c. In the final logistic regression model, only the R medial OFC was an independent predictor of A1c status (P= 0.017). The MD values/brain injury of the cingulate and R middle frontal cortex were not significant predictors of A1c status (Table 6.4).

Discussion

T2DM patients in this study with damage in the R medial OFC region of the brain are more likely to have uncontrolled glycemic status compared to having damage in other brain regions and/or having YFAS symptomatologies of food tolerance and food use during hazardous

situations. Frontal cortices are known to control executive function (cognitive processes to be able to make decisions or to carry out actions) and past T2DM studies have linked structural damage to these regions with depression, poor cognition, anxiety, poor sleep quality and poor T2DM self-care management (Cabrera-Mino et al., 2021; Choi, Roy, Freeby, Mullur, et al., 2020; Roy et al., 2023; Roy et al., 2020). While only the R frontal cortices were significant in this study, there are important functional differences in the hemispheres and subregions of the frontal cortices.

The L frontal cortices regulate routine, working memory-dependent processing whereas the R frontal cortices regulate task orientation and novel cognitive strategization (Goldberg et al., 1994). In our sample, there was a significant predictive relationship between the R medial OFC and A1c/glycemic status. It has been documented that the OFC not only regulates impulse control (which influences self-regulation of eating behaviors) and future thinking (influencing nutrition related goal planning behaviors), but researchers have found that injury to the OFC is associated with poor executive function, cognition and depression in T2DM patients (Cohen et al., 2011; Kumar et al., 2008; Roy et al., 2023; Roy et al., 2020; Watari et al., 2008). The findings of this study provide further evidence that the R frontal brain regions are key to unlocking further understanding of FA and T2DM glycemic status, especially since the previous dissertation study (manuscript two) revealed positive associations between the tissue damage in the frontal cortices and increasing YFAS scores among T2DM patients. Along with the fact that the regression analysis indicates that the two FA symptomatologies are intricately linked to, and are reflective of, OFC status. Specific brain injury to the OFC further elucidates the link between brain integrity to A1c outcomes, as previous studies have also shown the impact of glycemic status on brain integrity where A1c levels affect brain volume where for T2DM patients with

well-controlled A1c levels (< 6%), the overall brain volume was significantly greater than those with poorly controlled A1c levels of 7-7.9% (Erus et al., 2015).

The OFC sends information about reward and non-reward outcomes to the anterior cingulate cortex and the cingulate connects rewards to actions, thereby affecting emotions of reward or stress (Rolls, 2019). Which may explain why the cingulate brain area was not an independent predictor of A1c status. As the reward-punishment processing and memory are impaired via cingulate damage, changes in the cingulate and OFC can lead to impaired food experiences, thereby influencing T2DM self-management and A1c outcomes (Rolls, 2018). While cognition is a complex process, damage to the circuitry/connections between the cingulate and the OFC could explain why T2DM, and FA individuals might have issues managing decisions regarding food behaviors during stressful situations and T2DM self-management glucose checks/medication administration.

If there is impairment in brain structure which alters the signaling processes and T2DM patients have altered cognitive functioning, reward-punishment processing, and memory, these findings could be the neurological basis to the two most significant and common YFAS symptomatologies among T2DM patients: food tolerance and engaging in eating behaviors that can physically endanger themselves. Thus, the study findings suggest that poor cognition, decision-making and thereby FA behaviors such as food tolerance (marked increase in amount; marked decrease in effect) and hazardous food use are related to the tissue changes in the R medial OFC and these abnormal behaviors can be factors contributing to poor glycemic control status among T2DM subjects.

