

Dietary effects on impulsive choice:
An investigation of physiological moderators in rats and humans

by

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B.A., University of the Incarnate Word, 2014
M.S., Kansas State University, 2017

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Abstract

Unhealthful foods are convenient, ubiquitous, and inexpensive. Overconsumption of unhealthful foods can result in disease states such as obesity and Type 2 diabetes. In addition, to the physiological consequences of unhealthful foods, research in rats has shown that diets high in processed fat and sugar induce impulsive choice behavior. Research in humans has demonstrated a link between physiology and impulsive choice, but most investigations have not included diet. This dissertation is comprised of a series of studies that were designed to investigate diet, physiology, and impulsive choice in rats and humans. In Chapter 2, a novel impulsive choice task for food was developed to improve translational efficacy between rat and human models. Participants chose between a smaller amount of M&Ms after a shorter delay or a larger amount of M&Ms after a longer delay. The delay and magnitude of the reward was manipulated across trials. Participants always experienced the delay to reward and actually received the reward in one of the tasks. Results indicated that people were sensitive to delay and magnitude using this novel impulsive choice task for food. In Chapter 3, we investigated how a high-fat diet interacts with physiology (body fat percentage, insulin signaling, and inflammation) to predict impulsive choice in rats and humans. Using a parallel design, rats and humans were split into a Control or High-Fat diet, completed the impulsive choice task, and underwent physiology testing. High-fat diets induced a preference for the shorter delay in rats suggesting an inability to delay gratification, and this effect was not moderated by physiology. However, physiological measures interacted with diet to predict other aspects of impulsive choice (delay and magnitude sensitivity) in rats. High-fat diets were not predictive of impulsive choice in humans, but added sugar was predictive. While high-fat diets were not predictive of impulsive choice, physiology and diet interacted to predict impulsive choice. This evidence indicates that the relationship between

physiology (body fat percentage, insulin, and inflammation) and impulsive choice observed in the literature is moderated by diet. Therefore, the combination of physiology and diet are the most predictive of impulsive choice, especially in humans. These findings indicate that knowledge of dietary consumption and physiology can help us better understand impulsive choice, which can improve our ability to target individuals that could benefit from interventions to reduce impulsive choice with the goal of promoting more self-controlled food choices.

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Approved by:

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Chapter 1 - Physiological Mechanisms of Impulsive Choice

Impulsive choice behavior has become a variable of interest in understanding food choice because an unwillingness to wait for a larger reward may be associated with consumption of foods high in refined sugar and saturated fat. Indeed, more impulsive individuals are more likely to eat fast food (Garza, Ding, Owensby, & Zizza, 2016). There is also evidence to suggest that diet, especially consumption of refined high-fat and high-sugar foods, is associated with more impulsive behavior in humans (Dassen, Houben, & Jansen, 2015; Garza, Harris, & Bolding, 2013). These studies suggest that consumption of foods high in processed fat and sugar may affect impulsive choice and lead to chronic disease states, including obesity (Cordain et al., 2005). The dietary effects on behavior can be difficult to study in humans because dietary history is not easily controlled. Thus far, the research investigating diet, obesity, and impulsive choice in humans is correlational. Rat models can be used to parse the relationship between diet, obesity, and impulsive choice in humans.

Using a rat model to control for dietary history and experience, we were able to directly investigate the effects of diet on impulsive choice. The goal of the study was to determine how diet composition affected impulsive choice. Rats were fed either a chow control, high-fat, or high-sugar diet for 8 weeks. All groups had access to the same number of calories each day, and food intake did not differ between the dietary conditions prior to behavioral testing. After the dietary manipulation, rats were tested on an impulsive choice task where they chose between a smaller-sooner (SS) and a larger-later (LL) reward, with the SS being considered the impulsive choice. We found that high-fat and high-sugar diets resulted in a greater preference for the immediate reward compared to the chow control diet (Figure 1.1). Rats fed a high-fat or high-sugar rats were also more sensitive to delay, indicating that they were more impulsive (Steele,

Pirkle, & Kirkpatrick, 2017). Further, rats selectively bred for high-saccharine intake were more impulsive for food reward than rats bred for low-saccharine intake (Perry, Nelson, Anderson, Morgan, & Carroll, 2007). This research demonstrates that diet can affect impulsive choice behavior in rats.

Following on from our previous research, the studies in Chapter 3 investigated how diet and key physiological factors related to metabolic health interacted to predict impulsive choice using parallel designs in rats and humans. Body fat percentage, insulin signaling, and inflammation were measured because they have been implicated as important variables in understanding impulsive choice (Barlow, Reeves, McKee, Galea, & Stuckler, 2016; Eisenstein et al., 2015; Gassen et al., 2019; Isung et al., 2014), and they are all interrelated. Esposito and Giugliano (2006) outlined that diet can lead to insulin disruptions, inflammation, and obesity. In addition, adipose cells, which are directly related to body fat percentage, can produce inflammation (Esposito & Giugliano, 2006), and an inflammatory state can inhibit insulin signaling (Ezrokhi, Luo, Trubitsyna, & Cincotta, 2014). Therefore, diet can affect body fat percentage, insulin signaling, and inflammation making them possible candidates for understanding how diet affects impulsive choice.

In addition to body fat percentage, insulin signaling, and inflammation being affected by diet, these factors are all associated with disruptions in dopaminergic functioning (Daws et al., 2011; Johnson & Kenny, 2010; Narayanaswami, Thompson, Cassis, Bardo, & Dwoskin, 2013; Nash, 2017; Songab, Merlib, & Anismana, 1999; Wang et al., 2001). Disruptions in dopaminergic functioning can increase impulsive choice behavior in rats (Boomhower & Rasmussen, 2014; Pine, Shiner, Seymour, & Dolan, 2010), which may explain why these three factors are associated with impulsive choice (Barlow et al., 2016; Eisenstein et al., 2015; Gassen

et al., 2019; Isung et al., 2014). Altogether, an investigation of body fat percentage, insulin signaling, and inflammation can help us determine which factors predict impulsive choice and begin to uncover how diet and physiology interact to affect impulsive choice. Understanding the factors predictive of impulsive choice is particularly important because impulsivity is predictive of weight loss success (Nederkoorn, Jansen, Mulken, & Jansen, 2006).

Body fat percentage

Obesity is a potential factor that may help to explain how diet affects impulsive choice behavior. Obesity, as defined by the World Health Organization, is an abnormal or excessive accumulation of fat (Adab, Pallan, & Whincup, 2018). Evidence suggests that overconsumption of foods high in processed fat and sugar are associated with obesity in humans (Swinburn et al., 2011; Swinburn, Sacks, & Ravussin, 2009), and diets high in fat and sugar can increase body fat percentage (a measure of obesity) in rats as seen in Figure 1.2 (top; Steele, 2017). Previous research also indicates that obesity is associated with impulsive choice behavior (Barlow et al., 2016; Bickel et al., 2014; Rasmussen, Lawyer, & Reilly, 2010; Schiff et al., 2015).

When understanding obesity research, it is important to consider the measurement of obesity. Body mass index (BMI) is a common measure of obesity that is determined using height and weight making it an easy and cost effective method for quantifying obesity. However, it has been criticized because it cannot determine body fat distribution nor distinguish between lean and fat mass (Adab et al., 2018). Body fat percentage, especially when measured using imaging techniques that use dual energy x-ray absorptiometry (DEXA), are considered better assessments of obesity. Some studies have not found a relationship between obesity and impulsive choice when using BMI (Eisenstein et al., 2015; Gassen et al., 2019; Rasmussen et al., 2010), and others have only observed a relationship between body fat percentage and impulsive choice (Rasmussen

et al., 2010). Further, while high-fat and high-sugar diets induced impulsive choice behavior in rats, body weight was not correlated with impulsive choice as seen in Figure 1.2 (bottom; Steele et al., 2017). Body weight is often used as a measure of obesity in rats, and this research suggests that the relationship between obesity and impulsive choice observed in humans may not exist in rats. It is important to consider how obesity is measured when evaluating research and more precise measures of obesity are necessary to establish robust relationships. To address this issue, we used DEXA scans to measure body fat percentage in rats and humans as outlined in the translational studies in Chapter 3.

To better understand the relationship between body fat percentage and impulsive choice, we need to consider the underlying mechanisms of choice behavior. The most accepted process thought to underlie impulsive choice is delay discounting, where rewards that are farther in the future are valued less. Delay discounting is posited to take a hyperbolic form according to the following equation: $V = A / (1 + kD)$, where V is the subjective value of the reward, A the amount of the reward, D the delay to reward, and k is a free parameter thought to capture the individual discounting rate (Mazur, 2001; Odum, 2011). The discounting rate, k , represents an individual's sensitivity to delay. People with obesity are more impulsive than people with normal weight as evidenced by higher k -values. These higher k -values suggest that their subjective value of the reward decreases as a function of time more steeply compared to normal-weight individuals. This propensity to choose the more immediate reward, or conversely the inability to delay gratification, could make it difficult to make healthy choices when presented with numerous food choices each day (Wansink & Sobal, 2007), especially because convenient foods are often energy dense and high in fat (Isganaitis & Lustig, 2005).

Of note is the observation that the relationship between obesity and impulsive choice may only be observed when the impulsive choice task includes food choices as opposed to monetary choices (Rasmussen et al., 2010; Schiff et al., 2015). In addition, Barlow et al. (2016) conducted a systematic review of the literature on diet, obesity, and impulsive choice, and concluded that hypothetical, monetary impulsive choice tasks often found null results whereas studies using actual monetary rewards or hypothetical food rewards demonstrated a stronger relationship between obesity and impulsive choice. These results suggest that the obesity-impulsive choice relationship may be most likely observed in real-outcome tasks. Therefore, in Chapter 2, we reported on a study that developed a novel, real food impulsive choice task where participants experienced the delays and rewards. This task was then subsequently used in Chapter 3 to measure the relationship between diet, physiology, and impulsive choice. We expected that rats and people consuming a high-fat diet would be more impulsive and that body fat percentage would enhance this relationship. Therefore, for people or rats in the high-fat dietary group, those with higher body fat percentages would be more impulsive than those with lower body fat percentages.

Insulin signaling

The insulin and glucose systems are complex and work together to regulate glucose homeostasis. When the two systems are functioning normally, pancreatic β -cells secrete insulin in response to glucose in the blood, which clears glucose from the blood. Disruptions in glucose homeostasis are risk factors of Type 2 diabetes (Nathan et al., 2007). Measuring glucose, insulin, and C-peptide (a precursor to insulin) in response to a meal can elucidate the disruptions in the insulin system (Cobelli et al., 2014). Individuals could have high fasting glucose and be glucose tolerant; these factors can co-occur or be independent demonstrating the need for multiple

measures of insulin sensitivity (Nathan et al., 2007). Therefore, it is important to also consider insulin and C-peptide, in addition to glucose, to understand where the abnormalities originate. Considering glucose and insulin together can elucidate insulin sensitivity. Insulin sensitivity refers to how well insulin reduces blood glucose levels. Those who are insulin sensitive would need less insulin to dispose of glucose in the blood than someone who is less insulin sensitive. Considering glucose and C-peptide together can elucidate β -cell responsiveness, or the secretion of insulin in response to glucose. If someone has poor insulin sensitivity, the β -cells would need to secrete more insulin to dispose of glucose in the blood. Therefore, the β -cells can compensate for reduced insulin sensitivity by increasing insulin secretion. Understanding the degree of disruption is critical to fully understand how insulin might play a role in diet-induced impulsivity.

It has been proposed that diet can disrupt glucose homeostasis and alter insulin signaling (Esposito & Giugliano, 2006), and previous research shows that feeding rats diets high in fat and sugar alters insulin signaling as seen in Figure 1.3 (Arnold et al., 2014; Cao, Lu, Lewis, & Li, 2007; Posey et al., 2009). A study in our laboratory found that six weeks of exposure to high-fat and high-sugar diets resulted in significantly higher fasting blood glucose and insulin as well as higher insulin resistance, as measured by homeostatic model assessment (HOMA) values, compared to the chow control group (Figure 1.3). This suggests that disruptions in insulin signaling could affect impulsive choices.

One study found that reduced β -cell function, which can reduce insulin secretion, was associated with more impulsive choice behavior for money (Eisenstein et al., 2015). In addition, insulin sensitivity was associated with impulsive choice in people with high BMIs; people with reduced insulin sensitivity made more impulsive choices (Eisenstein et al., 2015). This

demonstrates the importance of insulin signaling in impulsive choice. Therefore, we tested the hypothesis that insulin signaling and diet interact to predict impulsive choice by investigating fasting glucose, insulin sensitivity, and insulin secretion. We expected that rats and people consuming a high-fat diet would be more impulsive for food, and that high fasting glucose levels, lower insulin sensitivity, and higher insulin secretion after a glucose load should enhance this relationship.

Inflammation

Another variable that could explain the effects of diet on impulsive choice behavior is inflammation. Interleukin-6 (IL-6) is a proinflammatory marker that is part of the inflammation response, and up to 35% of IL-6 is secreted from adipose cells (Esposito & Giugliano, 2006). While body fat percentage, is considered a major driver of inflammation because there is a strong positive correlation between the two variables (Vozarova et al., 2001), there is evidence that a single high-fat meal can induce inflammation in normal weight and obese individuals (Esposito & Giugliano, 2006).

In addition, a diet high in processed fat and sugar can result in cognitive deficits associated with brain inflammation in mice and rats, demonstrating a link between diet, inflammation, and behavior (Davidson et al., 2013; Pistell et al., 2010). Many of the cognitive deficits from diet are related to learning and memory impairments (Cordner & Tamashiro, 2015), but inflammation may contribute to the diet-induced impulsivity observed in rats (Steele, Pirkle, Davis, & Kirkpatrick, 2019; Steele et al., 2017). Recent evidence suggests that current levels of inflammation, as measured by IL-6 and TNF- α , predict impulsive choice in healthy individuals with normal BMIs (Gassen et al., 2019). This expands on evidence suggesting that inflammation is associated with impulsivity as measured by the self-report Karolinska Scale of Personality

questionnaire (Isung et al., 2014). However, neither of these studies in humans investigated the role of diet. Therefore, we tested the hypothesis that inflammation and diet interact to predict impulsive choice. We expected that rats and people consuming a high-fat diet would be more impulsive and that high inflammation levels would enhance this relationship. Therefore, for rats or humans in the high-fat dietary group, those with higher inflammation levels would be more impulsive than those with lower inflammation levels.

Translational approach to impulsive choice

The primary purpose of this dissertation was to provide a comprehensive investigation of diet and physiological factors related to metabolic health to uncover how body fat percentage, insulin signaling, and inflammation interact with diet to predict impulsive choice in rats and humans using translational methods. The investigations of physiology and impulsive choice in humans have not previously examined dietary factors (Eisenstein et al., 2015; Gassen et al., 2019; Rasmussen et al., 2010). However, it is essential that diet is considered given that it directly affects body fat percentage and metabolic health (Esposito & Giugliano, 2006) and behavior (Cordner & Tamashiro, 2015; Steele et al., 2019). Therefore, parallel designs in rats and humans were employed in the studies described in Chapter 3 to expand the current understanding of how physiology and impulsive choice are related by investigating the potential role of diet. Animal models allow us to answer questions using carefully designed experiments where we can control dietary history. This level of control provides valuable information, which can be used to inform human research and our understanding of disease. To improve the translational efficacy of this research, we first developed a novel impulsive choice task for food that closely resembles the impulsive choice tasks used in animals (Chapter 2). The relationship between obesity and impulsive choice is sometimes only observed with impulsive choice tasks

for actual monetary rewards or hypothetical food rewards (Barlow et al., 2016; Rasmussen et al., 2010; Schiff et al., 2015). The novel food task involves choices for actual food rewards, which more closely resembles the methods used in rats. Altogether, these studies provide an investigation of the inter-relationships between physiology, diet, and impulsive choice using parallel designs to uncover which individuals are most at risk for developing diet-induced obesity or impulsivity.

Figure 1.1 Mean proportion of LL choices as a function of the SS delay for rats fed a high-fat, high-sugar, or chow control diet. Error bars ($\pm$ SEM) were computed with respect to the estimated marginal means of the fitted generalized linear mixed-effects model. The secondary axis is included for interpretation of the b-values, which are in log odds. High-fat and high-sugar diets increased the preference for the shorter delay (intercept) and delay sensitivity (slope) compared to the chow diet.

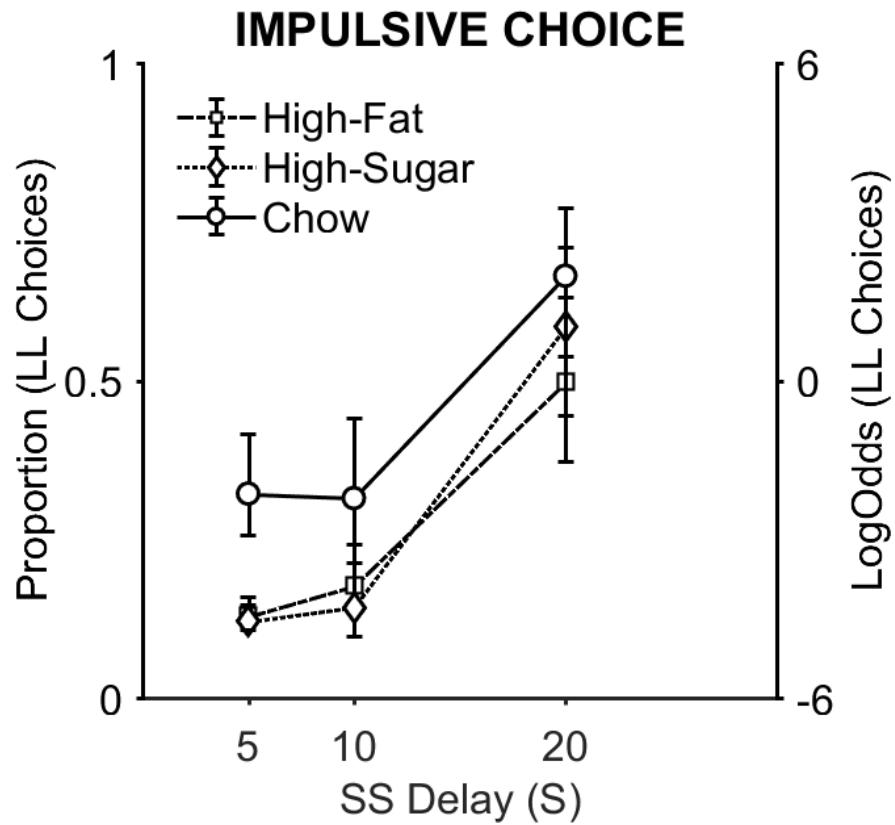


Figure 1.2. A: mean body fat percentage in the abdomen (+/- SEM from the model fit) as a function of months on the diet for all dietary conditions. High-fat and high-sugar diets increased body fat percentage after 9 months on the diet compared to the chow diet. B: The proportion of LL choices was not correlated with body weight.

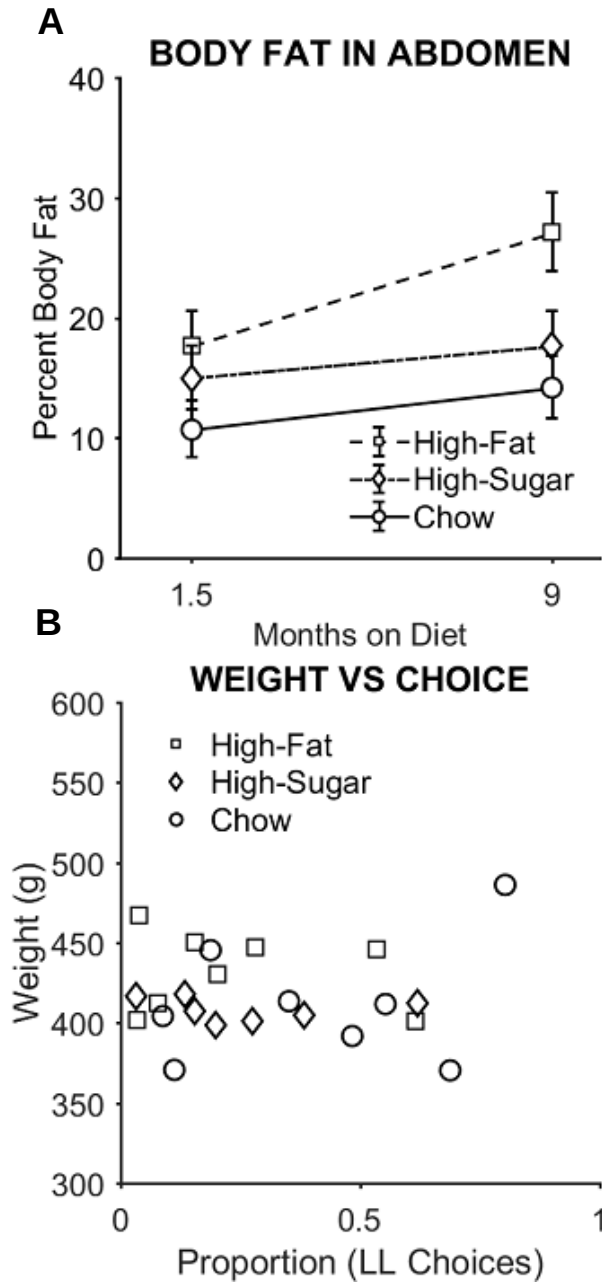
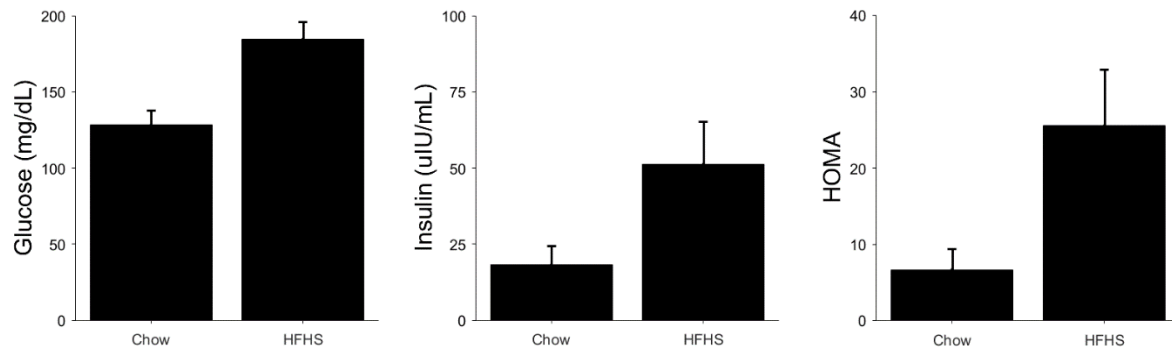


Figure 1.3. Mean differences ($\pm$ SE of the mean) in fasting glucose, fasting insulin, and HOMA ((Glucose*Insulin)/22.5, with glucose expressed as mmol/l and insulin expressed as μ U/ml) across the dietary conditions for males. HFHS = high-fat, high-sugar diet. HOMA (molar units) is an index to represent insulin resistance. The HFHS diet increased fasting glucose, fasting insulin, and HOMA compared to the chow diet.



Chapter 2 - Real versus Pseudo-Real Impulsive Food Choice Task

Impulsive choice is a widely studied construct because it is considered a trans-disease process that is predictive of several disorders and maladaptive behaviors (Bickel, Jarmolowicz, Mueller, Koffarnus, & Gatchalian, 2012; Bickel & Mueller, 2009) and is predictive of poor health and prosperity outcomes later in life (Schlam, Wilson, Shoda, Mischel, & Ayduk, 2013). For example, in the Marshmallow test, children made a choice at the age of four or five that predicted their SAT scores and social skills several years later, and even predicted weight status 30 years later (Schlam et al., 2013). The children were asked to choose between one marshmallow now or 2 marshmallows after a delay. This choice between a smaller amount now (SS) and a larger amount after a delay (LL) is the basis for impulsive choice tasks. The most common way to measure impulsive choice is to present participants with the choice between a large amount of money after a delay or a smaller amount of money available now (Odum, 2011). The choices are typically hypothetical: the participants will not receive the reward or wait for the delay. This allows researchers to obtain data on numerous choices to obtain a more graded measure of impulsive choice in comparison to the one-shot choice of the Marshmallow test. There are several variations of the impulsive choice task, which include potentially real rewards, consumable goods, and experiential tasks.

While body fat percentage and impulsive choice are related (Barlow et al., 2016), sometimes this relationship is only observed when the impulsive choice task includes food choices or real money choices as opposed to hypothetical monetary choices (Barlow et al., 2016; Rasmussen et al., 2010; Schiff et al., 2015). Currently, to our knowledge, there is only one established impulsive choice food task in humans (Hendrickson & Rasmussen, 2013; Hendrickson, Rasmussen, & Lawyer, 2015; Rasmussen et al., 2010). Participants choose

between a smaller number of bites after a shorter delay and a larger number of bites after a longer delay, and the rewards and the delays are hypothetical. Participants are asked to make each choice as though they would actually receive it.

