SEX DIFFERENCES IN EXERCISE-MEDIATED CHANGES IN DIET PREFERENCE AND ITS ASSOCIATED COGNITIVE AND METABOLIC OUTCOMES

BY

TIFFANY YATEEN YANG

DISSERTATION

Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Psychology
in the Graduate College of the
University of Illinois Urbana-Champaign, 2021

Urbana, Illinois

Doctoral Committee:

Assistant Professor Nu-Chu Liang, Chair
Associate Professor Ryan N. Dilger
Professor Janice M. Juraska
Assistant Professor Naiman Khan
Associate Professor Yuan-Xiang Pan

ABSTRACT

The modern environment contributes to the obesity epidemic by encouraging a sedentary lifestyle and increased intake of highly processed, energy dense foods. Females are more prone to develop disordered feeding behaviors, such as binge eating, and the prevalence of obesity is greater in females than males. However, obesity-related metabolic and cognitive dysregulation is more severe in males. One mechanism by which exercise may protect against these negative outcomes and restore energy homeostasis is through changes in macronutrient selection, specifically decreasing intake of high fat (HF) food. Sex differences in the susceptibility, outcomes, and exercise as a treatment intervention for obesity, however, have not been well-characterized. Moreover, how factors including diet, cognition, and peripheral metabolic function interact to potentially perpetuate the viscous feedback loop of maladaptive eating behavior and obesity in a sex-specific fashion is poorly understood. The goal of this dissertation was to investigate sex differences in the efficacy of exercise at attenuating the adverse cognitive and metabolic outcomes associated with long-term HF feeding. To this end, our lab has established a voluntary wheel running (WR) and two-diet choice model in rats. Using this paradigm, we found that the simultaneous introduction of WR and HF diet resulted in complete HF diet avoidance in WR rats whereas sedentary (Sed) rats maintained HF diet preference. There is also a sex difference in exercise-mediated changes in diet preference where male rats maintain HF diet avoidance and females reverse their initial HF diet avoidance. Chapter 2 examines the role of gonadal hormones on the expression and maintenance of HF diet avoidance during acute exercise. Chapter 3 extends the voluntary WR and two-diet choice paradigm used in Chapter 2 to assess sex differences in peripheral metabolic function and behavioral flexibility resulting from chronic HF feeding. In Chapter 4, an additional assessment of cognitive behavior was added where heightened impulsivity, a behavior associated with poor dietary self-regulation, binge eating, and obesity, was examined as both a potential vulnerability factor for and outcome of palatable diet preference. To more accurately mimic the fat and

carbohydrate intake in the modern environment, HF was replaced with a Western diet (WD). Impulsive choice was assessed before and after long-term WD exposure and preference in addition to WD-mediated metabolic adaptions. Results suggest that female, but not male, sex hormones as well as developmental factors are important for the expression of sex-typical diet choice patterns during exercise. The ability for exercise to improve peripheral metabolism, including glucose tolerance and insulin sensitivity, was greater in males than females. Although cognitive performance was only moderately improved in rats of both sexes, exercise did appear to have a beneficial effect on cognition. Taken together, the studies in this dissertation contribute to the knowledge of how sex differences in diet preference and exercise interact and lead to sex-specific physiological and behavioral adaptations.

ACKNOWLEDGEMENTS

First, I would like to thank my advisor, Dr. Nu-Chu Liang, for her guidance throughout my graduate school career. In addition, I would also like to thank my committee members, Dr. Ryan Dilger, Dr. Janice Juraska, Dr. Naiman Khan, and Dr. Yuan-Xiang Pan, for their expertise and advice. I am also grateful to have worked with some wonderful lab mates, Jim Choi, David Tkac, Francis Walter, and Dr. Weijie Xu, and numerous undergraduate assistants without whom this work would not have been possible. Finally, I would like to thank Holly Fairfield for all that she does beyond animal care.

I want to thank all my wonderful friends for their support and encouragement throughout the ups and downs of graduate school, especially Sara Westbrook, Carly Drzewiecki, and Kate Hamblen. Additionally, I am grateful to all my friends who have shared pictures and videos of their pets, and to all the cats I have cat-sat – Cow, Finn, Jax, and Randy – for keeping me entertained with their shenanigans.

Lastly, I want to thank my parents for their unwavering support throughout this challenging process and always believing in my success.

TABLE OF CONTENTS

CHAPTER 1: SEX DIFFERENCES IN THE INTERPLAY BETWEEN OBESITY, DIET, AND EXERCISE: COGNITIVE AND METABOLIC OUTCOMES

The globalization of the food industry has led to increased affordability and accessibility of food (Swinburn et al., 2011). To increase production and shelf life stability, foods have become more processed and, as an outcome, tend to have higher glycemic loads than unrefined foods (Foster-Powell et al., 2002). The modern obesogenic environment is not only saturated with food cues to eat, but also provides easy access to a variety of high-fat high-sugar foods (HFHS), which promotes overeating and weight gain (Okreglicka, 2015). Together, the overconsumption of highly palatable processed foods and living a sedentary lifestyle leads to a state of prolonged positive energy balance and exacerbates the development of obesity. Approximately 39% of the global population (Chooi et al., 2019) is considered to be overweight (body mass index (BMI) 25 – 30 kg/m^2) or obese (BMI ≥ 30 kg/m^2). Not only is the worldwide prevalence of obesity concerning, but also the rate at which it is increasing, e.g., 80% increase in incidence from 1980 to 2015 (Collaboration, 2017, Bluher, 2019, Chooi et al., 2019). For example, more than 30% of adults are considered obese within the United States (Bluher, 2019) and analyses project that based on current trends, nearly 50% of adults will be obese by the year 2030 (Ward et al., 2019).

Although obesity is typically classified based on excess body weight and fat, it is a complex disorder that affects whole body physiology including metabolic diseases such as type 2 diabetes, hypertension, stroke (Winocur et al., 2005, Kanoski et al., 2007, Martin et al., 2007) and cognitive disturbances such as depression, mild cognitive impairment, and Alzheimer's disease (Smith et al., 2011, Chen et al., 2017, Steenbergen and Colzato, 2017, Yang et al., 2018). These comorbidities severely impair quality of life and increase risk of morbidity and mortality. Obese individuals tend to have increased preference and intake for high-fat high-sugar (HFHS) foods (Drewnowski and Greenwood, 1983, Hill et al., 2012), which leads to excess weight and fat deposition. The typical Western diet (WD) contains ~40% calories from

both carbohydrates and fats (Okreglicka, 2015) and negatively influences both metabolic (Smith et al., 2011, Chen et al., 2017, Steenbergen and Colzato, 2017, Yang et al., 2018) and cognitive health (Martin et al., 2007). It is important to identify effective treatments to restore body weight homeostasis and mitigate disease risk for obesity and its comorbidities.

Behavioral treatment interventions aimed at restoring energy balance involve reducing caloric intake and increasing physical activity. The effectiveness of regular exercise at reducing body weight and fat is highly dependent on how quickly and whether individuals compensate for the increased energy demand from exercise (Beaulieu et al., 2017, Sparks, 2017, Beaulieu et al., 2020b, Foright et al., 2020). Moreover, exercise training appears to be more effective than diet control (Maesako et al., 2012) such that it decreases visceral fat and insulin resistance more than caloric restriction mediated-weight loss (Coker et al., 2009). A combination of exercise and diet, however, is the most effective method for body weight regulation. Exercise has also been implicated in influencing food preference. More specifically, individuals who are able to maintain long-term weight loss have decreased intake and preference for HF food (Klem et al., 2000, Beaulieu et al., 2017). Given that physically active individuals may cognitively choose to make healthier food selections, how exercise affects diet preference from a more physiological perspective to promote weight loss is unclear.

Distinct sex differences exist in the susceptibility and outcome of obesity. Obesity (Hudson et al., 2007, Flegal et al., 2010, Chooi et al., 2019) and disordered eating behavior (Klump et al., 2013, Hildebrandt et al., 2014) are more prevalent in women than men. However, the adverse metabolic and cognitive outcomes associated with obesity are generally more prevalent and severe in men (Espeland et al., 2018). As a treatment intervention for energy homeostasis and body weight regulation, exercise appears to have a greater efficacy in males (Anderson et al., 2001, Donnelly and Smith, 2005). Collectively, these studies highlight the need to include sex differences as a factor when developing treatment interventions to promote weight loss. Elucidating the mechanisms underlying sex differences in exercise and diet

preference and its associated physiological adaptions may help inform more effective interventions targeting weight loss and improve treatment outcomes.

SEX DIFFERENCES IN EXERCISE AND ENERGY BALANCE

Lifestyle-based treatment interventions for excessive weight gain involve changes in diet and exercise. Exercise can reverse some of the negative physiological impacts of obesity and improve overall body composition (Donnelly et al., 2009). Importantly, neither exercise nor diet alone is as effective at promoting weight and fat loss as regular exercise combined with caloric restriction (Shaw et al., 2006, Stiegler and Cunliffe, 2006, Coker et al., 2009). There is considerable sex and individual variability in response to exercise. That is, not all individuals decrease body weight or fat after regular, supervised exercise and are referred to as “non-responders” (Hammond et al., 2019). The percentage of non-responders is higher in women than men, such that roughly half of the women in a study increased body weight gain with exercise whereas the majority of men decreased body weight (Anderson et al., 2001, Donnelly and Smith, 2005). There is also an inverse correlation between physical activity and body fat in men but this relationship is absent in women (Bjorntorp, 1989, Westerterp and Goran, 1997, Paul et al., 2004). The rodent literature parallels the human literature. Studies have shown that exercise suppresses weight gain and adiposity to a greater extent in male than female rodents (Rolls and Rowe, 1979, Pitts, 1984, Cortright et al., 1997, Schroeder et al., 2010, Carrera et al., 2011) when lean (Bjorntorp, 1989, Cortright et al., 1997) and obese (Schroeder et al., 2010). Taken together, these results indicate that males are more responsive to the weight and fat loss effects than females. These sex differences in the physiological response to exercise likely influence the effectiveness of treatment outcomes.

Exercise increases energy expenditure, and the compensatory response to this energy deficit through changes in energy intake and food preference is highly variable in humans (Blundell and King, 1999, Scheurink et al., 1999, Melzer et al., 2005, King et al., 2009, Laskowski, 2012, Ebrahimi et al., 2013, Schubert et al., 2013, Donnelly et al., 2014).

Investigations into sex differences in the underlying the variable response to exercise in regards to energy balance in humans have been limited (Westerterp et al., 1992, Washburn et al., 2015). Currently, there is no clear consensus in the literature and some studies even report no sex differences in appetite and food intake in individuals engaging in regular exercise (Pomerleau et al., 2004, Hagobian et al., 2009, Ebrahimi et al., 2013, Thackray et al., 2016). In contrast, sex differences in exercise-mediated changes in food intake in rats are more apparent and consistent. After initiating a bout of exercise, male rats typically decrease food intake (Tokuyama et al., 1982, Looy and Eikelboom, 1989, Kawaguchi et al., 2005, Carrera et al., 2011). Female rats, however, vary in their response to voluntary WR and have been shown to both decrease (Tokuyama et al., 1982, Eckel and Moore, 2004) and increase (Carrera et al., 2011) food intake upon exercise. Sex-specific adaptations in energy balance in response to exercise may lead to different metabolic adaptations; however, the current literature is mostly limited to male subjects and precludes analysis of sex differences.

Beyond its effects on body weight regulation and energy balance, exercise can also influence diet preference. Studies from The National Weight Control Registry found that exercise alters dietary selection of macronutrients (Klem et al., 1997, Shick et al., 1998, Wing and Hill, 2001, Catenacci et al., 2014) among individuals who successfully maintained weight-loss ≥ 13.6 kg for at least 1 year. These individuals report that they exercise regularly and consume low-fat diets (Klem et al., 1997, Shick et al., 1998). Recent studies provide additional support for a role for exercise to decrease fat preference (Finlayson et al., 2011, Martin et al., 2019, Riou et al., 2019, Beaulieu et al., 2020a). Importantly, this shift in food preference was dependent on whether an individual responded to the weight loss effects of exercise. Non-responders that compensated for exercise and did not reduce body weight tended to increase liking and wanting for fatty foods (Finlayson et al., 2011, Sparks, 2017, Beaulieu et al., 2020b). These individuals also had a preference for fatty foods prior to the exercise intervention, which suggests that the loss of body weight and fat may work in combination with exercise to promote

a decrease in fat intake and preference. Currently, the biological mechanisms underlying the ability for exercise to influence diet preference have not been clearly elucidated.

Studies from our lab used a rodent model of voluntary exercise to address this gap in knowledge. In our voluntary wheel running (WR) and two-diet choice model, rats are given concurrent access to two diets (chow vs. palatable diet) and access to running wheels. Sedentary (Sed) rats given diet choice between chow and HF diet will prefer HF over chow diet. Although introducing WR to these Sed rats with an established preference for HF diet reduces intake and preference for the HF diet (Scarpace et al., 2010, Shapiro et al., 2011, Scarpace et al., 2012, Liang et al., 2015), a more robust effect is seen when WR and a novel HF diet are introduced together. With the simultaneous WR and two-diet choice paradigm, male rats show complete and persistent HF diet avoidance (Moody et al., 2015, Yang et al., 2017). In contrast, most female rats reverse their initial HF diet avoidance and establish preference for the HF diet within 2 weeks of WR and two-diet choice. Ovariectomized females express diet choice patterns similar to that of gonadally-intact males where they maintain HF diet avoidance for a longer period than intact cycling females (Moody et al., 2015). Results from these studies suggest sex hormones may underlie the sex difference in exercise-mediated changes in diet preference. To this end, Chapter 2 will assess the role for gonadal hormones in mediating the expression of sex-specific diet choice patterns during exercise.

SEX DIFFERENCES IN METABOLIC ADAPTATIONS TO DIET AND EXERCISE

Weight gain and increased abdominal adiposity potentiates dysregulated adipokine secretion (Ouchi et al., 2011, Kwon and Pessin, 2013, Jung and Choi, 2014) and insulin resistance (McNeilly et al., 2011, Kwon and Pessin, 2013) in metabolic organs (Zierath et al., 1997, Sabio et al., 2008, Blazquez et al., 2014, Boucher et al., 2014) that play a central role in the control of food intake and whole-body energy metabolism (Kim, 2016). Consumption of highly processed foods typical of the modern diet negatively influences metabolic health (Smith et al., 2011, Chen et al., 2017, Steenbergen and Colzato, 2017, Yang et al., 2018) and results in

larger spikes of blood glucose relative to unrefined food (Foster-Powell et al., 2002). A pattern of eating sugary, HF foods further perpetuates the cycle of excessive weight gain, abdominal adiposity, and metabolic dysregulation. Moreover, increased intake of dietary fat exacerbates the development of insulin resistance in peripheral organs, including the muscle, liver, and adipose (Zierath et al., 1997, Sabio et al., 2008, Blazquez et al., 2014, Boucher et al., 2014) and the brain (Clegg et al., 2011). Given that peripheral insulin resistance is correlated with central insulin resistance (Mielke et al., 2005) and HF feeding induces both central and peripheral insulin resistance (Clegg et al., 2011), the development of peripheral insulin resistance may also negatively impact cognitive health.

Impaired fasting blood glucose is associated with hepatic insulin resistance and involves decreased basal insulin secretion and suppressed insulin-mediated glucose uptake despite normal plasma insulin (Meyer et al., 2006, Abdul-Ghani et al., 2007). Elevated fasting blood glucose is an early indication of and risk factor for metabolic syndrome, which is comorbid with obesity and includes abdominal adiposity, hyperlipidemia, and insulin resistance (Festa et al., 2004). Indeed, obese individuals with elevated fasting blood glucose were more prone to develop metabolic syndrome (DeFina et al., 2012, Akter et al., 2017) and type 2 diabetes (DeFina et al., 2012). Higher fat intake also facilitates increased metabolic disturbances (i.e., glucose intolerance and insulin resistance) in humans (Storlien et al., 1996, Lichtenstein and Schwab, 2000, Vessby, 2000, Bisschop et al., 2001), and HF diet-induced insulin resistance appears to be greater in magnitude in males compared to females in humans (Hwang et al., 2010, Laredo et al., 2015, Shields et al., 2016, Arcones et al., 2019, Huebschmann et al., 2019). Impaired glucose tolerance is highly correlated with impaired skeletal muscle insulin resistance and generally involves both reduced insulin release and peripheral insulin resistance (Meyer et al., 2006, Abdul-Ghani et al., 2007). In regards to fat quality, saturated fats are more detrimental than unsaturated fat in the development of insulin resistance (Vessby et al., 2001). Replacing saturated with monosaturated fatty dietary acids was able to improve insulin sensitivity in

healthy individuals. Thus, specifically reducing saturated fat intake may be critical for substantially improving insulin action.

HF feeding has also been shown to impair glucose tolerance in animals and is associated with decreased basal and insulin-mediated glucose metabolism (Williams et al., 2014). Male rodents are more prone to weight gain and metabolic dysregulation with HF feeding than females (Elias et al., 2003, Amengual-Cladera et al., 2012, Barron et al., 2013, Underwood and Thompson, 2016). There are 3 main diets used in animal models of diet-induced obesity including high-carbohydrate (HC), HF, and HCHF diets (Rodriguez-Correa et al., 2020). Compared with HC and HCHF diets, HF diet induced the most significant weight and fat gain, increases in fasting blood glucose, and degree of insulin resistance (Panchal and Brown, 2011, Wong et al., 2016, Moreno-Fernandez et al., 2018, Lang et al., 2019, Rodriguez-Correa et al., 2020). A comprehensive study assessing the effects of 10%, 32%, and 45% fat diets on parameters including weight gain, fat composition, and insulin levels found a dose-dependent increase in all parameters as levels of dietary fat increased (Ghibaudi et al., 2002). Thus, it appears that fat intake is especially detrimental to glucose homeostasis. In selectively bred Sprague-Dawley diet-induced obese (DIO) and diet resistant (DR) prone rats, ~4 weeks of HF feeding resulted in glucose intolerance, dyslipidemia, and increased body weight and fat in DIO rats while the metabolic profile of DR rats was not negatively influenced (Levin et al., 1997, Madsen et al., 2010).

Sex differences in glucose homeostasis may contribute to the greater metabolic dysregulation from HF diet intake in males compared to females. Females have lower fasting blood glucose during fasting whereas men show impaired fasting glycaemia (Soeters et al., 2007, Mauvais-Jarvis, 2018, Lagou et al., 2021). During oral glucose tolerance tests (OGTT), females show elevated 2 h blood glucose concentrations after the glucose challenge (Sicree et al., 2008). Together, results from these studies suggest that men tend to exhibit impaired fasting glycaemia whereas women show glucose intolerance. Women are also more resistant to

developing insulin resistance than men when matched for physical fitness (Frias et al., 2001). However, women with lower fitness than men display insulin resistance. These studies suggest that not only are there sex differences in the metabolic outcome of obesity, but the sexes may also respond to exercise as a treatment intervention differently.

In rodents, females also appear to be more resistant against developing insulin resistance with long-term HF feeding (Basu et al., 2006, Medrikova et al., 2012). During OGTT the spike in blood glucose was lower in magnitude in females compared to males, and glucose levels returned to fasting levels more rapidly in females (Amengual-Cladera et al., 2012, Rudnicki et al., 2018). In contrast, another study has reported that females are less insulin sensitive and more prone to develop severe diabetes than males (Vital et al., 2006). Given the limited number of studies that include both sexes within the same study, it is unclear whether females remain more insulin sensitive with long-term HF feeding. We address this gap in knowledge in Chapters 3 and 4 by examining alterations in peripheral metabolism following chronic HF or WD preference in rats of both sexes.

As a weight loss intervention exercise not only facilitates the maintenance of a healthy body weight, but also improves metabolic health (Laskowski, 2012, Wegner et al., 2014). Exercise was able to improve fasting blood glucose within 7 days of exercise in non-diabetic (Trovati et al., 1984) and type 2 diabetic patients (Boule et al., 2005). Importantly, exercise does not always decrease fasting blood glucose but rather regulates it around a tighter physiological set point. In other words, exercise can decrease or increased blood glucose levels depending on pre-exercise levels,(i.e., reduced in those with high fasting blood glucose and elevated in those with low fasting blood glucose) (Norton et al., 2012). Exercise training leads to greater decreases in visceral fat and insulin resistance in obese individuals compared to dietary interventions (Coker et al., 2009, Maesako et al., 2012, Shakil-Ur-Rehman et al., 2017). However, exercise alone without other lifestyle changes was unable to completely reverse altered glucose metabolism in pre-diabetic individuals (Jenkins and Hagberg, 2011). Thus,

lifestyle changes including both diet and exercise may be necessary to restore glucose homeostasis.

The ability for exercise training to increase insulin sensitivity appears to be influenced by sex but not metabolic state (e.g., normal weight, diet- or genetically-induced obese, diabetic) (Goodyear et al., 1988, Bongbele et al., 1992, Tokuyama and Suzuki, 1998, Patterson et al., 2008, Gollisch et al., 2009, Beaudry et al., 2015). More specifically, exercise enhances glucose uptake in skeletal muscle and insulin sensitivity consistently in males but not females (Richter et al., 1982, Goodyear et al., 1988, Bongbele et al., 1992, Tokuyama and Suzuki, 1998, Gollisch et al., 2009, Beaudry et al., 2015). In contrast, females appear to be less responsive to the insulin-sensitizing and weight and fat loss effects of exercise (Tokuyama et al., 1982, Hill et al., 1989, Looy and Eikelboom, 1989, Donnelly et al., 2004, Kawaguchi et al., 2005, Carrera et al., 2011) than males. Presently, no study has characterized sex differences in the ability for exercise to rescue metabolic deficits from chronic HF exposure through changes in diet preference, which could help improve treatment outcomes for females.

SEX DIFFERENCES IN COGNITIVE RISK FACTORS AND OUTCOMES

Our modern environment is saturated with appetitive cues to eat and easy access to a variety of HFHS foods that stimulate hedonic eating. Poor cognitive control may be a vulnerability factor where individuals are unable to exert dietary self-regulation and overeat in the absence of physiological hunger (Smith et al., 2011), which is amplified by the presence of appetitive environmental cues (Hall et al., 2014, Hall et al., 2015). There appears to be a reciprocal influence between obesity and deficits in executive function (Sellaro and Colzato, 2017, Yang et al., 2018); however, whether these deficits are predictors or consequences of excessive weight gain are still unclear. The prefrontal cortex (PFC) is a central brain region responsible for cognitive processes relating to executive function, such as coordinating internal, goal-directed behavior (Dajani and Uddin, 2015, Edwards et al., 2018). Executive functions can be broken down into 3 separate domains including inhibitory control, working memory, and

cognitive flexibility (Khan et al., 2015). Cognitive flexibility is the domain that gives us the ability to adjust our eating attitudes (thoughts) and behaviors (goals) to adapt to the changing environment and engage in homeostatic eating.

HF feeding has been shown to induce region-specific deficits in PFC-mediated executive function (Kanoski et al., 2007, Stranahan et al., 2008, McNeilly et al., 2011, Aslani et al., 2015). This may in part be due to HF feeding-associated development of insulin resistance. Indeed, decreased resting state functional connectivity was shown to be inversely associated with insulin resistance (Musen et al., 2012). Results from studies using 2-deoxy-2[^{18}F]fluoro-D-glucose (FDG)-PET scans revealed that increased insulin resistance was associated the lower regional glucose metabolism in the prefrontal, cingulate, temporal, and insular cortices (Baker et al., 2011, Willette et al., 2015). This could lead to functional cognitive and behavioral changes associated with those regions. In addition, individuals with higher waist-to-hip ratios and abdominal adiposity have lower resting state PFC metabolism (Wright et al., 2016) and this dysregulation can occur prior to the development of insulin resistance (Volkow et al., 2009, Willeumier et al., 2011). Higher BMI and adiposity are also associated with lower total brain volume and region-specific structural changes in brain grey matter, including decreased hippocampal, temporal, cerebellar, orbitofrontal, and PFC volume (Debette et al., 2010, Smucny et al., 2012, Ursache et al., 2012, Medic et al., 2016, Wang et al., 2017a, Garcia-Garcia et al., 2018). Importantly, these structural changes are correlated with behavioral deficits such that individuals with lower PFC grey matter volume perform worse on tests of executive function (Walther et al., 2010). Functional neuroimaging data support the structural results. Lower glucose metabolism in the PFC is associated with impaired performance on neuropsychological tests of cognitive flexibility (e.g., Symbol Digit Modalities Test, Stroop Interferences, Wisconsin Card Sorting Task, etc.) (Lowe et al., 2019). Likewise, rodent studies have also shown that lesions to the PFC impair behavioral flexibility and increase perseverative responses (Eichenbaum et al., 1983, Murray et al., 2015). Taken together, these results provide evidence

that decreased PFC activation can lead to deficits in behavioral flexibility and could potentially influence food choice.

Sex differences in PFC-dependent tests of cognitive flexibility have not been extensively studied. To date, studies suggest a male advantage in the Iowa Gambling Task (Bolla et al., 2004, van den Bos et al., 2013). However, this task involves components for both cognitive flexibility and reward sensitivity and it is unclear which aspect is contributing to the observed sex difference (Evans and Hampson, 2015). Results from recent studies have shown both a male bias for better reversal learning as well as no sex difference in tests of cognitive flexibility (Shields et al., 2016). A neuroimaging study using marmosets reported sex differences in the correlation between reversal learning and resting state functional connectivity, which may have contributed to the poorer reversal learning in females (LaClair et al., 2019). Similarly, rodent studies of behavioral flexibility have primarily been limited to males. As a consequence, whether sex differences in reversal learning exist is uncertain (Hamilton and Brigman, 2015). Nevertheless, the small number of studies including rodents of both sexes suggest no sex difference (Grafe et al., 2017, Goodwill et al., 2018, Westbrook et al., 2018, Chowdhury et al., 2019) or a slight male bias (Bissonette et al., 2012). Thus, while the incidence of disordered eating is higher in females (Hudson et al., 2007, Flegal et al., 2010), it is uncertain whether poor behavioral flexibility could be a potential sex-specific vulnerability factor for non-homeostatic eating.

The vast majority of rodent studies in the field of diet and cognition have focused on hippocampal-dependent learning and memory and have utilized male subjects (Greenwood and Winocur, 1996, Winocur and Greenwood, 1999, 2005, Stranahan et al., 2008, Kanoski and Davidson, 2010, Valladolid-Acebes et al., 2011). To date, there have been a total of 3 studies that utilized the DIO and DR Sprague-Dawley rat model to study diet-induced changes in cognitive behavior. These studies have been limited to hippocampal-dependent learning and memory and only included male rats (Kanoski et al., 2010, Davidson et al., 2012, Davidson et

al., 2013). Nonetheless, studies assessing changes in PFC-sensitive behaviors found that HF feeding can induce deficits in PFC-dependent tests of behavioral flexibility (Kanoski et al., 2007, Stranahan et al., 2008, McNeilly et al., 2011, Aslani et al., 2015). A few studies have found that HF feeding impaired behavioral flexibility to a greater extent in males than females (Hwang et al., 2010, Laredo et al., 2015, Shields et al., 2016). The decrease in behavioral flexibility was correlated with decreased insulin sensitivity, but not body weight or blood glucose (McNeilly et al., 2011). In addition, the deficits in behavioral flexibility were associated with decreased spine density in the PFC and can occur before the development of insulin resistance (Bocarsly et al., 2015). Collectively, these studies suggest a bidirectional relationship between metabolic and cognitive function but precisely how these factors interact to influence flexible decision making in regards to food choice is unknown.

Improving cognitive flexibility in obese individuals may help with breaking persistent unhealthy habits and food choices and promote weight loss (Carels et al., 2014, Allom et al., 2018). One way by which cognitive flexibility can be improved is through exercise. This has been reliably demonstrated in both humans (Masley et al., 2009) and rodents (Brockett et al., 2015). Exercise reverses HF feeding-related cognitive impairments (Molteni et al., 2004, Kanoski and Davidson, 2010, Woo et al., 2013, Gibbons et al., 2014, Noble et al., 2014, Klein et al., 2016) whereas dietary changes (McNeilly et al., 2011, Boitard et al., 2016, McNeilly et al., 2016) and insulin sensitizing drugs (McNeilly et al., 2012) can only partially reverse deficits in behavioral flexibility. To our knowledge, no studies have directly examined sex differences in the interaction between diet and exercise on alterations in flexible responding. Chapter 3 will attempt to provide insight into this relationship by assessing if there are sex differences in the efficacy of exercise at rescuing HF-mediated impairments in behavioral flexibility.

IMPULSIVITY AS A VULNERABILITY FACTOR FOR AND OUTCOME OF OBESITY

Impulsivity is a multifaceted behavior that can be divided into impulsive action (i.e., the inability to inhibit a prepotent response) and impulsive choice (i.e., preference for smaller,

immediate rewards over larger, delayed rewards) (Broos et al., 2012, Weafer and de Wit, 2014). Impulsive action and choice are not correlated with each other in humans or rodents, and this behavioral dissociation (Broos et al., 2012, Weafer and de Wit, 2014) suggests that they have distinct neural correlates (Dalley et al., 2008, Peters and Buchel, 2011). Both aspects of impulsivity are strongly implicated in overeating and obesity (VanderBroek-Stice et al., 2017, Benard et al., 2019) and should be invested as separate constructs to elucidate the neurobiological mechanisms underlying the maladaptive behaviors associated with heightened impulsivity including compulsive overeating and binge-like eating behavior in addition to lack of dietary restraint (Fagundo et al., 2012, Benard et al., 2017), behaviors which are more common in females (Hudson et al., 2007, Flegal et al., 2010). Impulsive action has been consistently shown to predict binge-like overeating in humans (Meule et al., 2017) and rodents (Velazquez-Sanchez et al., 2014) whereas this relationship is less clear for impulsive choice (Smith et al., 2019). Conflicting reports including no association between overeating and impulsive choice (Moore et al., 2018) and a positive correlation between impulsivity and binge eating (Vickers et al., 2017) have been reported. Regardless, higher preference for smaller, immediate rewards was found to be associated with higher affect intensity and vulnerability for binge eating (Smith et al., 2019). Thus, heightened impulsivity may represent a vulnerable neurobiological phenotype for overeating and obesity (Dietrich et al., 2014). However, impulsivity is more commonly examined in the drug addiction field. Consequently, there exists a gap in knowledge regarding the predictive relationship between pre-clinical impulsivity and eating habits.

A lack of inhibitory control may increase the tendency to overconsume unhealthy, calorie-dense foods that, in turn, lead to more impulsive behavior in a vicious cycle that manifests as obesity. Increased PFC activation is associated with better self-control including resisting the desire to eat high calorie foods (Lopez et al., 2014) and overeating (Lopez et al., 2016, Han et al., 2018). Decreased PFC activation, however, is associated with poorer inhibitory control and higher BMI, both of which are key features of obesity (Lavagnino et al., 2016). In line

with this, obese individuals with and without comorbid binge eating disorder show deceased engagement of the PFC during a food specific passive viewing and response inhibition task (Rosch et al., 2020). Response inhibition appears to be inversely correlated with BMI at both the behavioral (increased impulsivity) and neural (reduced activation of frontal executive regions) levels (Batterink et al., 2010). Peripheral insulin resistance, however, was a better predictor of increased impulsive action than BMI (Eckstrand et al., 2017). In addition, obese women also show decreased engagement of executive control brain areas during a delay discounting task and made more impulsive choices than non-obese women (Stoeckel et al., 2013). Stoeckel et al. (2013) also report that the decreased activation in frontoparietal brain areas was associated with higher levels of impulsive behavior, which suggests a role of the PFC in impulsive choice behavior.

PFC hypoactivation is correlated with increased attentional impulsiveness and decreased response inhibition, which could explain the tendency to overeat palatable foods and contribute to altered metabolism (Hege et al., 2015). Selective insulin resistance in the PFC is also associated with deficits in impulse control and overeating (Winocur and Greenwood, 2005, Rasmussen et al., 2010), and these cognitive deficits were correlated with visceral adiposity (Kullmann et al., 2015). To further support the relationship between the PFC and impulsive choice, lesion studies in rodents have shown that inactivation of the PFC increased preference for the smaller immediate reward over the larger delayed reward (Mobini et al., 2002, Churchwell et al., 2009). Thus, it is possible that behavioral impulsivity leads to poor dietary self-regulation and metabolic dysregulation and may act to both promote and maintain excessive weight gain.

Sex differences in impulsivity may influence eating behavior, and the evidence for sex differences in impulsive choice for humans and rodents is mixed. In humans, impulsive choice behavior is influenced by reward delivery and type (real/hypothetical and drug/food/monetary) in addition to hormonal status (Smith and Hantula, 2008, Cross et al., 2011, Mitchell and Potenza,

2015, Weinstein and Dannon, 2015) and reports on sex differences are mixed (Mischel and Underwood, 1974, Kirby and Marakovic, 1996, Silverman, 2003, Reynolds et al., 2006, Beck and Triplett, 2009). The rodent literature parallels the human literature. Studies have reported higher levels of impulsive choice were reported in both males (Panfil et al., 2020) and females (Perry et al., 2007, Weafer and de Wit, 2014, Lukkes et al., 2016), whereas some reported no sex difference (Perry et al., 2008a, Hammerslag et al., 2019, Sackett et al., 2019). Hormonal status during testing may have influenced the assessment of impulsive choice where progesterone has been shown to be protective (Quinones-Jenab and Jenab, 2010, Swalve et al., 2016, Sjoberg and Cole, 2018, Swalve et al., 2018) and estrogen facilitative (Lynch et al., 2002, Carroll and Anker, 2010). These sex differences in impulsivity may influence the expression of disordered eating behavior.

HF feeding has been shown to increase impulsivity in rodents (Winocur and Greenwood, 2005, Robertson and Rasmussen, 2017, Steele et al., 2017). Studies examining impulsive choice specifically, however, have been rather limited and the results have been mixed – studies have reported no change (Garman et al., 2021) to increased (Steele et al., 2017) and decreased (Narayanaswami et al., 2013). The length of HF diet exposure was 2 weeks in Garman et al. (2021) and 8 weeks in Steele et al. (2017) and it is possible that changes in impulsive choice behavior do not become evident with shorter dietary exposure. In addition, Steele et al. (2017) supplemented chow with hydrogenated vegetable fat as a source of fat whereas Garman et al. (2021) used a 60% HF diet, and the different sources of dietary fat may have led to differential effects on impulsive choice. Narayanaswami et al. (2013) used DIO and DR Sprague-Dawley rats and found that with 8 weeks of 31.8% HF diet exposure, DIO rats made less impulsive choices than DR rats. All three studies utilized male rats and thus, it is unclear what the direction of effect would be in females. Given that females are more prone to develop disordered eating behavior males (Imperatori et al., 2013, Klump et al., 2013, Hildebrandt et al., 2014, Eneva et al., 2017), it would be of interest to determine if HF diet

negatively influences the cognitive control of feeding behavior. Differences in task design, length of HF diet exposure, and testing procedures also make it difficult to draw conclusions in regards to whether diet specifically increases impulsive choice behavior. Recent evidence points toward exercise being able to decrease impulsive choice in humans (Tate et al., 2015, Sofis et al., 2017, Albelwi et al., 2019) and female rodents (Strickland et al., 2016). Chapter 4 attempts to assess whether pre-clinical impulsivity can predict future palatable diet preference and the efficacy of exercise at attenuating diet-induced increases in impulsive choice behavior in rats of both sexes.

SUMMARY

Given the rapidly increasing rate at which the population is developing obesity, it is critical to determine suitable treatment interventions to combat the global health crisis. Sex differences in feeding behaviors and exercise have been studied separately and extensively. However, how exercise interacts with diet choice to influence sex-dependent cognitive and metabolic outcomes has been poorly characterized. In this dissertation, I address this gap in knowledge by first assessing the role of sex hormones in the expression of sex-specific palatable diet choice patterns during acute exercise (Chapter 2; Yang & Liang, 2018). Then, I examined the cognitive and metabolic outcomes resulting from sex differences in palatable diet preference and adaptation to exercise (Chapter 3; Yang, Gao, & Liang, 2020 and Chapter 4). I also investigated the potential for trait impulsivity as a vulnerability factor for palatable diet preference and the efficacy of exercise to attenuate diet-mediated increases in impulsivity (Chapter 4). The knowledge gained from the collection of studies in this dissertation will further characterize sex differences in this field and may provide insight towards developing sex-specific treatments to target weight loss and improve overall health.

CHAPTER 2: ROLE OF GONADAL HORMONES IN MEDIATING SEX-SPECIFIC DIET CHOICE PATTERNS DURING EXERCISE[1]

ABSTRACT

Habitual exercise is associated with decreased preference for high fat (HF) foods and may be a viable treatment intervention to promote weight loss and restore energy homeostasis for overweight and obese individuals. Past studies using a wheel running (WR) and two-diet choice (chow vs. HF) paradigm found that upon simultaneous introduction of a novel HF diet and WR, the majority of male WR rats persistently avoid the HF diet. HF diet avoidance is more transient in female WR rats that not only reverse HF diet avoidance, but also eventually establish a preference for the HF diet. The hormonal mechanism underlying this sex difference in exercise-mediated changes in diet preference is unclear. Given the influential role of estrogen signaling in feeding behavior, we hypothesized that estradiol is required for the reversal of HF diet preference in female WR rats. To test this, the duration of HF diet avoidance was compared among males, sham-operated females, and OVX rats with hormone replacement of oil vehicle, estradiol benzoate (E), progesterone (P), or both (E+P). Female and OVX E+P WR rats reversed HF diet avoidance more rapidly and frequently than males. E+P, but not E or P, replaced OVX WR rats significantly reversed HF diet avoidance. OVX oil rats avoided HF diet to the same extent as male rats during the first half diet choice but then sharply increased HF diet intake to the degree of preference. This incomplete elimination of sex differences suggests that developmental factors or androgens may partially mediate the maintenance of running-induced HF diet avoidance. To examine the role of androgens, male rats were sham-operated or orchiectomized (GDX). Both intact and GDX male WR rats persistently avoided the HF diet. Taken together, these results suggest that the activational effects of ovarian hormones play a role in female specific running-induced changes in diet choice patterns, but the activational effects of androgens are not required for the expression of HF diet avoidance in males.

