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Effects of a cafeteria diet on delay discounting in adolescent and adult rats: Alterations on dopaminergic sensitivity

Stephen H Robertson and Erin B Rasmussen

Abstract

Diet-induced obesity is a laboratory procedure in which nonhuman animals are chronically exposed to a high-fat, high-sugar diet (i.e. cafeteria diet), which results in weight gain, altered sensitivity to reward, and alterations in the dopamine D_2 system. To date, few (if any) studies have examined age-related diet-induced obesity effects in a rat model or have used an impulsive choice task to characterize diet-induced behavioral alterations in reward processes. We exposed rats to a cafeteria-style diet for eight weeks starting at age 21 or 70 days. Following the diet exposures, the rats were tested on a delay discounting task – a measure of impulsive choice in which preference for smaller, immediate vs larger, delayed food reinforcers was assessed. Acute injections of haloperidol (0.03–0.3 mg/kg) were administered to assess the extent to which diet-induced changes in dopamine D_2 influence impulsive food choice. Across both age groups, rats fed a cafeteria diet gained the most weight and consumed more calories than rats fed a standard diet, with rats exposed during development showing the highest weight gain. No age- or diet-related baseline differences in delay discounting were revealed, however, haloperidol unmasked subtle diet-related differences by dose-dependently reducing choice for the larger, later reinforcer. Rats fed a cafeteria diet showed a leftward shift in the dose-response curve, suggesting heightened sensitivity to haloperidol, regardless of age, compared to rats fed a standard diet. Results indicate that chronic exposure to a cafeteria diet resulted in changes in underlying dopamine D_2 that manifested as greater impulsivity independent of age at diet exposure.

Keywords

Cafeteria diet, delay discounting, diet-induced obesity, dopamine D_2 dysregulation, haloperidol, impulsivity

Correlational studies suggest that increases in obesity have been linked to a shift toward higher consumption of a diet high in fat and sugar (Dong et al., 2015; Nielsen et al., 2002; St-Onge et al., 2003). Experimental research supports these correlational studies by establishing a causal link between prolonged consumption of a high-fat, high-sugar diet and adiposity (Johnson and Kenny, 2010; Kanarek and Orthen-Gambill, 1982; Rolls et al., 1980; Vucetic et al., 2012; Woods et al., 2003). One relevant area of research is diet-induced obesity (DIO), which is an experimental preparation in which subjects (usually rodents) are given extended access to a high-fat, high-sugar diet and control animals are fed standard chow. One variation of the diet used in a DIO procedure is referred to as a cafeteria diet and consists of a variety of foods that are high in fat and refined carbohydrates (e.g. bacon, sausage, cheesecake, frosting, etc.; Johnson and Kenny, 2010; Rolls et al., 1980). DIO results in hyperphagia in free-feeding environments (Johnson and Kenny, 2010; Kanarek and Orthen-Gambill, 1982; Rolls et al., 1980) and increases in body fat (Johnson and Kenny, 2010; Kanarek and Orthen-Gambill, 1982; Rolls et al., 1980; Vucetic et al., 2012; Woods et al., 2003).

Several bodies of research have documented that DIO also alters dopaminergic function in the brain, especially in areas involved in reward. First, imaging studies show that animals fed a high-fat diet have lower activity in the ventral tegmental area (VTA) and nucleus accumbens (NAc) compared to those fed a control diet (Val-Laillet et al., 2011). Neural imaging research with obese humans also shows reduced striatal activity in response to consumption of a high-fat, high-sugar liquid

compared to lean participants (Stice et al., 2009a; Stice et al., 2009b). Second, high-fat diets, compared to control diets, can directly alter dopaminergic brain reward areas, via downregulation of D_2 receptor densities in the striatum (Johnson and Kenny, 2010), reductions of DA in the NAc shell (Geiger et al., 2009), and lower dopamine D_2 receptor gene expression in the VTA (Vucetic et al., 2012). Third, a high-fat diet can alter behavioral sensitivity to dopaminergic D_2 compounds in behavioral economic tasks that use food as a reinforcer (Boomhower and Rasmussen, 2014; Robertson et al., 2017). Taken together, these studies demonstrate that diet can influence dopaminergic D_2 function in the brain, especially in areas involved in reward.

Researchers have identified delay discounting as a behavioral process that is influenced by dopamine-rich neural areas, such as the striatum (Bickel et al., 2011, 2014). Delay discounting refers to the tendency for an outcome to become devalued as a function of the delay to its receipt. Behavior that is especially sensitive to delayed outcomes is considered a facet of impulsivity. Delay discounting is assessed by arranging a series of choices between a single food pellet delivered immediately versus multiple food pellets delivered after a

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brief delay. By establishing preferences for more immediate outcomes (impulsive choices), researchers can then assess factors, such as diet or specific drugs (e.g. Boomhower and Rasmussen, 2014; Evenden and Ryan, 1996; Koffarnus et al., 2011) that alter these patterns.

Impulsive food-related choices have been shown with obese humans (Hendrickson and Rasmussen, 2013, 2016; Rasmussen et al., 2010) and in some animal models of obesity (Boomhower et al., 2013). One animal model of obesity is the Zucker rat, in which obesity is the result of a homozygous *fa/fa* “fatty” allele pattern and lean Zucker rats (controls) have heterozygous *fa/Fa* or homozygous *Fa/Fa* alleles (Beck, 2000; Sahu, 2004; Zucker and Zucker, 1961). Boomhower et al. (2013) used the delay discounting task with lean and obese Zucker rats and found that obese Zucker rats tolerated significantly shorter delays than lean Zucker rats. As such, a higher sensitivity to delayed outcomes may be one factor that promotes obesogenic patterns of behavior.

In addition, diet has also been shown to affect dopaminergic sensitivity during impulsive choice tasks. Boomhower and Rasmussen (2014) investigated the extent to which chronic exposure to a high-fat diet versus a standard diet altered impulsive food choice. Following exposure to a high-fat or a standard diet, researchers tested rats on a delay discounting task. Researchers found no baseline differences in delay discounting as a function of diet; however, rats fed a high-fat diet were more sensitive to acute injections of haloperidol (a D_2 antagonist), such that they showed higher impulsivity under haloperidol than rats fed a standard diet. These changes are consistent with diet-related changes that affect D_2 structure and function in the brain (Baladi, et al., 2012; Boomhower and Rasmussen, 2014; Geiger et al., 2009; Johnson and Kenny, 2010; Robertson et al., 2017; Val-Laillet et al., 2011; Vucetic et al., 2012).

