



# Food quality and motivation: A refined low-fat diet induces obesity and impairs performance on a progressive ratio schedule of instrumental lever pressing in rats



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## HIGHLIGHTS

- High fat diets (HFDs) cause obesity and cognitive impairment in rodents.
- HFDs are also highly refined obscuring the causal factors in their effects.
- We fed rats a refined or unrefined low-fat diet (LFD).
- The refined LFD induced significant weight gain and motivational impairment.
- Therefore, diet quality, not fat, is a cause of obesity and cognitive impairment.

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## ABSTRACT

**Introduction:** Purified high-fat diet (HFD) feeding causes deleterious metabolic and cognitive effects when compared with unrefined low-fat diets in rodent models. These effects are often attributed to the diet's high content of fat, while less attention has been paid to other mechanisms associated with the diet's highly refined state. Although the effects of HFD feeding on cognition have been explored, little is known about the impact of refined vs. unrefined food on cognition. We tested the hypothesis that a refined low-fat diet (LFD) increases body weight and adversely affects cognition relative to an unrefined diet.

**Materials and methods:** Rats were allowed ad libitum access to unrefined rodent chow (CON, Lab Diets 5001) or a purified low-fat diet (REF, Research Diets D12450B) for 6 months, and body weight and performance on an instrumental lever pressing task were recorded.

**Results:** After six months on their respective diets, group REF gained significantly more weight than group CON. REF rats made significantly fewer lever presses and exhibited dramatically lower breaking points than CON rats for sucrose and water reinforcement, indicating a chronic reduction of motivation for instrumental performance. Switching the rats' diet for 9 days had no effect on these measures.

**Conclusions:** Diet-induced obesity produces a substantial deficit in motivated behavior in rats, independent of dietary fat content. This holds implications for an association between obesity and motivation. Specifically, behavioral traits comorbid with obesity, such as depression and fatigue [1], may be effects of obesity rather than contributing causes. To the degree that refined foods contribute to obesity, as demonstrated in our study, they may play a significant contributing role to other behavioral and cognitive disorders.

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## 1. Introduction

The consumption of refined, processed foods (REF), a major component of the Western diet, is linked to poor health outcomes in human

populations [2–4], including obesity, diabetes, and cardiovascular disease [5,6]. Statistics from the United States Centers for Disease Control currently report that 35.7% of U.S. adults and approximately 17% of children and adolescents are obese, and these trends are not limited to the U.S. [7–9].

Furthermore, the rapid transition to a Western diet of processed foods over the past few decades has resulted in a wholesale shift from one type of food to another. The transition from traditional diets

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including large proportions of locally-grown and harvested plants and animals to industrial diets heavy in mechanically-separated, minced, saturated with artificial flavors and preservatives, salted, and otherwise altered food has been linked to dramatic increases in rates of overweight and obesity among members of traditional ethnic and cultural groups in developing countries [6,10]. In fact, the strength of this connection is so reliable that a percent increase in obesity among these cultural groups can be predicted in accordance with the degree of increase in food-processing [5].

Despite the large body of evidence linking the Western REF diet to elevated cardiometabolic disease risk, less attention has been directed at its relationship to cognition. Most experimental work has investigated the metabolic and cognitive effects of a purified high-fat diet (HFD) in animal models. These effects are often attributed to the diet's high content of fat, while less attention has been paid to other mechanisms associated with the diet's highly refined state. Although the effects of HFD feeding on cognition have been explored [11–15], little is known about the impact of refined vs. unrefined food on cognition, and it remains difficult to disentangle the effects of dietary fat from the effects of HFD-induced obesity. As cognition is a function of brain physiology, any impairment in brain functioning at the mechanistic level may result in cognitive impairments. Brain systems known to be involved in the dysregulation of appetite and consummatory behavior include the hypothalamus [16], hippocampus [17,18], and striatum [19], which also involve the striatal dopamine D<sub>2</sub> receptor [20], the mesolimbic dopamine (DA) pathway [21], and the orbitofrontal cortex (OFC, [22]). As these systems also play a role in cognitive functions, such as motivation, attention, learning and memory, and behavioral control, we may also expect impairments in these cognitive processes.

