The Utility of Behavioral Economics in Expanding the Free-Feed Model of Obesity

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Abstract

Animal models of obesity are numerous and diverse in terms of identifying specific neural and peripheral mechanisms related to obesity; however, they are limited when it comes to behavior. The standard behavioral measure of food intake in most animal models occurs in a free-feeding environment. While easy and cost-effective for the researcher, the free-feeding environment omits some of the most important features of obesity-related food consumption—namely, properties of food availability, such as effort and delay to obtaining food. Behavior economics expands behavioral measures of obesity animal models by identifying such behavioral mechanisms. First, economic demand analysis allows researchers to understand the role of effort in food procurement, and how physiological and neural mechanisms are related. Second, studies on delay discounting contribute to a growing literature that shows that sensitivity to delayed food- and food-related outcomes is likely a fundamental process of obesity. Together, these data expand the animal model in a manner that better characterizes how environmental factors influence food consumption.

Key words: behavioral economics, delay discounting, economic demand, free-feeding, obesity

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I. Animal Models

Laboratory researchers often use reductionist methods to simplify mechanisms involved in rather complex phenomena, such as medical and psychological disorders. The use of animal models is one manner in which more simple systems and behaviors, and their causes and influences, can be isolated and understood.

The most fundamental properties of animals models have been a topic of discussion for decades (e.g., see McKinney, 1977; Robbins & Sahakian, 1979; Robinson & Becker, 1986; Torjman et al., 2007). Three criteria seem to be especially relevant to psychological and health-related disorders, which often incorporate behavior: behavioral similarity, physiological similarity, and treatment sensitivity. Behavioral similarity refers to the degree to which behavior characterized by the animal model is similar to that exhibited in humans. Physiological similarity refers to underlying mechanisms that accompany the behavioral change, which are generally neural or peripheral. Treatment sensitivity would indicate the degree to which a treatment (e.g., in most cases, a drug) changes both the underlying mechanism and the behavior of interest, and the degree to which the same drugs lead to amelioration of symptoms in humans and non-humans.

Few animal models meet all three of these criteria. More often, a model will satisfy one or two of the criteria. In some rare cases, all of the criteria are met, but the causes for physiological and behavioral change are mimicked or induced by other variables. For example, it is difficult to create a model of schizophrenia in non-humans in which stereotypic behavior can be examined. However, dopaminergic compounds can be used to induce stereotypies in animals

that are in some ways similar, and, like humans, reflect dopaminergic involvement (see Geyer & Markou, 2002 for review). Nonetheless, the cumulative use of animal models in research can provide critical information that together can be used to first understand specific mechanisms, eventually leading to the development of effective treatments for diseases and disorders.

1.1 Animal Models of Obesity.

There are dozens to hundreds of animal models of obesity (Speakman, Hambly, Mitchell, & Krol, 2007; Lutz & Woods, 2012). Given that the incidence of obesity has dramatically increased in the USA and other industrialized nations in the last two to three decades (Centers for Disease Control and Prevention, 2012; National Center for Health Statistics, 2012), and because obesity is a health-related problem that involves many of the systems in the body (e.g., adiposity, pancreatic, hypothalamic), a large variety of animal models have been developed to better understand how specific systems are affected—from the molecular level to the behavioral level. This paper is not meant to review these types of models, or to comment to a great extent about the degree to which they meet the three criteria for a strong animal model. Rather, we wish to describe them to provide a general context for a central issue.

Models for obesity are generally separated into several categories, though the details of the grouping can differ from one review to another (cf. Kaiyala & Schwartz, 2011; Leibel, 2008; Schwartz et al., 2003; Lutz & Woods, 2012; Speakman et al., 2007; Woods, 2009). For the purposes of this paper, we will group them as follows:

1.1.1. Environmental models. A number of animal models use environmental conditions to induce obesity and these are usually dietary in nature, emphasizing exposure to palatable diets for specified time periods (see Speakman et al., 2007; West & York, 1998). Dietary models reflect strong ecological validity in terms of cause-and-effect relations observed in humans. One

example is the high fat diet. In this model, rodents (though, there are others—see West & York, 1998) are chronically fed either a diet high in fat or a standard nutritionally balanced diet. Rats exposed to the high-fat diet exhibit hyperphagia, which results in excessive weight gain and adiposity, compared to controls (e.g., Warwick et al., 2000; West & York, 1998; Woods et al., 2003).

The high-fat diet model appears to meet all three properties of a strong animal model of obesity. Johnson and Kenny (2010), for example, exposed basic laboratory rats for 40 days to either standard chow, an extended high-fat diet in which a diet high in fat (e.g., frosting, cheesecake, etc.) was in place for 23 hours per day, and a reduced exposure group that only received a high-fat diet for one hour per day. Rats exposed to the extended high fat diet ate 2-3 times more kcalories (kcal) than rats in the standard chow condition and gained more than twice as much weight across the 40-day period. In addition, these rats showed a 75% reduction in dopamine D₂ receptors in the striatum of the brain compared to controls and those in the reduced exposure group, both of which showed modest reductions in D₂ densities and little weight gain. Other studies have shown similar effects (Warwick et al., 2000; West & York, 1998; Woods et al., 2003).