To ensure that the participants' choices reflect what they would choose if they were going to experience the actual delay and reward, researchers may use an impulsive choice task with potentially real rewards. For a potentially real reward, participants are instructed that they will receive one of their choices at the conclusion of the experiment. The goal is to encourage participants to respond as though they are receiving each of their chosen rewards by delivering a randomly sampled reward. While it is well established that hypothetical and potentially real monetary rewards can result in similar choice functions (Lawyer, Schoepflin, Green, & Jenks, 2011; Odum, 2011; Robertson & Rasmussen, 2018), there is limited and mixed evidence on consumable goods (e.g., food). One study found that potentially real cigarettes were discounted more steeply than hypothetical cigarettes (Green & Lawyer, 2014), but another study found that hypothetical and potentially real food rewards were not discounted differently (Robertson & Rasmussen, 2018).

One challenge with the hypothetical food and money tasks is that they do not reflect the way choices are made in real life, where people usually experience the consequences of their choices. In addition, the discrepancy in methods between animal research (which exclusively deliver real consequences) and human research (with hypothetical consequences) makes it difficult to compare results across species for translational purposes. Experiential discounting tasks (EDTs) for use with human participants have been developed to address some of the limitations of hypothetical tasks. In EDTs, participants receive the reward and experience the delays, such as having to wait 30 s before they can bank a monetary reward. These tasks are thus

more similar to rodent tasks (Reynolds & Schiffbauer, 2004). While EDTs more closely resemble the tasks used in rodents, they have received criticism for several major deviations from the rodent procedures (Smits, Stein, Johnson, Odum, & Madden, 2013). Specifically, previously-developed EDTs: (1) have probabilistic outcomes, whereas rodent procedures have certain outcomes; (2) do not impose an inter-trial interval after the choice; (3) result in points as opposed to rewards such as food that can be consumed during the session.

Given these important considerations for measuring impulsive choice behavior coupled with the criticisms of current experiential discounting tasks, the goal of this experiment was to create a real reward, real delay impulsive food choice task that addressed the criticisms outlined in Smits et al. (2013) by delivering certain outcomes and including an inter-trial interval. The current experiment also compared a pseudo-real reward, real delay task (similar to the previous EDTs) and a novel real reward, real delay task. Further, a hypothetical, monetary impulsive choice questionnaire (Kirby, Petry, & Bickel, 1999) was used as a benchmark for comparison. This experiment should provide a novel way to understand impulsive food choices, which can help uncover the critical variables that affect real world impulsive choices.

Method

Participants

Fifty participants (26 female) in Riley County, KS were recruited through fliers and word of mouth. The average age of the participants was 23.3 (SD = 3.7) years old. After signing up, participants were contacted and asked not to eat or drink for at least four hours before their session. The participants reported the time of their last meal at the beginning of the session to confirm they had not eaten in the last 4 hr. Participants were also asked to “circle one of the lines for how you are feeling right now” on the Holt Satiety Index, which ranges from extremely

hungry to extremely satisfied (Holt, Brand Miller, Petocz, & Farmakalidis, 1995). Participants were not asked to report how hungry they were to avoid biasing them toward the hungry side of the scale. The study description indicated that they would make choices for M&Ms. Participants were compensated with \$5 and a small snack of mini M&Ms administered during the choice task. Individuals were excluded from participation if they were under the age of 18, non-fluent in English, diagnosed with a metabolic disorder (e.g., diabetes) or eating disorder, had extremely restrictive eating habits (e.g., no carb diet), were taking medication that can impact hunger/appetite, or were a smoker. Participants self-reported that these exclusion criteria did not apply. The study was approved by the Institutional Review Board at Kansas State University.

Apparatus

The choice tasks were conducted on a Dell computer. MATLAB 2018a controlled the experimental procedures and collected data. During the real food choice task, the pieces of candy were delivered through a feeder (Med-Associates, St. Albans, VT, ENV-203-MINI) into a small plastic bowl. The feeder was controlled by a transitor to transitor logic interface coupled with a 28V DC Adapter (Med-Associates, St. Albans, VT, SG-230R). The adapter connected the feeder, a DC power supply (Med-Associates, St. Albans, VT, SG-500T), and a digital input/output card (National Instruments, Austin, TX; PCIe-6509). Computerized control of the feeder was controlled through the Data Acquisition Toolbox in MATLAB 2018a with millisecond timing precision.

Procedure

Participants arrived in the laboratory and read the informed consent form before indicating the time since their last meal and their subjective hunger on the Holt Satiety Index. Then, they completed both the pseudo-real and real reward impulsive food choice tasks in a

counterbalanced order (Figure 2.1). Next, the participants completed a demographic questionnaire and the Kirby questionnaire.

Measures

Impulsive choice tasks

To measure impulsive choice behavior, participants chose between SS versus LL rewards, with the SS choice characterized as the impulsive choice. Each participant completed two tasks: a pseudo-real food choice task and a real food choice task. In the pseudo-real food choice task, participants chose pseudo-real rewards and experienced the delay to reward. In the real food choice task, the participants obtained the actual food reward after they experienced the delay. Participants sat at a computer and they were presented with 25 choices where the SS option delivered 1-4 mini M&Ms after a short delay and the LL option delivered 4 or 5 mini M&Ms after a longer delay. The delays ranged from 5 to 30 s (Table 2.1). The number of mini M&Ms and the delay to reward were indicated on the screen (e.g., 1 M&M in 5 s or 5 M&Ms in 25 s).

Figure 2.2 depicts the combinations of delay and magnitude ratios (delay ratio = SS delay/LL delay; magnitude ratio = SS magnitude/LL magnitude). Each participant experienced each magnitude/delay ratio combination once so that participants could earn 120 mini M&Ms maximum (~1 oz; 141 kcal; 42% fat, 54% carbs, 4% protein). The choice parameters were distributed equally across the two halves as consumption during the real food choice task may affect choices in the second half of the task. Each half included at least one trial with each delay and magnitude ratio.

Upon arrival, participants were asked to set aside their phone and there were no clocks in the room so as to encourage reliance on their internal timing mechanisms when making and

waiting for their choices. The instructions were as follows: “During this 45-min session, you are going to make a bunch of choices. You will be presented with two options on the screen and you will choose which ever option that you want. After making that choice by pressing “F” or “J”, you must wait that amount of time and press that key again to receive the reward. You may press that key as many times as you want, but the response after that amount of time will result in the food delivered to the bowl (or store).” A 30-s intertrial interval (ITI) commenced following delivery of the reward during which blank white screen was shown. The ITI and fixed number of trials ensured that choosing the LL was the optimal choice assuming that maximum reward earning was the participant’s goal. For the real reward impulsive choice task, participants were instructed that “There will be a blank screen following your choice. This time is intended for you to eat the M&Ms. The next choice will pop up automatically. There is water here for you in case you need it.” For the pseudo-real reward impulsive choice task, participants were instructed that “There will be a blank screen following your choice, and the next choice will pop up automatically.” The water was available during the pseudo-real task, but their attention was not drawn to it. Details about the length of the task were ambiguous. Participants did not know if the session was a set amount of time or if their choice influenced how long they were in the session.

During the pseudo-real reward impulsive food choice task, the participants chose their preferred option and waited the delay before they were able to “store” the pieces of candy on the screen. The participants did not receive any food rewards to consume, but they could see the number of mini M&Ms they had earned in their store. They were asked to make the choice as though they were going to receive those M&Ms after the specified amount of time. During the real reward impulsive food choice task, the participants received their choice and consumed the food reward, but they could not see the number of mini M&Ms they had earned. The mini

M&Ms were delivered through a feeder (see Apparatus) following the first response after the delay elapsed.

Kirby questionnaire

For the choice task, participants answered a series of 27 questions consisting of choices between immediate (smaller-sooner, SS) and delayed (larger-later, LL) rewards (Kirby, 2009). For example, a choice could be \$15 now versus \$35 in 13 days (Table 2.2). A single question appeared on the screen and advanced to the next question after the response occurred; the 27 questions were presented randomly intermixed. Instructions for the choice task were: "In the task that follows, you will have the opportunity to choose between different amounts of money available after different delays. The test consists of about 30 questions, such as the following: Would you rather have \$10 in 30 days or \$2 now? You will not receive any of the rewards that you choose, but you should make your decisions as though you were really going to get the rewards you choose."

Data analysis

For the impulsive food choice tasks, repeated measures logistic regressions were conducted to determine differences in the proportion of LL choices made during the impulsive choice task. For the delay analysis, the fixed effects included task (pseudo-real or real), delay ratio, and intercept. Delay ratio assessed sensitivity to delay and was scaled so that the intercept represented the largest difference in delays (SS/LL-5/25), or a preference for the shorter delay. For the magnitude analysis, the fixed effects included task (pseudo-real or real), magnitude ratio, and intercept. Magnitude ratio assessed sensitivity to magnitude and was scaled so that the intercept represented the largest difference in magnitudes (SS/LL-1/5), or a preference for the larger magnitude. Impulsive choice is characterized by greater sensitivity to delay and lower

sensitivity to magnitude (Wileyto, Audrain-McGover, Epstein, & Lerman, 2004; Young, 2018). This analysis technique allows the two aspects of impulsive choice to be characterized. Task was included as a categorical predictor to determine similarities in performance across food choice tasks. Half and order were included as categorical predictors, but adding these predictors did not improve the Akaike Information Criterion (AIC; Burnham & Anderson, 2002) so they were not incorporated into the final model. The random effects structure included intercept as well as the interaction between delay (or magnitude ratio) and task. The interaction between delay (or magnitude ratio) and task was included as a random effect to obtain individual slope estimates for each task for analysis of the individual differences. For the Kirby Questionnaire, individual k values were determined using the Wileyto et al. (2004) approach. The k values obtained from the Kirby Questionnaire were correlated with performance on the real reward impulsive food choice tasks as a benchmark for comparison to a commonly used hypothetical discounting task. The k values were correlated with preference for the shorter delay, delay sensitivity, preference for the larger delay, and magnitude sensitivity (Wileyto et al., 2004; Young, 2018).

Results

Impulsive choice

The full model outputs are in Table 2.3. Delay and magnitude were analyzed in separate models. There was a significant effect of delay and magnitude ratio, such that the proportion of LL choices changed as the delay and magnitude ratios changed. However, there were no main effects of task or interaction between task and delay (or magnitude) ratio. This suggests that performance was similar across real and pseudo real tasks, consistent with the visual depiction of the data in Figure 2.3.

Inter-task correlations

Delay intercept ($r = 0.96$), delay slope ($r = 0.97$), magnitude intercept ($r = 0.95$), and magnitude slope ($r = 0.88$) were all highly correlated for the pseudo-real and real impulsive choice tasks, $ps < .001$ (Figure 2.4). However, performance on the Kirby Questionnaire did not correlate very well with preference for the shorter delay, delay sensitivity, preference for the larger magnitude, or magnitude sensitivity on the real impulsive choice task (Figure 2.5). Delay intercept, delay ratio, magnitude intercept from the real and pseudo-real task were not significantly correlated with the k values obtained from the regression analysis ($rs < 0.15$, $ps > .31$). However, k -values were significantly correlated with the magnitude slope on the pseudo-real ($r = 0.30$, $p = .04$) and real ($r = 0.28$, $p = 0.047$) choice tasks. Thus, whether or not individuals experience consequences (rewards and delays) appears to affect choice behavior.

Discussion

This experiment established a novel impulsive choice task designed to improve translational efficacy between rodents and humans. In addition, a real food task may be a better indicator of obesity as it may better approximate real world food choices (Barlow et al., 2016). Participants completed a real reward, real delay impulsive choice task for food and a pseudo-real reward, real delay impulsive choice task for food in a counterbalanced order. Mixed effects logistic regressions were used to parse apart different aspects of choice: preference for the shorter delay, preference for the larger magnitude, sensitivity to delay, and sensitivity to magnitude (Steele et al., 2019; Steele et al., 2017). The results suggest that participants were sensitive to delay and magnitude of the reward. Further, participants responded similarly on the pseudo-real and real tasks, suggesting that the experience of actual outcomes may not be necessary in the EDTs.

When comparing the novel tasks to the Kirby questionnaire, the results indicate that performance on the real impulsive choice task was not correlated with the k values obtained from the Kirby questionnaire. This is a common finding in studies that use experiential discounting tasks (Reynolds, Richards, & De Wit, 2006; Reynolds & Schiffbauer, 2004). The lack of a correlation between the food choice tasks and the Kirby questionnaire suggests that the tasks are picking up on different processes. Hypothetical choice tasks may be more likely to reflect intentions whereas real choice tasks should reflect actual choices. The Marshmallow test, as an example of real choice tasks, is predictive of real-world outcomes most likely because it is an actual choice (CITE). The real food impulsive choice task developed in this study is an improvement on Marshmallow task because it is not purely a one-shot task. Rather, the choice parameters utilized in this current study provides a graded choice behavior and allows bias and sensitivity to delays and magnitude to be parsed. However, k was moderately associated with magnitude slope. This is a novel finding based on the analysis used in this experiment. While k is commonly used as a measure for delay sensitivity, this measure actually combines sensitivity to delay and magnitude (Young, 2017). Our analysis method parses apart preference for the shorter delay, preference for the larger reward, sensitivity to delay, and sensitivity to magnitude. Because k is associated with magnitude sensitivity on the experiential tasks used in this study, it is possible that the hypothetical impulsive choice tasks measure sensitivity to magnitude more so than sensitivity to delay. People are poor at perceiving time (Eagleman, 2008) and may focus on the reward amounts instead of the delays. Consistent with this idea, a recent study showed that individuals primarily paid attention to the amount of money, not the delay to reward on a hypothetical impulsive choice task (Amasino, Sullivan, Kranton, & Huettel, 2019). Because participants experience the delays to reward in our task, this may draw attention to the delays.

This may explain why experiential discounting and hypothetical discounting tasks are not well correlated (Reynolds et al., 2006; Reynolds & Schiffbauer, 2004). Further research should disentangle the effects of delay and reward magnitude on impulsive choice in the different tasks.

Altogether, we have developed an impulsive choice task for food that closely resembles the tasks used in rodents, thus improving translation between animal and human models. Participants received certain rewards, received the consumable reward during the session, waited for the delay, and experienced the inter-trial interval addressing several of the previous concerns of experiential discounting tasks (Smits et al., 2013). Understanding impulsive choice for rewards with short delays provides a close translation to animal models and may have implications for food choices in real life. For example, Appelhans et al. (2018) imposed a 25-s delay to unhealthy snack options in three vending machines on the campus of an academic medical center. This simple intervention slightly increased healthy snack purchases. This demonstrates that short delays have the potential to impact actual food choices. Future research should determine how impulsive choices on our novel task relates to actual food choices. Experiential discounting tasks, especially for real rewards, may predict impulsive food choices in real time better than hypothetical tasks. Indeed, obesity and impulsive choice are most strongly related on impulsive choice tasks for food (Barlow et al., 2016). Therefore, utilizing a real food impulsive choice to uncover how diet and physiology interact to predict impulsive choice may be the most applicable. Many food choices in real life include delays to more healthful options, and it is important to understand if choice in a laboratory task can predict how individuals choose in real life.

Figure 2.1. All participants completed the real food choice task or the pseudo-real food choice task in a counterbalanced order. Following both food choice tasks, participants completed the demographic and Kirby questionnaires.

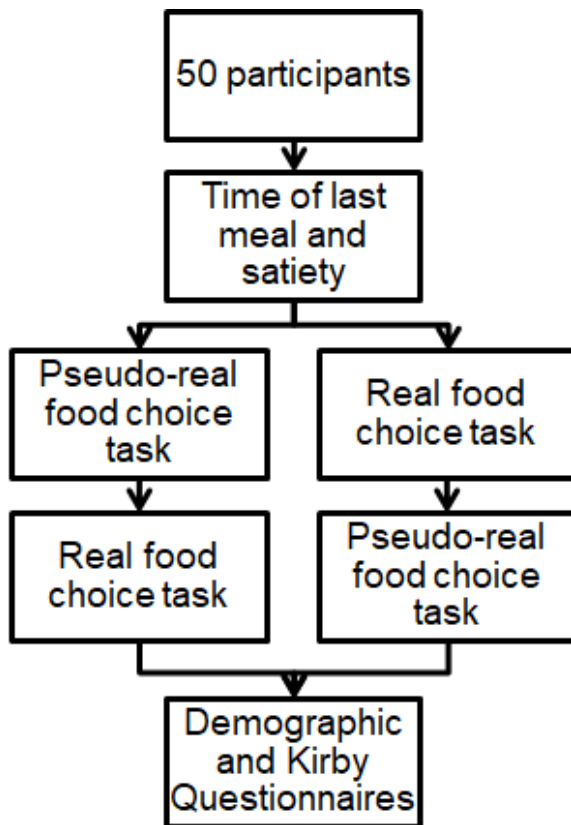


Figure 2.2. The delay and magnitude ratios that were used in the pseudo-real and real food impulsive choice task, where delay ratio = SS delay/LL delay and magnitude ratio = SS magnitude/LL magnitude.

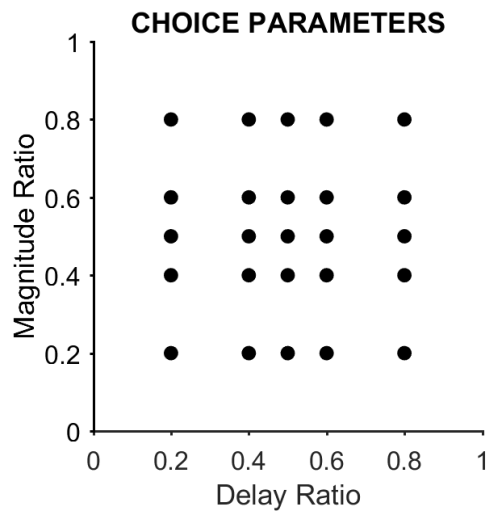


Figure 2.3. Mean proportion of larger-later (LL) choices in the real and pseudo-real tasks as a function of delay (A) and magnitude (B) ratio. The left panel includes participants who received the pseudo-real task first and the right includes participants who received the real task first. Error bars ($\pm$ SEM) were computed with respect to the estimated marginal means of the fitted generalized linear mixed-effects model. There were no intercept or slope differences for each task regardless of which task was completed first.

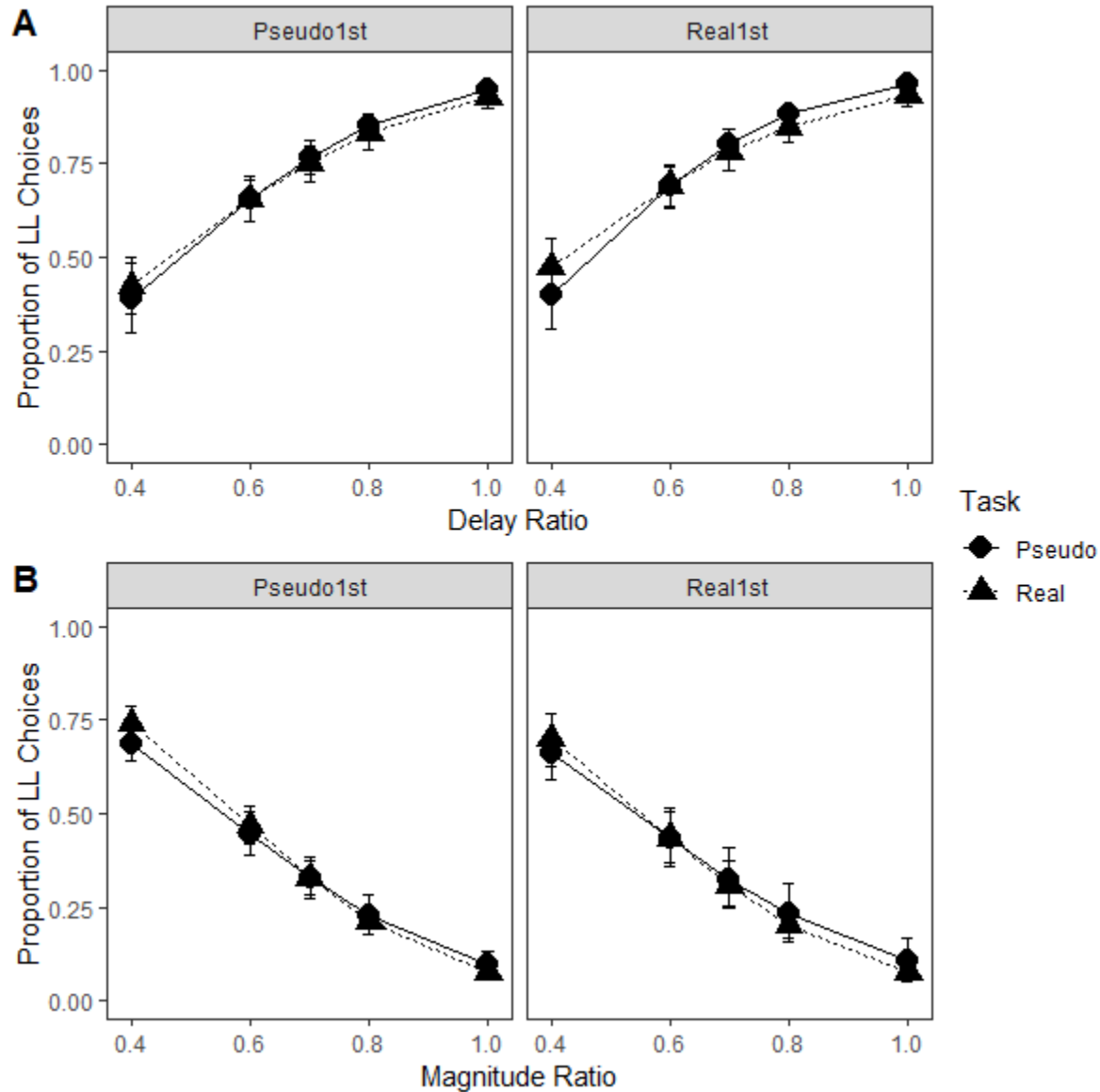


Figure 2.4. Correlation between performance on pseudo-real and real food choice tasks. The intercept and slope estimates for each individual were obtained from the generalized mixed effects model random effects coefficients. A and B depict the correlations for the estimates obtained from the delay ratio model for intercept (A) and slope (B). C and D depict the correlations for the estimates obtained from the magnitude ratio model for intercept (C) and slope (D). Performance on the pseudo-real and real food choice tasks were highly correlated.

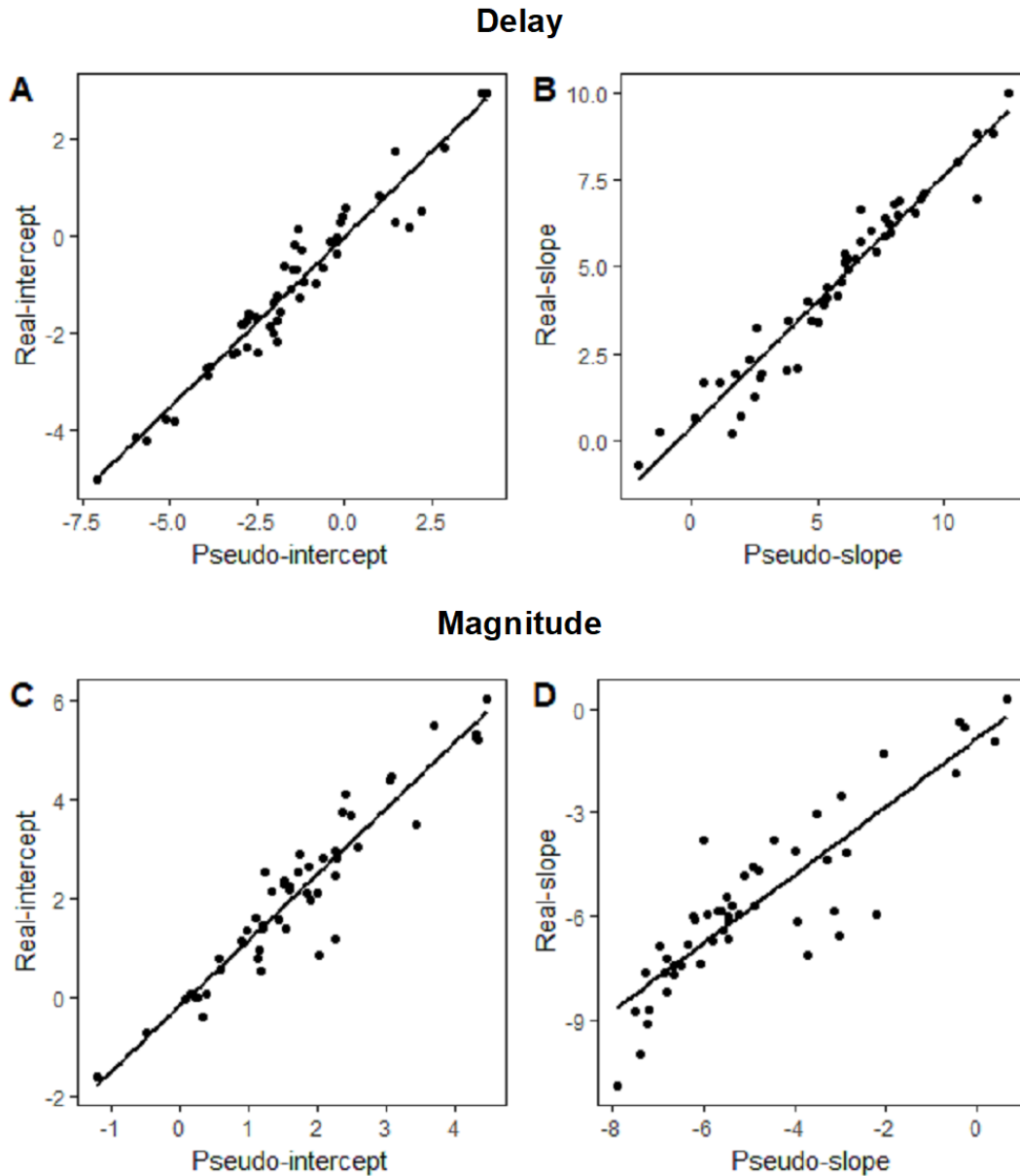


Figure 2.5. Correlation between individuals' performance on the real food tasks and the logarithm of the k -values obtained from the Kirby questionnaire. The intercept and slope estimates for each individual on the real food task were obtained from the generalized mixed effects model random effects coefficients. A and B depict the correlation between the k values (log-transformed) obtained from the Kirby questionnaire and the estimates obtained from the delay ratio model intercept (A) and slope (B). C and D depict the correlation between the k values obtained from the Kirby questionnaire and the estimates obtained from the magnitude ratio model for intercept (C) and slope (D). Log (k) was not correlated with delay intercept, delay slope, or magnitude intercept. However, log (k) was moderately correlated with magnitude slope. Overall, the measurements from the Kirby questionnaire were not well correlated with the measurements from the real food task.