Many factors differ between refined diets typical of Western industrialized nations, and the unrefined diets that are more characteristic of the non-industrial subsistence cultures as well as health-conscious individuals in industrialized societies. Thus, we chose to compare the effects on cognitive function of an obesogenic REF diet to those of a control diet composed primarily of unrefined ingredients. This approach has strong ecological validity because it approximates the differences between typically refined and unrefined diets consumed by individuals in our society. Characterizing the relationships between a refined diet, obesity, and cognitive function will enable experimental investigations of the causal components of the refined diet that affect health and develop effective interventions that may have practical, real-world significance as treatments.

In the present study, we test the hypothesis that a refined low-fat diet increases body weight and adversely affects cognition relative to an unrefined diet. Rats were allowed ad libitum access to unrefined rodent chow (CON) or a purified low-fat diet (REF) for six months, and body weight and performance on an instrumental lever pressing task were recorded. The lever press task consisted of instrumental lever pressing on progressive-ratio (PR) schedules of reinforcement. In a PR schedule, reinforcement is delivered only after completing a greater number of responses than previously required. The number of lever presses required for reinforcement increases progressively in fixed steps based on the PR ratio. For example, a PR3 schedule requires 3 lever presses for the first reinforcer, then 6, then 9, and so on until the end of the session. PR schedules provide a sensitive assay for motivation [23,24]. The lower the intrinsic motivation of the subject, the sooner should they reach a breaking point and “give up” on making any further instrumental responses. In each experiment, rats received two sessions on a PR3 schedule of reinforcement followed by two sessions on a PR5 schedule of reinforcement.

The REF diet, despite closely matching the macronutrient ratio of the CON diet, differed in the nature of those macronutrients. In particular, the refining process breaks down complex foods into their simple constituents that are more easily absorbed through the intestines and assimilated into the body [4]. This may be one of the major factors for why junk foods are so addictive and obesogenic. Notably, the REF diet

consisted largely of simple sugars and refined flour. The CON diet, on the other hand, contained more whey, soy, vegetables, fish meal, and complex carbohydrates. Refining into the simple constituents also can affect the flavor profile, texture, and other features of the food to change its palatability and reward value [25].

We hypothesize that REF diet feeding leads to greater weight gain and greater disruption of motivation processes than CON feeding. Specifically, we should observe less persistence in lever-pressing and earlier breaking points in rats consuming a REF diet. To gauge the generality of motivational impairments, we assessed the effect of diet on PR schedules of lever pressing for either a 20% sucrose solution (Experiments 1 and 3) or water (Experiment 2) on PR3 and PR5 schedules of reinforcement.

## 2. General methods

### 2.1. Subjects

Thirty-two experimentally-naïve female Long Evans rats (*Rattus norvegicus*) acquired from Harlan (Indianapolis, IN) served as subjects. Subjects were pair-housed in transparent plastic tubs with a wood-shaving substrate in a vivarium maintained on a 12-h light/dark cycle. Experiments were conducted during the dark portion of the cycle. Prior to the beginning of Experiment 1, a progressive food restriction schedule was imposed so that each cage of pair housed rats received 25 g of their respective diets (REF or CON) daily. Subjects were randomly assigned to either the REF diet or the CON diet ( $n_s = 16$ ).

### 2.2. Diets

The REF (Research Diets 12450B) and CON (Lab Diets 5001) diets were 20% protein vs. 28% protein, 70% vs. 58% carbohydrate, and 10% vs. 13% fat, respectively. The diets, both commercially available rodent chows, differed in the amount of refinement and processing that went into their production (see Appendix for diet sheets provided by the manufacturers). The Lab Diets 5001 was also selected as the CON diet because it is a common diet in other behavioral experiments, including in our laboratory.

### 2.3. Apparatus

Behavioral training was conducted in a small room containing eight Skinner boxes. Each Skinner box measured 30 × 25 × 20 cm ( $L \times W \times H$ ) and was housed in a separate sound-and-light attenuating environmental isolation chest (ENV-008, Med Associates, Georgia, VT, USA). The front and back walls and ceiling of the chamber were constructed of clear Plexiglas, the side walls were made of aluminum, and the floors were constructed of stainless steel rods measuring 0.5 cm in diameter, spaced 1.5 cm center-to-center. The enclosure was dimly illuminated by a 28-V bulb (ENV-215M, Med Associates) house light located 2 cm from the top of the left-side chamber wall.