With humans, a diet high in fat also leads to heightened caloric intake and weight gain (e.g., Lissner et al., 1987; Schrauwen & Westerterp, 2000). Moreover, imaging studies show a similar reduction of striatal dopamine D₂ receptors inversely correlated to BMI, which supports a common neurobiological mechanism (Wang et al., 2001). These data support that there is similarity between humans and rodents in terms of behavioral change by way of increased food intake and weight gain, identify at least one common neurobiological mechanism, and show that the common cause is diet related; therefore, the first two properties of a strong animal model are

met. In addition, in terms of drug sensitivity, compounds that block D₂ receptors (e.g., anti-psychotic drugs like haloperidol and olanzepine) are associated with increased caloric weight gain in rats (e.g., Cooper et al., 2005; Cooper et al., 2007) and humans (e.g., Moisan, Grégoire, Gaudet, & Cooper, 2005; Zipursky et al., 2005). Therefore, there is reasonable evidence that all three criteria for a strong animal model are met with high-fat diet.

1.1.2 Genetic models. Compared to environmental models, far more models that are genetic in nature have been developed to understand how expression of specific genes influence physiological and behavioral changes involved in obesity (Speakman et al., 2007). While genetic differences in humans generally account for less variability in obesity compared to environmental differences (especially diet), genetic models can isolate which genes control specific peptides, hormones, or receptors involved in obesity, which can lead to effective drug development that targets these systems. Genetic models can be divided into the following subcategories:

1.1.2.1. Single-gene loss of function. There are at least ten single-gene loss of function models that have been developed to characterize the extent to which variations in specific dominant and recessive allele combinations result in phenotypic differences that lead to obesity (Speakman et al., 2007). Three frequently used mouse models—all of which involve leptin impairment—are the *ob/ob*, *db/db*, and *s/s* strains (Lutz & Woods, 2012). The obese Zucker rat, which possesses the recessive *fa/fa* allele combination, is a single-gene rat model. Within three weeks of age, the *fa/fa* Zucker rat eats more, weighs more, and has higher adiposity than lean Zucker rats that possess one or two dominant lean alleles (see Beck, 2000; Sahu, 2004 for reviews; Zucker & Zucker, 1961). One of the main target impairments in the Zucker strain, as well as other single-gene models, is leptin regulation, though leptin also affects endocannabinoid

and dopaminergic regulation (both of which are also differentially affected in the Zucker rat [DiMarzo et al., 2001; Fetissov et al., 2002]). In addition to hyperphagia, these impairments are associated with alterations in sensitivity to food reinforcement (e.g., Boomhower et al., 2013; Rasmussen & Huskinson, 2008; Rasmussen et al., 2012).

1.1.2.2. Transgenic models. Transgenic models are those in which genes have been modified by either introducing new DNA or by deleting specific genes. For obesity, there are hundreds of genes that when mutated or expressed in transgenic models lead to increased body weight and adiposity (Speakman et al., 2007), and many are related to impairments in leptin or in leptin-related function. Knockout mouse models include those in which genes known to affect a specific system associated with obesity are deleted and compared to a wildtype control. Perhaps the best example is the proopiomelanocortin (POMC) model, in which the model lacks POMC or a POMC-derived peptide. POMC, which is a direct target of leptin, is a precursor to α -melanocyte-stimulating hormone (α -MSH)—a satiety hormone that reduces feeding and increases energy expenditure by activating melanocortin 3 and 4 receptors in the hypothalamus. If POMC is reduced or missing, then satiety via the α -MSH pathway is inhibited, creating a constant appetitive state (Lutz & Woods, 2012). Other knockouts, such as the POMC/AgRP and the MC4R are similar in that they target the melanocortin system.

1.1.2.3. Epigenetic and polygenic models. Research is also progressing toward more complex models of obesity. The field of epigenetics examines the degree to which environmental events influence expression of specific genes, and this has been applied to obesity. Some models focus on the perinatal environment, i.e., fetal programming. Research on gestational undernutrition, for example, suggests that prenatally undernourished organisms, when reared postnatally in conditions of food abundance, exhibit hyperphagia, larger body mass, and larger

fat cells compared to non-prenatally deprived controls (e.g., Beall et al., 2004; Jones & Friedman, 1982; Vickers, et al., 2000). Some studies, however, show that higher levels of prenatal undernutrition can lead to lean perinatal body mass (compared to controls on a standard diet) that persists to adulthood (Wakley & Rasmussen, 2009). Over-feeding pregnant dams, especially with a high-fat diet, also can lead to continuously obese offspring compared to those fed a standard prenatal diet (e.g., Levin & Govek, 1998; Sullivan et al., 2011). In addition, other areas of research examine the combined efforts of multiple genes by using molecular map markers (e.g., Dietrich et al., 1996). These types of studies that examine the influence of several factors that combine to create higher body mass and adiposity move research closer toward understanding the complexities of human obesity.

2.1 Free feeding as a behavioral dependent variable and its limitations

While animal models of obesity are numerous and diverse in terms of identifying genetic and environmental influences on physiological functions, they appear uncomplicated when it comes to behavior. One of the most important dependent variables related to obesity is food intake or caloric consumption, because it plays a direct role in increasing body mass. The most frequently used behavioral dependent variable in obesity is hyperphagia, in which food intake in the obese group is greater than the control group.