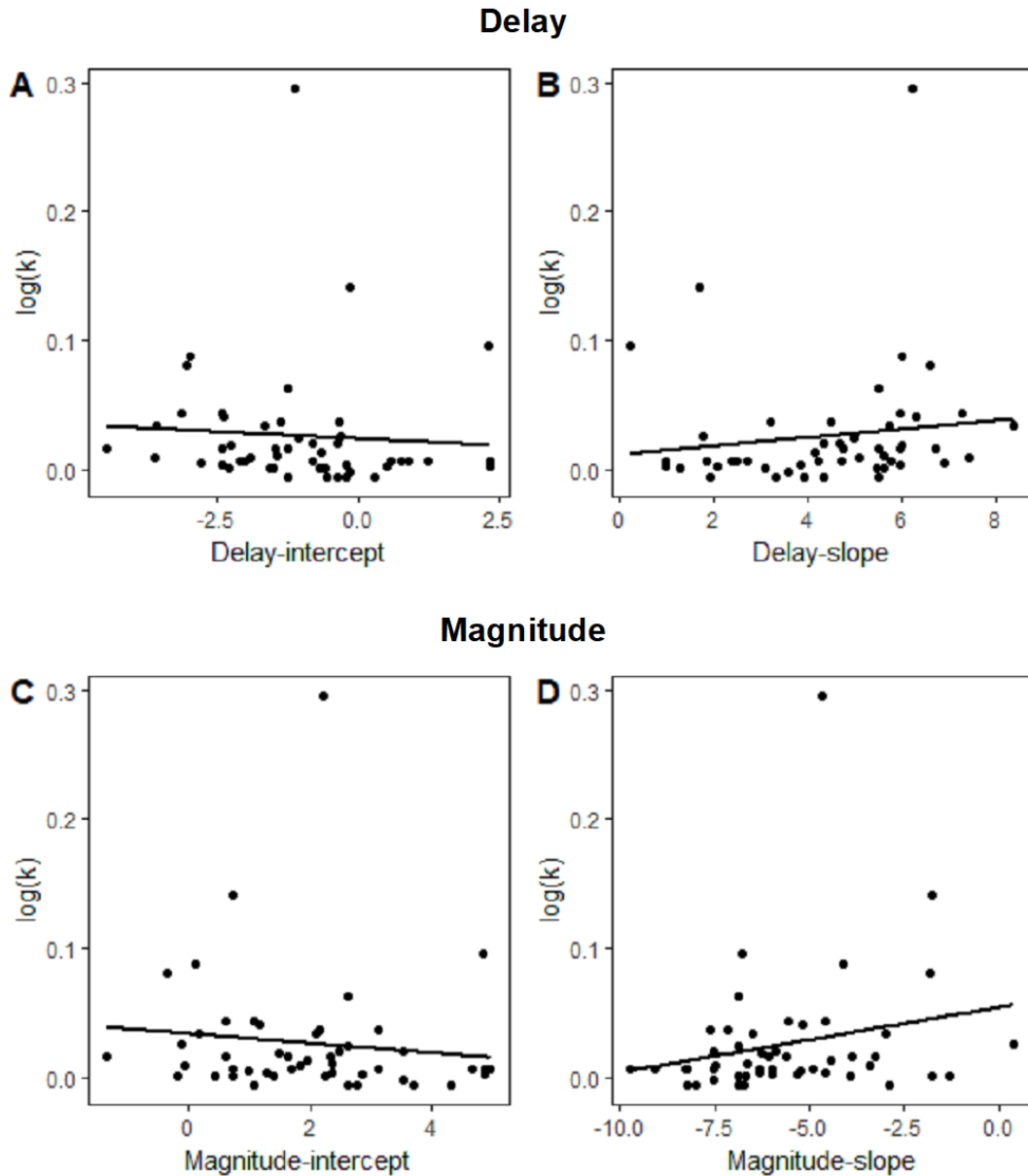


Table 2.1. Individual items for the real and pseudo-real impulsive food choice tasks. The smaller-sooner (SS) and larger-later (LL) delays were in seconds. Items 1-13 were experienced in the first half of the session and items 14-25 were experienced in the second half. Within each half, the items were delivered in a random order.

Item	SS Amount	LL Amount	SS Delay	LL Delay	Delay Ratio	Mag Ratio
1	1	5	5	25	0.2	0.2
2	2	4	5	25	0.2	0.5
3	4	5	5	25	0.2	0.8
4	2	5	10	25	0.4	0.4
5	3	5	10	25	0.4	0.6
6	1	5	15	30	0.5	0.2
7	2	4	15	30	0.5	0.5
8	4	5	15	30	0.5	0.8
9	2	5	15	25	0.6	0.4
10	3	5	15	25	0.6	0.6
11	1	5	20	25	0.8	0.2
12	2	4	20	25	0.8	0.5
13	4	5	20	25	0.8	0.8
14	2	5	5	25	0.2	0.4
15	3	5	5	25	0.2	0.6
16	1	5	10	25	0.4	0.2
17	2	4	10	25	0.4	0.5
18	4	5	10	25	0.4	0.8
19	2	5	15	30	0.5	0.4
20	3	5	15	30	0.5	0.6
21	1	5	15	25	0.6	0.2
22	2	4	15	25	0.6	0.5
23	4	5	15	25	0.6	0.8
24	2	5	20	25	0.8	0.4
25	3	5	20	25	0.8	0.6

Table 2.2. Individual items for the Kirby questionnaire (Kirby et al., 1999). The smaller-sooner (SS) and larger-later (LL) delays were in days. The questions were presented individually in a random order.

Item	SS Amount	SS Delay	LL Amount	LL Delay
1	\$34	0	\$35	186
2	\$28	0	\$30	179
3	\$22	0	\$25	136
4	\$25	0	\$30	80
5	\$19	0	\$25	53
6	\$24	0	\$35	29
7	\$14	0	\$25	19
8	\$15	0	\$35	13
9	\$11	0	\$30	7
10	\$54	0	\$55	117
11	\$47	0	\$50	160
12	\$54	0	\$60	111
13	\$49	0	\$60	89
14	\$40	0	\$55	62
15	\$34	0	\$50	30
16	\$27	0	\$50	21
17	\$25	0	\$60	14
18	\$20	0	\$55	7
19	\$78	0	\$80	162
20	\$80	0	\$85	157
21	\$67	0	\$75	119
22	\$69	0	\$85	91
23	\$55	0	\$75	61
24	\$54	0	\$80	30
25	\$41	0	\$75	20
26	\$33	0	\$80	14
27	\$31	0	\$85	7

Table 2.3. Full model output of the fixed effects from the logistic regression models conducted on all choices in the impulsive choice tasks for food. Delay ratio and magnitude ratio were analyzed separately. The model included the fixed effects of the overall intercept, task (pseudo, real) as a categorical predictor, and delay or magnitude ratio a continuous predictor. Further details of the modeling are provided in the methods section. Delay ratio and magnitude ratio were significant predictors of impulsive choice. Task and the interaction between task and delay (or magnitude) ratio did not predict impulsive choice.

Analysis	Predictor	<i>b</i>	SE	<i>z</i>	<i>p</i>
Delay	Intercept	-1.36	0.33	-4.09	< .001
	Delay ratio	5.22	0.58	9.05	< .001
	Task	-0.23	0.13	-1.77	0.077
	Delay ratio × Task	0.57	0.31	1.85	0.064
Magnitude	Intercept	2.00	0.26	7.59	< .001
	Magnitude ratio	-5.45	0.51	-10.70	< .001
	Task	-0.21	0.13	-1.58	0.114
	Magnitude ratio × Task	0.42	0.32	1.31	0.191

Chapter 3 - Physiological Moderators

Our previous research indicated that a diet high in processed fat increased impulsive choice (Steele et al., 2019; Steele et al., 2017), body fat percentage (Figure 1.2, top), and insulin resistance (Figure 1.3) in rats. Given that obesity as measured by BMI and body fat percentage (Barlow et al., 2016; Bickel et al., 2014; Rasmussen et al., 2010; Schiff et al., 2015), insulin signaling (Eisenstein et al., 2015), and inflammation (Gassen et al., 2019) are associated with impulsive choice in humans, it is proposed that disruptions in body fat percentage, insulin signaling, and/or inflammation may interact with diet to predict impulsive choice. Thus far, diet, body fat percentage, insulin signaling, and inflammation have been investigated separately providing an accumulation of evidence that these factors may be important. However, it is unclear how these factors are related to each other, and most investigations related to impulsive choice in humans do not measure diet.

The overall goal of this chapter was to use translational methods to determine how diet interacts with body fat percentage, insulin signaling, and inflammation to predict impulsive choice. These studies determined the extent to which these three factors interacted with diet to predict impulsive choice. The key factors of interest were measured and/or manipulated using a parallel design in animals and humans (

Figure 3.1). The subjects were assigned to a dietary condition (Control or High Fat) before experiencing the impulsive choice tasks. Notably, the novel impulsive choice task for food described in Chapter 2 was used in this experiment to employ more similar behavioral assessments across species. Rats and humans experienced the consequence of their choice (delay and reward). In addition, the physiological measures of body fat percentage, insulin sensitivity and insulin secretion following 75 g of glucose, and inflammation were obtained. Subjects underwent an oral glucose tolerance test (OGTT) to determine functioning of key aspects of the insulin system (insulin sensitivity and insulin secretion). The fasting blood sample was also used to measure IL-6 as an indicator of inflammation. Finally, body fat percentage was measured using a dual-energy x-ray absorptiometry (DEXA) scan. A DEXA scan uses x-ray technology to measure body composition, including body fat percentage. The human participants went through the same procedure as the rats except that diet was measured through the Automated Self-Administered 24-Hour (ASA24) Dietary Assessment Tool instead of being manipulated through exposure to the diets.

We expected that rats and people consuming a high-fat diet would have disruptions in physiology and impulsive choice. Specifically, we expected the high-fat group to have higher body fat percentages, higher fasting glucose levels, reduced insulin sensitivity, higher insulin secretion, and higher inflammation. In addition, we expected the high-fat group to be more impulsive. We hypothesized that this relationship between diet and impulsive choice would be moderated by physiology such that higher body fat percentages, reduced insulin sensitivity, higher insulin secretion, and higher inflammation should strengthen the relationship between diet and impulsive choice.

Rat model

Method

Animals. Forty-eight male Sprague-Dawley rats (Charles River, NY) arrived at Kansas State University at 21-25 days of age and weighing 34-50 g. Females were not used in this study because previous research showed that females had some differences in regard to the effects of diet on impulsive choice, fasting glucose, fasting insulin, and HOMA values. Specifically, a high-fat/high-sugar group made more self-controlled choices than the chow group. In addition, the groups did not differ in fasting glucose, fasting insulin, or HOMA values. Altogether, a mixed sex sample was not feasible for this current project because the effect sizes for females are not within the confidence intervals for males. We would have needed to study sex as a separate independent variable, which would have at least doubled the number of animals needed to complete the study, which was not feasible for the scope of this project. Upon arrival, rats were individually housed in clear shoe box cages to allow for measurement of food intake and controlled delivery of the diets. Rats were maintained on a 12:12 hr light:dark cycle with lights on at 7 am. All behavioral testing was conducted in the dark portion of the cycle. All procedures and research were conducted in accordance with IACUC and AAALAC guidelines.

Dietary manipulation. Rats were randomly assigned into two eucaloric groups (Control or High Fat) and underwent an 8-week diet manipulation before beginning behavioral testing. The control group (C) received an all chow diet (LabDiet 5001; 3.36 kcal/g). The high-fat group (HF) received 60% of their calories from chow (LabDiet 5001; 3.36 kcal/g) and 40% of their calories from hydrogenated vegetable oil, a type of processed saturated fat. The supplement was used instead of commercial diets that control for vitamins and protein across groups to more closely model human diets. When people consume diets high in fat and sugar, they are often

deficient in minerals and low in protein. Using the dietary supplement increases translation to humans who are consuming diets with poor nutritional value. Table 3.1 outlines the macronutrient breakdown for both groups; the chow and supplement combined to make up the macronutrient breakdown. Each day the rats received 60% of their calories as chow on top of the cage. The remaining 40% of the calories was placed in the cage. The chow group received 40% of the chow inside the cage to control for experience with the food in the cage. To ensure that the rats consumed their daily food ration, the number of calories administered were based on the number of calories consumed ad libitum during development in a previous study (Leibowitz, Lucas, Leibowitz, & Jhanwar, 1991). The number of calories increased each week as the rats aged to match the expected number of calories that they would consume at the corresponding age.

The rats continued to receive their diet during behavioral testing. To ensure the rats were willing to work for food during behavioral testing, the rats were restricted to a 4-hr eating window. The food was removed after 4 hr of feeding and food intake was measured. The rats fasted for 18 hr prior to behavioral testing. During behavioral testing, rat received pellets in the chamber. The food received during testing was subtracted from the chow placed on the top of the cage to continue to maintain equivalent calorie distribution.

Food intake during behavioral testing was not analyzed because part of the daily food ration was received in the apparatus. This made it difficult to interpret consumption because some rats received more of their food in the experiment versus home cage and these foods were delivered under different conditions. One week prior to behavioral testing, the groups differed in their intake of chow received in the food hopper, which made up 60% of the calories from each

diet, $F(1,120) = 46.42$, $p < .001$. Group HF ($M = 11.62$ g, $SD = 3.00$) ate more chow than Group C ($M = 6.77$ g, $SD = 2.68$).

Apparatus. The behavioral tasks were conducted in 24 operant chambers (Med Associates, St. Albans, VT), each housed within a sound-attenuating, ventilated box (74 x 38 x 60 cm). Each operant chamber (25 x 30 x 30) was equipped with a stainless steel grid floor; two stainless steel walls (front and back); and a transparent polycarbonate side wall, ceiling, and door. Two pellet dispensers (ENV-203), mounted on the outside of the front wall of the operant chamber, delivered 45-mg food pellets (Product #F0165, Bio-Serv, Flemington, NJ) to a food cup (ENV-200R7) that was centered on the lower section of the front wall. Head entries into the food magazine were transduced by an infrared photobeam (ENV-254). Two retractable levers (ENV-112CM) were located on opposite sides of the food cup. The chamber was also equipped with a house light (ENV-215) that was centered at the top of the chamber's front wall, as well as two nose-poke key lights (ENV-119M-1) that were each located above the left and right levers. Water was always be available from a sipper tube that protruded through the back wall of the chamber. Experimental events were controlled and recorded with 2-ms resolution by the software program MED-PC IV (Tatham & Zurn, 1989).

Procedure. As depicted in

Figure 3.1, rats underwent an 8-week dietary manipulation before beginning behavioral testing. Rats completed initial training before beginning two impulsive choice tasks. The impulsive choice tasks were separated with a buffer task. Following the completion of behavioral testing, the rats completed an oral glucose tolerance test. This was conducted at the end of the study to measure disruptions of the glucose system. Fasting blood samples were used to measure fasting IL-6. The rats received a DEXA scan to measure body fat percentage.

Behavioral testing

Initial training. Rats completed three sessions of initial training to establish lever pressing. During the first training session, rats received magazine training and lever-press training. The magazine training consisted of delivery of 60 food pellets into a food cup through a random time 60-s schedule. Following magazine training, lever-press training rewarded lever presses with a fixed-ratio (FR) 1 schedule of reinforcement. Left and right levers were trained separately in 6 sub-blocks of 10 food deliveries, resulting in a total of 30 pellets per lever. Following the first training session, the rats continued lever-press training during two sessions. First, lever pressing was rewarded on a FR1 schedule of reinforcement. Left and right levers were trained separately in 6 sub-blocks (3 blocks per lever). Following the FR1 training, both levers were inserted and lever pressing were rewarded on a random ratio (RR) 3 schedule of reinforcement, followed by an RR5 schedule of reinforcement. For both the RR3 and RR5 block, each of the four sub-blocks consisted of 5 food deliveries per a lever.

Impulsive choice task. After acquisition of lever pressing, the rats began the impulsive choice task. To measure impulsive choice behavior, rats chose between smaller-sooner (SS) versus larger-later (LL) rewards in two impulsive choice tasks – delay manipulation and magnitude manipulation – to allow for delay and magnitude sensitivity to be parsed apart,

respectively. Each session consisted of 60 trials and lasted until all trials were completed or 2 hr elapsed. A 10-s interval began each session before the rats were presented with forced and free choice trials, randomly intermixed throughout the session. On free choice trials, the rats were presented with a choice between two levers, SS versus LL, with lever assignments counterbalanced across rats. After the initial press, a delay to the reward was initiated and the first response after the delay caused the lever to retract, food to be delivered, and a 90-s ITI to begin. There was a forced choice block at the beginning of each session where rats received 4 SS forced-choice trials and 4 LL-forced choice trials. After the forced choice block, there were 54 trials randomly intermixed (42 free-choice trials, 6 SS forced-choice trials, and 6 LL forced-choice trials).

For the delay manipulation, the SS choice always delivered 2 pellets and the LL reward always delivered 5 pellets. There were 12 sessions where the delays were changed. For the magnitude manipulation, the SS delay was always 10 s and the LL delay was always 25 s. There were 12 sessions where the magnitudes changed. The SS lever was switched before beginning the magnitude manipulation in the impulsive choice task. The parameters and number of session for the delay and magnitude manipulations are in Table 3.2.

Buffer task. A modification of the initial training was used in between each task to minimize the carryover effects from one task to another (Wang, Marshall, & Kirkpatrick, 2017). It consisted of three sessions. The first session delivered FR1 → RR3 → RR5 schedules where each schedule was one block with 20 reinforcers earned on each lever, constituting three blocks in total. The last two sessions consisted of three blocks of RR5 with 20 reinforcers on each lever per block. A 5-min inter-block interval (IBI) was delivered for both sessions.

Physiological Measures

Rats completed all behavioral testing before beginning the physiological testing. To measure insulin sensitivity, rats completed an oral glucose tolerance test after an 18 hr fast. This test measures postprandial response to glucose by collecting blood at several time points. A glucose tolerance test beverage (Fisherbrand, 40-102-5FB) was administered by oral dosing via syringe at a dose of 1.2 g carbohydrates/kg of body weight. Habituation commenced after completion of all behavioral testing to ensure the rats would consume the beverage quickly during the oral glucose tolerance test. Rats were administered 2 mL of the beverage via a syringe for 2 days prior to the oral glucose tolerance test. Before consumption and 15, 30, 60, and 120 min after consumption (Berthiaume & Zinker, 2002), blood was drawn from the tail using a tail snip to measure glucose with a Bayer contour glucose meter. Only glucose levels were obtained at each of the time points following consumption because this blood sampling procedure did not result in enough blood for additional samples. Before administration of the glucose, 0.3 mL of blood was collected from the tail, blood samples were centrifuged and plasma was be stored at -80° C. The samples were shipped to the Radioimmunoassay and Biomarkers Core of the University of Pennsylvania Diabetes Research Center (DRC) to determine the amount of IL-6 in the plasma using enzyme-linked immunoassay (ELISA) kits (r6000B). All samples were below the level of detection (62.5 pg/ml), so we were not able to determine IL-6 levels from the samples.

A Lunar PIXImus small animal densitometer (Lunar-General Electric, Madison, WI) measured body fat percentage to confirm the dietary effects on body composition. Rats received a fatal dose (1 ml) of pentobarbital sodium and the scan was completed while they were deeply anesthetized. Because this piece of equipment was specific for small animals (i.e. mice), the

measurements focused on abdominal fat stores, as visceral adipose tissue in the abdomen increases the risk of obesity-related diseases (Bjorndal, Burri, Staalesen, Skorve, & Berge, 2011). The region of interest spanned the abdomen from the 12th rib to the top of the pelvic girdle.

Data analysis. All analyses were conducted in R (version 3.5.3). To confirm the effects of diet on each of the physiological variables and determine whether the physiological variables were related, a series of regressions were performed (see Physiological variables). Further, moderation analyses were conducted to determine if physiological variable interact with diet to predict impulsive choice behavior (see Physiological variables and impulsive choice). For all analyses, diet was effect coded (C=1; F=-1). Other scaling and analysis approaches are described below.

Impulsive choice. Impulsive choice behavior on the delay and magnitude manipulation were modeled through separate analyses to parse apart preference and sensitivity to delay or magnitude. Generalized mixed effects logistic regressions were conducted using the lme4 package in R. The SS delay was scaled so that the intercept represented the largest difference between delays (SS/LL-5/25), or a preference for the shorter delay. The LL magnitude was scaled so that the intercept represents the largest difference between magnitudes (SS/LL-1/5), or a preference for the larger magnitude reward. Delay and magnitude ratio were included as continuous variables to test for delay and magnitude sensitivity. Intercept and delay (or magnitude) ratio were tested as possible random effects. While the models including intercept and ratio as random effects were the best based on the Akaike Information Criterion (AIC; Burnham & Anderson, 2002), the intercept only model was used in all analyses to avoid over-parameterization because as the intercept and slope were significantly correlated ($r_s > .54$).

Physiological variables. Body fat percentage in the abdomen as measured by the DEXA scan was used in the body fat analysis. Fasting glucose and glucose incremental area under the curve (iAUC) from the oral glucose tolerance test were used in the glucose response analyses. Diet was tested as a predictor of each of the physiological factors (body fat percentage, fasting glucose, glucose response) using a linear regression. Correlations were also conducted to determine how the physiological factors were related. Each of the key factors was continuous. Body fat was log-transformed and glucose iAUC was square root-transformed to normalize the measures.

Physiological variables and impulsive choice. Moderation analyses were conducted to determine if any of the physiological variables (body fat percentage, fasting glucose, and glucose response) altered the size or direction of the effect of diet on impulsive choice. Generalized mixed effects logistic regressions were conducted using the lme4 package in R. Glucose response was quantified by the incremental area under the curve (iAUC). In the moderation analyses, the physiological variables were tested as moderators through separate models using a theory-driven approach. The fixed effects included the interaction between each physiological variable (body fat percentage, fasting glucose, glucose response), dietary condition, and delay or magnitude ratio. The two-way interaction (e.g., Body Fat Percentage $\times$ Diet) indicates whether body fat percentage moderated the effects of diet on preference for shorter delay/larger magnitude. The three-way interaction (e.g., Body Fat Percentage $\times$ Diet $\times$ Delay or Magnitude Ratio) indicates whether body fat percentage moderated the effects of diet on sensitivity to delay/magnitude. Each of the physiological variables was mean-centered. Coefficient comparisons were conducted on significant three-way interactions with the emmeans package in

R. The 1st quartile, mean, and 3rd quartile values were used to probe the slopes within each group. Only the slopes within each group were compared.

