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Diet and vigilance

An obesogenic refined low-fat diet disrupts attentional and behavioral control processes in a vigilance task in rats

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ABSTRACT

Diets consisting of refined foods (REF) are associated with poor physical (e.g., obesity and diabetes) and mental (e.g., depression) health and impaired cognition. Few animal studies have explored the causal links between diet processing and health. Instead, most studies focus on the role of macronutrients, especially carbohydrate and fat concurrently with how processed are the ingredients. We previously showed that a REF low fat diet (LFD) caused greater adiposity and impaired motivation compared to an unrefined control (CON) diet consisting of similar macronutrient ratios (Blaisdell et al., 2014). Here we test the hypothesis that the same REF LFD adversely affects attentional processes and behavioral control relative to the CON diet.

Rats with ad libitum access to the REF diet for two months gained greater adiposity than rats consuming the CON diet. Rats then completed training on a vigilance task involving pressing the correct lever signaled by a brief visual cue whose onset varied across trials. A REF diet reduced accuracy when there was a delay between the start of the trial and cue onset. Poorer accuracy was due to increased premature responses, reflecting impulsivity, and omissions, indicating an inability to sustain attention. These results corroborate the links between consumption of refined foods, obesity, and poor cognition in humans. We discuss the possible causal models that underlie this link.

1. Introduction

Processed and refined foods (REF) are major contributors to poor physical health as reported by observational, epidemiological studies (Caraher and Coveney, 2003; Cordain et al., 2005; Lindeberg, 2010). Consumption of REF diets is also linked to poor mental health and cognitive function, including impairments in attention and concentration, impulsivity, and clinical diagnosis of ADHD (Agranat-Meged et al., 2005; Davis, 2010; Johnson and Kenny, 2010; Pellow et al., 2011), mood disorders such as major depressive disorder (MDD) and anxiety (Akbaraly et al., 2009; Jacka et al., 2010), autism spectrum disorder (ASD) (Wilson, 2013), substance abuse (including food addiction) (Liu et al., 2010), and poor mental functioning/low IQ (Sigman and Whaley, 1998). Children and individuals of low socioeconomic status (Halfon et al., 2013) may be particularly vulnerable to the effects of a REF diet. There also exist strong links between consumption of REF diets with Alzheimer's disease (AD) and cognitive decline (Greenwood and Winocur, 2005; Kanoski and Davidson, 2011).

Many of these conditions are linked to dysregulation of mesolimbic dopamine (DA) (Campbell and Eisenberg, 2007). Early or chronic intake of a REF diet is also associated with behavioral problems and poor school and work performance stemming from impaired focus and concentration (Benton, 2008; Liu et al., 2004; Fu et al., 2007). Consumption of REF diets early in childhood is associated with increased hyperactivity later in childhood (Wiles et al., 2009). Dysregulation of attention is a defining feature of some psychopathologies, such as ADHD, and drug addiction is often comorbid with these conditions (Biederman et al., 1995), and may contribute to aggression and anti-social behavior in children (Benton, 2008). REF diets are also deficient in a number of key nutrients that play an important role in brain development. Deficiencies in these micronutrients can thus lead to developmental cognitive

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disorders (Bryan et al., 2004). Thus, it is critical to understand how our modern food environment may be contributing to impairments in attention and behavioral control.

While human epidemiological science suggests a strong link between consuming REF diets and poor physical and mental health, well-controlled experiments are difficult to perform in humans, thereby necessitating an animal model—such as the rodent—with which to determine causal relationships. Not surprisingly, a large literature has accumulated reporting on the negative impact of "Western Diets" in rodent physical health (Martin et al., 2010) as well as brain and cognition (Davidson et al., 2014; Freeman et al., 2014). Despite this large and growing literature, there are few studies that investigate the relationship between degree of **refinement** independent of macronutrient (carbohydrate, fat, and protein) ratio (e.g., high-fat versus low-fat diets, etc.). To clarify terminology, whole foods are those whose ingredients derive from whole food sources, whereas refined foods are those made from ingredients that have been separated and isolated from the original whole food context, such as sugar and flour, industrial seed oils, and isolate proteins, such as whey, casein, and soy (see Spreadbury, 2012). This is important because diets can promote health or induce harm despite being high or low in fat or carbohydrate. For example, high-fat, low-carbohydrate (HF/LC) diets have been experimentally shown in rodents to sometimes cause poor health typically when they also contain sugar (Freeman et al., 2014) or maintain good health typically when they are ketogenic (involve the use of ketone bodies as a metabolic fuel substrate) (Douris et al., 2015; Kennedy et al., 2011). Likewise, low-fat, high-carbohydrate (LF/HC) diets have been experimentally shown in rodents to sometimes cause poor health, especially when high in sugar (Coelho et al., 2010; Lombardo et al., 1996), or maintain good health (Reeves et al., 1993), typically when containing more whole grains.