While adult animal models have been used to understand diet-related obesity, to our knowledge, no animal models have been used to study the behavioral effects of a high-fat, high-sugar diet in a developing rodent that would be analogous to a human in child and adolescent development (e.g. Ozane and Hales, 2004). Development is characterized by a myriad of neural changes. Neural areas related to self-control (e.g. prefrontal cortex) and reward (e.g. striatal regions) follow different developmental trajectories, such that regions involved in reward tend to mature earlier than the regions involved in self-control (Andersen, 2003; Casey et al., 2008; Gogtay et al., 2004; Kalsebeek et al., 1988), which results in relatively more influence from neural areas related to reward and may promote impulsive patterns of behavior. Indeed, researchers have documented that, in humans, children and adolescents tend to show steeper patterns of delay discounting relative to adults (Green et al., 1994; Hendrickson and Rasmussen, 2016).

Since childhood obesity predicts adult obesity (Biro and Wien, 2010; Guo and Chumlea, 1999) and diet-induced disruptions of dopamine D_2 function leads to dysregulation of the neural reward systems, it is possible that early exposure to a cafeteria-style diet may promote persistent impulsive behavior patterns that may create long-term problems, such as obesity. Experiments focused on characterizing obesity in an animal model analogous to childhood and adolescent developmental stages should allow researchers to assess the extent to which development and dietary history may affect impulsive food choice.

The current study used a 2×2 experimental design to investigate the extent to which a cafeteria diet versus a standard diet interacted with development (21 d vs 73 d of age when dietary exposure begins) to influence rates of delay discounting and changes in dopamine D_2 function. The current study had two primary aims. First, we assessed the extent to which diet and age at diet onset resulted in differences in weight gain, caloric consumption, and baseline rates of delay discounting. Second, we assessed the extent to which diet and age resulted in changes in sensitivity to a dopamine D_2 antagonist, haloperidol.

Methods

Subjects and diets

Male Sprague-Dawley rats ($n=60$), age 21 d (ADOL) or 70 d (ADULT), were obtained from a commercial breeder (Simonsen, Gilroy, California, USA) and individually housed in plexiglass shoebox cages with ad libitum access to water. Diet exposures began at either 21 d of age ($n=30$) or 73 d of age ($n=30$). The ages of these rats were selected to correspond to human adolescent and adult developmental phases, respectively (Sengupta, 2013). Each rat was randomly assigned to either a cafeteria-style diet or standard chow. Rats fed a cafeteria diet received daily unlimited access to cooked sausage (3.17 kcal/g), cheesecake (4.23 kcal/g), potato chips (5.71 kcal/g), frosting (4.24 kcal/g), M&Ms (5.01 kcal/g), Twix (5.01 kcal/g), and free access to standard chow (3.0 kcal/g). Rats exposed to the standard diet received unlimited access to standard chow. Rats were allowed 23 h access to their respective diets daily for eight weeks. Food was weighed prior to its placement in each rat’s home cage and, after 23 h, excess food was removed, weighed, and replaced with fresh food. After the diet exposures, 10 rats with the lowest body weight from the standard chow group within each age group and 10 rats with the highest body weight from the cafeteria diet group within each age group were used for behavioral testing. Using the rats with the highest (DIO) and lowest (standard diet) body weights is a standard practice (e.g. Boomhower and Rasmussen, 2014; Huang et al., 2003; 2006; Johnson and Kenny, 2010; Levin and Keese, 1998; Robertson et al., 2017) used to maximize the differences in weights and D_2 in the striatum between groups (Johnson and Kenny, 2010; Wang et al., 2001), as well as to ensure that the animals were a model of obesity, and not simply an evaluation of the effects of a cafeteria diet, per se. The Idaho State University Institutional Animal Care and Use Committee approved all procedures.

Apparatus

Seven Coulbourn Habitest (Coulbourn Instruments, Whitehall, Pennsylvania, USA) standard operant chambers individually placed in a sound-attenuating cubicle, equipped with two levers and stimulus lights, and a receptacle for reinforcer deliveries were used. Reinforcers were 45 mg grain-based Precision pellets (Bioserv, Frenchtown, New Jersey, USA; 3.35 kcal/g). White noise was generated via a speaker situated on the top-right corner of the left wall. The chamber was ventilated via a 5×5 cm fan on the top-left corner of the left wall. Experimental events and data collection were controlled with

a 0.01-s resolution using GraphicState software (Coulbourn Instruments, Whitehall, Pennsylvania, USA) on a Windows-based computer.

Behavioral testing

Training. Following the eight-week diet exposure, rats were trained to lever press in a series of three-hour sessions. At the start of lever press training, rats that were exposed starting at age 21 d were 77 d old and rats that were exposed starting at age 73 d were 129 d old; thus, for both groups, behavioral testing began during adulthood. During this portion of the experiment, rats' weights were reduced to 85% of their free feeding body weight at the final day of diet exposure by restricting post-session access to their respective diets. Lever-press training for both levers was accomplished in a manner similar to other studies (see Boomhower et al., 2013 for details). After the rats successfully pressed each lever 60 times, they completed two additional sessions in which both levers were active to screen for side biases. Any side biases were corrected via shaping (i.e. reinforcing successive approximations) lever pressing to the unfavored lever. If the rats did not complete this sequence in seven days, they were trained to lever press via shaping. After completing two sessions in which both levers were pressed 60 times, the rats were considered trained and delay discounting testing commenced.

Delay discounting. During delay discounting testing, rats were maintained at 85% free feeding body weight to establish food as a reinforcer. Weights were maintained with food delivered during each session, as well as providing a supplemental amount of each rat's respective diet following the daily session (amount varied for each rat each day). Delay discounting sessions lasted 1.5 h or until all trials were completed. The delay discounting procedure was a modified version of Evenden and Ryan's (1996) procedure used by Boomhower and Rasmussen (2014). Generally, the procedure was arranged such that a response on one lever resulted in the delivery of a single 45 mg grain-based pellet immediately and a response on the other lever resulted in the delivery three 45 mg grain-based pellets after a delay. Each session consisted of five blocks of discrete trials consisting of two forced-choice and 10 free-choice trials. For the forced choice trials, rats experienced each contingency (i.e. one forced-choice trial for the single-pellet lever and one for the three-pellet option) in a randomly selected order. Following the forced choice trials, ten free choice trials commenced in which both levers were operational and rats could select either outcome. For each trial, the rat could make one of three choices: (a) select the one-pellet option (smaller, sooner (SS)), (b) select the three-pellet option (larger, later (LL)), or (c) make no response (an omission). If the rat chose the SS option, a single pellet was delivered immediately followed by the initiation of the intertrial interval (ITI). If the rat chose the LL option, three pellets were delivered following the specified delay, after which the ITI commenced. If the rat did not make a response after 30 s (an omission), the ITI commenced. During the ITI, all lights were extinguished and levers were not active. The duration of the ITI was such that each trial following a lever press or omission was held at one minute. For instance, if the delay was 20 s, the rat would press the lever, wait 20 s for the pellet, and then a 40 s ITI commenced.