Results and Discussion

Dietary effects

Impulsive choice: delay

Rats overall made more SS choices at the intercept (delay ratio = 0.2), $z = -3.82$, $p < .001$, $b = -0.65$, $SE = .17$. There was a main effect of group such that Group C made significantly more LL choices than Group HF when the delays were maximally different (ratio = 0.2), $z = 3.30$, $p < .001$, $b = 0.56$, $SE = .17$. Rats fed a high-fat diet had a greater preference for the shorter delay, replicating previous research (Steele et al., 2017). There was a significant effect of delay ratio, such that rats made more LL choices as the delays became more similar, $z = 40.10$, $p < .001$, $b = 4.40$, $SE = .11$. However, there were no group differences in slope, $z = -0.83$, $p = .41$, $b = -0.09$, $SE = .11$ (Figure 3.2, A), indicating that there were no group differences in delay sensitivity contrary to previous findings (Steele et al., 2019; Steele et al., 2017). The null findings for the dietary effects on delay sensitivity may be a result of the parameters or shortened nature of the current tasks. The current task used a larger number of delay combinations. The task in the present experiment also changed delays after 2 days of exposure, while rats experienced each delay for 15 or more days in previous experiments (Steele et al., 2019; Steele et al., 2017). The group differences in delay sensitivity might be affected by learning and acquisition of the task. Indeed, short and long-term consumption of high-fat diets in rats results in learning and memory deficits on a variety of tasks (Cordner & Tamashiro, 2015). If rats fed a high-fat diet take longer to learn the task parameters, then the shortened task used in the current study could limit their ability to adjust their behavior to the new parameters. Therefore, the HF group may have had a

steeper slope in previous experiments because the rats had more time to learn the delays and adjust their behavior. Overall, a HF diet increased impulsive choice as demonstrated by a greater preference for the shorter delay, or an inability to delay gratification.

Impulsive choice: magnitude

Rats overall made more LL choices at the intercept (magnitude ratio = 0.2), $z = 9.91$, $p < .001$, $b = 1.64$, $SE = .17$. There was no main effect of group, $z = 1.17$, $p = .24$, $b = 0.19$, $SE = .17$. This suggests that there are no group differences in preference for the larger magnitude when the magnitudes were maximally different. There was a significant effect of magnitude ratio, such that rats made fewer LL choices as the magnitudes became more similar, $z = -34.85$, $p < .001$, $b = -3.75$, $SE = .11$. There was a significant Group $\times$ Magnitude Ratio interaction such that the control group had shallower slopes than the HF group, $z = 3.89$, $p < .001$, $b = 0.42$, $SE = .11$ (Figure 3.2, B). Therefore, rats fed a high-fat diet had greater magnitude sensitivity than the control group. Previous studies have found that high-fat diets result in lower magnitude sensitivity compared to the control group (Steele et al., 2019). Despite the differences in slopes, the high-fat rats made more SS choices, consistent with Steele et al. (2019). The task differences could explain the different findings in these two studies. The SS magnitude was manipulated in this study, while the LL magnitude was manipulated in the previous study (Steele et al., 2019). Previous research has found differences in impulsive choice depending on magnitude order (Smith, Peterson, & Kirkpatrick, 2016). In addition, the effects of amphetamine on impulsive choice depends on how the parameters are manipulated (Maguire, Henson, & France, 2014). It is possible that the same is true of dietary effects on impulsive choice. In addition, the shortened task could have affected these outcomes because the rats did not have as much time to adjust to

the changes in magnitude. Overall, the high-fat diet resulted in greater magnitude sensitivity under the current set of parameters and testing conditions.

Physiological variables

The dietary effects on the physiological variables are shown in Table 3.3. All physiological measures were obtained after completion of behavioral testing. There were significant group differences in body fat percentage (log-transformed), body weight, and fasting glucose, such that Group HF had higher body fat percentages, body weights, and fasting glucose levels, consistent with our previous research (Figure 1.2 and Figure 1.3) and previous literature (Posey et al., 2009). Therefore, body fat percentage and fasting glucose may help to explain the dietary effects on impulsive choice. There were no group differences in glucose response as measured by glucose iAUC following a glucose load suggesting that rats fed a high-fat diet were still glucose tolerant following long-term exposure to a high-fat diet. It is possible that the calorie restriction imposed to ensure motivation to work in the operant chambers was protective against deficits in glucose response (Larson-Meyer et al., 2006; Wing et al., 1994). Indeed, previous research has found that rats fed a high-fat diet with matched calories to the low-fat diet did not show differences in glucose tolerance (Posey et al., 2009).

Individual differences

Body weight was not correlated with body fat percentage, $r = .13$, $p = .39$ (Figure 3.3, A), suggesting that body weight and body fat percentage may be detecting different stages of obesity. Specifically, rats may show differences in body fat percentage before showing differences in body weight. Previous research has shown that rats fed a high-sugar diet did not differ from control rats in body weight, but the rats fed a high-sugar diet had higher body fat percentages (Steele et al., 2019). Therefore, changes in body composition may occur prior to

changes in weight status. It has also been proposed that body fat percentage is primarily under the control of diet, while body weight is more affected by genetics in rats (Schemmel, Mickelsen, & Gill, 1970). Altogether, body weight may not be the best measure of obesity given that body weight was not correlated with body fat percentage.

Body fat percentage was correlated with fasting glucose, $r = .46$, $p = .001$ (Figure 3.3, B). Glucose iAUC was not correlated with body fat percentage, $r = .22$, $p = .14$ (Figure 3.3, C) or fasting glucose, $r = -0.04$, $p = .81$ (Figure 3.3, D). Previous research has shown that glucose iAUC is associated with body fat percentage (Posey et al., 2009). However, the high-fat diet did not induce changes in glucose iAUC, so this may explain the lack of correlation between glucose iAUC, body fat percentage, and fasting glucose. While fasting glucose levels and glucose iAUC are measuring two aspects of the glucose system, individuals can have high fasting glucose levels and an intact glucose response (Nathan et al., 2007). Therefore, there does not necessarily have to be a relationship between fasting glucose and glucose iAUC. Altogether, the two factors that were affected by diet (body fat percentage and fasting glucose) were related.

Physiological moderators

Body fat percentage, fasting glucose, and glucose response were analyzed in separate models. The models included the fixed effects of Group (Control vs. High Fat), Delay (or Magnitude) Ratio, and Body Fat Percentage (or Fasting Glucose or Glucose Response). Intercept was included as a random effect. The full model output for body fat percentage (Table 3.4), fasting glucose (Table 3.5), and glucose response (Table 3.6) are included, and significant findings are discussed below.

Body fat percentage

Body fat percentage and diet interacted to predict delay sensitivity (Figure 3.4, A). Coefficient comparisons indicated that sensitivity to delay (the slope of the choice function) increased systematically from lower, $b = 4.31$, to higher body fat percentages, $b = 6.43$, for the control group, $z = -5.38$, $p < .001$, as seen in Figure 3.4. Higher slopes are associated with steeper delay discounting. The slope effects are consistent with previous literature demonstrating that obesity is associated with steeper delay discounting (Barlow et al., 2016). However, sensitivity to delay decreased from lower, $b = 6.37$, to higher body fat percentages, $b = 4.70$, for the high-fat group, $z = 5.56$, $p < .001$, and the rats with the highest body fat percentages in both groups tended to make more LL choices, although this was not significant.

The current findings are in contrast to the trend found when further analyzing the data in Steele et al. (2019). An exploratory analysis of the interaction between diet and body fat percentage in Steele et al. (2019) indicated that rats with higher body fat percentages had greater delay sensitivity if they were fed a high-fat diet. The different trends may be a result of the shortened task. It is possible that high amounts of body fat exasperate the diet-induced deficits in learning and memory (Cordner & Tamashiro, 2015), which could have made it more difficult for them to learn the parameters in the current study. Overall, body fat percentage interacted with diet to affect delay sensitivity differentially depending on diet.

Diet and body fat percentage interacted to predict magnitude sensitivity (Figure 3.4, B). Coefficient comparisons indicated that sensitivity to magnitude decreased from lower, $b = -6.14$, to higher body fat percentages, $b = -4.42$, for the high-fat group, $z = -5.49$, $p < .001$. However, sensitivity to magnitude did not change significantly from lower, $b = -3.29$, to higher body fat

percentages, $b = -3.80$, for the control group, $z = 1.52$, $p = .28$. Therefore, rats fed a high-fat diet and with higher body fat percentages showed lower magnitude sensitivity.

Impulsive choice is characterized by high delay sensitivity and low magnitude sensitivity (Wileyto et al., 2004; Young, 2018). Overall, higher body fat percentage was associated with high delay sensitivity for the control rats and low magnitude sensitivity for the high-fat rats suggesting that body fat percentage and dietary fat intake interact to predict different aspects of impulsive choice. The analysis technique used allows for these aspects of impulsive choice to be parsed. We expected that higher body fat percentages would exaggerate the dietary effects on impulsive choice (e.g. higher delay and lower magnitude sensitivity). While our hypothesis was partially confirmed, deficits in learning may explain the opposite effect for delay sensitivity as outlined previously (Cordner & Tamashiro, 2015). Although, the control rats exhibited the relationship between delay sensitivity and body fat percentage that is seen in humans (Barlow et al., 2016). It is also the case that preexisting differences in body fat percentage were not investigated. We did not have a baseline assessment of body fat percentage, so preexisting differences in body fat or amount of fat gained could explain susceptibility to dietary effects on impulsive choice or obesity. Future research should investigate how preexisting differences in body fat percentage affect susceptibility to diet-induced obesity and impulsivity.

Fasting glucose

Diet and fasting glucose interacted to predict delay sensitivity (Figure 3.5, A). Coefficient comparisons indicated that sensitivity to delay decreased from lower, $b = 5.55$, to higher fasting glucose levels, $b = 4.39$, for the HF group, $z = 4.30$, $p < .001$. However, sensitivity to delay did not change significantly from lower, $b = 4.20$, to higher fasting glucose levels, $b = 4.54$, for the control group, $z = -1.22$, $p = .42$. The results indicate that rats with higher fasting glucose had

reduced delay sensitivity for the HF group. These results for the high-fat group are consistent with the effects reported in the body fat percentage section. The consistent effects may stem from the correlation between body fat percentage and fasting glucose whereby this constellation of effects promotes deficits in learning and memory. Indeed, high fasting glucose levels are associated with impairments in memory in non-human primates (Djelti et al., 2017). Therefore, obtaining stability in choice behavior may take more time and be especially critical in studies utilizing a high-fat diet. Future research should investigate the relationship between diet, physiology, and impulsive choice when stable responding has been obtained to ensure that the rats have learned the task parameters and are making an informed choice.

Diet interacted with fasting glucose levels to predict magnitude sensitivity (Figure 3.5, B). Coefficient comparisons indicated that sensitivity to magnitude increased from lower, $b = -3.09$, to higher fasting glucose levels, $b = -3.76$, for the control group, $z = 2.75$, $p = .02$. However, sensitivity to magnitude did not change significantly from lower, $b = -4.69$, to higher fasting glucose levels, $b = -4.11$, for the high-fat group, $z = -2.07$, $p = .10$. While there were similar patterns for fasting glucose and body fat percentage for delay sensitivity, these patterns were not the same for magnitude sensitivity. Therefore, the connection between body fat percentage and fasting glucose may point to a mechanism by diet affects delay sensitivity.

Glucose response

Diet interacted with glucose iAUC to predict delay sensitivity (Figure 3.6, A). Coefficient comparisons indicated that sensitivity to delay decreased from lower, $b = 5.35$, to higher glucose iAUCs, $b = 3.70$, for the control group, $z = 8.56$, $p < .001$. However, sensitivity to delay did not change significantly for the HF group from lower, $b = 4.44$, to higher glucose iAUCs, $b = 4.53$, $z = -0.50$, $p = .87$. Glucose iAUC also moderated the effect of diet on magnitude sensitivity

(Figure 3.6, B). Coefficient comparisons indicated that sensitivity to magnitude was increased from lower, $b = -2.72$, to higher glucose iAUCs, $b = -4.48$, for the control group, $z = 10.03$, $p < .001$. However, magnitude sensitivity did not significantly change for the high-fat group from lower, $b = -4.29$, to higher glucose iAUCs, $b = -4.08$, $z = -1.09$, $p = .52$. Altogether, higher glucose iAUC was associated with lower delay sensitivity and higher magnitude sensitivity for the control group indicating fewer impulsive choices. It is possible that glucose iAUCs may not be associated with disease state for the control group given that the means were in the normal range (Table 3.3). Given that insulin is critical for food intake, higher glucose iAUCs may suggest that insulin is lower which can alter food intake (Posey et al., 2009). Future research should investigate how insulin alters impulsive choice.

Overall summary

The overall effects of the HF diet in the current study differed from previous investigations, which reported that the HF diet increased delay sensitivity (Steele et al., 2019; Steele et al., 2017). The present study did not find any effect on delay sensitivity, but instead reported an overall increase in impulsive choices. It is possible that this is a result of learning and memory deficits as HF diets are associated with cognitive deficits due to impairments of hippocampal functioning (Cordner & Tamashiro, 2015). The present task provided more limited experience on each set of choice parameters so that we could collect a larger number of choice parameter values to better correspond with the human choice task. The HF rats may not have been able to fully learn the choice parameters to generate asymptotic choice behavior. Examining the role of learning and memory processes in impulsive choice could be a fruitful avenue for future research.

Moderation analyses were conducted to determine whether the physiological factors measured (body fat percentage, fasting glucose, and glucose response) changed the strength or direction of the dietary effects on impulsive choice. While the high-fat diet increased preference for the immediate option, none of the physiological factors affected preference for the more immediate option. This could be because the HF diet was creating more homogeneous choice functions by driving choices towards the SS, which could impair the ability to detect individual differences. Causal methodology should be used to determine how physiological variables might be affecting choice. For example, administering insulin to determine if diet-induced impulsive choice is reduced could suggest that insulin signaling is interacting with diet. The current study provides correlational evidence that dietary fat intake and physiological variables are related to impulsive choice, and future research should expand on these findings to determine the direction of the relationship.

Overall, long-term exposure to a high-fat diet led to higher body fat percentages and fasting glucose levels as well as deficits in impulsive choice. There was an interaction between physiological variables and impulsive choice. We expected that higher body fat percentages and higher fasting glucose levels would exaggerate the dietary effects on impulsive choice leading to greater sensitivity to delay and lower sensitivity to magnitude. However, we only partially supported our hypothesis given that greater disruptions in these variables were associated with lower sensitivity to delay and magnitude in the high-fat group. This suggests that body fat percentage and dietary fat intake primarily affect the magnitude aspect of impulsive choice. Future research should better understand the circumstances under which dietary fat intake and body fat percentage interact to predict impulsive choice.

Differences in reward value may explain the opposite effects for the control and high-fat group due to the nature of the food pellets used in the behavioral tasks. The control group earned reinforcers that had more sugar (25% monosaccharides and disaccharides) than the chow received in the home cage. It is possible that the pellets earned in the study were more palatable than the home cage diet, which may have resulted in increased preferences for larger rewards. On the other hand, the pellets earned in the choice task may have been less palatable than the home cage diets in the HF group due to their lower fat content. Indeed, a previous study found that HF diets resulted in reduced willingness to work for food pellets and led to greater preference for fat over sugar (Steele et al., 2019). Together, this suggests that rats fed a high-fat diet may not value the reinforcers in the behavioral testing chamber as much as the food received in the home cage. The altered valuation of reinforcers may also interact with the physiological variables. Future research should investigate how different types of reinforcers alter the expression of the dietary effects on impulsive choice.

For the control group, higher body fat percentages were predictive of greater delay sensitivity as expected based on the relationship between body fat percentage and impulsive choice in humans (Rasmussen et al., 2010). In addition, higher fasting glucose levels were predictive of greater magnitude sensitivity. Higher glucose iAUCs predicted lower delay sensitivity and greater magnitude sensitivity. Therefore, for the control group, higher fasting glucose levels and higher glucose iAUCs were predictive of less impulsive choices. It is possible that higher fasting glucose levels and glucose iAUCs may not be associated with a disease state in the control group given that the means were in the normal range (Table 3.3). Given that insulin is critical for food intake, higher fasting glucose levels and higher glucose iAUCs may suggest that insulin is lower altering performance on the impulsive choice for food (Posey et al.,

2009). Future research should investigate how insulin alters impulsive choice. Overall, physiological factors interacted with dietary fat intake to predict impulsive choice, and the direction of the relationship between physiology and impulsive choice depended on dietary history.

Human model

Method

Participants. Sixty participants (68% Caucasian) were recruited through flyers and news releases in Riley County, Kansas. Participants were screened based on diet and physical activity as described in the procedure section. The sex, age, and physical activity characteristics of the groups is in Table 3.7. Participants were compensated with a DEXA scan (\$250 value) plus \$20 at the completion of the experiment. The study was approved by the Institutional Review Board at Kansas State University.

Procedure. The overall procedure is depicted in Figure 3.1. Participants completed an online screening and two test sessions. As part of the screening process, participants completed the informed consent form and the International Physical Activity Questionnaire (IPAQ). Following this initial online survey, participants completed the Automated Self-Administered 24-Hour (ASA24) Dietary Assessment Tool for three days (two week days and one weekend day). Participants were placed into Groups C and HF based on the percentage of calories consumed from fat. The original plan was to match the rat macronutrient break down, such that Group HF would consist of participants who reported consuming >50% of their calories from fat. However, after collecting 30 responses of screening data, none of the participants consumed more than 50% of their calories from fat. Given this constraint, thirty participants completed all three days of the ASA24 food recall, and we used these data to create an extreme groups design.

The first quartile was used as the cut off for Group C and the third quartile was used as the cut off for Group HF. Therefore, Group HF must have consumed 40% or more of their calories from fat. The C group must have consumed less than 35% of their calorie from fat, which is the recommended amount ("2015–2020 Dietary Guidelines for Americans," 2015). A breakdown of the dietary group's macronutrient consumption is in Table 3.8.

The IPAQ was used to control for physical activity across the two groups using a matched groups design. People with high levels of physical activity have lower levels of inflammation (Teeman et al., 2016), and exercise decreases impulsive choice (Sofis, Carrillo, & Jarmolowicz, 2017; Strickland, Feinstein, Lacy, & Smith, 2016), so the matched groups assignment controlled for exercise in our diet groups.

For both testing sessions, the participants reported the time of their last meal at the beginning of the session. For the first testing session, participants were instructed not to eat anything for 4 hr before the session. Upon arrival, participants completed the impulsive food choice test. For the second testing session, participants were instructed not to eat anything for 10 hr before the session. Upon arrival, an indwelling catheter was placed for the oral glucose tolerance test (OGTT), which took approximately 2.5 hr. At the end of the session, the DEXA scan was completed.

Measures

Dietary assessment. Participants completed the Automated Self-Administered 24-Hour (ASA24) Dietary Assessment Tool, online dietary 24 hr recall, for three days (2 week days and 1 weekend day). The participants were given a unique ID and password, and they logged in to the website to report the food and drink they consumed the prior day. The average percentage of

calories from protein, fat, carbohydrates, added sugar, and saturated fat across the 3 days of recall were calculated for dietary assignment.

International Physical Activity Questionnaire (IPAQ). The IPAQ: Short Last 7 Days Self-Administered Format was administered as part of the screening processes. The IPAQ includes 4 questions about the kinds of physical activities completed in the last 7 days. For example, participants were asked how many days they did vigorous activity and how long they typically spent doing that type of activity on those days. In addition, participants reported how much time they typically spent sitting during the week. Multiples of the resting metabolic rate (MET) were obtained and multiplied by the minutes performed to obtain MET-minutes, a measure of physical activity

Impulsive choice tasks. The real reward impulsive food choice task (Chapter 2, Measures) and the Kirby questionnaire (Chapter 2, Measures) were used to measure impulsive choice.

Oral glucose tolerance test (OGTT). The test was performed after a 10 hr overnight fast (no food or beverages other than water). For example, if the participant came in for testing at 7:00AM, then he/she needed to finish any eating by 9:00PM the evening before. An indwelling catheter was placed to collect blood at the start of the visit before consuming a glucose tolerance test beverage (Fisherbrand, 40-102-5FB) and was used for blood collection throughout the 2-hr test. Before consumption and 15, 30, 45, 60, 90, and 120 min after consumption, blood was drawn from the indwelling catheter with approximately 5 mL being drawn at each time point. Blood samples were centrifuged and plasma was stored at -80° C. The samples were shipped to the Radioimmunoassay and Biomarkers Core of the University of Pennsylvania Diabetes Research Center (DRC) to determine amount of insulin, C-peptide, and IL-6 in the plasma using

radioimmunoassay kits (EMD Millipore, St Louis MO). Glucose was measured with a Bayer contour glucose meter. This test allows for insulin sensitivity and insulin secretion to be parsed apart using glucose, insulin, and C-peptide to determine if there are disruptions in the insulin system (Cobelli et al., 2014). Inflammation levels were determined using the fasting blood sample collected during the oral glucose tolerance test by measuring IL-6.

Body fat percentage. Body fat percentage of the full body was measured by dual-energy X-ray absorptiometry (GE prodigy, Lunar-General Electric, Madison, WI). Participants were asked to remove any metal (jewelry, belts, etc) and shoes before lying down in a supine position for approximately ten minutes while the DEXA scanned the individual. Participants were instructed to lay still for the duration of the scan.

Data analysis. All analyses were conducted in *R* (version 3.5.3). To determine if there were group differences in each of the physiological variables and determine whether the physiological variables were related, a series of regressions were performed. Further, moderation analyses were conducted to determine how the physiological factors interact with diet. These regressions were the same as described in the rat model.

Impulsive choice.

The same approach used in the rat model was used for the human model. While the model including slope as a random effect was better than the intercept only model, the slope and intercept were highly correlated, so only intercept was included as a random effect to avoid over-parameterization. We also tested to see whether sex and half were significant predictors of choice. Half referred to the first and second half of the task; the choice parameters were distributed equally across two halves to determine whether consumption during the real food choice task affected choices in the second half of the task. For delay ratio, the model that

included half was only .4 AIC points better than the model that did not include sex or half. The model that included sex was 3.5 AIC points worse than the model that did not include sex or half. Therefore, the intercept model without sex or half was used in subsequent analyses. For magnitude ratio, the model that included half was .3 points better than the model that included sex. The model that did not include sex or half was worse by 1.2 points. The AICs are similar and these variables are not theoretically meaningful so as to justify their inclusion; there would need to be a clear improvement in AIC value for these variables to be included in the model (Symonds & Moussalli, 2011). Thus, the intercept model without sex or half was used in subsequent analyses.

Physiological variables and impulsive choice. Moderation analyses were conducted to determine if any of the physiological variables (body fat percentage, fasting glucose, insulin sensitivity, insulin secretion, and inflammation) altered the size or direction of the effect of diet on impulsive choice. The approach used in the rat model for the moderation analyses were used in the human model. Insulin sensitivity was derived using the ogttMetrics package in R (Stubbs et al., 2017). Insulin secretion was measured using the postprandial C-peptide-to-glucose ratio (PCGR) by dividing incremental area under the curve (iAUC) for C-peptide by the iAUC for glucose (Lee et al., 2014). Coefficient comparisons were conducted using the emmeans package in R.

Results and Discussion

Dietary effects

Impulsive choice

For the delay model, there was no main effect of group, $z = -0.67$, $p = .51$, $b = -0.11$. There was a significant effect of delay ratio, such that participants made more LL choices as the

delays became more similar, $z = 4.54$, $p < .001$, $b = 1.30$. There were no group differences in slope, $z = -0.54$, $p = .59$, $b = -0.15$ (

Figure 3.7, A). For the magnitude model, there was no main effect of group, $z = -1.49$, $p = .14$, $b = -0.24$. There was a significant effect of magnitude ratio, such that participants made more SS choices as the magnitudes became more similar, $z = -4.34$, $p < .001$, $b = -1.24$. There were no group differences in slope, $z = 0.99$, $p = .32$, $b = 0.32$ (

Figure 3.7, B). Overall, dietary fat consumption as measured by a 24-h recall did not predict impulsive choice. This may be a result of the short-term nature of the dietary assessment. Research investigating the dietary effects on impulsive choice and cognition in rodents typically examine the effects of long-term diet on behavior (Pistell et al., 2010; Steele et al., 2019; Steele et al., 2017). Investigating diet over the past year may better approximate the results found in rats.

It is also possible that the types of fat are important for predicting impulsive choice. Our rats consumed a diet high in processed, saturated fat (13.6% of calories) mainly from lard, whereas the high-fat group in humans only consumed 6.7% of their calories from saturated fat. There is evidence in rats that a very high-fat diet consisting of lard produced cognitive impairments, while a diet consisting of 41% of the calories from fat did not disrupt cognition (Pistell et al., 2010). The diets utilized in Pistell et al. (2010) also had different types of fat, which may influence how dietary fat affects behavior. It has been proposed that the high amount of fat from lard results in neuroinflammation, which affects behavior (Pistell et al., 2010). The people in the high-fat group consumed 45% of their calories from fat on average, with a small proportion being from saturated fat, suggesting that their diet might not result in cognitive impairments. Therefore, the macronutrient composition and the type of fat could have differential effects on behavior. Future research should investigate the complexities of a high-fat diet to better understand how fat consumption might affect impulsive choice. It is also important to note that the sample used in the current study may have more healthful diets than the typical population because Riley County is fairly affluent and well educated, with many of the participants being staff, students, and faculty at Kansas State University. Indeed, more than 50% of the participants consumed between 1500 and 2500 calories suggesting that most of the

participants were consuming calories within the dietary guidelines and consistent with their metabolic rates. These factors likely affect the types of fats the participants consume. It is possible that people from areas with higher amounts of food insecurity or with less of an emphasis on education may exhibit different dietary patterns.