A review of these studies suggests the hypothesis that diet quality may be a critical factor determining a diet's healthfulness. In the cases where a diet is healthy, it is generally composed of fewer artificially-derived (e.g., synthetic or isolated) ingredients and instead incorporates ingredients derived from a whole-food source. On the other hand, a substantially higher percentage of unhealthy diets appear to be composed of refined and purified ingredients, such as refined flour and sugar, industrially-refined oils, and protein isolates such as casein or soy isolate. The combination of fat, sugar, and salt in REF diets has been optimized to lead to overconsumption by laboratory rodents, such as on cafeteria diets including refined foods (Johnson and Kenny, 2010). In addition, commercial REF diets designed for rodents, such as the one used in this study, tend to be deficient in many important fatty acids and nutrients, such as Omega-3 (n3) poly unsaturated fatty acids (PUFA) and naturally-occurring trans-fatty acids that are beneficial to health (vaccenic acid, conjugated linoleic acid, etc.).

To address the issue of diet quality directly, we recently compared in rats the effects on motivation of consumption of two low-fat diets that had similar macronutrient ratios but that differed substantially in the degree of refinement of their ingredients (Blaisdell et al., 2014). Rats consuming a REF diet were compared to rats consuming a healthy control (CON) diet. Not only was the REF diet obesogenic; it also resulted in impairments in motivation assessed using a progressive ratio (PR) schedule of instrumental lever pressing. Rats on the REF diet took longer breaks between bouts of lever pressing for either food (sucrose solution) or water, suggesting a general impairment in motivation to perform the task as effort increased to receive each additional reinforcer (food or water). Finally, when some of the rats on each diet were switched to being fed the other diet for nine days, no changes in motivation-based performance were observed. Rats that had consumed the healthy CON diet for 9 days following months of consuming the REF diet continued to show motivational impairments, whereas rats that had chronically consumed the CON diet but switched to the REF diet for 9 days showed no signs of developing impairments in motivation as a result of the short time on the refined diet.

In this paper, we further investigate the effects of consuming the obesogenic low-fat REF diet on attentional and behavioral control processes in the rat. We developed a Two-Choice Visual Discrimination Procedure (2CVDP) to assess vigilance, defined as sustained attention to detect a brief stimulus event. In this task, each trial begins with the simultaneous insertion of two choice levers followed by a brief presentation of a light over one of the two levers. The rat must wait for the light to appear after which it has a brief period of time in which to press the lever under the light to earn a food reinforcer. The 2CVDP has been successfully used in rodents to dissociate and isolate attentional processes from processes of working memory, motivation, and general motor capacity (Ward et al., 2012). This task has been used to reveal specific impairments in sustained attention, but not working memory, that result from medial prefrontal lesions (Kahn et al., 2012). Thus, we applied this task to test the hypothesis that consuming a REF diet would cause impairments in sustained attention in rats.

2. Methods

2.1. Subjects

Thirty-two experimentally-naïve female Long Evans rats (*Rattus norvegicus*) from Harlan (Indianapolis, IN) served as subjects. Our sample size was chosen based on prior work in our lab showing significant effects of the diets used on weight and motivation using the same sample size (Blaisdell et al., 2014). 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 beginning the experiment, a progressive food restriction schedule was imposed so that each cage of pair housed rats received approximately 25 g (7 pellets) of standard rat chow (LabDiets 5001). Body weights were recorded every other day for the duration of the experiment.

2.2. Diets

The REF diet (Research Diets D12450B) was 20% protein, 70% carbohydrate, and 10% fat. The primary ingredients of the REF diet included Casein (200 g) and L-Cystine (3 g) as the protein sources; sucrose (350 g), corn starch (315 g), and maltodextrin (35 g) as the carbohydrate sources; cellulose (50 g) for fiber; soybean oil (25 g) and lard (20 g) as the sources of fats; and vitamin, minerals, and artificial coloring. The CON diet (LabDiets 5001) was 28% protein, 58% carbohydrate, and 13% fat. The primary ingredients of the CON diet included in order of quantity: corn meal, soybean meal, beet pulp, fish meal, oats, brewer's yeast, cane molasses, alfalfa meal, whey, wheat germ, porcine fat, porcine meat, vitamins and minerals. The diets, both commercially available rodent chows, differed in the amount of refinement and purification that went into their production (see Appendix for diet sheets provided by the manufacturers). The REF diet was more energy dense, at 3.85 kcal/g than was the CON diet at 3.02 kcal/g of metabolizable energy.