No delay (0-s) probe testing. Prior to experiencing delays, rats completed a series of tests that consisted of five blocks of 10 discrete choice trials as described above; however, both the one-pellet and three-pellet alternatives were delivered immediately. Each rat completed these tests until it pressed the three-pellet option 90% of the time in each block. This step is critical to demonstrate that the rat is sensitive to amount, prior to implementing delays.

Delay discounting. Following the completion of 0-s probe testing, delays were introduced. The initial delay sequence consisted of blocks of delays of 0, 1, 2, 4, and 8 s. If responding for the LL alternative remained above 50% across all delay blocks, a second delay sequence consisting of blocks of delays of 0, 2, 4, 8, and 16 s was introduced. Again, if choice for the LL alternative remained above 50%, a final sequence of delays consisting of 0, 5, 10, 20, and 40 s was introduced. The order in which the delays were presented (i.e. ascending or descending) was counterbalanced across rats. Each delay sequence was in place for at least five sessions. These sessions were run six days a week. A 0-s probe test was conducted once weekly in order to check that the rats remained sensitive to amount. The benefit of using this procedure is that it allows researchers to establish a baseline and then assess drug-induced changes in sensitivity to delay and amount within a single session (Madden and Johnson, 2010).

Baseline behavior was considered stable when (a) the total responses for the LL option did not show an increasing or decreasing trend across the last five sessions, (b) the responses for the LL response for a given session did not vary by more than 20% of the grand mean of the previous five sessions, (c) choice for the three-pellet alternative in the 0-s delay block was at least 90% across the last five sessions, and (d) the rat chose the three-pellet option 90% in the 0-s probe session for that week (Boomhower and Rasmussen, 2014; Huskinson, et al., 2012). One rat (standard diet exposed at age 21 d) was excluded from analysis due to unstable baseline and was not moved to drug testing.

Haloperidol challenges. After baseline responding was stable, acute haloperidol challenges commenced. Acute intraperitoneal (i.p.) injections were administered 20 min prior to the experimental session to ensure that the drug was behaviorally active. Injections (0, 0.03, 0.1, and 0.3 mg/kg) were administered once per week on the same day. The lower doses (0.03 and 0.1 mg/kg) were administered in a randomized order prior to the largest dose (0.3 mg/kg), which was administered last. Vehicle sessions were conducted the day before a haloperidol injection.

During haloperidol challenges, rats received four days of testing without drug (non-injection controls) and one day of 0-s probe testing without drug. All rats were required to pass the 0-s probe test in two sessions or less by selecting the three-pellet option for at least 90% of each trial in order to undergo the vehicle and drug testing for that week. One adult (Rat S28) completed some vehicle and drug testing sessions, though did not meet the 0-s probe criteria after repeated testing. This rat's data were included in the analysis because the pattern of results was the same with or without inclusion.

Drug

Haloperidol (Sigma-Aldrich, USA) was dissolved in a 1:1:18 vehicle solution of lactic acid (Sigma-Aldrich, USA), buffering agent,

and saline (1 mL/kg). Both drug and vehicle solutions (which included the lactic acid, buffering agent, and saline) were held at a pH of 7 and were administered in a 1 mg/mL volume. Haloperidol has a half-life of 14.5–36.7 h (Kudo and Ishizaki, 1999); therefore, the drug was likely active during behavioral testing.

Statistical analyses

Statistical analyses were performed using IBM SPSS Version 23.0 (IBM SPSS Statistics for Macintosh, Version 23.0, IBM Corp., Armonk, New York, USA). For both weight gain and caloric consumption, data were averaged into weekly bins. Weight gain was calculated by subtracting the average weight for each week of diet exposure from the average weight for week one of diet exposure. Group differences in weight gain and caloric consumption were assessed using mixed analyses of variance (ANOVAs), with week as the repeated measure and diet (cafeteria vs standard) and age (21 vs 73 d) as between-subject factors.

Baseline data. Delay discounting data were quantified in two manners. First, percentage choice for the LL option from the last three sessions for each delay on the terminal delay sequence was averaged for each rat. Second, baseline rates of delay discounting were also assessed by examining indifference points. Indifference points were determined by fitting a best-fit function to each delay discounting curve for each rat. The indifference point was interpolated by finding the delay value at which the line generated by the best-fit function corresponded to 50% LL choice (GraphPad Prism version 7.00 for MacOS X, GraphPad Software, La Jolla, California, USA). Indifference points are shown in Table 1. Given that interpretations using area-under-the-curve (AUC) for baseline data are limited because animals reached indifference at different delay sequences, we do not provide this analysis. That is, because AUC is restricted to a value of 0–1, it is difficult to directly compare AUC across rats on different delay sequences. Baseline percentage LL choice was analyzed using a mixed Analysis of Variance (ANOVA) with delay block as the repeated measure and age (ADOL vs ADULT) at diet exposure, diet type, and delay sequence (ascending vs descending) as between-subject variables. Baseline indifference points were analyzed using a 2 (cafeteria vs standard diet) × 2 (ADOL vs ADULT) × 2 (ascending vs descending sequence) ANOVA.

Drug data. The three sessions of vehicle data were averaged for each rat and then across each diet and age condition. Data for each dose of haloperidol are from a single session. Percentage choice LL under drug conditions was analyzed using a mixed ANOVA with delay block for each dose as repeated measures and age at diet exposure and diet type as between-subject variables. We also analyzed drug data by plotting the means for each dose against delay for AUC analysis, in which trapezoids were fitted to the area beneath the discounting curve and then the area of each trapezoid was summed (Myerson et al., 2001; Reed et al., 2012). Larger values indicate lower levels of delay discounting. AUC was analyzed using a mixed ANOVA with dose as the repeated measure and age at diet exposure and diet as between subject factors. Finally, to measure drug sensitivity, haloperidol data were expressed as percentage of vehicle for both percentage choice LL and AUC and analyzed using a mixed ANOVA with

dose as the repeated measure and diet and age at diet exposure as between-subject factors.

Results

Weight gain and food intake

Figure 1 (top panel) shows weight gain across the dietary exposure period. A mixed ANOVA (week as repeated measure, age and diet as between-subject factors) showed weight gain increased across week for all groups, $F(1.64, 59.11)=2411.93$, $p<0.001$, $\eta_p^2=0.99$. There was also a main effect of diet, $F(1, 36)=31.71$, $p<0.001$, $\eta_p^2=0.47$, in which DIO had higher weight gain, and age, $F(1, 36)=1302.04$, $p<0.001$, $\eta_p^2=0.97$, in which adolescent rats had higher weight gain. There was no diet × age interaction ($p=0.27$). In addition, there was a week × diet interaction, $F(1.64, 59.11)=25.38$, $p<0.001$, $\eta_p^2=0.41$, a week × age interaction, $F(1.64, 59.11)=839.32$, $p<0.001$, $\eta_p^2=0.96$, and a week × diet × age interaction, $F(1.64, 59.11)=4.64$, $p=0.02$, $\eta_p^2=0.11$, such that adolescent rats with DIO exposure had the highest weight gain by the last week.

