RAT STRAIN DIFFERENCES IN BINGE EATING: IMPLICATIONS FOR GENETIC DIFFERENCES

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A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

PSYCHOLOGY- MASTER OF ARTS

2013

ABSTRACT

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Binge eating is a significantly heritable phenotype, but efforts to identify specific risk genes have fallen short. Identification of animal strain differences in risk for binge eating could highlight genetic differences across animals that can be exploited in future animal and molecular genetic research. The current study aimed to explore strain differences in risk for binge eating in Sprague-Dawley versus Wistar female rats using the Binge Eating Resistant/Binge Eating Prone model. A sample of male Sprague Dawley rats, a known low-risk group for binge eating, was included as a comparison group. A total of 83 rats (23 Wistar female, 30 Sprague-Dawley female, 30 Sprague-Dawley male) completed a protocol of intermittently administered, palatable food. Binge eating prone (BEP) and binge eating resistant (BER) rats were identified using a tertile approach. Sprague-Dawley female rats consumed the highest amount of palatable food and were more likely to be classified as BEP compared to Wistar female and Sprague-Dawley male rats. Wistar female rats were not significantly different from Sprague-Dawley male rats in their palatable food intake and tendency to be classified as BER rather than BEP. Sprague-Dawley female rats appear to be a particularly vulnerable strain for binge eating. Comparisons between this strain and others could help identify specific genetic/biological factors that differentiate this strain from lower risk strains. The opioid and dopaminergic systems, linked to binge eating in humans, are possible candidates to explore. Strain differences in these reward processes and their genetic/biological underpinnings could help increase understanding of individual differences in risk for binge eating in humans.

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Introduction

Eating disorders are significant psychological disorders that are affected by both biological and genetic factors. Of the primary eating disorders, Anorexia Nervosa (AN), Bulimia Nervosa (BN) and Binge Eating Disorder (BED), binge eating is a core feature of each disorder (Keel, Heatherton, Dorer, Joiner, & Zalta, 2006; Wade, Bergin, Tiggemann, Bulik, & Fairburn, 2006). Binge eating involves consumption of extremely large amounts of food in a short period of time while experiencing a loss of control during the episode (American Psychiatric Association [APA], 2000). In addition, binge eating is associated with elevated rates of obesity (Spitzer et al., 1993; Stice, Cameron, Killen, Hayward, & Taylor, 1999; Stice, Presnell, & Spangler, 2002) and psychopathology such as major depression (Telch & Stice, 1998).

Previous research has suggested that genetic factors may contribute to binge eating. Twin studies have shown that eating disorders are significantly heritable at around 50-83% (Klump, Bulik, Kaye, Treasure, & Tyson, 2008). Importantly, binge eating itself is also heritable with estimates ranging from 50-82% (Bulik, Sullivan, & Kendler, 1998). While these data have indicated the importance of genetic factors, molecular genetic research has been relatively inconclusive in identifying specific risk genes for binge eating. Interestingly, specific genes within the opioid/dopaminergic systems (e.g., mu-opioid receptor, dopamine D2 receptor) that contribute to reward processes have been associated with binge eating and the types of palatable food consumed during a binge episode (Davis et al., 2009). Further understanding of underlying genetic factors within these systems may help to gain increased insight into binge eating.

While findings from human studies have been helpful in further understanding binge eating, animal studies offer a unique perspective for understanding binge eating risk by providing the opportunity to study behaviors in the absence of psychosocial influences found in human

research (Klump et al., 2011). For example, body dissatisfaction and peer influences are psychosocial influences that have been shown to contribute to the development of binge eating in humans (Stice et al., 2002; Vincent & McCabe, 2000). Animals likely do not experience these same risk factors for development of binge eating, and therefore, animal models can more easily isolate biological and genetic factors that influence binge eating.

To more clearly study biological and genetic differences, animal models, particularly rodent models, frequently use genetically diverse outbred strains. Outbred rat strains start as "inbred" strains, in that the strain begins by inbreeding rats from the same strain line. However, over time, the strain multiples by breeding unrelated rats from the same strain, which serves to increase genetic heterogeneity and produce an "outbred" (rather than purely "inbred") strain. This heterogeneity within the outbred strain allows for discovery of differential phenotypes within the strain, which is similar to the diversity found in a human population. Importantly, even though an outbred strain is heterogeneous, animals within the same strain are still more similar to each other than animals of different outbred strains, since rats from the same outbred strain were bred from the same initial parental animals. Taken together, these genetic features of outbred strains allow for identification of extreme phenotypes within a strain, but also the examination of strain differences in these phenotypes.