The significant finding in this study possibly challenges past FA studies in non-T2DM subjects involving functional brain imaging. Among humans, the nutritional state of fasting

versus being fed increased brain activation to pictures of high-calorie over low-calorie foods in the ventral striatum, amygdala, anterior insula, and medial and lateral orbitofrontal cortex (OFC) (Goldstone et al., 2009). Though hunger makes all food appealing, Goldstone et al. (2009) study further demonstrated the hedonic value of certain types of food through the brain reward system bias towards high-calorie versus low-calorie foods as there was a positive correlation with medial and lateral OFC activation during fasting. Knowing OFC regulates eating behaviors especially during fasting, it will be interesting to further investigate if T2DM patients who have greater tissue impairment in the OFC have poorly controlled glycemic status and still have cravings for high-calorie foods when they are NOT fasting. The altered brain structure could be the basis for the abnormal tissue activity and thereby an affinity towards high-calorie foods and poor glycemic outcomes as the cognitive functions that are regulated by the OFC are impaired. Either way, if there is already brain injury among T2DM patients, it causes one to reconsider if the type of food or addictive substances is truly the basis of influence on brain processing like upon the brains of those with SRAD as postulated in prior FA studies (Gearhardt et al., 2009b; Gearhardt, Davis, et al., 2011; Schulte et al., 2015).

Potential Treatments

Since the R medial OFC is a brain region of concern for A1c status in T2DM, cognitive behavior therapy (CBT) is a potential intervention that can improve the functions regulated by this impaired brain region through cognitive restructuring. Interventions such as CBT can modulate behaviors through education that motivates, leads, and enables participants to comply with health promotion and T2DM self-care behaviors. CBT has had a positive effect on T2DM self-management where participants have been able to achieve statistically significantly improved emotional adaptation, self-efficacy to overcome barriers, and A1c levels in multiple

studies (Ghoreishi et al., 2019; Pan et al., 2020; Safren et al., 2014). Treatment with CBT in T2DM have lowered/improved depression scores and increased medication adherence and self-monitoring of blood (Safren et al., 2014). In non-T2DM populations, several studies have reported CBT has helped improve gray matter volumes or activity in the prefrontal cortices and OFC (Jensen et al., 2012; Ritchey et al., 2011; Seminowicz et al., 2013). However, the impact of CBT on brain status in T2DM remains to be explored.

Another potential neuroprotective, preventative, and therapeutic treatment is resveratrol. This is a polyphenol product naturally occurring in grapes, berries, and medicinal plants (Zhang et al., 2020). Resveratrol has been successfully tested in animal models, in T2DM, and Alzheimer's samples to improve the brain's metabolic profile and cognitive function, to decrease insulin resistance, and to induce anti-inflammatory and antioxidant effects (Moussa et al., 2017; Silveira et al., 2019; Wong et al., 2016; Zhang et al., 2020). CBT, along with such nutritional supplementation that operate on the molecular level (e.g., resveratrol), are non-invasive, novel ways to protect against T2DM-related cognitive dysfunction due to the underlying damage to the brain regions that regulate cognition and executive function behaviors.

Limitations

A limitation in the findings could be due to the greater representation of controlled T2DM patients (~ 66%), which could be a limiting factor in not detecting differences in FA as a predictor between the glycemic control groups. It should be noted that the small sample size of patients could be a restrictive factor where type II error occurred and there could have been significant findings for FA or other brain areas as predictors of A1c status or A1c group differences in YFAS symptomatologies and brain damage in the left frontal cortices. However, the sample size of this study was adequately powered to be able to detect the significant brain

damage findings (0.759 to 1.108, Cohen's d) (see Table 6.2) and to identify an independent predictor of A1c status. Though A1c levels are important to T2DM brain integrity, this study did not consider how disease duration such as newly diagnosed versus chronic impacts FA and brain tissue integrity. In fact, an inclusion-criteria for the R01 study are that patients must be on stable T2DM medication therapy (no changes in medications or dosages in previous 6 weeks) and this limits recruitment of newly diagnosed/unstable T2DM populations due to high risks of acute changes in brain tissue. Hence, that is why there may not have been significant differences between controlled and uncontrolled T2DM patients in disease duration, because the duration in diabetes history was similar but not statistically significant, 10.26±7.297 versus 12.27±5.884 respectively (t=-0.788, P =0.437).