Each chamber was equipped with a liquid-dipper (ENV-202M, Med Associates) that could be lowered into a trough of sucrose solution (20% by volume) or water reward and then raised. When in the raised position, a small well (0.05 cm<sup>3</sup>) at the end of the dipper arm that contained reward protruded up into the drinking receptacle. Delivery of reward served as the appetitive reinforcer. Each chamber also contained one 3.5-cm wide retractable lever (ENV-112CM, Med Associates), located on the metal wall of the chamber, 8 cm to the left of the drinking receptacle and resting 6.5 cm above the floor grid. During training, the lever protruded into the chamber. Ventilation fans in each enclosure and a white noise generator on a shelf outside of the enclosures provided a constant 62-dB(A) background noise.

### 3. Experiment 1: progressive ratio schedule of sucrose reinforcement

#### 3.1. Procedure

##### 3.1.1. Operant training

Rats received one day of exposure to the chamber with levers retracted. During this 30-min session, rats learned to consume sucrose delivered every  $20 \pm 15$  s. Following this session, levers were extended into the chamber and rats were trained to press the lever for sucrose reinforcement. In each 30-min session, reward was delivered on a Continuous Reinforcement schedule (CRF) in which each lever press was followed by the delivery of sucrose. Additionally, sucrose was delivered every 120 s, noncontingent on bar press behavior. Once rats made a minimum of 50 lever presses in a single session, subsequent sessions were extended to 60-min duration and reinforcement was delivered on a fixed-ratio 3 (FR3) schedule of reinforcement, for which reinforcement was delivered after every three lever presses. Noncontingent reward was discontinued during this and subsequent sessions. Once rats had made 50 lever presses in each of two sessions of FR3, rats were moved to progressive ratio training.

Rats received two 30-min sessions of lever press training on a progressive ratio 3 (PR3) schedule of reinforcement. On a PR3 schedule, the number of lever pressing required for delivery of reinforcement increased by 3 after every trial (i.e. 3, 6, 9, etc.). Subsequently, rats received a single 60-min session of FR5 lever press training, followed by two 30-min sessions of PR5 lever press training. On a PR5 schedule, the number of lever presses required for reinforcement increased by 5 after every trial (i.e., 5, 10, 15, etc.).

### 4. Experiment 2: progressive ratio schedule of water reinforcement

Experiment 2 investigated if similar results on the lever press persistence task would be obtained if water reinforcement replaced the sucrose solution. Specifically, we wanted to determine if the higher sucrose content of the REF diet (which contained up to 35% sucrose) (Research Diets, Inc., 2006) caused the 20% sucrose reward to be relatively less rewarding for the rats on REF diet than for the rats on the CON diet. Such an effect could indirectly negatively affect their motivation to lever press for the reward without directly impairing their general motivation.

#### 4.1. Subjects & diets

Rats were fed ad lib on their respective diet (REF or CON), but were water restricted. Water was available for 60 min daily following the completion of each daily behavioral training session.

#### 4.2. Procedure

The rats received the exact same procedure as described for Experiment 1 except a) magazine training was omitted, and b) water was used as the reward instead of sucrose solution.

### 5. Experiment 3: progressive ratio schedule of sucrose reinforcement

Our main goal in Experiment 3 was to control for the order effects which may have been responsible for the rats' greater rate of lever pressing for water reinforcement, as compared with 20% sucrose solution, by repeating the experiment with sucrose reinforcement following the completion of the water reinforcement study, resulting in an A–B–A design (where "A" = sucrose reinforcement and "B" = water reinforcement).

#### 5.1. Subjects & diets

Rats were food restricted as in Experiment 1 and had ad lib access to water while in the home cage.

#### 5.2. Procedure

The rats received the exact same procedure as described for Experiment 1 except that magazine training and operant lever press training on the CRF schedule were omitted. Thus, rats began the procedure of Experiment 3 with a session of FR3 training.