In relation to binge eating, identifying specific outbred strains with more or less binge eating behaviors would make it possible to narrow the search for potential genetic and biological risk factors. Follow-up research could then use information on phenotypic and genetic strain differences to identify potential risk genes for binge eating. To date, however, no studies have examined strain differences in binge eating in animal models, although, several animal models of binge eating exist that would be appropriate for such investigations. One in particular is the

Binge Eating Resistant/Binge Eating Prone (BER/BEP) model, a well-established model of binge eating that has been successfully utilized in animal research (Boggiano et al., 2007; Klump et al., 2011; Oswald, Murdaugh, King, & Boggiano, 2011). The BER/BEP model does an excellent job of representing binge eating behaviors as they appear in humans, and there are several features of the model that make it ideal for studying binge eating. The BER/BEP model identifies binge eating prone and binge eating resistant rats based on intermittent, palatable food intake by examining four-hour intakes of palatable food during a 24-hour feeding test. Four-hour intakes have been shown to be a reliable time frame in which to observe binge eating behaviors in rats (Boggiano et al., 2007), and is similar to binge eating patterns observed in humans which occurs over a short period of time. The feeding tests are administered every few days which models the intermittent pattern typically seen in binge eating patterns in humans. Similar to humans, food consumed during binge episodes in binge eating prone rats is typically palatable and high fat foods (rather than chow) that lack nutritional value (Boggiano et al., 2007; Boggiano, Dorsey, Thomas, & Murdaugh, 2009; Klump et al., 2011; Oswald et al., 2011). While cognitive symptoms of binge eating are more difficult to model, research has also provided evidence that binge eating prone rats will endure painful foot-shock for the opportunity to consume palatable food (Oswald et al., 2011) showing that rats may experience a loss of control over binge eating, much like is present in humans (Klump et al., 2011). Furthermore, binge eating prone animals do not differ in their body weight when compared to binge eating resistant animals (Boggiano et al., 2007). This is similar to data showing that women with BN typically are not overweight but are of average weight. In sum, while it is difficult to model all aspects of human binge eating in an animal model, overall, the BER/BEP model has strong face validity as it is able to model many key features of binge eating behaviors as it appears in humans.

To date, all studies of the BER/BEP model have used rats from the outbred Sprague-Dawley strain, though other outbred strains have the possibility to show more or less vulnerability for binge eating. Although no studies have specifically examined strain differences in binge eating, one study examined strain differences in taste preferences of 17 liquid taste compounds (Tordoff, Alarcon, & Lawler, 2008). This study used 14 different rat strains, three of which were outbred strains (including Sprague-Dawley and Wistar), and found that the Sprague-Dawley strain had a stronger preference for the sweet compounds, and fell in the highest preference category. This provides indirect evidence that the Sprague-Dawley strain may indeed be particularly vulnerable to consumption of highly palatable food. Notably, another strain showed a lack of preference for sweet solutions; the Wistar rat strain never fell in the highest preference for the sweet compounds, suggesting that it may represent a particularly low risk strain for palatable food consumption. As previously mentioned, preference for sweetness is present in binge eating, as binge foods tend to be highly palatable food that are high-fat, high-sweet foods. This suggests that the Sprague-Dawley strain may be a particularly high-risk strain for binge eating, while the Wistar strain may be a low-risk strain that exhibits a lack of preference for sweetness and binge eating.

The aim of the current study was to examine this possibility by directly comparing binge eating proneness between 30 Sprague-Dawley rats and 23 Wistar rats phenotyped as binge eating resistant versus binge eating prone. The objective of the first aim was to examine differences in palatable food intake between Sprague-Dawley female rats and Wistar female rats during feeding tests. Like the research showing Sprague-Dawley rats having a greater preference for sweet solutions, it was predicted that the Sprague-Dawley female rats would consume a larger amount of palatable food than Wistar female rats across testing days. The second aim directly determined

if strain differences in binge eating proneness are present. Much like hypotheses about palatable food intake, it was predicted that the Sprague-Dawley female rats would exhibit higher rates of binge eating proneness compared to the Wistar female rats.

Importantly, in both analyses, female rats were examined, but a group of Sprague-Dawley male rats was also included as a comparison group. Previous research has shown that Sprague-Dawley male rats exhibit lower rates of palatable food intake and binge eating prone phenotypes than the Sprague-Dawley female rats (Klump, Racine, Hildebrandt, & Sisk, submitted). The inclusion of a male comparison group also helped determine whether the level of binge eating proneness observed in Wistar female rats fell closer to a known low-risk group, (i.e., the Sprague-Dawley male rats), or a more high-risk binge eating prone group (i.e., the Sprague-Dawley female rats).