The bottom of Figure 1 shows mean weekly caloric intake across the diet exposure period. A mixed ANOVA revealed that across all groups, there was a main effect of week that trended toward significance, $F(7, 252)=1.95$, $p=0.06$, $\eta_p^2=0.05$. There was also a main effect of diet, $F(1, 36)=703.42$, $p<0.001$, $\eta_p^2=0.95$, in which DIO rats consumed the most kcal, a trending effect of age, $F(1, 36)=51.47$, $p=0.06$, $\eta_p^2=0.59$, in which adults consumed more kcal, and a diet × age interaction, $F(1, 36)=42.51$, $p<0.001$, $\eta_p^2=0.54$, such that adults in the DIO group had the highest consumption. There was also a week × diet interaction, $F(7, 252)=8.99$, $p<0.001$, $\eta_p^2=0.20$, a week × age interaction, $F(7, 252)=4.63$, $p<0.001$, $\eta_p^2=0.11$, and week × diet × age interaction, $F(7, 252)=4.24$, $p<0.001$, $\eta_p^2=0.11$.

Baseline and vehicle delay discounting

Differences in baseline percentage choice LL were tested using a repeated measures ANOVA with diet, age, and delay sequence as between-subjects factors (data not shown). There was an effect of delay, $F(4, 124)=246.98$, $p<0.001$, $\eta_p^2=0.89$. There were no other diet or age-related main effects (p 's > 0.22) or interactions (p 's > 0.16). We also analyzed the data after converting the percentage larger, later values into percentage of the 0-s block for each delay and found a main effect of delay, $F(4, 116)=104.68$, $p<0.001$, $\eta_p^2=0.78$. There were no other main effects (p 's > 0.157) or interactions (p 's > 0.071). For indifference points, no main effects (p 's > 0.18) or interactions (p 's > 0.28) were revealed.

Data from the vehicle condition are presented in Figure 2. The top panel shows mean percentage choice for the LL option as a function of delay. A mixed ANOVA revealed a main effect of delay, $F(4, 140)=272.935$, $p<0.001$, $\eta_p^2=0.89$, such that percentage LL choice decreases with delay. There was also a main effect of diet, $F(1, 35)=6.88$, $p=0.01$, $\eta_p^2=0.16$, such that DIO rats showed higher percentage LL choice. There was a delay × diet interaction, $F(4, 140)=4.62$, $p=0.002$, $\eta_p^2=0.12$, such that rats fed a standard diet showed lower percentage choice LL across the delays. There were no main effects of age ($p=0.50$)

Table 1. Shows the delay sequence and delay at which indifference was reached for each rat from each diet and age condition.

Rat ID	Delay sequence	ASC/DESC	Indifference point (s)
D1	0–8 s	ASC	4.23
D2	0–8 s	DESC	3.24
D3	0–40 s	DESC	20.06
D7	0–40 s	ASC	15.14
D8	0–40 s	ASC	31.95
D9	0–16 s	DESC	9.00
D10	0–40 s	DESC	19.98
D11	0–16 s	ASC	8.07
D13	0–40 s	DESC	28.83
D15	0–40 s	DESC	9.81
D17	0–40 s	ASC	30.27
D18	0–16 s	DESC	12.73
D20	0–40 s	DESC	11.81
D21	0–40 s	ASC	26.79
D24	0–40 s	ASC	10.09
D26	0–40 s	DESC	13.69
D27	0–40 s	ASC	34.03
D28	0–40 s	ASC	17.06
D29	0–40 s	DESC	10.49
D30	0–40 s	DESC	21.70
S1	0–16 s	DESC	7.96
S2	0–40 s	DESC	32.87
S5	0–40 s	ASC	17.86
S6	0–40 s	ASC	14.97
S9	0–40 s	ASC	12.37
S10	0–40 s	DESC	10.33
S12	0–40 s	DESC	11.21
S13	0–16 s	ASC	10.35
S14	0–8 s	ASC	7.70
S16	0–40 s	DESC	9.13
S17	0–16 s	DESC	13.10
S19	0–40 s	ASC	13.81
S22	0–16 s	ASC	5.02
S23	0–40 s	ASC	15.94
S26	0–40 s	DESC	18.42
S25	0–40 s	DESC	16.46
S28	0–16 s	ASC	5.51
S29	0–40 s	ASC	7.89
S30	0–40 s	DESC	19.98

ASC: ascending; DESC: descending.

D1–D15 (diet-induced obesity (DIO), age 21 d), D17–D30 (DIO, age 73 d), S1–S14 (standard, age 21 d), S16–S30 (standard, age 73 d). The delay sequence column shows the range of delays presented to each rat. The ASC/DESC column notes if the rat was tested in an ASC or a DESC order. The indifference (s) column shows the indifference point derived from the best-fit function.

and no other interactions (p 's>0.37). The bottom panel of Figure 2 shows the average AUC for vehicle injection sessions. An ANOVA revealed a main effect of diet, $F(1, 35)=4.55$, $p=0.04$, $\eta_p=0.12$. There were no other main effects or interactions (p 's>0.65). In addition, we compared rates of delay discounting during baseline and vehicle testing using a mixed ANOVA and revealed no differences in rates of discounting ($p=0.51$).

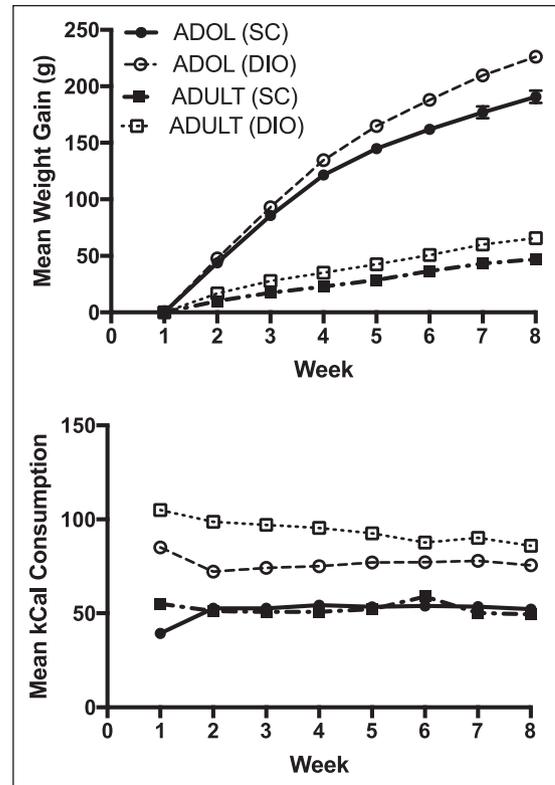


Figure 1. Mean weight gain for rats that continued to behavioral testing ($n=40$; top panel), and mean food consumption expressed in kcal ($n=40$) across the eight-week diet exposure period for each group (adolescent (ADOL) standard chow (SC)=black circles; ADOL diet-induced obesity (DIO)=white circles; adult (ADULT) SC=black squares; ADULT DIO=white circles). Error bars represent one standard error of the mean (SEM). Some error bars are obscured by the data point.