We conducted an exploratory analysis on the percentage of calories from added sugar. based on our previous research in rats that has shown that diets high in added sugar induced a greater preference for the shorter delay as seen in Figure 1.1 (Steele et al., 2019; Steele et al., 2017). There were a significant interaction between percentage of calories from added sugar and delay ratio, such that delay sensitivity increased from lower, $b = -2.01$, to higher, $b = 4.68$, amounts of added sugar, $z = 4.21$, $p < .001$, $b = 2.66$, $SE = .63$ (Figure 3.8, A). For the magnitude task, there was a main effect of percentage of calories from added sugar, $z = 3.11$, $p = .002$, $b = 1.08$, $SE = .35$. This suggests that people who consume more added sugar have a greater preference for the larger magnitude when the magnitudes were maximally different. There was a significant Added Sugar $\times$ Magnitude Ratio interaction such that magnitude sensitivity increased as percentage of calories from added sugar went from lower, $b = 2.31$, to higher, $b = -4.86$, amounts of sugar, $z = -4.49$, $p < .001$, $b = -2.86$, $SE = .64$ (Figure 3.8, B). Therefore, percentage of calories from added sugar predicted greater delay sensitivity and great magnitude sensitivity on an impulsive choice for food suggesting that people who consume more sugar are unwilling to wait for the reward, yet also want the larger reward.

The type of food reward received during the task could affect behavior on these tasks. The rats chose between different amounts of grain pellets, whereas the humans made choices about different amounts of M&Ms. For the HF rats, they earned a reward that was likely lower value than their home cage diet. For the humans, they earned a food type that is likely greater in

value than the average value of their daily food intake, particularly for the control group. This difference in reward type could be critical for understanding how diet interacts with physiology to predict impulsive choice. It is also important to note that people who consume low amount of sugar did not perform as would be expected on the impulsive choice task as indicated by the negative slope for delay ratio. It is possible that people who consume small amounts of sugar in their regular diet were not motivated by the parameters of the task. Participants indicated that they enjoyed M&Ms in order to participate in the study. However, they may not have enjoyed consuming the rewards during the task. Together, this suggests that people who consume low amounts of sugar may not value the reinforcers in the task. This valuation of reinforcers may also interact with the physiological variables. Future research should investigate how different types of reinforcers alter the relationship between diet and impulsive choice.

Physiological variables

There were no group differences in body fat percentage, body mass index (BMI), fasting glucose, insulin sensitivity, insulin secretion, or inflammation (Table 3.7). We predicted that there would be differences between the two dietary groups, such that the high-fat group would have higher body fat percentages, higher BMIs, higher fasting glucose levels, lower insulin sensitivity, higher insulin secretion, and higher inflammation given previous research connecting diet to these variables (Esposito & Giugliano, 2006; Posey et al., 2009). The fact that we did not find group differences in the physiological measures for humans may explain why we did not find the dietary effects on impulsive choice that we observed in rats.

It is possible that the short-term diet did not reflect dietary history even though research suggests that people have stable dietary patterns over a two-year period (Borland, Robinson, Crozier, & Inskip, 2008). It is also possible that we did not see differences because human diets

are varied and not under experimental control. We did not account for types of fat (saturated versus unsaturated) or sources of fat (avocados versus processed oils). Further, the proportion of calories from fat was not as distinct across groups in the humans (>40%) as compared to the rats (48%). The small difference in average intake between the groups in humans may explain why group differences in impulsive choice were not observed. Future research should investigate these complexities to determine if there are aspects of a high-fat diet that best predict disruptions in physiology and cognition in humans.

Kirby questionnaire

Group, $t = 1.30$, $p = .2$, did not predict performance on the Kirby questionnaire consistent with the finding that dietary fat intake did not predict performance on the real food impulsive choice task.

Individual differences

The correlation between the physiological variables is shown in Figure 3.9. Body fat percentage and BMI (inverse transformed) were negatively correlated, $r = -0.57$, $p < .001$ (Figure 3.9, A), such that higher body fat percentages were associated with higher BMIs. Note that the negative relationship is a result of the transformation of BMI for analysis purposes. This is consistent with previous research showing that BMI is correlated with body fat percentage as measured by a DEXA scan (Adab et al., 2018). While these two measures of obesity were significantly correlated, the moderate correlation could explain the fact that some studies find that BMI is related to impulsive choice, while others only find that body fat percentage is related to impulsive choice (Barlow et al., 2016).

Body fat percentage was positively correlated with inflammation levels, $r = .54$, $p < .001$ (Figure 3.9, E), consistent with the hypothesis that body fat may be a source of inflammation

(Esposito & Giugliano, 2006). Fasting glucose levels were negatively associated with insulin sensitivity indicating that those with higher fasting glucose had worse insulin sensitivity, $r = -0.32$, $p = .02$ (Figure 3.9, F). While fasting glucose and low insulin sensitivity often co-occur, there are independent consistent with the weak correlation (Nathan et al., 2007). No other physiological variables were correlated, $ps > .08$. Given the Esposito and Giugliano (2006) model, we would have expected to see a relationship between body fat percentage and insulin signaling as well as a relationship between inflammation and insulin signaling.

Performance on the real food impulsive choice task was not related to impulsive choice as measured by the Kirby questionnaire, $rs < .05$, $ps > .69$. This is consistent with the results from Chapter 2 (Figure 2.5). Altogether, this suggests that the real food impulsive choice task and the Kirby questionnaire are not measuring the same construct possibly as a result of the reward durations, amounts, or type. In addition, the hypothetical versus experiential aspect of the choice task could alter behavior. Future research should disentangle the key variables that affect performance on these tasks.

Physiological moderators

All physiological measures were analyzed in separate models to determine how they interacted with dietary fat intake to predict impulsive choice. The models included the fixed effects of Group (Control vs. High Fat), Delay (or Magnitude) Ratio, and Body Fat Percentage (or Fasting Glucose or Insulin Sensitivity or Insulin Secretion or Inflammation). Intercept was included as a random effect. The full model outputs for body fat percentage (Table 3.10), fasting glucose (Table 3.11), insulin sensitivity (Table 3.12), insulin secretion (Table 3.13), and inflammation (Table 3.14) are included in tables, and significant findings are discussed below. In

addition, group did not interact with any of the physiological variables to predict impulsive choice as measured by the Kirby questionnaire, $t_s < 1.80$, $p_s > .08$.

Body fat percentage

Body fat percentage interacted with dietary fat intake to predict delay sensitivity (Figure 3.10, A). Coefficient comparisons indicated that sensitivity to delay increased from lower, $b = 0.43$, to higher body fat percentages, $b = 2.59$, for the high-fat group, $z = -3.33$, $p = .003$. This is consistent with previous literature demonstrating that obesity is associated with steeper impulsive choice functions, or higher k -values (Barlow et al., 2016). However, sensitivity to delay did not change significantly from lower, $b = 0.98$, to higher body fat percentages, $b = 1.30$, for the control group, $z = -0.61$, $p = .82$. Therefore, body fat percentage interacted with dietary fat intake to affect delay sensitivity.

Body fat percentage predicted preference for the larger magnitude such that people with high body fat percentages had a higher preference for the larger reward, $b = 0.55$, than people with lower body fat percentages, $b = 0.05$. Body fat percentage interacted with dietary fat intake to predict magnitude sensitivity (Figure 3.10, B). Coefficient comparisons indicated that sensitivity to magnitude increased from lower, $b = -0.32$, to higher body fat percentages, $b = -2.90$, for the high-fat group, $z = 3.89$, $p < .001$. However, sensitivity to magnitude did not change from lower, $b = -0.71$, to higher body fat percentages, $b = -1.20$, for the control group, $z = 0.94$, $p = .61$. These results indicate that body fat percentage is associated with both increased delay and magnitude sensitivity for people who are consuming a high-fat diet. This expands our current knowledge of body fat percentage and impulsive choice. The current evidence in the field suggests that sensitivity to delay is related to body fat percentage especially for food reward (Rasmussen et al., 2010). Our analysis technique further suggests that people consuming a high-

fat diet and that also have higher body fat percentages have a greater preference for the larger reward and greater magnitude sensitivity compared to those with lower body fat percentages. The inconsistent findings regarding the relationship between impulsive choice and obesity in the literature may stem from the dietary patterns of the participants where the relationships are more likely to be observed in studies where the participants consume higher amounts of dietary fat (Barlow et al., 2016). Knowledge of both body fat percentage and dietary fat intake can better predict impulsive choices than either alone

Together the findings from the current study suggest that people who consume a high-fat diet and who have higher body fat percentages are less willing to wait for rewards and prefer larger rewards. Within the context of the impulsive choice tasks, an individual with the combination high delay sensitivity and high magnitude sensitivity would not be characterized as impulsive (Wileyto et al., 2004; Young, 2018). It is not possible to have “more now” within the construction of these tasks. However, when considering food choice people make every day, the fast food culture and highly processed foods make it possible to have large amounts of highly palatable, energy dense foods relatively immediately. Therefore, it is important to determine how behavior on the real food impulsive choice task predicts actual food choices as preferences for more-now may be important indicators of obesity that are not typically being measured in choice tasks.

Fasting glucose

Fasting glucose predicted preference for the shorter delay such that people with high fasting glucose levels had a higher preference for the shorter delay, $b = -0.81$, than people with lower fasting glucose levels, $b = -0.25$. Fasting glucose levels interacted with dietary fat intake to predict delay sensitivity (Figure 3.11, A). Coefficient comparisons indicated that sensitivity to

delay increased from lower, $b = 0.15$, to higher fasting glucose levels, $b = 2.22$, for Group C, $z = -2.46$, $p = .04$. However, sensitivity to delay did not change significantly from lower, $b = 1.50$, to higher fasting glucose levels, $b = 1.42$, for Group HF, $z = 0.13$, $p = .99$. Fasting glucose also interacted with dietary fat intake to predict magnitude sensitivity (Figure 3.11, B). Coefficient comparisons indicated that sensitivity to magnitude increased from lower, $b = -0.27$, to higher fasting glucose levels, $b = -2.13$, for Group C, $z = 2.68$, $p = .02$. However, sensitivity to magnitude did not change significantly from lower, $b = -1.75$, to higher fasting glucose levels, $b = -1.40$, for Group HF, $z = -0.64$, $p = .80$. Altogether, these findings suggest that people with higher fasting glucose levels exhibited a preference for the shorter delay, or an inability to delay gratification, regardless of dietary fat intake. In addition, people in the control group with higher fasting glucose levels were more sensitive to changes in delay and magnitude similar to the findings for added sugar and body fat percentage. This suggests that higher fasting glucose levels are inducing an unwillingness to wait for a reward and a desire for larger amounts of the reward. To our knowledge, this is the first investigation of fasting glucose and impulsive choice, and the results indicate that high levels of fasting glucose may predict impulsive food choices in people consume dietary fat within the recommended ranges.

Insulin sensitivity and secretion

Insulin sensitivity refers to how well insulin reduces blood glucose levels; those who are insulin sensitive would need less insulin to dispose of glucose in the blood than someone who is less insulin sensitive. While we expected to see that people in Group HF with poorer insulin sensitivity would be more sensitive to delay, insulin sensitivity did not interact with dietary fat intake to predict delay sensitivity (Figure 3.12, A) or magnitude sensitivity (Figure 3.12, B). Previous research has found that, for people with obesity, lower levels of insulin sensitivity were

associated with higher delay sensitivity (Eisenstein et al., 2015). Insulin is secreted in response to glucose. If an individual is not insulin sensitive, the body would need to secrete more insulin to deal with the glucose load. Insulin secretion interacted with dietary fat intake to predict delay sensitivity (Figure 3.13, A). However, coefficient comparisons were unable to localize the effect, $ps > .25$. Previous literature did not find a relationship between insulin secretion and delay sensitivity (Eisenstein et al., 2015). Altogether, we were not able to detect an interaction between dietary fat intake, insulin signaling (insulin sensitivity or secretion), and impulsive choice. It is possible that our population was too homogenous to detect differences in insulin signaling; dietary groups did not differ in their body fat percentage, fasting glucose, insulin sensitivity, insulin secretion, or inflammation levels. There may not be large enough disruptions in insulin signaling to detect differences.

Inflammation

IL-6 levels interacted with dietary group to predict preference for the larger magnitude (Figure 3.14, B). While there is a trend for people with higher levels of inflammation to make more SS choices in Group C, this effect could not be localized, $z = 1.89$, $p = .14$. Gassen et al. (2019) found that current inflammation levels (IL-6 and TNF- α) as measured in plasma were predictive of impulsivity in a sub-clinical population. They tightly controlled for other sources of inflammation by excluding participants who were sick recently and by asking participants to avoid inflammation altering activities such as exercise and alcohol for 48 hr prior to testing. In addition, that study included 159 participants. Therefore, future research investigating the relationship between inflammation and impulsive choice should consider a larger sample size and methods to control for outside sources of inflammation. IL-6 is considered a proinflammatory cytokine that is related to adiposity as demonstrated in this current study, but it

is also affected by other factors. It is important to consider these other factors when trying to uncover how inflammation is affecting behavior.

Overall summary

Self-reported dietary fat intake was not predictive of impulsive choice. However, an exploratory analysis of added sugar found that people who consumed higher amounts of sugar had greater delay sensitivity, greater preference for the larger magnitude, and increased magnitude sensitivity. The moderation analyses demonstrated a similar pattern of behavior. For the high-fat group, higher body fat percentages were associated with greater delay sensitivity and greater magnitude sensitivity. For the control group, higher fasting glucose levels were associated with greater delay sensitivity and greater magnitude sensitivity.

High delay sensitivity and low magnitude sensitivity are typically viewed as characteristics of impulsive choice (Wileyto et al., 2004; Young, 2018). The high delay sensitivity and high magnitude sensitivity (and preference) observed on the real food impulsive choice task suggests that those individuals are unwilling to wait for the reward, yet also want the larger reward. While participants cannot have larger amounts immediately in the context of the task, this finding is important to consider in relation to food choices made outside of the laboratory. People rarely decide between a small amount now and a larger amount later. Rather, people can have large amounts of palatable, energy dense food now. Therefore, greater delay and magnitude sensitivity could be problematic. Future research should investigate how choice on the real food impulsive choice task relates to actual food choices.

Comparison of rat and human models

There is emerging evidence that body fat, glucose/insulin function, and inflammation are related to impulsive choice (Barlow et al., 2016; Eisenstein et al., 2015). We conducted a

translational assessment of impulsive choice, dietary fat and sugar, body composition, and metabolic outcomes in rats and humans. These studies utilized parallel designs, and we developed a novel impulsive choice task for food to improve translation.

Dietary effects

Following an 8-week dietary manipulation, rats fed a high-fat diet had higher body fat percentages and higher fasting glucose levels compared to rats fed a control diet. However, glucose response did not differ. These changes in physiology were seen even though both groups had access to the same number of calories each day. In addition to changes in body fat percentage and fasting glucose, rats fed a high-fat diet had a greater preference for the shorter delay and greater magnitude sensitivity compared to rats fed a control diet. This demonstrates that a high-fat diet can alter impulsive choice, replicating previous research (Steele et al., 2019; Steele et al., 2017). Compared to the control group, the high-fat diet consisted of fewer vitamins, less protein, and more fat. Further, the high-fat group consumed more calories even though rats were only allowed access to 100 calories per day. These factors are likely driving the complex relationships between diet, physiological variables, and choice. Future research should investigate which factors or constellation of factors contribute to the relationship between diet, physiological variables, and choice.

Human participants in this study completed a 24-h dietary recall for three days prior to behavioral and physiological testing. An extreme groups design was used to create two dietary groups to resemble the dietary manipulation used in the rats. People who reported consuming a high-fat diet did not differ in any of the physiological measures from the control group, nor did they exhibit differences in impulsive choice. When comparing the macronutrient composition for the groups across species in Table 3.1 and Table 3.8, it is important to note that the HF and C

diets were more distinct for the rats. The C diet for rats had only 13% of calories from fat, while the HF diet had 48%. For the humans, the C diet had 31% of calorie from fat, while the HF had 45%. Further, the HF diet in rats was composed of 13.6% of calories from processed, saturated fat mostly from lard, whereas the high-fat group in humans only consumed 6.7% of their calories from saturated fat. It is also unknown whether the saturated fat consumed by the human participants were natural or processed saturated fats. Research in mice demonstrates that a high-fat diet from lard can induce cognitive deficits whereas butter fats did not produce these effects (Pistell et al., 2010). Therefore, the type of fat is likely an important contributor the effects of diet on impulsive choice.

An exploratory analysis found that the proportion of calories from added sugar was predictive of impulsive choice in humans, such that people who consumed more added sugar were more sensitive to changes in delay and magnitude. Our previous research in rats has shown that long-term consumption of a diet high in sugar can increase delay sensitivity and lead to more impulsive choices (Steele et al., 2019; Steele et al., 2017). It is possible that the added sugar analysis is more comparable to the rat studies because both include refined sugar, whereas the high-fat diets may be more variable between the two species. Fast food consumption (Garza et al., 2016) and unhealthy eating (Dassen et al., 2015; Garza et al., 2013) have been linked to delay sensitivity. However, to our knowledge, this is the first study to look at macronutrient composition and impulsive choice in humans. In addition, this is the first study to investigate delay and magnitude sensitivity when considering dietary fat intake and impulsive choice in humans.

There are some important considerations regarding the measurement of diet in humans. We measured short term diet, which can give a snap shot of what people consumed during the

few days before the experimental sessions. However, diet is relatively stable for up to 2 years (Borland et al., 2008), so the present dietary assessment may be a valid indicator of longer-term diet. Nevertheless, it is possible that a measurement of diet over the course of the year may be a better predictor of impulsive choice. These measures require that participants report average portions of food consumed in the last year. On the other hand, people perform poorly at estimating portion sizes (Schwartz & Byrd-Bredbenner, 2006), so there are limitations to these measures as well. Altogether, there are pros and cons to different dietary assessments, and a comprehensive tool available at <https://dietassessmentprimer.cancer.gov/> outlines different dietary assessments and provides recommendations for assessments depending on the research question.

Dietary history from childhood might also predict impulsive choice in adulthood. The rats received the same diet starting early in development for 8 weeks before behavioral testing (corresponding to 8 years in humans; Sengupta, 2013). In previous studies, some of the dietary effects remained even after rats were removed from the unhealthy diets (Steele et al., 2017; Wang et al., 2015). Therefore, childhood diet may be predictive of choice later in life just as impulsive choice is predictive of weight status later in life (Schlam et al., 2013). People could be consuming a healthy diet now, but poor dietary history may lead to lingering effects on cognition. The effects of childhood dietary history likely depend on the age of the participant. For example, college students may be highly influenced by their dietary history from childhood given that they recently lived at home, while older individuals may not be affected by childhood dietary history. Further, childhood or current socio-economic status (SES) may affect diet. In fact, people with lower SES purchase foods higher in fat and lower in nutrients (Appelhans et al., 2012). Sex is another important factor. The current study did not use female rats, but the human

study included both males and females. This could have important implications for the translation of the results. Altogether, the dietary history of the rodents is relatively controlled compared to the human participants, and future research should investigate how age, dietary history, SES, and sex affect the relationship between current diet, physiological variables, and impulsive choice.

Physiological moderators

The interaction between physiological variables (body fat percentage, insulin signaling, and inflammation) and dietary fat intake was tested as a predictor of impulsive choice. There is extensive evidence that obesity and impulsive choice are related in humans (Barlow et al., 2016). However, some previous reports have not found a relationship between BMI/body weight and impulsive choice in humans (Eisenstein et al., 2015; Gassen et al., 2019; Nederkoorn, Smulders, Havermans, Roefs, & Jansen, 2006; Rasmussen et al., 2010) and rats (Steele et al., 2017). This study suggests that dietary fat intake and body fat percentage interact to predict impulsive choice. For people consuming a high-fat diet, higher body fat percentage was predictive of greater sensitivity to delay and magnitude. Control rats showed a similar effect for delay sensitivity. However, high-fat rats showed the opposite effect; higher body fat percentage was predictive of lower sensitivity to delay and magnitude. This demonstrates that additional information about dietary fat intake can help us better understand those that might be more at risk for impulsive tendencies. The patterns in the human data suggest that those people who have high delay sensitivity and high magnitude sensitivity may be at high risk given that they are unwilling to wait and want larger amounts of reward suggesting they may be more prone to eat large amounts of convenient, energy-dense, highly palatable foods. This is particularly important because impulsivity is predictive of weight loss success (Nederkoorn, Jansen, et al., 2006).

Several components of the glucose and insulin system were tested. High fasting glucose was predictive of preference for a shorter delay in humans regardless of group. In addition, in the control group, higher fasting glucose levels were predictive of greater delay and magnitude sensitivity in humans. High fasting glucose was predictive of magnitude sensitivity in the control rats as well. However, this is not consistent with the results in rats where high-fat diet coupled with high fasting glucose levels predicted lower sensitivity to delay. To our knowledge, this is the first investigation of the relationship between fasting glucose and impulsive choice demonstrating that fasting glucose is an important predictor of impulsive choice. Insulin sensitivity and insulin secretion were not predictive of impulsive choice, partially replicating previous research (Eisenstein et al., 2015). Poorer glucose response (i.e. higher AUC) was associated with lower delay sensitivity and higher magnitude sensitivity for control rats. It is important to note that we are missing part of the story for rats. Because we were unable to obtain a large enough blood sample at each time point, we only measured glucose. Knowing the corresponding insulin values would help us uncover the relationship between glucose and insulin in response to a glucose load.

Inflammation values were not able to be obtained from the rats because they were below the level of detection, which is not uncommon in the field (Shapiro, Tumer, Gao, Cheng, & Scarpace, 2011). Future work should investigate neuroinflammation given that high-fat diets induce neuroinflammation that is associated with cognitive impairments (Kanoski & Davidson, 2011; Pistell et al., 2010). Therefore, neuroinflammation could explain why there are dietary effects on impulsive choice. In humans, inflammation interacted with dietary fat intake to predict preference for the larger magnitude, but we could not localize this effect. Previous research has found that current levels of inflammation are predictive of impulsive choice, even in subclinical

populations (Gassen et al., 2019). The previous study tightly controlled for other sources of inflammation, and they also had a larger sample size of 159 participants. It is possible that the current study was underpowered. Future research should determine how diet might moderate the effects of inflammation on impulsive choice.

Summary and implications

High-fat diets induced a preference for the shorter delay in rats indicating poor delay gratification, and this effect was not moderated by physiological variables. However, physiological measures interacted with dietary fat intake to predict other aspects of impulsive choice (delay and magnitude sensitivity) in rats. High-fat diets were not predictive of impulsive choice in humans, but added sugar was predictive. While high-fat diets were not predictive of impulsive choice, physiology and dietary fat intake interacted to predict impulsive choice. This evidence indicates that the relationship between physiology (body fat percentage and insulin sensitivity) and impulsive choice observed in the literature (Barlow et al., 2016; Eisenstein et al., 2015) is moderated by dietary fat intake. Therefore, body fat percentage and dietary fat intake are more predictive of impulsive choice than either factor alone. Future research should investigate how impulsive choice using the novel impulsive choice task for food predicts food choice and weight loss treatment outcomes.

Figure 3.1. Procedure. Overview of the procedures and their timeline for the rat model (left) and human translational model (right). SD = Sprague Dawley, ASA24 = 24 h dietary recall; DEXA = dual energy x-ray absorptiometry.