Another potential study limitation is the time gap (4-12 months) between the parent R01 investigation's A1c and MRI data capture and the current study's YFAS measures. However, the glycemic management was already stable at the time and the A1c trends were being monitored and were also consistent. In addition, the YFAS questionnaire was validated to assess an individual's eating behavior in the prior 12 months and the cross-sectional design makes it challenging to determine any causal relationships between FA and MD values at certain brain regions among T2DM patients.

Conclusion

The findings of this study show that within a sample of T2DM patients with significant tissue alterations in three brain areas associated with A1c status, only brain tissue injury of the R medial OFC/executive decision-making was an independent predictor of glycemic control status. Thus, strong urges to overeat may be explained by a breakdown of cognitive and behavioral control systems that are related to the structural and microstructural brain damage that have also

been linked to poor T2DM glycemic outcomes. The remaining question that is yet to be answered is: does treatment of a specific brain region (R medial OFC) improve dietary choices and thereby, glycemic outcomes in T2DM? Perhaps the overlap in brain areas found in this study and in the prior dissertation studies (frontal cortices), could be the link to understanding overeating in T2DM patients and may be key factors in improving glycemic outcomes. The causal pathway of FA and brain structural changes in T2DM have not been established, but this study provides insight into the potential underlying pathophysiological mechanisms and adverse effects of poor T2DM glycemic control on brain physiology. YFAS was not intended to discriminate and determine glycemic control but identify individuals with symptomatology likened to that of SRAD. With this in consideration, it may be important to consider therapies that can promote neurogenesis and/or protect brain areas, instead of methods which primarily or solely depend upon client T2DM self-management education or addiction counseling. Such neurobiological interventions may be of greater help for T2DM patients to improve their dietary self-management, glycemic control, and health status.

These at-risk patients may benefit from preventative and therapeutic interventions, such as CBT or nutritional treatments (e.g. resveratrol) that can reverse brain changes or improve poor cognition by providing neuroprotection for the R medial OFC (Ghoreishi et al., 2019; Pan et al., 2020; Safren et al., 2014; Seminowicz et al., 2013; Zhang et al., 2020). While the findings of this investigation contribute to the growing body of neuroimaging T2DM studies, this study can also help clinicians pinpoint the neurobiological characteristics of FA behaviors among T2DM patients. By incorporating considerations of these neurological factors into current interventions there may be opportunities to improve T2DM dietary self-management and glycemic outcomes.