A concern about the use of hyperphagia as a main dependent variable is that it generally occurs in laboratory conditions in which food is readily available. In many of the studies using animal models of obesity, the environment is the rodent's homecage in which a large amount of food is accessible by way of a wire or mesh cage top, or a receptacle that can hold an excessive amount of food—often much more than the rodent can physically eat. The amount of food that is left over (in g) can be quantified and subtracted from what was originally offered (e.g., Becker

& Grinkler, 1977; Huszar et al., 1997; West & York, 1998; Warwick et al., 2000; Weide et al., 2003; Woods et al., 2003). The effort required for food is minimal—often just a small number of steps or the animal simply lifting its snout to the cage top.

The validity of animal models of obesity, in terms of the use of free-feeding as a model of food consumption, becomes questionable when one considers the context in which food intake takes place. A large and substantive literature shows that food intake depends highly on the extent to which food is readily available. Part of this literature is supported by epidemiological studies in which physical distance to sources of high-fat food, such as fast-food restaurants, are inversely related to rates of obesity (Davis & Carpenter, 2009; Jeffrey et al., 2006; Maddock, 2004). Similarly, studies that take place in more naturalistic human environments demonstrate that when unhealthy food is proximate, overeating occurs (Wansink et al., 2006; Wansink & Payne, 2008). Conversely, in areas where supermarkets or other food providers (e.g., food banks) offer healthier options, such as fruits and vegetables, individuals are more likely to purchase and eat healthier food and have lower levels of obesity (Hanks et al., 2012; Jeffrey et al., 1994; Martin et al., 2013; Moreland et al., 2006; Wang et al., 2007). These findings support the notion that physical proximity and availability of food influences its consumption.

Studies that focus specifically on the food choices of the individual in an experimental setting also support the idea that effort can reduce food consumption. One study by Smith and Epstein (1991) examined choices for moderately-preferred, low-calorie food vs. highly-preferred, high-calorie food in obese children. Access to the moderately-preferred food was placed under a variable ratio (VR) 2 schedule of reinforcement, in which only two responses on average were required for access to the food. For the highly preferred food, response requirements for accessing food ranged from a VR 2 to a VR 32 schedule of reinforcement.

Participants preferred to work for the highly preferred food until the response requirements were increased to the VR 16 schedule; at that point preference shifted to the less preferred food. In a similar study (Saelens & Epstein, 1996), obese and non-obese adults chose to eat food under a range of VR schedules (2 to 32) or engage in low-response cost (under a VR 2) sedentary activities. Non-obese individuals switched from food to sedentary activities when VRs increased. Obese individuals, however, were more likely to persist in earning food reinforcers with higher response requirements. This shows again that preference for food will change when accessibility increases, but there are individual differences to this sensitivity to effort.

Another factor that influences food accessibility in humans is the *monetary* cost of food. One way to quantify food cost is to examine the cost per calorie (Drewnowski, 2010). When quantified in this manner, it becomes clear that there is a disparity in food cost such that healthy food is more expensive per calorie compared to unhealthy food (Drewnowski & Darmon, 2005a; Drewnowski & Darmon, 2005b; Drewnowski, 2010). Thus, from the perspective of food accessibility, one would predict that food that is more expensive in terms of monetary price would be consumed less. It has been demonstrated that if the prices of healthy food are lowered, consumption of these foods increase (Jeffery et al., 1994; French et al., 1997). Said simply, when access to healthy, low calorie food options is costly in terms of physical effort or money, and access to high calorie, nutrient dense food is more available or less expensive, obesity is more likely.

2.1.1 *Demand*. A second literature showing a relation between food availability and consumption comes from the area of behavioral economics. One well-supported area of research describes the extent to which consumption of commodities changes as a function of price; that is, increases in price lead to predictable decreases in consumption (see Bickel & Vuchinich, 2000;

Hursh, 1980; 1984; Hursh & Silberberg, 2008). In the behavioral laboratory, animals will lever-press to produce food pellets. The number of responses required for a food pellet is varied from low to high (usually under fixed ratio (FR) schedules of reinforcement) and the degree to which consumption varies as a function of price (i.e., demand) can be characterized mathematically. Demand, the relation between consumption and price, offers a framework from which one can understand the conditions under which food consumption occurs under a range of prices, which is important to understand in the context of animal models of obesity.

The MC4R knockout is a good example. This mouse model is one in which the melanocortin-4 receptor is rendered inactive, which results in hyperphagia and obesity (Huszar et al., 1997; Weide et al., 2003). Atalayer et al (2010) tested MC4R mice in a demand procedure in which all of the daily food was earned in 23-h operant testing sessions (i.e., closed economy). They found that under low-effort conditions (i.e., FR 2), MC4R mice ate 25% more and were 60% larger in body mass compared to wildtype controls. Under higher response requirements (i.e., FR 30-50), however, MC4R mice consumed significantly *fewer* reinforcers compared to low-effort conditions and earned significantly fewer food reinforcers than wildtypes. That is, the pattern of hyperphagia observed under low effort or free feeding conditions was not only attenuated, but the differences in food consumption between the lean and obese groups were reversed by the added effort requirement.