[1]Data from this chapter are published in Yang, TY & Liang, NC (2018). Ovarian hormones mediate running-induced changes in high fat diet choice patterns in female rats. *Horm Behav*, *100*, 81-93.

RATIONALE

Disordered eating behaviors, such as binge eating, is more common in females than males (Hudson et al., 2007, Flegal et al., 2010) and contributes to the development of obesity. Regular physical activity is a way to restore energy balance with non-homeostatic eating. However, females do not consistently reduce body weight or adiposity in response to exercise (Bjorntorp, 1989, Anderson et al., 2001, Paul et al., 2004, Donnelly and Smith, 2005) and often compensate for the increased energetic requirement with increased food intake leading to weight gain (Cortright et al., 1997, Carrera et al., 2011, Riou et al., 2019). Recent research focusing on the impact of exercise on changes in macronutrient preference and consumption (Beaulieu et al., 2017, Beaulieu et al., 2020b) found that chronic exercise is associated with decreased fat intake (Martin et al., 2019, Riou et al., 2019, Beaulieu et al., 2020a). Whether exercise directly mediates decreased preference for HF food is unclear because humans may be more mindful and consciously make healthier food choices after exercising. To this end, our laboratory utilized a WR and two-diet choice model to examine the relationship between exercise and diet preference in rats of both sexes. Male rats express complete and persistent HF diet avoidance whereas females reverse their avoidance. Removal of ovarian hormones through OVX appears to increase the persistency of HF diet avoidance to be similar to that of gonadally-intact males (Moody et al., 2015).

Central or peripheral estradiol administration has been shown to suppress food intake, adiposity, and body weight (Wade and Gray, 1979, Asarian and Geary, 2002, Santollo et al., 2010, Eckel, 2011). In contrast, progesterone administration alone has no effect on these measures (Wade and Gray, 1979, Gray and Wade, 1981, Asarian and Geary, 2006, Yu et al., 2011). Given the lack of effect of progesterone, these results suggest that estradiol plays a more influential role than progesterone in feeding behavior. In orchiectomized males, high dose testosterone decreases food intake, adiposity, and body weight (Gray et al., 1979). This suppression of food intake is likely due to the aromatization of testosterone into estrogenic

metabolites (Nunez et al., 1980, Siegel et al., 1981) rather than testosterone action itself. Taken together, these studies implicate sex hormones as probable candidates underlying the expression of sex-specific diet choice patterns during exercise.

Gonadal hormones play a major role in the control food intake and feeding behavior (Asarian and Geary, 2013, Begg and Woods, 2013). Replacement with estradiol alone is often sufficient to restore estrus associated feminine behavior (e.g., food intake, physical activity, lordosis, etc.), and OVX rats are commonly primed with estradiol or both estradiol and progesterone prior to behavioral tests (Sodersten and Eneroth, 1981, Olster and Blaustein, 1988, Apostolakis et al., 1996). However, very few studies have investigated the effects of progesterone alone (Zucker, 1969, Frye and Walf, 2004) and do not allow us to tease apart whether both ovarian hormones are required for the expression of female-typical behavior.

In the present study, we first examined whether ovarian hormones are necessary for the female-typical shift from HF diet avoidance to preference while wheel running. Diet choice patterns were compared among intact males, sham-operated females, and OVX rats with oil vehicle (O), estradiol benzoate (E), progesterone (P), or both (E+P) replacement. Given that diet choice patterns did not differ among WR gonadally-intact male and OVX rats (Moody et al., 2015) and that estradiol is more influential in regulating food intake than progesterone (Wade and Gray, 1979, Geary and Asarian, 1999, Asarian and Geary, 2002, Butera, 2010, Eckel, 2011), we hypothesized that estradiol signaling in OVX rats is required for the expression of female-specific diet choice patterns. The partial elimination of sex differences with OVX led us to question if androgens played a role in mediating the persistency of HF diet avoidance in males. Thus, diet choice patterns were compared between sham-operated or orchiectomized (GDX) males.

METHODS

Subjects

Subjects were 48 male (250-275g) and 100 female (150-175g) Sprague-Dawley rats (Envigo, Indianapolis, IN) that were ~7-8 weeks old upon arrival. Rats were individually housed in polyethylene tubs on a 12:12 light-dark cycle (lights on at 0200 h) with ad lib access to a standard chow diet (3.1 kcal/g, 58% carbohydrate, 24% protein, and 18% fat; Teklad global 2018, Teklad Diets, Madison, WI) and tap water during habituation. After habituation, male rats were left undisturbed while female rats underwent either sham or bilateral OVX surgery (Idris, 2012) for the hormone replacement component of the study. Female rats were vaginally lavaged daily during the middle of the light cycle (0800 h) beginning 5 days post-surgery; afterwards, vaginal cytology was inspected to track estrous stage and verify successful OVX surgery and hormone replacement. A separate set of male rats were sham-operated or orchiectomized (Idris, 2012) at the same time point for the androgen component of the study.

Macronutrient	Description	Unit	Teklad 2018 (3.1 kcal/g)	45% HF Diet (4.74 kcal/g)
Protein	Total	% kcal	24	20
Carbohydrate	Sucrose	% kcal	-	17
	Other carbohydrates	% kcal	58	18
Fat	Total	% kcal	18	45
	Saturated fats	% of total fat (wt)	0.9	31.4
	Monounsaturated fats	% of total fat (wt)	1.3	35.5
	Polyunsaturated fats	% of total fat (wt)	3.4	33.1

Table 2.1. Macronutrient composition of chow and HF diet.

Wheel running and two-diet choice

Body weight, food, and water intake in addition to estrous stage and running activity was recorded daily at 0800 h. See Figure 2.1 for a timeline of the experiment and Table 2.1 for diet composition. After recovering from surgery, WR rats were transferred to running wheel cages with the wheel locked while Sed rats remained in their regular cages. A novel 45% HF diet (4.73 kcal/g, 35% carbohydrate, 20% protein, and 45% fat; Research Diets D12451) was introduced 2 h before dark onset (1200 h) to all rats 3-4 days after the acclimatization period. Running wheels were unlocked at the same time as the introduction of HF diet for the WR rats. The

position of the food hoppers was alternated daily to prevent the development of side preference for both Sed and WR rats. The acclimatization period for the running wheel cages was one day shorter for the hormone replacement than androgen component to ensure all hormone replaced rats would receive an injection the day before and on the day the wheels were unlocked. Daily voluntary wheel running activity was recorded and analyzed through the Vital View Software System (Starr Life Sciences, Oakmont, PA) on the computer. The WR and the two-diet choice procedure continued for 18 days.

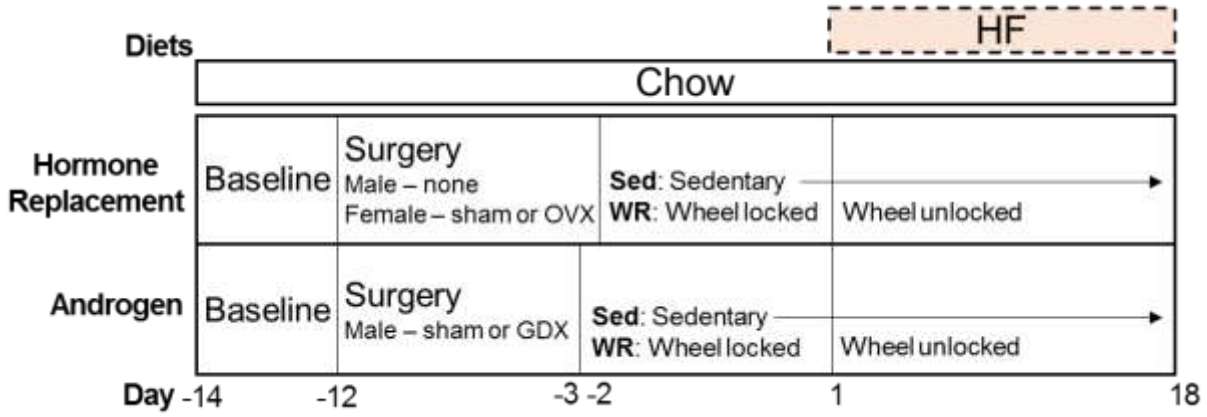

Figure 2.1. Timeline of experiment. OVX: ovariectomy, GDX: orchiectomy; Sed: sedentary, WR: wheel running; HF: high fat.

Hormone replacement

The dose and schedule of hormone replacement was determined based on literature (Asarian and Geary, 2002, 2013) demonstrating that these doses not only normalized food intake and body weight of OVX rats to that of gonadally-intact females, but also closely mimics the cyclical peaks of plasma estradiol and progesterone (al-Dahan and Thalmann, 1996) observed during the estrous cycle in intact female rats. Hormone replacement began 8 days after surgery in 4-day cycles. β-Estradiol 3-benzoate (Cat. #E8518-5G; Sigma, St. Louis, MO) and progesterone (Cat. #S3547-1L; Sigma, St. Louis, MO) was dissolved in sesame oil to achieve a concentration of 2 µg/0.1 mL and 0.5 mg/0.1 mL, respectively. OVX rats were injected subcutaneously (s.c.) during the middle of the light cycle once every 4 days with oil, estradiol

benzoate, or progesterone or an injection of estradiol benzoate and progesterone on the 1st and 3rd day, respectively.

Data analysis

Raw data included daily measurements of body weight, chow and HF diet intake, and running activity. During the wheel running and two-diet choice period, daily chow and HF diet intake (kcal) was compared among Sed and WR rats. HF diet preference was calculated by raking daily HF diet intake (kcal) and dividing it by the rat's total daily energy intake (kcal). A ratio > 0.5 indicated preference for HF diet.

Daily body weight, HF diet preference, total energy intake, and running activity were analyzed separately using 3-way mixed-model ANOVAs. Between-subjects factors included hormone (male, female, OVX O, OVX E, OVX P, and OVX E+P) and exercise (Sed vs. WR) for the hormone replacement component and group (male vs. GDX) and exercise (Sed vs. WR) for the androgen component. The within-subjects factor was time (18 days) for both components. Diet choice patterns were analyzed using a 4-way mixed-model ANOVA with hormone and exercise as the between-subjects factors and diet (chow vs. HF) and time as the within-subjects factors. Post-hoc Fisher's LSD tests were performed when significant main effects or interactions were identified. Data are presented as mean ± standard error of the mean (SEM).

RESULTS

Running activity

Analysis of running activity with a mixed model ANOVA revealed that all rats increased running activity over time [time and hormone x time: $F(17,918) = 97.053$ and $F(85,918) = 9.959$, respectively, both $p < 0.0001$]. Differences in hormone replacement were reflected in activity levels [hormone $F(5,54) = 30.58$, $p < 0.0001$]. Running activity in OVX O and OVX P WR rats was relatively stable and similar to males (post-hoc M vs. OVX O or OVX P, all $p > 0.13$) but significantly lower than female, OVX E, and OVX E+P rats (post-hoc tests all $p < 0.0001$). Hormone replacement with estradiol benzoate restored running activity to the level of intact

females [post-hoc F vs. OVX E or OVX E+P, both $p > 0.15$]. In the androgen component, a mixed model ANOVA revealed that GDX males ran less than sham-operated males [hormone $F(1,14) = 27.53$, $p < 0.0001$] and did not show the same type of escalation in running activity seen in intact males starting from the 8th day of the WR period (post- hoc all $p < 0.05$).

Hormone replacement

Wheel running and two-diet choice. Diet choice patterns differed among Sed and WR rats [diet, exercise x diet, and exercise x diet x time: $F(1,108) = 23.30$ and 303.99, respectively, and $F(85,1836) = 48.54$, all $p < 0.0004$]. There was no influence of sex or hormone replacement in Sed rats, such that they all consumed significantly more HF than chow diet [Figure 2.2A - F; diet x time: $F(17,1836) = 12.23$, $p < 0.0001$; hormone x diet: $F(5,108) = 0.87$, $p = 0.50$].

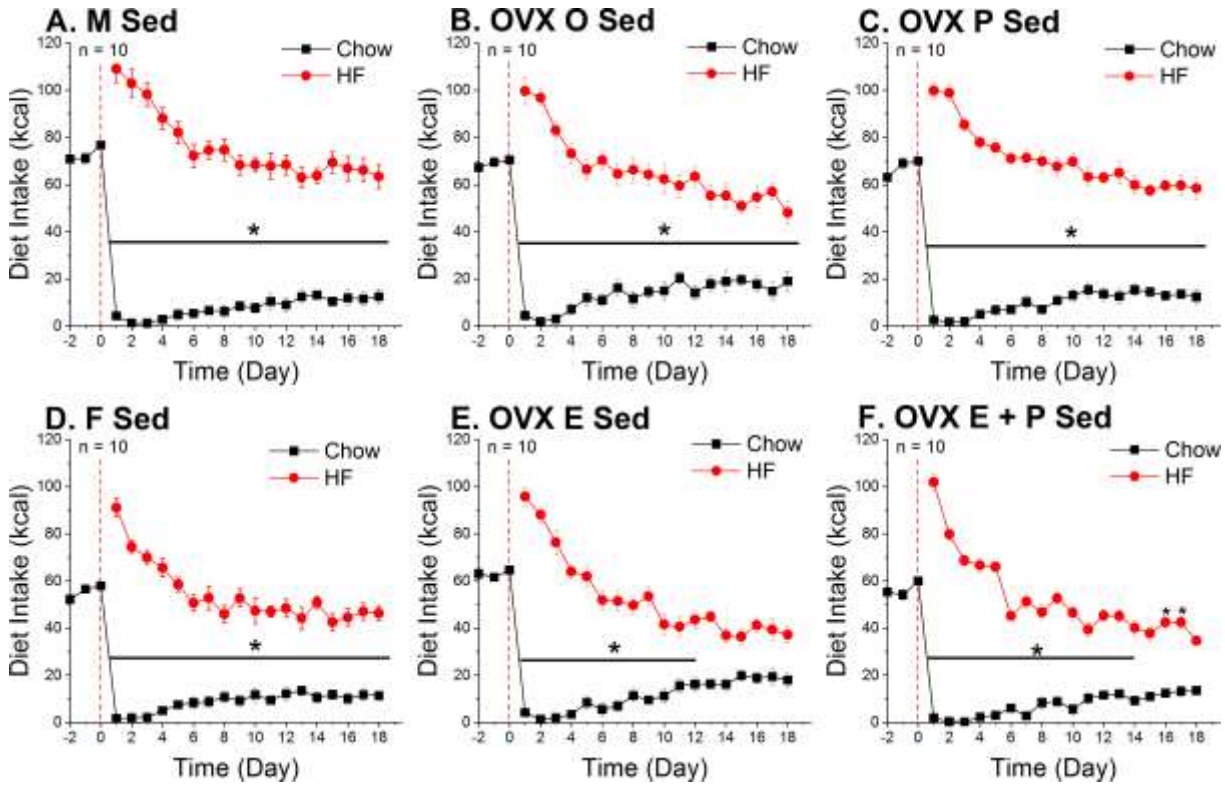

Figure 2.2. Diet choice patterns in sedentary (Sed) rats. The dashed red vertical line denotes the start of the two-diet choice and WR period. (A – F) All Sed rats consumed more HF than chow diet. *chow vs. HF, $p < 0.05$

There was a significant effect of hormone replacement on diet choice among WR rats [Figure 2.3 A-F; hormone, exercise, and hormone x exercise: $F(5,108) = 23.82$, 28.37, and

16.68, respectively, all $p < 0.0001$]. Compared to female and OVX groups, male WR rats persistently avoided HF diet through the duration of the WR and two-diet choice period [hormone x exercise x diet x time: $F(85, 1836) = 2.15$, $p < 0.0001$]. During the first 11 days of diet choice, diet choice patterns of OVX O WR rats were similar to males in which they avoided HF diet. By the 13th day, however, OVX O WR rats began to reverse HF diet avoidance and had diet choice patterns more similar to females. Male WR rats consumed significantly less HF diet compared to female, OVX O, and OVX E+P WR rats (post-hoc all $p < 0.05$). HF diet intake did not differ among F and all OVX WR groups (post-hoc all $p > 0.10$).

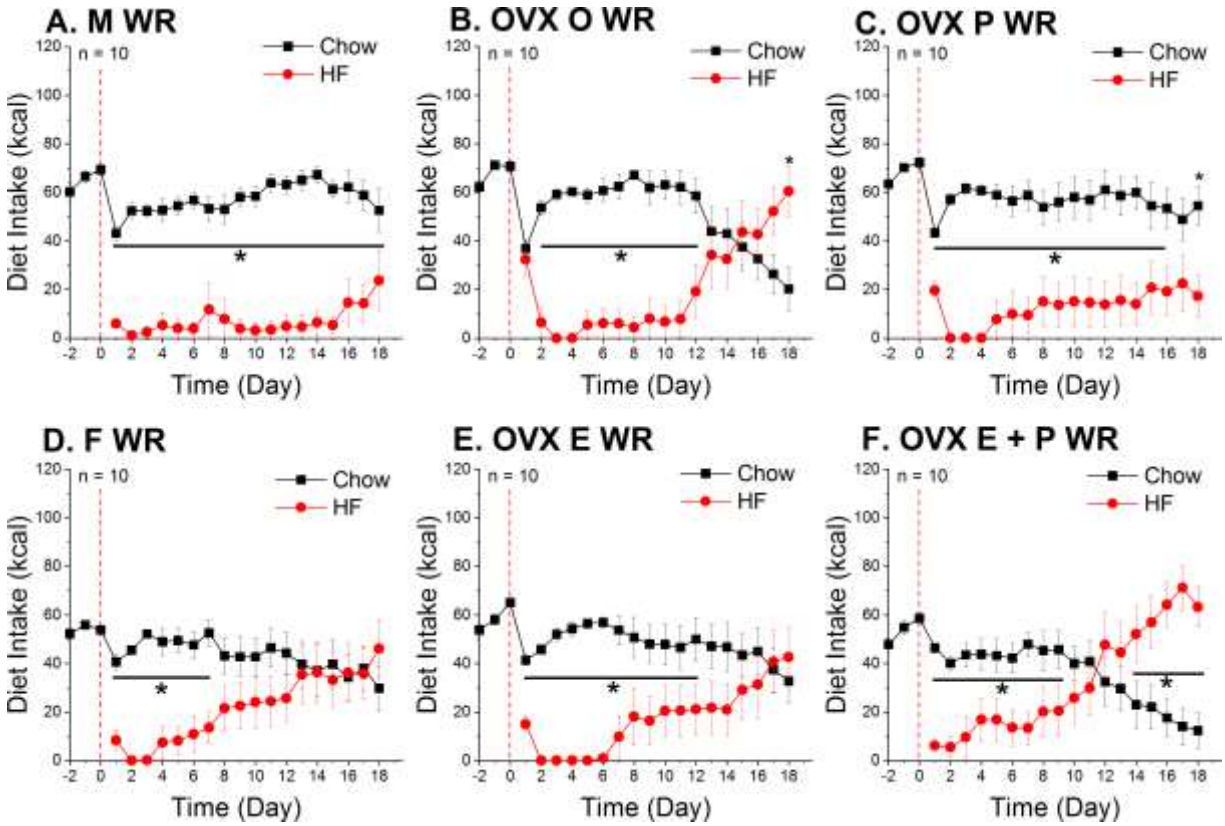

Figure 2.3. Diet choice patterns among wheel running (WR) rats. The dashed red vertical line denotes the start of the two-diet choice and WR period. (A) Male rats persistently avoided HF diet throughout the experimental period. (B) OVX O rats avoided HF diet for the first half of the diet choice period but sharply reversed HF diet avoidance. (C) Progesterone replacement alone did not lead to the reversal of HF diet avoidance. (D) Intact F WR rats initially avoided HF diet but gradually reversed their HF diet avoidance with time. (E) OVX E WR rats increased intake of HF diet but did not significantly reverse their initial HF diet avoidance. (F) Replacement with both E + P led to the complete reversal of HF diet avoidance. *chow vs. HF, $p < 0.05$

Both exercise and hormone replacement had an effect on HF diet preference [Table 2.1; exercise and hormone x exercise: $F(1,108) = 354.77$ and $F(5,108) = 2.42$, both $p < 0.05$]. In the WR condition, HF diet preference ratio was lower in males compared to both female and OVX E+P rats (post-hoc both $p < 0.01$) but only trended towards significance when compared to OVX O rats (post-hoc $p = 0.054$). That is, M WR rats persistently avoided HF diet whereas F and O and E+P hormone replaced OVX WR groups reversed HF diet avoidance by the end of the 18-day diet choice period. E and P replaced OVX WR rats expressed diet choice patterns in between that of male and female rats such that their HF diet preference did not differ significantly from that of males or females. On the last day of the experimental period, M and OVX P WR rats had similar HF preference ratios of 0.26 ± 0.10 and 0.23 ± 0.10, respectively. This was lower than the HF diet preference ratios in F (0.56 ± 0.10), OVX E (0.51 ± 0.10), OVX E+P (0.84 ± 0.10), and OVX O (0.73 ± 0.10) WR rats.

Post-hoc comparisons		***p*-value** (Fisher's LSD)
Male	Female OVX E+P OVX O	$p < 0.02$ $p < 0.0002$ $p = 0.054$
Male & Female	OVX E OVX P	$p > 0.10$
Female	OVX E+P OVX O	$p > 0.13$

Table 2.2. Fisher's LSD post-hoc tests of HF diet preference ratio among WR rats. HF diet preference differed significantly between WR males that avoided HF diet and OVX E+P rats that reversed HF diet avoidance. OVX E and OVX P rats expressed diet choice patterns in between that of males and females. HF diet preference did not differ among intact females, OVX E+P, and OVX O rats.

Total energy intake and body weight. Exercise decreased total daily energy intake [exercise $F(1,108) = 28.37$, $p < 0.0001$]. Furthermore, hormone replacement also significantly affected daily energy intake [hormone and hormone x exercise $F(5,108) = 23.82$ and 16.68, respectively, both $p < 0.0001$]. In the Sed condition, OVX led increased food intake in OVX O and OVX P rats such that their daily energy intake was comparable to males (post-hoc $p >$

0.07). M WR rats reduced energy intake to levels similar to females (post-hoc $p > 0.86$). OVX O and OVX P rats had significantly higher energy intakes than males (post-hoc $p < 0.05$), but only OVX O rats had significantly higher energy intake than females (post-hoc $p < 0.01$). Daily energy intake in OVX E and E+P rats did not significantly differ from females (post-hoc all $p > 0.23$) in either the Sed or WR condition.

Exercise suppressed body weight gain in WR rats [exercise, exercise x time, hormone x exercise x time, $F(1,108) = 57.180$, $F(18,1944) = 65.842$, and $F(90,1944) = 4.594$, all $p < 0.0001$]. Estrogen replacement alone was able to suppress OVX-associated weight gain in both Sed and WR rats [hormone and hormone x exercise, $F(5,108) = 319.53$ and 30.03, respectively, both $p < 0.02$]. Body weight did not differ among F, OVX E, or OVX E+P (post-hoc tests, all $p > 0.08$) or OVX O and OVX P (post-hoc $p > 0.58$) rats in either the Sed or WR condition. Additionally, OVX O and OVX P WR rats had weighed more than F, OVX E, and OVX E+P WR rats (post-hoc OVX E or OVX E+P vs. OVX O or OVX P, all $p < 0.0001$). In both the Sed and WR condition, male rats had the higher body weights than all the other groups (post-hoc M vs. all groups, all $p < 0.0001$).

Androgen

Wheel running and two-diet choice. A mixed model ANOVA [hormone (2) x exercise (2) x diet (2) x time (18)] revealed that diet choice patterns differed among Sed and WR rats [exercise and diet x exercise: $F(1,24) = 65.53$ and 314.81, respectively, both $p < 0.0001$] such that Sed rats expressed opposite diet choice patterns. More specifically, all Sed rats consumed significantly more HF than chow diet (Figure 2.4 A & B) where WR rats avoided HF diet (Figure 2.4 C & D). There was no effect of androgen removal on diet choice between intact and GDX male either Sed and WR conditions [diet, hormone x diet, and hormone x exercise $F(1,24) = 2.48$, 1.81, and 2.47 all $p > 0.12$]. Both sham-operated and GDX WR males avoided HF diet and had similar chow intake (both post-hoc $p > 0.47$).

Analysis of HF diet preference ratios with a 3-way mixed model ANOVA [hormone (2) x exercise (2) x time (18)] revealed the same relationship where exercise led to significantly lower HF diet preference. In addition, there was no difference in HF diet preference between sham-operated and GDX WR rats [exercise $F(1,24) = 357.81$, $p < 0.0001$; hormone and hormone x exercise $F(1,24) = 1.41$ and 0.003, both $p > 0.24$].

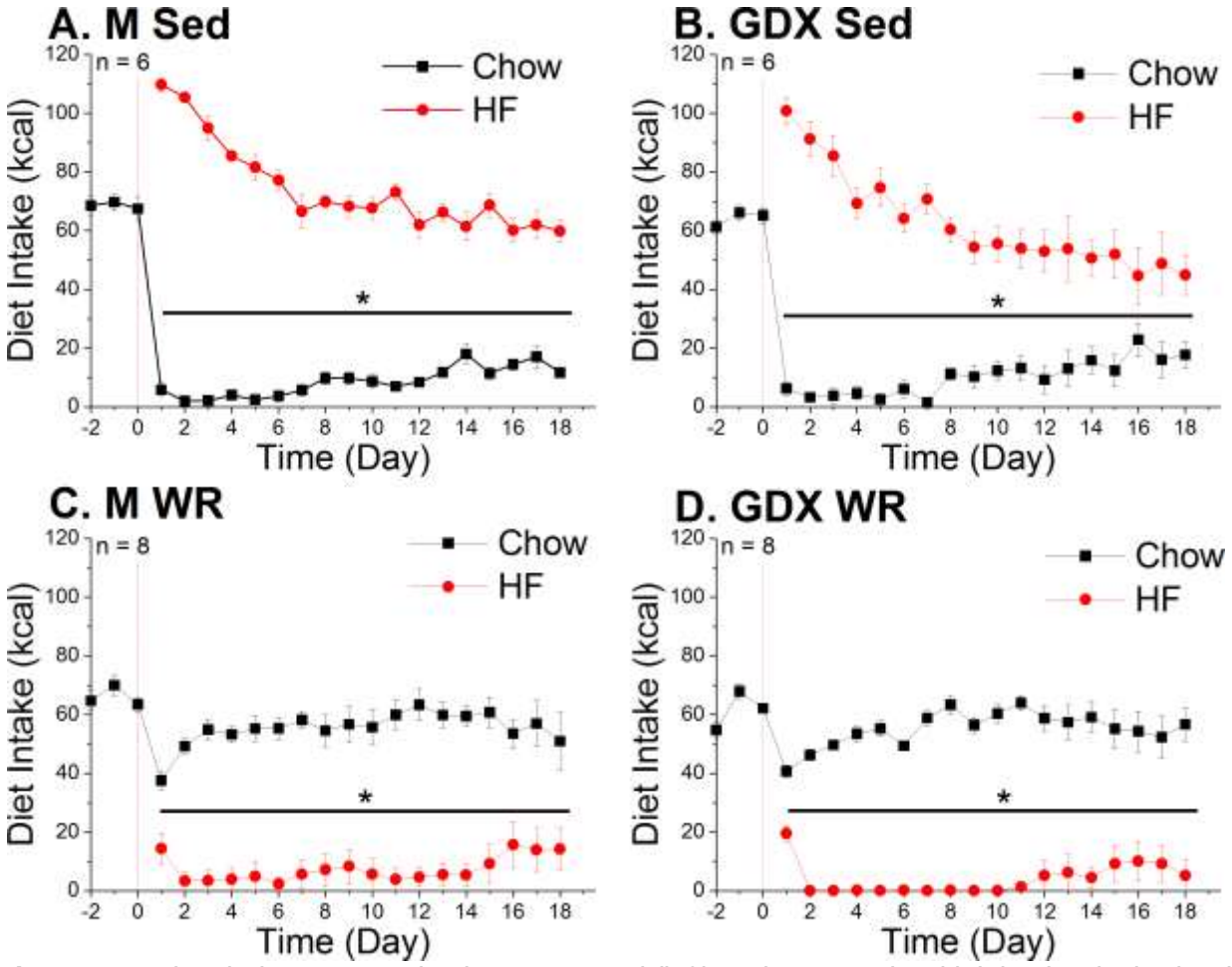

Figure 2.4. Diet choice patterns in sham-operated (left) and GDX males (right). The dashed red vertical line denotes the start of the two-diet choice and WR period. (A & B) All Sed rats consumed more HF than chow diet. (C & D) M WR and GDX WR rats maintained HF diet avoidance throughout the WR and two-diet choice period. *chow vs. HF, $p < 0.05$

Total energy intake and body weight. Sham-operated males had higher energy intake and body weights compared to GDX rats while Sed [hormone $F(1,24) = 10.74$ and 7.76, respectively, both $p < 0.02$]. Exercise suppressed total energy intake and body weight [exercise $F(1,24) = 65.53$ and 10.70, respectively, both $p < 0.01$] in both sham-operated and GDX males.

Nevertheless, total energy intake and body weight did not differ between sham-operated and GDX WR groups [hormone x exercise $F(1,24) = 2.47$ and 0.93, respectively, both $p > 0.12$].

DISCUSSION

The present study aimed to investigate the role of gonadal hormones in exercise-mediated changes in HF diet preference. In regards to the influence of ovarian hormones, we found that the timing and frequency of HF diet avoidance reversal differed among wheel running rats (Figure 2.3). The majority of male WR rats maintained persistent HF diet avoidance whereas female and E+P replaced OVX rats reversed HF diet avoidance and more quickly than the few males that eventually reversed their initial avoidance. Without hormone replacement, OVX rats expressed similar degrees of HF diet avoidance as males during the first half of the WR and two-diet choice period but sharply increased HF diet intake and preference to the level of intact females. Finally, estrogen or progesterone replacement alone in running OVX rats was not sufficient to significantly reverse HF diet avoidance, which suggests that both ovarian hormones are necessary for the expression of female-typical diet choice patterns. In males, orchiectomy did not affect the persistency of HF diet avoidance (Figure 2.4 C & D). The incomplete elimination of sex differences in OVX rats and lack of effect of GDX suggests that in addition to ovarian hormones, developmental factors contribute to the earlier and more frequent reversal of HF diet avoidance in female WR rats.

The result that diet preference in orchiectomized males did not differ from sham-operated males (Figure 2.4) is consistent with the notion that testosterone is less influential than estrogen (Mauvais-Jarvis et al., 2013) in regards to the neural control of food intake (Nunez et al., 1980). Testosterone, however, is important during development. The testosterone surge that occurs by postnatal day 10 masculinizes and defeminizes certain regions of the perinatal brain (MacLusky and Naftolin, 1981, Arnold and Gorski, 1984, McCarthy, 1994, Bakker and Baum, 2008) and in the absence of testosterone, the central nervous system is structurally organized in a female fashion, which does not require ovarian hormones (Phoenix et al., 1959, Jost et al.,

1973, Baum, 1979, MacLusky and Naftolin, 1981, Bakker et al., 2006, McCarthy, 2008, Lenz et al., 2012). Thus, the developmental organization of behavior during the sensitive period could explain why non-hormone replaced OVX rats (OVX O) eventually reversed HF diet avoidance. However, the activational consequences of gonadal hormone release (i.e., altered patterns of hormone secretion and changes in sensitivity to hormones) starting from puberty appear to exert a greater influence on food intake and metabolism (Bell and Zucker, 1971, Wade, 1972, Gustafsson and Stenberg, 1976). In line with this notion, we found that hormone replacement with both ovarian hormones resulted in the most complete female-typical pattern of behavior, which suggests that the activational consequences of ovarian hormones may play a key role in mediating changes in HF diet preference. This finding is similar to other types of female-specific behavior. For example, while estrogen alone can induce lordosis in OVX rats (Sodersten and Eneroth, 1981), an optimal dose of estrogen followed by progesterone results in more complete displays of sexual behaviors in female rats (Pfaff, 1970, Moss and McCann, 1973, Pfaff et al., 2006).

The efficiency of energy metabolism during different states of energy requirement (exercise vs sedentary) differs between male and females (Tarnopolsky et al., 1990, Tate and Holtz, 1998, D'Eon and Braun, 2002). Estrogen facilitates increased lipid oxidation and reduced carbohydrate utilization (Gorski et al., 1976, Ellis et al., 1994), and progesterone potentiates these effects (Matute and Kalkhoff, 1973). In contrast, testosterone favors carbohydrate utilization over lipid oxidation (Braun et al., 2005). Thus, differences in the efficiency of fuel substrate utilization where the HF diet is a more efficient fuel source for females during a state of increased energy demand could explain running-associated sex differences in HF diet choice (Hill et al., 1986, Cortright and Koves, 2000).

Sex differences in novelty and neophobia could explain why male rats express more persistent HF diet avoidance throughout the two-diet choice and wheel running period compared to females. Male rats have longer approach latencies and appear to prefer familiar to

novel objects when given a choice (Russell, 1975) and will approach and consume a novel food more slowly than females (Modlinska et al., 2015). Although the novelty of the HF diet likely wears off, higher levels of neophobia in males from their first exposure may persist and promote the maintenance of HF diet avoidance and contribute to the sex difference in diet preference. The effect of novelty, however, might not be as persistent in OVX rats. Thus, they subsequently reversed HF diet avoidance and behaved more similarly to females for the rest of the experiment. In support of this, a recent study found that after 6 weeks of chronic, unpredictable stress, OVX rats increase latency to feed in a novelty suppressed feeding test and have similar profiles of anxiety-like behavior to males (Mahmoud et al., 2016). This could explain why OVX rats behaved similarly to males and avoided HF diet during the first 11 days of the two-diet choice and wheel running period. Further studies are necessary to test whether differences in novelty response corresponds to food neophobia and whether or not food neophobia differs between male, female, and OVX rats while wheel running.

The factors contributing to the greater susceptibility for females to develop disordered eating behaviors and the deleterious effects of HF diet are unclear. We found that first, OVX partially eliminated sex differences and GDX had no effect on the persistency of exercise-mediated HF diet avoidance and second, both ovarian hormones were necessary for the expression of female-typical diet choice patterns. In contrast to males, the majority of female rats with running wheel access failed to maintain HF diet avoidance, which could contribute to the higher susceptibility for developing obesity and its associated comorbid conditions in females (Hudson et al., 2007, Flegal et al., 2010). Moreover, females are less responsive to exercise as a method of weight loss (Hill et al., 1989, Donnelly et al., 2004, Caudwell et al., 2014). Sex-dependent responses to exercise as a treatment intervention underscores the importance of determining which neural circuits are involved in mediating exercise-associated changes in palatable diet preference in both sexes. Elucidating the neurobiological mechanisms underlying exercise-mediated changes in diet preference in both sexes could provide novel

insight towards developing sex-specific treatments for disordered eating behaviors and lead to better outcomes.

CHAPTER 3: SEX DIFFERENCES IN THE INTERACTION BETWEEN CHRONIC HIGH FAT FEEDING-ASSOCIATED DEFICITS IN PERIPHERAL METABOLISM AND COGNITIVE FUNCTION[2]

ABSTRACT

Food resources were limited prior to industrialization. In contrast, our modern environment provides easy access to a variety of energy dense, palatable foods and is saturated with food cues to eat. Maladaptive dietary choices, including overconsumption of high fat (HF) foods, exacerbates to the development of obesity, metabolic syndrome, and cognitive dysfunction. The current study assessed whether exercise-mediated changes in HF diet preference would lead to sex specific outcomes in metabolic and cognitive health in sedentary (Sed) and wheel running (WR) rats of both sexes. To this end, we extended the WR and two-diet choice (chow vs. HF) paradigm from Chapter 2 to ~6 weeks in order to investigate the efficacy of exercise at reversing HF diet-induced impairment in peripheral metabolism and cognition, hypothesizing that exercise would be more protective against the deleterious effects of HF feeding in males. All WR rats avoided HF diet upon running initiation, and male rats maintained lower HF diet preference for a longer period than females. WR induced suppression of body weight and fat deposition to a greater extent in males than females. These results may have contributed to sex differences in glucose tolerance and insulin profile, such that improvements were only seen in males. Exercise enhanced learning to escape on the Barnes maze in WR rats of both sexes. During tests of reversal learning, only female WR rats increased the number of errors committed, suggesting a sex-dependent effect of exercise on behavioral flexibility. Taken together, our results suggest that exercise is more effective at attenuating HF-associated metabolic deficits in males, and highlights the importance of developing sex-specific treatment interventions for energy homeostasis and cognitive dysfunction.

[2]Data from this chapter are published in Yang, TY, Gao, Z, & Liang, NC (2020). Sex-dependent wheel running effects on high fat diet preference, metabolic outcomes, and performance on the Barnes maze in rats. *Nutrients*, *12(9)*, 2721.

RATIONALE

The industrial revolution not only sparked a shift in food availability, but also the way foods are processed including higher use of refined sugars and saturated fats. This type of high-fat and high-sugar diet has been termed the “Western diet” (WD) and is highly palatable and promotes overeating. Making maladaptive and nutritionally unhealthy food choices increase the risk of obesity, metabolic syndrome, and cognitive dysregulation, which may be further exacerbated by living a sedentary lifestyle. The overconsumption of HF food is associated with increased abdominal adiposity, weight gain, peripheral metabolic dysregulation, and cognitive deficits (Winocur et al., 2005, Kanoski et al., 2007, Martin et al., 2007, Cifre et al., 2018). Deficits in behavioral flexibility may result in the inability to appropriately adapt dietary choices to external environmental and internal visceral cues (Kakoschke et al., 2018, Favieri et al., 2019) and promote rigid diet choices in a viscous cycle that facilitates the development of obesity (Perpina et al., 2017, Edwards et al., 2018).