Acute drug challenges

Figure 3 shows mean percentage choice for the LL option as a function of delay for each drug dose. Each panel represents a group with adolescents in the top panels and adults in the bottom panels. Standard chow groups are represented on the left; cafeteria diet (DIO) on the right. There was a main effect of delay, $F(4, 140)=228.92$, $p<0.001$, $\eta_p=0.87$ and a main effect of dose, $F(3, 105)=132.96$, $p<0.001$, $\eta_p=0.79$. While there was no main effect of diet ($p=0.68$), there were several diet-related interactions. There was a delay×diet interaction, $F(4, 140)=6.24$, $p<0.001$, $\eta_p=0.52$ and a dose×diet interaction, $F(3, 105)=34.90$, $p=0.03$, $\eta_p=0.08$. In addition, there was a delay×dose interaction, $F(4.8, 168.04)=26.70$, $p<0.001$, $\eta_p=0.43$. There was no main effect of age or any other interactions (p 's>0.20). AUC (not shown) values decreased dose-dependently, $F(3, 105)=102.76$, $p<0.001$, $\eta_p=0.75$. A dose×diet interaction approached significance, $F(3, 105)=2.30$, $p=0.08$, $\eta_p=0.06$. No interactions were revealed (p 's>0.41).

Percentage of vehicle

Because there were differences in groups with the vehicle data (Figure 2) and to more clearly show the diet×dose interactions from Figure 3, Figure 4 (top) shows data on drug sensitivity

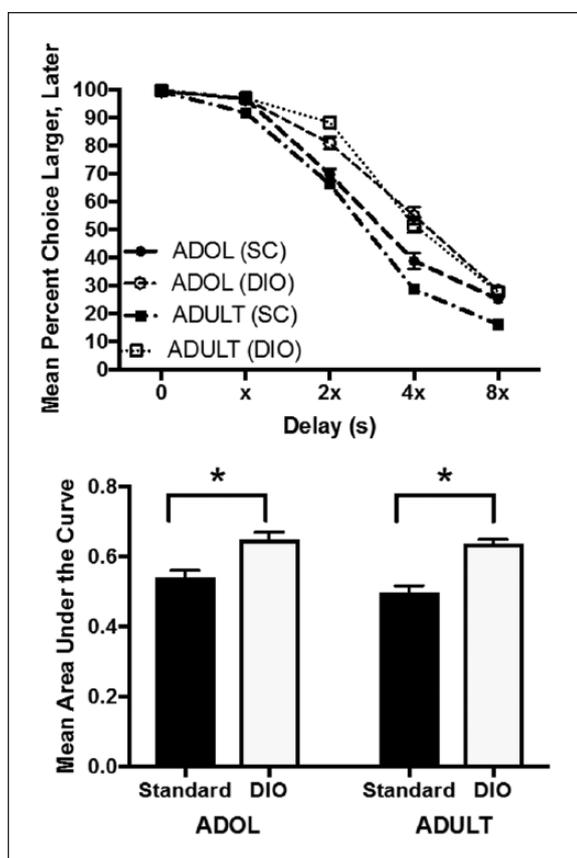


Figure 2. Top panel shows mean percentage choice for the larger, later (LL) alternative across all delays tested on the terminal sequence for each group (adolescent (ADOL) 21 standard chow (SC)=black circles; ADOL 21 diet-induced obesity (DIO)=white circles; adult (ADULT) SC=black squares; ADULT DIO=white circles) following an injection of vehicle. Bottom panel shows mean area-under-the-curve (AUC) for each group following vehicle injections. Error bars represent one standard error of the mean (SEM). Some error bars are obscured by the data point.

with mean percentage LL choice under the terminal delay sequence as a function of dose. Data are expressed as percentage of vehicle. Percentage choice for the LL option decreased as a function of dose, $F(3, 105)=145.17, p<0.001, \eta_p=0.81$. There was also a main effect of diet, $F(1, 35)=6.14, p<0.02, \eta_p=0.15$. A dose \times diet interaction that approached significance was also revealed, $F(3, 105)=2.57, p=0.058, \eta_p=0.07$, such that animals fed the cafeteria diet, regardless of age, demonstrated a sensitivity to the 0.1 mg/kg dose of haloperidol relative to animals fed a standard diet. No main effect of age or a diet \times age interaction was found (p 's >0.55).

The bottom of Figure 4 shows mean AUC values expressed in terms of percentage of vehicle. AUC decreased as a function of dose, $F(3, 105)=145.10, p<0.001, \eta_p=0.81$. There was a main effect of diet, $F(1, 35)=5.81, p<0.02, \eta_p=0.14$. In addition, there was a dose \times diet interaction that approached significance, $F(3, 105)=2.56, p=0.059, \eta_p=0.07$, such that rats fed a cafeteria diet showed greater sensitivity to the 0.1 mg/kg dose relative to animals fed a standard diet. No main effect of age or a diet \times age interaction was apparent (p 's >0.54).

Because there were interactions with diet, delay, and dose in the aforementioned analyses (Figures 3 and 4), we more carefully examined amount and delay parameters. We started with the 0-s delay, in which delay to both SS and LL alternatives were held constant at 0-s, but amount differed. This specific condition tested for sensitivity to amount. Figure 5 shows mean percentage LL choice during the 0-s block of the delay discounting task as a function of dose. A mixed ANOVA (dose as repeated measures and diet and age as between-subject factors) revealed a main effect of dose, $F(2.19, 76.79)=89.65, p<0.001, \eta_p=0.72$. There was also a main effect of diet, $F(1, 35)=5.81, p=0.02, \eta_p=0.14$, such that DIO rats showed a higher sensitivity to haloperidol. In addition, a dose \times diet interaction trended toward significance, $F(2.19, 76.79)=2.74, p=0.07, \eta_p=0.07$, such that DIO rats were particularly sensitive to the injections at the 0.1 (at both ages) and 0.3 (ADOL only) mg/kg doses. There were no other main effects or interactions revealed (p 's >0.18).