### 6. Experiment 4: effect of dietary cross-over on progressive ratio schedule of sucrose reinforcement

In a recent study [26] in which rats consumed either a cafeteria diet (which induced obesity) or a chow diet, rats switched from chow to cafeteria diet became hyperphagic and had increased dopamine expression in the ventral tegmental area (VTA) compared to rats switched from cafeteria to chow. Rats switched from a cafeteria to a chow diet, however, became hypophagic, had reduced white and brown adipose tissue mass, as well as lowered plasma leptin and fasting glucose, compared to rats remaining on the cafeteria diet. Furthermore, rats switched from a cafeteria to chow diet showed increased corticotropin-releasing hormone mRNA expression in the dorsal hypothalamus compared to rats that remained on a chow diet. This suggests that removal from a highly palatable diet can induce acute activation of the HPA (hypothalamic–pituitary–adrenal) axis, heightening stress sensitivity. These findings are consistent with the observation that, when stressed, humans seek out highly-palatable 'comfort' foods to attempt to reduce the activity in the chronic stress-response network and reduce anxiety [27].

We assessed whether a short-term switch in diets would result in similar acute changes in motivation in our task. To test this, we used a cross-over design in which half of the rats maintained on each diet were switched to the alternate diet for a period of nine days. Specifically, eight of the rats eating a CON diet were switched to a REF diet (CON-REF) and half of the rats eating the REF diet were switched to the CON diet (REF-CON), each for nine days, while the remainder of the rats in each condition continued to eat their respective diets (i.e., CON-CON and REF-REF). Per the procedure outlined in Ref. [26], rats were fasted for one day prior to the start of Experiment 4.

## 7. Results

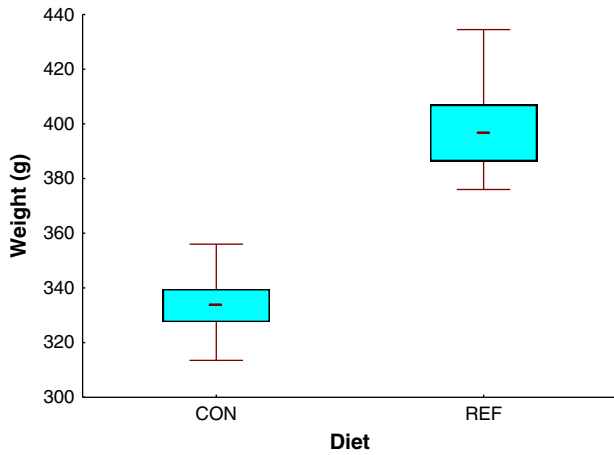
#### 7.1. Weight

By the start of Experiment 1 (at which point rats had spent 6 months on their respective diet), rats had greatly diverged in weight depending on dietary condition. REF rats ( $M = 396.69$ ,  $SEM = 10.27$ ) weighed significantly more than did CON rats ( $M = 333.56$ ,  $SEM = 6.02$ ),  $t(30) = 5.30$ ,  $p < .001$  (Fig. 1).