The highly processed foods associated with the typical WD tend to have higher glycemic loads (Foster-Powell et al., 2002) than unrefined foods and pose a threat to metabolic health (Smith et al., 2011, Chen et al., 2017, Steenbergen and Colzato, 2017, Yang et al., 2018). Exercise appears to be more effective than diet control at improving metabolic function (Maesako et al., 2012). For example, exercise training-mediated weight loss led to greater decreases in visceral fat and hepatic insulin resistance in obese men and women compared with caloric restriction-mediated weight loss (Coker et al., 2009). Changes in body weight, adiposity, and food intake and preference in humans is variable (Blundell and King, 1999, King et al., 2009, Ebrahimi et al., 2013, Schubert et al., 2013, Donnelly et al., 2014, Castro et al., 2020) and depends on whether individuals compensate for energetic demand from exercise and how responsive they are to positive outcomes of regular exercise (Sparks, 2017, Beaulieu et al., 2020b). Female rodents also differ in response to exercise in regards to body weight and food intake (Tokuyama et al., 1982, Eckel and Moore, 2004, Carrera et al., 2011). On the other hand,

males consistently decrease energy intake, body weight, and adiposity (Tokuyama et al., 1982, Looy and Eikelboom, 1989, Kawaguchi et al., 2005, Carrera et al., 2011) with exercise training. Given the considerably less variability in rodents and the limited number of studies of sex differences in energy homeostasis (Westerterp et al., 1992, Washburn et al., 2015) in humans, a rat model provides a good avenue for investigating sex differences in the interplay between exercise and peripheral metabolic function.

Cognitive function is negatively influenced by long-term consumption of HF diet in humans (Greenwood and Winocur, 2005) and rodents (Winocur and Greenwood, 2005) alike. The literature has focused on HF feeding-related hippocampal impairment of spatial learning and memory (Greenwood and Winocur, 1996, Winocur and Greenwood, 1999, 2005, Stranahan et al., 2008, Kanoski and Davidson, 2010, Valladolid-Acebes et al., 2011); however, HF diet can also alter prefrontal cortex (PFC)-mediated executive function, including behavioral flexibility (Kanoski et al., 2007, Stranahan et al., 2008, McNeilly et al., 2011, Aslani et al., 2015, Mekari et al., 2020). The few studies that examined PFC-dependent cognition found that HF feeding led to decreased behavioral flexibility in rats (Kanoski et al., 2007, Stranahan et al., 2008, McNeilly et al., 2011, Aslani et al., 2015), which was reversed by dietary (Boitard et al., 2016, McNeilly et al., 2016) and exercise (Woo et al., 2013), but not drug (McNeilly et al., 2012), interventions. Decreased behavioral flexibility was correlated with decreased insulin sensitivity, but not body weight or plasma glucose level (McNeilly et al., 2011). Taken together, these studies suggest that HF diet and insulin resistance may interact to promote the development and maintenance of cognitive rigidity which exercise may counteract.

Sex differences in the metabolic and cognitive outcomes of HF feeding may differentially affect the cognitive control of feeding behavior in males and females. As seen in both the human and animal literature, the metabolic (Elias et al., 2003, Amengual-Cladera et al., 2012, Barron et al., 2013, Underwood and Thompson, 2016) and cognitive (Hwang et al., 2010, Laredo et al., 2015, Shields et al., 2016) effects of chronic HF feeding appear to be more

deleterious in males than females. However, the prevalence of obesity (Hudson et al., 2007, Flegal et al., 2010) and mild cognitive impairment (Seshadri et al., 1997, Lin et al., 2015) is higher in females than males. The opposite effect in regards to cognitive outcomes was seen in rodents such that behavioral flexibility is more negatively impacted by HF diet in males (Hwang et al., 2010, Laredo et al., 2015, Shields et al., 2016). While exercise has been shown to attenuate HF-mediated disruptions in learning and memory (Nara et al., 1997, Molteni et al., 2004, Greenwood and Winocur, 2005, Winocur and Greenwood, 2005, Coker et al., 2009, Maesako et al., 2012, Gibbons et al., 2014, Noble et al., 2014, Loprinzi et al., 2019, Park et al., 2019), these studies primarily focus on hippocampal-mediated behavior (Molteni et al., 2004, Noble et al., 2014, Park et al., 2019) rather than the PFC (Klein et al., 2016). Additionally, these studies rarely include both sexes within the same experiment so direct assessments of sex differences cannot be made. Thus, whether exercise is able to protect against cognitive dysregulation to the same extent in both male and female rats with long-term HF feeding is unclear.

Studies have shown that exercise can reverse HF-induced deficits in metabolic and cognitive function (Molteni et al., 2004, Woo et al., 2013, Gibbons et al., 2014, Noble et al., 2014, Klein et al., 2016). To our knowledge, no study has investigated sex differences in the efficacy of voluntary exercise at reversing deficits metabolic and behavioral flexibility resulting from chronic HF feeding. The current study seeks to address this gap in knowledge by extending the WR and two-diet choice used in Chapter 2 to ~6 weeks, a period of time that is sufficient to induce diet-induced obesity (Buettner et al., 2007), to examine whether 1) higher HF diet preference increases susceptibility to the negative consequences of HF diet intake and 2) exercise can reverse HF-associated metabolic and cognitive dysfunction with long-term exposure to HF diet. We hypothesized that WR females would have the worst performance on the Barnes maze based on the likelihood that they will reverse HF diet avoidance. We also predict to find a positive relationship between increased HF diet preference with peripheral

insulin resistance, which will be associated with poorer performance on the Barnes maze. Results from this study could provide insight into the development of sex-specific prevention and treatment options to maintaining energy homeostasis.

METHODS

Subjects

The subjects for this experiment included 24 male (250-275 g) and 24 female (150-175 g) Sprague-Dawley rats (Envigo, Indianapolis, IN) that were ~7-8 weeks old upon arrival. Rats were group housed on a standard 12:12 light-dark cycle (lights on at 0700 h). During habituation, rats had ad lib access to a standard chow diet and tap water. During the experimental period, rats had diet choice between standard, high carbohydrate chow and a 45% HF diet.

Wheel running and two-diet choice

Body weight, food intake, and fluid intake was recorded daily during the dark cycle at 0800 h. See Figure 3.1 for a timeline of the experiment. After habituation, rats became individually housed such that sedentary (Sed) moved into sedentary tubs and wheel running (WR) rats were moved into running wheel cages (13” diameter wheel; Mini Mitter, Starr Life Sciences, Oakmont, PA) with the wheel locked. The wheels were unlocked for the WR rats after a 4-day acclimation period and a novel HF diet was simultaneously introduced to both Sed and WR rats 2 h before dark onset (1700 h). Running activity was recorded and analyzed daily following daily care (VitalView, Starr Life Sciences, Oakmont, PA, USA). The wheel running and two-diet choice procedures continued for ~6 weeks after which the rats were sacrificed and retroperitoneal, mesenteric, and gonadal fat pads were dissected and weighed.

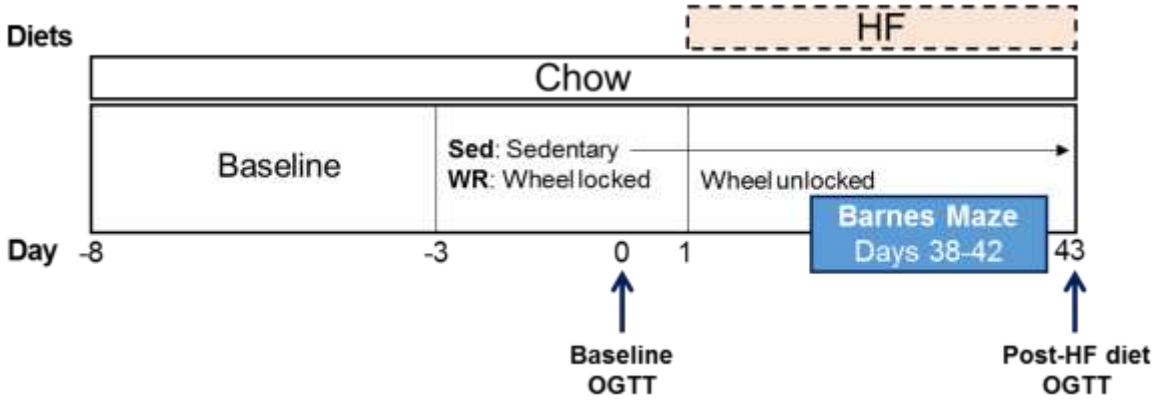

Figure 3.1. Timeline of experiment. Sed: sedentary, WR: wheel running; HF: high fat; OGTT: oral glucose tolerance test.

Oral glucose tolerance test

Two OGTTs were performed for this experiment, one at baseline (BL) and one after HF diet exposure (post-HF) to examine within-group effects of HF diet on glucose tolerance. Baseline OGTT was performed the day before the wheels were unlocked (day 0), and post-HF OGTT was performed the day of sacrifice (day 44), which was two days after the end of the Barnes maze. On the day of OGTT, food was removed 3 h after dark onset (1400 h) where rats consumed ~60% kcal of their usual daily diet intake. Complete overnight fasting enhances insulin-stimulated glucose utilization; thus, rats were only moderately fasted to allow for the assessment of insulin action in a more physiological context (Ayala et al., 2006, Bowe et al., 2014). Baseline/fasting glucose was assessed at 0 min through a tail nick using a handheld glucometer (AlphaTRAK2, Abbott, Abbott Park, IL) after which rats were challenged with a 2 g/kg of 20% glucose dissolved in distilled water through oral gavage. Both blood glucose measurements and tail blood was collected at 15, 30, 60, and 120 min from the time the rats were gavaged using the same tail nick during baseline sampling. Tail blood was centrifuged at 870 × g for 15 min at 4 °C and ~25 µL of plasma was collected for each sampling time point. Tail blood plasma was stored at −80 °C until the samples were processed for plasma insulin concentrations using the Rat Ultrasensitive Insulin ELISA (ALPCO, Salem, NH) according to manufacturers' protocol.

Barnes maze

During the last week of the WR and two-diet choice period, all rats were trained on the Barnes maze starting 2.5 h after light onset (0930 h). A concealed overhead-mounted camera aimed directly at the center of the maze was used to film each trial, which was operated using a computer from the adjacent room. Five visuospatial cues were placed in the room and their location was held constant during training and reversal learning. For both training and reversal learning trials, a trial ended when the rat entered the escape box or after the allotted time had elapsed. The maze and escape box were cleaned using a non-alcohol-based coverage spray between each rat to eliminate odor cues.

After daily care, rats were single caged in standard tubs and moved to the room adjacent to the testing room for at least 1 h of habituation prior to testing. There were 4 trials/day during training (total of 16 trials/day) with 4 different starting locations (Figure 3.2). Rats were placed on the edge of the maze with their nose pointed away from the center of the maze. All rats finished a trial at the first starting location with an inter-trial interval of at least 30 min before being testing began for the second starting location. In other words, all rats completed a trial from the same starting location before the next round of trials began. The order of the starting locations was the same for each training day. If a rat failed to find the escape box within the allotted time of 90 s, they were gently guided into the box which was then covered. Rats were allowed to remain in the escape box for 15 s before being returned to their home cage.

On the fifth day of behavioral testing, rats were placed at the center of the maze facing away from the escape box for a probe trial to verify they learned the task. The procedures were the same from testing. After the probe trial, the escape box was rotated 180°, but none of the visuospatial cues were moved. For the 3 reversal learning trials with 30 min inter-trial intervals, rats were given 150 s to locate the new location of the escape box and allowed to remain in the box for 15 s. If a rat failed to locate the new location, they were gently guided into the escape box and remained there for 15 s.

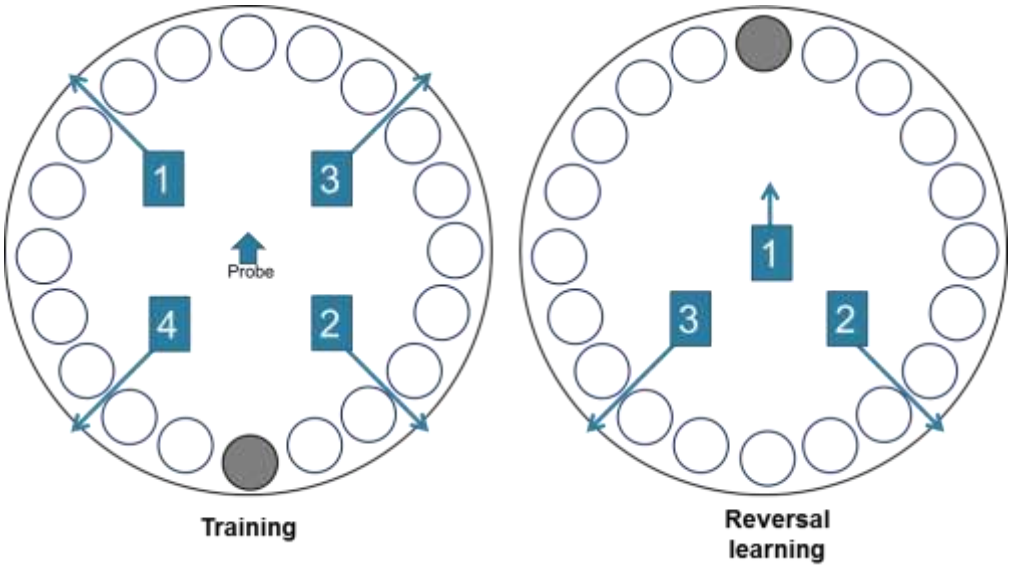

Figure 3.2. Starting locations on the Barnes maze for training (left) and reversal learning (right) trials. Rats underwent 4 trials/day during training and a probe trial followed by 3 reversal learning trials during testing.

Data analysis

Statistical analyses were performed using Statistica 13.3 (TIBCO, Palo Alto, CA, USA). Data are presented as the mean ± standard error of the mean (SEM). Post hoc Fisher's LSD tests were performed when significant main effects or interactions were identified.

Raw data from the WR and two-diet choice period included weekly body weight and 6 weekly averages of chow and HF diet intake, daily energy intake, and running activity. These measures were analyzed separately using 3-way mixed model ANOVAs with sex (male vs. female) and exercise (Sed vs. WR) as between-subject factors and time (6 weeks) as the within-subject factor. Diet choice was analyzed using a 4-way mixed model ANOVA with sex and exercise as the between-subject factors and diet (chow vs. HF) and time as the within-subject factors. Retroperitoneal, mesenteric, and gonadal fat pad weights were analyzed separated with a 2-way ANOVA with sex and exercise as the between-subject factors.

Raw data from OGTT included blood glucose and plasma insulin measurements. Baseline OGTT and post-HF OGTT results were analyzed separately using a 3-way mixed model ANOVAs with sex and exercise as between-subject factors, and time (0, 15, 30, 60, and

120 min) as the within-subjects factor. Glucose and insulin area under curve (AUC) results were analyzed separately using a 2-way mixed model ANOVA with sex and exercise as the between-subject factors and time (baseline vs. post-HF) as the within-subjects factor. Trunk insulin plasma was analyzed with a 2-way ANOVA with sex and exercise as the between-subject factors. Separate correlation analyses were performed to determine if there was a relationship between either glucose or insulin AUC during OGTT and trunk plasma insulin levels with average HF diet preference ratio.

Latency to enter the escape box and errors during training and testing on the Barnes maze was manually scored. At least two individuals video scored the training and testing portion of the Barnes maze for all rats. An error was recorded each time the rat poked its nose into a hole other than the one leading to the escape box. Training and testing data were analyzed using a 3-way mixed model ANOVA with sex and exercise as the between-subject factors and trial (daily average) as the within-subject factor.

RESULTS

Wheel running and two-diet choice

Diet choice patterns were similar to the results from the shorter paradigm in Chapter 2. Male and female Sed rats consumed more HF than chow diet and gradually decreased HF and increased chow intake over time (Figure 3.3 A & B). In contrast, WR rats expressed opposite diet choice patterns and increased HF diet intake over time [Figure 3.3 C & D; time × exercise and time × diet × exercise $F(5,220) = 42.28$ and 37.35, respectively, both $p < 0.001$]. With the extended paradigm (2 vs. 6 weeks), there were no sex differences in HF diet preference such that all rats reversed their initial HF diet avoidance (Figure 3.3 E & F). However, ~64% of M WR rats had HF diet preference ratios less than 0.5, which suggests that they preferred HF over chow diet for less than half of the 6 week diet choice period. Additionally, female WR rats reversed HF diet avoidance earlier than males (week 2 vs. 5) and had higher levels of HF diet preference [time × sex × exercise $F(5,220) = 3.92$, $p < 0.05$].

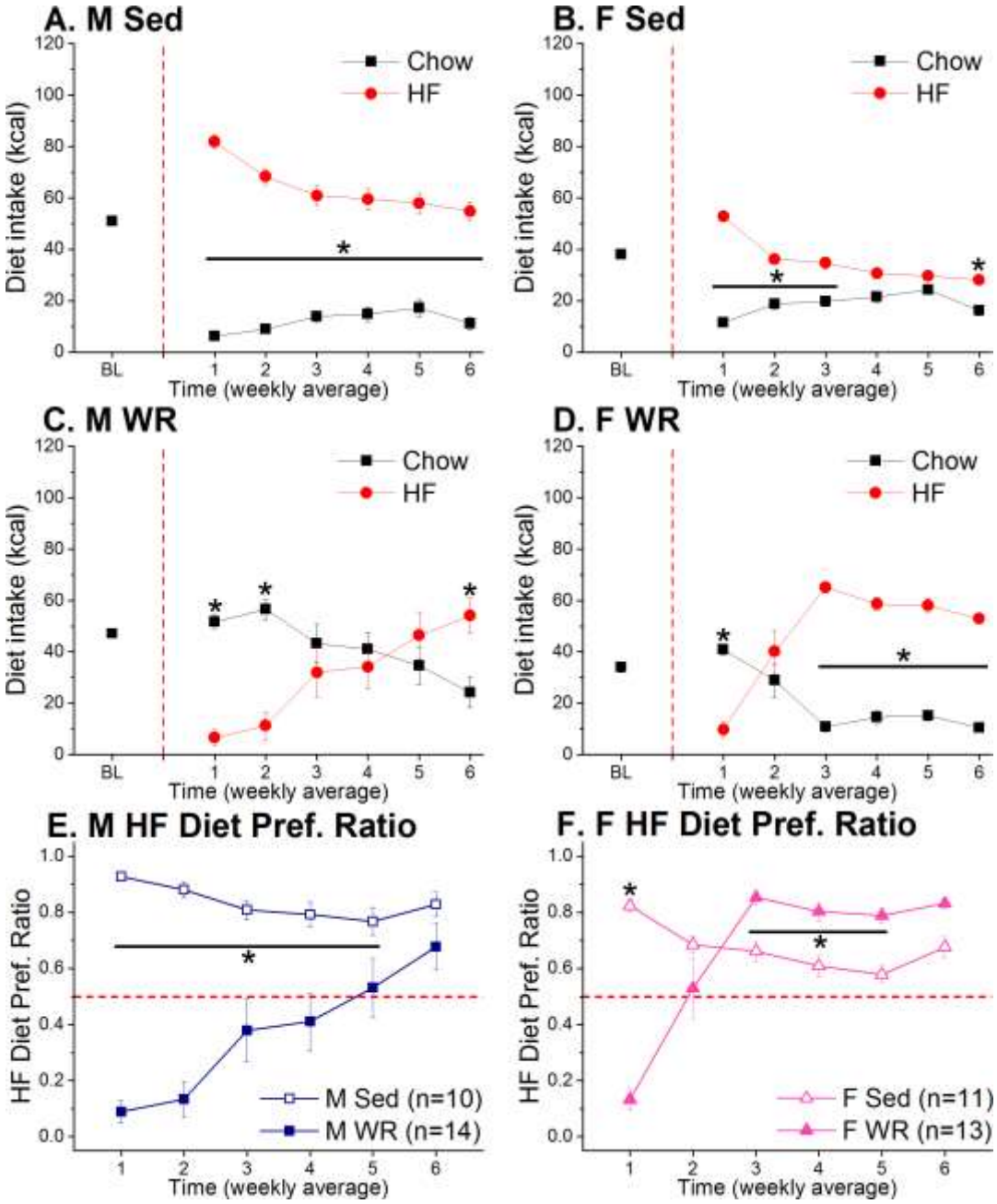

Figure 3.3. Diet choice and HF diet preference ratios in males and female rats. The vertical and horizontal dashed red lines denote the start of the two-diet choice and WR period and preference for HF diet where any value greater than 0.5 indicates a preference for HF diet, respectively. (A) Sedentary male rats maintained higher intake of HF than chow diet throughout the experiment. *chow vs. HF, $p < 0.05$ (B) There was a period of 2 weeks during which female Sed rats did not show a preference for HF diet. *chow vs. HF, $p < 0.05$ (C) Male WR rats increased HF diet intake across time and consumed significantly more HF than chow during the last week of the WR and two-diet choice period. *chow vs. HF, $p < 0.05$ (D) Female WR rats sharply increased HF diet intake after which they began consuming more HF than chow diet. *chow vs. HF, $p < 0.05$. (E & F) HF diet preference went in opposite directions among Sed and WR rats in both sexes. * Sed vs. WR, $p < 0.05$.

Running activity and energy intake

Running activity was higher in females than males (Figure 3.4 A) and both sexes showed an inverted-U shaped curve in running activity such that activity peaked and subsequently decreased to levels similar to baseline [time × sex $F(5,125) = 9.73$, $p < 0.001$]. The increased energetic requirement from exercise led to sex-specific adaptations [Figure 3.4 B; sex × exercise $F(1,440 = 28.26$, $p < 0.001$] across time [time × sex × exercise $F(5,220) = 4.97$, $p < 0.001$]. Exercise initially suppressed energy intake in males, after which they increased food intake to levels similar to their Sed counterparts (post hoc $p > 0.15$). In contrast, females compensated for the additional energy demand from WR earlier than males and consumed more food than F Sed rats (post hoc $p < 0.001$).

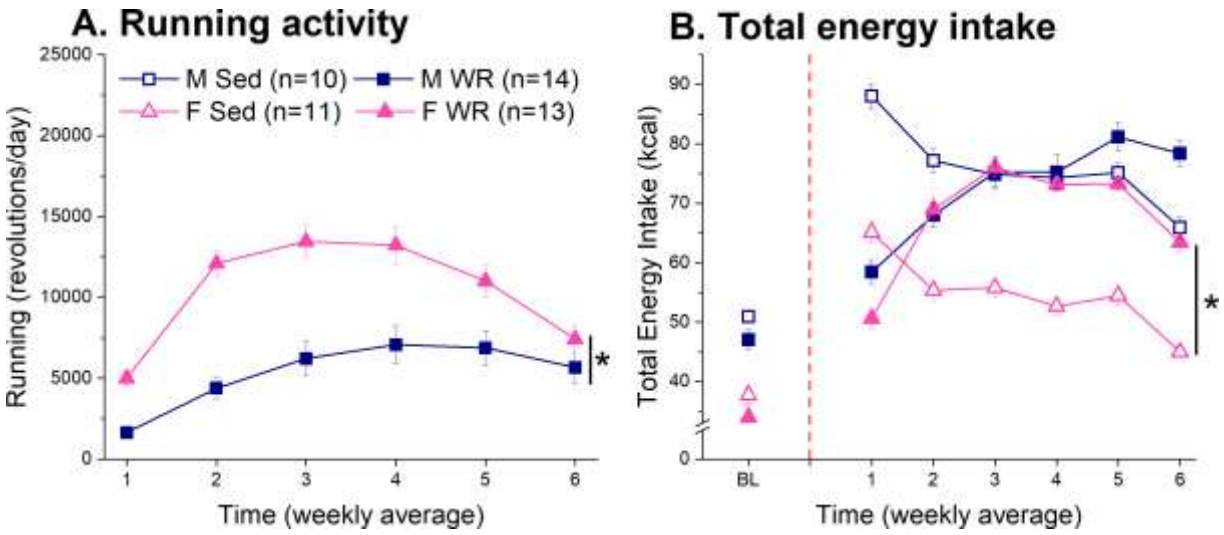

Figure 3.4. Running activity and total energy intake. (A) Female rats ran more than males, and both sexes showed and inverted-U trend in running activity. *Male vs. female, $p < 0.05$. (B) Female WR rats had higher energy intake than their Sed counterparts and there was no difference between Sed and WR males. *Sed vs. WR, $p < 0.05$.

Body weight and adiposity

Exercise-associated changes in daily energy intake led to suppressed body weight gain in rats of both sexes [exercise $F(1,44) = 29.16$, $p < 0.001$]. However, the effect of exercise was greater in magnitude in males than females (Figure 3.5 A). At the end of the experiment, there was a 10% difference in body weight between Sed and WR males and only a 2% differences in females. Decreased body weight gain with exercise was reflected in visceral adiposity (Figure

3.5 B). Retroperitoneal and mesenteric fat was decreased in WR rats [exercise $F(1,44) = 11.62$ and 10.47, respectively, both $p < 0.01$] in both sexes [sex x exercise $F(1,44) = 1.26$ and 3.68, respectively, both $p > 0.06$]. There was a trend towards a sex difference in the mesenteric fat ($p = 0.061$) and post hoc analyses suggests that the exercise effect was driven by males. Gonadal fat was only decreased in M WR rats, and there was no difference between female Sed and WR rats [sex x exercise $F(1,44) = 8.16$, $p < 0.01$; post hoc male Sed vs. WR $p < 0.01$ and female Sed vs. WR $p > 0.49$].

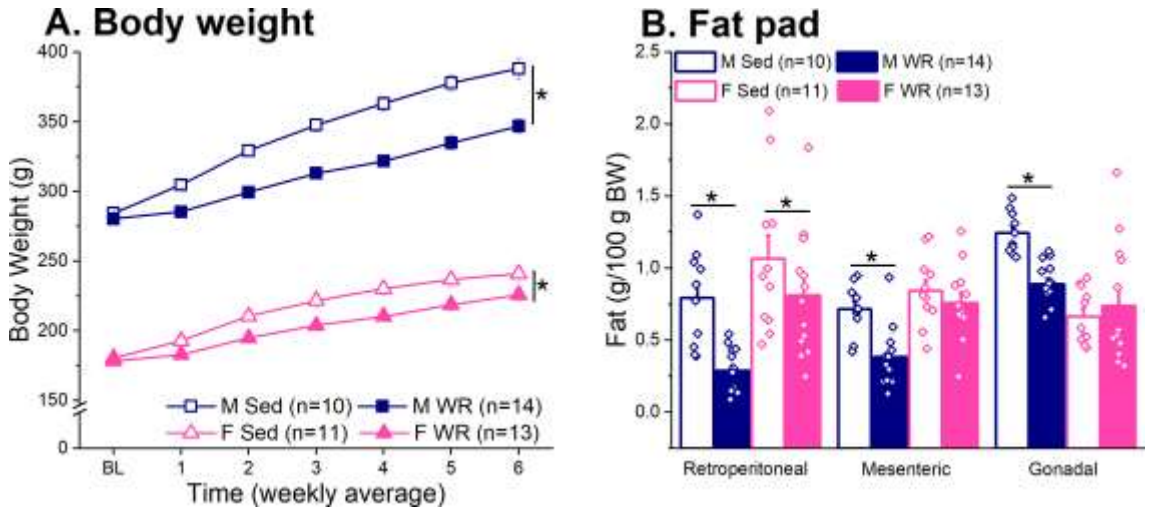

Figure 3.5. Body weight and fat composition. (A) Exercise led to suppressed body weight in both sexes, and this effect was more pronounced in males than females. *Sed vs. WR, $p < 0.05$. (B) Exercise suppressed retroperitoneal, mesenteric, and gonadal fat in males and had a limited effect in females with only an observable decrease in the retroperitoneal fat pad. *Sed vs. WR, $p < 0.05$.

Oral glucose tolerance test (OGTT)

During baseline conditions where rats were maintained on chow diet only, there were no group differences during OGTT [Figure 3.6 A; time × sex × exercise $F(4,176) = 1.78$, $p > 0.32$]. After 6 weeks of chronic HF feeding, fasting blood glucose levels were higher in females than males [Figure 3.6 B; time × sex $F(4,172) = 5.26$, $p < 0.001$; post hoc 0 min males vs. females 103.33 vs. 116.61 mg/dL, $p < 0.05$]. Blood glucose returned to fasting levels by 120 min in females but not males (post hoc 0 min vs. 120 min female $p > 0.32$ and male $p < 0.001$). Analyses comparing baseline and post-HF glucose AUC during OGTT revealed that exercise decreased glucose AUC from baseline in males, but this effect was absent in females [Figure

3.6 C; time × sex × exercise $F(1,43) = 6.81$, $p < 0.05$; post hoc male WR BL vs. HF $p < 0.01$ and female WR BL vs. HF $p > 0.12$].

No differences in insulin levels during OGTT were observed at baseline [Figure 3.6 D; time × sex × exercise $F(4,156) = 0.85$, $p > 0.49$]. There was a trend for exercise to decrease plasma insulin during the post-HF OGTT [Figure 3.6 E; sex × exercise $F(1,41) = 2.87$, $p = 0.09$], and this effect appeared to be driven by males. In support of this, a one-way ANOVA revealed a group difference at 0 min where only M WR rats had lower plasma insulin levels after long-term HF feeding [group $F(1,42) = 4.05$, $p < 0.05$; post hoc male Sed vs. WR $p < 0.01$ and female Sed vs. WR $p > 0.13$]. The amount of insulin produced to clear the same amount of glucose across time following the glucose challenge was not affected by exercise experience [time × exercise $F(4,164) = 1.61$, $p > 0.17$]. Analysis of insulin AUC during OGTT revealed a sex difference in the ability for exercise to suppress HF feeding-related increases in insulin [Figure 3.6 F; time × sex × exercise effect ($F(1,35) = 5.29$, $p < 0.05$]. The increase in insulin from baseline in males (post hoc M Sed BL vs. HF $p < 0.001$) was attenuated by exercise (post hoc M WR BL vs. HF $p > 0.06$). Moreover, M WR rats had lower post-HF insulin AUCs than their Sed counterparts (post hoc HF M Sed vs. M WR $p < 0.001$). In contrast, exercise did not appear mitigate HF-related increases in insulin in females (post hoc F Sed and F WR BL vs. HF both $p < 0.01$ and HF F Sed vs. F WR $p > 0.98$).

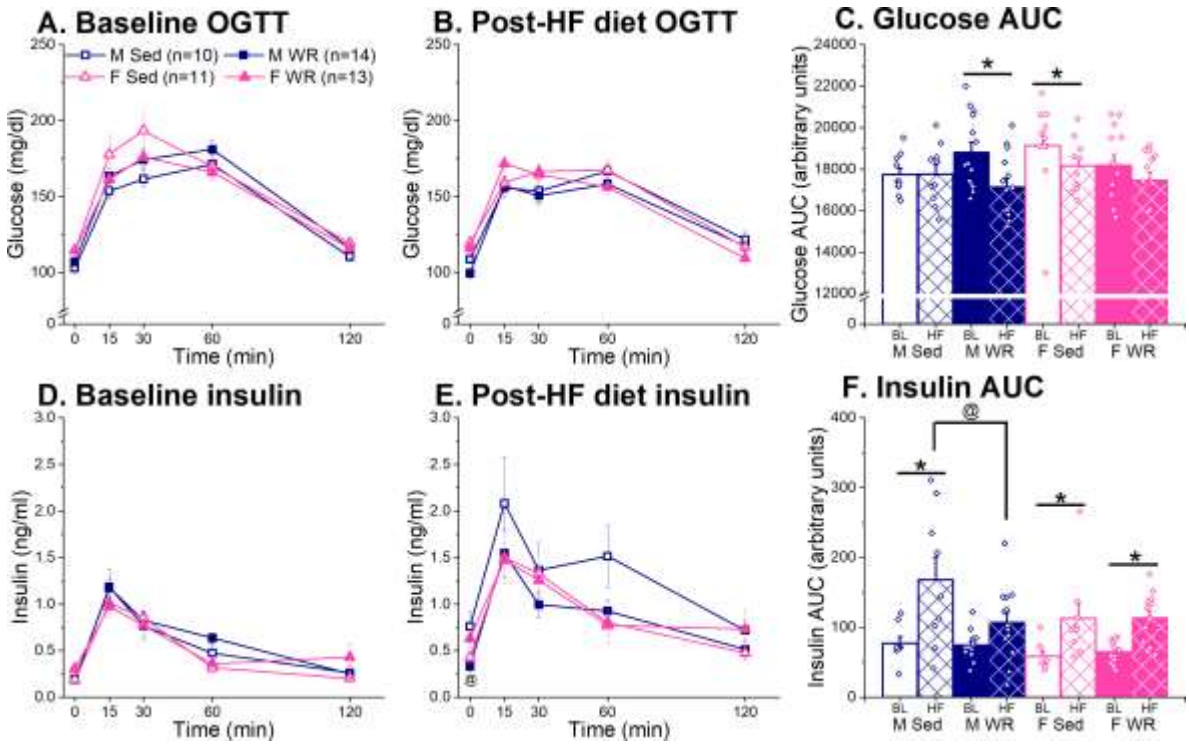

Figure 3.6. Blood glucose (top row) and plasma insulin (bottom row) results from an OGTT at baseline (BL) and post-HF diet exposure. (A) There were no group differences in blood glucose at BL. (B) Blood glucose levels following an oral glucose challenge retuned to fasting levels faster in females than males. (C) Relative to baseline, male WR and female Sed rats showed improved glucose clearance post-HF diet exposure. *BL vs. HF, $p < 0.05$. (D) There were no group differences in plasma insulin at BL. (E) Exercise decreased fasting plasma insulin levels in males but not females after long-term HF feeding. @M Sed vs. WR, $p < 0.05$. (F) Male WR rats had lower insulin AUC than their Sed counterparts. In contrast, both Sed and WR females had higher insulin AUC post-HF diet compared to chow BL. *BL vs. HF, $p < 0.05$, @HF M Sed vs. WR, $p < 0.05$.

At the end of the experiment, F WR rats had higher trunk plasma insulin levels than their Sed counterparts [F Sed 0.44 ± 0.06, and F WR 0.69 ± 0.06 ng/mL; sex × exercise $F(1,44) = 31.40$, $p < 0.001$; post hoc female Sed vs. WR $p < 0.05$] whereas this effect was reversed in males [M Sed 1.04 ± 0.10, M WR 0.54 ± 0.05; post hoc male Sed vs. WR $p < 0.001$]. A regression analysis on the relationship between average HF diet preference and trunk plasma insulin revealed that in males, higher preference for HF diet was associated with higher plasma insulin [Figure 3.7 A; $F(1,22) = 7.72$, $R = 0.51$, $p < 0.01$]; however, this relationship was not observed in females [Figure 3.7 B; $F(1,22) = 0.95$, $R = 0.01$ $p > 0.94$]. No associations were found between average HF diet preference and either glucose or insulin AUC.

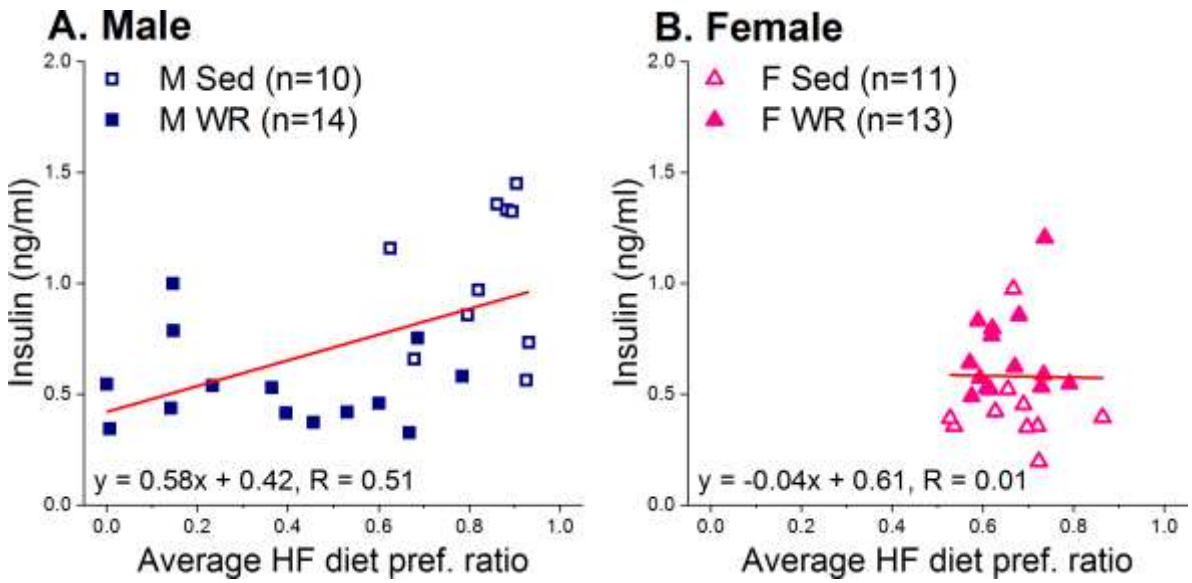

Figure 3.7. Correlation between trunk plasma insulin levels at the end of the experiment and the average ratios of HF diet preference. (A) There was a moderate, positive correlation between HF diet preference and trunk plasma insulin in males. (B) There was no relationship between HF diet preference and trunk plasma insulin levels in females.

Barnes maze

During training, males were slower to located the escape box relative to females [sex and trial × sex $F(1,43) = 66.58$ and $F(3,129) = 7.59$, respectively, both $p < 0.001$]. Exercise training decreased latency to locate the escape box in rats of both sexes [Figure 3.8 A & C; trial × exercise and trial × sex × exercise $F(3,129) = 4.23$ and 2.00, $p < 0.01$ and $p > 0.11$, respectively]. Similarly, exercise reduced the number of errors made during the task acquisition/learning in rats of both sexes [Figure 3.8 B & D; trial x exercise and trial × sex × exercise $F(3,129) = 3.37$ and 0.65, respectively, $p < 0.05$ and $p > 0.58$]. Male rats did, however, make more errors on average than females during training [sex $F(1,43) = 5.25$, $p < 0.05$].