Our laboratory also has demonstrated that predictable patterns emerge with obese Zucker (*fa/fa*) rats when food consumption requires a range of low to high response requirements (Rasmussen et al., 2010; 2012). Under free-feeding conditions, obese Zuckers eat 2-3 times more food than lean Zucker rats (Kowalski et al., 1998; Rasmussen et al., 2010); the *fa/fa* allele pattern accounts for about 92% of the variability in the free-feeding data (Rasmussen et al.,

2010). When Zucker rats (*fa/fa*) earned food pellets contingent upon a fixed number of responses (i.e. FR schedules), however, a different pattern emerged. Under low FRs (i.e., 5-50), obese rats had significantly higher food consumption than lean rats. At higher FRs (i.e., 90-300), however, there were no differences between lean and obese rats. Importantly, the *fa/fa* allele pattern contributed no more than 14% of the variability when food was consumed under the FRs, whereas the price of food (FR) accounted for *up to 85%* of the variability in food consumption. As such, hyperphagia in obese Zucker rats (*fa/fa*) can be considered the result of a low-effort environment and is attenuated in environments in which effort is required to procure food.

So far, with two animal models of obesity, food consumption is reduced as a function of response requirement, and importantly, effort requirements for food reduce the differences between obese and lean rodents. This fuller characterization of consumption patterns can elucidate the extent to which genes for obesity interact with effort in terms of producing differences in food consumption. In addition, it should be noted that these patterns of consumption under low- vs. high-effort conditions also can be easily quantified and compared between lean and obese rats using free parameters of the demand equation (Rasmussen, Reilly, Buckley, & Boomhower, 2012; Rasmussen, Reilly, & Hillman, 2010).

2.1.2. Quantification of demand and its relation to obesity. A demand curve describes the relation between consumption and price—as price increases, consumption decreases. Typically, the slope of the demand curve is negative, though it positively accelerates. Features of demand curves can be described as elastic and inelastic (Hursh, 1980; 1984). Inelasticity refers to consumption that changes very little as a function of effort requirement. Elasticity refers to a price-related reduction in consumption. For instance, consumption may remain inelastic at low fixed ratio (FR) values but become elastic at higher FR values (Hursh, 1980; Rasmussen et al.,

2010; Rasmussen et al., 2012). The point of elasticity, or unit elasticity, represents the point at which demand moves from inelastic to elastic. More technically, it is the point at which a 1% increase in price results in a 1% decrease in consumption (Hursh & Silberberg, 2008).

Demand is a particularly useful framework because one can quantify aspects of demand by fitting equations to the data (Hursh & Silberberg, 2008). The most recent model is exponential in nature (also called the essential value model) and takes the form of:

$$\log Q = \log Q_0 + k(e^{-\alpha QP} - 1) \quad (1)$$

where Q represents consumption and P represents price. The value k represents the range of reinforcers earned transformed into log units. The free parameter α represents the rate of decline in consumption as a function of price (P). The higher the α value, the more sensitive to price behavior is (and the less value it is stated to have). Q_0 is also a free parameter value and represents consumption at the lowest price.

Importantly, the exponential equation quantifies elasticity (α), a measure that is relevant to food available at higher-effort conditions. The free parameter Q_0 , on the other hand, is relevant to food available at a very low cost and may be highly relevant to conditions like free-feeding. In the context of obesity, then, these free parameter values can give detailed information about the extent to which low- and high-effort requirements for food can be quantified and compared, especially in animal models. In the Rasmussen et al. (2010) paper, for example, obese Zucker rats had significantly higher Q_0 values than lean rats, suggesting higher consumption at lower FR values. This, incidentally, was also consistent with the free-feeding data. When FR values increased, however, consumption declined in a similar manner between both groups. In other words, there were no differences in elasticity (α values).

We have also examined aspects of demand in the diet induced (DIO) model of obesity (Robertson et al., unpublished results). Here, rats were exposed to high-fat or control diets for 16 weeks; the rats exposed to high-fat diet ate 25% more kcals than rats fed standard chow and gained significantly more weight. Afterward, under a closed economy, all rats earned all of their food, and received re-exposure to their respective diets twice a week. We tested behavior under a variety of FR schedules (i.e., 5-300). Not surprisingly, consumption was greatest in both groups under low-effort conditions and declined with FR; however, there were no differences in consumption at low effort (no differences in Q_0 values) or high effort (no differences in α values) conditions. Thus, effort, whether low or high, reduced any differences in food value that were due to diet exposure.

Possible neuromechanisms. Demand procedures, when used with techniques from behavioral pharmacology, can identify potential neural mechanisms that underlie effort-based food procurement. Thus, when combined, behavioral economics and behavioral pharmacology provide a powerful framework for assessing environment and neural interactions that mediate problematic patterns of eating that may lead to obesity.

Endocannabinoids are one class of neurotransmitters that appear to be related to food intake and effort-based food consumption. DiMarzo et al. (2001) showed that higher levels of endocannabinoid, 2-AG, is related to heightened food intake in free-feeding conditions. Indeed, 2-AG levels are also higher in the obese Zucker rat (DiMarzo et al., 2001). In addition, endocannabinoids appear to also be involved in effort-related food procurement. Rasmussen and Huskinson (2008) showed that when obese and lean Zucker rats were allowed to free feed, obese Zucker rats ate 2-3 times more food than lean Zucker rats and rimonabant—a drug that blocks the endocannabinoid CB1 receptor (and also serves as an inverse agonist)—reduced free food

intake in both groups. When these same rats were required to work for food under progressive ratio schedules of reinforcement, the breakpoints (i.e. response requirement at which food no longer maintains behavior) did not differ between groups—that is, the reinforcing properties of food were similar. However, when rimonabant was administered acutely, the drug significantly reduced both groups' mean breakpoints, such that the obese Zucker rats showed greater reductions and at lower doses than the lean controls. Group differences in sensitivity to the drug suggest that disparities in the endocannabinoid system exist between the two strains and are relevant to effort-based food procurement.