#### 7.2. Lever pressing

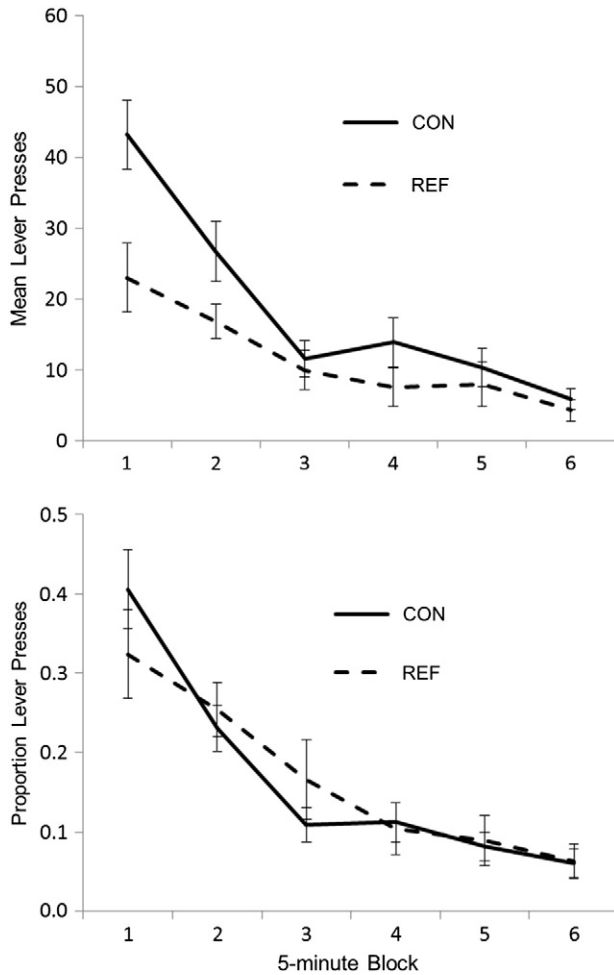
We first analyzed the effect of diet on the total number of lever presses made within a session for the PR3 and PR5 schedules of reinforcement of Experiment 1. A 2 (Diet)  $\times$  2 (PR) mixed ANOVA revealed main effects of both Diet,  $F(1, 30) = 6.27$ ,  $p < .02$ , and PR,  $F(1, 30) = 12.80$ ,  $p < .01$ , but there was no interaction. Analysis of the lever presses made within consecutive 5-min blocks revealed differences in total rates of lever pressing in the first block of the session,  $F(1, 30) = 8.59$ ,  $p < .01$  (Fig. 2, top panel), with a Block  $\times$  Diet interaction  $F(1, 30) = 2.62$ ,  $p < .05$ . Nevertheless, the proportional rate of decline observed within session was similar between the two diet conditions (Fig. 2, bottom panel), indicating that Diet had no effect on within-session changes in satiation.

We next analyzed the effect of reinforcer type (sucrose solution or water) on rates of lever pressing. Because differences between Experiments 1 and 2 could be due to reinforcer type or training-order effects, we utilized an ABA design with sucrose reinforcement in Experiments 1



**Fig. 1.** Mean weight (grams) in the CON and REF groups at the beginning of Experiment 1. Center line indicates mean, box indicates standard error of the mean, and whiskers show range of values for each condition.

and 3 and water reinforcement in Experiment 2. A 2 (Diet: REF or CON) × 2 (PR: 3 or 5) × 3 (Experiment: 1, 2, or 3) mixed ANOVA performed on mean rates of lever pressing revealed main effects of Diet,  $F(1, 30) = 12.50, p < .01$ , Experiment,  $F(2, 60) = 21.13, p < .001$ ; and PR,  $F(1, 30) = 16.54, p < .001$ ; a two-way interaction between Experiment and PR,



**Fig. 2.** Mean (top panel) and proportion (bottom panel) lever presses made by rats in the CON and REF groups during successive 5-minute blocks of the first progressive ratio 3 (PR3) session of instrumental lever pressing in Experiment 1. Error bars denote standard errors of the means.

$F(2, 60) = 7.97, p < .001$ , and a three-way interaction between Experiment, PR, and Diet,  $F = 7.97, p < .001$ . Fig. 3 reveals that overall total lever presses were higher for CON rats compared to REF rats. Also, response rates increased from Experiments 1 to 2, but held relatively steady between Experiments 2 and 3, with the exception for CON rats on a PR5 schedule of water reinforcement.