Both male and female rats decreased latency [sex × exercise $F(1,43) = 1.80$, $p > 0.18$] and errors committed [sex × exercise $F(1,43) = 1.67$, $p > 0.20$] during the probe trial, and there were no effects of sex or exercise. During reversal learning, there was no evidence of sex differences of an effect of exercise for latency or errors [sex × exercise $F(1,43) = 0.79$ and 0.15, respectively, both $p > 0.37$]. There was a difference in the percent increase in errors made

between the probe and reversal trials. A factorial ANOVA revealed that F WR rats had a larger increase in errors made than their Sed counterparts [sex × exercise $F(1,34) = 6.48$, $p < 0.05$; female Sed vs. WR post hoc $p < 0.05$], but there was no difference between Sed and WR males (post hoc male Sed vs. WR $p > 0.10$).

All rats used a non-spatial serial search strategy (i.e., a clockwise or counterclockwise sequential search) rather than a direct search strategy where the rats utilize visuospatial cues (i.e., signs in the testing room to find the escape box). Despite not using the visual cues, decreased latency and errors across time provides evidence that all rats learned the task. Sprague-Dawley rats have poor visual acuity biasing them towards using a serial search strategy (Gawel et al., 2019); however, visual acuity has not been shown to be correlated with deficits in learning and memory issues in mice tested on the Barnes maze (O'Leary et al., 2011). Our results for latency and errors made are also comparable to what has been reported in the literature (Rosenfeld and Ferguson, 2014, Gawel et al., 2019).

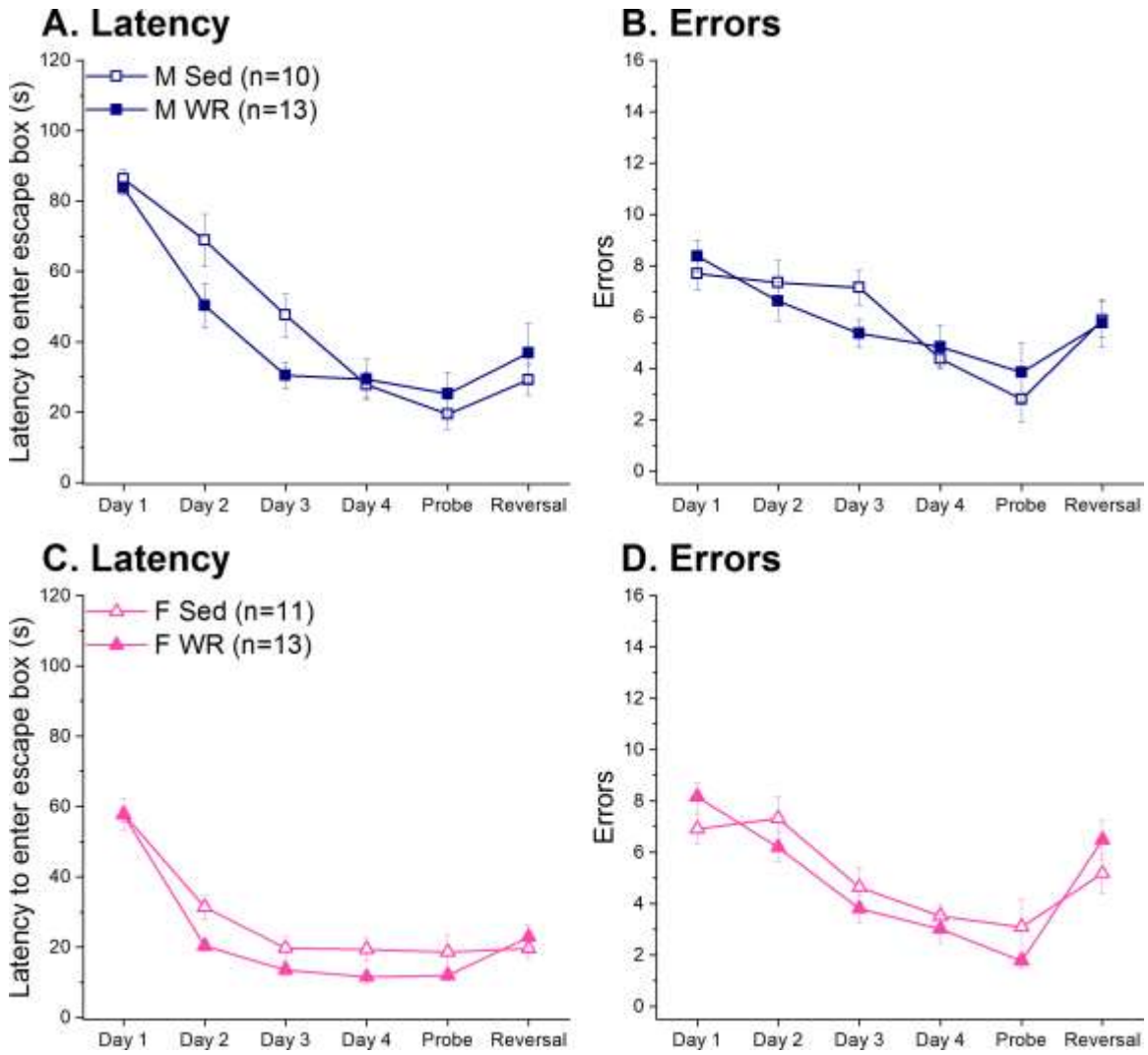

Figure 3.8. Barnes maze results for males (M, top) and females (F, bottom). (A & C) Both male and female rats decreased latency to locate the escape box across training days. (B & D) All rats made fewer errors across training days when searching for the escape box.

DISCUSSION

The efficacy at which exercise can attenuate the adverse metabolic and cognitive outcomes of prolonged HF-feeding is unclear. To this end, we used a long-term WR and two-diet choice model to examine the relationship between increased HF diet preference and its associated metabolic and cognitive outcomes, and if exercise can attenuate these negative effects with chronic HF feeding. We found that both male and female rats reversed HF diet avoidance, and this shift in diet preference occurred earlier in females than males (Figure 3.3). The positive effects of exercise including suppressed body weight and fat deposition (Figure 3.5), which may have contributed to improved metabolic function, were only observed in males (Figure 3.6). Exercise equally improved learning and memory as evidenced by decreased latency and errors made to locate the escape box on the Barnes maze in rats of both sexes (Figure 3.8). Although the rats' use of a spatial search strategy limited the interpretation of changes in behavioral flexibility, female WR rats showed some impairment and were the only group to increase the number of errors made from the probe to reversal learning trials when compared to their Sed controls. Thus, it appears that sex differences in running-induced changes in diet choice patterns led to sex-specific outcomes in regards to the protective effect of exercise on peripheral metabolism and cognition.

Diet choice patterns during WR were similar to our short-term WR and two-diet choice experiment in Chapter 2 (Figure 3.3). Although all rats reversed HF diet avoidance, males maintained this avoidance for a longer duration than females. In females, feeding behavior appears to be palatability-driven rather than by physiological hunger or metabolic state (Tapia et al., 2019, Buczek et al., 2020). These factors may contribute to the higher incidence of binge eating behavior increased female susceptibility to binge eating (Hudson et al., 2007, Klump et al., 2013) and development of obesity (Perpina et al., 2017, Edwards et al., 2018). In addition, females have higher reward sensitivity than males (Lynch, 2006, Carroll and Anker, 2010). As a result, WR may not be a sufficient substitute for the reinforcing effects of HF diet (Spierling et

al., 2018). Male rats are more responsive to the naturally rewarding effects of voluntary WR (Belke and Wagner, 2005) such that WR can decrease drug-seeking behavior (Peterson et al., 2014, Zhou et al., 2016). Exercise may not be able to combat the lack of dietary restraint (Day et al., 2012) and propensity towards palatability-driven eating in the absence of hunger via stimulation of the reward system in females (Buczek et al., 2020) leading them to reverse HF diet avoidance earlier than males.

With exercise training, the extent of decreased HF diet preference, energy intake, body weight, and adiposity was greater in males than females and may have contributed to our finding that glucose metabolism was only improved in males. In line with this, studies have shown that males are also more responsive to exercise-mediated improvements in insulin sensitivity and glucose tolerance (Hill et al., 1989, Donnelly et al., 2004, Caudwell et al., 2014). One potential explanation for the limited beneficial effects of exercise in females could be that because females compensated for the increased energy requirement from exercise by increasing daily energy intake more rapidly than males (Carrera et al., 2011, Foright et al., 2020), leading to a lower magnitude of body weight and fat loss. This suggests that without a concurrent loss of body weight and fat, exercise has a limited effect on improving peripheral metabolic function in females (Nara et al., 1997, Coker et al., 2009, Maesako et al., 2012). A combination of diet and exercise may be optimal to promote weight loss and improve insulin sensitivity for females. Although male WR rats also reversed HF diet avoidance, this reversal occurred later than females and despite increased HF diet intake, it appears that exercise training can attenuate HF-induced impairments in glucose tolerance (Vallerand et al., 1986, Goodyear et al., 1991, Bongbele et al., 1992, Goodyear and Kahn, 1998, Tokuyama and Suzuki, 1998, LaPier et al., 2001, Latour et al., 2001, Gollisch et al., 2009, Lamontagne et al., 2013). In addition, the relationship between increased HF diet preference and insulin levels was only present in males (Figure 3.7). Taken together, the positive metabolic effects of exercise appear to be influenced by both the slower compensatory response to exercise (Beaulieu et al.,

2017, Beaulieu et al., 2020b, Foright et al., 2020) and longer maintenance of low HF diet preference in males.

Learning on the Barnes maze was improved with exercise training (Figure 3.8) independent of sex (Betancourt et al., 2017, Villanueva Espino et al., 2020). This is consistent with reports in the literature where exercise has been shown to reverse cognitive deficits resulting from HF feeding (Molteni et al., 2004, Kanoski and Davidson, 2010, Woo et al., 2013, Gibbons et al., 2014, Noble et al., 2014, Klein et al., 2016). While we found that females had faster escape latencies than males (i.e,. no male advantage) during training, reports on sex differences in learning visuospatial tasks are inconsistent (Bucci et al., 1995, Jonasson, 2005, O'Leary et al., 2011, Locklear and Kritzer, 2014). There was, however, evidence of sex differences during reversal learning such that female, but not male, WR rats increased errors made from the probe to reversal learning trials compared to their Sed controls. This suggests that female WR rats had the worst behavioral flexibility and conflicts with the literature stating more pronounced PFC-related cognitive dysfunction with HF feeding in males (Hwang et al., 2010, Laredo et al., 2015, Shields et al., 2016). Importantly, all rats used a non-spatial search strategy, which may be more efficient and not uncommon given the low visual acuity of Sprague-Dawley rats (Locklear and Kritzer, 2014) compared to other commonly used strains such as Long-Evans and Wistar rats (Locklear and Kritzer, 2014, Sadeghian et al., 2019). Our interpretation and analysis of the behavioral flexibility results are thus limited and confounded by two factors 1) rats did not use the spatial cues to located the escape box and 2) task acquisition may be weaker when learning without utilizing spatial cues. Obesity typically results in mild cognitive impairment (Seshadri et al., 1997, Lin et al., 2015) and the Barnes maze may not be a sufficiently sensitive behavioral task to tap into the complex nature of cognition. Future studies should include a variety of behavioral tasks to tap into different facets of cognition to directly assess if chronic HF feeding impairs specific rather than global domains of cognitive function

sex dependently whereby some component-specific impairments are more influential in the control of feeding behavior.

In the present study, we examined the metabolic and cognitive outcomes of sex-specific diet choice patterns with long-term HF feeding in Sed and WR rats. The protective effect of exercise at attenuating peripheral metabolic dysregulation was specific to males. However, both male and female rats improved performance on the Barnes maze. The lack of improvement in metabolic function in females did not appear to affect exercise-associated improvements in cognitive performance on the Barnes maze. Thus, there appears to be differential protective effects of aerobic exercise in terms of metabolic and cognitive health. On the whole, although the metabolic effects of chronic HF feeding and preference led to worse outcomes in females, exercise remains a suitable intervention for both sexes to protect against diet-associated declines in cognitive ability.

CHAPTER 4: ROLE OF EXERCISE IN MEDIATING ALTERATIONS IN PERIPHERAL METABOLISM AND IMPULSIVE CHOICE WITH CHRONIC WESTERN DIET EXPOSURE

ABSTRACT

Higher levels of impulsivity may increase the temptation to overeat energy dense foods in the modern obesogenic environment and may contribute to the development of obesity. However, it is unclear if heightened impulsivity is a cause or outcome of consuming Western style diets that are high in both processed fat and sugar. The present study examined impulsive choice before and after Western diet (WD) exposure using our established long-term wheel running (WR) and two-diet choice model in rats of both sexes. We hypothesized that higher levels of impulsivity would be associated with higher WD preference that would further increase future impulsive choice behavior, which exercise would attenuate. To this end, delayed discounting, a measure of impulsive choice, was assessed at baseline with all rats maintained in sedentary housing and a control diet. Then, rats were divided into naïve, sedentary (Sed), or WR groups for the 5-week WR and two-diet choice period after which all rats underwent an oral glucose tolerance test. Subsequently, all rats were re-tested on impulsive choice followed by an insulin tolerance test (ITT). All Sed rats preferred WD over the control diet, and all WR rats reversed WD avoidance with females reversing earlier than males. Exercise-mediated suppression of body weight and adiposity was more evident in males that also showed improved glucose clearance. There was no effect of exercise on insulin sensitivity; however, WR rats of both sexes had a faster recovery of hypoglycemia during ITT compared to their Sed and naïve counterparts. No sex or group differences in impulsivity were observed at baseline, and all rats made more impulsive choices following WD exposure independent of diet, sex, or exercise. Improvements to the study design including extending the length of diet exposure, employing a consistent housing and weight-restriction procedure, and using a more palatable food reinforcer may be necessary to tease apart the relationship between diet and impulsive choice and whether exercise can attenuate increases in impulsivity from chronic consumption of high energy diets.

RATIONALE

Consumption of palatable food may lead to pathological changes in the brain and behavior that promote a cycle of overeating and weight gain. One vulnerable neurobiological phenotype that contributes to compulsive overeating and binge-like eating behavior is impulsivity (VanderBroek-Stice et al., 2017, Benard et al., 2019). Weaker inhibitory control may increase the tendency to overconsume unhealthy, calorie-dense foods, and make poor dietary choices in the modern obesogenic environment that, in turn, lead to more impulsive behavior (Steele et al., 2017). Unchecked, this pattern of feeding behavior may lead to the development of obesity, which detrimentally impacts cognitive and metabolic function.

Impulsivity is a multifaceted behavior that can be divided into two neurally dissociable parts (Broos et al., 2012, Weafer and de Wit, 2014): impulsive action (i.e., poor inhibitory control) and impulsive choice (i.e., inability to delay short-term gratification). Impulsive action has been consistently shown to predict binge-like overeating in humans (Meule et al., 2017) and rodents (Velazquez-Sanchez et al., 2014). Contrasting reports in regards to the relationship between excessive overeating and impulsive choice have been found including no relationship (Moore et al., 2018) and binge-eating females displaying higher levels of impulsive choice (Vickers et al., 2017). Thus, it is unclear whether obese-prone individuals have a vulnerable neurobiological phenotype that lends itself to binge-like eating behavior or whether it is a consequence of increased palatable diet intake.

The limited studies utilizing a delay discounting task on the effect of chronic HF feeding on subsequent increases in impulsive choice are mixed, ranging from no change (Garman et al., 2021), decreased in obesity prone rats relative to obesity resistant rats (Narayanaswami et al., 2013), and increased impulsive choice behavior when maintained on a HF diet (Steele et al., 2017). The effect of HF diet may be sensitive to the length of palatable diet exposure and methodological differences in the assessment of impulsive choice. Moreover, it is unclear whether the HF-associated increase in impulsive choice is transient given that rats maintained

on either a HF or high-sugar diet made more impulsive choices while on the palatable diet but were no different from controls when switched back to a chow diet (Steele et al., 2017). The aforementioned studies only utilized male rats; therefore, it is unclear whether females would more consistently show increased levels of impulsive choice behavior given that they are more likely to engage in binge-eating behavior than male rats (Imperatori et al., 2013, Klump et al., 2013, Hildebrandt et al., 2014, Eneva et al., 2017).

Reports on gender differences in impulsive choice vary depending on reward type (real vs. hypothetical, drug vs. food) and hormones (Smith and Hantula, 2008, Cross et al., 2011, Mitchell and Potenza, 2015, Weinstein and Dannon, 2015) and are mixed in humans (Mischel and Underwood, 1974, Kirby and Marakovic, 1996, Silverman, 2003, Reynolds et al., 2006, Beck and Triplett, 2009). There is a lack of consensus in the literature in regards to sex differences in impulsive choice in rodents with studies reporting higher levels in males (Panfil et al., 2020), females (Perry et al., 2007, Weafer and de Wit, 2014, Lukkes et al., 2016), or no sex difference (Perry et al., 2008a, Hammerslag et al., 2019, Sackett et al., 2019). In contrast to humans in which impulsive choice is associated with hormone concentrations, a recent study found that female rats display higher levels of impulsive choice than males and that this effect was independent of estrous stage (Hernandez et al., 2020). The majority of studies on sex differences in impulsivity are typically in the field of drug addiction and use drug, rather than food, reinforcers. However, the motivational processes (e.g., trait impulsivity, physiological state, reward sensitivity) underlying overeating and problematic drug use may be different such that these maladaptive behaviors lead to different metabolic outcomes and disease states. It is important to characterize these sex differences in the susceptibility for impulsivity-based overeating in order to optimize sex-specific prevention and treatment interventions.

Exercise promotes weight loss and improves insulin sensitivity and may thus be able to attenuate weight and insulin-associated increases in impulsivity. Indeed, initial evidence in human studies suggests that exercise can decrease impulsive choice (Tate et al., 2015, Sofis et

al., 2017, Albelwi et al., 2019). The one rodent study utilizing female rats reported similar findings (Strickland et al., 2016). However, it is unclear whether the effect of exercise on attenuating increases in impulsivity would be more pronounced in males based on the fact that males are more response to the weight and fat loss effects of exercise than females (Pitts, 1984, Cortright et al., 1997, Anderson et al., 2001, Donnelly and Smith, 2005, Schroeder et al., 2010).

Whether impulsive choice can predict palatable diet preference during exercise or is an outcome of chronic palatable diet preference is unclear. Moreover, how additional factors such as sex, exercise, and metabolic function interact with impulsivity and HF feeding has not been examined. The hypothesis was twofold: first, we hypothesized that baseline impulsivity would predict future Western diet preference, and that females would display higher levels of impulsive choice than males in addition to increased peripheral insulin resistance and second, we hypothesized that exercise would attenuate metabolic and cognitive outcomes of chronic Western diet exposure to a greater extent in males than females. To test this hypothesis, we measured impulsive choice before and after chronic Western diet exposure in sedentary and wheel running rats that had long-term access to diet choice between a control and Western diet. Investigating the role of impulsivity in palatable diet preference may lead to new insights regarding sex differences in vulnerability to and response to pathological feeding behavior.

METHODS

Subjects

The subjects in this experiment included 32 male (250 – 275 g) and 32 female (150 – 175 g) Sprague-Dawley rats (Envigo, Indianapolis, IN) that were ~7-8 weeks old upon arrival. A timeline of the experiment and experimental diet composition are summarized in Figure 4.1 and Table 4.1. During habituation, rats were group housed in same sex pairs on a reversed 12:12 light/dark cycle (lights on at 1930) and maintained on ab lib water and chow (3.1 kcal/g; Teklad global 2018, Teklad Diets, Madison, WI). Daily measurements of body weight, food intake, and

fluid intake occurred during the dark cycle at 0730 h. Chow was replaced with the control diet (3.9 kcal/g; 10% fat, 73% carbohydrate, 17% protein; D14042701, Research Diets, New Brunswick, NJ) before the baseline assessment of impulsive choice which lasted ~3 weeks. During the behavioral testing period, rats were moderately food restricted and maintained at 85-95% of their free feeding weight. After baseline behavioral testing, rats were single caged and ad lib access to food was returned. Rats were divided into three groups (n = 10-11/group): a naïve control group maintained on the control diet and a sedentary (Sed) group with diet choice between the control and Western diet (WD; 4.7 kcal/g; 40% fat, 43% carbohydrate, 17% protein; D12079B, Research Diets, New Brunswick, NJ) that were housed in conventional cages, and a WR group that had access to both diet choice and WR and were housed in running wheel cages (13” diameter wheel; Mini Mitter, Starr Life Sciences, Oakmont, PA).

Rats were maintained on the WR and two-diet protocol for the duration of the experiment. After ~5 weeks on the experimental procedures, all rats underwent an oral glucose tolerance test (OGTT) after which they were re-tested on impulsive action which lasted ~2 weeks. An insulin tolerance test (ITT) was performed the day after behavioral testing concluded. Rats were euthanized the day following ITT.

Macronutrient	Unit	Control diet (3.9 kcal/g)	Western diet (4.74 kcal/g)
Protein	% kcal	17	17
Carbohydrate	% kcal	73	43
Fat	% kcal	10	40
Total		**100**	**100**
Source	**Unit**		
Casein, 80 mesh	kcal (*g*)	780 (*195*)	780 (*195*)
DL-Methionine	kcal (*g*)	12 (*3*)	12 (*3*)
Corn starch	kcal (*g*)	2780 (*695*)	200 (*5*)
Maltodextrin 10	kcal (*g*)	600 (*150*)	400 (*100*)
Sucrose	kcal (*g*)	0 (*0*)	1364 (*341*)
Cellulose BW200	kcal (*g*)	0 (*50*)	0 (*50*)
Milk fat, anhydrous	kcal (*g*)	383 (*42.5*)	1800 (200)
Corn oil	kcal (*g*)	90 (*10*)	90 (*10*)
Ethoxyquin	kcal (*g*)	0 (*0.04*)	0 (*0.04*)
Mineral mix S10001	kcal (*g*)	0 (*35*)	0 (*35*)
Calcium carbonate	kcal (*g*)	0 (*4*)	0 (*4*)
Vitamin mix V10001	kcal (*g*)	40 (*10*)	40 (*10*)
Choline bitartrate	kcal (*g*)	0 (*2*)	0 (*2*)
Cholesterol	kcal (*g*)	0 (*0*)	0 (1.5)
Total		**4685 (*1196.59*)**	**4686 (*1001.54*)**

Table 4.1. Nutrient composition of the low-fat control diet and Western diet.

Wheel running and two-diet choice

The wheel running and two-diet choice protocol that began after baseline assessment of impulsive choice was executed the same way as Chapter 3 with a few modifications. First, Western diet (WD) was used in place of HF diet as the palatable diet, and a control diet matched to the WD diet was used in place of chow diet. Second, a naïve control group for each sex that only had access to the control diet was added to the group design. The experimental protocol ran uninterrupted for ~5 weeks and was maintained for the duration of the experiment during OGTT, impulsive choice re-test, and ITT. During the impulsive choice re-test, rats were mildly food restricted and had 1 h access to both diets right before dark onset (1700 h).

On the day of sacrifice, food and fluid was removed ~2.5-3.5 h before light onset (1600 – 1700 h) and all rats underwent an intraperitoneal (i.p.) insulin challenge (1 U/kg Humulin R U-100; Eli Lilly; Indianapolis, Indiana) at 1900 h. 45 min after the injection, rats were sacrificed via rapid decapitation and brains were collected and frozen on powered dry ice. Trunk blood

plasma was collected for assessment of plasma insulin levels, and carcasses were saved for post-mortem dissection of the retroperitoneal, mesenteric, and gonadal fat pads.

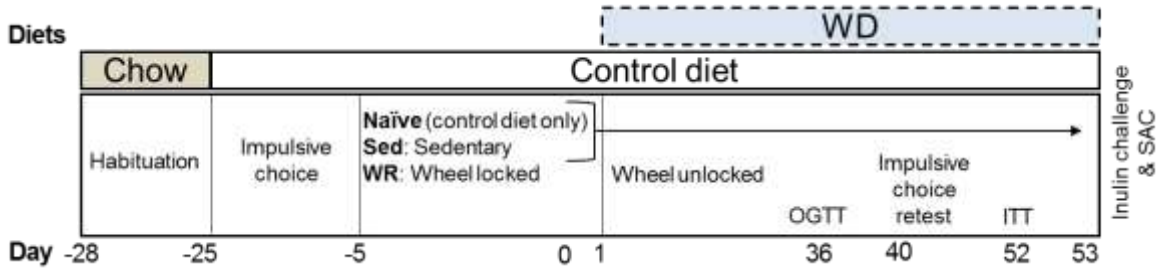

Figure 4.1. Timeline of experiment. Sed: sedentary, WR: wheel running; OGTT: oral glucose tolerance test; ITT: insulin tolerance test; SAC: sacrifice

Oral glucose tolerance test (OGTT) and insulin tolerance test (ITT)

After ~5 weeks of WR and two-diet choice, all rats underwent an OGTT. The procedures for OGTT were identical to that of Chapter 3.

After the re-test of impulsive choice, all rats underwent an ITT the day before sacrifice. Food was removed 3.5 h before light onset (1600 h) and baseline (0 min) blood glucose assessment began at 2000 h through a tail nick using an AlphaTRAK2 handheld glucometer. Then, rats were challenged with an i.p. injection of 0.56 U/kg Humulin R U-100 (Eli Lilly; Indianapolis, Indiana). Blood glucose was assessed 15, 30, and 90 min following the insulin challenge using the same tail nick from baseline.

Impulsive choice

Impulsive choice (Foscue et al., 2012, Hammerslag et al., 2019) was assessed at baseline and re-tested following WD exposure. After 5 days of food restriction, rats were given ~10 BioServ pellets (3.6 kcal/g; Bio-serv, #F0021; Frenchtown, NJ) that would later serve as reinforcers in their home cage. Rats underwent one day of magazine training where they were placed in the operant chamber with pellet delivery occurring at variable time intervals ranging from 60 – 120 s at 5 s intervals (i.e., 60, 65, 70… or 110, 115, 120 s) under a variable time (VT) 90 s schedule of delivery averaging to 90 s. This was done for acclimate the rat to the operant

box and make the food trough more salient. During the 45 min session, all levers were retracted, and the cue and house lights were not illuminated.

Lever assignments were counterbalanced, such that half of the males and females had the left lever assigned as the smaller sooner lever (1 pellet) and the right lever assigned as the larger later lever (3 pellets) whereas the other halves of each sex had the reverse assignments. These lever assignments were maintained constant throughout all sessions and through both baseline and post-WD assessment of impulsive choice.

After magazine training, rats underwent lever press training consisting of 45 trials per session. The first 2 sessions of lever press training also included autoshaping where pellets were delivered following a VT90 schedule in addition to when the rat pressed the lever to promote task acquisition. A session ended after 45 min had elapsed or after 45 trials, whichever occurred first. Training days for the smaller sooner and larger later lever were alternated daily and all rats were trained starting with the smaller sooner lever. Importantly, there was no delay associated with the larger later lever during lever press training and pellet delivered occurred 1 s after the lever press. During lever press training, only one lever was extended at a time and only the cue light above the active/extended lever was illuminated. Once a rat pressed the lever, the cue light above it extinguished, the lever retracted, and the number of pellets associated with that lever was delivered. After pellet delivery, the house light was illuminated signaling the intertrial interval (ITI) that lasted a total of 20 s after which it extinguished. Lever press training ended when rats achieved a total of 45 trials in 2 consecutive days.

During lever press training, handshaping occurred in the afternoon the same day if a rat earned less than 10 pellets on any day during lever press training. These sessions were identical to lever press training sessions except that crushed pellet bait was placed on the active lever every ~10 min and rats were also reinforced by the experimenter for successive approximations of the lever press behavior whereby a pellet was placed on the active lever for the rat to consume.

Two forced choice sessions consisting of 25 trials per session were conducted to ensure rats would press both levers and associate one with a delay. A trial began with free choice during which both levers were extended and the cue light above each lever was illuminated. After a lever press occurred, the cue lights above both levers extinguished and both levers retracted. If a rat chose to press the smaller sooner lever, 1 pellet was delivered after 1 s and if a rat chose to press the larger later lever, 3 pellets were delivered after 5 s. After pellet delivery and the associated delay, the house light illuminated to signal the ITI, which lasted for 20 s after which it extinguished. Then, the lever the rat did not press before was extended and the cue light above it was illuminated. Rats were required to press the previously not chosen lever during the forced choice portion of that trial. The event sequence following the lever press was the same as the free choice portion of the trial. After the forced choice portion, a new trial started with both levers extended and the cue light about each lever illuminated where rats once again had free choice.

Rats then underwent pre-training. A session ended after 45 min had elapsed or after 45 trials, whichever occurred first. Sessions began with both levers extended and the cue light above each lever illuminated. After a lever press, both levers retracted and the cue lights above the levers extinguished and the number of pellets associated with that lever was delivered after 1 s regardless of whether the rat chose the smaller sooner or larger later lever. The house light was illuminated for 20 s to signal the ITI following pellet delivery. Following the ITI, the house light extinguished and a new trial began with both levers extended and the cue light above each lever illuminated. Pre-training ended after a rat achieved a total of 45 trials in 2 consecutive days.

Then, all rats underwent discrimination training where sessions were identical to that of pre-training except omission errors were introduced. A session ended after 45 trials and there was no session time limit. An omission error occurred if a rat does not make a response during the choice phase during which both levers are extended. If no lever press occurred after 60 s,

then there was no pellet delivery and the trial moved directly into the ITI where the house light was illuminated for 20 s and extinguished before a new trial. Discrimination training ended after a rat selected the larger later lever ≥ 80% of the time in 3 consecutive days.

During the 5 testing sessions, the sessions were identical to that of discrimination training except a delay period was introduced for the larger later lever and increased each day from 5, 15, 30, 50, to 75 s (Figure 4.2). All rats proceeded to the next delay phase the following day regardless of performance. The delay period for the smaller sooner lever was maintained at 1 s throughout testing. A session ended after 45 trials and there was no session time limit.

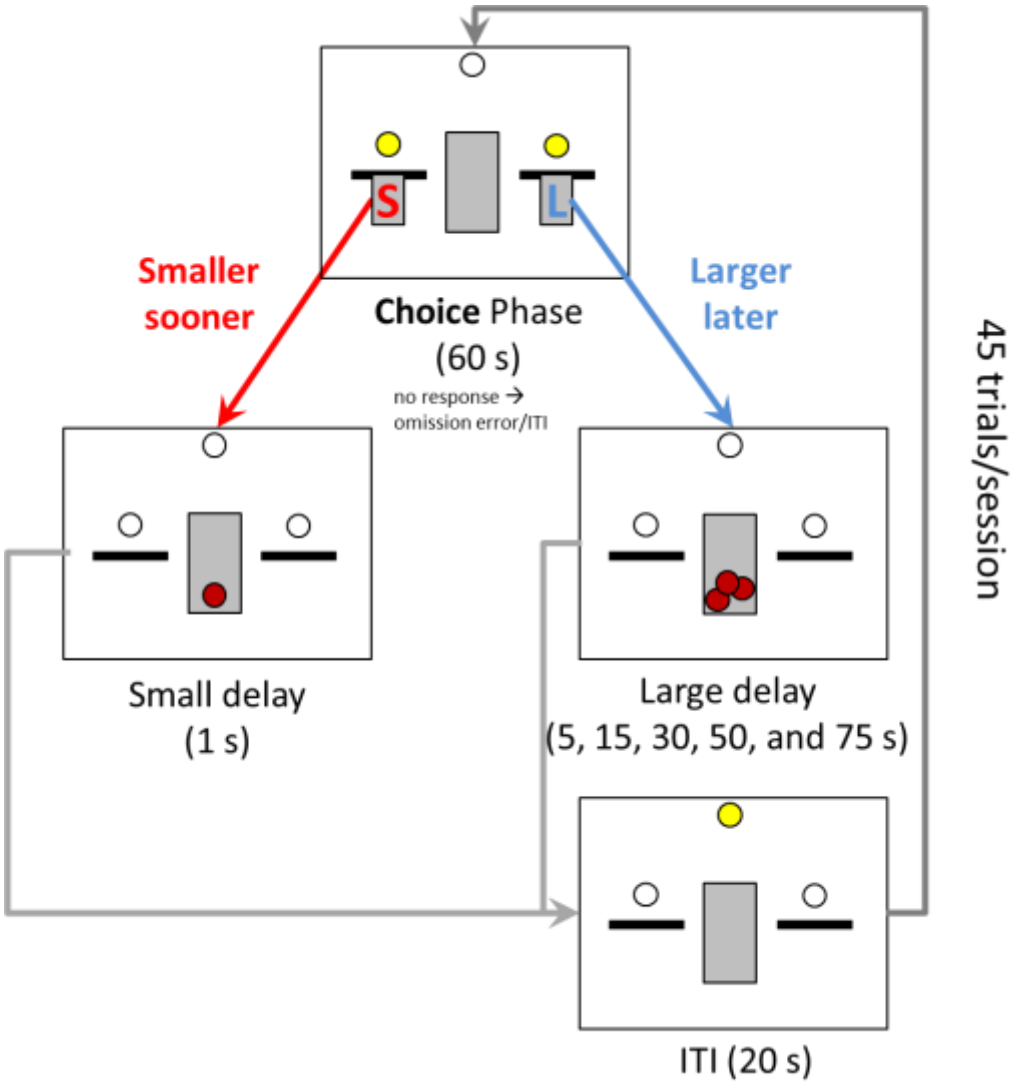

Figure 4.2. Workflow for assessment of impulsive choice. A trial begins with the choice phase where rats choose between the smaller sooner lever (1 pellet delivered after 1 s) or the larger later lever (3 pellets delivered after 5/15/30/50/75 s) after which the trial moves into the ITI. No response during the choice phase results in an omission error where the trial moves directly into the ITI. Sessions end after 45 trials and there is no session time limit. Choosing the smaller sooner lever more frequently suggests increased impulsive choice. ITI: intertrial interval

Statistical analysis

Statistical analyses were performed using Statistica 13.3 (TIBCO, Palo Alto, CA, USA). Data are presented as the mean ± standard error of the mean (SEM). Post hoc Fisher's LSD and Tukey's HSD tests were performed when significant main effects or interactions were identified.

Raw data during the uninterrupted WR and two-diet choice portion of the experiment included weekly body weight and weekly averages of total energy intake, and running activity. Separate 3-way mixed model ANOVAs with sex (male vs. female) and exercise (Sed vs. WR vs. naïve) as between-subject factors and time (5 weeks) as the within-subject factor was used to analyze body weight and total energy intake. Running activity was analyzed using a 2-way mixed model ANOVA with sex as the between-subject measure and time as the within-subject measure.

Diet choice patterns in Sed and WR rats were analyzed using a 4-way mixed model ANOVA with sex and exercise as the between-subject factors and diet (control diet vs. WD) and time as the within-subject factors. WD preference ratios were calculated by dividing daily intake of WD (kcal) by total daily energy intake (kcal) and average weekly WD preference was analyzed using a 3-way mixed model ANOVA with sex and exercise as the between-subject factors and time as the within-subject factor. Retroperitoneal, mesenteric, and gonadal fat pads were normalized to body weight and analyzed separately using 2-way factorial ANOVAs with sex and exercise as the between-subject factors.

The raw data from OGTT and ITT from each sex were analyzed separately. Plasma glucose and insulin concentrations from OGTT were analyzed using a 2-way mixed model ANOVAs with exercise as the between-subject factor and time (0, 15, 30, 60, 120 min) as the within-subject factor. Glucose and insulin area under curve (AUC) results from OGTT were analyzed separately using 2-way ANOVAs with sex and exercise as the between-subject factors. Plasma glucose data from ITT was analyzed to assess insulin sensitivity using a 2-way

mixed model ANOVAs with exercise as the between-subject factor and time (0, 15, and 30 min) as the within-subject factor. The first 30 min of ITT involves glucose translocation and uptake into the muscle and adipose thereby decreasing blood glucose levels and is a measure of insulin resistance (Durham and Truett, 2006, Ajala et al., 2012). After the nadir of blood glucose that occurs ~30min, the counter-regulatory response to hypoglycemia becomes initiated to bring glucose levels back to baseline. The counter-regulatory response involves the activation of the sympathetic nervous system and release of counter-regulatory hormones including epinephrine, corticosterone, and glucagon, which promote hepatic glycogenolysis to promote glucose release (Durham and Truett, 2006, Ajala et al., 2012). Thus, the blood glucose concentration 90min (Durham and Truett, 2006, Ajala et al., 2012) after the insulin challenge in ITT was used to assess deficits in the counter-regulatory response using a 2-way factorial ANOVA with sex and exercise as the between-subject factors.

A larger later preference ratio was calculated by taking the larger later lever presses and dividing it by total number of level presses and used as an index of impulsive choice behavior. Data from baseline was analyzed using a 1-way ANOVA with sex as the between-subject factor and delay (5, 15, 30. 50, 75s) as the within-subject factor. Re-test data was analyzed similarly with the addition of exercise as a between-subject factor. Then, to assess changes in impulsive choice behavior, a 4-way mixed model ANOVA was performed with the additional within-subject factor of time (baseline vs. post-WD).

To assess changes in the rate of discounting, the preference ratio for the larger later lever from the 5 days of impulsive choice testing were fit to a non-linear exponential function: $LL\ pref.ratio = e^{-kD}$ where *D* is the delay to the reward and *k* (the slope) serves as an index of the rate of delay discounting and reward sensitivity (Odum, 2011, Ucha et al., 2019). A larger *k*-value indicates a steeper slope/decreased preference for the larger later lever and suggests increased impulsive choice behavior (Odum, 2011). The *k*-parameter or slope at baseline and post-WD exposure was first analyzed separately using a 1-way or 2-way ANOVA, respectively.