To examine aspects of delay sensitivity that may have played a role in DIO rats' sensitivity to haloperidol in the discounting data, we investigated the role of order (ascending or descending) of the delays imposed. Figure 6 (top) shows percentage LL choice as a function of delay for each diet group and whether the rats were assigned to the ascending or descending delay sequence. Age was collapsed across diet conditions due to the lack of differences observed in previous and present analyses. A mixed ANOVA (dose as the repeated measure, diet and delay sequence as between-subject factors) revealed that percentage LL choice decreased as a function of increases in delay, $F(4, 140)=77.98, p<0.001, \eta_p=0.69$. There was a delay \times diet interaction, $F(4, 140)=3.36, p=0.01, \eta_p=0.09$, such that rats fed a high-fat diet showed a lower preference for the LL alternative. There was a delay \times sequence interaction, $F(4, 140)=3.48, p=0.01, \eta_p=0.09$, such that lower delays in the descending sequence showed lower percentage LL choice. Importantly, there was also a diet \times sequence interaction that approached significance, $F(1, 35)=3.76, p=0.06, \eta_p=0.10$, such that rats fed a cafeteria diet exposed to a descending sequence showed a larger reduction in percentage LL choice. No other main effects or interactions were revealed (p 's >0.25).

One reason why DIO rats may have showed higher discounting in the descending delay sequence is because experiencing longer delays first may have made them especially sensitive to delay. Therefore, examining omissions made during these sessions would provide some additional information on this mechanism. Figure 6 (bottom) shows percentage trials omitted following an injection of 0.1 mg/kg of haloperidol for each diet group exposed to an ascending vs descending delay sequence. A mixed ANOVA (dose as the repeated measure and diet and delay sequence as between-subject factors) revealed a delay \times sequence interaction, $F(4, 140)=4.26, p=0.003, \eta_p=0.11$, such that more omissions occurred at lower delays. We also found a diet \times sequence interaction, $F(1, 35)=4.23, p=0.05, \eta_p=0.11$, such that rats fed a cafeteria diet that were exposed to a descending delay sequence showed the most omission. No other main effects or interactions were revealed (p 's >0.17).

Discussion

In the current study, rats given chronic access to a cafeteria diet showed higher levels of weight gain compared to rats fed a

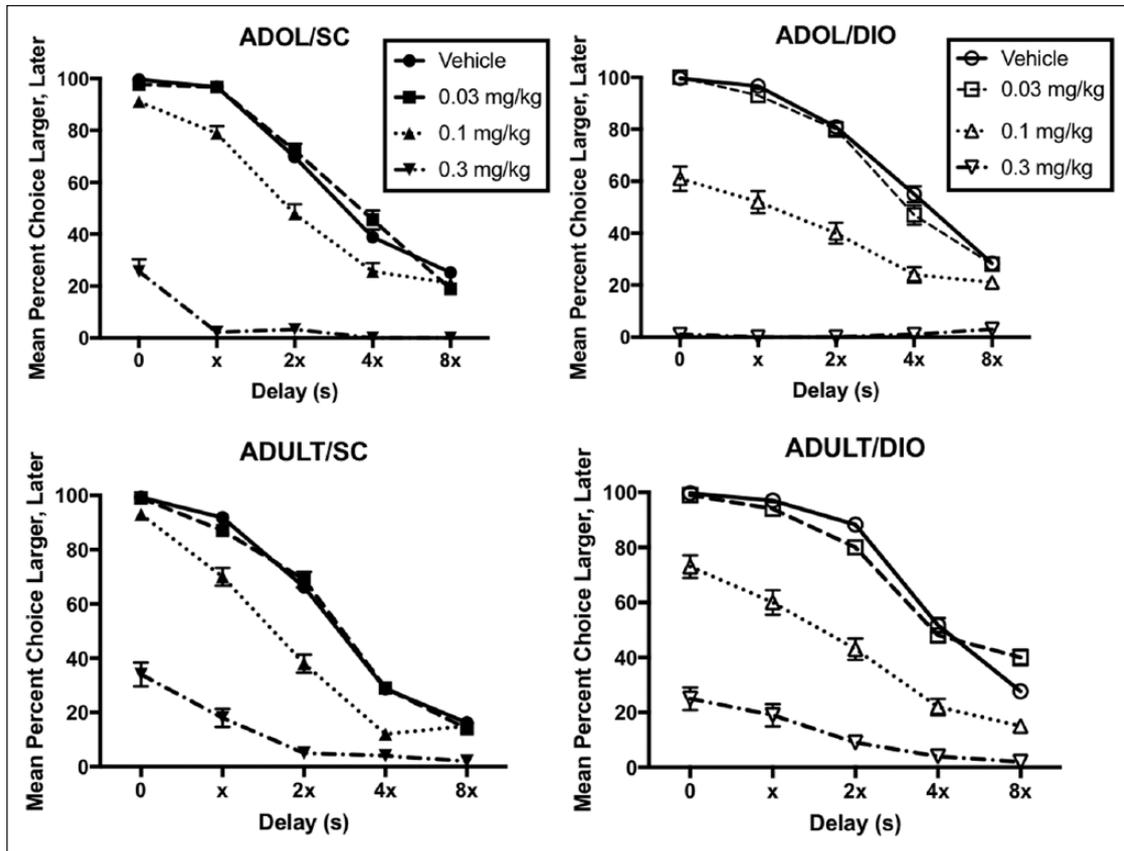


Figure 3. Percentage choice for the three-pellet alternative as a function of delay following an injection of 0, 0.03 mg/kg, 0.1 mg/kg, and 0.3 mg/kg of haloperidol for each group (adolescent (ADOL) standard chow (SC)=top left; ADOL diet-induced obesity (DIO)=top right; adult (ADULT) SC=bottom left; ADULT DIO=bottom right). Error bars represent one standard error of the mean (SEM). Some error bars are obscured by the data point.

standard diet within each age group. Rats that were exposed to their respective diets starting at age 21 d showed greater weight gain across the diet exposure period than rats that started diet exposures at age 70 d. This is likely because, at age 21 d, rats have a much lower body mass than rats at age 70 d and are in a developmental period characterized by active growth (Sengupta, 2013). Within each age group, rats fed a cafeteria diet gained more weight relative to rats fed a standard diet. These findings support research that DIO results in excessive weight gain and higher caloric intake compared to standard diet controls (Boomhower and Rasmussen, 2014; Johnson and Kenny, 2010; Robertson et al., 2017; Rolls et al., 1980).

We found no differences as a function of diet or age in baseline levels of delay discounting, which is consistent with a previous report on delay discounting following DIO (Boomhower and Rasmussen, 2014), but is inconsistent with a previous report on a genetic model of obesity (Boomhower et al., 2013). There are a number of reasons for this discrepancy. First, different patterns of food consumption may result from a dietary model of obesity, which tends to target alterations in dopamine function related to food reward, than from the Zucker genetic model of obesity, which tends to target leptin-based alterations (see review by Rasmussen et al., 2016). (Though, leptin and dopamine can neuromodulate one another – see review by Oswal and Yeo, 2010 – for more information.) Second, Boomhower et al. (2013)

quantified delay discounting using an adjusting delay procedure, whereas the current report used a modified Evenden and Ryan (1996) procedure. Third, the previous report used sucrose pellets and the current report used grain-based pellets, thus palatability may have played a role in discounting rate. These procedural differences may have contributed to differences in delay discounting observed between the genetic and dietary models of obesity.