As an exploratory aim of the study, the feeding behavior (i.e., palatable food intake and chow intake) and body weights of animals in both the binge eating prone and binge eating resistant groups from both strains were examined for potential strain differences in the nature of the binge eating prone phenotype. Previous research has shown that binge eating prone Sprague-Dawley female rats do not differ in body weight or daily chow intake from the binge eating resistant Sprague-Dawley female rats on feeding test days or non-feeding test days (Boggiano et al., 2007). By contrast, the feeding behaviors of Sprague-Dawley male rats are more complicated. While the male Sprague-Dawley BER/BEP animals do not differ in their body weight, there is a difference in their chow intake on feeding test days. Binge eating prone male rats consume less chow than the binge eating resistant male rats, suggesting that they may be compensating for over eating palatable on food by decreasing their chow intake (i.e., they replace part of their chow intake with the palatable food) (Klump et al., submitted). These

findings provide more evidence of strain differences in the nature of binge eating prone phenotype across groups.

Method

Animals

A convenience sample of 83 animals of both the Sprague-Dawley and Wistar strains were obtained for the study. Sixty Sprague-Dawley rats (females, n = 30, males, n=30) were obtained on approximately postnatal day 60 from Harlan (Madison, Wisconsin). Twenty-three female Wistar rats were also obtained from Dr. James Galligan (Department of Pharmacology and Toxicology, MSU) on approximately postnatal day 46-53. Importantly, this Wistar rat group was comprised of both wild-type animals (n=12) and serotonin transporter knock-out animals (n=11). All animals were exposed to the BER/BEP model as part of a larger study aiming to examine differences in binge eating proneness between wild-type and serotonin knock-out Wistar female rats. Analyses showed no significant differences in palatable food intake between the wild-type and knock-out Wistar rat groups suggesting that removal of this serotonin the serotonin transporter was not important for binge eating behaviors (see Table 1). Therefore, all Wistar rats were combined into one group to allow for examination of strain differences in binge eating.

The animals were individually housed in clear plexiglass cages (45 x 23 x 21 cm) that were outfitted with a wire cage lid. The animals were given ad lib access to both chow (Rodent diet 8640; Harlan Teklad Global Diets, Madison, WI) and water. Temperature was held at 21 ± 2ºC, and the room was on a light cycle allowing for 12 hours of light, and 12 hours of dark (on at 2400h, off at 1200h). Animals were treated in accordance with the *NIH Guide for the Care and Use of Laboratory Animals,* and all protocols were approved by the Michigan State University Institutional Animal Care and Use Committee.

Experimental Design

The study design followed the well-established Binge Eating Resistant/Binge Eating Prone (BER/BEP) model of binge eating (Boggiano et al., 2007; Oswald et al., 2011), with modifications to feeding test frequency. Instead of the tests being administered 1-2 times per week for two weeks (Boggiano et al., 2007), the current study administered feeding tests three times per week (Monday, Wednesday, and Friday) over the course of two weeks. This is a modification that has been used previously in our lab (Klump et al., 2011; Klump et al., submitted) and has been useful for generating more feeding test data for determining binge eating status. Administering feeding tests three times per week showed highly similar results to those observed in other studies of the BER/BEP model (Boggiano et al., 2007).

Animals were run in three different cohorts to accommodate the collection of palatable food, chow, and body weight measurements under the time constraints (see Table 2 for a breakdown of sample sizes in each cohort). A total of seven identical feeding tests were done, though only six will be included in data analyses. During testing of the first cohort, there was a malfunction with the air conditioning resulting in high temperatures that may have affected the data from feeding test 3. I therefore excluded data from this feeding test for Cohort 1. To account for the uneven number of tests across cohorts, I subsequently removed feeding test 3 data from Cohorts 2 and Cohort 3 as well.

Each day prior to dark onset (1200h), daily body weight and chow measurements were recorded. Chow was in pellet form to make locating spillage in the bedding easier. Any spillage detected after searching the bedding was added to the chow measurement. All body weight and chow measurements were taken to the nearest tenth of a gram using an electronic scale.

On feeding test days, the rats had ad lib access to chow, water, and palatable food for the entirety of the feeding test (24 hours). Feeding tests began at 1200h when 50-80 grams of new chow were added to the cage, and 15-25 grams of palatable food (i.e., Betty Crocker Creamy Vanilla Frosting, General Mills Inc., Minneapolis, MN) were placed in small Petri dishes. The palatable food dish was hung inside the cage via wire hook and was left in position for the full 24 hours of the feeding tests. Both chow and palatable food were weighed at the 1, 4, and 24-hour time points using the same weighing and rounding cutoffs described above. The feeding tests were administered identically each time following the same procedures described.