Impulsive choice behavior from baseline and post-WD exposure was compared using a 3-way mixed model ANOVA.

RESULTS

Wheel running and two-diet choice

All Sed rats consumed significantly more WD than control diet [diet x exercise $F(1,39) = 38.18$, and diet x exercise x time $F(4,156) = 6638.00$, both $p < 0.001$; Figure 4.3A & B]. Diet choice patterns differed among male and female rats [diet x sex x exercise $F(1,39) = 4.42$, $p < 0.05$] and male WR rats maintained lower preference for WD diet than females across time [diet x sex x exercise x time $F(4,156) = 4.92$, $p < 0.001$; Figure 4.3C & D]. In addition, male WR rats reversed their initial WD avoidance at week 4 (post hoc WD vs. control diet weeks 1 – 3 all $p < 0.05$ and week 4 $p > 0.99$), 1 week later than female rats (post hoc WD vs. control diet weeks 1 and 2 both $p < 0.05$ and week 3 $p > 0.99$). In addition, male WR rats never consumed more WD than control diet whereas female WR rats consumed more WD than control diet during the last 2 weeks of WR and two-diet choice (post hoc WD vs. control diet weeks 4 and 5 both $p < 0.05$). During impulsivity re-test where rats were food restricted, however, all rats consumed significantly more WD than control diet [diet $F(1,39) = 134.09$, $p < 0.001$] independent of sex or exercise [diet x sex x exercise $F(1,39) = 0.10$, $p > 0.75$].

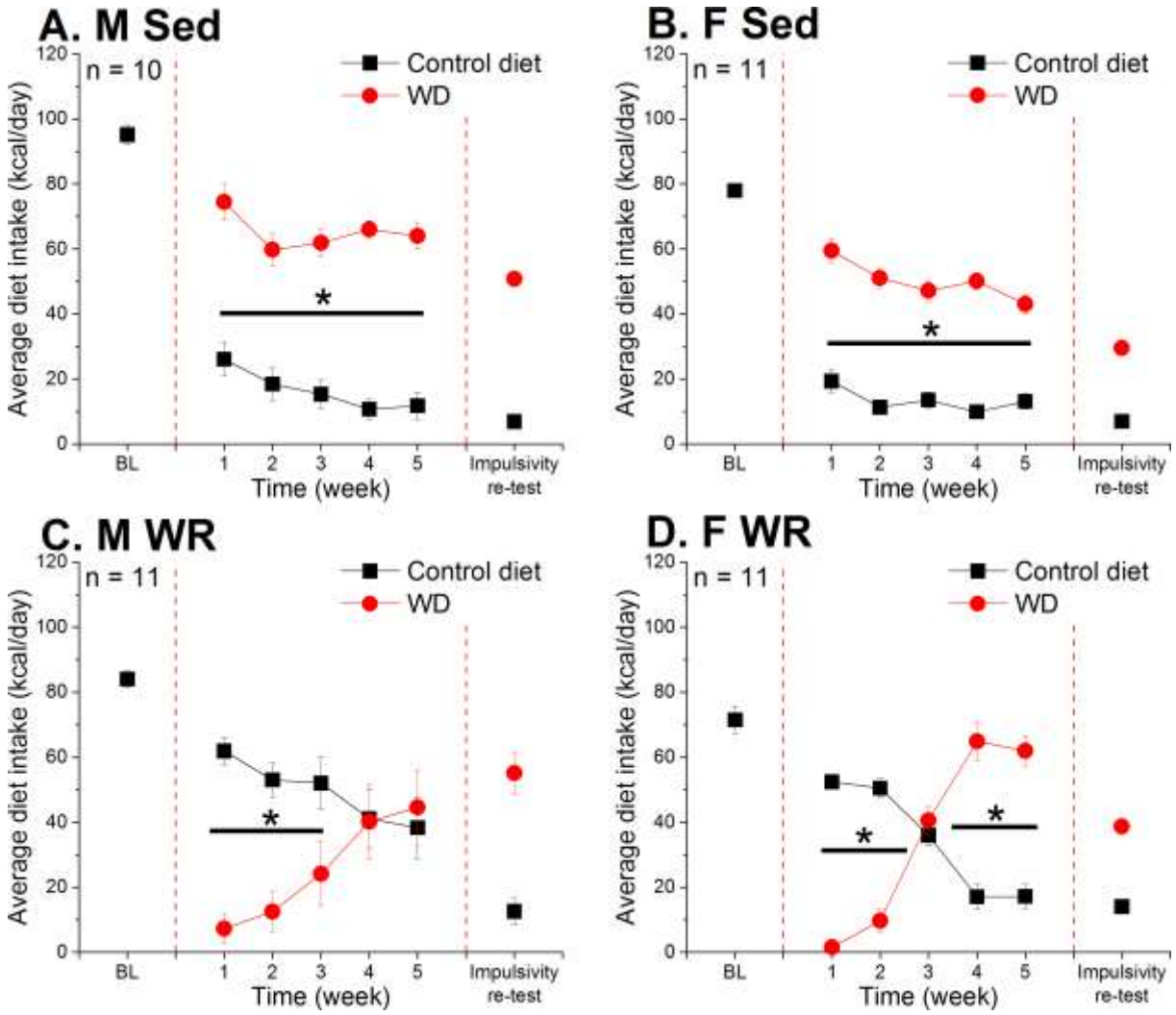

Figure 4.3. Diet choice patterns among sedentary and wheel running rats. (A & B) All Sed rats consumed more WD than control diet. *: control diet vs. WD, $p < 0.05$ (C) Male WR rats reversed their initial avoidance of WD after 4 weeks of two-diet choice. *: control diet vs. WD (D) After 3 weeks of two-diet choice, female WR rats sharply reversed their initial avoidance and started consuming significantly more WD than control diet. *: control diet vs. WD, $p < 0.05$; Sed: sedentary; WR: wheel running; WD: Western diet; BL: baseline

Similar effects were seen in regards to WD preference where exercise led to lower WD preference overall [exercise $F(1,39) = 54.99$ and sex x exercise x time $F(4,156) = 7.79$, both $p < 0.001$]. However, WR males maintained lower WD preference compared to their Sed counterparts for the entire 5 weeks (all $p < 0.001$; Figure 4.4A) whereas WR females were only able to maintained a decreased preference for WD for the first 3 weeks (post hoc all $p < 0.01$; Figure 4.4B) of the WR and two-diet choice period. All rats preferred WD diet during impulsivity

re-test, and there was no effect of sex or exercise on WD preference [sex and exercise F(1,39) = 1.40 and 3.83, respectively, both p > 0.05].

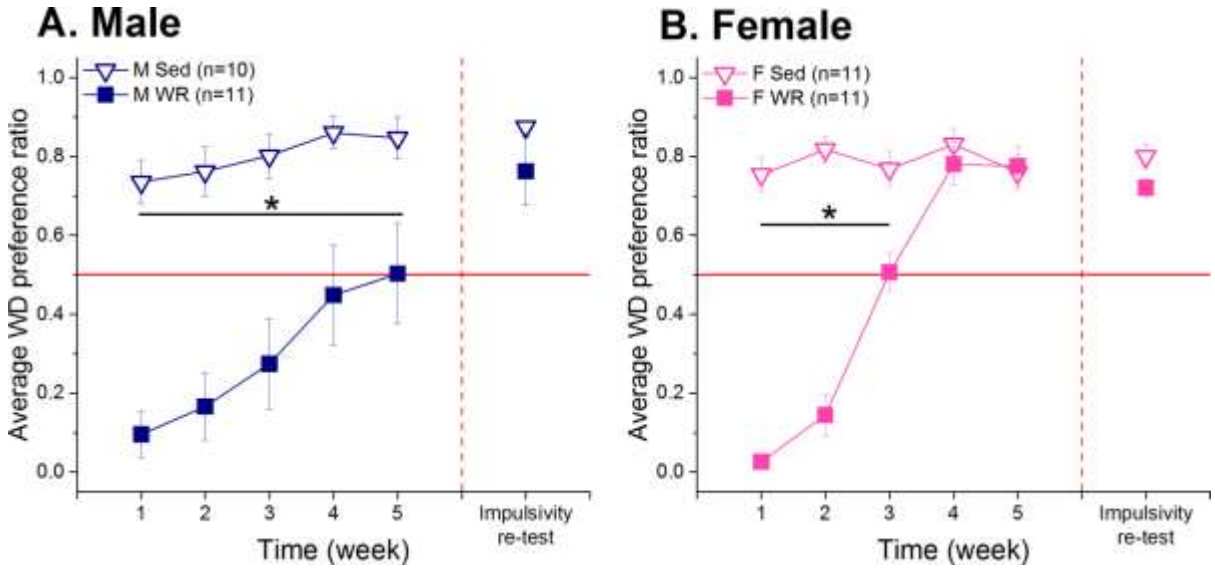

Figure 4.4. Western diet preference. (A) Male WR rats maintained low WD preference throughout the two-diet choice period and only established a preference for WD during the impulsivity re-test while under a food restriction regimen. *: Sed vs. WR, p < 0.05 (B) Female WR rats only maintained lower preference for WD for 3 weeks after which their WD preference did not differ their Sed counterparts. Sed: sedentary; WR: wheel running; *: Sed vs. WR, p < 0.05

Running activity and energy intake

Running activity was higher in females than males [sex F(1,20) = 27.44, p < 0.001]. This sex difference in WR activity was maintained during the impulsive choice re-test during which rats were moderately food restricted (Figure 4.5A). Both male and female WR rats had lower energy intake across time [exercise F(2,58) = 29.82, p < 0.001 and exercise x time F(8,232) = 97.18, p < 0.001]. There was also a sex difference in regards to how male and female rats compensated for the increased energetic requirement of exercise [sex x exercise F(2,58) = 15.41, p < 0.001]. Exercise led to an initial suppression of energy intake in males after which their intake recovered to the level of their naïve controls (post hoc p > 0.68) but still lower than their Sed counterparts (post hoc p < 0.05; Figure 4.5B). In contrast, female WR rats increased their energy intake to higher than both the naïve and Sed groups (post hoc both p < 0.05; Figure

4.5C). In addition, the introduction of WD led to higher energy intake in rats of both sexes (post hoc both $p < 0.001$).

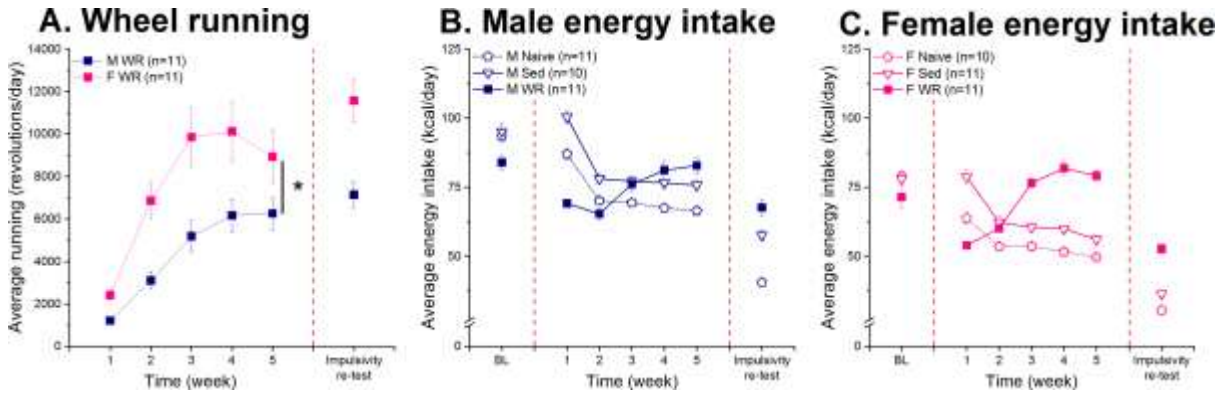

Figure 4.5. Wheel running and total energy intake. (A) Female rats had high levels of running wheel activity compared to males. *Male vs. female, $p < 0.05$ (B) Male running rats did not consume more food intake than the naïve and Sed rats to reflect their increased energy expenditure until the 5th week of the running + two-diet choice regimen. (C) Female rats compensated for the increased energy demand from exercise more rapidly than males.

Body weight and adiposity

Body weight gain was suppressed in WR rats of both sexes [exercise $F(2,58) = 31.16$, $p < 0.001$] relative to their Sed counterparts (Figure 4.6A). The sex difference in body weight (sex $F(1,58) = 1123.88$, $p < 0.001$] may have blocked the sex x exercise effect [$F(2,58) = 2.50$, $p > 0.09$]; thus, the sexes were analyzed separately to assess group differences. In males, WR rats weighed significantly less than both the Sed and naïve groups [exercise $F(2, 29) = 22.51$, $p < 0.001$; post hoc WR vs. Sed or naïve, both $p < 0.001$ and Sed vs. naïve $p > 0.05$]. In contrast, female WR rats had lower body weights only when compared to their Sed counterparts but not naïve controls [$F(2,29) = 9.67$, $p < 0.001$; post hoc WR vs. Sed $p < 0.001$ and WR vs. naïve $p > 0.13$].

There were no sex differences in the composition of the retroperitoneal or mesenteric fat pads [sex $F(1,58) = 2.06$ and 2.97, respectively, both $p > 0.09$ and sex x exercise $F(2,58) = 1.31$ and 2.16, respectively, both $p > 0.12$; Figure 4.6B]. However, given that there was a sex difference in body weight, the sexes were analyzed separately in a 1-way ANOVA to assess the effect of exercise within each sex [$F(2,58) = 29.49$ and 2.76, respectively, both $p < 0.05$]. Due to

sex differences in gonadal fat composition, the sexes were also analyzed separately for this fat pad. Exercise decreased retroperitoneal adiposity in male WR rats relative to both their Sed and naïve counterparts [$F(2,29) = 22.12$, $p < 0.001$; post hoc M WR vs. Sed and naïve, all $p < 0.001$]. The effect of exercise was more limited in the mesenteric fat pad [$F(2,29) = 8.56$, $p < 0.01$; post hoc M WR vs. Sed $p < 0.01$ and M WR vs. naïve $p > 0.08$]. In females, exercise reduced retroperitoneal fat composition relative to WD-preferring Sed rats but not their naïve controls [$F(2,29) = 12.13$, $p < 0.001$; post hoc F WR vs. Sed $p < 0.001$ and F WR vs. naïve $p > 0.59$]. There was no effect of exercise in the mesenteric fat pad [$F(2,29) = 0.18$, $p > 0.83$]. Exercise reduced gonadal fat in both male and female rats [$F(2,29) = 13.11$ and 5.00, both $p < 0.05$]. In both sexes, WR was able to attenuate WD-associated gonadal fat deposition (WR vs. Sed post hoc both $p < 0.05$).

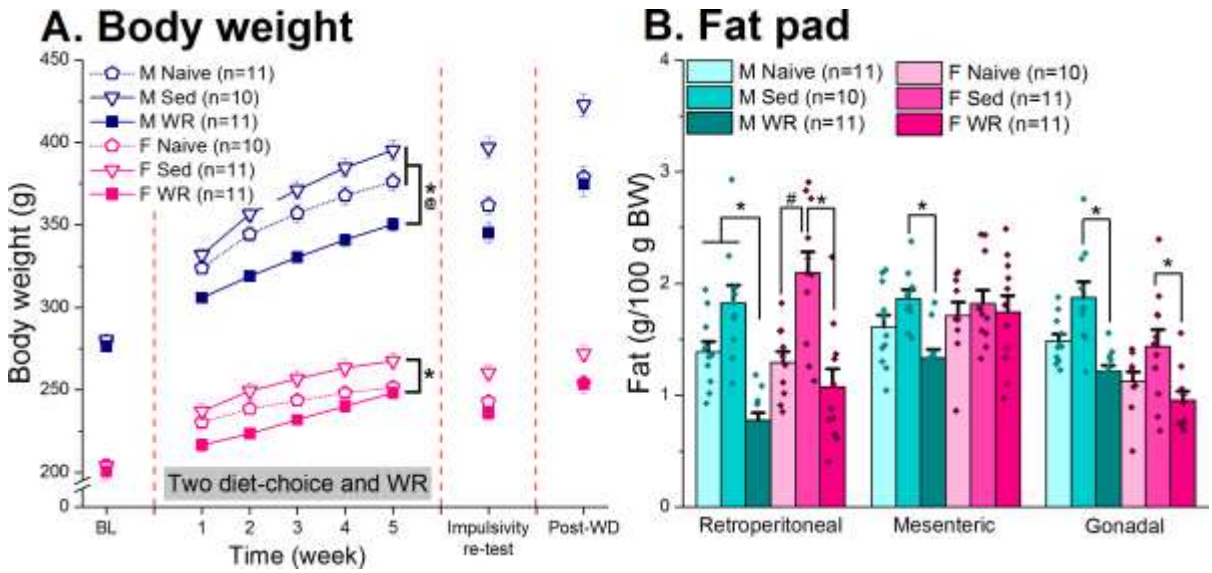

Figure 4.6. Body weight and adiposity. (A) Exercise suppressed body weight gain in rats of both sexes. *: Sed vs. WR, $p < 0.05$; @: Naïve vs. WR, $p < 0.05$ (B) Male rats show reduced fat deposition in the retroperitoneal, mesenteric, and gonadal fat pads whereas there was no effect of exercise in females for the mesenteric fat pad and only suppressed adiposity in the retroperitoneal and gonadal fat pads. *: Sed vs. WR, $p < 0.05$; #: Naïve vs. Sed, $p < 0.05$

Oral glucose tolerance test

Throughout the blood sampling period of OGTT, male WR rats had lower blood glucose than both Sed and naïve groups [exercise $F(2,29) = 3.48$, $p < 0.05$ and exercise x time $F(8,116) = 2.71$, $p < 0.01$; Figure 4.7A] at baseline (post hoc 0 min M WR vs. Sed or naïve both $p < 0.05$) and end of OGTT (post hoc 120 min M WR vs. Sed or naïve both $p < 0.05$). The effect of exercise did not reach statistical significance in females [exercise $F(2,29) = 2.79$, $p > 0.07$; Figure 4.7B]. There was a sharp increase in plasma glucose 15 min following the oral glucose challenge in female WR rats [exercise x time $F(8,116) = 2.30$, $p < 0.05$] when compared to their naïve controls (post hoc $p < 0.001$).

Analysis of glucose AUC revealed that males cleared the glucose load faster than females [sex $F(1,58) = 12.95$, $p < 0.001$; Figure 4.7C]. In males, exercise led to improved clearance compared with the Sed group [sex x exercise $F(2,58) = 3.42$, $p < 0.05$; post hoc M WR vs. Sed $p < 0.05$]. In females, exercise led to improved clearance compared to their naïve control (post hoc F WR vs. naïve $p < 0.05$).

Male rats had higher plasma insulin than females during OGTT [sex $F(1,55) = 21.64$, $p < 0.001$]. There was a sex x exercise interaction [$F(2,55) = 6.44$, $p < 0.01$; Figure 4.7D] such that M WR rats had lower insulin compared with their Sed and naïve groups (post hoc both $p < 0.01$) whereas there was no effect of exercise in females (post hoc F WR vs. Sed or naïve both $p > 0.44$; Figure 4.7E).

Analysis of insulin AUC revealed that male rats produced more insulin to clear the glucose load than females [sex $F(1,55) = 21.12$, $p < 0.001$; Figure 4.7F]. There was a sex difference in the effect of exercise [sex x exercise $F(2,66) = 5.33$, $p < 0.01$] such that in males, exercise reduced the amount of insulin measured during OGTT compared to both Sed and naïve males (post hoc both $p < 0.01$) whereas this effect was absent in females (post hoc both $p > 0.99$).

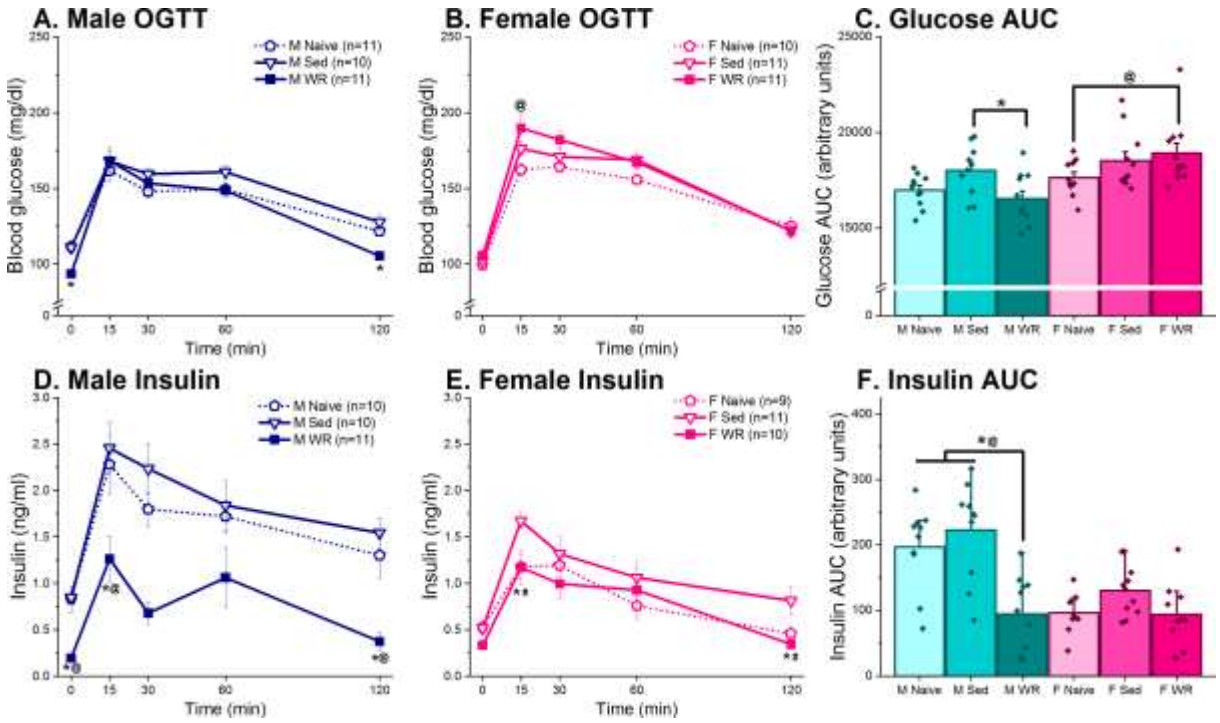

Figure 4.7. Results of the oral glucose tolerance test. (A & B) Exercise resulted in decreased blood glucose in males but not females. *: Sed vs. WR, $p < 0.05$, @: Naïve vs. WR, $p < 0.05$ (C) Male WR rats had lower glucose AUC than rats without access to exercise. In contrast, female WR rats had higher glucose AUC compared to their naïve controls. *: Sed vs. WR, $p < 0.05$, @: Naïve vs. WR, $p < 0.05$ (D & E) Plasma insulin concentrations during OGTT was decreased in male WR rats relative to their Sed and naïve counterparts at baseline, 15, and 120 min. In contrast, female WR rats were not different from their naïve controls but did have lower insulin than their Sed counterparts at 15 and 120 min. *: Sed vs. WR, $p < 0.05$, @: Naïve vs. WR, $p < 0.05$, #: Naïve vs. Sed, $p < 0.05$ (F) Exercise decreased the amount of insulin required to clear the same glucose load in males but not females. *: Sed vs. WR, $p < 0.05$, @: Naïve vs. WR, $p < 0.05$

Insulin tolerance test

To assess insulin sensitivity in the periphery, blood glucose data from the first 30 min following the insulin challenge was analyzed. Females had lower blood glucose during ITT than males [sex $F(1,55) = 13.05$, $p < 0.001$]. Exercise increased plasma glucose in male WR rats compared to both the Sed and naïve groups [sex x exercise $F(2,55) = 6.03$, $p < 0.01$; post hoc both $p < 0.01$; Figure 4.8A] whereas there was no effect of exercise in females (F WR vs. Sed or naïve both $p > 0.61$; Figure 4.8B). AUC of blood glucose during the first 30 min did not reveal any effects [sex x exercise $F(2,51) = 0.57$, $p > 0.57$; Figure 4.8C].

The counter-regulatory response was assessed using the 90 min timepoint, and results revealed a main effect of exercise [$F(1,51) = 5.82$, $p < 0.01$] such that male and female WR rats of both sexes had higher blood glucose than their Sed and naïve counterparts [sex x exercise $F(1,51) = 0.35$, $p > 0.70$].

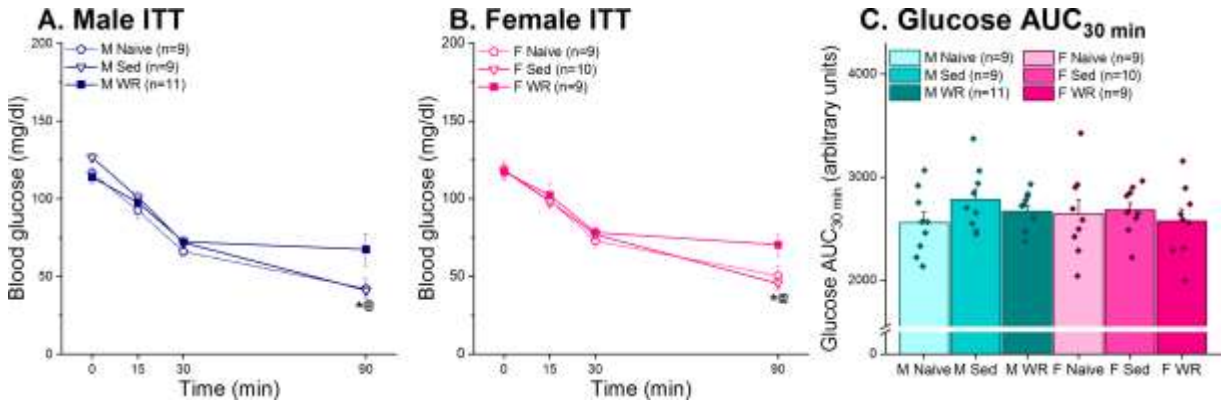

Figure 4.8. Results of the insulin tolerance test. (A & B) All rats significantly reduced blood glucose levels during the first 30 min after the insulin injection. At 90 min post-injection, however, male and female WR rats had higher blood glucose levels. *: Sed vs. WR, $p < 0.05$, @: Naïve vs. WR, $p < 0.05$ (C) Analysis of glucose AUC during the first 30 min following the insulin challenge did not reveal sex differences or an effect of exercise.

Impulsive choice

There were no sex differences at baseline [sex $F(1,62) = 0.69$, $p > 0.40$ and sex x delay $F(4,246) = 1.03$, $p > 0.39$; Figure 4.9]. All rats decreased preference for the larger later lever across testing days [delay $F(4,248) = 240.37$, $p < 0.001$]. During the post-WD re-test, there was no effect of exercise or sex x exercise interaction [$F(2,58) = 0.37$ and 1.07, respectively, both $p < 0.35$]. Mirroring their baseline behavior, all rats decreased preference for the larger later lever with increased delay [$F(4,232) = 186.07$, $p < 0.001$]. When impulsive choice behavior was compared between baseline and post-WD exposure, there was no effect of exercise or sex x exercise interaction [$F(2,58) = 0.11$ and 0.42, respectively, both $p > 0.66$]. All rats had decreased preference for the larger later lever during the re-test [time $F(1,58) = 130.73$, $p < 0.001$ and time x sex x exercise $F(2,58) = 0.85$, $p < 0.43$].

Analysis of the slope revealed no sex differences at baseline [$F(1,60) = 0.03$, $p > 0.86$] or re-test [$F(1,56) = 1.14$, $p > 0.29$] in terms of the rate of discounting. There was an increase in

impulsive choice behavior during the re-test from baseline for all rats [time $F(1,54) = 9.42$, $p < 0.01$ and time x sex x exercise $F(2,540) = 0.09$, $p > 0.91$]. However, there was no effect of exercise [$F(1,54) = 0.13$, $p > 0.87$] or sex x exercise [$F(2,54) = 0.47$, $p > 0.62$].

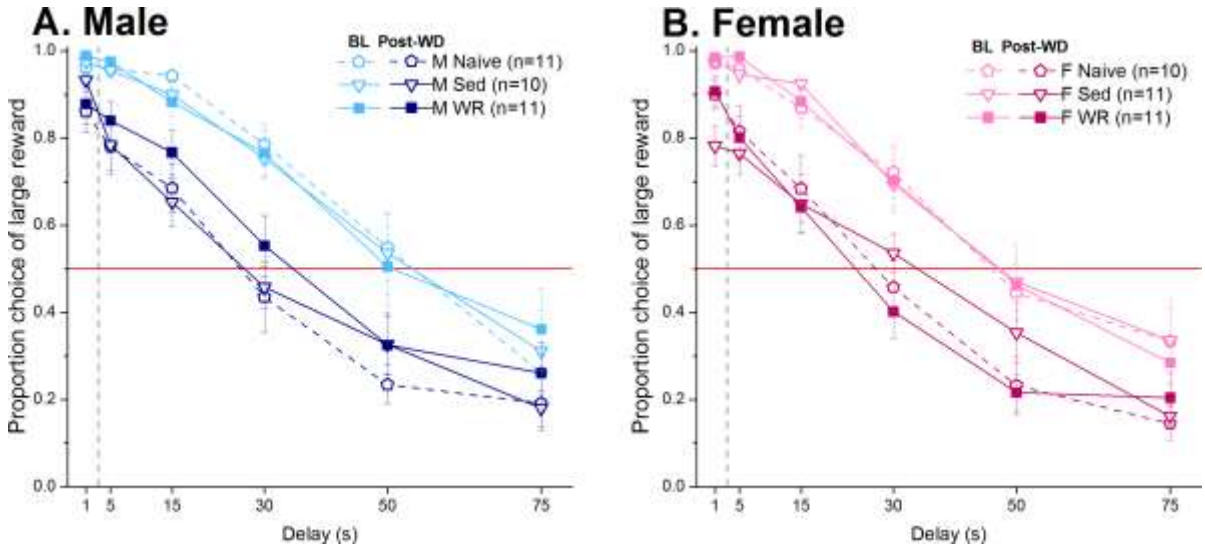

Figure 4.9. Assessment of impulsive choice before and after Western Diet exposure. (A) All male rats showed higher levels of impulsive choice behavior during the impulsivity re-test. Male WR rats maintained preference for the larger reward whereas male Sed and naïve rats had decreased preference at the 30s delay. (B) All female rats showed a faster decrease in preference for the large reward during the post-WD re-test relative to baseline. Female WR rats appeared to decrease preference for the large reward more quickly than their Sed and naïve counterparts as the delay interval increased. BL: baseline, WD: western diet

Regression analyses with sex and exercise as covariates did not reveal any predictive ability of average baseline impulsivity [$F(1,38) = 0.64$, $p > 0.42$] or rate of discounting [$F(1,38) = 0.09$, $p > 0.76$] on future average WD preference. In addition, there was no relationship between the rate of discounting post-WD exposure with average WD preference [$F(1,37) = 0.72$, $p > 0.40$].

DISCUSSION

The present study assessed if baseline levels of impulsivity could predict future western diet preference and whether preference for WD would lead to increased impulsivity, which exercise may attenuate, in rats of both sexes. Diet choice patterns among Sed and WR rats (Figure 4.3) were consistent with results of chapter 3 that used HF diet as the palatable diet

(Yang et al., 2020). Exercise suppressed weight gain and visceral adiposity to a greater extent in males than females. Results from an OGTT show that WD exposure decreased glucose clearance in rats of both sexes (Figure 4.7A & B) and was attenuated by exercise in males but not females. There were no changes in insulin sensitivity following long-term WD exposure; however, exercise improved the counter-regulatory response to hypoglycemia in WR rats of both sexes during the ITT (Figure 4.8A & B). At baseline, there were no sex differences in impulsive choice. During the re-test, all rats displayed higher levels of impulsivity regardless of diet, sex, or exercise. More specifically, WD did not lead to increased impulsivity and post-WD impulsivity was not associated with WD preference during the two-diet choice and WR period. Taken together, these results suggest that exercise is more beneficial in males, and that the extent to which WD influences impulsive choice is limited.

Female WR rats sharply reversed their initial avoidance for WD and compensated for the increased energy requirement of exercise earlier and more rapidly than males. Faster adaptation to exercise may have led to a more rapid development of fat preference. Indeed, studies have reported that individuals who compensate for exercise (less weight loss than expected) increased liking and wanting for HF food (Finlayson et al., 2011, Martin et al., 2019). The shift to preferring WD occurred ~1 week later compared to our previous study using HF diet in female rats (Yang et al., 2020). The delayed shift may be partially mediated by diet palatability, such that the WD diet is 5% lower in fat than the 45% HF diet making the HF diet the more palatable diet (Benton, 2005). Studies utilizing both HF diet and WD found that without diet choice, rats maintained on HF diet had higher caloric intake of HF diet than WD (Wilson et al., 2007, Kosari et al., 2012). Following the shift in diet preference, females started to consume more WD than the control diet. Unlike males, exercise had a limited effect at attenuated WD-related weight gain, adiposity, and glucose intolerance in females (Pitts, 1984, Cortright et al., 1997, Anderson et al., 2001, Donnelly and Smith, 2005, Schroeder et al., 2010). Furthermore, not only was glucose clearance not improved in female WR rats, but they also had slower

glucose clearance than their naïve controls (Figure 4.7C). These findings suggest that exercise is more protective against the deleterious metabolic effects of WD feeding in males than females.

Chronic WD feeding did not induce insulin resistance as assessed through ITT. This is in contrast with the majority of studies that find a consistent effect of increased insulin resistance following WD feeding (Moreno-Fernandez et al., 2018, Kopp, 2019). Rats were maintained on an ab lib feeding schedule with two-diet choice for 5 weeks. The length of WD exposure leading to deleterious metabolic effects appears to be variable, ranging from 30 d (Prada et al., 2005) to 10 weeks (Derkach et al., 2017). Moreover, there is some evidence that the fat content may play a more influential role in the development of insulin resistance, such that HF but not high-fat high-sugar fed mice developed insulin resistance (Omar et al., 2012). In the present study, the assessment of insulin sensitivity occurred after the impulsivity re-test. Food restriction during behavioral testing may have improved peripheral metabolism and blocked our ability to detect changes in insulin sensitivity. Short-term dietary restriction has been shown to not only alter body composition, but also improve glucose tolerance and insulin sensitivity (Escriva et al., 2007, Matyi et al., 2018). Extending the length of WD exposure and performing ITT during ab lib feeding would provide a better assessment as to whether WD negatively impacts peripheral metabolic function that would be attenuated by exercise.

Wheel running improved the counter-regulatory response to hypoglycemia in both male and female rats (Figure 4.8A & B). This may be due to increased awareness of hypoglycemia (McNeilly et al., 2017, Farrell et al., 2020) from previous exercise experience, such that exercise induces a counter-regulatory response to hypoglycemia in a similar manner as an insulin challenge (Galassetti et al., 2006, Lee et al., 2020). It would be worthwhile to determine if exercise (Marliss and Vranic, 2002) could serve as a less invasive method (Gaisano et al., 2012) to improve the counter-regulatory response and reduce future risk of hypoglycemia, especially for patients with type 1 diabetes.

There were no sex differences in impulsive choice at baseline (Perry et al., 2008a, Hammerslag et al., 2019, Sackett et al., 2019) and western diet exposure did not lead to increased impulsive choice in rats of either sex. This is in contrast with previous studies using male rats that report increased impulsivity following 8 weeks of a fat supplemented chow diet (Steele et al., 2017, Steele et al., 2019) but in agreement with a study that found no change after 2 weeks of 60% HF diet exposure (Garman et al., 2021). One potential explanation is methodological differences such that our delay discounting task involved increasing the delay component for the large reward (Garman et al., 2021) whereas the laboratory that reported an effect of HF diet increased the delay component for the small reward (Steele et al., 2017, Steele et al., 2019). Another possible reason for the lack of diet-induced increases in impulsivity may be that the dietary effect is only present in rats that were highly impulsive prior to chronic WD feeding. Evidence from a study using cocaine injections found that increased impulsive choice was only present in rats pre-categorized as being highly impulsive (Cho et al., 2018a). In addition to sources of dietary fat, the way impulsive choice is tested may tap into different factors including sensitivity to temporal delay and reward magnitude (Hamilton et al., 2015, Peterson et al., 2015) and may contribute to the lack of consensus in the literature in regards to the effect of diet-induced changes in impulsivity.

The length of WD exposure prior to behavioral testing may be a critical factor when assessing changes in impulsivity. Longer exposure to the energy dense diet leads to increased weight gain and adiposity (Steele et al., 2017, Steele et al., 2019), which may further promote increases in impulsive choice behavior. In line with this, BMI was found to be positively correlated with impulsive choice (Meyre et al., 2019). Another study found opposite results such that there was no association between BMI and impulsivity; however; results suggested a bidirectional effect of western diet and impulsivity before the development of obesity (Lumley et al., 2016, Steele et al., 2019). Although results are mixed, BMI is not an accurate reflection of fat composition and evidence suggests a positive relationship between body fat and impulsivity

(Rasmussen et al., 2010). To motivate task performance, rats were moderately food restricted during behavioral testing in the present study and may have lost some body fat, which may have influenced their levels of impulsivity. Moreover, the lack of ad lib access to WD during behavioral testing may have also influenced the rats' impulsive choice behavior. It would be of interest to assess impulsive choice while rats are maintained on an ad lib feeding schedule of the palatable diet. Presently, it remains unclear whether body weight gain, adiposity, or dietary fat content is more influential in mediating changes in impulsivity. Future studies including diets with differing fat composition ranging from low to high would help elucidate the relative importance of fat in mediating diet-induced increases in impulsivity.