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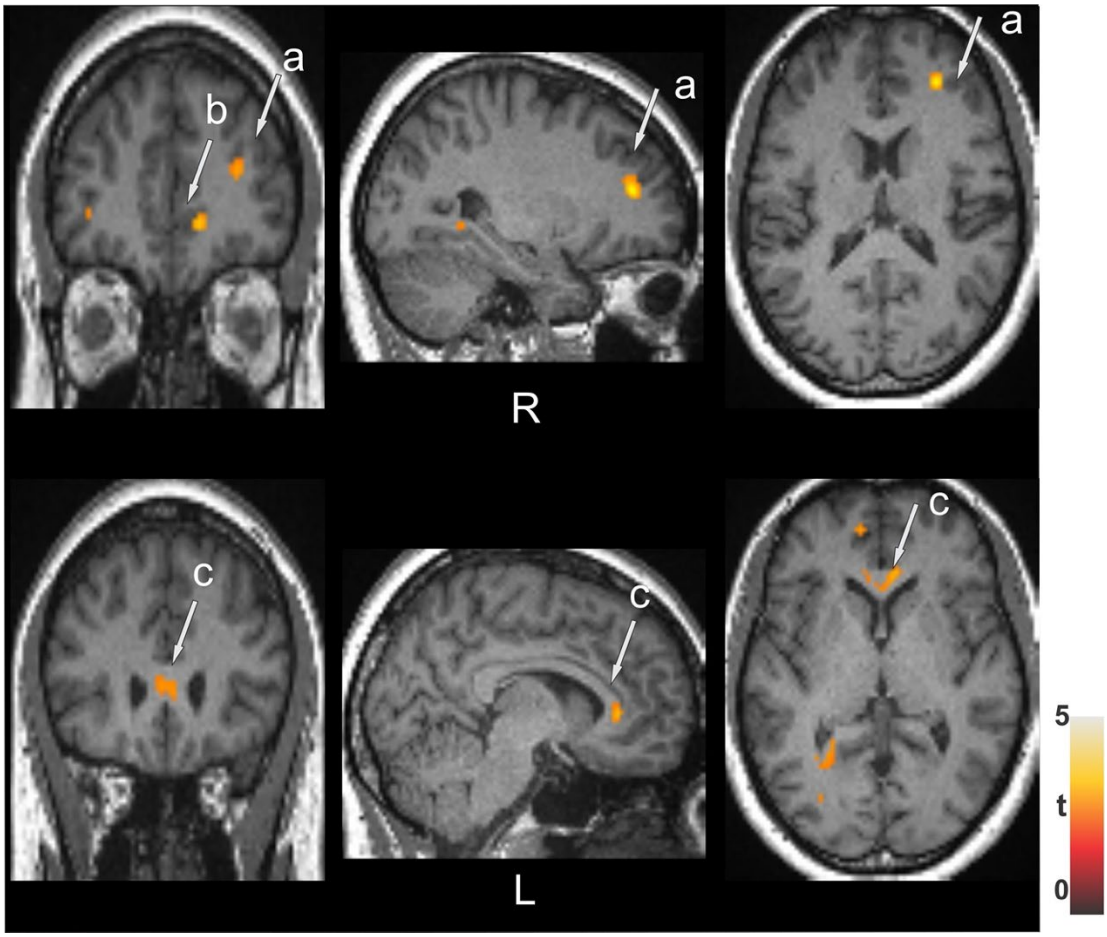
Figure 6.1 Brain sites in T2DM patients that show significant damage in relation to A1c Status



Brain regions with increased MD values in T2DM patients emerged in Frontal (a. Middle -Right, b. Medial Orbital -Right), and cingulate gyrus regions (c). All brain images are shown in neurological convention, with the left side of the brain on the left side of the axial and coronal images (*L=Left, R= Right*), and the color bar represents *t*-statistic.

Table 6.1 Differences in demographic and clinical characteristics between controlled Type 2 Diabetes Mellitus (T2DM) and uncontrolled T2DM (N=32)

	Controlled T2DM Mean±SD	**Uncontrolled T2DM Mean±SD**	***P*-value**
Gender (men/women)	N=21(9/12)	N=11(7/4)	0.458[a]
Age (years)	57.195±8.225	58.855±7.062	0.575
BMI (kg/m^2)	28.948±5.316	29.061±7.488	0.961
A1c	5.952±0.523	8.218±1.359	<0.001**[1]
Duration of Diabetes History	10.26±7.297	12.27±5.884	0.437
Racial Background			
White	n=4(19%)	n=4(36.4%)	
Asian	n=5(23.8%)	n=3(27.3%)	0.710[b]
Hispanic	n=7(33.3%)	n=2(18.2%)	
Other	n=5(23.8%)	n=2(18.2%)	
Socioeconomic Status			
< $100K annual gross income	n=7(33.3%)	n=6(54.5%)	0.246[a]
≥$100k	n=14(66.7%)	n=5(45.5%)	
Education			
<4-year college	n=4(19%)	n=4(36.4%)	0.397[b]
≥4-year college	n=17(81%)	n=7(63.6%)	

BMI, body mass index

[a]Calculated with Pearson Chi-Square; [b]Calculated with Fisher's Exact Test

***P* <0.001

[1]Cohen's d effect size: -2.536

Table 6.2 FA in T2DM (N=32)

YFAS 2.0 Symptom Criterion in Entire Sample	**T2DM (N=32) Yes/No (%)**		
6) Food Tolerance 10) Food Use During Hazardous Situations	Yes 4 (12.5%); No 28 (87.5%) Yes 14 (43.75%); No 18 (56.25%)		
YFAS 2.0 Symptom Criterion by A1c Status Groups	**Controlled T2DM (n=21) Yes (%)**	**Uncontrolled T2DM (n=11) Yes (%)**	***P*-value**
6) Food Tolerance 10) Food Use During Hazardous Situations	3 (14.3%) 9 (42.9%)	1 (9.1%) 5 (45.5%)	1[a] 0.888[b]