Data Analyses

Data Preparation. In order to account for differences in body weight/size across sex and possibly strain, palatable food and chow intakes were standardized (intake(g)/body weight(g)$^{2/3}$) by body weight prior to analyses.

Strain Differences in Palatable Food Intake. A one-way analysis of variance (ANOVA) with Tukey's post hoc t-tests was used to examine mean differences in palatable food intake across the three study groups (e.g., Wistar females, Sprague-Dawley females, and Sprague-Dawley male rats) at the 1-hour, 4-hour, and 24-hour time points.

Strain Differences in Proportion of Binge Eating Resistant and Binge Eating Prone Groups. Using methods established by Boggiano et al. (2007) and Klump et al. (2011), animals were identified as binge eating resistant (BER) or binge eating prone (BEP) by examining the 4-hour time point of palatable food across the six feeding tests. The 4-hour food intake measurement in particular has been used in previous studies using the BER/BEP model and has proven to be an accurate measurement of binge eating (Boggiano et al., 2007; Klump et al., 2011; Oswald et al., 2011). Animals scoring in the top tertile a majority of the time, and never

falling in the bottom tertile, were classified as binge eating prone. Conversely, animals scoring in the bottom tertile the majority of the time, and never falling in the top tertile, were classified as binge eating resistant. It is important to note that by using this categorical method, some animals may not meet these classification requirements and therefore, are excluded from categorical analyses. A classification for what is used as the majority of feeding tests has varied across previous studies. Some have required three out of six, four out of six, and five out of six feeding tests of scoring in the top or bottom tertile to determine BEP/BER status respectively (Klump et al., 2011, Klump et al., submitted). All three classifications were used to explore whether strain differences were present across all classifications or just some classifications. The tertiles for determining BER/BEP groups were calculated using a combined total group (all animals from both strains) in order to assign BER/BEP status.

Previous studies have compared the proportion of binge eating resistant and binge eating prone categorical phenotypes using chi-squares analyses. These differences were explored here using 2 (BER/BEP) x 3 (strain group) chi-square tests followed by two-proportion z-tests to compare the proportion of binge eating resistant versus binge eating prone phenotypes across Wistar female, Sprague-Dawley female, and Sprague-Dawley male rats. However, given the small sample size in the Wistar group, and due to the BER/BEP categorical approach, which excludes some animals from analyses, a continuous BER/BEP variable approach was also used. This approach uses a binge eating prone "count" variable that counts the number of times each rat scored in the highest tertile (i.e., highest PF intake) across the six feeding tests (score range 0-6). Likewise, a binge eating resistant count variable was calculated using the number of times each rat scored in the lowest tertile (i.e., lowest PF intake) during the six feeding tests (score range 0-6). Importantly, this allows for the inclusion all animals in analyses. A one-way

ANOVA with Tukey's post hoc t-tests will be used to compare the average count variable across both strain and sex.

Exploratory Analyses - Strain Differences in the Nature of Binge Eating Resistant and Binge Eating Prone Groups. The feeding behavior and body weights of animals in the binge eating prone and binge eating resistant categories from the Sprague-Dawley and Wistar strains were examined for potential strain differences in the nature of the binge eating prone phenotype. Specifically, I used multiple regression to examine whether strain type (Wistar versus Sprague-Dawley) interacts with the binge eating prone or binge eating resistant phenotypes to predict palatable food intake, chow intake, and body weights. Analyses were conducted separately for feeding test versus non-feeding test days.

Results

Strain Differences in Palatable Food Intake. Results from ANVOAs examining mean differences in palatable food intake across study groups (e.g., Wistar female rats, Sprague-Dawley female rats, and Sprague-Dawley male rats) are summarized in Table 3[1]. Findings suggested that there were significant differences across groups, with Sprague-Dawley female rats consuming significantly higher amounts of palatable food across all time points (i.e., 1-hour, 4-hour, and 24-hours). Although Wistar female and Sprague-Dawley male rats consistently consumed lower amounts of palatable food than the Sprague-Dawley females, differences between the two groups varied depending upon the time frame examined (e.g., Wistar females consumed significantly less palatable food at the 1-hour time point than Sprague Dawley males, whereas Sprague Dawley males consumed significantly less at 24 hours). Nonetheless, overall,

[1] Aim 1 and aim 2 analyses were also run excluding serotonin knock-out Wistar rats. Results from these analyses showed the same patterns indicating no specific influences of the knock-out animals on study results (data not shown).

results were remarkably consistent in suggesting medium-to-large differences (see effect sizes – Table 3) in palatable food intake between the Sprague Dawley female and both the Wistar female and Sprague-Dawley male groups.