Regardless of diet, sex, or exercise, all rats were more impulsive during the re-test. A potential explanation is that motivation to work for the dustless precision pellet was reduced following WD exposure. Indeed, studies have shown that following exposure to a high fat or a high fat high sugar diet lead to decreased motivation and sensitivity to the reward magnitude (la Fleur et al., 2007, Steele et al., 2019). It is unclear whether a more palatable reward such as a sucrose pellet would increase motivation and allow for a better assessment of impulsive choice. A progressive ratio test assessing breakpoint would provide more insight into changes in motivation for the food reward and should be included in future studies. In addition, the change in rearing conditions from pair housing at baseline to individual housing during the re-test may have may have led to increased impulsive choice behavior during the re-test (Figure 4.9). Previous research is mixed with some studies suggesting that the social isolation stress decreases (Hellemans et al., 2005, Liu et al., 2017) impulsive choice whereas others found increased (Perry et al., 2008b, Kirkpatrick et al., 2013, Kirkpatrick et al., 2014, Wang et al., 2017b) impulsivity or no effect (Baarendse et al., 2013). The studies that found increased impulsive choice ranged from variable delays for the larger lever within the a test session based on task performance (e.g., increased delay when the larger lever was selected) (Perry et al., 2008b), intermixing fixed, forced, and free choice trials within a test session (Kirkpatrick et al.,

2014), and increasing the reward magnitude for the larger lever across test sessions (Kirkpatrick et al., 2014, Wang et al., 2017b) with delays. Studies with similar task designs to the present study with no delay for the small reward delivery and consistent reward magnitude for both the smaller and larger levers have found opposite results with decreased (Hellemans et al., 2005, Liu et al., 2017) or no change (Baarendse et al., 2013) in impulsive choice following social isolation. In contrast, we found increased impulsive choice behavior. However, changes in impulsive choice following social isolation may not be evident until a challenge (e.g., drug) is made (Liu et al., 2017) and the rats in the present study experienced long-term WD exposure. These inconsistent results may result from differences in task design (increasing delay interval vs. reward magnitude) and rearing conditions (isolated vs. socially or novelty enriched) (Peterson et al., 2015) and requires further investigation.

Hunger tends to increase impulsive choice for food when assessed using delay discounting paradigms in humans (Raynor and Epstein, 2003, Wang and Dvorak, 2010, Wang et al., 2018, Skrynka and Vincent, 2019) and rodents (Prince et al., 2020). Food restriction during impulsive choice testing led to body weights ~90-95% (postnatal day ~80) of their pre-test body weights during baseline and ~97-103% (postnatal day ~140) during the re-test. Although we found that rats were more impulsive during the re-test, this contrasting result from the known literature may result from 1) rats were still growing (Snider et al., 2016) during the baseline impulsivity assessment and may be more sensitive to the effects of food restriction; 2) rats were closer to their pre-test body weights during the re-test leading to decreased motivation to lever press for the food reinforcer (Wayner and Rondeau, 1976); and 3) rats were previously exposed to the reinforcer and tend to decrease responding for the same reinforcer types with habitual exposure (Epstein et al., 2008, McSweeney and Murphy, 2009). These factors may have influenced motivation to perform the task and could have blocked our ability to detect WD-induced changes in impulsive choice behavior. Future studies should consider using a different reinforcer for each round of testing.

There was a slight difference in feeding conditions in that during baseline, rats only had access to the control diet and an appropriate amount was left in the home cage to maintain rats at ~90% of their free feeding weight whereas during the re-test, rats had access to two diets and both hoppers were left in the home cage for ~1 h. A recent study found no difference in delay discounting in regards to the method of food restriction (amount vs. temporal) when weights were restricted to a similar extent (Tapp et al., 2020); however, body weights during the re-test suggest less weight-restriction and may have influenced impulsive choice behavior. Together, changes in housing conditions and feedings schedules between baseline and re-test impulsivity may have blocked our ability to detect subtle diet and exercise-mediated changes in impulsive choice. For consistency, future studies should aim for similar pre-test free-feeding weights if performing more than one assessment of impulsivity using consistent feeding schedules.

The present study investigated the relationships between exercise, palatable diet preference, and peripheral metabolic function with impulsivity. There were sex-specific outcomes of exercise on peripheral metabolic function, such that exercise had a higher efficacy at preventing WD-mediated weight gain, adiposity, and glucose intolerance in males. Although there were no significant signs of insulin resistance, exercise improved the counter-regulatory response to hypoglycemia in both sexes and could be a potential treatment for patients with type 1 diabetes who have become habituated to recurring hypoglycemia (Conn et al., 2008, Yardley and Sigal, 2015). Given that no significant effect of impulsive choice was found, changes in the experimental design including extending the length of diet exposure, including diets varying in fat composition, and testing impulsivity without food restriction, may reveal more nuanced effects of western diet on impulsive choice. It is of importance to determine if there is a relationship between impulsivity and palatable food intake as it could offer insight into whether heightened impulsivity is a vulnerable phenotype to overeating and significant weight gain.

CHAPTER 5: GENERAL DISCUSSION

Epidemiological studies have shown that the prevalence of obesity (Hudson et al., 2007, Flegal et al., 2010) is higher in women than men; however, the adverse metabolic and cognitive outcomes of obesity are more prevalent and severe in males (Smith et al., 2011, Kautzky-Willer et al., 2016, Li et al., 2017, Ogurtsova et al., 2017, Espeland et al., 2018). As a method to restore energy balance, exercise has a greater efficacy at promoting body weight and fat loss and recusing metabolic deficits in males than females (Hill et al., 1989, Donnelly et al., 2004, Caudwell et al., 2014). Collectively, these studies suggest that sex differences in eating behavior and the subsequent cognitive and metabolic outcomes may be mediated by different underlying mechanisms. Despite the fact that sex-specific feeding behavior may differentially confer heightened vulnerability for obesity and its comorbid health outcomes, most research focuses on males. Thus, sex differences in the development of and treatment for excessive weight gain have not been well characterized. The goal of this dissertation was to address this gap in knowledge by examining how sex differences in the interaction between diet preference and exercise interact and lead to sex-specific behavioral adaptations and outcomes. The findings are summarized below in Figure 5.1.

	Measure	Male	Female	
Diet	**Diet choice**	Maintained HF diet avoidance	Reversed HF diet avoidance	M < **F**
	Sex hormones	Not required	Required	
Metabolic outcomes	**Body weight and adiposity**	Suppressed	Slightly suppressed	**M** > F
	Oral glucose tolerance test	Improved glucose tolerance and insulin sensitivity	No change	**M** > F
	Insulin tolerance test	Improved counter-regulatory response	Improved counter-regulatory response	M = F
Cognitive outcomes	**Spatial learning and memory**	Improved learning	Improved learning	M = F
	Behavioral flexibility	No change	Potential deficits	**M** > F
	Impulsive choice	No change	No change	M = F

Figure 5.1. Summary of the findings from the studies in this dissertation. The interaction between exercise and diet led to sex-specific diet choice patterns and in turn, both metabolic and cognitive outcomes. Although exercise improved metabolic health to a greater extent in males, it still had some efficacy for females. Some sex differences in cognitive function were observed, but exercise appeared to have a positive effect in rats of both sexes.

Work in this dissertation highlights the complexity of energy balance and feeding behavior and how exercise interacts with both factors to influence cognitive and metabolic outcomes. In three empirical studies, I used a WR and two-diet choice rat model to first assess the role of gonadal hormones in the expression of sex-specific diet choice patterns during acute exercise (Chapter 2). Then, I examined sex differences in long-term palatable diet preference and the cognitive and metabolic consequences of chronic palatable diet preference (Chapters 3 & 4) as well as trait cognitive vulnerability for palatable diet preference (Chapter 4). Each of these studies contributes to the overall aim of this dissertation by investigating whether sex differences in response to the interaction between diet and exercise lead to sex-specific cognitive and metabolic adaptations.

In Chapter 2, I provide evidence that acute exercise mediates changes in HF diet preference in rats of both sexes. More specifically, male WR rats maintained HF diet avoidance whereas females initiated but eventually reversed HF diet avoidance. OVX did not completely eliminate sex differences, which suggests that both activational and organizational effects of sex hormones are involved in the expression of sex-typical diet choice patterns during exercise.

Indeed, the post-pubertal masculinized females behave similarly to intact males and have lower levels of palatable food intake and binge eating behavior compared to control females (Klump et al., 2017, Culbert et al., 2018). Hormone replacement with both estrogen and progesterone was required for the expression of female typical diet choice patterns and add to the sparse literature on the discrete effects of estrogen and progesterone separately (Sodersten and Eneroth, 1981, Olster and Blaustein, 1988, Apostolakis et al., 1996). In line with research showing a more influential role of estrogen than testosterone in feeding behavior (Nunez et al., 1980, Asarian and Geary, 2013, Begg and Woods, 2013), removal of male sex hormones did not alter diet choice patterns in males. Together, the results from our study suggest female, but not male, sex hormones are required for the expression of sex-typical diet choice patterns during exercise.

Chapter 3 extended the acute paradigm used in Chapter 2 and showed that with long-term WR and two-diet choice, all rats reversed HF diet avoidance. Importantly, the reversal of HF diet avoidance occurred earlier and more rapidly in females. The finding that exercise suppressed fat preference and intake in all WR rats supports recent findings that exercise decreases fat preference in humans (Finlayson et al., 2011, Martin et al., 2019, Riou et al., 2019, Beaulieu et al., 2020a). Female rats compensated for the additional energy requirement from exercise and more readily established a preference for HF diet than males. In line with this, humans who compensate for exercise do not reduce fat preference (Finlayson et al., 2011, Sparks, 2017, Beaulieu et al., 2020b). In Chapter 4, I replaced the HF with a WD and used a control diet as the high carbohydrate diet and replicated the diet choice results from Chapter 3.

The studies in this dissertation focused on outcomes of long-term palatable diet preference rather than the underlying neurobiological mechanisms. Given its role in controlling food intake, the gut-brain axis is a good candidate future research into the underlying mechanisms of how diet and exercise interact to mediate energy homeostasis. Altered secretion of anorexigenic gut peptides including glucagon-like peptide 1 (GLP-1) and reduced oral taste threshold and gastrointestinal sensitivity to fat have been observed in obese individuals (Stewart

et al., 2011, Lean and Malkova, 2016, Dirksen et al., 2019). Increased palatable diet intake in WR rats may have blunted postprandial GLP-1 secretion and altered fat intake/preference. Additionally, HF diet reduces energy intake to a lesser extent in obese relative to lean subjects, and obese subjects tended to have greater energy intake after a HF meal (Brennan et al., 2012). A decreased response to the satiating effects of fat (Little et al., 2007) may partially explain why all WR rats reversed HF diet avoidance with long-term exposure. Exercise increases GLP-1 secretion, which may contribute to enhanced satiety (Martins et al., 2010, Sumithran et al., 2011, Schubert et al., 2014), and GLP-1 decreases preference for sweet and fatty foods (Kadouh et al., 2020). Together, these studies suggest that GLP-1 could potentially be influencing diet preference during exercise. Future research could investigate how chronic fat intake and exercise interact to affect GLP-1 release and whether that leads to a diminished response to the satiating effects of fat and promote overeating.

The metabolic results from Chapter 2 – 4 are consistent with previous studies reporting greater efficacy for exercise to improve whole body composition and peripheral metabolism in males (Perreault et al., 2008). Females more readily adapted to the increased energy requirement of exercise than males (Tokuyama et al., 1982, Looy and Eikelboom, 1989, Kawaguchi et al., 2005, Carrera et al., 2011) and this may have led to a decrease in efficacy for exercise to suppress weight gain and adiposity in females compared to males (Bjorntorp, 1989, Anderson et al., 2001, Paul et al., 2004, Donnelly and Smith, 2005). In line with this, a combination of diet and exercise appears to be the most effective at promoting weight loss than either method alone (Coker et al., 2009, Donnelly et al., 2009, Maesako et al., 2012). These results point toward the need to develop sex-specific methods to target body weight regulation and energy balance.

Exercise may facilitate weight loss through the release of myokines, such as interleukin-6 (IL-6) and irisin, which mediate muscle-organ crosstalk to the brain (Pedersen and Febbraio, 2012, Pedersen, 2019). Enhanced IL-6 release from adipose tissue accompanies the chronic,

low-grade inflammation associated with obesity and the consumption of HF diet (Hotamisligil, 2006). In contrast, muscle-derived IL-6 release during exercise appears to play more of a role in metabolism than the inflammatory response (Pedersen, 2019) and is central to exercise-induced fat loss (Wedell-Neergaard et al., 2019). Central, but not peripheral, infusion of IL-6 suppresses feeding and improves glucose tolerance and is associated with suppressed weight gain and adiposity (Timper et al., 2017). Sex differences in IL-6 release are unclear but depend on the duration and intensity of exercise (Pedersen et al., 2001), and we report sex differences in running activity with females displaying higher activity levels than males. Moreover, GLP-1 release during exercise is occurs through an IL-6-dependent manner, and both GLP-1 and IL-6 have been implicated in mediating insulin action (Ellingsgaard et al., 2011, Ellingsgaard et al., 2020). The greater improvement in body composition and overall metabolic profile in male WR rats may be mediated by sex differences in muscle release of IL-6 and central IL-6 signaling during exercise that future studies could explore.

In Chapters 3 and 4, we found that male WR rats show improved glucose tolerance and insulin sensitivity relative to their Sed counterparts whereas this effect was absent in females (Vallerand et al., 1986, Goodyear et al., 1991, Bongbele et al., 1992, Goodyear and Kahn, 1998, Tokuyama and Suzuki, 1998, LaPier et al., 2001, Latour et al., 2001, Gollisch et al., 2009, Lamontagne et al., 2013). The female rats in our studies may not have sufficiently reduced body weight and adiposity to influence insulin signaling (Perreault et al., 2008). To date, this is the first study to investigate the effects of exercise and diet in regards to changes in peripheral function in rats of both sexes and adds novel insight to the field. One potential mechanism that could mediate improved insulin sensitivity is exercised-induced muscle-derived irisin release. As a myokine, irisin improves metabolism by increasing glucose uptake and browning of adipose tissue (Rabiee et al., 2020). It also influences energy balance by increasing central anorexigenic peptide expression (Natalicchio et al., 2020) and reducing food intake (Ferrante et al., 2016). It

would be worthwhile to assess how diet and exercise influence irisin action to mediate changes in whole-body metabolism in future studies.

The crosstalk between the gut-brain axis and gut microbiome may also influence the metabolic outcomes of HF feeding. Indeed, administration of a GLP-1 agonist led to changes in the gut microbiota and was associated with improved glucose and lipid metabolism in addition to weight loss (Zhao et al., 2018, Madsen et al., 2019). Dietary macronutrient sources and intake can modify the composition and function of gut microbiota (Madsen et al., 2017), and it appears that HF feeding rather than obesity drives changes in these properties (Xiao et al., 2017). The different diet choice patterns among male and female rats may have led to obesogenic gut microbiomes (Ridaura et al., 2013) and influenced body composition and metabolic fitness (Collins et al., 2016). For example, the association between gut microbiota composition and visceral fat mass was stronger than nutrient intake (Le Roy et al., 2019). Developing a greater understanding of host, gut microbiota, and environmental interactions may provide a novel avenue to treat the obese phenotype.

We did not find a significant effect of palatable diet exposure on impairing behavioral flexibility (Chapter 3) or enhancing impulsive choice (Chapter 4) despite extensive literature in human studies showing a robust association between deficits in PFC-mediated executive function, including cognitive flexibility, and impulsivity with overeating and obesity (Dietrich et al., 2014, Sellaro and Colzato, 2017, Yang et al., 2018, Smith et al., 2019). Although we do not report robust diet effects, our results inform improvements to general methodology and task design to tap into the nuanced nature of PFC-mediated cognition, which is relatively understudied (Greenwood and Winocur, 1996, Winocur and Greenwood, 1999, 2005, Stranahan et al., 2008, Kanoski and Davidson, 2010, Valladolid-Acebes et al., 2011). Future work is necessary to investigate whether increasing the length of diet exposure or fat content would lead to more evident impairment of PFC-sensitive behaviors.

No studies have investigated sex differences in the interaction between exercise and diet preference on behavioral flexibility or impulsive choice. In Chapter 3, we found that all WR rats improved learning faster than their Sed counterparts on the Barnes maze (Murray et al., 2009, Gibbons et al., 2014). Female WR rats increased errors made from the probe to reversal learning trial, suggesting some evidence of behavioral inflexibility (Kanoski et al., 2007, Stranahan et al., 2008, McNeilly et al., 2011, Aslani et al., 2015). Our results add to the literature characterizing sex differences in the effect of HF diet exposure on PFC-sensitive behavior. Female rats in our study consumed more HF diet than males, and HF feeding is associated with decreased circulating irisin levels and secretion leading to muscle insulin resistance (Yang et al., 2015). Moreover, irisin levels are negatively associated with cognitive flexibility in obese individuals (Fagundo et al., 2016), and may have altered executive function in female WR rats. Future work could look into the neuroprotective role irisin, which is co-localized with the gut peptide neuropeptide Y (NPY) in the paraventricular nucleus of the hypothalamus (Ferrante et al., 2016), plays in the brain via the MAPK pathway (Rabiee et al., 2020) and how it influences feeding behavior, insulin signaling , and cognition.

There was no evidence for baseline impulsivity at predicting future WD preference and or any effect of sex, diet, or exercise on increasing impulsive choice behavior after chronic WD feeding (Chapter 4). This is the first study that has included rats of both sexes in the assessment of exercise and diet-related changes in impulsive choice. Our results lend support to the one study that reports no change in impulsive choice and adds the finding of no change in impulsive choice (Garman et al., 2021) and is in contrast to other reports of increased (Steele et al., 2017) and decreased (Narayanaswami et al., 2013) impulsive choice. Thus, our results provide novel insight into the ability, or lack thereof, for impulsive choice to predict future palatable diet preference and suggest that impulsive choice behavior may be relatively stable against dietary challenges. Future studies are required to determine whether extending the duration of palatable diet exposure would lead to increases in impulsive choice that exercise

would rescue. In addition, increased preference for a smaller, immediate reward is associated with decreased dopamine $D_{2/3}$ receptor availability in the nucleus accumbens core (Barlow et al., 2018) as well as diet-induced obese rats that engage in compulsive-like feeding behavior (Johnson and Kenny, 2010, van de Giessen et al., 2013). Exercise increases striatal $D_{2/3}$ receptor expression and can attenuate methamphetamine-induced decreases in receptor availability (Vuckovic et al., 2010, Cho et al., 2018b). Determining whether exercise can attenuate HF-mediated neural adaptations in $D_{2/3}$ receptor expression and if it is associated with maladaptive behavioral and cognitive outcomes would provide another avenue to treat overeating and weight gain.

In conclusion, the research in this dissertation suggests a role of sex hormones in mediating sex-specific exercise-mediated diet choice patterns that lead to divergent metabolic outcomes and potentially nuanced changes in cognitive functions. Exercise appears to be sufficient to reverse adverse diet-mediated effects on metabolism in males; however, females may need concurrent weight loss with changes in dietary and exercise habits to show improvements in peripheral metabolism. Although there does not appear to be a sex difference in the ability for exercise to enhance cognition, it is a multi-faceted construct and whether exercise has the same efficacy at improving cognition function in all domains is unclear. More work needs to be done to determine if cognitive flexibility or trait impulsivity confer increased vulnerability for developing and maintaining disordered feeding behavior. Sex differences in the cognitive control of feeding behavior could underlie the gender disparity of obesity and disordered eating, both of which are more prevalent in females. Results from studies in this dissertation suggest that treatment interventions for restoring energy balance, such as exercise, need to be tailored to each sex in order to address the sex-specific metabolic and cognitive dysregulation resulting from long-term palatable diet intake and sedentary behaviors.

REFERENCES

Abdul-Ghani MA, Matsuda M, Balas B, DeFronzo RA (2007) Muscle and liver insulin resistance indexes derived from the oral glucose tolerance test. Diabetes Care 30:89-94.

Ajala O, Lockett H, Twine G, Flanagan DE (2012) Depth and duration of hypoglycaemia achieved during the insulin tolerance test. Eur J Endocrinol 167:59-65.

Akter R, Nessa A, Husain MF, Wahed F, Khatun N, Yesmin M, Nasreen S, Tajkia T (2017) Effect of Obesity on Fasting Blood Sugar. Mymensingh Med J 26:7-11.

al-Dahan MI, Thalmann RH (1996) Progesterone regulates gamma-aminobutyric acid B (GABAB) receptors in the neocortex of female rats. Brain Res 727:40-48.

Albelwi TA, Rogers RD, Kubis HP (2019) Exercise as a reward: Self-paced exercise perception and delay discounting in comparison with food and money. Physiol Behav 199:333-342.

Allom V, Mullan B, Smith E, Hay P, Raman J (2018) Breaking bad habits by improving executive function in individuals with obesity. BMC Public Health 18:505.

Amengual-Cladera E, Llado I, Gianotti M, Proenza AM (2012) Sex differences in the effect of high-fat diet feeding on rat white adipose tissue mitochondrial function and insulin sensitivity. Metabolism 61:1108-1117.

Anderson JW, Konz EC, Frederich RC, Wood CL (2001) Long-term weight-loss maintenance: a meta-analysis of US studies. Am J Clin Nutr 74:579-584.

Apostolakis EM, Garai J, Fox C, Smith CL, Watson SJ, Clark JH, O'Malley BW (1996) Dopaminergic regulation of progesterone receptors: brain D5 dopamine receptors mediate induction of lordosis by D1-like agonists in rats. J Neurosci 16:4823-4834.

Arcones AC, Cruces-Sande M, Ramos P, Mayor F, Jr., Murga C (2019) Sex Differences in High Fat Diet-Induced Metabolic Alterations Correlate with Changes in the Modulation of GRK2 Levels. Cells 8.

Arnold AP, Gorski RA (1984) Gonadal steroid induction of structural sex differences in the central nervous system. Annu Rev Neurosci 7:413-442.

Asarian L, Geary N (2002) Cyclic estradiol treatment normalizes body weight and restores physiological patterns of spontaneous feeding and sexual receptivity in ovariectomized rats. Horm Behav 42:461-471.

Asarian L, Geary N (2006) Modulation of appetite by gonadal steroid hormones. Philos Trans R Soc Lond B Biol Sci 361:1251-1263.

Asarian L, Geary N (2013) Sex differences in the physiology of eating. Am J Physiol Regul Integr Comp Physiol 305:R1215-1267.

Aslani S, Vieira N, Marques F, Costa PS, Sousa N, Palha JA (2015) The effect of high-fat diet on rat's mood, feeding behavior and response to stress. Transl Psychiatry 5:e684.

Ayala JE, Bracy DP, McGuinness OP, Wasserman DH (2006) Considerations in the design of hyperinsulinemic-euglycemic clamps in the conscious mouse. Diabetes 55:390-397.

Baarendse PJ, Counotte DS, O'Donnell P, Vanderschuren LJ (2013) Early social experience is critical for the development of cognitive control and dopamine modulation of prefrontal cortex function. Neuropsychopharmacology 38:1485-1494.

Baker LD, Cross DJ, Minoshima S, Belongia D, Watson GS, Craft S (2011) Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. Arch Neurol 68:51-57.

Bakker J, Baum MJ (2008) Role for estradiol in female-typical brain and behavioral sexual differentiation. Front Neuroendocrinol 29:1-16.

Bakker J, De Mees C, Douhard Q, Balthazart J, Gabant P, Szpirer J, Szpirer C (2006) Alpha-fetoprotein protects the developing female mouse brain from masculinization and defeminization by estrogens. Nat Neurosci 9:220-226.

Barlow RL, Gorges M, Wearn A, Niessen HG, Kassubek J, Dalley JW, Pekcec A (2018) Ventral Striatal D2/3 Receptor Availability Is Associated with Impulsive Choice Behavior As Well As Limbic Corticostriatal Connectivity. Int J Neuropsychopharmacol 21:705-715.
Barron AM, Rosario ER, Elteriefi R, Pike CJ (2013) Sex-specific effects of high fat diet on indices of metabolic syndrome in 3xTg-AD mice: implications for Alzheimer's disease. PLoS One 8:e78554.
Basu R, Dalla Man C, Campioni M, Basu A, Klee G, Toffolo G, Cobelli C, Rizza RA (2006) Effects of age and sex on postprandial glucose metabolism: differences in glucose turnover, insulin secretion, insulin action, and hepatic insulin extraction. Diabetes 55:2001-2014.
Batterink L, Yokum S, Stice E (2010) Body mass correlates inversely with inhibitory control in response to food among adolescent girls: an fMRI study. Neuroimage 52:1696-1703.
Baum MJ (1979) Differentiation of coital behavior in mammals: a comparative analysis. Neurosci Biobehav Rev 3:265-284.
Beaudry JL, Dunford EC, Leclair E, Mandel ER, Peckett AJ, Haas TL, Riddell MC (2015) Voluntary exercise improves metabolic profile in high-fat fed glucocorticoid-treated rats. J Appl Physiol (1985) 118:1331-1343.
Beaulieu K, Hopkins M, Blundell J, Finlayson G (2017) Impact of physical activity level and dietary fat content on passive overconsumption of energy in non-obese adults. Int J Behav Nutr Phys Act 14:14.
Beaulieu K, Hopkins M, Gibbons C, Oustric P, Caudwell P, Blundell J, Finlayson G (2020a) Exercise Training Reduces Reward for High-Fat Food in Adults with Overweight/Obesity. Med Sci Sports Exerc 52:900-908.
Beaulieu K, Oustric P, Finlayson G (2020b) The Impact of Physical Activity on Food Reward: Review and Conceptual Synthesis of Evidence from Observational, Acute, and Chronic Exercise Training Studies. Curr Obes Rep 9:63-80.
Beck RC, Triplett MF (2009) Test-retest reliability of a group-administered paper-pencil measure of delay discounting. Exp Clin Psychopharmacol 17:345-355.
Begg DP, Woods SC (2013) The endocrinology of food intake. Nat Rev Endocrinol 9:584-597.
Belke TW, Wagner JP (2005) The reinforcing property and the rewarding aftereffect of wheel running in rats: a combination of two paradigms. Behav Processes 68:165-172.
Bell DD, Zucker I (1971) Sex differences in body weight and eating: organization and activation by gonadal hormones in the rat. Physiol Behav 7:27-34.
Benard M, Bellisle F, Kesse-Guyot E, Julia C, Andreeva VA, Etile F, Reach G, Dechelotte P, Tavolacci MP, Hercberg S, Peneau S (2019) Impulsivity is associated with food intake, snacking, and eating disorders in a general population. Am J Clin Nutr 109:117-126.
Benard M, Camilleri GM, Etile F, Mejean C, Bellisle F, Reach G, Hercberg S, Peneau S (2017) Association between Impulsivity and Weight Status in a General Population. Nutrients 9.
Benton D (2005) Can artificial sweeteners help control body weight and prevent obesity? Nutr Res Rev 18:63-76.
Betancourt E, Wachtel J, Michaelos M, Haggerty M, Conforti J, Kritzer MF (2017) The impact of biological sex and sex hormones on cognition in a rat model of early, pre-motor Parkinson's disease. Neuroscience 345:297-314.
Bisschop PH, de Metz J, Ackermans MT, Endert E, Pijl H, Kuipers F, Meijer AJ, Sauerwein HP, Romijn JA (2001) Dietary fat content alters insulin-mediated glucose metabolism in healthy men. Am J Clin Nutr 73:554-559.
Bissonette GB, Lande MD, Martins GJ, Powell EM (2012) Versatility of the mouse reversal/set-shifting test: effects of topiramate and sex. Physiol Behav 107:781-786.
Bjorntorp PA (1989) Sex differences in the regulation of energy balance with exercise. Am J Clin Nutr 49:958-961.

Blazquez E, Velazquez E, Hurtado-Carneiro V, Ruiz-Albusac JM (2014) Insulin in the brain: its pathophysiological implications for States related with central insulin resistance, type 2 diabetes and Alzheimer's disease. Front Endocrinol (Lausanne) 5:161.
Bluher M (2019) Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol 15:288-298.
Blundell JE, King NA (1999) Physical activity and regulation of food intake: current evidence. Med Sci Sports Exerc 31:S573-583.
Bocarsly ME, Fasolino M, Kane GA, LaMarca EA, Kirschen GW, Karatsoreos IN, McEwen BS, Gould E (2015) Obesity diminishes synaptic markers, alters microglial morphology, and impairs cognitive function. Proc Natl Acad Sci U S A 112:15731-15736.
Boitard C, Parkes SL, Cavaroc A, Tantot F, Castanon N, Laye S, Tronel S, Pacheco-Lopez G, Coutureau E, Ferreira G (2016) Switching Adolescent High-Fat Diet to Adult Control Diet Restores Neurocognitive Alterations. Front Behav Neurosci 10:225.
Bolla KI, Eldreth DA, Matochik JA, Cadet JL (2004) Sex-related differences in a gambling task and its neurological correlates. Cereb Cortex 14:1226-1232.
Bongbele J, Gutierrez A, Cardin S, Lavoie JM (1992) Effect of physical training on insulin response to intravenous glucose in male peripubertal rats. J Appl Physiol (1985) 73:1227-1231.
Boucher J, Kleinridders A, Kahn CR (2014) Insulin receptor signaling in normal and insulin-resistant states. Cold Spring Harb Perspect Biol 6.
Boule NG, Weisnagel SJ, Lakka TA, Tremblay A, Bergman RN, Rankinen T, Leon AS, Skinner JS, Wilmore JH, Rao DC, Bouchard C, Study HF (2005) Effects of exercise training on glucose homeostasis: the HERITAGE Family Study. Diabetes Care 28:108-114.
Bowe JE, Franklin ZJ, Hauge-Evans AC, King AJ, Persaud SJ, Jones PM (2014) Metabolic phenotyping guidelines: assessing glucose homeostasis in rodent models. J Endocrinol 222:G13-25.
Braun B, Gerson L, Hagobian T, Grow D, Chipkin SR (2005) No effect of short-term testosterone manipulation on exercise substrate metabolism in men. J Appl Physiol (1985) 99:1930-1937.
Brennan IM, Luscombe-Marsh ND, Seimon RV, Otto B, Horowitz M, Wishart JM, Feinle-Bisset C (2012) Effects of fat, protein, and carbohydrate and protein load on appetite, plasma cholecystokinin, peptide YY, and ghrelin, and energy intake in lean and obese men. Am J Physiol Gastrointest Liver Physiol 303:G129-140.
Brockett AT, LaMarca EA, Gould E (2015) Physical Exercise Enhances Cognitive Flexibility as Well as Astrocytic and Synaptic Markers in the Medial Prefrontal Cortex. Plos One 10.
Broos N, Schmaal L, Wiskerke J, Kostelijk L, Lam T, Stoop N, Weierink L, Ham J, de Geus EJ, Schoffelmeer AN, van den Brink W, Veltman DJ, de Vries TJ, Pattij T, Goudriaan AE (2012) The relationship between impulsive choice and impulsive action: a cross-species translational study. PLoS One 7:e36781.
Bucci DJ, Chiba AA, Gallagher M (1995) Spatial learning in male and female Long-Evans rats. Behav Neurosci 109:180-183.
Buczek L, Migliaccio J, Petrovich GD (2020) Hedonic Eating: Sex Differences and Characterization of Orexin Activation and Signaling. Neuroscience 436:34-45.
Buettner R, Scholmerich J, Bollheimer LC (2007) High-fat diets: modeling the metabolic disorders of human obesity in rodents. Obesity (Silver Spring) 15:798-808.
Butera PC (2010) Estradiol and the control of food intake. Physiol Behav 99:175-180.
Carels RA, Burmeister JM, Koball AM, Oehlhof MW, Hinman N, LeRoy M, Bannon E, Ashrafioun L, Storfer-Isser A, Darby LA, Gumble A (2014) A randomized trial comparing two approaches to weight loss: differences in weight loss maintenance. J Health Psychol 19:296-311.

Carrera O, Cerrato M, Vazquez R, Sineiro C, Gutierrez E (2011) Gender dimorphic effects of voluntary running in laboratory rats depends on maturational status. Q J Exp Psychol (Hove) 64:823-832.
Carroll ME, Anker JJ (2010) Sex differences and ovarian hormones in animal models of drug dependence. Horm Behav 58:44-56.
Castro EA, Carraca EV, Cupeiro R, Lopez-Plaza B, Teixeira PJ, Gonzalez-Lamuno D, Peinado AB (2020) The Effects of the Type of Exercise and Physical Activity on Eating Behavior and Body Composition in Overweight and Obese Subjects. Nutrients 12.
Catenacci VA, Odgen L, Phelan S, Thomas JG, Hill J, Wing RR, Wyatt H (2014) Dietary habits and weight maintenance success in high versus low exercisers in the National Weight Control Registry. J Phys Act Health 11:1540-1548.
Caudwell P, Gibbons C, Finlayson G, Naslund E, Blundell J (2014) Exercise and weight loss: no sex differences in body weight response to exercise. Exerc Sport Sci Rev 42:92-101.
Chen FT, Chen SR, Chu IH, Liu JH, Chang YK (2017) Multicomponent Exercise Intervention and Metacognition in Obese Preadolescents: A Randomized Controlled Study. J Sport Exerc Psychol 39:302-312.
Cho BR, Kwak MJ, Kim WY, Kim JH (2018a) Impulsive Action and Impulsive Choice Are Differentially Expressed in Rats Depending on the Age at Exposure to a Gambling Task. Front Psychiatry 9:503.
Cho J, Kim D, Jang J, Kim J, Kang H (2018b) Treadmill running suppresses the vulnerability of dopamine D2 receptor deficiency to obesity and metabolic complications: a pilot study. J Exerc Nutrition Biochem 22:42-50.
Chooi YC, Ding C, Magkos F (2019) The epidemiology of obesity. Metabolism 92:6-10.
Chowdhury TG, Wallin-Miller KG, Rear AA, Park J, Diaz V, Simon NW, Moghaddam B (2019) Sex differences in reward- and punishment-guided actions. Cogn Affect Behav Neurosci 19:1404-1417.
Churchwell JC, Morris AM, Heurtelou NM, Kesner RP (2009) Interactions between the prefrontal cortex and amygdala during delay discounting and reversal. Behav Neurosci 123:1185-1196.
Cifre M, Palou A, Oliver P (2018) Cognitive impairment in metabolically-obese, normal-weight rats: identification of early biomarkers in peripheral blood mononuclear cells. Mol Neurodegener 13:14.
Clegg DJ, Gotoh K, Kemp C, Wortman MD, Benoit SC, Brown LM, D'Alessio D, Tso P, Seeley RJ, Woods SC (2011) Consumption of a high-fat diet induces central insulin resistance independent of adiposity. Physiol Behav 103:10-16.
Coker RH, Williams RH, Yeo SE, Kortebein PM, Bodenner DL, Kern PA, Evans WJ (2009) The impact of exercise training compared to caloric restriction on hepatic and peripheral insulin resistance in obesity. J Clin Endocrinol Metab 94:4258-4266.
Collaboration NCDRF (2017) Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. Lancet 390:2627-2642.
Collins KH, Paul HA, Hart DA, Reimer RA, Smith IC, Rios JL, Seerattan RA, Herzog W (2016) A High-Fat High-Sucrose Diet Rapidly Alters Muscle Integrity, Inflammation and Gut Microbiota in Male Rats. Sci Rep 6:37278.
Conn VS, Hafdahl AR, Lemaster JW, Ruppar TM, Cochran JE, Nielsen PJ (2008) Meta-analysis of health behavior change interventions in type 1 diabetes. Am J Health Behav 32:315-329.
Cortright RN, Chandler MP, Lemon PW, DiCarlo SE (1997) Daily exercise reduces fat, protein and body mass in male but not female rats. Physiol Behav 62:105-111.

Cortright RN, Koves TR (2000) Sex differences in substrate metabolism and energy homeostasis. Can J Appl Physiol 25:288-311.
Cross CP, Copping LT, Campbell A (2011) Sex differences in impulsivity: a meta-analysis. Psychol Bull 137:97-130.
Culbert KM, Sinclair EB, Hildebrandt BA, Klump KL, Sisk CL (2018) Perinatal testosterone contributes to mid-to-post pubertal sex differences in risk for binge eating in male and female rats. J Abnorm Psychol 127:239-250.
D'Eon T, Braun B (2002) The roles of estrogen and progesterone in regulating carbohydrate and fat utilization at rest and during exercise. J Womens Health Gend Based Med 11:225-237.
Dajani DR, Uddin LQ (2015) Demystifying cognitive flexibility: Implications for clinical and developmental neuroscience. Trends Neurosci 38:571-578.
Dalley JW, Mar AC, Economidou D, Robbins TW (2008) Neurobehavioral mechanisms of impulsivity: fronto-striatal systems and functional neurochemistry. Pharmacol Biochem Behav 90:250-260.
Davidson TL, Hargrave SL, Swithers SE, Sample CH, Fu X, Kinzig KP, Zheng W (2013) Inter-relationships among diet, obesity and hippocampal-dependent cognitive function. Neuroscience 253:110-122.
Davidson TL, Monnot A, Neal AU, Martin AA, Horton JJ, Zheng W (2012) The effects of a high-energy diet on hippocampal-dependent discrimination performance and blood-brain barrier integrity differ for diet-induced obese and diet-resistant rats. Physiol Behav 107:26-33.
Day CJ, McHale S, Francis J (2012) Individual differences and preference for dietary fat using the Fat Preference Questionnaire((c)) in a UK sample. Appetite 58:679-686.
Debette S, Beiser A, Hoffmann U, Decarli C, O'Donnell CJ, Massaro JM, Au R, Himali JJ, Wolf PA, Fox CS, Seshadri S (2010) Visceral fat is associated with lower brain volume in healthy middle-aged adults. Ann Neurol 68:136-144.
DeFina LF, Vega GL, Leonard D, Grundy SM (2012) Fasting glucose, obesity, and metabolic syndrome as predictors of type 2 diabetes: the Cooper Center Longitudinal Study. J Investig Med 60:1164-1168.
Derkach KV, Bondareva VM, Trashkov AP, Chistyakova OV, Verlov NA, Shpakov AO (2017) [Metabolic and hormonal indices in rats with prolonged model of metabolic syndrome induced by high-carbohydrate and high-fat diet]. Adv Gerontol 30:31-38.
Dietrich A, Federbusch M, Grellmann C, Villringer A, Horstmann A (2014) Body weight status, eating behavior, sensitivity to reward/punishment, and gender: relationships and interdependencies. Front Psychol 5:1073.
Dirksen C, Graff J, Fuglsang S, Rehfeld JF, Holst JJ, Madsen JL (2019) Energy intake, gastrointestinal transit, and gut hormone release in response to oral triglycerides and fatty acids in men with and without severe obesity. Am J Physiol Gastrointest Liver Physiol 316:G332-G337.
Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW, Smith BK, American College of Sports M (2009) American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. Med Sci Sports Exerc 41:459-471.
Donnelly JE, Herrmann SD, Lambourne K, Szabo AN, Honas JJ, Washburn RA (2014) Does increased exercise or physical activity alter ad-libitum daily energy intake or macronutrient composition in healthy adults? A systematic review. PLoS One 9:e83498.
Donnelly JE, Smith B, Jacobsen DJ, Kirk E, Dubose K, Hyder M, Bailey B, Washburn R (2004) The role of exercise for weight loss and maintenance. Best Pract Res Clin Gastroenterol 18:1009-1029.