YFAS, Yale Food Addiction Scale
[a]Calculated with Fisher's Exact Test
[b]Calculated with Pearson's Chi-Square

Table 6.3 Differences in FA and brain damage between patients with controlled T2DM and uncontrolled T2DM (N=32)

Brain Regions (MD values- mm^2/s**)**	**Controlled T2DM Mean±SD**	**Uncontrolled T2DM Mean±SD**	**Statistic**	***P*-value**	**Effect Size**
Cingulate	$1.08\times10^{3}\pm0.11\times10^{-3}$	$0.908\times10^{3}\pm0.11\times10^{-3}$	t=2.324	0.027*	0.865
R Frontal Middle	$0.84\times10^{3}\pm0.05\times10^{-3}$	$0.81\times10^{3}\pm0.03\times10^{-3}$	t=2.040	0.05*	0.759
R Frontal Medial Orbital	$0.84\times10^{3}\pm0.04\times10^{-3}$	$0.80\times10^{3}\pm0.04\times10^{-3}$	t=2.976	0.006*	1.108
L Frontal Superior	$0.76\times10^{3}\pm0.04\times10^{-3}$	$0.761\times10^{3}\pm0.02\times10^{-3}$	t=-0.186	0.854	-0.09

MD, Mean Diffusivity; *L=Left, R= Right*,

*$P < 0.05$

Table 6.4 Logistic regression analysis of predictors of A1c Status (N=32)

Predictors	***Step 0 -Variables Not in Equation*** ***P-values***	***Step 1*** ***P-values***	***Exp(B)***
YFAS Symptom 6	0.673	0.738	-
YFAS Symptom 10	0.888	0.933	-
Cingulate	0.027*	0.745	-
R Frontal Middle	0.048*	0.699	-
R Frontal Medial Orbital	0.007*	0.017*	<0.001*

YFAS, Yale Food Addiction Scale
Logistic regression of model -Forward Stepwise (Likelihood ratio):
χ^2= 8.945 (1), *P*-value = 0.003*
Nagelkerke R^2=33.7%
Percentage correct = 68.8
*$P < 0.05$

CHAPTER SEVEN

Dissertation Summary

Chapter Seven: Dissertation Summary

Since FA is associated with brain changes and T2DM patients are prone to brain changes, this dissertation study sheds light on the additional impact that FA may have on brain tissue integrity and on glycemic outcomes T2DM patients. The overlap in brain areas found in two studies (manuscript two and manuscript three), frontal cortices, could be the link to understanding overeating in T2DM patients and may be key factors in improving glycemic outcomes. The causal pathway of FA and brain structural changes in T2DM have not been established, but this dissertation study provides insight into the potential underlying pathophysiological mechanisms and adverse effects of poor T2DM glycemic control on brain physiology.

In this dissertation study, the overarching aim was to explore relationships between FA, impulsivity, brain tissue injury, and glycemic outcomes. Manuscript one, showed positive associations between FA symptomatologies and glycemic outcomes (A1c), while impulsivity was not associated with A1c. A subset of questions pertaining to food tolerance and food use during physically hazardous situations from the YFAS 2.0 tool that are linked to A1c, may be useful in clinical practice to help assess patient's food behaviors. Future studies exploring the significance of these two FA symptomatologies could be beneficial, as in manuscript two, there were specific areas of brain tissue injury that were associated with FA symptomatologies from the YFAS 2.0 tool. While which brain injury sites that were specifically associated with food tolerance or food use during physically hazardous situations were not investigated, manuscript two revealed that increases in the number of FA symptomatologies that a patient endorsed were associated with brain tissue injury in sites regulating executive decision making, memory - auditory/visual, motor functioning, and emotions. Altogether, the current dissertation study and

past structural T2DM MRI findings expose the complications that can drive or result from the development and progression of T2DM-related structural changes to specific sites in the brain as they are associated with functional changes in cognition, mood, and FA. Manuscript three uncovered that among T2DM patients in this dissertation study, specific tissue damage in the R medial OFC predicts A1c status, and causality is yet to be determined. Since directionality of the relationship between structural or functional changes seen in specific brain areas has not been well-identified, this is a potential future area of study as it would be beneficial to develop large longitudinal studies to better understand the progression, impact, and risk factors that either delay or accelerate the development of T2DM-related brain damage.