Strain Differences in the Proportion of Binge Eating Resistant and Binge Eating Prone Groups. Using a categorical approach, animals were classified as binge eating prone or binge eating resistant using the 3/6, 4/6, and 5/6 feeding test classifications. Across all classifications, chi-square tests indicated significant differences in the proportion of binge eating prone versus binge eating resistant rats across rat strain (3/6 classification: χ^2 [2, N = 34] = 26.41, p < .001; 4/6 classification: χ^2 [2, N = 25] = 25.00, p < .001; 5/6 classification: χ^2 [2, N = 14] = 14.00, p < .001). Follow-up z-tests showed that there was a significantly higher proportion of binge eating prone animals, and a lower proportion of binge eating resistant animals, in the Sprague-Dawley female rats as compared to all other groups (see Table 4). By contrast, the Sprague-Dawley male rats and Wistar female rats produced the opposite results, with more binge eating resistant, and fewer binge eating prone, phenotypes compared to the Sprague-Dawley female rats. Very similar results were obtained in the ANOVAs examining the binge eating proneness/resistance count variable (see Table 5). Binge eating prone tertile counts were significantly higher in the Sprague-Dawley female rats, while binge eating resistant counts were significantly higher in the Sprague-Dawley male and Wistar female rats (all *p's* < 001).

Exploratory Analyses - Strain Differences in the Nature of Binge Eating Resistant and Binge Eating Prone Groups. Results from the regression testing whether strain group (i.e., Sprague-Dawley female rats, Sprague-Dawley male rats, and Wistar female rats) and binge group (binge eating resistant vs. binge eating prone) affected differences in chow intake,

palatable food intake, or body weight are presented in Table 6. Because no Wistar female rats were categorized as binge eating prone (see above), here, the focus was on the BER/BEP tertile count variable instead of the BER/BEP categorical groupings. Notably, the binge eating resistant tertile count x strain group and binge eating prone tertile count x strain group interactions were of most interest in these analyses, since the interactions directly test whether differences in the nature of the BER/BEP phenotypes (e.g., chow intake, body weight, or palatable food intake) are present across strains.

As expected, the pattern of results for main effects was largely consistent with prior ANOVA findings in the full sample of rats. There were significant main effects of strain group for chow intake and body weight ($p < .001$) (see Table 6), with the male Sprague-Dawley rats consuming more chow and weighing more than the other two groups ($p < .001$). Additionally, animals with greater binge eating prone counts showed higher consumption of palatable food ($p's < .01$) and animals with more binge eating resistant counts showed lower palatable food consumption ($p's < .01$). There were no significant main effects of BER/BEP counts on chow intake, with the exception that binge eating prone counts were positively associated with 4-hour chow intake. Importantly, there were no significant tertile count x strain group interactions for palatable food, chow intake, or body weight suggesting that levels of chow intake and palatable food intake did not differ significantly between binge eating prone counts or the binge eating resistant counts from each group.

Discussion

This was the first study to examine rat strain differences in binge eating proneness. Results supported hypotheses that the Sprague-Dawley female strain is a particularly vulnerable strain to binge eating behaviors while the Wistar female rat strain is particularly resistant to

binge eating. Furthermore, the Wistar female strain is similar to a previously determined low-risk strain for binge eating, the Sprague-Dawley males. Importantly, there were no differences in the nature of the binge eating prone phenotype in regards to palatable food or chow intake. These significant results provide evidence that differences in binge eating expand beyond sex differences, such that animals differing in genetic backgrounds (rather than just sex) differ in their propensity to binge eat.

Previous research has been relatively inconclusive in identifying specific genes for binge eating in humans. Exploration of possible genetic differences between the Wistar and Sprague-Dawley rat strains may provide insight into underlying genetic mechanisms that could be fruitfully exploited in future human work. Promising candidates include genes within the opioid and dopaminergic systems that underlie reward processes. Intake of palatable food, much like the ingestion of substances of abuse, has been linked to these reward processes in both animal and human work (Berridge, 2009). Indeed, previous research has focused on how the opioid and dopaminergic systems differentially promote increased "liking" (i.e., a hedonic response when consuming palatable food associated with opioid system) versus "wanting" (i.e., the motivation to seek a reward associated with the dopaminergic system) of rewarding stimuli, including palatable foods (Berridge, 2009). Importantly, increased "liking" and "wanting" in response to palatable food has been found in individuals who binge eat as compared to controls, and specific opioid genes (e.g., the mu-opioid receptor gene) have been linked to hedonic "liking" in binge eaters (Davis et al., 2009). Taken together, these data suggest that increased liking and wanting of palatable food could lead to increased risk for binge eating in humans, binge eating prone rats, and furthermore, Sprague-Dawley female rats in general. New pharmacological research showing significant reductions in liking responses to sweet food in binge eaters following mu-

opioid receptor antagonist administration add further support for this hypothesis (Ziauddeen et al., 2012).