A second study (Rasmussen et al., 2012) supports the findings from Rasmussen and Huskinson (2008), but used demand analysis. Obese and lean Zucker rats earned sucrose under FR schedules that varied between 5 and 300 responses. Before some sessions, rimonabant or a vehicle was acutely administered. Under vehicle, there were no differences in consumption between groups. Rimonabant, however, dose-dependently increased elasticity (α values) for food for both lean and obese Zucker rats. Across doses of rimonabant, obese rats had significantly lower elasticity values than lean rats, showing again that rimonabant unmasked neurochemical differences between lean and obese rats that were effort-related. In addition, rimonabant dose-dependently reduced Q_0 values; however, obese rats had significantly higher values than lean rats in vehicle and drug conditions. These results support other studies that show that rimonabant reduces free-food intake and extends the findings to effort-related conditions (Arnone et al., 1997; McLaughlin et al., 2003; Rowland et al., 2001).

From a pharmacological similarity standpoint, rimonabant has been shown to be effective at reducing food intake and weight in humans in randomized clinical trials (Després et al., 2005; Van Gaal et al., 2005; Pi-Sunyer et al., 2006; Christensen et al., 2007). However, rimonabant

was not approved by the FDA for use in humans as randomized clinical trials show that it slightly increases the risk of suicidal ideation (see Christensen et al., 2007; Food and Drug Administration, 2007). One interpretation of this is that while rimonabant blocks food reinforcer efficacy, it may also block the efficacy of other reinforcers, such as activity (Rasmussen & Hillman, 2011). As such, a general blocking of reinforcement may enhance depression, suicidal ideation, or suicidal attempts.

There is also evidence that suggests that dopamine (DA) in the nucleus accumbens (NAc) is a mechanism of effort-based responding (Salamone & Correa, 2012; Salamone et al., 2012). In one study, DA-depleted rats (rats that had DA in the NAc depleted via a neurotoxic lesion) and control rats were presented with choices between a preferred food available under an FR 5 schedule or a less preferred food that was freely available (Cousins & Salamone, 1994). They found that rats with DA depletion showed a preference for less preferred free-food compared to a preferred food available for a cost, whereas the control rats showed a preference for the preferred food available for a cost. In another condition, in which all rats only had access to food under an FR 5 schedule of reinforcement, both DA depleted and control rats showed similar levels of effort-dependent food consumption. Thus, when offered a choice, DA depleted rats allocated more behavior to the less effortful alternative; however, if they did not have a choice they responded in an identical fashion as controls, which indicates that the value of food was not affected by DA depletion, only the sensitivity to effort. Other studies support this finding (Aberman & Salamone, 1999; Cousins et al., 1996). Thus, DA depletions appear to make rats more sensitive to effort requirements related to food procurement. These findings are particularly interesting given that research shows prolonged exposure to a high-fat, high sugar diet leads to reductions in DA₂ receptor density (Geiger et al., 2009; Johnson & Kenny, 2010). In

addition, other research shows that individuals who are obese are also more likely to have a particular polymorphism of the DRD2 allele pattern which is associated with alterations in D₂ receptor densities and differences in sensitivities to effort-based (VR schedules) food reinforcement (Epstein, Temple, Neiderhiser, Salis, Erbe, & Leddy, 2007). To date, however, dopaminergic function in high-fat diet exposed rats, other rodent models, or humans studies that specifically examine the dopamine D₂ system have yet to be explored with effort-related tasks. More research is needed in this area.

2.1.3 Summary

For many of the existing animal models of obesity, eating behavior has been examined only in a single, low-effort context and has led researchers to conclude that obese animals are hyperphagic. However, demand procedures and analyses allow researchers to assess how food consumption changes across different effort requirements and has shown that, as effort associated with accessing food increases, eating decreases, often resulting in unimpressive differences between obese and healthy-weight controls. Moreover, similar effort-induced reductions in food consumption are observed in humans in both experimental laboratory studies and correlational studies with food environments. In these situations, consumer demand theory would predict that individuals would over consume food with lower prices (in terms of effort or money), which would lead to an obesogenic environment. Therefore, behavioral economic studies with demand expand the behavioral feature of animal models of obesity by more carefully characterizing behavioral similarity by identifying an effort-based mechanism.

Demand procedures can also be used to enhance the second and third properties of animal models. By combining techniques from behavioral pharmacology, researchers can elucidate underlying neural mechanisms that mediate effortful food procurement. Thus far,

endocannabinoids (specifically at the CB1 receptor) and DA have been implicated. In addition, relevant treatments that target these substrates can be identified and developed. Therefore, all three criteria for a strong animal model are supported with demand analyses.

3.1 Delay Discounting and Obesity

We have argued that effort is a missing feature of the free-feeding environment that may be critical in terms of modeling human behavior. Another related feature of the free-feeding environment is immediacy to food. In this type of environment, food is acquired with minimal delay. It is likely that adding a delay to the receipt of food may alter eating patterns and that individual differences in sensitivity to delay may be a mechanism of obesity.