If there is already brain injury among T2DM patients, it causes one to reconsider if the type of food or addictive substances are truly the basis of influence on brain processing and development as in the brains of those with substance-related use and addictive disorders (SRAD) as postulated in prior FA studies (Gearhardt et al., 2009; Gearhardt et al., 2011; Schulte et al., 2015). Possible reasons that FA and impulsivity were not predictors of A1c status stems from the development of the YFAS 2.0 and BIS-11tools, which were not intended to discriminate and determine glycemic control, especially since YFAS 2.0 was designed to identify individuals with SRAD symptomatologies. Items within the tools might not capture the nuances of impulsivity or FA behaviors most relevant to T2DM management and A1c levels.

Despite suggested similarities in behaviors between FA and substance abuse, there are other complex differences to consider between the characterization of FA and substance addiction. For example, Ziauddeen and Fletcher (2013) questions the dependability of utilizing the DSM-IV criteria for substance dependence as the framework for FA. Since substance addiction is a disorder fraught with vulnerable risk factors that impact its natural history and

course, there needs to be longitudinal studies that also explore the natural history of the FA syndrome. Since there are limitations to the prevailing phenotypic-based definition and measurement of FA, Ziauddeen and Fletcher (2013) recommends exploring FA from a neurobehavioral syndrome perspective where there are core measurable FA behaviors such as the inability to control consumption and increased motivation to consume and persistently consume despite negative consequences (Deroche-Gamonet et al., 2004; Everitt et al., 2008). Therein lies additional concerns: whether YFAS 2.0/BIS-11 tools have discriminant qualities of assessing FA/impulsivity traits versus the state of the patient, in which the situation, environment, or state of the patient at the time of completing the questionnaires could be varied, manipulated, and influenced due to other confounding factors not accounted for in the dissertation study.

The skeptics of the current FA model identified impulsivity and compulsivity as important endophenotypes and key vulnerability factors in the development of an addiction model, where they can be prospectively or retrospectively correlated with the duration of FA (Ziauddeen and Fletcher (2013). Despite the biological similarities between food and drug consumption, the food intake process differs in that it increases glucose in the brain as the pleasurable activity activates the brain through fast sensory signals and through slow ingestion processes (Gearhardt et al., 2009b). Unlike food, drugs have direct pharmacological effect when activating the same reward system (Volkow & Wise, 2005). And though dopamine release due to FA does not equate to addictive properties, the increase in dopamine release has been associated with greater perceptions of reward of both food and psychoactive substances (Volkow et al., 2002). No matter the differences between the food and drug consumption process, future scientific studies that continue to utilize the FA model could explore which type of brain abnormality in substance-related use and addictive disorders should be considered the true

hallmark of FA to compare with the brain changes of T2DM patients, and furthermore, whether the brain injury areas associated with FA (as discovered in manuscript two) are associated with glycemic outcomes.

This dissertation study deepens our knowledge and enhances understanding of food behaviors among T2DM patients where the brain may play the key role to improving T2DM glycemic outcomes. Collectively, the three manuscripts suggest that the potential interventions that focus on promoting neurogenesis and/or protecting specific brain areas of injury (e.g., cognitive brain training, neurofeedback, mesenchymal stem cell therapies, and nutritional supplementation) may help with food behaviors in people with T2DM. The clinical implications from the dissertation findings illuminates future research opportunities that can investigate how these therapies could be the future of T2DM treatment and if they can help improve cognitive/functional impairments related to brain tissue injury, glycemic control, and overall health status of T2DM patients. The future looks promising, especially with growing scientific evidence that the brain has influence over physical responses and health conditions. This dissertation paves the way for clinicians to consider brain health in T2DM dietary self-care management and to explore brain tissue targeted therapies to improve food behaviors and glycemic outcomes in people with T2DM.