Though there were no differences between baseline and vehicle data, rats fed a chronic high-fat, high-sugar diet showed lower rates of delay discounting following an injection of vehicle. This is notable because it suggests differences between diet groups were apparent without drug on board. One interpretation of the diet-related difference with the vehicle data is that a small perturbation, such as a vehicle injection, was enough to create small enough differences in the distributions that combined with dietary history to manifest as a diet-based difference. More research is needed to more carefully examine this. It was surprising, however, that rats exposed to the cafeteria diet were more self-controlled (greater preference for the larger-later outcome) than rats in the standard chow diet condition. There could be three reasons for this observation: an insensitivity to delay, a heightened sensitivity to amount, or both.

Haloperidol dose-dependently reduced the percentage choice for larger, later food outcomes; that is, the drug increased impulsive choice, for both diet and age conditions. This has been

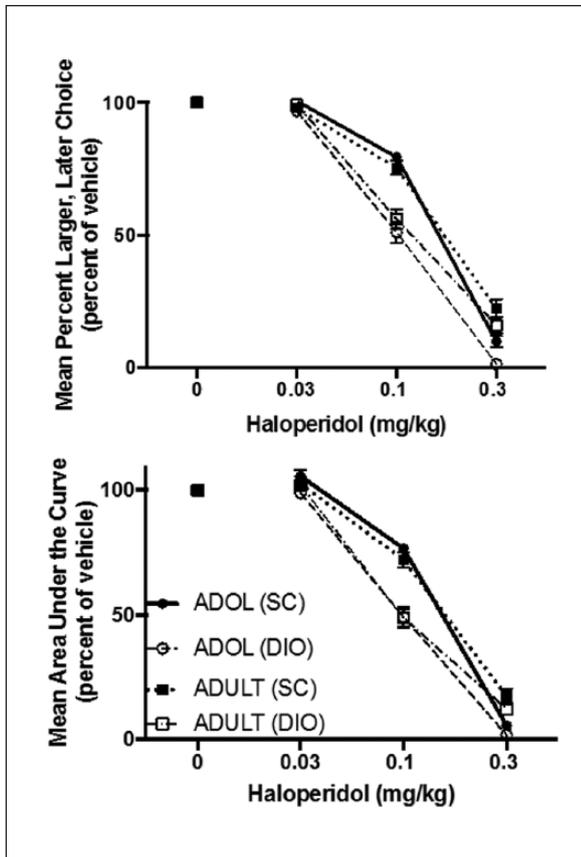


Figure 4. Mean percentage choice (percentage of vehicle) for the three-pellet alternative (top) and mean area-under-the-curve (AUC) values (bottom) as a function of haloperidol dose (adolescent (ADOL) standard chow (SC)=black circles; ADOL diet-induced obesity (DIO)=white circles; adult (ADULT) SC=black squares; ADULT DIO=white circles). Error bars represent one standard error of the mean (SEM). Some error bars are obscured by the data point.

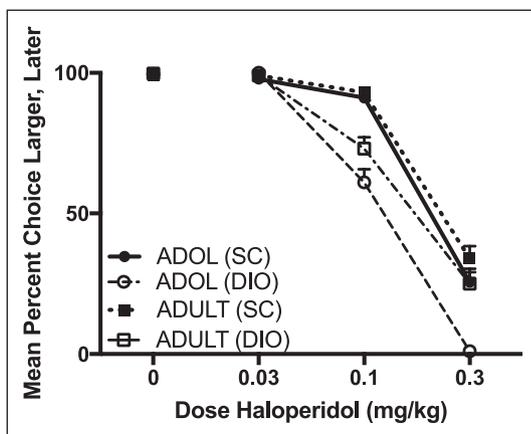


Figure 5. Percentage larger, later (LL) choice during the no delay (0-s) block of the delay discounting task as a function of dose for each group (adolescent (ADOL) standard chow (SC)=black circles; ADOL diet-induced obesity (DIO)=white circles; adult (ADULT) SC=black squares; ADULT DIO=white circles). Error bars represent one standard error of the mean (SEM). Some error bars are obscured by the data point.

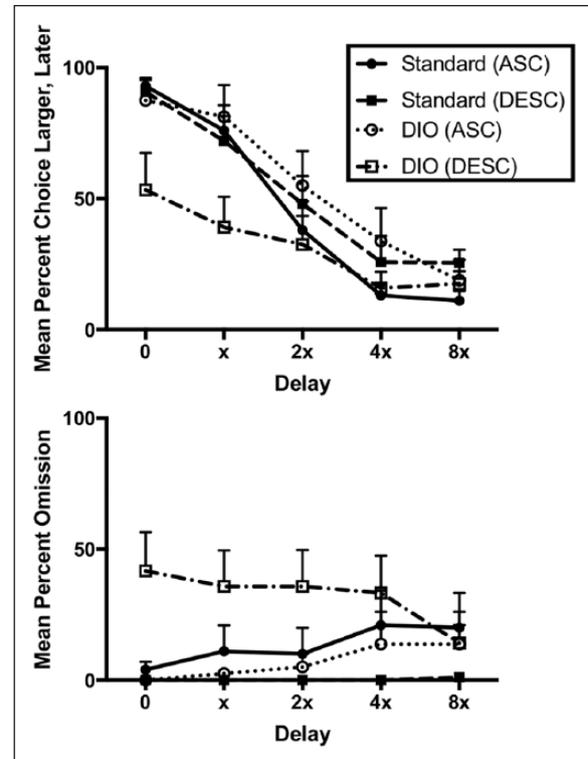


Figure 6. Mean percentage choice for larger, later (LL) (top), and mean percentage omission (bottom) as a function of delay following 0.1 mg/kg of haloperidol for each diet group, displayed for ascending (ASC) or descending (DESC) delay sequences (standard ASC=black circle; standard DESC=black square; diet-induced obesity (DIO) ASC=white circle; DIO DESC=white square). Error bars represent one standard error of the mean (SEM). Some error bars are obscured by the data point.

shown in other studies (Boomhower and Rasmussen, 2014; Koffarnus et al., 2011). Koffarnus et al. (2011) found that 0.1 mg/kg of haloperidol reduced preference for the LL alternative in standard laboratory rats. As such, the finding that all rats showed some shift in delay discounting following an injection of haloperidol is consistent with previous research.