Research has isolated the nucleus accumbens as a key brain area for these liking and wanting signals in response to palatable food (Berridge, 2009; Stice, Spoor, Ng, & Zald, 2009). Moreover, this increased activation of the nucleus accumbens in response to palatable food has been shown in women who binge eat (Wang et al., 2012). Critically, preliminary research also suggests increased activation of the nucleus accumbens in binge eating prone rats. Binge eating prone Sprague-Dawley female rats showed increased activation in the nucleus accumbens core and shell in response to palatable food as compared to binge eating resistant rats (Gradl, Klump, & Sisk, in preparation). Translating this information to strain differences, it is possible that Sprague-Dawley females' heightened sensitivity to the rewarding properties of palatable food in the nucleus accumbens contributes to their increased rates of binge eating prone phenotypes. Moreover, strain differences in these phenotypes and brain activation patterns could result from risk genes/variants within the opioid and dopamine systems that differentiate the Sprague-Dawley females from other rat strains (e.g., Wistars). Future research should examine if liking, wanting, and their underlying neurobiological processes contribute to binge eating prone phenotypes and the overall increased vulnerability of the Sprague-Dawley female rats.

Importantly, the current study also found Wistar female rats to be a particularly resistant group to binge eating. Despite ad lib access to palatable food during feeding tests, a substance generally preferred by all rats, the Wistar female rats consistently consumed small amounts across the study. Further exploration of the Wistar female rat strain could increase understanding of mechanisms underlying the resistance to binge eating observed in some eating disorders (e.g., anorexia nervosa (AN), restricting subtype). The AN restricting subtype is characterized by low

body weight and caloric restriction in the absence of binge eating (APA, 2000). Currently, there is one predominant animal model of these restricting eating disorders which is the Activity Based Anorexia (ABA) model. This model uses of a protocol of restricted food and ad lib running wheel access to categorize animals as “prone” or “resistant” to activity based anorexia. Prone and resistant classifications are based on body weight that is lost across the study period (Dixon, Ackert, & Eckel, 2003). For example, those rats losing a large amount of body weight within first few study days are classified as prone and vice versa for resistant. Animals who are more prone to activity based anorexia have increased running wheel activity despite their severe weight loss (Dixon et al., 2003). While a range of behavioral data (e.g., food intake, running wheel activity) can be collected, ABA only models one aspect of the restricting AN disorder – weight loss in the presence of food restriction and exercise. Several other key behaviors make up this disorder, including a resistance to developing binge eating, even in the presence of access to palatable food and extreme dietary restriction. By utilizing the Wistar female rat strain, the binge eating resistance component of AN could be further elucidated. Moreover, it would be interesting to combine the two models by incorporating access to palatable food into the ABA model (i.e., Do ABA prone rats binge eat when exposed to palatable food?) and food restriction/activity levels into the BER/BEP model (i.e., Do BER rats run excessively in response to food intake?). Specifically, examination of activity levels in the BER/BEP model context could further differentiate possible strain differences in a model of compensatory behaviors between the prone Sprague-Dawley female and Wistar female rat strains.

The current study was not without its limitations. First, the sample size was small across all strain groups. The use of both categorical and continuous variables partially addressed this limitation. The categorical approach used more stringent criteria for phenotypic binge eating

prone and binge eating resistant classifications, while the continuous approach increased statistical power by including all animals in analyses. Nonetheless, it would be important to replicate these results with larger sample sizes.

Second, although the binge eating prone/binge eating resistant model powerfully evaluates overconsumption of palatable food in binge eating, it is unable to model the cognitive aspects of binge eating common in clinical eating disorders (e.g., weight and shape concerns, loss of control over eating). Although data suggest that some of these cognitive features may be present (e.g., foot shock experiments that are suggestive of a loss of control over eating in binge eating prone rats; see Oswald et al., 2011), more data are needed to further examine this possibility. Finally, this naturalistic study only describes strain differences in behavior; underlying, neurobiological mechanisms of effects were not explored. Future research should examine potentially influential mechanisms, such as opioid and dopaminergic modulation of reward processes. These mechanisms might contribute to strain differences in the BER/BEP model and, in turn, this knowledge could be used to significantly increase the understanding of risk for binge eating in humans.