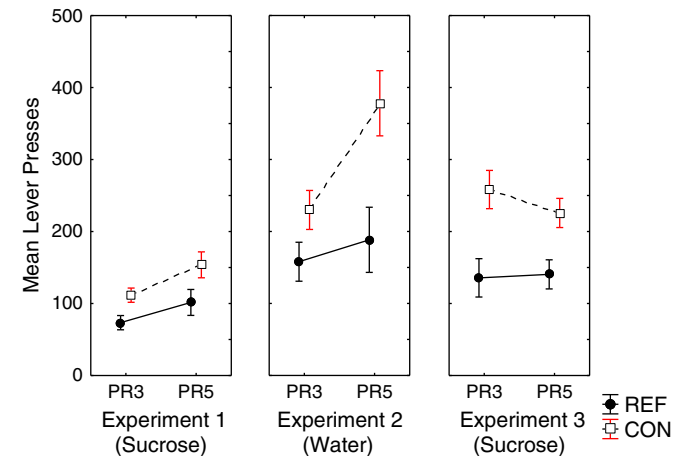
The increase in response rates between Experiments 1 and 2 suggests that rats were responding at pre-asymptotic levels during Experiment 1 but had reached asymptote by Experiment 2. Thus, we conducted a separate mixed ANOVA on lever-press data from just Experiments 2 and 3. This analysis revealed a main effect of Diet,  $F(1, 30) = 11.32, p < .01$ , Experiment,  $F(1, 30) = 5.09, p < .05$ , and PR,  $F(1, 30) = 9.96, p < .01$ , a two-way interaction between Experiment and PR,  $F(1, 30) = 20.78, p < .001$ , and a three-way interaction,  $F(1, 30) = 11.76, p < .01$ . Planned comparisons using the error term from the three-way interaction revealed REF rats lever pressed significantly less than did CON rats for Experiment 2 PR5 and Experiment 3, PR3 and PR5,  $p < .01$ .

**7.3. Breaking points**

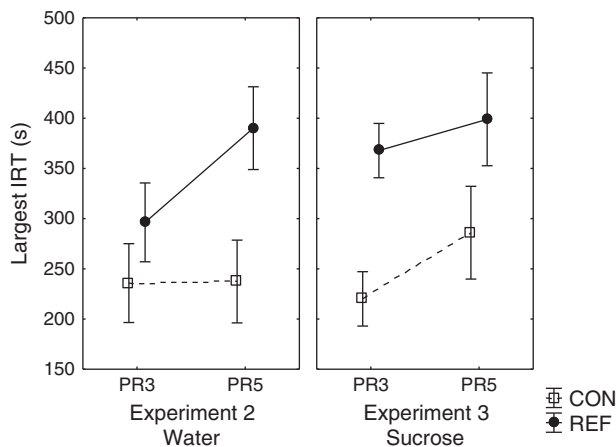
Rates of lever pressing are affected by many factors other than motivation, such as satiety, sensory adaptation, habituation, and hyperactivity. The breaking point on a PR schedule is thought to more directly reflect the motivational component of instrumental lever pressing, independent of these other factors. A breaking point is the time at which a subject gives up on making a reinforced response. In our procedure, we identified the largest inter-response time (IRT) as an indicator of the breaking point. A three-way mixed ANOVA with Diet as the between subject factor, and Experiment (2 or 3) and PR (3 or 5) as within-subject factors conducted on the largest IRT data revealed only a main effect of Diet,  $F(1, 30) = 8.91, p < .01$  (Fig. 4). Specifically, rats on the REF diet exhibited larger breaking points (i.e., took longer breaks between responses) than did rats on the CON diet, suggesting impaired motivation in the REF diet rats. This was true for both water (Experiment 2) and sucrose (Experiment 3) reinforcement, and on both PR schedules of reinforcement.

**7.4. Cross-over experiment**

Rat's weights did not significantly change after nine days of feeding on the alternative diet (REF → CON, CON → REF),  $F < 1.0$ . A three-way mixed ANOVA with Prior Diet (REF, CON) and Current Diet (REF, CON) as between-group factors and PR schedule (PR3, PR5) as a repeated measure revealed only a main effect of PR, but no other main-effects



**Fig. 3.** Mean lever presses made by rats in the CON and REF groups on the PR3 and PR5 schedules of reinforcement when reinforced with sucrose solution (Experiments 1 and 3; left and right panels, respectively) and water (Experiment 2, middle panel). Error bars denote standard errors of the means.



**Fig. 4.** Largest interresponse times (IRTs) in seconds between successive lever presses made by rats in the CON and REF groups on the PR3 and PR5 schedules of reinforcement when reinforced with water (Experiment 2, left panel) and sucrose solution (Experiment 3, right panel). Error bars denote standard errors of the means.

or interactions were observed. Thus, REF rats fed the CON diet for nine days still showed similar levels of impaired motivation as did REF rats that did not receive the CON diet. Likewise, CON rats fed the REF diet for nine days did not exhibit any impairment in motivation relative to CON rats that had no exposure to the REF diet.