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APPENDICES

Appendix A. YFAS 2.0 Scoring

Each question falls under a DSM V Substance-Related and Addictive Disorders (SRAD) symptom criterion (Criterion #1-11) or clinical impairment/distress (Criterion #12):

1) Substance taken in larger amount and for longer period than intended

Questions #1, #2, #3

2) Persistent desire or repeated unsuccessful attempts to quit

Questions #4, #25, #31, # 32

3) Much time/activity to obtain, use, recover

Questions #5, #6, #7

4) Important social, occupational, or recreational activities given up or reduced

Questions #8, #10, #18, #20

5) Use continues despite knowledge of adverse consequences (e.g., emotional problems, physical problems)

Questions, #22, #23

6) Tolerance (marked increase in amount; marked decrease in effect)

Questions #24, #26

7) Characteristic withdrawal symptoms; substance taken to relieve withdrawal

Questions #11, #12, #13, #14, #15

8) Continued use despite social or interpersonal problems

Questions #9, #21, #35

9) Failure to fulfill major role obligation (e.g., work, school, home)

Questions #19, #27

10) Use in physically hazardous situations

Question #28, #33, #34

11) Craving, or a strong desire or urge to use

Questions #29, #30

12) Use causes clinically significant impairment or distress

Questions #16, #17

Each question has a different threshold: 0 = threshold not met, 1 = threshold is met

1) Once a month: #9, #10, #19, #27, #33, #35
2) Two to three times a month: #8, #18, #20, #21, #34
3) Once a week: #3, #11, #13, #14, #22, #28, #29
4) Two to three times a week: #5, #12, #16, #17, #23, #24, #26, #30, #31, #32
5) Four to six times a week: #1, #2, #4, #6, #7, #15, #25

After computing the threshold for each question, sum up the questions under each criterion (e.g., Tolerance, Withdrawal, Clinical Significance, etc.). If the score for the symptom criterion is ≥ 1, then the criterion has been met and is scored as 1. If the score = 0, then the symptom criterion has not been met and is scored as 0.

Example:

Tolerance: (#24 =1) + (#26 = 0) = 1, Criterion Met

Craving (#29=0) + (#30 = 0), Criterion Not Met

Failure to fulfill role obligations (#19 =1) + (#27 = 1), Criterion Met and scored as 1

For the symptom count scoring option, add up all of the scores for each of the 11 criteria (e.g., Tolerance, Withdrawal, Use Despite Negative Consequence). Do not add clinical significance to the score. This score should range from 0 to 11 (0 symptoms to 11 symptoms.)

For the “diagnosis” scoring option, a participant can meet for mild, moderate, or severe food addiction. Both the symptom count score and the clinical significance criterion are used.

No Food Addiction = 1 or fewer symptoms

No Food Addiction = Does not meet criteria for clinical significance

Mild Food Addiction = 2 or 3 symptoms and clinical significance

Moderate Food Addiction = 4 or 5 symptoms and clinical significance

Severe Food Addiction = 6 or more symptoms and clinical significance

Note. Retrieved from: https://sites.lsa.umich.edu/fastlab/yale-food-addiction-scale/. (Gearhardt et al., 2016)

Neuroinvesting: Build a New Investing Brain, Wai-Yee Chen.

Published 2013 by John Wiley & Sons Singapore Pte. Ltd.

Appendix B: Barratt Impulsiveness Scale (Revised)

Introduction: People differ in ways they act and think under various situations. Ernest Barratt developed the Barratt Impulsiveness Scale Test in 1995 to measure a person's level of impulsiveness.[1] This is a revised test incorporating my comments to help you identify and be aware of ways in which you react and think as an investor.