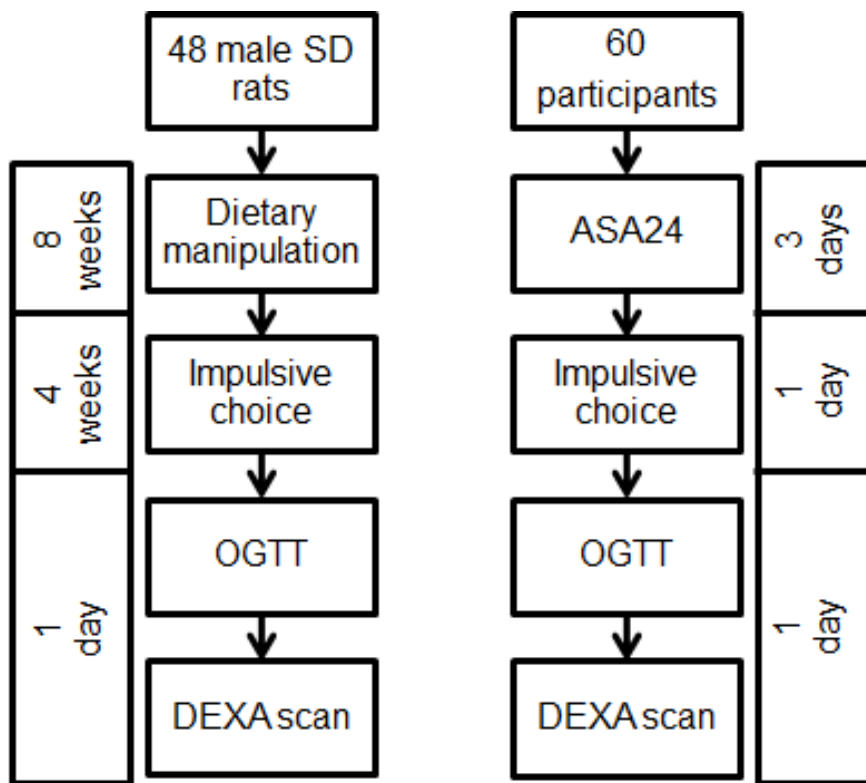


Figure 3.2. Dietary effects on choice in rats. Mean proportion of larger-later (LL) choices for each group as a function of delay/magnitude ratio in rats. A: Impulsive choice: delay task performance. Rats fed a high-fat diet made more SS choices at the delay intercept compared to rats fed a chow diet, but there were no differences in delay slope. B: Impulsive choice: magnitude task performance. Rats fed a high-fat diet had a steeper magnitude slope compared to rats fed a chow diet, but there were no differences at the magnitude intercept. The delay and magnitude ratios were the SS / LL delay or magnitude, respectively. Smaller ratios indicate a larger difference in the delays or magnitudes. HF = high-fat; C = control. Error bars (+/- SEM) were computed with respect to the estimated marginal means of the fitted generalized linear mixed-effects model.

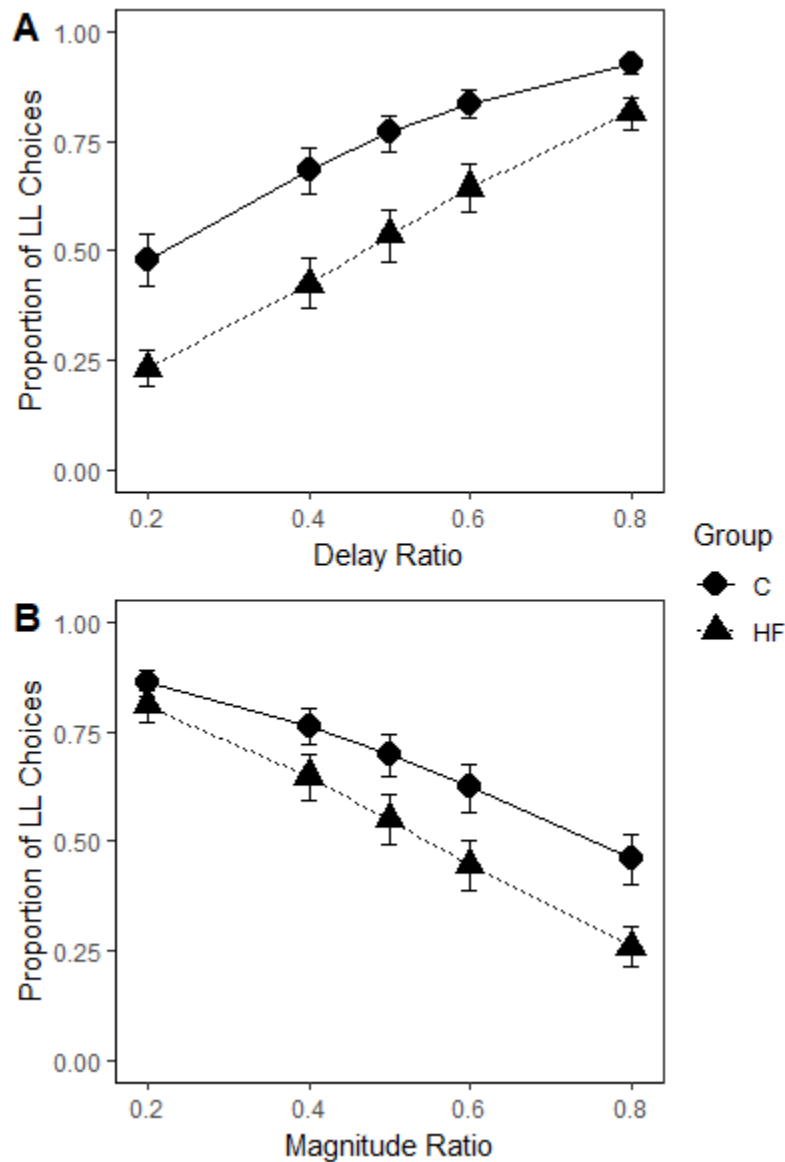


Figure 3.3. Correlations between physiological variables in rats. The correlation between the physiological measures in rats. iAUC = incremental area under the curve. Body weight was not correlated with body fat (A). Body fat was significantly correlated with fasting glucose (B) and glucose iAUC (C). Fasting glucose was not correlated with glucose iAUC (D)

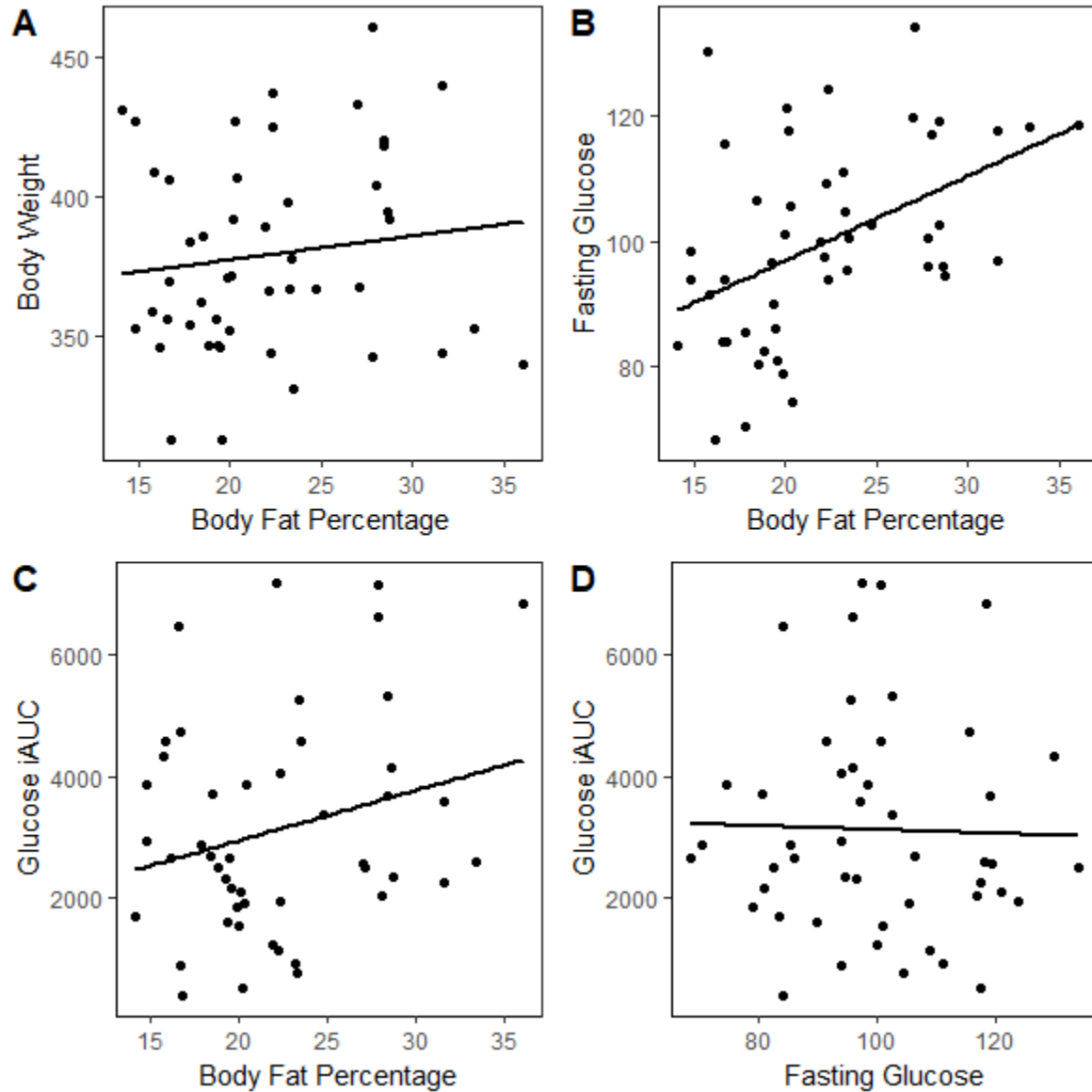


Figure 3.4. Body fat percentage and choice in rats. Mean proportion of larger-later (LL) choices for each group as a function of body fat percentage and delay/magnitude ratio in rats. A: Impulsive choice: delay task performance. Sensitivity to delay (the slope of the choice function) increased systematically from lower to higher body fat percentages for the control group. However, sensitivity to delay decreased from lower, to higher body fat percentages for the high-fat group. B: Impulsive choice: magnitude task performance. Sensitivity to magnitude did not change significantly from lower to higher body fat percentages for the control group. However, sensitivity to magnitude decreased from lower to higher body fat percentages for the high-fat group. The delay and magnitude ratios were the SS / LL delay or magnitude, respectively. Smaller ratios indicate a larger difference in the delays or magnitudes. HF = high-fat; C = control; PBF = percent body fat. Error bars (+/- SEM) were computed with respect to the estimated marginal means of the fitted generalized linear mixed-effects model.

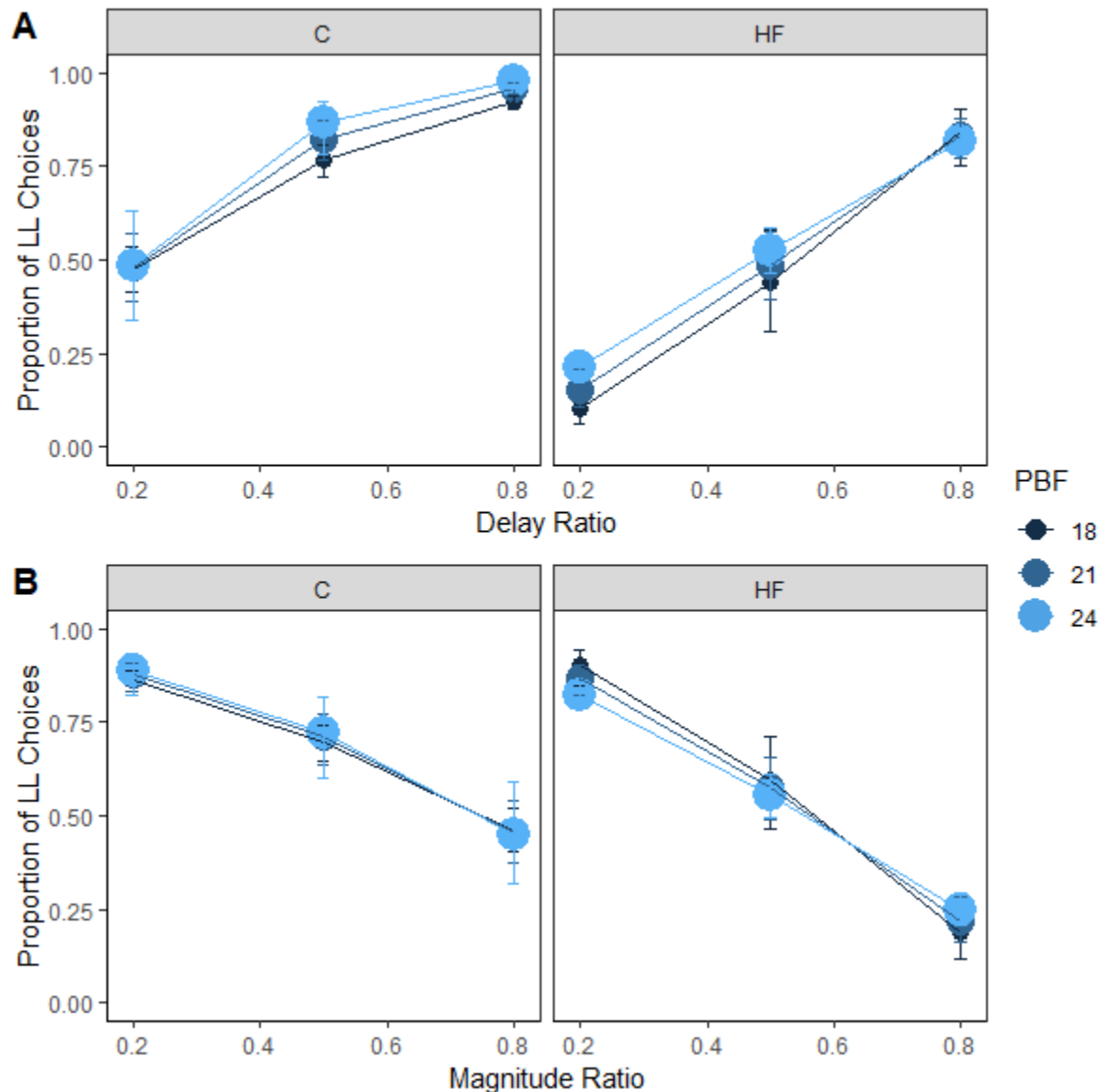


Figure 3.5. Fasting glucose and choice in rats. Mean proportion of larger-later (LL) choices for each group as a function of fasting glucose and delay/magnitude ratio in rats. A: Impulsive choice: delay task performance. Sensitivity to delay did not change significantly from lower to higher fasting glucose levels for the control group. However, sensitivity to delay decreased from lower to higher fasting glucose levels for the high-fat group. B: Impulsive choice: magnitude task performance. Sensitivity to magnitude increased from lower, $b = -3.09$, to higher fasting glucose levels for the control group. However, sensitivity to magnitude did not change significantly from lower to higher fasting glucose levels for the high-fat group. The delay and magnitude ratios were the SS / LL delay or magnitude, respectively. Smaller ratios indicate a larger difference in the delays or magnitudes. HF = high-fat; C = control; FG = fasting glucose. Error bars ($\pm$ SEM) were computed with respect to the estimated marginal means of the fitted generalized linear mixed-effects model.

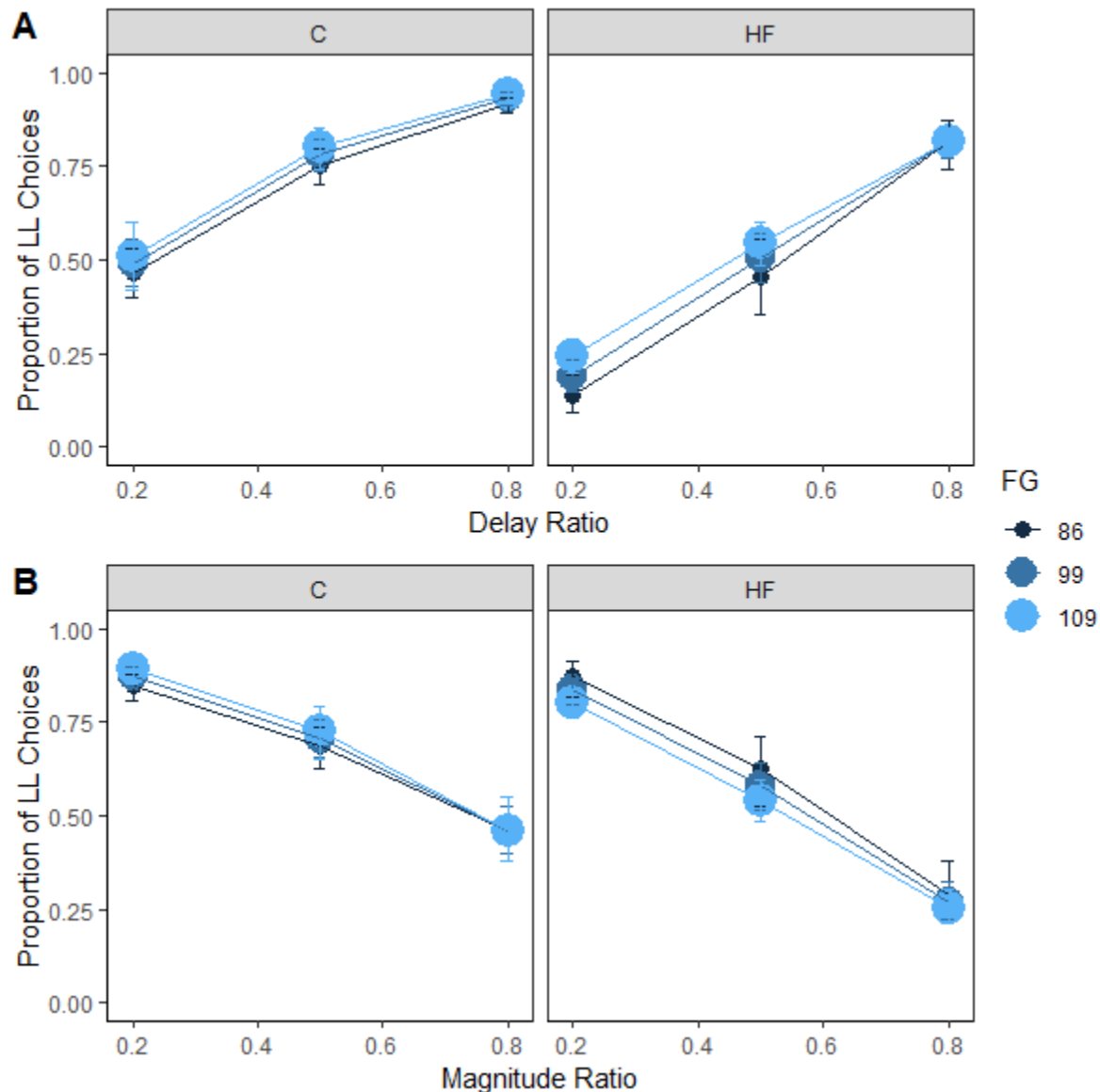


Figure 3.6. Glucose response and choice in rats. Mean proportion of larger-later (LL) choices for each group as a function of glucose response and delay/magnitude ratio in rats. A: Impulsive choice: delay task performance. Sensitivity to delay decreased from lower to higher glucose iAUCs for the control group. However, sensitivity to delay did not change significantly for the high-fat group from lower to higher glucose iAUCs. B: Impulsive choice: magnitude task performance. Sensitivity to magnitude increased from lower to higher glucose iAUCs for the control group. However, magnitude sensitivity did not significantly change for the high-fat group from lower to higher glucose iAUCs. The delay and magnitude ratios were the SS / LL delay or magnitude, respectively. Smaller ratios indicate a larger difference in the delays or magnitudes. HF = high-fat; C = control; sqrt.iAUC = incremental area under the curve-square root transformed. Error bars ($\pm$ SEM) were computed with respect to the estimated marginal means of the fitted generalized linear mixed-effects model.

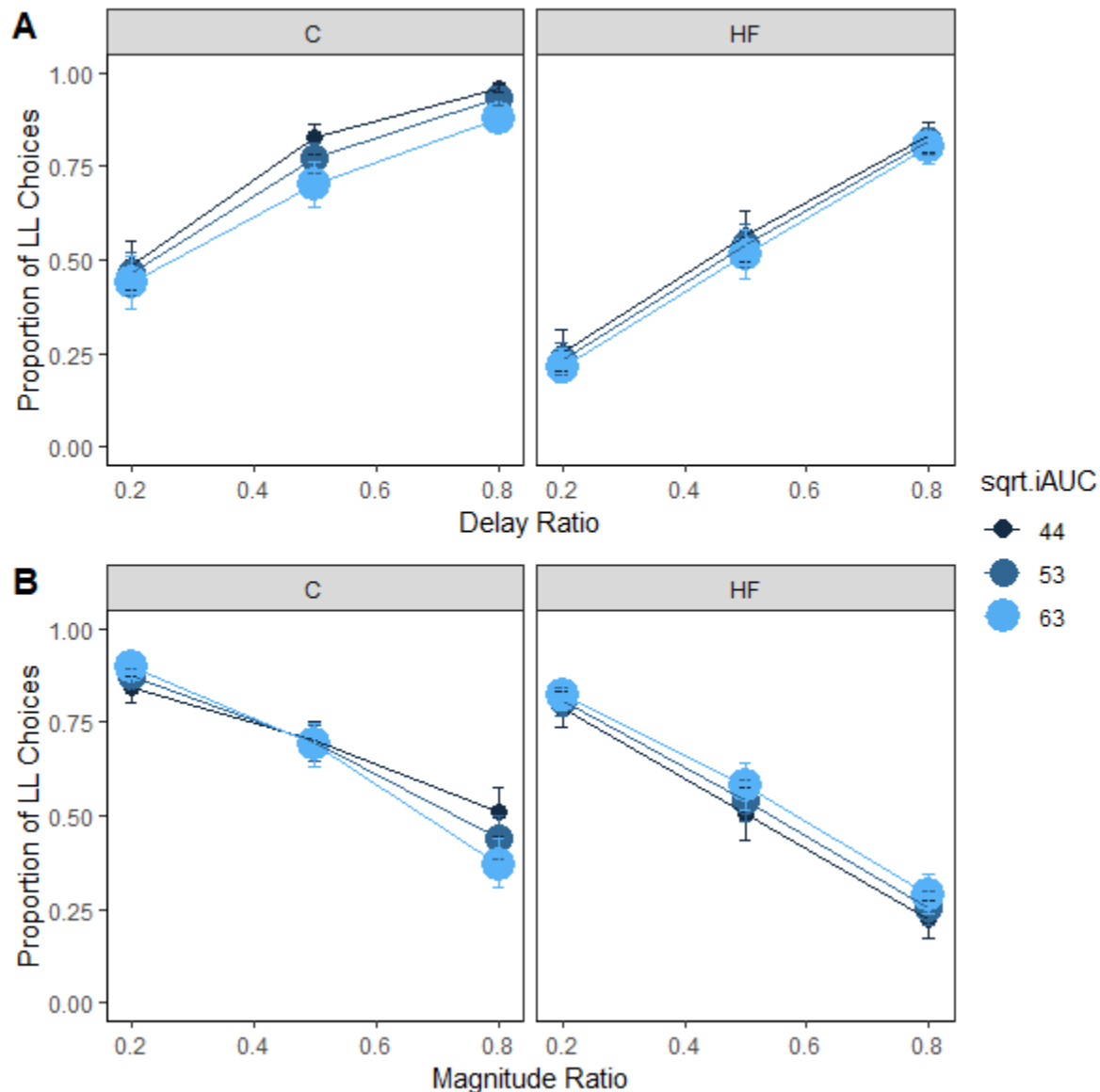


Figure 3.7. Dietary effects in humans. Mean proportion of larger-later (LL) choices for each group as a function of delay (A) and magnitude (B) ratio in humans. The delay and magnitude ratios were the SS / LL delay or magnitude, respectively. Smaller ratios indicate a larger difference in the delays or magnitudes. HF = high-fat; C = control. Error bars (+/- SEM) were computed with respect to the estimated marginal means of the fitted generalized linear mixed-effects model. There were no group difference in intercept or slope for delay (A) or magnitude (B) ratio.