Rats fed a cafeteria diet showed a higher behavioral sensitivity to haloperidol; that is, they became more impulsive for food than the rats fed the standard chow diet. Specifically, at the 0.1 mg/kg dose, rats fed a cafeteria diet showed a reduced tendency to select the LL option than the rats fed a standard diet, regardless of age. This finding is consistent with previous research that has demonstrated that adult rats fed a high-fat diet showed higher behavioral sensitivity to a 0.1 mg/kg dose than rats fed a standard rat chow diet (Boomhower and Rasmussen, 2014; Robertson et al., 2017). This also supports studies documenting diet-induced changes in dopaminergic D_2 that likely affect the reward areas of the brain (Baladi, et al., 2012; Boomhower and Rasmussen, 2014; Geiger et al., 2009; Johnson and Kenny, 2010; Robertson et al., 2017; Val-Laillet et al., 2011; Vucetic et al., 2012).

One possible explanation for the observation that DIO rats showed a lower preference for the LL alternative under haloperidol was, in part, influenced by drug-induced changes in sensitivity to amount. Under the 0-s block, in which there is no delay associated with either food option, haloperidol created a

preference for the smaller, sooner option for some rats – and this was more pronounced in the DIO groups.

In addition to changes in sensitivity to amount, the diet-induced sensitivity to haloperidol can also be explained by a heightened sensitivity to delay. We controlled for ascending and descending order of delays by randomly assigning rats to these two conditions. Rats exposed to standard chow did not differ in terms of discounting whether they received the delays in ascending or descending order. However, DIO rats that received the delays in descending order showed significantly higher impulsivity than those in the ascending delay condition; DIO rats in the ascending delay sequence were statistically indistinguishable from the standard chow groups. A closer inspection of the omission data suggests that DIO rats that experienced the delays in descending order exhibited omissions on over 40% of the trials (including short delays). These omissions were likely not due to drug-related motor effects, because the DIO group that received the delays in ascending order (and the standard diet groups) did not show greater than 5–10% of omissions during these sessions – even at the larger delays. Thus, DIO animals exposed initially to the highest delays were more sensitive to delay. It should be noted that other research using dopaminergic agonists shows that delay sequence interacts with drugs effects on delay discounting. For instance, amphetamine and methylphenidate produce increases in preferences for larger, later food in standard laboratory rats exposed to an ascending, but not descending, delay sequence (Orsini et al., 2017; Tanno et al., 2014). As such, the dopaminergic-influenced changes in discounting rates, whether influenced by drugs or diet, can be impacted by delay sequence.

One surprising finding was the consistent lack of age-related differences in the behavioral data. The rationale for investigating developmental aspects of DIO was influenced by the competing decision systems theory (Bickel et al., 2011, 2014). According to this theory, DA-rich reward areas (e.g. striatal) and prefrontal regions involved in self-control interact to influence impulsive choice patterns. The extent to which one area exerts more influence over the other, in part, determines the extent to which a pattern of impulsivity is evident. In theory, diet-induced changes in D_2 may lead to striatal regions overriding the influence of prefrontal regions. During development, the reward-related striatal regions develop prior to the prefrontal regions, which is thought to influence higher levels of impulsivity in childhood and adolescence (Galvan, 2010; Geier and Luna, 2009). We hypothesized that by using a high-fat, high-sugar diet to dysregulate dopamine D_2 systems during development, it is possible to disrupt the neural development of self-control and reward regions, which would result in a tendency to engage in impulsive patterns of food intake that would persist across development. However, we found no age effects in any of the data.

One possibility that could account for the lack of age differences in discounting is that studies have demonstrated human adolescents and adults differ in terms of delay discounting for money (Green et al., 1994; Hendrickson and Rasmussen, 2016) but not for food (Hendrickson and Rasmussen, 2016). This could reflect differences between discounting rates for secondary, non-consumable reinforcers vs. primary, consumable reinforcers, respectively. Perhaps discounting for food is something that remains stable across the lifespan. More research is needed in this area to determine the extent to which commodity-specific discounting differs across age.

One limitation of this study is that we only investigated a single pellet type (i.e. grain-based pellets). Grain-based pellets are similar in palatability and macronutrient content to the standard chow. In the current study, we opted to use grain-based pellets in order to control for introducing a pellet that differed in terms of palatability and macronutrient content from the standard diet. However, it is possible that rats would show differences in delay discounting using pellets with different palatability and/or macronutrient content. In particular, given that rats fed a cafeteria diet had an extended dietary history of palatable food with a high caloric content from fat and sugar, it is possible that using a less palatable grain-based pellet is not sufficient to observe between-group differences in food impulsivity at baseline. A second limitation is that, although we observed differences in sensitivity to a D_2 antagonist, we are uncertain what brain regions and specific mechanisms are driving these effects. Some possibilities may be reductions in D_2 receptor expression in the striatum (Johnson and Kenny, 2010), reductions in D_2 receptor expression in the VTA (Vucetic et al., 2012), or lower availability of synaptic dopamine (Geiger et al., 2009). These considerations should be assessed in future studies.

Other limitations concern the nature of the cafeteria diet and obesity. First, as previously noted, the practice of selecting the heaviest rats from the cafeteria fed group and the standard diet fed group is conventional in DIO research (Boomhower and Rasmussen, 2014; Huang et al., 2003, 2006; Johnson and Kenny, 2010; Levin and Keesey, 1998; Robertson et al., 2017) and allows researchers to test rats that are more prone, rather than resistant, to DIO. This could be viewed as a limitation because it is possible that only rats that are obesity-prone show sensitivity to dopaminergic compounds prior to diet exposure, which has been demonstrated in a prior study (Vollbrecht et al., 2015). We were not able to disentangle the factors in the current study that contribute to obesity-prone vs. obesity-resistant rats (e.g. pre-existing pharmacological sensitivities) and to be certain that sensitivity to the dopaminergic compound was specific to dietary exposure. However, given that the study of obesity, per se, is a study of factors that underlie the development and maintenance of extreme body mass (Wang et al., 2001), these methods are ecologically valid and appropriate in the context of characterizing an animal model of obesity. Future studies, though, could parse the effects of diet and obesity-proneness in a more controlled manner.

Conclusion

The current findings offer evidence that prolonged exposure to a cafeteria diet leads to subtle changes in behaviors that are unmasked by dopaminergic compounds, especially those that act on the D_2 receptor subtype. The findings also show that at least two specific behavioral mechanisms – sensitivity to delay and sensitivity to amount – drove the diet-induced changes in delay discounting. The study also supports diet-induced alterations in dopamine D_2 by extending neural endpoints involved in reward processes (e.g. Baladi, et al., 2012; Boomhower and Rasmussen, 2014; Geiger et al., 2009; Johnson and Kenny, 2010; Robertson et al., 2017; Val-Laillet et al., 2011; Vucetic et al., 2012) to more complex behavioral mechanisms such as food impulsivity. Future research should seek to characterize environmental factors that influence sensitivity to haloperidol following DIO, with a focus

on disentangling the relative roles of sensitivity to delay and sensitivity to amount and to identify specific neural mechanisms that underlie these alterations.

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