Donnelly JE, Smith BK (2005) Is exercise effective for weight loss with ad libitum diet? Energy balance, compensation, and gender differences. Exerc Sport Sci Rev 33:169-174.
Drewnowski A, Greenwood MR (1983) Cream and sugar: human preferences for high-fat foods. Physiol Behav 30:629-633.
Durham HA, Truett GE (2006) Development of insulin resistance and hyperphagia in Zucker fatty rats. Am J Physiol Regul Integr Comp Physiol 290:R652-658.
Ebrahimi M, Rahmani-Nia F, Damirchi A, Mirzaie B, Asghar Pur S (2013) Effect of Short-term Exercise on Appetite, Energy Intake and Energy-regulating Hormones. Iran J Basic Med Sci 16:829-834.
Eckel LA (2011) The ovarian hormone estradiol plays a crucial role in the control of food intake in females. Physiol Behav 104:517-524.
Eckel LA, Moore SR (2004) Diet-induced hyperphagia in the rat is influenced by sex and exercise. Am J Physiol Regul Integr Comp Physiol 287:R1080-1085.
Eckstrand KL, Mummareddy N, Kang H, Cowan R, Zhou M, Zald D, Silver HJ, Niswender KD, Avison MJ (2017) An insulin resistance associated neural correlate of impulsivity in type 2 diabetes mellitus. PLoS One 12:e0189113.
Edwards CG, Walk AM, Thompson SV, Mullen SP, Holscher HD, Khan NA (2018) Disordered Eating Attitudes and Behavioral and Neuroelectric Indices of Cognitive Flexibility in Individuals with Overweight and Obesity. Nutrients 10.
Eichenbaum H, Clegg RA, Feeley A (1983) Reexamination of functional subdivisions of the rodent prefrontal cortex. Exp Neurol 79:434-451.
Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB (2003) Lower cognitive function in the presence of obesity and hypertension: the Framingham heart study. Int J Obes Relat Metab Disord 27:260-268.
Ellingsgaard H, Hauselmann I, Schuler B, Habib AM, Baggio LL, Meier DT, Eppler E, Bouzakri K, Wueest S, Muller YD, Hansen AM, Reinecke M, Konrad D, Gassmann M, Reimann F, Halban PA, Gromada J, Drucker DJ, Gribble FM, Ehses JA, Donath MY (2011) Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells. Nat Med 17:1481-1489.
Ellingsgaard H, Seelig E, Timper K, Coslovsky M, Soederlund L, Lyngbaek MP, Wewer Albrechtsen NJ, Schmidt-Trucksass A, Hanssen H, Frey WO, Karstoft K, Pedersen BK, Boni-Schnetzler M, Donath MY (2020) GLP-1 secretion is regulated by IL-6 signalling: a randomised, placebo-controlled study. Diabetologia 63:362-373.
Ellis GS, Lanza-Jacoby S, Gow A, Kendrick ZV (1994) Effects of estradiol on lipoprotein lipase activity and lipid availability in exercised male rats. J Appl Physiol (1985) 77:209-215.
Eneva KT, Murray S, O'Garro-Moore J, Yiu A, Alloy LB, Avena NM, Chen EY (2017) Reward and punishment sensitivity and disordered eating behaviors in men and women. J Eat Disord 5:6.
Epstein LH, Robinson JL, Temple JL, Roemmich JN, Marusewski A, Nadbrzuch R (2008) Sensitization and habituation of motivated behavior in overweight and non-overweight children. Learn Motiv 39:243-255.
Escriva F, Gavete ML, Fermin Y, Perez C, Gallardo N, Alvarez C, Andres A, Ros M, Carrascosa JM (2007) Effect of age and moderate food restriction on insulin sensitivity in Wistar rats: role of adiposity. J Endocrinol 194:131-141.
Espeland MA, Carmichael O, Yasar S, Hugenschmidt C, Hazzard W, Hayden KM, Rapp SR, Neiberg R, Johnson KC, Hoscheidt S, Mielke MM, Action for Health in Diabetes Research G (2018) Sex-related differences in the prevalence of cognitive impairment among overweight and obese adults with type 2 diabetes. Alzheimers Dement 14:1184-1192.
Evans KL, Hampson E (2015) Sex differences on prefrontally-dependent cognitive tasks. Brain Cogn 93:42-53.

Fagundo AB, de la Torre R, Jimenez-Murcia S, Aguera Z, Granero R, Tarrega S, Botella C, Banos R, Fernandez-Real JM, Rodriguez R, Forcano L, Fruhbeck G, Gomez-Ambrosi J, Tinahones FJ, Fernandez-Garcia JC, Casanueva FF, Fernandez-Aranda F (2012) Executive functions profile in extreme eating/weight conditions: from anorexia nervosa to obesity. PLoS One 7:e43382.

Fagundo AB, Jimenez-Murcia S, Giner-Bartolome C, Aguera Z, Sauchelli S, Pardo M, Crujeiras AB, Granero R, Banos R, Botella C, de la Torre R, Fernandez-Real JM, Fernandez-Garcia JC, Fruhbeck G, Rodriguez A, Mallorqui-Bague N, Tarrega S, Tinahones FJ, Rodriguez R, Ortega F, Menchon JM, Casanueva FF, Fernandez-Aranda F (2016) Modulation of Irisin and Physical Activity on Executive Functions in Obesity and Morbid obesity. Sci Rep 6:30820.

Farrell CM, McNeilly AD, Fournier P, Jones T, Hapca SM, West D, McCrimmon RJ (2020) A randomised controlled study of high intensity exercise as a dishabituating stimulus to improve hypoglycaemia awareness in people with type 1 diabetes: a proof-of-concept study. Diabetologia 63:853-863.

Favieri F, Forte G, Casagrande M (2019) The Executive Functions in Overweight and Obesity: A Systematic Review of Neuropsychological Cross-Sectional and Longitudinal Studies. Front Psychol 10:2126.

Ferrante C, Orlando G, Recinella L, Leone S, Chiavaroli A, Di Nisio C, Shohreh R, Manippa F, Ricciuti A, Vacca M, Brunetti L (2016) Central inhibitory effects on feeding induced by the adipo-myokine irisin. Eur J Pharmacol 791:389-394.

Festa A, D'Agostino R, Jr., Hanley AJ, Karter AJ, Saad MF, Haffner SM (2004) Differences in insulin resistance in nondiabetic subjects with isolated impaired glucose tolerance or isolated impaired fasting glucose. Diabetes 53:1549-1555.

Finlayson G, Caudwell P, Gibbons C, Hopkins M, King N, Blundell J (2011) Low fat loss response after medium-term supervised exercise in obese is associated with exercise-induced increase in food reward. J Obes 2011.

Flegal KM, Carroll MD, Ogden CL, Curtin LR (2010) Prevalence and trends in obesity among US adults, 1999-2008. JAMA 303:235-241.

Foright RM, Johnson GC, Kahn D, Charleston CA, Presby DM, Bouchet CA, Wellberg EA, Sherk VD, Jackman MR, Greenwood BN, MacLean PS (2020) Compensatory eating behaviors in male and female rats in response to exercise training. Am J Physiol Regul Integr Comp Physiol.

Foscue EP, Wood KN, Schramm-Sapyta NL (2012) Characterization of a semi-rapid method for assessing delay discounting in rodents. Pharmacol Biochem Behav 101:187-192.

Foster-Powell K, Holt SH, Brand-Miller JC (2002) International table of glycemic index and glycemic load values: 2002. Am J Clin Nutr 76:5-56.

Frias JP, Macaraeg GB, Ofrecio J, Yu JG, Olefsky JM, Kruszynska YT (2001) Decreased susceptibility to fatty acid-induced peripheral tissue insulin resistance in women. Diabetes 50:1344-1350.

Frye CA, Walf AA (2004) Estrogen and/or progesterone administered systemically or to the amygdala can have anxiety-, fear-, and pain-reducing effects in ovariectomized rats. Behav Neurosci 118:306-313.

Gaisano HY, Macdonald PE, Vranic M (2012) Glucagon secretion and signaling in the development of diabetes. Front Physiol 3:349.

Galassetti P, Tate D, Neill RA, Richardson A, Leu SY, Davis SN (2006) Effect of differing antecedent hypoglycemia on counterregulatory responses to exercise in type 1 diabetes. Am J Physiol Endocrinol Metab 290:E1109-1117.

Garcia-Garcia I, Michaud A, Dadar M, Zeighami Y, Neseliler S, Collins DL, Evans AC, Dagher A (2018) Neuroanatomical differences in obesity: meta-analytic findings and their validation in an independent dataset. Int J Obes (Lond).

Garman TS, Setlow B, Orsini CA (2021) Effects of a high-fat diet on impulsive choice in rats. Physiol Behav 229:113260.
Gawel K, Gibula E, Marszalek-Grabska M, Filarowska J, Kotlinska JH (2019) Assessment of spatial learning and memory in the Barnes maze task in rodents-methodological consideration. Naunyn Schmiedebergs Arch Pharmacol 392:1-18.
Geary N, Asarian L (1999) Cyclic estradiol treatment normalizes body weight and test meal size in ovariectomized rats. Physiol Behav 67:141-147.
Ghibaudi L, Cook J, Farley C, van Heek M, Hwa JJ (2002) Fat intake affects adiposity, comorbidity factors, and energy metabolism of sprague-dawley rats. Obes Res 10:956-963.
Gibbons TE, Pence BD, Petr G, Ossyra JM, Mach HC, Bhattacharya TK, Perez S, Martin SA, McCusker RH, Kelley KW, Rhodes JS, Johnson RW, Woods JA (2014) Voluntary wheel running, but not a diet containing (-)-epigallocatechin-3-gallate and beta-alanine, improves learning, memory and hippocampal neurogenesis in aged mice. Behav Brain Res 272:131-140.
Gollisch KS, Brandauer J, Jessen N, Toyoda T, Nayer A, Hirshman MF, Goodyear LJ (2009) Effects of exercise training on subcutaneous and visceral adipose tissue in normal- and high-fat diet-fed rats. Am J Physiol Endocrinol Metab 297:E495-504.
Goodwill HL, Manzano-Nieves G, LaChance P, Teramoto S, Lin S, Lopez C, Stevenson RJ, Theyel BB, Moore CI, Connors BW, Bath KG (2018) Early Life Stress Drives Sex-Selective Impairment in Reversal Learning by Affecting Parvalbumin Interneurons in Orbitofrontal Cortex of Mice. Cell Rep 25:2299-2307 e2294.
Goodyear LJ, Hirshman MF, Horton ED, Knutson SM, Wardzala LJ, Horton ES (1991) Exercise training normalizes glucose metabolism in a rat model of impaired glucose tolerance. Metabolism 40:455-464.
Goodyear LJ, Hirshman MF, Knutson SM, Horton ED, Horton ES (1988) Effect of exercise training on glucose homeostasis in normal and insulin-deficient diabetic rats. J Appl Physiol (1985) 65:844-851.
Goodyear LJ, Kahn BB (1998) Exercise, glucose transport, and insulin sensitivity. Annu Rev Med 49:235-261.
Gorski J, Stankiewicz B, Brycka R, Kiczka K (1976) The effect of estradiol on carbohydrate utilization during prolonged exercise in rats. Acta Physiol Pol 27:361-367.
Grafe LA, Cornfeld A, Luz S, Valentino R, Bhatnagar S (2017) Orexins Mediate Sex Differences in the Stress Response and in Cognitive Flexibility. Biol Psychiatry 81:683-692.
Gray JM, Nunez AA, Siegel LI, Wade GN (1979) Effects of testosterone on body weight and adipose tissue: role of aromatization. Physiol Behav 23:465-469.
Gray JM, Wade GN (1981) Food intake, body weight, and adiposity in female rats: actions and interactions of progestins and antiestrogens. Am J Physiol 240:E474-481.
Greenwood CE, Winocur G (1996) Cognitive impairment in rats fed high-fat diets: a specific effect of saturated fatty-acid intake. Behav Neurosci 110:451-459.
Greenwood CE, Winocur G (2005) High-fat diets, insulin resistance and declining cognitive function. Neurobiol Aging 26 Suppl 1:42-45.
Gustafsson JA, Stenberg A (1976) On the obligatory role of the hypophysis in sexual differentiation hepatic metabolism in rats. Proc Natl Acad Sci U S A 73:1462-1465.
Hagobian TA, Sharoff CG, Stephens BR, Wade GN, Silva JE, Chipkin SR, Braun B (2009) Effects of exercise on energy-regulating hormones and appetite in men and women. Am J Physiol Regul Integr Comp Physiol 296:R233-242.
Hall P, Tran B, Lowe C, Vincent C, Mourtzakis M, Liu-Ambrose T, Prapavessis H, Gidron Y (2015) Expression of executive control in situational context: Effects of facilitating versus restraining cues on snack food consumption. Health Psychol 34:539-546.

Hall PA, Lowe C, Vincent C (2014) Executive control resources and snack food consumption in the presence of restraining versus facilitating cues. J Behav Med 37:587-594.
Hamilton DA, Brigman JL (2015) Behavioral flexibility in rats and mice: contributions of distinct frontocortical regions. Genes Brain Behav 14:4-21.
Hamilton KR, Mitchell MR, Wing VC, Balodis IM, Bickel WK, Fillmore M, Lane SD, Lejuez CW, Littlefield AK, Luijten M, Mathias CW, Mitchell SH, Napier TC, Reynolds B, Schutz CG, Setlow B, Sher KJ, Swann AC, Tedford SE, White MJ, Winstanley CA, Yi R, Potenza MN, Moeller FG (2015) Choice impulsivity: Definitions, measurement issues, and clinical implications. Personal Disord 6:182-198.
Hammerslag LR, Belagodu AP, Aladesuyi Arogundade OA, Karountzos AG, Guo Q, Galvez R, Roberts BW, Gulley JM (2019) Adolescent impulsivity as a sex-dependent and subtype-dependent predictor of impulsivity, alcohol drinking and dopamine D2 receptor expression in adult rats. Addict Biol 24:193-205.
Hammond BP, Stotz PJ, Brennan AM, Lamarche B, Day AG, Ross R (2019) Individual Variability in Waist Circumference and Body Weight in Response to Exercise. Med Sci Sports Exerc 51:315-322.
Han JE, Boachie N, Garcia-Garcia I, Michaud A, Dagher A (2018) Neural correlates of dietary self-control in healthy adults: A meta-analysis of functional brain imaging studies. Physiol Behav 192:98-108.
Hege MA, Stingl KT, Kullmann S, Schag K, Giel KE, Zipfel S, Preissl H (2015) Attentional impulsivity in binge eating disorder modulates response inhibition performance and frontal brain networks. Int J Obes (Lond) 39:353-360.
Hellemans KG, Nobrega JN, Olmstead MC (2005) Early environmental experience alters baseline and ethanol-induced cognitive impulsivity: relationship to forebrain 5-HT1A receptor binding. Behav Brain Res 159:207-220.
Hernandez CM, Orsini C, Wheeler AR, Ten Eyck TW, Betzhold SM, Labiste CC, Wright NG, Setlow B, Bizon JL (2020) Testicular hormones mediate robust sex differences in impulsive choice in rats. Elife 9.
Hildebrandt BA, Klump KL, Racine SE, Sisk CL (2014) Differential strain vulnerability to binge eating behaviors in rats. Physiol Behav 127:81-86.
Hill JO, Talano CM, Nickel M, DiGirolamo M (1986) Energy utilization in food-restricted female rats. J Nutr 116:2000-2012.
Hill JO, Thiel J, Heller PA, Markon C, Fletcher G, DiGirolamo M (1989) Differences in effects of aerobic exercise training on blood lipids in men and women. Am J Cardiol 63:254-256.
Hill JO, Wyatt HR, Peters JC (2012) Energy balance and obesity. Circulation 126:126-132.
Hotamisligil GS (2006) Inflammation and metabolic disorders. Nature 444:860-867.
Hudson JI, Hiripi E, Pope HG, Jr., Kessler RC (2007) The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry 61:348-358.
Huebschmann AG, Huxley RR, Kohrt WM, Zeitler P, Regensteiner JG, Reusch JEB (2019) Sex differences in the burden of type 2 diabetes and cardiovascular risk across the life course. Diabetologia 62:1761-1772.
Hwang LL, Wang CH, Li TL, Chang SD, Lin LC, Chen CP, Chen CT, Liang KC, Ho IK, Yang WS, Chiou LC (2010) Sex differences in high-fat diet-induced obesity, metabolic alterations and learning, and synaptic plasticity deficits in mice. Obesity (Silver Spring) 18:463-469.
Idris AI (2012) Ovariectomy/orchidectomy in rodents. Methods Mol Biol 816:545-551.
Imperatori C, Innamorati M, Tamburello S, Continisio M, Contardi A, Tamburello A, Fabbricatore M (2013) Gender differences in food craving among overweight and obese patients attending low energy diet therapy: a matched case-control study. Eat Weight Disord 18:297-303.

Jenkins NT, Hagberg JM (2011) Aerobic training effects on glucose tolerance in prediabetic and normoglycemic humans. Med Sci Sports Exerc 43:2231-2240.
Johnson PM, Kenny PJ (2010) Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. Nat Neurosci 13:635-641.
Jonasson Z (2005) Meta-analysis of sex differences in rodent models of learning and memory: a review of behavioral and biological data. Neurosci Biobehav Rev 28:811-825.
Jost A, Vigier B, Prepin J, Perchellet JP (1973) Studies on sex differentiation in mammals. Recent Prog Horm Res 29:1-41.
Jung UJ, Choi MS (2014) Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. Int J Mol Sci 15:6184-6223.
Kadouh H, Chedid V, Halawi H, Burton DD, Clark MM, Khemani D, Vella A, Acosta A, Camilleri M (2020) GLP-1 Analog Modulates Appetite, Taste Preference, Gut Hormones, and Regional Body Fat Stores in Adults with Obesity. J Clin Endocrinol Metab 105.
Kakoschke N, Aarts E, Verdejo-Garcia A (2018) The Cognitive Drivers of Compulsive Eating Behavior. Front Behav Neurosci 12:338.
Kanoski SE, Davidson TL (2010) Different patterns of memory impairments accompany short- and longer-term maintenance on a high-energy diet. J Exp Psychol Anim Behav Process 36:313-319.
Kanoski SE, Meisel RL, Mullins AJ, Davidson TL (2007) The effects of energy-rich diets on discrimination reversal learning and on BDNF in the hippocampus and prefrontal cortex of the rat. Behav Brain Res 182:57-66.
Kanoski SE, Zhang Y, Zheng W, Davidson TL (2010) The effects of a high-energy diet on hippocampal function and blood-brain barrier integrity in the rat. J Alzheimers Dis 21:207-219.
Kautzky-Willer A, Harreiter J, Pacini G (2016) Sex and Gender Differences in Risk, Pathophysiology and Complications of Type 2 Diabetes Mellitus. Endocr Rev 37:278-316.
Kawaguchi M, Scott KA, Moran TH, Bi S (2005) Dorsomedial hypothalamic corticotropin-releasing factor mediation of exercise-induced anorexia. Am J Physiol Regul Integr Comp Physiol 288:R1800-1805.
Khan NA, Raine LB, Drollette ES, Scudder MR, Hillman CH (2015) The relation of saturated fats and dietary cholesterol to childhood cognitive flexibility. Appetite 93:51-56.
Kim JB (2016) Dynamic cross talk between metabolic organs in obesity and metabolic diseases. Exp Mol Med 48.
King NA, Hopkins M, Caudwell P, Stubbs RJ, Blundell JE (2009) Beneficial effects of exercise: shifting the focus from body weight to other markers of health. Br J Sports Med 43:924-927.
Kirby KN, Marakovic NN (1996) Delay-discounting probabilistic rewards: Rates decrease as amounts increase. Psychon Bull Rev 3:100-104.
Kirkpatrick K, Marshall AT, Clarke J, Cain ME (2013) Environmental rearing effects on impulsivity and reward sensitivity. Behav Neurosci 127:712-724.
Kirkpatrick K, Marshall AT, Smith AP, Koci J, Park Y (2014) Individual differences in impulsive and risky choice: effects of environmental rearing conditions. Behav Brain Res 269:115-127.
Klein C, Jonas W, Iggena D, Empl L, Rivalan M, Wiedmer P, Spranger J, Hellweg R, Winter Y, Steiner B (2016) Exercise prevents high-fat diet-induced impairment of flexible memory expression in the water maze and modulates adult hippocampal neurogenesis in mice. Neurobiol Learn Mem 131:26-35.
Klem ML, Wing RR, Chang CC, Lang W, McGuire MT, Sugerman HJ, Hutchison SL, Makovich AL, Hill JO (2000) A case-control study of successful maintenance of a substantial

weight loss: individuals who lost weight through surgery versus those who lost weight through non-surgical means. Int J Obes Relat Metab Disord 24:573-579.
Klem ML, Wing RR, McGuire MT, Seagle HM, Hill JO (1997) A descriptive study of individuals successful at long-term maintenance of substantial weight loss. Am J Clin Nutr 66:239-246.
Klump KL, Culbert KM, Sisk CL (2017) Sex Differences in Binge Eating: Gonadal Hormone Effects Across Development. Annu Rev Clin Psychol 13:183-207.
Klump KL, Racine S, Hildebrandt B, Sisk CL (2013) Sex differences in binge eating patterns in male and female adult rats. Int J Eat Disord 46:729-736.
Kopp W (2019) How Western Diet And Lifestyle Drive The Pandemic Of Obesity And Civilization Diseases. Diabetes Metab Syndr Obes 12:2221-2236.
Kosari S, Badoer E, Nguyen JC, Killcross AS, Jenkins TA (2012) Effect of western and high fat diets on memory and cholinergic measures in the rat. Behav Brain Res 235:98-103.
Kullmann S, Heni M, Veit R, Scheffler K, Machann J, Haring HU, Fritsche A, Preissl H (2015) Selective insulin resistance in homeostatic and cognitive control brain areas in overweight and obese adults. Diabetes Care 38:1044-1050.
Kwon H, Pessin JE (2013) Adipokines mediate inflammation and insulin resistance. Front Endocrinol (Lausanne) 4:71.
la Fleur SE, Vanderschuren LJ, Luijendijk MC, Kloeze BM, Tiesjema B, Adan RA (2007) A reciprocal interaction between food-motivated behavior and diet-induced obesity. Int J Obes (Lond) 31:1286-1294.
LaClair M, Febo M, Nephew B, Gervais NJ, Poirier G, Workman K, Chumachenko S, Payne L, Moore MC, King JA, Lacreuse A (2019) Sex Differences in Cognitive Flexibility and Resting Brain Networks in Middle-Aged Marmosets. eNeuro 6.
Lagou V, Magi R, Hottenga JJ, Grallert H, Perry JRB, Bouatia-Naji N, Marullo L, Rybin D, Jansen R, Min JL, Dimas AS, Ulrich A, Zudina L, Gadin JR, Jiang L, Faggian A, Bonnefond A, Fadista J, Stathopoulou MG, Isaacs A, Willems SM, Navarro P, Tanaka T, Jackson AU, Montasser ME, O'Connell JR, Bielak LF, Webster RJ, Saxena R, Stafford JM, Pourcain BS, Timpson NJ, Salo P, Shin SY, Amin N, Smith AV, Li G, Verweij N, Goel A, Ford I, Johnson PCD, Johnson T, Kapur K, Thorleifsson G, Strawbridge RJ, Rasmussen-Torvik LJ, Esko T, Mihailov E, Fall T, Fraser RM, Mahajan A, Kanoni S, Giedraitis V, Kleber ME, Silbernagel G, Meyer J, Muller-Nurasyid M, Ganna A, Sarin AP, Yengo L, Shungin D, Luan J, Horikoshi M, An P, Sanna S, Boettcher Y, Rayner NW, Nolte IM, Zemunik T, Iperen EV, Kovacs P, Hastie ND, Wild SH, McLachlan S, Campbell S, Polasek O, Carlson O, Egan J, Kiess W, Willemsen G, Kuusisto J, Laakso M, Dimitriou M, Hicks AA, Rauramaa R, Bandinelli S, Thorand B, Liu Y, Miljkovic I, Lind L, Doney A, Perola M, Hingorani A, Kivimaki M, Kumari M, Bennett AJ, Groves CJ, Herder C, Koistinen HA, Kinnunen L, Faire U, Bakker SJL, Uusitupa M, Palmer CNA, Jukema JW, Sattar N, Pouta A, Snieder H, Boerwinkle E, Pankow JS, Magnusson PK, Krus U, Scapoli C, de Geus E, Bluher M, Wolffenbuttel BHR, Province MA, Abecasis GR, Meigs JB, Hovingh GK, Lindstrom J, Wilson JF, Wright AF, Dedoussis GV, Bornstein SR, Schwarz PEH, Tonjes A, Winkelmann BR, Boehm BO, Marz W, Metspalu A, Price JF, Deloukas P, Korner A, Lakka TA, Keinanen-Kiukaanniemi SM, Saaristo TE, Bergman RN, Tuomilehto J, Wareham NJ, Langenberg C, Mannisto S, Franks PW, Hayward C, Vitart V, Kaprio J, Visvikis-Siest S, Balkau B, Altshuler D, Rudan I, Stumvoll M, Campbell H, van Duijn CM, Gieger C, Illig T, Ferrucci L, Pedersen NL, Pramstaller PP, Boehnke M, Frayling TM, Shuldiner AR, Peyser PA, Kardia SLR, Palmer LJ, Penninx BW, Meneton P, Harris TB, Navis G, Harst PV, Smith GD, Forouhi NG, Loos RJF, Salomaa V, Soranzo N, Boomsma DI, Groop L, Tuomi T, Hofman A, Munroe PB, Gudnason V, Siscovick DS, Watkins H, Lecoeur C, Vollenweider P, Franco-Cereceda A, Eriksson P, Jarvelin MR, Stefansson K, Hamsten A, Nicholson G, Karpe F, Dermitzakis ET, Lindgren

CM, McCarthy MI, Froguel P, Kaakinen MA, Lyssenko V, Watanabe RM, Ingelsson E, Florez JC, Dupuis J, Barroso I, Morris AP, Prokopenko I, Meta-Analyses of G, Insulin-related traits C (2021) Sex-dimorphic genetic effects and novel loci for fasting glucose and insulin variability. Nat Commun 12:24.
Lamontagne J, Jalbert-Arsenault E, Pepin E, Peyot ML, Ruderman NB, Nolan CJ, Joly E, Madiraju SR, Poitout V, Prentki M (2013) Pioglitazone acutely reduces energy metabolism and insulin secretion in rats. Diabetes 62:2122-2129.
Lang P, Hasselwander S, Li HG, Xia N (2019) Effects of different diets used in diet-induced obesity models on insulin resistance and vascular dysfunction in C57BL/6 mice. Sci Rep-Uk 9.
LaPier TL, Swislocki AL, Clark RJ, Rodnick KJ (2001) Voluntary running improves glucose tolerance and insulin resistance in female spontaneously hypertensive rats. Am J Hypertens 14:708-715.
Laredo SA, Steinman MQ, Robles CF, Ferrer E, Ragen BJ, Trainor BC (2015) Effects of defeat stress on behavioral flexibility in males and females: modulation by the mu-opioid receptor. Eur J Neurosci 41:434-441.
Laskowski ER (2012) The role of exercise in the treatment of obesity. PM R 4:840-844; quiz 844.
Latour MG, Shinoda M, Lavoie JM (2001) Metabolic effects of physical training in ovariectomized and hyperestrogenic rats. J Appl Physiol (1985) 90:235-241.
Lavagnino L, Arnone D, Cao B, Soares JC, Selvaraj S (2016) Inhibitory control in obesity and binge eating disorder: A systematic review and meta-analysis of neurocognitive and neuroimaging studies. Neurosci Biobehav Rev 68:714-726.
Le Roy CI, Bowyer RCE, Castillo-Fernandez JE, Pallister T, Menni C, Steves CJ, Berry SE, Spector TD, Bell JT (2019) Dissecting the role of the gut microbiota and diet on visceral fat mass accumulation. Sci Rep 9:9758.
Lean ME, Malkova D (2016) Altered gut and adipose tissue hormones in overweight and obese individuals: cause or consequence? Int J Obes (Lond) 40:622-632.
Lee MH, Vogrin S, Paldus B, Jayawardene D, Jones HM, McAuley SA, Obeyesekere V, Gooley J, La Gerche A, MacIsaac RJ, Sundararajan V, Jenkins AJ, Ward GM, O'Neal DN (2020) Glucose and Counterregulatory Responses to Exercise in Adults With Type 1 Diabetes and Impaired Awareness of Hypoglycemia Using Closed-Loop Insulin Delivery: A Randomized Crossover Study. Diabetes Care 43:480-483.
Lenz KM, Nugent BM, McCarthy MM (2012) Sexual differentiation of the rodent brain: dogma and beyond. Front Neurosci 6:26.
Levin BE, Dunn-Meynell AA, Balkan B, Keesey RE (1997) Selective breeding for diet-induced obesity and resistance in Sprague-Dawley rats. Am J Physiol 273:R725-730.
Li W, Qiu Q, Sun L, Yue L, Wang T, Li X, Xiao S (2017) Sex differences in obesity and cognitive function in a cognitively normal aging Chinese Han population. Neuropsychiatr Dis Treat 13:2405-2410.
Liang NC, Bello NT, Moran TH (2015) Wheel running reduces high-fat diet intake, preference and mu-opioid agonist stimulated intake. Behav Brain Res 284:1-10.
Lichtenstein AH, Schwab US (2000) Relationship of dietary fat to glucose metabolism. Atherosclerosis 150:227-243.
Lin KA, Choudhury KR, Rathakrishnan BG, Marks DM, Petrella JR, Doraiswamy PM, Alzheimer's Disease Neuroimaging I (2015) Marked gender differences in progression of mild cognitive impairment over 8 years. Alzheimers Dement (N Y) 1:103-110.
Little TJ, Horowitz M, Feinle-Bisset C (2007) Modulation by high-fat diets of gastrointestinal function and hormones associated with the regulation of energy intake: implications for the pathophysiology of obesity. Am J Clin Nutr 86:531-541.

Liu YP, Wilkinson LS, Robbins TW (2017) 'Waiting impulsivity' in isolation-reared and socially-reared rats: effects of amphetamine. Psychopharmacology (Berl) 234:1587-1601.
Locklear MN, Kritzer MF (2014) Assessment of the effects of sex and sex hormones on spatial cognition in adult rats using the Barnes maze. Horm Behav 66:298-308.
Looy H, Eikelboom R (1989) Wheel running, food intake, and body weight in male rats. Physiol Behav 45:403-405.
Lopez RB, Hofmann W, Wagner DD, Kelley WM, Heatherton TF (2014) Neural predictors of giving in to temptation in daily life. Psychol Sci 25:1337-1344.
Lopez RB, Milyavskaya M, Hofmann W, Heatherton TF (2016) Motivational and neural correlates of self-control of eating: A combined neuroimaging and experience sampling study in dieting female college students. Appetite 103:192-199.
Loprinzi PD, Ponce P, Zou L, Li H (2019) The Counteracting Effects of Exercise on High-Fat Diet-Induced Memory Impairment: A Systematic Review. Brain Sci 9.
Lowe CJ, Reichelt AC, Hall PA (2019) The Prefrontal Cortex and Obesity: A Health Neuroscience Perspective. Trends Cogn Sci 23:349-361.
Lukkes JL, Thompson BS, Freund N, Andersen SL (2016) The developmental inter-relationships between activity, novelty preferences, and delay discounting in male and female rats. Dev Psychobiol 58:231-242.
Lumley J, Stevenson RJ, Oaten MJ, Mahmut M, Yeomans MR (2016) Individual differences in impulsivity and their relationship to a Western-style diet. Pers Indiv Differ 97:178-185.
Lynch WJ (2006) Sex differences in vulnerability to drug self-administration. Exp Clin Psychopharmacol 14:34-41.
Lynch WJ, Roth ME, Carroll ME (2002) Biological basis of sex differences in drug abuse: preclinical and clinical studies. Psychopharmacology (Berl) 164:121-137.
MacLusky NJ, Naftolin F (1981) Sexual differentiation of the central nervous system. Science 211:1294-1302.
Madsen AN, Hansen G, Paulsen SJ, Lykkegaard K, Tang-Christensen M, Hansen HS, Levin BE, Larsen PJ, Knudsen LB, Fosgerau K, Vrang N (2010) Long-term characterization of the diet-induced obese and diet-resistant rat model: a polygenetic rat model mimicking the human obesity syndrome. J Endocrinol 206:287-296.
Madsen L, Myrmel LS, Fjaere E, Liaset B, Kristiansen K (2017) Links between Dietary Protein Sources, the Gut Microbiota, and Obesity. Front Physiol 8:1047.
Madsen MSA, Holm JB, Palleja A, Wismann P, Fabricius K, Rigbolt K, Mikkelsen M, Sommer M, Jelsing J, Nielsen HB, Vrang N, Hansen HH (2019) Metabolic and gut microbiome changes following GLP-1 or dual GLP-1/GLP-2 receptor agonist treatment in diet-induced obese mice. Sci Rep 9:15582.
Maesako M, Uemura K, Kubota M, Kuzuya A, Sasaki K, Hayashida N, Asada-Utsugi M, Watanabe K, Uemura M, Kihara T, Takahashi R, Shimohama S, Kinoshita A (2012) Exercise is more effective than diet control in preventing high fat diet-induced beta-amyloid deposition and memory deficit in amyloid precursor protein transgenic mice. J Biol Chem 287:23024-23033.
Mahmoud R, Wainwright SR, Chaiton JA, Lieblich SE, Galea LA (2016) Ovarian hormones, but not fluoxetine, impart resilience within a chronic unpredictable stress model in middle-aged female rats. Neuropharmacology 107:278-293.
Marliss EB, Vranic M (2002) Intense exercise has unique effects on both insulin release and its roles in glucoregulation: implications for diabetes. Diabetes 51 Suppl 1:S271-283.
Martin B, Pearson M, Kebejian L, Golden E, Keselman A, Bender M, Carlson O, Egan J, Ladenheim B, Cadet JL, Becker KG, Wood W, Duffy K, Vinayakumar P, Maudsley S, Mattson MP (2007) Sex-dependent metabolic, neuroendocrine, and cognitive responses to dietary energy restriction and excess. Endocrinology 148:4318-4333.

Martin CK, Johnson WD, Myers CA, Apolzan JW, Earnest CP, Thomas DM, Rood JC, Johannsen NM, Tudor-Locke C, Harris M, Hsia DS, Church TS (2019) Effect of different doses of supervised exercise on food intake, metabolism, and non-exercise physical activity: The E-MECHANIC randomized controlled trial. Am J Clin Nutr 110:583-592.
Martins C, Kulseng B, King NA, Holst JJ, Blundell JE (2010) The effects of exercise-induced weight loss on appetite-related peptides and motivation to eat. J Clin Endocrinol Metab 95:1609-1616.
Masley S, Roetzheim R, Gualtieri T (2009) Aerobic Exercise Enhances Cognitive Flexibility. J Clin Psychol Med S 16:186-193.
Matute ML, Kalkhoff RK (1973) Sex steroid influence on hepatic gluconeogenesis and glucogen formation. Endocrinology 92:762-768.
Matyi S, Jackson J, Garrett K, Deepa SS, Unnikrishnan A (2018) The effect of different levels of dietary restriction on glucose homeostasis and metabolic memory. Geroscience 40:139-149.
Mauvais-Jarvis F (2018) Gender differences in glucose homeostasis and diabetes. Physiol Behav 187:20-23.
Mauvais-Jarvis F, Clegg DJ, Hevener AL (2013) The role of estrogens in control of energy balance and glucose homeostasis. Endocr Rev 34:309-338.
McCarthy MM (1994) Molecular aspects of sexual differentiation of the rodent brain. Psychoneuroendocrinology 19:415-427.
McCarthy MM (2008) Estradiol and the developing brain. Physiol Rev 88:91-124.
McNeilly AD, Gallagher JR, Huang JT, Ashford MLJ, McCrimmon RJ (2017) High-Intensity Exercise as a Dishabituating Stimulus Restores Counterregulatory Responses in Recurrently Hypoglycemic Rodents. Diabetes 66:1696-1702.
McNeilly AD, Gao A, Hill AY, Gomersall T, Balfour DJK, Sutherland C, Stewart CA (2016) The effect of dietary intervention on the metabolic and behavioural impairments generated by short term high fat feeding in the rat. Physiol Behav 167:100-109.
McNeilly AD, Williamson R, Balfour DJ, Stewart CA, Sutherland C (2012) A high-fat-diet-induced cognitive deficit in rats that is not prevented by improving insulin sensitivity with metformin. Diabetologia 55:3061-3070.
McNeilly AD, Williamson R, Sutherland C, Balfour DJ, Stewart CA (2011) High fat feeding promotes simultaneous decline in insulin sensitivity and cognitive performance in a delayed matching and non-matching to position task. Behav Brain Res 217:134-141.
McSweeney FK, Murphy ES (2009) Sensitization and habituation regulate reinforcer effectiveness. Neurobiol Learn Mem 92:189-198.
Medic N, Ziauddeen H, Ersche KD, Farooqi IS, Bullmore ET, Nathan PJ, Ronan L, Fletcher PC (2016) Increased body mass index is associated with specific regional alterations in brain structure. Int J Obes (Lond) 40:1177-1182.
Medrikova D, Jilkova ZM, Bardova K, Janovska P, Rossmeisl M, Kopecky J (2012) Sex differences during the course of diet-induced obesity in mice: adipose tissue expandability and glycemic control. Int J Obes (Lond) 36:262-272.
Mekari S, Neyedli HF, Fraser S, O'Brien MW, Martins R, Evans K, Earle M, Aucoin R, Chiekwe J, Hollohan Q, Kimmerly DS, Dupuy O (2020) High-Intensity Interval Training Improves Cognitive Flexibility in Older Adults. Brain Sci 10.
Melzer K, Kayser B, Saris WH, Pichard C (2005) Effects of physical activity on food intake. Clin Nutr 24:885-895.
Meule A, de Zwaan M, Muller A (2017) Attentional and motor impulsivity interactively predict 'food addiction' in obese individuals. Compr Psychiatry 72:83-87.
Meyer C, Pimenta W, Woerle HJ, Van Haeften T, Szoke E, Mitrakou A, Gerich J (2006) Different mechanisms for impaired fasting glucose and impaired postprandial glucose tolerance in humans. Diabetes Care 29:1909-1914.