APPENDIX

Table 1

Means, Standard Deviations, and Effect Sizes for 1-hour, 4-hour, and 24-hour Palatable Food Intake

	Mean (Standard Deviation)			
Time	Wistar WT	Wistar KO	*p*	Cohen's *d*
1-hour	.08 (.02)	.08 (.02)	0.64	0
4-hour	.23 (.02)	.22 (.03)	0.12	0.39
24-hour	.39 (.04)	.36 (.03)	0.65	0.85

Note. WT = wild type; KO = knock out

Table 2
Sample Size of Rat Strains by Gender and Cohort

	Cohort 1 (N = 30)	Cohort 2 (N = 42)	Cohort 3 (N = 11)
Sprague-Dawley Female	15 (50%)	13 (30%)	2 (18%)
Sprague-Dawley Male	15 (50%)	12 (29%)	3 (27%)
Wistar Female	0 (0%)	17 (41%)	6 (55%)

Note. Values are Ns for each group and the percent total of each cohort.

Table 3

Means, and Standard Deviations, Effect Sizes, and ANOVA for 1-hour, 4-hour, and 24-hour Palatable Food Intake

	Mean (Standard Deviation)				ANOVA
Time	Sprague-Dawley Females	Sprague-Dawley Males	Wistar Females	Cohen's *d*	*F*(df,df,)
1-hour	.14 (.03)[a]	.12 (.03)[b]	.08 (.02)[c]	0.66-2.26	27.23 (2,82)***
4-hour	.30 (.05)[a]	.22 (.04)[b]	.23 (.03)[b]	1.80	34.69 (2,82)***
24-hour	.42 (.04)[a]	.30 (.05)[b]	.38 (.04)[c]	0.95-2.66	57.82 (2,82)***

Note. Cohen's *d* = medium to large effect sizes. Superscripts of different values denote significant differences between groups at $p < .001$.

***$p < .001$

Table 4

Differences in the Proportion of Categorical BER and BEP Phenotypes Using Combined Group Tertiles (N = 83 rats, 30 Sprague-Dawley Female, 30 Sprague-Dawley Male, 23 Wistar Female)

Status	Sprague-Dawley Female	Sprague-Dawley Male	Wistar Female
		3/6 tertile classification (50%)	
BER	1 (3%)[a]	8 (27%)[b]	5 (22%)[b]
BEP	19 (63%)[a]	1 (3%)[b]	0 (0%)[b]
		4/6 tertile classification (67%)	
BER	0 (0%)[a]	6 (20%)[b]	4 (17%)[b]
BEP	15 (50%)[a]	0 (0%)[b]	0 (0%)[b]
		5/6 tertile classification (83%)	
BER	0 (0%)[a]	6 (20%)[b]	1 (4%)[a]
BEP	7 (23%)[a]	0 (0%)[b]	0 (0%)[b]

Note. Superscripts of different values denote significant differences at $p < .001$.

Table 5

Means, and Standard Deviations, and ANOVA for BER/BEP Counts Based on 4-hr Combined Group Tertiles

	Mean (Standard Deviation)			ANOVA
Status	Sprague-Dawley Females	Sprague-Dawley Males	Wistar Females	*F*(df,df)
BER	0.57 (1.04)[a]	3.07 (1.72)[b]	2.43 (1.27)[b]	26.19 (2,82)***
BEP	3.27 (1.76)[a]	1.30 (1.21)[b]	1.17 (.94)[b]	20.73 (2,82)***

Note. Superscripts of different values denotes significant differences at $p < .001$.

***$p < .001$

Table 6

Results from Multiple Regressions Examining the Influence of BER/BEP Count and Strain Group on Chow Intake, Body Weight, and Palatable Food Intake