One manner in which sensitivity to delay, a facet of impulsivity, has been tested is with delay discounting. Delay discounting is a decrease in the subjective value of a reward as delay to its receipt increases (Ainslie, 1975; Madden & Bickel, 2010; Rachlin et al., 1991). In the delay discounting paradigm, a series of choices between two outcomes is arranged: a smaller amount of an outcome delivered immediately versus a larger amount delivered after a delay (see, e.g., Madden & Johnson, 2010). A pattern of selecting the smaller, sooner option is suggestive of impulsive behavior, while consistent selection of the larger, later choice indicates a more self-controlled pattern (Madden et al., 1997). In animal research, an adjusting-delay or adjusting-amount procedure is often used to quantify impulsive choice. For the former, the subject (often a rodent) is exposed to both options in forced-choice trials and then makes choices in the free-choice trials. If the rodent chooses the larger, delayed amount in the majority of free-choice trials, the delay to the larger reward is titrated (reduced, in this case) until there is indifference between the two options (that is, 50% of the behavior is allocated to the smaller, sooner reward). The indifference point is used as a measure of impulsivity—lower indifference points refer to

greater impulsivity. Adjusting-amount procedures, in which delays are held constant while amounts of the larger, delayed outcome are manipulated are also used and allow impulsive behavior to be assessed (see Madden & Johnson, 2010).

We have examined impulsive food choice patterns using rodent models of obesity. Boomhower et al. (2013) examined differences in impulsive choice between genetically lean and obese Zucker rats. Both groups of rats were presented with a choice of receiving one sucrose pellet immediately after a standard delay of one second, or two sucrose pellets after an adjusting delay that systematically increased or decreased by one second, depending upon previous choices. Obese Zucker rats showed adjusting delays that were half as long as lean controls, suggesting obese Zuckers were more impulsive. In a separate condition, rats chose between one sucrose pellet after a 5-sec delay for the smaller reward or an adjusting delay for three sucrose pellets. More self-controlled choices were observed for both groups in the 5-sec standard delay condition compared to the 1 sec standard delay. Obese Zucker rats, however, still showed a greater sensitivity to delay, as they exhibited lower adjusting delays than lean Zuckers. In addition, both groups of rats showed a “magnitude effect”, in that adjusting delays increased for both lean and obese rats when the larger, later amount increased from two pellets to three sucrose pellets.

3.1.1. Possible neuromechanisms. The relation between delay discounting and obesity may have an underlying pharmacological mechanism related to the dopamine system, in particular the D₂ receptor. Boomhower and Rasmussen (2014) examined effects of haloperidol, a dopamine D₂ antagonist, on the discounting patterns of rats previously fed a standard chow diet versus rats fed a high-fat diet. Haloperidol dose-dependently increased impulsive choice for food in both groups of rats. However, rats fed the high-fat diet showed a greater sensitivity to the

drug. This suggests that high-fat diet, which changes dopamine D₂ receptors (Johnson & Kenny, 2010) may manifest as changes in food-related impulsivity.

3.1.2. Human discounting and obesity. The delay discounting paradigm has also been applied to humans. Here, researchers pose a series of hypothetical choices to participants in which they choose between a relatively small monetary outcome (e.g., \$10) available immediately and a larger delayed monetary outcome (e.g., \$100 in 1 day; Rachlin, 1995; Rachlin et al., 1991). Over the course of the choices, the smaller, sooner amount is adjusted incrementally to identify the point at which the individual “switches” from choosing the larger, delayed amount to choosing the smaller, sooner amount. This value, termed the *indifference point* represents the current subjective value of the larger reward. The series of choices is presented repeatedly across several different delay periods (e.g., one week, one month, six months), yielding indifference point values that typically decrease as a function of the delays (larger delays yield smaller indifference point values). The pattern of these indifference point values can be described using a hyperbolic discounting function (Mazur, 1987):

$$V = A / (1 + kD) \quad (2)$$

where, V represents the indifference point (or subjective value) of the delayed reward, A is the amount of the delayed reward, D is the delay of the reward, and k is a free parameter that quantifies the rate of decay of the reward value as delay increases, or the relative degree of discounting. In general, the value of the outcome is equal to the amount, but loses value with delay. Specifically, the hyperbolic pattern describes a steep decrease of subjective value at shorter delays and asymptotes with larger delays. Subjective value also decreases as a function of k , which represents an individual difference variable of sensitivity to delay, or impulsivity. Higher k values refer to greater sensitivity to delay, or higher impulsivity. The area under the

curve (AUC) of the discounting function is also used as an atheoretical measure of discounting; lower AUC values, which reflect a steeper discounting curve are indicative of more impulsive choice.

The repeated selection of the more impulsive choice (i.e. smaller, sooner) has been linked to a number of health-related outcomes such as drug addiction (Baker et al., 2003; Bickel & Marsh, 2001; Kirby et al., 1999; Konecky & Lawyer, 2015), gambling (Dixon et al., 2003; Petry, 2001), and obesity (Hendrickson & Rasmussen, 2013; Jarmolowicz et al., 2014; Rasmussen et al., 2010; Schlam et al., 2013; Weller et al., 2008). Because steep delay discounting is observed across a number of disorders it has been considered a trans-disease process (Bickel, et al., 2012; Bickel & Mueller, 2009). The understanding of delay discounting may prove useful in the development of treatments across a wide array of problems (Hamilton et al., 2015), in particular, obesity.