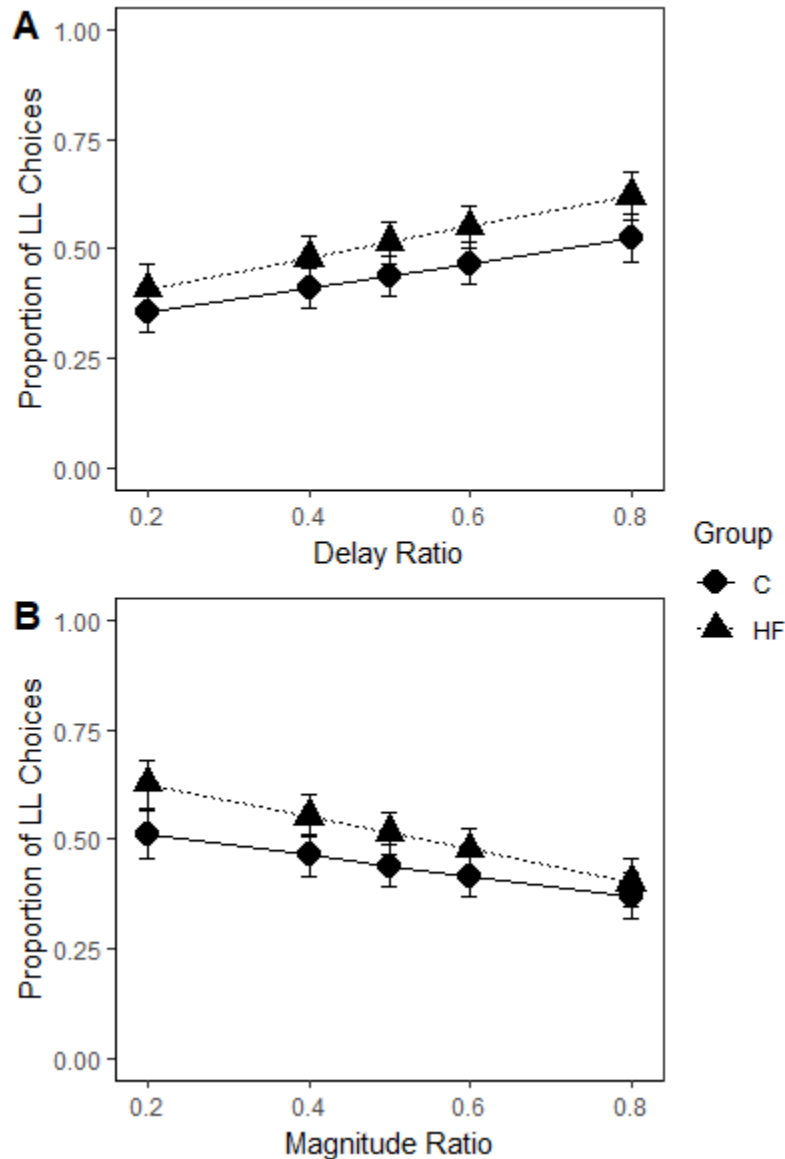


Figure 3.8. Mean proportion of larger-later (LL) choices as a function of percentage of calories consumed from sugar and delay (A) and magnitude (B) ratio in humans. The delay and magnitude ratios were the SS / LL delay or magnitude, respectively. Smaller ratios indicate a larger difference in the delays or magnitudes. Error bars ($\pm$ SEM) were computed with respect to the estimated marginal means of the fitted generalized linear mixed-effects model. There was a significant interaction between percentage of calories from added sugar and delay ratio, such that delay sensitivity increased from lower to higher amounts of added sugar. People who consume more added sugar had a greater preference for the larger magnitude when the magnitudes were maximally different. Magnitude sensitivity increased as percentage of calories from added sugar went from lower to higher amounts of sugar.

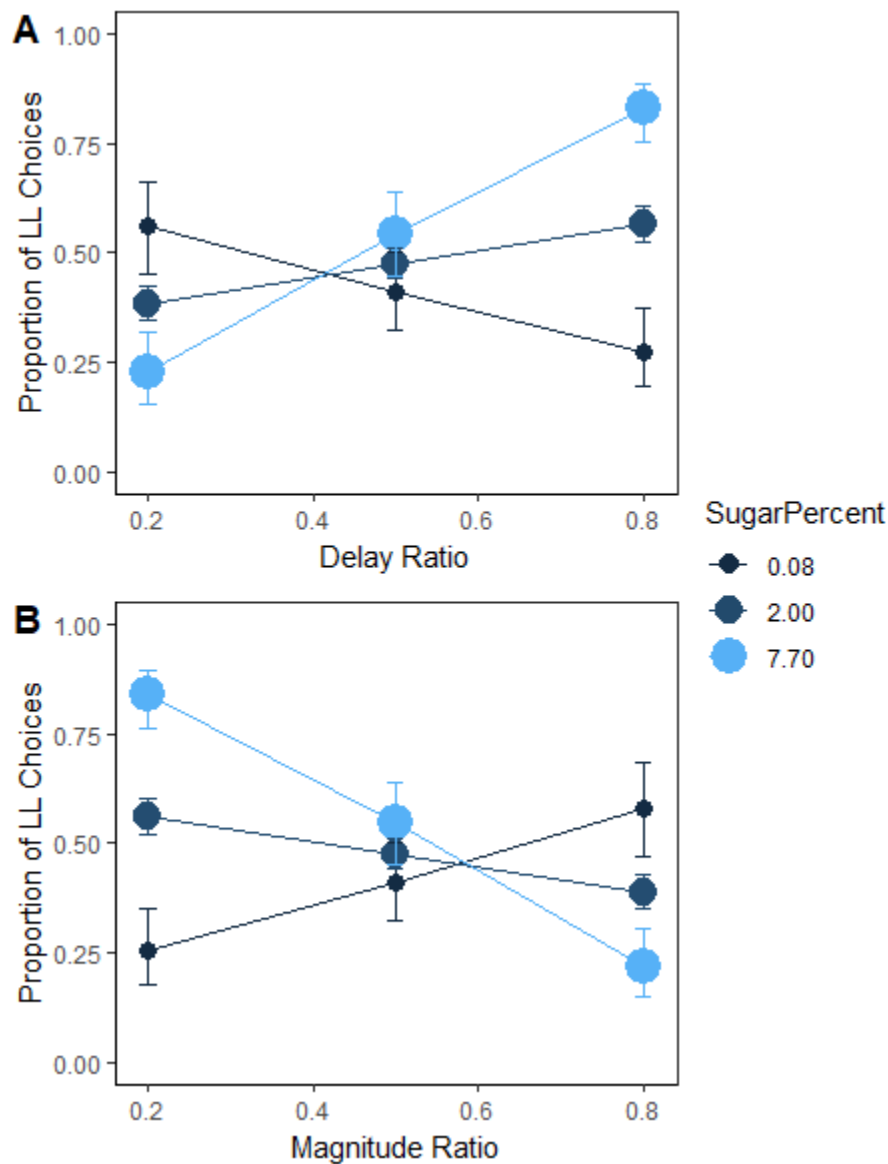


Figure 3.9. Correlations between physiological variables in humans. Body fat percentage was significantly correlated with the inverse of body mass index (A), fasting glucose (B), and inflammation (E). Insulin sensitivity and fasting glucose were significantly correlated (F). All correlations were not significant.

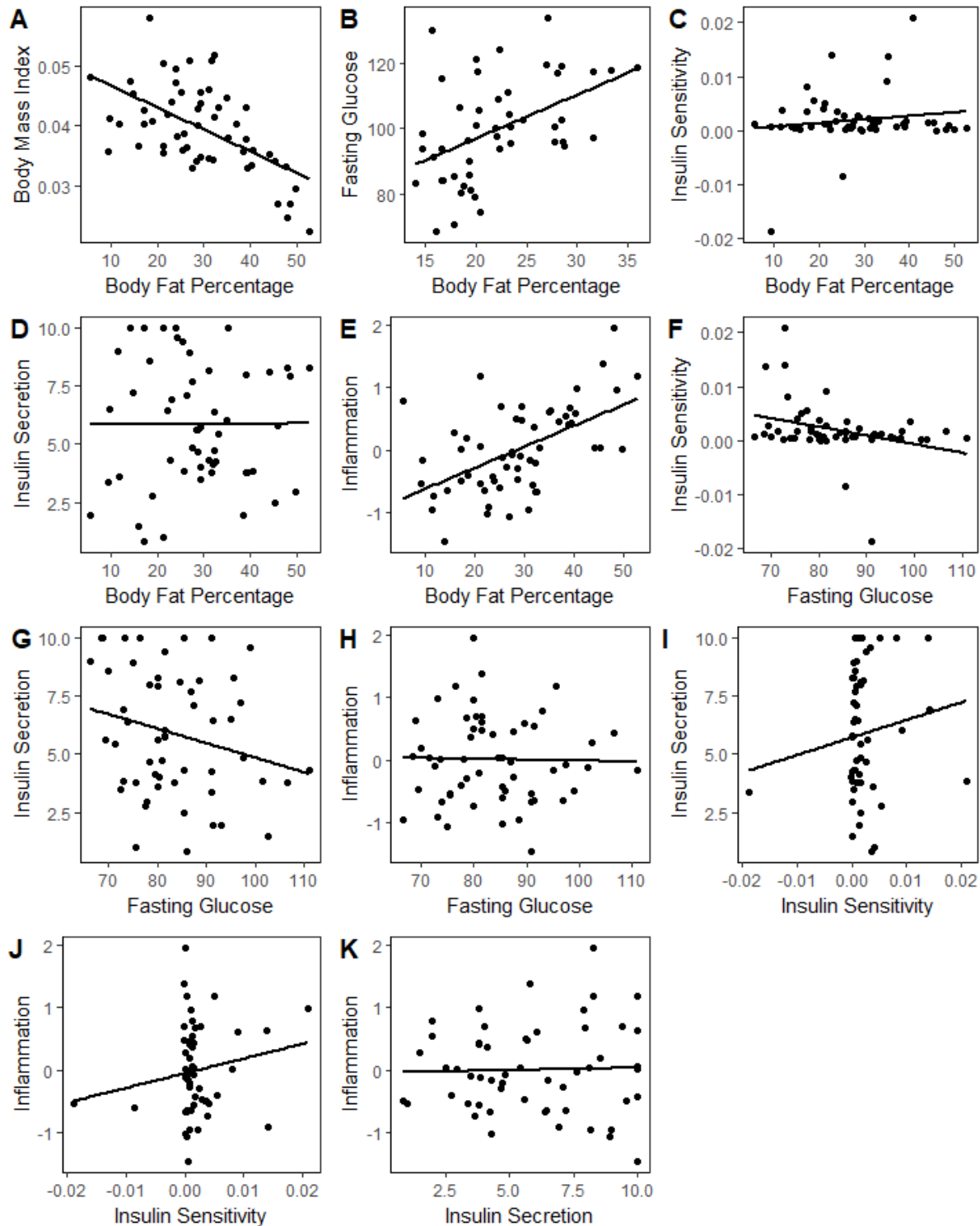


Figure 3.10. Body fat percentage and choice in humans. Mean proportion of larger-later (LL) choices for each group as a function of body fat percentage and delay (A) and magnitude (B) ratio in humans. Sensitivity to delay or magnitude did not change significantly from lower to higher body fat percentages for the control group. However, sensitivity to delay and magnitude increased from lower to higher body fat percentages for the high-fat group. The delay and magnitude ratios were the SS / LL delay or magnitude, respectively. Smaller ratios indicate a larger difference in the delays or magnitudes. HF = high-fat; C = control; PBF = percent body fat. Error bars ($\pm$ SEM) were computed with respect to the estimated marginal means of the fitted generalized linear mixed-effects model.

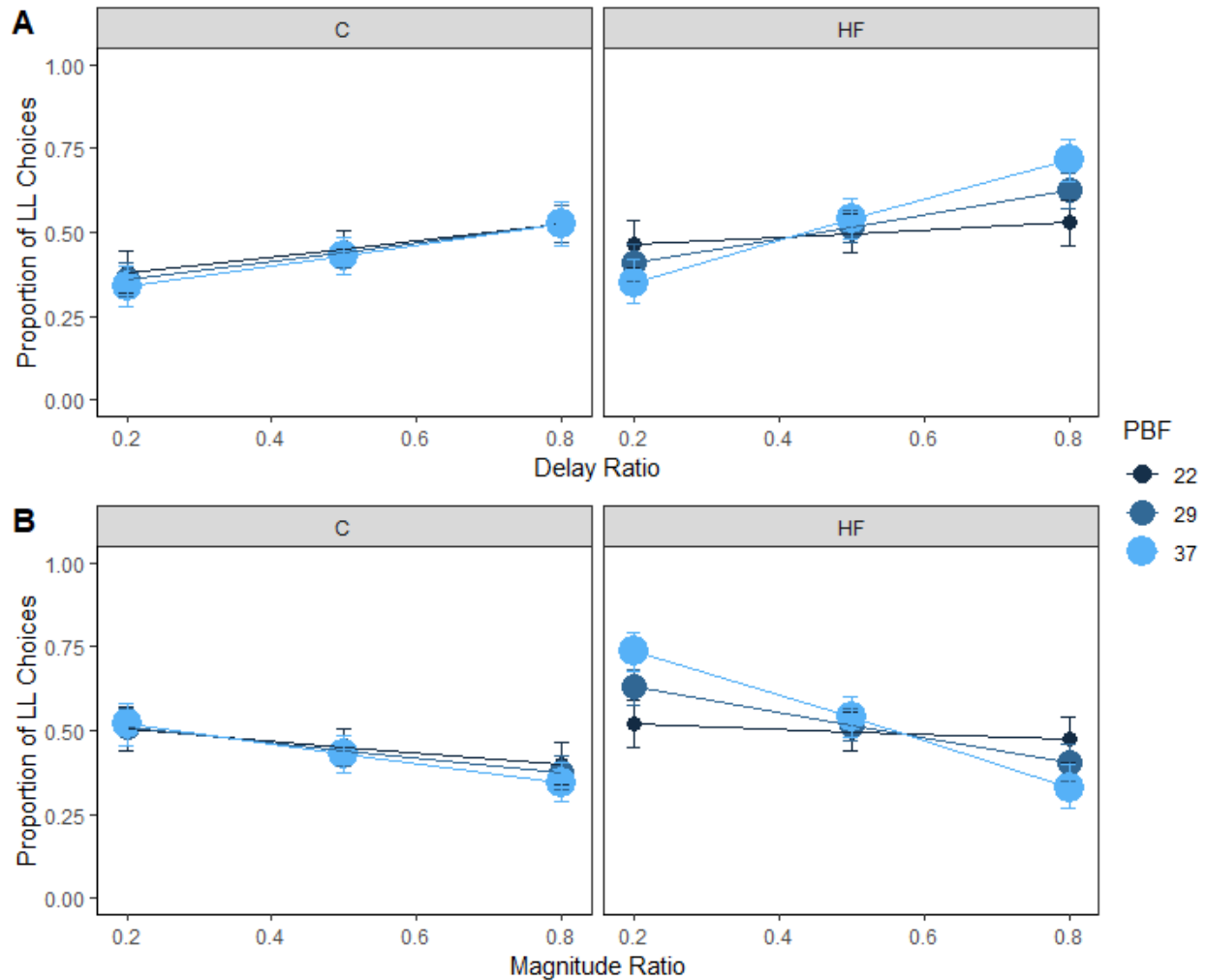


Figure 3.11. Fasting glucose and choice in humans. Mean proportion of larger-later (LL) choices for each group as a function of fasting glucose and delay (A) and magnitude (B) ratio in humans. Sensitivity to delay and magnitude increased from lower to higher fasting glucose levels for the control group. However, sensitivity to delay and magnitude did not change significantly from lower to higher fasting glucose levels for the high-fat group. The delay and magnitude ratios were the SS / LL delay or magnitude, respectively. Smaller ratios indicate a larger difference in the delays or magnitudes. HF = high-fat; C = control; FG = fasting glucose. Error bars (+/- SEM) were computed with respect to the estimated marginal means of the fitted generalized linear mixed-effects model.

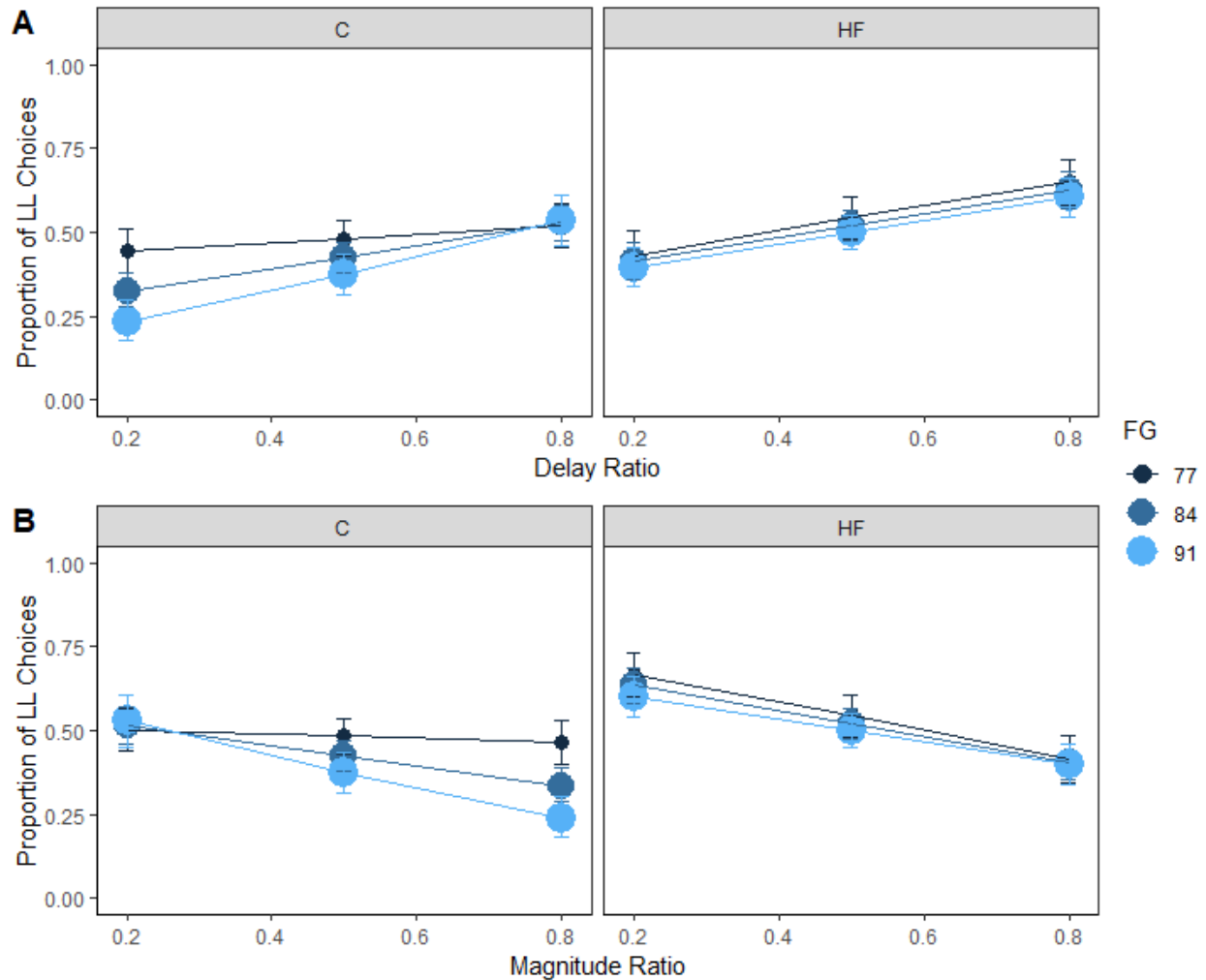


Figure 3.12. Insulin sensitivity and choice in humans. Mean proportion of larger-later (LL) choices for each group as a function of insulin sensitivity and delay (A) and magnitude (B) ratio in humans. Insulin sensitivity did not interact with diet to predict delay sensitivity or magnitude sensitivity. The delay and magnitude ratios were the SS / LL delay or magnitude, respectively. Smaller ratios indicate a larger difference in the delays or magnitudes. HF = high-fat; C = control; SI = insulin sensitivity. Error bars ($\pm$ SEM) were computed with respect to the estimated marginal means of the fitted generalized linear mixed-effects model.

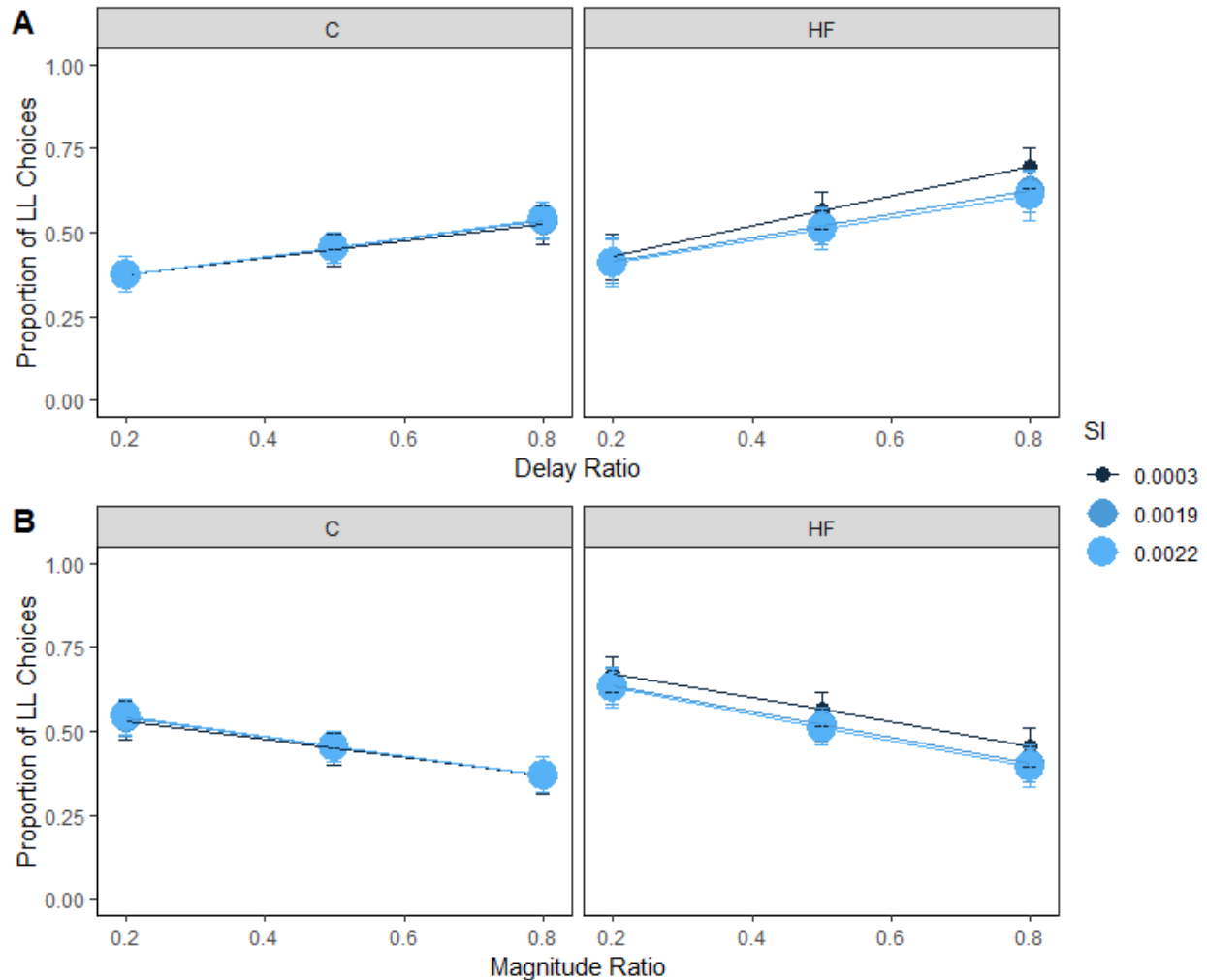


Figure 3.13. Insulin secretion and choice in humans. Mean proportion of larger-later (LL) choices for each group as a function of insulin secretion and delay (A) and magnitude (B) ratio in humans. Insulin secretion interacted with diet to predict delay sensitivity. However, coefficient comparisons were unable to localize the source of the effect. Insulin secretion did not interact with diet to predict magnitude sensitivity. The delay and magnitude ratios were the SS / LL delay or magnitude, respectively. Smaller ratios indicate a larger difference in the delays or magnitudes. HF = high-fat; C = control; invsqrtPCGR = insulin secretion-inverse square root transformed. Error bars (+/- SEM) were computed with respect to the estimated marginal means of the fitted generalized linear mixed-effects model.