BER Count Models				BEP Count Models			
	B (SE)	*t*	*p*		B (SE)	*t*	*p*
Chow 4-HR FT (R^2 =.70)				**Chow 4-HR FT** (R^2 = .78)			
BER Count	-.01 (.01)	-2.49	.02	BEP Count	.03 (.01)	3.87	<.001
Wistar – SD (F)	.06 (.01)	4.49	<.001	Wistar – SD (F)	.05 (.01)	5.00	<.001
Wistar – SD (M)	.11 (.01)	10.35	<.001	Wistar – SD (M)	.10 (.01)	9.90	<.001
Wistar – SD (F) * BER Count	-.01 (.01)	-.92	.36	Wistar – SD (F) * BEP Count	-.01 (.01)	-.99	.33
Wistar – SD (M) * BER Count	.01 (.01)	1.83	.07	Wistar – SD (M) * BEP Count	-.02 (.01)	-1.98	.05
Chow NFT (R^2= .66)				**Chow NFT** (R^2 = .69)			
BER Count	.003 (.01)	.49	.63	BEP Count	.002 (.00)	.26	.79
Wistar – SD (F)	.02 (.01)	1.82	.07	Wistar – SD (F)	.02 (.01)	1.53	.13
Wistar – SD (M)	.09 (.01)	9.17	<.001	Wistar – SD (M)	.09 (.01)	8.57	<.001
Wistar – SD (F) * BER Count	.01 (.01)	1.17	.24	Wistar – SD (F) * BEP Count	-.01 (.01)	-1.65	.10
Wistar – SD (M) * BER Count	-.002 (.01)	-.39	.70	Wistar – SD (M) * BEP Count	.002 (.01)	.28	.78
BW FT (R^2=.94)				**BW FT** (R^2 = .94)			
BER Count	-1.61 (2.39)	-.68	.50	BEP Count	-3.23 (3.24)	-1.00	.32
Wistar – SD (F)	21.04 (5.47)	3.85	<.001	Wistar – SD (F)	24.43 (5.10)	4.79	<.001
Wistar – SD (M)	123.23 (4.23)	27.85	<.001	Wistar – SD (M)	126.73 (4.94)	25.64	<.001
Wistar – SD (F) * BER Count	2.07 (3.50)	.59	.56	Wistar – SD (F) * BEP Count	2.67 (3.57)	.75	.47
Wistar – SD (M) * BER Count	1.23 (2.85)	.43	.67	Wistar – SD (M) * BEP Count	4.13 (3.90)	1.06	.29
BW NFT (R^2 =.94)				**BW NFT** (R^2 = .94)			
BER Count	-2.00 (2.56)	-.85	.40	BEP Count	-2.86 (3.20)	-.89	.38
Wistar – SD (F)	20.25 (5.40)	3.75	<.001	Wistar – SD (F)	23.91 (5.04)	4.74	<.001
Wistar – SD (M)	121.90 (4.36)	27.96	<.001	Wistar – SD (M)	125.36 (4.89)	25.65	<.001
Wistar – SD (F) * BER Count	2.06 (3.45)	.60	.55	Wistar – SD (F) * BEP Count	2.41 (3.53)	.68	.50
Wistar – SD (M) * BER Count	1.89 (2.80)	.68	.50	Wistar – SD (M) * BEP Count	3.43 (3.86)	.89	.38

Table 6 (cont'd)

PF 4-hour (R^2 = .76)				**PF 4-hour** (R^2 = .84)			
BER Count	-.02 (.00)	-4.03	<.001	BEP Count	.02 (.01)	4.64	<.001
Wistar – SD (F)	.02 (.01)	2.37	.02	Wistar – SD (F)	.02 (.01)	2.67	<.01
Wistar – SD (M)	.01 (.01)	.67	.51	Wistar – SD (M)	-.01 (.01)	-1.26	.21
Wistar – SD (F) * BER Count	-.01 (.01)	-1.24	.22	Wistar – SD (F) * BEP Count	.002 (.01)	.38	.71
Wistar – SD (M) * BER Count	-.002 (.01)	-.31	.76	Wistar – SD (M) * BEP Count	.002 (.01)	.32	.75
PF 24-hour (R^2 = .77)				**PF 24-hour** (R^2 = .77)			
BER Count	-.02 (.01)	-3.72	.002	BEP Count	.02 (.01)	2.64	.01
Wistar – SD (F)	.01 (.01)	.39	.70	Wistar – SD (F)	-.002 (.01)	-2.00	.85
Wistar – SD (M)	-.06 (.01)	-6.12	<.001	Wistar – SD (M)	-.08 (.01)	-6.92	<.001
Wistar – SD (F) * BER Count	-.001 (.01)	-.09	.93	Wistar – SD (F) * BEP Count	.001 (.01)	.07	.94
Wistar – SD (M) * BER Count	-.004 (.01)	-.66	.51	Wistar – SD (M) * BEP Count	.003 (.01)	.37	.71

Note: Wistar – SD (F) = dummy coded strain group variable for comparison of Sprague-Dawley female rats to Wistar female rats; Wistar – SD (M) = dummy coded strain group variable for comparison of Sprague-Dawley male rats to Wistar female rats; HR = hour, FT = feeding test days, NFT = non-feeding test days, BW = body weight, PF = palatable food

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