Obesity appears to be a predictor for delay discounting for money; that is obese individuals tend to discount more steeply for money than healthy-weight individuals (Jarmolowicz et al., 2014; Weller et al., 2008). There is also a growing literature that shows obese individuals are more likely to discount steeply for food (Applehans et al., 2012; Hendrickson & Rasmussen, 2013; Hendrickson et al., 2015; Rasmussen et al., 2010; Schlam et al., 2013). Schlam et al. (2013), for example, showed that a single food-choice question presented to 4-year olds predicted obesity 30 years later. Essentially, 4-year-old children were given the “marshmallow test”—a choice between one edible now (a marshmallow or cookie, though in some cases, pennies were used) vs. waiting for two edibles after a delay. Children who had difficulties waiting for the larger, delayed outcome were more likely to be obese 30 years

later than those who waited longer. Indeed, it is possible that the pattern of choosing immediate food outcomes was a lifelong pattern that increased risk of obesity in this sample.

Rasmussen et al. (2010) examined percent body fat (PBF) as a possible predictor for impulsive food choice in adults. Participants completed computerized adjusting-amount discounting tasks for hypothetical food and hypothetical money. Results revealed percent body fat was a predictor for food discounting--participants in the top quartile for percent body fat discounted food at a much steeper rate than those in the bottom quartile. This effect was domain specific, meaning that percent body fat was only a predictor for hypothetical food outcomes, but not for hypothetical money outcomes, though the monetary outcomes that were used were small (\$1-10). Similar to Rasmussen et al. (2010), Hendrickson and Rasmussen (2013) and Hendrickson et al. (2015) replicated percent body fat as a predictor for food discounting, but not for money discounting. Hendrickson et al. (2015) also observed a “magnitude effect” for both food and monetary outcomes; that is, individuals showed a greater sensitivity to delay for smaller, delayed outcomes (e.g., 8 bites in 1 hour) than for larger, delayed outcomes (e.g. 40 bites in 1 hour). These studies suggest that individuals with a higher percent body fat are more sensitive to delayed food outcomes and are more likely to exhibit impulsive choice patterns for food, but tend to be less impulsive when presented with higher, delayed food amounts relative to lower, delayed food amounts.

The data presented here suggest a number of implications. First, that whether rat or human, obese organisms tend to discount food-related outcomes at a steeper rate than lean controls. Second, human and animal data also show magnitude effects for food discounting; that is, smaller amounts of food (like money) are discounted more steeply than larger amounts of food (Boomhower et al., 2013; Hendrickson et al., 2013). Third, the data also suggest that

impulsive choice patterns are malleable. Animal studies show that specific drugs and simply increasing the delay to the smaller, sooner food outcome can result in more self-controlled food choice patterns. With humans, mindful eating can also change impulsive choice patterns (Hendrickson & Rasmussen, 2013). Using a college sample, we randomly assigned participants to one of two conditions – a 50-min mindful eating condition or a 50-min DVD control. Participants first completed baseline delay discounting tasks (using a computerized adjusting-amount procedure) for both food and money. Then, participants in both groups were also given four pieces of food (a fruit, a vegetable, a cracker, and a sweet) to sample. Participants in the DVD-based control group were told to eat the food however they wanted as they viewed a 50-min clip of a DVD about the food pyramid. Those assigned to the mindful eating group were instructed by having a researcher lead them in a 50-min mindful eating procedure, a modification of the “raisin exercise” (Kabat-Zinn, 1994). Here, the participants were instructed to deliberately attend to features of the food and their physiological responses to them in an objective manner. They also wrote down their observations to assure the researchers that the exercise was followed. The mindful group demonstrated increases in area-under-the-curve values (more self-controlled choice) for food relative to baselines. This effect was specific to food, as the money-related outcomes did not change after mindful eating. Moreover, the control group’s impulsive choice patterns for food or money did not change after viewing the DVD. This effect was replicated recently with adolescents and adults (Hendrickson & Rasmussen, under review).

4.1 Conclusions

We must carefully consider the experimental setting when conducting research on excessive consumption of reinforcers, especially those that have implications for addictive behaviors. Ahmed (2010), for example, described a validation crisis in the substance abuse

literature by identifying limitations with the experimental setting. Specifically, he identified that cocaine self-administration is inflated when a non-drug alternative is omitted from the experimental setting; he also pointed out that a single-response option is not ecologically valid in terms of representing real-world choices. Perhaps there also exists a validation crisis in obesity research by using free-feeding models as a standard procedure for measuring food intake. The free-feeding environment arranges conditions that lead to a high degree of food availability. As a result, maximal food intake is observed, which often inflates differences between lean and obese rodents.

Studies from behavioral economics offer a stronger characterization of behavior compared to free-feeding that captures aspects of food availability, namely effort-based and delay-based properties of food reinforcement. Studies from demand show strongly and repeatedly that food consumption decreases as a function of response requirement. Differences between lean and obese rats become trivial when effort is involved. Moreover, demand analysis can help identify specific neurotransmitter systems that are involved with effort-based food procurement, such as the endocannabinoid system. Requiring effort in food procurement provides a more ecologically valid model, as well, because experimental studies with humans and correlational studies with humans in the natural world add support that food consumption decreases as a function of effort-related and monetary-related cost.

Delay discounting is another area of behavioral economics that incorporates aspects of food availability, namely, delay to receipt of food. Studies consistently show that rats and humans that are obese demonstrate stronger preferences for immediate food and food-related outcomes over larger, delayed outcomes compared to lean or healthy-weight controls. These

studies also show magnitude effects across species (including humans) and that delay discounting can be changed or manipulated.