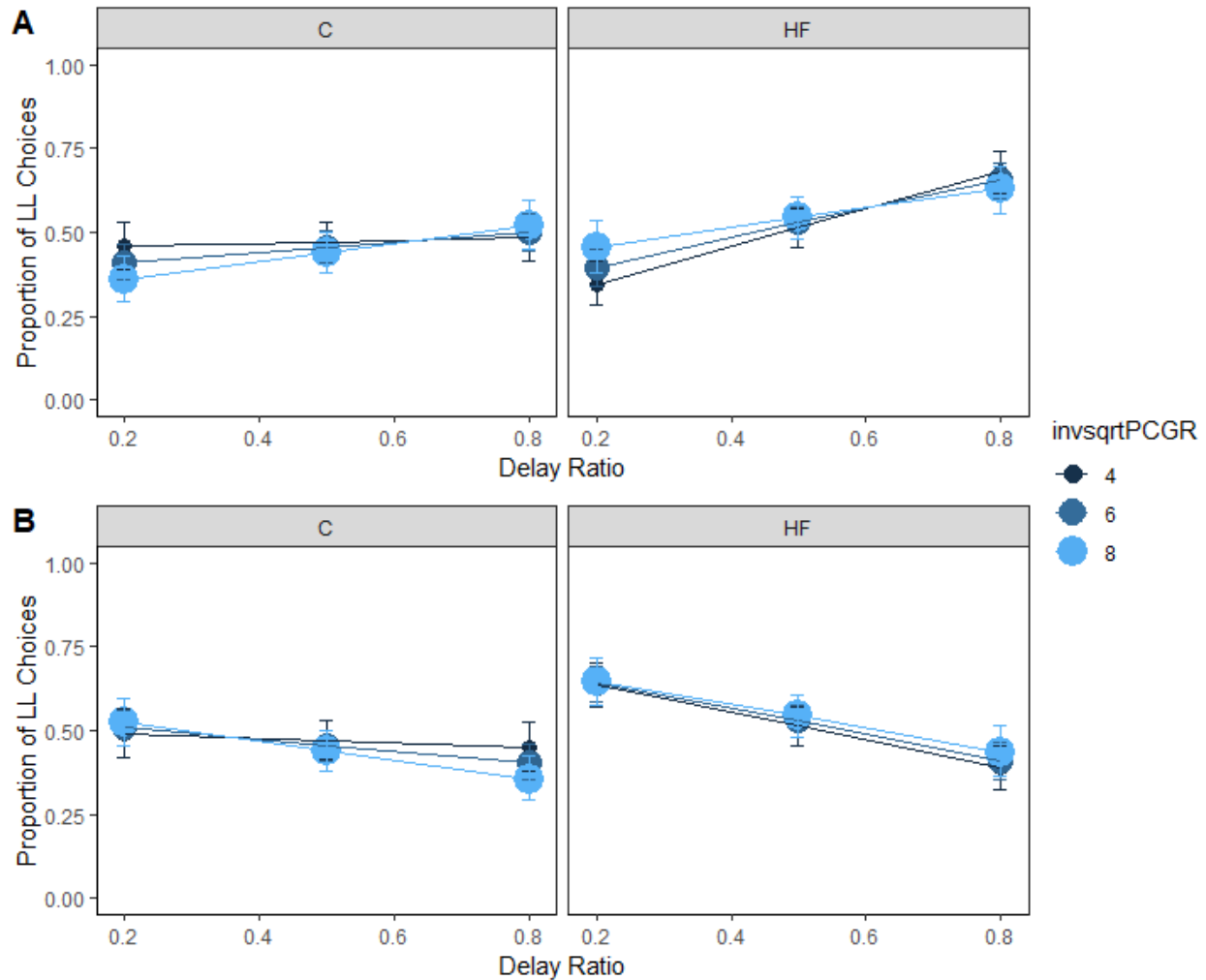


Figure 3.14. Inflammation and choice in humans. Mean proportion of larger-later (LL) choices for each group as a function of inflammation and delay (A) and magnitude (B) ratio in humans. Inflammation did not interact with diet to predict delay or magnitude sensitivity. The delay and magnitude ratios were the SS / LL delay or magnitude, respectively. Smaller ratios indicate a larger difference in the delays or magnitudes. HF = high-fat; C = control; IL6 = inflammation. Error bars (+/- SEM) were computed with respect to the estimated marginal means of the fitted generalized linear mixed-effects model.

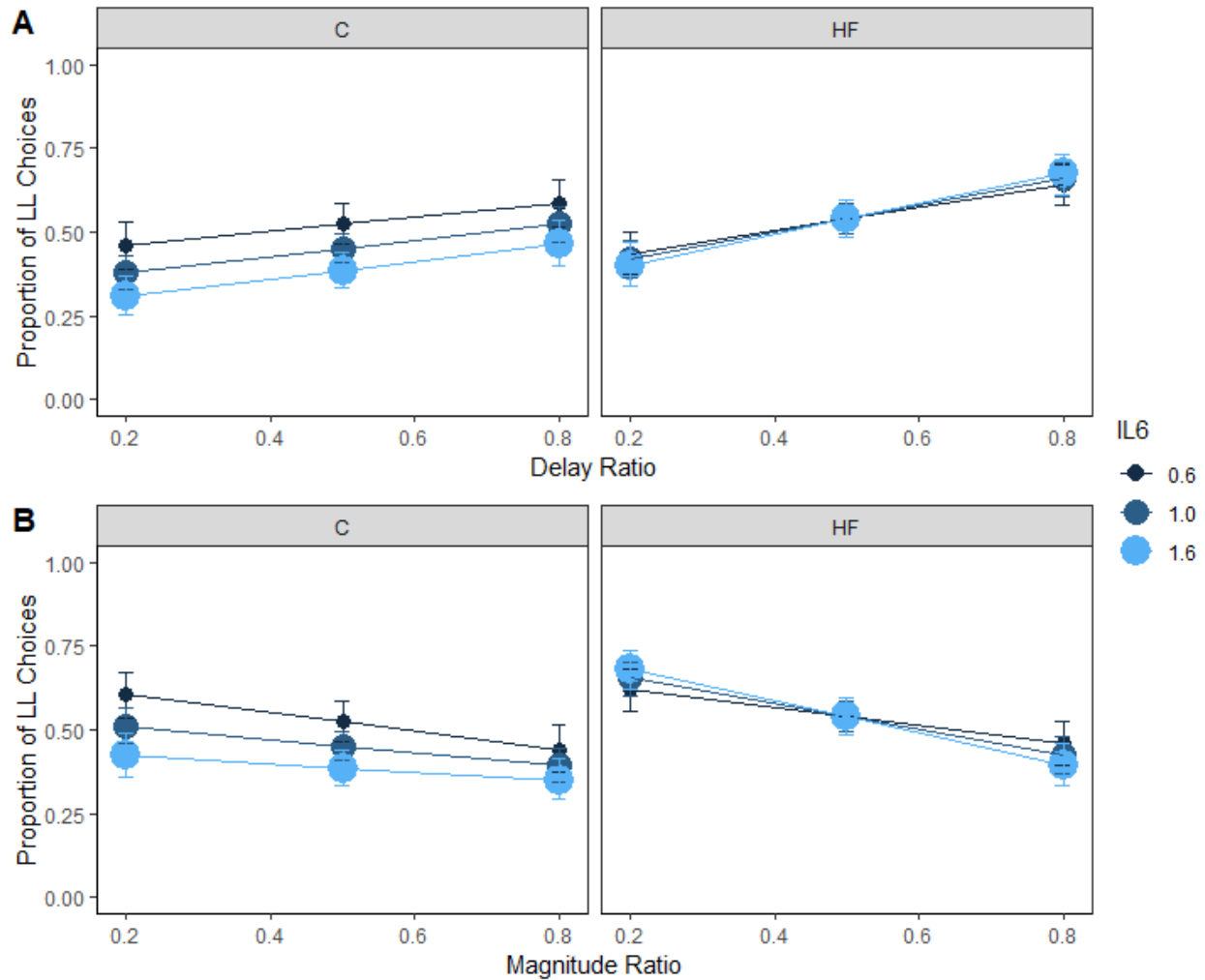


Table 3.1. Macronutrient composition in rats. Macronutrient composition of the control (Chow) and high-fat (HF) diets in rats.

Macronutrient composition		
	Chow	HF
Fat (%)	13.77	47.99
Protein (%)	28.55	17.22
Carbohydrates (%)	57.68	34.79
Added sugar (%)	7.46	4.50
Saturated fat (%)	3.94	13.58

Table 3.2. Choice parameters for rats. The parameters and number of sessions for the delay and magnitude manipulations of the impulsive choice task in rats. SS = smaller-sooner; LL = larger-later; Sess = sessions; Amt = amount.

Delay Manipulation					Magnitude Manipulation				
SS Delay	LL Delay	SS Amt	LL Amt	# sess	SS Delay	LL Delay	SS Amt	LL Amt	# sess
5	25	2	5	4	10	25	1	5	4
10	25	2	5	2	10	25	2	5	2
15	30	2	5	2	10	25	2	4	2
15	25	2	5	2	10	25	3	5	2
20	25	2	5	2	10	25	4	5	2

Table 3.3. Dietary effects on physiology in rats. Group differences in physiological measures for rats.

Characteristic	Control (n = 24)	High-Fat (n = 24)	<i>p</i>
Body fat (%)	18.25 (±2.64)	25.96 (±4.60)	<.001
Body weight (g)	363.54 (±30.66)	394.75 (±33.59)	.001
Fasting glucose (mg/dl)	93.13 (±14.01)	106.44 (±14.55)	.002
Glucose response (iAUC)	2959.48 (±1724.41)	3274.92 (±1852.09)	.53

Values are presented as mean (±standard deviation). Means and standard deviations are based on the raw values.

Table 3.4. Body fat percentage and choice in rats. Body fat moderation model output for rats from a logistic regression with the fixed effects of Group (Control vs. High Fat), Slope (Delay or Magnitude Ratio), and Body Fat Percentage.

	Delay				Magnitude			
	<i>b</i>	SE	<i>z</i>		<i>b</i>	SE	<i>z</i>	
(Intercept)	-0.90	0.26	-3.48	***	1.92	0.24	7.85	***
Group	0.82	0.26	3.16	**	0.04	0.24	0.16	
Slope	5.46	0.18	30.16	***	-4.41	0.17	-26.23	***
BF	1.34	1.14	1.18		-0.63	1.05	-0.61	
Slope × Group	-0.06	0.18	-0.33		0.85	0.17	5.09	***
Group × BF	-1.21	1.14	-1.07		1.45	1.05	1.39	
Slope × BF	0.69	0.75	0.91		1.84	0.70	2.63	**
Slope × Group × BF	5.76	0.75	7.65	***	-3.40	0.70	-4.85	***

* $p < .05$

** $p < .01$

*** $p < .001$

BF = percentage body fat

Table 3.5. Fasting glucose and choice in rats. Fasting glucose model output for rats from a logistic regression with the fixed effects of Group (Control vs. High Fat), Slope, and Fasting Glucose.

	Delay				Magnitude			
	<i>b</i>	SE	<i>z</i>		<i>b</i>	SE	<i>z</i>	
(Intercept)	-0.75	0.19	-4.04	***	1.78	0.18	9.80	***
Group	0.71	0.19	3.82	***	0.15	0.18	0.82	
Slope	4.65	0.13	36.66	***	-3.92	0.12	-32.00	***
FG	0.02	0.01	1.63		-0.002	0.01	-0.20	
Slope × Group	-0.26	0.13	-2.06	*	0.45	0.12	3.72	***
Group × FG	-0.01	0.01	-0.94		0.02	0.01	1.71	
Slope × FG	-0.02	0.01	-2.12	*	-0.002	0.01	-0.25	
Slope × Group × FG	0.03	0.01	3.88	***	-0.03	0.01	-3.37	***

* $p < .05$

** $p < .01$

*** $p < .001$

FG = fasting glucose

Table 3.6. Glucose response and choice in rats. Glucose response moderation model output for rats from a logistic regression with the fixed effects of Group (Control vs. High Fat), Slope, and Glucose Response.

	Delay				Magnitude			
	<i>b</i>	SE	<i>z</i>		<i>b</i>	SE	<i>z</i>	
(Intercept)	-0.67	0.17	-4.00	***	1.66	0.17	10.06	***
Group	0.52	0.17	3.12	**	0.24	0.17	1.45	
Slope	4.52	0.11	40.25	***	-3.87	0.11	-35.11	***
iAUC	-0.01	0.01	-1.03		0.02	0.01	1.76	
Slope × Group	0.04	0.11	0.37		0.32	0.11	2.87	**
Group × iAUC	0.00	0.01	0.08		0.01	0.01	0.62	
Slope × iAUC	-0.04	0.01	-5.83	***	-0.04	0.01	-5.96	***
Slope × Group × iAUC	-0.04	0.01	-6.52	***	-0.05	0.01	-7.56	***

* $p < .05$

** $p < .01$

*** $p < .001$

iAUC = incremental area under the curve

Table 3.7. Demographic characteristics in humans. Characteristics of dietary groups in humans.

Characteristic	Control (n = 30)	High-Fat (n = 30)	<i>p</i>
Sex, male/female	21/9	17/13	.42
Age, yr	30.93 ($\pm$ 12.96)	34.47 ($\pm$ 12.12)	.18
Total MET	5023 ($\pm$ 4184)	3580 ($\pm$ 3571)	.12

Values are presented as mean ($\pm$ standard deviation). Means and standard deviations are based on the raw values. A chi-square test was used to compare frequencies of sex across groups. MET = multiples of the resting metabolic rate.

Table 3.8. Macronutrient composition in humans. Macronutrient composition of the different dietary groups in humans.

Characteristic	Control (n = 30)	High-Fat (n = 30)	<i>p</i>
Calories (kcal)	1823 (±551)	2102 (±516)	.03
Fat (%)	31.30 (±4.18)	45.17 (±4.59)	<.001
Protein (%)	17.16 (±5.30)	18.59 (±4.30)	.26
Carbohydrates (%)	51.27 (±7.96)	37.43 (±7.10)	< .001
Added sugar (%)	2.92 (±1.63)	1.97 (±1.13)	.011
Saturated fat (%)	4.51 (±1.23)	6.72 (±1.55)	<.001

Values are presented as mean (±standard deviation). Means and standard deviations are based on the raw values.

Table 3.9. Dietary effects on physiology in humans. Group differences in physiological measures for humans.

Characteristic	Control (n = 30)	High-Fat (n = 30)	<i>p</i>
PBF (%)	29.17 (±11.99)	28.38 (±10.44)	.79
BMI (kg/m ²)	25.75 (±4.45)	26.54 (±6.07)	.77
FG (mg/dl)	82.25 (±8.48)	85.83 (±10.95)	.16
SI (min ⁻¹ /μU·ml ⁻¹)	0.003 (±0.007)	0.001 (±0.001)	.33
PCGR (c-peptide iAUC/glucose iAUC)	0.09 (±0.29)	0.09 (±0.21)	.72
IL-6 (pg/ml)	0.04 (±0.62)	-0.02 (±0.78)	.77

Values are presented as mean (±standard deviation). Means and standard deviations are based on the raw values. PBF = body fat percentage; BMI = body mass index; FG = fasting glucose; SI = insulin sensitivity; PCGR = insulin secretion; IL-6 = inflammation.

Table 3.10. Body fat percentage and choice in humans. Body fat moderation model output for humans from a logistic regression with the fixed effects of Group (Control vs. High Fat), Slope, and Body Fat Percentage.

	Delay				Magnitude			
	<i>b</i>	SE	<i>z</i>		<i>b</i>	SE	<i>z</i>	
(Intercept)	-0.48	0.16	-3.00	**	0.29	0.16	1.81	
Slope	1.30	0.29	4.50	***	-1.25	0.29	-4.31	***
BF	-0.02	0.01	-1.46		0.03	0.01	2.20	*
Group	-0.10	0.16	-0.66		-0.25	0.16	-1.56	
Slope × BF	0.08	0.03	2.96	**	-0.10	0.03	-3.63	***
Slope × Group	-0.17	0.29	-0.58		0.31	0.29	1.06	
Group × BF	0.01	0.01	0.64		-0.03	0.01	-1.94	
Slope × Group × BF	-0.06	0.03	-2.19	*	0.07	0.03	2.46	*

* $p < .05$

** $p < .01$

*** $p < .001$

BF = percentage body fat

Table 3.11. Fasting glucose and choice in humans. Fasting glucose model output for humans from a logistic regression with the fixed effects of Group (Control vs. High Fat), Slope, and Fasting Glucose.

	Delay				Magnitude			
	<i>b</i>	SE	<i>z</i>		<i>b</i>	SE	<i>z</i>	
(Intercept)	-0.54	0.16	-3.38	***	0.31	0.16	1.94	
Slope	1.43	0.29	4.86	***	-1.40	0.29	-4.75	***
FG	-0.04	0.02	-2.29	*	-0.01	0.02	-0.36	
Group	-0.19	0.16	-1.17		-0.24	0.16	-1.53	
Slope × FG	0.06	0.03	1.84		-0.05	0.03	-1.69	
Slope × Group	-0.03	0.29	-0.09		0.16	0.29	0.54	
Group × FG	-0.03	0.02	-1.68		0.01	0.02	0.81	
Slope × Group × FG	0.06	0.03	2.01	*	-0.08	0.03	-2.49	*

*p<.05

**p<.01

***p<.001

FG = fasting glucose

Table 3.12. Insulin sensitivity and choice in humans. Insulin sensitivity model output for humans from a logistic regression with the fixed effects of Group (Control vs. High Fat), Slope, and Insulin Sensitivity.

	Delay				Magnitude			
	<i>b</i>	SE	<i>z</i>		<i>b</i>	SE	<i>z</i>	
(Intercept)	-0.43	0.17	-2.46	*	0.37	0.16	2.31	*
Slope	1.26	0.33	3.79	***	-1.43	0.30	-4.75	***
SI	-16.95	96.86	-0.18		-23.75	38.11	-0.62	
Group	-0.08	0.17	-0.47		-0.21	0.16	-1.29	
Slope × SI	-109.66	194.77	-0.56		-98.39	58.79	-1.67	
Slope × Group	-0.17	0.33	-0.51		0.26	0.30	0.87	
Group × SI	16.09	96.86	0.17		46.16	38.52	1.20	
Slope × Group × SI	158.25	194.77	0.81		69.31	57.88	1.20	

*p<.05

**p<.01

***p<.001

SI = insulin sensitivity

Table 3.13. Insulin secretion and choice in humans. Insulin secretion model output for humans from a logistic regression with the fixed effects of Group (Control vs. High Fat), Slope, and Insulin Secretion.

	Delay				Magnitude			
	<i>b</i>	SE	<i>z</i>		<i>b</i>	SE	<i>z</i>	
(Intercept)	-0.39	0.16	-2.45	*	0.31	0.16	1.93	
Slope	1.20	0.30	4.01	***	-1.13	0.30	-3.79	***
PCGR	0.01	0.06	0.10		0.02	0.06	0.35	
Group	0.03	0.16	0.21		-0.28	0.16	-1.74	
Slope × PCGR	-0.02	0.12	-0.21		-0.07	0.12	-0.64	
Slope × Group	-0.59	0.30	-1.96		0.45	0.30	1.50	
Group × PCGR	-0.10	0.06	-1.64		0.01	0.06	0.19	
Slope × Group × PCGR	0.24	0.12	2.07	*	-0.14	0.12	-1.17	

*p<.05

**p<.01

***p<.001

PCGR = insulin secretion

Table 3.14. Inflammation and choice in humans. Inflammation model output for humans from a logistic regression with the fixed effects of Group (Control vs. High Fat), Slope, and Inflammation.

	Delay				Magnitude			
	<i>b</i>	SE	<i>z</i>		<i>b</i>	SE	<i>z</i>	
(Intercept)	-0.41	0.15	-2.68	**	0.34	0.15	2.20	*
Slope	1.32	0.29	4.50	***	-1.19	0.29	-4.06	***
IL6	-0.39	0.23	-1.69		-0.23	0.23	-1.02	
Group	-0.08	0.15	-0.54		-0.30	0.15	-1.92	
Slope × IL6	0.36	0.43	0.84		-0.14	0.43	-0.33	
Slope × Group	-0.33	0.29	-1.13		0.39	0.29	1.32	
Group × IL6	-0.25	0.23	-1.08		-0.50	0.23	-2.16	*
Slope × Group × IL6	-0.10	0.43	-0.24		0.73	0.43	1.68	

* $p < .05$

** $p < .01$

*** $p < .001$

IL6 = inflammation

Chapter 4 - Discussion

Unhealthful foods have physiological and behavioral consequences. Our previous research demonstrated that diets high in processed fats and sugars induced impulsive choice in rats (Steele et al., 2019; Steele et al., 2017). Impulsive choice is marked by an unwillingness to wait for a larger reward. Understanding impulsive choice is critical because it is linked to obesity (Barlow et al., 2016), diet (Dassen et al., 2015; Garza et al., 2013), and weight loss success (Nederkooorn, Jansen, et al., 2006). There is accumulating evidence that body fat percentage, insulin signaling, and inflammation are related to impulsive choice (Barlow et al., 2016; Eisenstein et al., 2015; Gassen et al., 2019), but diet is not typically investigated along with physiological factors to understand impulsive choice in humans. In Chapter 1, we reviewed the evidence demonstrating that dietary fat intake, body fat percentage, insulin signaling, and inflammation are interrelated. This provided the foundation for the physiological measures used in our studies.

We conducted an assessment of dietary fat intake, physiological markers, and impulsive choice in rats and humans. This approach will provide a better understanding of who is most likely at risk for diet-induced impulsivity and provides an avenue to promote self-control. We used a translational approach with parallel designs in rats and humans. Investigating dietary effects in rats allowed us to understand how diets high in processed fats contribute to physiology and behavior because dietary history can be tightly controlled. Using a rat model, we found that diets high in processed fat induced impulsive choice and altered physiology. Interestingly, the high-fat diet induced a preference for shorter delays, but this effect was not moderated by physiology. Rather, delay and magnitude sensitivity were predicted by the interaction between

dietary fat intake and physiology. The rat model is complemented by the human model, which can more easily be applied in a clinical setting.

Beyond understanding the same factors in rats and humans, we sought to improve the translational methods by developing a novel impulsive choice task for food in Chapter 2. Impulsive choice tasks in rats and humans provide subjects with the choice between a smaller reward after a shorter delay or a larger reward after a longer delay. However, rat and human tasks diverge one important way – rats experience the consequences of their choices, whereas humans do not. Rats wait for the delay period and then they receive the actual reward that they chose. In contrast, most human tasks used in previous research are hypothetical. In our novel task, participants experienced the delay to the reward and received the reward. This novel task is more similar to rat tasks and expands the impulsive choice tasks for food. There are few impulsive choice tasks for food, but research indicates that some of the relationships between physiological variables and impulsive choice may only be expressed when measuring impulsive food choices (Rasmussen et al., 2010; Schiff et al., 2015). Indeed, in the current study, the physiological variables predicted impulsive choice on the real food task, but not the Kirby questionnaire. Therefore, this task may be a better assessment for understanding and predicting choices related to food. Future studies should also consider reward type. The HF rats received food in their impulsive choice task that may have been valued less due to the lower fat content, and this difference could have been responsible for some of species differences. In addition, the human participants worked for M&Ms, which is presumably a high valued reward for most people. People who consumed lower amounts of sugar had inverted choice functions suggesting that the type of reward and motivation to earn that reward may affect impulsive choice when actually receiving the reward. The novel impulsive choice task for food provides an avenue for

better translation of rodent research, and future research should uncover the role of other factors such as reward type, motivation, dietary history, sex, and age.

Using this novel impulsive choice task for food, we conducted a translational study on the relationship between diet and impulsive choice in rats and humans. High-fat diets in rats induced a preference for the shorter delay confirming previous findings (Steele et al., 2017), but this was not the case in humans. The difference in macronutrient breakdown may explain these effects. While we sought to create dietary groups in humans that were similar to the rats with respect to macronutrient composition, there are several key differences that may explain the differences in the relationship between diet and impulsive choice including the use of males only, type of fat (saturated vs unsaturated), source of fat, and differences in vitamin content of the diets. Interestingly, added sugar predicted a preference for the shorter delay and greater sensitivity to changes in delay and magnitude. This is consistent with previous findings in rats (Steele et al., 2019; Steele et al., 2017). The added sugar in humans may relate better to the high-sugar diets in rats because there is less discrepancy regarding the types and sources compared to fat. Together, this finding demonstrates the need to create better parallels between dietary conditions in rats and humans to improve the translation from rat to human models.

While previous research has found that body fat percentage, insulin sensitivity, and inflammation are associated with impulsive choice (Barlow et al., 2016; Eisenstein et al., 2015; Gassen et al., 2019), the current study expanded on the current literature by investigating the dietary effects on these relationships. Our results suggest that body fat percentage was associated with impulsive choice for people that were consuming a diet high in fat. Therefore, the relationship between body fat percentage and impulsive choice observed in the field (Barlow et al., 2016) may depend on diet. This suggests that diet should be included as a factor when trying

to predict impulsive choice. We also found that fasting glucose was predictive of a greater preference for the shorter delay regardless of dietary fat intake, and fasting glucose was predictive of greater sensitivity to delay and magnitude in the control group. This is the first investigation of the relationship between fasting glucose and impulsive choice to our knowledge.

Therefore, dietary fat intake and physiological variables interacted to predict impulsive choice, suggesting that physiology and diet could be risk factors for impulsive food choices (Dassen et al., 2015; Garza et al., 2016; Garza et al., 2013; Guerrieri et al., 2007). Diet, body fat percentage, and fasting glucose are all feasible measures to obtain, and these measures could be signs of early disease risk. Therefore, obtaining these measures could give researchers or practitioners a quick assessment of risk of impulsive choices that could ultimately lead to diet-induced obesity. This information can be used in clinical settings, such as obesity treatment programs, to improve treatment outcomes. Dietary and physiological measures, in combination, could be used to identify individuals most at risk for impulsive choice so that behavioral interventions could be used as a primary preventative measure or in conjunction with the traditional obesity treatment program. There are various behavioral interventions that could be used to target impulsive choice in these individuals (Peterson, Hill, Marshall, Stuebing, & Kirkpatrick, 2015; Rung & Madden, 2018; Smith, Panfil, Bailey, & Kirkpatrick, in press). Together, these factors could inform treatment and possibly predict treatment success (Nederkoorn, Jansen, et al., 2006). Intervening to improve physiology and behavior at this point could reduce the risk of developing diet-related disease such as obesity and Type-2 diabetes.

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