Meyre D, Mohamed S, Gray JC, Weafer J, MacKillop J, de Wit H (2019) Association between impulsivity traits and body mass index at the observational and genetic epidemiology level. Sci Rep 9:17583.
Mielke JG, Taghibiglou C, Liu L, Zhang Y, Jia Z, Adeli K, Wang YT (2005) A biochemical and functional characterization of diet-induced brain insulin resistance. J Neurochem 93:1568-1578.
Mischel W, Underwood B (1974) Instrumental ideation in delay of gratification. Child Dev 45:1083-1088.
Mitchell MR, Potenza MN (2015) Importance of sex differences in impulse control and addictions. Front Psychiatry 6:24.
Mobini S, Body S, Ho MY, Bradshaw CM, Szabadi E, Deakin JF, Anderson IM (2002) Effects of lesions of the orbitofrontal cortex on sensitivity to delayed and probabilistic reinforcement. Psychopharmacology (Berl) 160:290-298.
Modlinska K, Stryjek R, Pisula W (2015) Food neophobia in wild and laboratory rats (multi-strain comparison). Behav Processes 113:41-50.
Molteni R, Wu A, Vaynman S, Ying Z, Barnard RJ, Gomez-Pinilla F (2004) Exercise reverses the harmful effects of consumption of a high-fat diet on synaptic and behavioral plasticity associated to the action of brain-derived neurotrophic factor. Neuroscience 123:429-440.
Moody L, Liang J, Choi PP, Moran TH, Liang NC (2015) Wheel running decreases palatable diet preference in Sprague-Dawley rats. Physiol Behav 150:53-63.
Moore CF, Blasio A, Sabino V, Cottone P (2018) Impulsive choice does not predict binge-like eating in rats. Behav Pharmacol 29:726-731.
Moreno-Fernandez S, Garces-Rimon M, Vera G, Astier J, Landrier JF, Miguel M (2018) High Fat/High Glucose Diet Induces Metabolic Syndrome in an Experimental Rat Model. Nutrients 10.
Moss RL, McCann SM (1973) Induction of mating behavior in rats by luteinizing hormone-releasing factor. Science 181:177-179.
Murray AJ, Knight NS, Cochlin LE, McAleese S, Deacon RM, Rawlins JN, Clarke K (2009) Deterioration of physical performance and cognitive function in rats with short-term high-fat feeding. FASEB J 23:4353-4360.
Murray AJ, Woloszynowska-Fraser MU, Ansel-Bollepalli L, Cole KL, Foggetti A, Crouch B, Riedel G, Wulff P (2015) Parvalbumin-positive interneurons of the prefrontal cortex support working memory and cognitive flexibility. Sci Rep 5:16778.
Musen G, Jacobson AM, Bolo NR, Simonson DC, Shenton ME, McCartney RL, Flores VL, Hoogenboom WS (2012) Resting-state brain functional connectivity is altered in type 2 diabetes. Diabetes 61:2375-2379.
Nara M, Takahashi M, Kanda T, Shimomura Y, Kobayashi I (1997) Running exercise improves metabolic abnormalities and fat accumulation in sucrose-induced insulin-resistant rats. Obes Res 5:348-353.
Narayanaswami V, Thompson AC, Cassis LA, Bardo MT, Dwoskin LP (2013) Diet-induced obesity: dopamine transporter function, impulsivity and motivation. Int J Obes (Lond) 37:1095-1103.
Natalicchio A, Marrano N, Biondi G, Dipaola L, Spagnuolo R, Cignarelli A, Perrini S, Laviola L, Giorgino F (2020) Irisin increases the expression of anorexigenic and neurotrophic genes in mouse brain. Diabetes Metab Res Rev 36:e3238.
Noble EE, Mavanji V, Little MR, Billington CJ, Kotz CM, Wang C (2014) Exercise reduces diet-induced cognitive decline and increases hippocampal brain-derived neurotrophic factor in CA3 neurons. Neurobiol Learn Mem 114:40-50.
Norton L, Norton K, Lewis N (2012) Exercise training improves fasting glucose control. Open Access J Sports Med 3:209-214.

Nunez AA, Siegel LI, Wade GN (1980) Central effects of testosterone on food intake in male rats. Physiol Behav 24:469-471.
O'Leary TP, Savoie V, Brown RE (2011) Learning, memory and search strategies of inbred mouse strains with different visual abilities in the Barnes maze. Behav Brain Res 216:531-542.
Odum AL (2011) Delay discounting: I'm a k, you're a k. J Exp Anal Behav 96:427-439.
Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, Cavan D, Shaw JE, Makaroff LE (2017) IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract 128:40-50.
Okreglicka K (2015) Health effects of changes in the structure of dietary macronutrients intake in western societies. Rocz Panstw Zakl Hig 66:97-105.
Olster DH, Blaustein JD (1988) Progesterone facilitation of lordosis in male and female Sprague-Dawley rats following priming with estradiol pulses. Horm Behav 22:294-304.
Omar B, Pacini G, Ahren B (2012) Differential development of glucose intolerance and pancreatic islet adaptation in multiple diet induced obesity models. Nutrients 4:1367-1381.
Ouchi N, Parker JL, Lugus JJ, Walsh K (2011) Adipokines in inflammation and metabolic disease. Nat Rev Immunol 11:85-97.
Panchal SK, Brown L (2011) Rodent models for metabolic syndrome research. J Biomed Biotechnol 2011:351982.
Panfil K, Bailey C, Davis I, Mains A, Kirkpatrick K (2020) A time-based intervention to treat impulsivity in male and female rats. Behav Brain Res 379:112316.
Park HS, Park SS, Kim CJ, Shin MS, Kim TW (2019) Exercise Alleviates Cognitive Functions by Enhancing Hippocampal Insulin Signaling and Neuroplasticity in High-Fat Diet-Induced Obesity. Nutrients 11.
Patterson CM, Dunn-Meynell AA, Levin BE (2008) Three weeks of early-onset exercise prolongs obesity resistance in DIO rats after exercise cessation. Am J Physiol Regul Integr Comp Physiol 294:R290-301.
Paul DR, Novotny JA, Rumpler WV (2004) Effects of the interaction of sex and food intake on the relation between energy expenditure and body composition. Am J Clin Nutr 79:385-389.
Pedersen BK (2019) Physical activity and muscle-brain crosstalk. Nat Rev Endocrinol 15:383-392.
Pedersen BK, Febbraio MA (2012) Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat Rev Endocrinol 8:457-465.
Pedersen BK, Steensberg A, Schjerling P (2001) Muscle-derived interleukin-6: possible biological effects. J Physiol 536:329-337.
Perpina C, Segura M, Sanchez-Reales S (2017) Cognitive flexibility and decision-making in eating disorders and obesity. Eat Weight Disord 22:435-444.
Perreault L, Ma Y, Dagogo-Jack S, Horton E, Marrero D, Crandall J, Barrett-Connor E, Diabetes Prevention P (2008) Sex differences in diabetes risk and the effect of intensive lifestyle modification in the Diabetes Prevention Program. Diabetes Care 31:1416-1421.
Perry JL, Nelson SE, Anderson MM, Morgan AD, Carroll ME (2007) Impulsivity (delay discounting) for food and cocaine in male and female rats selectively bred for high and low saccharin intake. Pharmacol Biochem Behav 86:822-837.
Perry JL, Nelson SE, Carroll ME (2008a) Impulsive choice as a predictor of acquisition of IV cocaine self- administration and reinstatement of cocaine-seeking behavior in male and female rats. Exp Clin Psychopharmacol 16:165-177.
Perry JL, Stairs DJ, Bardo MT (2008b) Impulsive choice and environmental enrichment: effects of d-amphetamine and methylphenidate. Behav Brain Res 193:48-54.

Peters J, Buchel C (2011) The neural mechanisms of inter-temporal decision-making: understanding variability. Trends Cogn Sci 15:227-239.
Peterson AB, Hivick DP, Lynch WJ (2014) Dose-dependent effectiveness of wheel running to attenuate cocaine-seeking: impact of sex and estrous cycle in rats. Psychopharmacology (Berl) 231:2661-2670.
Peterson JR, Hill CC, Kirkpatrick K (2015) Measurement of impulsive choice in rats: same- and alternate-form test-retest reliability and temporal tracking. J Exp Anal Behav 103:166-179.
Pfaff D (1970) Nature of sex hormone effects on rat sex behavior: specificity of effects and individual patterns of response. J Comp Physiol Psychol 73:349-358.
Pfaff DW, Sakuma Y, Kow LM, Lee AWL, Easton A (2006) Hormonal, Neural, and Genomic Mechanisms for Female Reproductive Behaviors, Motivation, and Arousal. Knobil and Neill's Physiology of Reproduction, Vols 1 and 2, 3rd Editon 1825-1920.
Phoenix CH, Goy RW, Gerall AA, Young WC (1959) Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. Endocrinology 65:369-382.
Pitts GC (1984) Body composition in the rat: interactions of exercise, age, sex, and diet. Am J Physiol 246:R495-501.
Pomerleau M, Imbeault P, Parker T, Doucet E (2004) Effects of exercise intensity on food intake and appetite in women. Am J Clin Nutr 80:1230-1236.
Prada PO, Zecchin HG, Gasparetti AL, Torsoni MA, Ueno M, Hirata AE, Corezola do Amaral ME, Hoer NF, Boschero AC, Saad MJ (2005) Western diet modulates insulin signaling, c-Jun N-terminal kinase activity, and insulin receptor substrate-1ser307 phosphorylation in a tissue-specific fashion. Endocrinology 146:1576-1587.
Prince A, Murphy ES, Lupfer G (2020) Effects of Food Restriction and Pre-Training Length on Delay Discounting in Male Wistar Rats. Psychol Rec 70:91-98.
Quinones-Jenab V, Jenab S (2010) Progesterone attenuates cocaine-induced responses. Horm Behav 58:22-32.
Rabiee F, Lachinani L, Ghaedi S, Nasr-Esfahani MH, Megraw TL, Ghaedi K (2020) New insights into the cellular activities of Fndc5/Irisin and its signaling pathways. Cell Biosci 10:51.
Rasmussen EB, Lawyer SR, Reilly W (2010) Percent body fat is related to delay and probability discounting for food in humans. Behav Processes 83:23-30.
Raynor HA, Epstein LH (2003) The relative-reinforcing value of food under differing levels of food deprivation and restriction. Appetite 40:15-24.
Reynolds B, Ortengren A, Richards JB, de Wit H (2006) Dimensions of impulsive behavior: Personality and behavioral measures. Pers Indiv Differ 40:305-315.
Richter EA, Garetto LP, Goodman MN, Ruderman NB (1982) Muscle glucose metabolism following exercise in the rat: increased sensitivity to insulin. J Clin Invest 69:785-793.
Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, Griffin NW, Lombard V, Henrissat B, Bain JR, Muehlbauer MJ, Ilkayeva O, Semenkovich CF, Funai K, Hayashi DK, Lyle BJ, Martini MC, Ursell LK, Clemente JC, Van Treuren W, Walters WA, Knight R, Newgard CB, Heath AC, Gordon JI (2013) Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science 341:1241214.
Riou ME, Jomphe-Tremblay S, Lamothe G, Finlayson GS, Blundell JE, Decarie-Spain L, Gagnon JC, Doucet E (2019) Energy Compensation Following a Supervised Exercise Intervention in Women Living With Overweight/Obesity Is Accompanied by an Early and Sustained Decrease in Non-structured Physical Activity. Front Physiol 10:1048.
Robertson SH, Rasmussen EB (2017) Effects of a cafeteria diet on delay discounting in adolescent and adult rats: Alterations on dopaminergic sensitivity. J Psychopharmacol 31:1419-1429.

Rodriguez-Correa E, Gonzalez-Perez I, Clavel-Perez PI, Contreras-Vargas Y, Carvajal K (2020) Biochemical and nutritional overview of diet-induced metabolic syndrome models in rats: what is the best choice? Nutrition & Diabetes 10.
Rolls BJ, Rowe EA (1979) Exercise and the development and persistence of dietary obesity in male and female rats. Physiol Behav 23:241-247.
Rosch SA, Schmidt R, Luhrs M, Ehlis AC, Hesse S, Hilbert A (2020) Evidence of fNIRS-Based Prefrontal Cortex Hypoactivity in Obesity and Binge-Eating Disorder. Brain Sci 11.
Rosenfeld CS, Ferguson SA (2014) Barnes maze testing strategies with small and large rodent models. J Vis Exp e51194.
Rudnicki M, Abdifarkosh G, Rezvan O, Nwadozi E, Roudier E, Haas TL (2018) Female Mice Have Higher Angiogenesis in Perigonadal Adipose Tissue Than Males in Response to High-Fat Diet. Front Physiol 9:1452.
Russell PA (1975) Sex-Differences in Rats Response to Novelty Measured by Activity and Preference. Q J Exp Psychol 27:585-589.
Sabio G, Das M, Mora A, Zhang Z, Jun JY, Ko HJ, Barrett T, Kim JK, Davis RJ (2008) A stress signaling pathway in adipose tissue regulates hepatic insulin resistance. Science 322:1539-1543.
Sackett DA, Moschak TM, Carelli RM (2019) Prelimbic Cortical Neurons Track Preferred Reward Value and Reflect Impulsive Choice during Delay Discounting Behavior. J Neurosci 39:3108-3118.
Sadeghian A, Fathollahi Y, Javan M, Shojaei A, Kosarmadar N, Rezaei M, Mirnajafi-Zadeh J (2019) Spatial Learning and Memory in Barnes Maze Test and Synaptic Potentiation in Schaffer Collateral-CA1 Synapses of Dorsal Hippocampus in Freely Moving Rats. Basic Clin Neurosci 10:461-468.
Santollo J, Katzenellenbogen BS, Katzenellenbogen JA, Eckel LA (2010) Activation of ERalpha is necessary for estradiol's anorexigenic effect in female rats. Horm Behav 58:872-877.
Scarpace ET, Matheny M, Strehler KY, Shapiro A, Cheng KY, Tumer N, Scarpace PJ (2012) Simultaneous introduction of a novel high fat diet and wheel running induces anorexia. Physiol Behav 105:909-914.
Scarpace PJ, Matheny M, Zhang Y (2010) Wheel running eliminates high-fat preference and enhances leptin signaling in the ventral tegmental area. Physiol Behav 100:173-179.
Scheurink AJ, Ammar AA, Benthem B, van Dijk G, Sodersten PA (1999) Exercise and the regulation of energy intake. Int J Obes Relat Metab Disord 23 Suppl 3:S1-6.
Schroeder M, Shbiro L, Gelber V, Weller A (2010) Post-weaning voluntary exercise exerts long-term moderation of adiposity in males but not in females in an animal model of early-onset obesity. Horm Behav 57:496-505.
Schubert MM, Desbrow B, Sabapathy S, Leveritt M (2013) Acute exercise and subsequent energy intake. A meta-analysis. Appetite 63:92-104.
Schubert MM, Sabapathy S, Leveritt M, Desbrow B (2014) Acute exercise and hormones related to appetite regulation: a meta-analysis. Sports Med 44:387-403.
Sellaro R, Colzato LS (2017) High body mass index is associated with impaired cognitive control. Appetite 113:301-309.
Seshadri S, Wolf PA, Beiser A, Au R, McNulty K, White R, D'Agostino RB (1997) Lifetime risk of dementia and Alzheimer's disease. The impact of mortality on risk estimates in the Framingham Study. Neurology 49:1498-1504.
Shakil-Ur-Rehman S, Karimi H, Gillani SA (2017) Effects of supervised structured aerobic exercise training program on fasting blood glucose level, plasma insulin level, glycemic control, and insulin resistance in type 2 diabetes mellitus. Pak J Med Sci 33:576-580.
Shapiro A, Cheng KY, Gao Y, Seo DO, Anton S, Carter CS, Zhang Y, Tumer N, Scarpace PJ (2011) The act of voluntary wheel running reverses dietary hyperphagia and increases leptin signaling in ventral tegmental area of aged obese rats. Gerontology 57:335-342.

Shaw K, Gennat H, O'Rourke P, Del Mar C (2006) Exercise for overweight or obesity. Cochrane Database Syst Rev CD003817.
Shick SM, Wing RR, Klem ML, McGuire MT, Hill JO, Seagle H (1998) Persons successful at long-term weight loss and maintenance continue to consume a low-energy, low-fat diet. J Am Diet Assoc 98:408-413.
Shields GS, Trainor BC, Lam JC, Yonelinas AP (2016) Acute stress impairs cognitive flexibility in men, not women. Stress 19:542-546.
Sicree RA, Zimmet PZ, Dunstan DW, Cameron AJ, Welborn TA, Shaw JE (2008) Differences in height explain gender differences in the response to the oral glucose tolerance test- the AusDiab study. Diabet Med 25:296-302.
Siegel LI, Nunez AA, Wade GN (1981) Effects of androgens on dietary self-selection and carcass composition in male rats. J Comp Physiol Psychol 95:529-539.
Silverman IW (2003) Gender differences in delay of gratification: A meta-analysis. Sex Roles 49:451-463.
Sjoberg EA, Cole GG (2018) Sex Differences on the Go/No-Go Test of Inhibition. Arch Sex Behav 47:537-542.
Skrynka J, Vincent BT (2019) Hunger increases delay discounting of food and non-food rewards. Psychon Bull Rev 26:1729-1737.
Smith CL, Hantula DA (2008) Methodological considerations in the study of delay discounting in intertemporal choice: A comparison of tasks and modes. Behav Res Methods 40:940-953.
Smith E, Hay P, Campbell L, Trollor JN (2011) A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment. Obes Rev 12:740-755.
Smith KE, Mason TB, Crosby RD, Engel SG, Wonderlich SA (2019) A multimodal, naturalistic investigation of relationships between behavioral impulsivity, affect, and binge eating. Appetite 136:50-57.
Smucny J, Cornier MA, Eichman LC, Thomas EA, Bechtell JL, Tregellas JR (2012) Brain structure predicts risk for obesity. Appetite 59:859-865.
Snider TH, McGarry KG, Babin MC, Jett DA, Platoff GE, Jr., Yeung DT (2016) Acute toxicity of phorate oxon by oral gavage in the Sprague-Dawley rat. Fundam Toxicol Sci 3:195-204.
Sodersten P, Eneroth P (1981) Serum levels of oestradiol-17 beta and progesterone in relation to sexual receptivity in intact and ovariectomized rats. J Endocrinol 89:45-54.
Soeters MR, Sauerwein HP, Groener JE, Aerts JM, Ackermans MT, Glatz JF, Fliers E, Serlie MJ (2007) Gender-related differences in the metabolic response to fasting. J Clin Endocrinol Metab 92:3646-3652.
Sofis MJ, Carrillo A, Jarmolowicz DP (2017) Maintained Physical Activity Induced Changes in Delay Discounting. Behav Modif 41:499-528.
Sparks LM (2017) Exercise training response heterogeneity: physiological and molecular insights. Diabetologia 60:2329-2336.
Spierling SR, Kreisler AD, Williams CA, Fang SY, Pucci SN, Kines KT, Zorrilla EP (2018) Intermittent, extended access to preferred food leads to escalated food reinforcement and cyclic whole-body metabolism in rats: Sex differences and individual vulnerability. Physiol Behav 192:3-16.
Steele CC, Pirkle JRA, Davis IR, Kirkpatrick K (2019) Dietary effects on the determinants of food choice: Impulsive choice, discrimination, incentive motivation, preference, and liking in male rats. Appetite 136:160-172.
Steele CC, Pirkle JRA, Kirkpatrick K (2017) Diet-induced impulsivity: Effects of a high-fat and a high-sugar diet on impulsive choice in rats. PLoS One 12:e0180510.

Steenbergen L, Colzato LS (2017) Overweight and Cognitive Performance: High Body Mass Index Is Associated with Impairment in Reactive Control during Task Switching. Front Nutr 4:51.
Stewart JE, Seimon RV, Otto B, Keast RS, Clifton PM, Feinle-Bisset C (2011) Marked differences in gustatory and gastrointestinal sensitivity to oleic acid between lean and obese men. Am J Clin Nutr 93:703-711.
Stiegler P, Cunliffe A (2006) The role of diet and exercise for the maintenance of fat-free mass and resting metabolic rate during weight loss. Sports Med 36:239-262.
Stoeckel LE, Murdaugh DL, Cox JE, Cook EW, 3rd, Weller RE (2013) Greater impulsivity is associated with decreased brain activation in obese women during a delay discounting task. Brain Imaging Behav 7:116-128.
Storlien LH, Baur LA, Kriketos AD, Pan DA, Cooney GJ, Jenkins AB, Calvert GD, Campbell LV (1996) Dietary fats and insulin action. Diabetologia 39:621-631.
Stranahan AM, Norman ED, Lee K, Cutler RG, Telljohann RS, Egan JM, Mattson MP (2008) Diet-induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle-aged rats. Hippocampus 18:1085-1088.
Strickland JC, Feinstein MA, Lacy RT, Smith MA (2016) The effects of physical activity on impulsive choice: Influence of sensitivity to reinforcement amount and delay. Behav Processes 126:36-45.
Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A, Proietto J (2011) Long-term persistence of hormonal adaptations to weight loss. N Engl J Med 365:1597-1604.
Swalve N, Smethells JR, Carroll ME (2016) Progesterone attenuates impulsive action in a Go/No-Go task for sucrose pellets in female and male rats. Horm Behav 85:43-47.
Swalve N, Smethells JR, Younk R, Mitchell J, Dougen B, Carroll ME (2018) Sex-specific attenuation of impulsive action by progesterone in a go/no-go task for cocaine in rats. Psychopharmacology (Berl) 235:135-143.
Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML, Gortmaker SL (2011) The global obesity pandemic: shaped by global drivers and local environments. Lancet 378:804-814.
Tapia MA, Lee JR, Weise VN, Tamasi AM, Will MJ (2019) Sex differences in hedonic and homeostatic aspects of palatable food motivation. Behav Brain Res 359:396-400.
Tapp DN, Zerkle HL, McMurray MS (2020) Extent of food restriction affects probability but not delay-based decision-making. J Exp Anal Behav 114:179-192.
Tarnopolsky LJ, MacDougall JD, Atkinson SA, Tarnopolsky MA, Sutton JR (1990) Gender differences in substrate for endurance exercise. J Appl Physiol (1985) 68:302-308.
Tate CA, Holtz RW (1998) Gender and fat metabolism during exercise: a review. Can J Appl Physiol 23:570-582.
Tate LM, Tsai PF, Landes RD, Rettiganti M, Lefler LL (2015) Temporal discounting rates and their relation to exercise behavior in older adults. Physiol Behav 152:295-299.
Thackray AE, Deighton K, King JA, Stensel DJ (2016) Exercise, Appetite and Weight Control: Are There Differences between Men and Women? Nutrients 8.
Timper K, Denson JL, Steculorum SM, Heilinger C, Engstrom-Ruud L, Wunderlich CM, Rose-John S, Wunderlich FT, Bruning JC (2017) IL-6 Improves Energy and Glucose Homeostasis in Obesity via Enhanced Central IL-6 trans-Signaling. Cell Rep 19:267-280.
Tokuyama K, Saito M, Okuda H (1982) Effects of wheel running on food intake and weight gain of male and female rats. Physiol Behav 28:899-903.
Tokuyama K, Suzuki M (1998) Intravenous glucose tolerance test-derived glucose effectiveness in endurance-trained rats. Metabolism 47:190-194.

Trovati M, Carta Q, Cavalot F, Vitali S, Banaudi C, Lucchina PG, Fiocchi F, Emanuelli G, Lenti G (1984) Influence of physical training on blood glucose control, glucose tolerance, insulin secretion, and insulin action in non-insulin-dependent diabetic patients. Diabetes Care 7:416-420.
Ucha M, Roura-Martinez D, Contreras A, Pinto-Rivero S, Orihuel J, Ambrosio E, Higuera-Matas A (2019) Impulsive Action and Impulsive Choice Are Differentially Associated With Gene Expression Variations of the GABAA Receptor Alfa 1 Subunit and the CB1 Receptor in the Lateral and Medial Orbitofrontal Cortices. Front Behav Neurosci 13:22.
Underwood EL, Thompson LT (2016) High-fat diet impairs spatial memory and hippocampal intrinsic excitability and sex-dependently alters circulating insulin and hippocampal insulin sensitivity. Biol Sex Differ 7:9.
Ursache A, Wedin W, Tirsi A, Convit A (2012) Preliminary evidence for obesity and elevations in fasting insulin mediating associations between cortisol awakening response and hippocampal volumes and frontal atrophy. Psychoneuroendocrinology 37:1270-1276.
Valladolid-Acebes I, Stucchi P, Cano V, Fernandez-Alfonso MS, Merino B, Gil-Ortega M, Fole A, Morales L, Ruiz-Gayo M, Del Olmo N (2011) High-fat diets impair spatial learning in the radial-arm maze in mice. Neurobiol Learn Mem 95:80-85.
Vallerand AL, Lupien J, Deshaies Y, Bukowiecki LJ (1986) Intensive exercise training does not improve intravenous glucose tolerance in severely diabetic rats. Horm Metab Res 18:79-81.
van de Giessen E, la Fleur SE, Eggels L, de Bruin K, van den Brink W, Booij J (2013) High fat/carbohydrate ratio but not total energy intake induces lower striatal dopamine D2/3 receptor availability in diet-induced obesity. Int J Obes (Lond) 37:754-757.
van den Bos R, Homberg J, de Visser L (2013) A critical review of sex differences in decision-making tasks: focus on the Iowa Gambling Task. Behav Brain Res 238:95-108.
VanderBroek-Stice L, Stojek MK, Beach SRH, vanDellen MR, MacKillop J (2017) Multidimensional assessment of impulsivity in relation to obesity and food addiction. Appetite 112:59-68.
Velazquez-Sanchez C, Ferragud A, Moore CF, Everitt BJ, Sabino V, Cottone P (2014) High trait impulsivity predicts food addiction-like behavior in the rat. Neuropsychopharmacology 39:2463-2472.
Vessby B (2000) Dietary fat and insulin action in humans. Br J Nutr 83 Suppl 1:S91-96.
Vessby B, Uusitupa M, Hermansen K, Riccardi G, Rivellese AA, Tapsell LC, Nalsen C, Berglund L, Louheranta A, Rasmussen BM, Calvert GD, Maffetone A, Pedersen E, Gustafsson IB, Storlien LH, Study K (2001) Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: The KANWU Study. Diabetologia 44:312-319.
Vickers SP, Goddard S, Brammer RJ, Hutson PH, Heal DJ (2017) Investigation of impulsivity in binge-eating rats in a delay-discounting task and its prevention by the d-amphetamine prodrug, lisdexamfetamine. J Psychopharmacol 31:784-797.
Villanueva Espino LA, Silva Gomez AB, Bravo Duran DA (2020) Cognitive training increases dendritic arborization in the dorsal hippocampal CA1 and CA3 neurons of female and male Long-Evans rats. Synapse 74:e22140.
Vital P, Larrieta E, Hiriart M (2006) Sexual dimorphism in insulin sensitivity and susceptibility to develop diabetes in rats. J Endocrinol 190:425-432.
Volkow ND, Wang GJ, Telang F, Fowler JS, Goldstein RZ, Alia-Klein N, Logan J, Wong C, Thanos PK, Ma Y, Pradhan K (2009) Inverse association between BMI and prefrontal metabolic activity in healthy adults. Obesity (Silver Spring) 17:60-65.
Vuckovic MG, Li Q, Fisher B, Nacca A, Leahy RM, Walsh JP, Mukherjee J, Williams C, Jakowec MW, Petzinger GM (2010) Exercise elevates dopamine D2 receptor in a mouse model of Parkinson's disease: in vivo imaging with [(1)(8)F]fallypride. Mov Disord 25:2777-2784.

Wade GN (1972) Gonadal hormones and behavioral regulation of body weight. Physiol Behav 8:523-534.
Wade GN, Gray JM (1979) Gonadal effects on food intake and adiposity: a metabolic hypothesis. Physiol Behav 22:583-593.
Walther K, Birdsill AC, Glisky EL, Ryan L (2010) Structural brain differences and cognitive functioning related to body mass index in older females. Hum Brain Mapp 31:1052-1064.
Wang H, Wen B, Cheng J, Li H (2017a) Brain Structural Differences between Normal and Obese Adults and their Links with Lack of Perseverance, Negative Urgency, and Sensation Seeking. Sci Rep 7:40595.
Wang MZ, Marshall AT, Kirkpatrick K (2017b) Differential effects of social and novelty enrichment on individual differences in impulsivity and behavioral flexibility. Behav Brain Res 327:54-64.
Wang XT, Dvorak RD (2010) Sweet future: fluctuating blood glucose levels affect future discounting. Psychol Sci 21:183-188.
Wang XT, Reed RN, Baugh LA, Fercho KA (2018) Resource forecasting: Differential effects of glucose taste and ingestion on delay discounting and self-control. Appetite 121:101-110.
Ward ZJ, Bleich SN, Cradock AL, Barrett JL, Giles CM, Flax C, Long MW, Gortmaker SL (2019) Projected U.S. State-Level Prevalence of Adult Obesity and Severe Obesity. N Engl J Med 381:2440-2450.
Washburn RA, Honas JJ, Ptomey LT, Mayo MS, Lee J, Sullivan DK, Lambourne K, Willis EA, Donnelly JE (2015) Energy and Macronutrient Intake in the Midwest Exercise Trial 2 (MET-2). Med Sci Sports Exerc 47:1941-1949.
Wayner MJ, Rondeau DB (1976) Schedule dependent and schedule induced behavior at reduced and recovered body weight. Physiol Behav 17:325-336.
Weafer J, de Wit H (2014) Sex differences in impulsive action and impulsive choice. Addict Behav 39:1573-1579.
Wedell-Neergaard AS, Lang Lehrskov L, Christensen RH, Legaard GE, Dorph E, Larsen MK, Launbo N, Fagerlind SR, Seide SK, Nymand S, Ball M, Vinum N, Dahl CN, Henneberg M, Ried-Larsen M, Nybing JD, Christensen R, Rosenmeier JB, Karstoft K, Pedersen BK, Ellingsgaard H, Krogh-Madsen R (2019) Exercise-Induced Changes in Visceral Adipose Tissue Mass Are Regulated by IL-6 Signaling: A Randomized Controlled Trial. Cell Metab 29:844-855 e843.
Wegner M, Helmich I, Machado S, Nardi AE, Arias-Carrion O, Budde H (2014) Effects of exercise on anxiety and depression disorders: review of meta- analyses and neurobiological mechanisms. CNS Neurol Disord Drug Targets 13:1002-1014.
Weinstein A, Dannon P (2015) Is Impulsivity a Male Trait Rather than Female Trait? Exploring the Sex Difference in Impulsivity. Current Behavioral Neuroscience Reports 2:9-14.
Westbrook SR, Hankosky ER, Dwyer MR, Gulley JM (2018) Age and sex differences in behavioral flexibility, sensitivity to reward value, and risky decision-making. Behav Neurosci 132:75-87.
Westerterp KR, Goran MI (1997) Relationship between physical activity related energy expenditure and body composition: a gender difference. Int J Obes Relat Metab Disord 21:184-188.
Westerterp KR, Meijer GA, Janssen EM, Saris WH, Ten Hoor F (1992) Long-term effect of physical activity on energy balance and body composition. Br J Nutr 68:21-30.
Willette AA, Bendlin BB, Starks EJ, Birdsill AC, Johnson SC, Christian BT, Okonkwo OC, La Rue A, Hermann BP, Koscik RL, Jonaitis EM, Sager MA, Asthana S (2015) Association of Insulin Resistance With Cerebral Glucose Uptake in Late Middle-Aged Adults at Risk for Alzheimer Disease. JAMA Neurol 72:1013-1020.

Willeumier KC, Taylor DV, Amen DG (2011) Elevated BMI is associated with decreased blood flow in the prefrontal cortex using SPECT imaging in healthy adults. Obesity (Silver Spring) 19:1095-1097.
Williams LM, Campbell FM, Drew JE, Koch C, Hoggard N, Rees WD, Kamolrat T, Thi Ngo H, Steffensen IL, Gray SR, Tups A (2014) The development of diet-induced obesity and glucose intolerance in C57BL/6 mice on a high-fat diet consists of distinct phases. PLoS One 9:e106159.
Wilson CR, Tran MK, Salazar KL, Young ME, Taegtmeyer H (2007) Western diet, but not high fat diet, causes derangements of fatty acid metabolism and contractile dysfunction in the heart of Wistar rats. Biochem J 406:457-467.
Wing RR, Hill JO (2001) Successful weight loss maintenance. Annu Rev Nutr 21:323-341.
Winocur G, Greenwood CE (1999) The effects of high fat diets and environmental influences on cognitive performance in rats. Behav Brain Res 101:153-161.
Winocur G, Greenwood CE (2005) Studies of the effects of high fat diets on cognitive function in a rat model. Neurobiol Aging 26 Suppl 1:46-49.
Winocur G, Greenwood CE, Piroli GG, Grillo CA, Reznikov LR, Reagan LP, McEwen BS (2005) Memory impairment in obese Zucker rats: an investigation of cognitive function in an animal model of insulin resistance and obesity. Behav Neurosci 119:1389-1395.
Wong SK, Chin KY, Suhaimi FH, Fairus A, Ima-Nirwana S (2016) Animal models of metabolic syndrome: a review. Nutr Metab (Lond) 13:65.
Woo J, Shin KO, Park SY, Jang KS, Kang S (2013) Effects of exercise and diet change on cognition function and synaptic plasticity in high fat diet induced obese rats. Lipids Health Dis 12:144.
Wright RS, Cole AP, Ali MK, Skinner J, Whitfield KE, Mwendwa DT (2016) Examining the Influence of Measures of Adiposity on Cognitive Function in Middle Age and Older African Americans. Arch Clin Neuropsychol 31:23-28.
Xiao L, Sonne SB, Feng Q, Chen N, Xia Z, Li X, Fang Z, Zhang D, Fjaere E, Midtbo LK, Derrien M, Hugenholtz F, Tang L, Li J, Zhang J, Liu C, Hao Q, Vogel UB, Mortensen A, Kleerebezem M, Licht TR, Yang H, Wang J, Li Y, Arumugam M, Wang J, Madsen L, Kristiansen K (2017) High-fat feeding rather than obesity drives taxonomical and functional changes in the gut microbiota in mice. Microbiome 5:43.
Yang T, Xu WJ, York H, Liang NC (2017) Diet choice patterns in rodents depend on novelty of the diet, exercise, species, and sex. Physiol Behav 176:149-158.
Yang TY, Gao Z, Liang NC (2020) Sex-Dependent Wheel Running Effects on High Fat Diet Preference, Metabolic Outcomes, and Performance on the Barnes Maze in Rats. Nutrients 12.
Yang Y, Shields GS, Guo C, Liu Y (2018) Executive function performance in obesity and overweight individuals: A meta-analysis and review. Neurosci Biobehav Rev 84:225-244.
Yang Z, Chen X, Chen Y, Zhao Q (2015) Decreased irisin secretion contributes to muscle insulin resistance in high-fat diet mice. Int J Clin Exp Pathol 8:6490-6497.
Yardley JE, Sigal RJ (2015) Exercise strategies for hypoglycemia prevention in individuals with type 1 diabetes. Diabetes Spectr 28:32-38.
Yu Z, Geary N, Corwin RL (2011) Individual effects of estradiol and progesterone on food intake and body weight in ovariectomized binge rats. Physiol Behav 104:687-693.
Zhao L, Chen Y, Xia F, Abudukerimu B, Zhang W, Guo Y, Wang N, Lu Y (2018) A Glucagon-Like Peptide-1 Receptor Agonist Lowers Weight by Modulating the Structure of Gut Microbiota. Front Endocrinol (Lausanne) 9:233.
Zhou Y, Zhao M, Zhou C, Li R (2016) Sex differences in drug addiction and response to exercise intervention: From human to animal studies. Front Neuroendocrinol 40:24-41.
Zierath JR, Houseknecht KL, Gnudi L, Kahn BB (1997) High-fat feeding impairs insulin-stimulated GLUT4 recruitment via an early insulin-signaling defect. Diabetes 46:215-223.

Zucker I (1969) Hormonal Determinants of Sex Differences in Saccharin Preference, Food Intake and Body Weight. Physiology & Behavior 4:595-&.