## 8. General discussion

Rats fed a purified low-fat diet (REF) for over six months gained significantly more weight than rats fed an unpurified diet (CON). Following this, they showed lower motivation to perform an instrumental lever press task. Specifically, REF diet rats made fewer lever presses, with the largest differences confined to the first few minutes of the session, and exhibited larger breaking points, as evidenced by larger maximum IRTs. Notably, impairment of motivation induced by the REF diet was independent of the within-session drop in lever press response rates which was largely due to changes in satiety. Also, extended consumption of a REF diet resulted in a persistent impairment in motivation that was not affected by nine days of consuming a CON diet. Likewise, nine days of consuming a REF diet was insufficient to induce changes in body weight, or impair motivation for rats that had previously consumed the CON diet. This has potential implications for human diet.

An important result was that motivation to lever press was impaired not only in food-restricted rats working for food reinforcement (sucrose), but also in water-restricted rats working for water reinforcement. The non-specificity of the impairment suggests that the REF diet affected general mechanisms of motivation rather than those specific to the feeding behavioral system. Taken together, these findings lend support to the hypothesis raised by scientists [28,29] and journalists [30] that obesity may not be the result of impaired motivation (lethargy). Rather, an obesogenic diet, such as that consisting of highly processed, refined foods, may induce obesity and disrupt motivational mechanisms of the central nervous system. This hypothesis awaits further empirical scrutiny and does not necessarily rule out the lack of will power as a contributing factor to obesity. Nevertheless, others have found that depletion of dopamine (DA) in the nucleus accumbens (NAc) results in increased effort-avoidance [31]. It is possible that an obesogenic REF diet dysregulates dopamine signaling in the NAc and other parts of the mesolimbic DA pathway, thereby impairing motivation to engage effort to obtain reward. Support for this hypothesis comes from experimental evidence that rats that gained significant amounts of weight on a highly-palatable diet displayed progressive reductions in the rewarding properties of brain stimulation [20]. Investigation of the NAc and other parts of the mesolimbic DA pathway is required to test this intriguing hypothesis.

While the REF diet serves as a model for a human junk food diet, more research is needed to investigate which of the many factors that differ between the two diets have the greatest impact on behavior and cognition. The lipid component of the REF diet consists of soybean oil and lard. The CON diet lipids are derived primarily from lard. Soybean oil is high in omega-6 PUFA and exhibits pro-inflammatory physiological effects in some contexts [32] and may contribute to cognitive impairment [33]. In particular, diets high in linoleic acid cause rats to gain excessive weight on a high fat diet [34]. The protein content of the CON diet derived from a variety of sources, including fish meal, whey, pork meat, and ground meal from cereal grains and legumes. Protein in the REF diet, however, was derived almost entirely from casein. Another major difference between the two diets was their carbohydrate content. Carbohydrate in the CON diet derived largely from unrefined starches and polysaccharides, such as ground corn, beet pulp, molasses, oats, alfalfa, and wheat germ. The REF diet derived its carbohydrates from refined corn starch and the disaccharide sucrose. Thus, the REF chow tasted sweeter than did the CON chow. Due to the high sucrose content, the REF chow had a much higher fructose content, which has been shown to promote leptin resistance and obesity in rodents [35,36]. Finally, the REF diet was highly refined; that is, its ingredients had been broken down into simple components and reconstituted into compact pellets. There is evidence that the exact same nutrients dysregulate appetite and impair satiety mechanisms to promote obesity when ingested as refined flours instead of as whole foods [4,22,25,37]. It is likely that the aspects of the REF diet that are obesogenic and disrupt normal cognitive function will prove multifactorial in nature.

Our current results in the rat model encourage investigation of the effects of highly-processed “junk food diets” in motivation and engagement in effortful tasks in humans. It may be that obese individuals are similarly less motivated to engage in rewarded action, or show a marked avoidance of effortful tasks, compared to non-obese individuals. If a refined diet can impair motivation, what other cognitive functions are impaired? These results call for further investigation of the effects of a REF diet on cognition, including attention, impulsivity, and working memory.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.physbeh.2014.02.025>.

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