Directions: Read each statement and circle the appropriate number on the right side of this page. Do not spend too much time on any statement. Answer quickly and honestly. Refer to Table B.1.

Scores
1 *Rarely/Never*
2 *Occasionally*
3 *Often*
4 *Almost Always/Always*

Scoring system: Before adding up your scores in each section, reverse the scores of reverse questions; for example, if your score on a reverse score question was 4, then reverse it to 1.

Then add up all your scores for the section.

Table B.1 Revised Barratt Impulsiveness Scale 1

Attentional Facet	Scores
I.	1 2 3 4
1. I don't "pay attention."	1 2 3 4
2. I concentrate easily.	1 2 3 4
3. I "squirm" at plays or lectures.	1 2 3 4
4. I am a steady thinker.	1 2 3 4
5. I am restless at the theater or lectures.	1 2 3 4

(*Continued*)

Table B.1 (*Continued*)

II.	1 2 3 4
6. I have "racing" thoughts.	1 2 3 4
7. I change hobbies.	
8. I often have extraneous thoughts when thinking.	
Reverse score questions are: *2* and *4*	
Your scores for Attentional Facet I: _____	
Your scores for Attentional Facet II: _____	
Comment: if your scores were low on both then you have a good attention span and cognitive stability, the qualities of nonimpulsivity.	
Motor Facet	
I.	
9. I do things without thinking.	1 2 3 4
10. I make up my mind quickly.	1 2 3 4
11. I am happy-go-lucky.	1 2 3 4
12. I "act" on impulse.	1 2 3 4
13. I act on the spur of the moment.	1 2 3 4
14. I buy things on impulse.	1 2 3 4
15. I spend or charge more than I earn.	1 2 3 4
II.	1 2 3 4
16. I change jobs.	1 2 3 4
17. I change residences.	1 2 3 4
18. I can think only about one thing at a time.	1 2 3 4
19. I am future oriented.	1 2 3 4
Reverse score question is *19*	
Your score for Motor Facet I: _____	
Your score for Motor Facet II: _____	
Comment: If you scored low on both, then you have good control of your motor actions and persevere in holding off on impulsive actions.	
The answer to question 10 needs to be qualified. My assessment differs from the standard low score for nonimpulsivity. I accept a higher score for this question because I believe that an investor's ability to make up his or her mind quickly with a quality decision is a positive factor. The ability to make a quick and yet not impulsive decision is the skill of an excellent instinctual investor. I see a mid to high score in this question as positive.	
Planning Facet	
I.	
20. I plan tasks carefully.	
21. I plan trips well ahead of time.	1 2 3 4
22. I am self-controlled.	1 2 3 4
23. I am a careful thinker.	1 2 3 4
24. I plan for job security.	1 2 3 4
25. I say things without thinking.	1 2 3 4
II.	1 2 3 4
26. I save regularly.	1 2 3 4
27. I like to think about complex problems.	1 2 3 4
28. I am easily bored when solving thought problems.	1 2 3 4
29. I am more interested in the present than in the future.	1 2 3 4
30. I like puzzles.	
Reverse score questions are: *20, 21, 22, 23, 24, 26, 27,* and *30*	

Table B.1 (*Continued*)

Your score for Planning Facet I: _____
Your score for Planning Facet II: _____
Comment: If you scored low on both, then you have good self-control in planning for your future and possess the cognitive ability for complexity, the reverse of an impulsive attitude.

With question 29, my assessment differs from the standard score. I accept a higher score for nonimpulsivity. While one's attitude of planning for the future is a sign of nonimpulsivity, for an investor, the ability to *focus on the present decision* and not be distracted by the prospects of future profits or an out-of-proportion fear of past or future losses is an asset. A higher score for those reasons is acceptable for this question and does not detract from being nonimpulsive.

Source: http://www.impulsivity.org/pdf/BIS11English.pdf, with author's revision incorporated in the scale.

Note. Retrieved from https://onlinelibrary.wiley.com/doi/pdf/10.1002/9781118638279.app2.

(Patton et al., 1995)