It should also be noted that animal and human studies on delay discounting for food and some studies with effort that we have mentioned (e.g., Saelens & Epstein, 1996 and Smith & Epstein, 1991) incorporate choice as part of the food environment. Choice is an inherent part of the context of eating; there is always a choice to eat or to engage in a different behavior. Moreover, when there is more than one food option available (as with most food choices), there are properties of the food options besides relative effort and delay to food that compete for behavioral allocation. These properties include relative amount, macronutrient content, palatability, freshness, and caloric content, just to name a few (see Epstein, Leddy, Temple, & Faith, 2007 for a review of these). There are also individual difference factors related to obesity that can affect behavioral allocation to food options. For example, we used the generalized matching relation to quantify sensitivity to relative amounts of food in obese and lean rats. Lean and obese Zucker rats pressed two levers under concurrent variable interval variable interval (conc VI VI) schedules of reinforcement food pellets, which programmed different reinforcer rates on each lever. We found that obese Zucker rats were highly sensitive to differences in relative amounts of food, while lean rats tended to undermatch or allocate less behavior to larger amounts of food (Buckley & Rasmussen, 2012). This sensitivity allowed obese rats to earn more food reinforcers than lean rats overall. In addition, when rats pressed levers for grain vs. sucrose flavored pellets concurrently, lean and obese rats showed stronger preference (i.e., bias) toward sucrose; however, the obese rats did not show biases that were stronger than lean rats—bias across the two groups was similar. Obese rats simply earned more pellets than lean rats (Buckley & Rasmussen, 2014). Studies on obesity which incorporate choice as part of the

procedures are critically important to understanding food as a reinforcer that varies in relation to other reinforcers.

Behavioral economics allows researchers to collaborate with those from other fields to identify relevant neurotransmitter systems and neurobiological substrates. For example, dopamine D₂ in the nucleus accumbens is likely involved in effort-based responding (Salamone et al 2012, Salamone & Correia, 2012) and striatal D₂ also changes with high-fat diet exposure (Johnson & Kenny, 2010). In addition, endocannabinoids, specifically those that activate the CB1 receptor, are involved in both low- and high-effort food-seeking behaviors (e.g. Rasmussen & Huskinson, 2008; Rasmussen et al., 2012). More studies are needed, however, that identify specific neural mechanisms that are likely involved in these types of behaviors. For example, fMRI studies that use human participants may be able to reveal activation of specific substrates during effort-based food seeking tasks. In addition, techniques used in animal studies, such as electricalphysiological measures, biochemical assays, and immunohistochemistry may reveal more about specificity than behavioral pharmacology studies, which typically identify relevant neurotransmitter systems but not necessarily specific structures.

Because animal studies from demand and delay discounting provide a fuller characterization of behavior, and they also describe what is observed in humans, they support the first property of a good animal model: behavioral similarity. In addition, behavioral pharmacological studies that employ demand and delay discounting procedures support the literature by adding studies on neurochemical substrates and pharmacological similarity of these mechanisms—two additional properties of a strong animal model. Therefore behavioral economics can expand what we know about food intake related to animal models of obesity by incorporating availability aspects of the food environment.

Finally, obesity may be relevant to the *reinforcer pathology* view of health disorders posited by Bickel et al. (2012; 2014) and Carr et al. (2011). A reinforcer pathology, usually applied to substance abuse, is one in which two behavioral characteristics are evident: one, discounting for an outcome (such as a drug, or other outcomes such as money) is particularly steep, and 2) demand for an outcome, such as a drug of abuse, is especially inelastic. One might apply aspects of this framework to obesity, which, like substance abuse, is often viewed as an addictive behavior. The data presented here suggest that obese individuals, like individuals diagnosed with substance abuse disorders, are likely to show steep delay discounting, especially with food related outcomes, which is consistent with a reinforcer pathology.

As for the second characteristic, though, demand analysis with animal models in open and closed economies does not necessarily reveal that food is more inelastic with obese organisms. Rather, food consumption is highest only in low-effort conditions. Therefore, inelasticity for food might be irrelevant to a reinforcer pathology for obese individuals. There may be a simple reason for this-- higher body mass may make high-effort food-seeking especially burdensome. While lean organisms may show greater elasticity for food simply because food has less essential value to them, obese individuals may show elasticity for food because activity toward food seeking is especially challenging. This idea is supported by a recent study from our laboratory (Peterson et al., unpublished results) in which human participants used the Food Purchasing Task (Epstein et al., 2007), a simple self-report demand task in which individuals report how many portions of their favorite food (note: this could be a low-energy or high-energy food) they would buy as a function of monetary price vs. effort-based price (stairs they would have to climb to receive it). Self-reported portions decreased as a function of monetary price and effort-related price for both obese and lean individuals, and in a

manner that was well characterized by the essential value demand equation (Hursh & Silberberg, 2008). While Epstein et al. (2007) originally found greater elasticity in women for low-energy (healthy foods) compared to obese women using the monetary price measure, we found no differences between groups for monetary price. With effort-related *stair climbing*, however, obese individuals showed greater elasticity values compared to healthy-weight individuals; that is, they reported they would “buy” fewer portions of their favorite food only when they had to engage in an effortful task. This suggests that general sensitivity to price may be differentially related to obesity. Perhaps there are at least two different types of prices (perhaps more!)—effort-based price and monetary price—that may differentially predict obesity with varying types of individuals. Further research with humans and non-humans is necessary to elucidate obesity-related behavioral processes.

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