2.3. Apparatus

Behavioral training was conducted in a small room containing eight conditioning chambers. Each conditioning chamber measured $30 \times 25 \times 20$ cm (L x W x H) and was housed in separate sound-attenuating and light-attenuating environmental isolation chests (ENV-008, Med Associates, Georgia, VT). The front and back

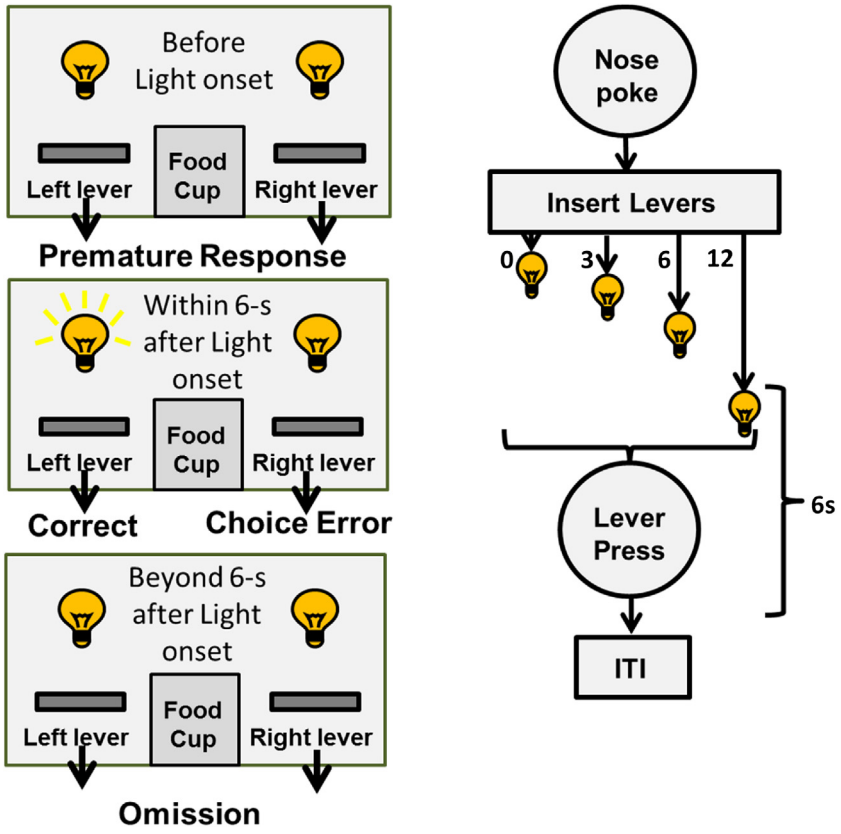

Fig. 1. Left panels: Schematic of front panel of the rat chamber equipped with two lights, each above one of two levers. One lever to the left, the other to the right of the food cup. The top panel shows the outcome of pressing a lever prior to light onset. The middle panel shows two possible outcomes with a lever press within 6-s after light onset. The lower panel shows the outcome of failing to press the lever within 6-s after light onset. Right panel: Diagram of trial structure. Each trial began with a nose poke into the food cup, which caused the levers to insert into the chamber. One of the two lights would illuminate for 1-s duration, either immediately with lever insertion, or following a delay of 3, 6, or 12 s. A trial ended when a lever was pressed within 6 s of light onset, or 6 s after light onset if no lever press was made.

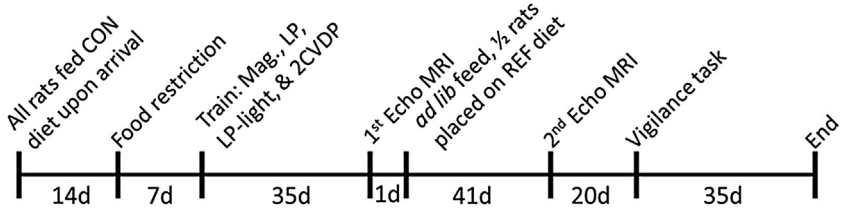

Fig. 2. Timeline of experiment. Mag = magazine training, LP = lever press training, 2CVDP = two-choice visual discrimination procedure, d = days.

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 kept dark except during the presentation of a light stimulus.

Each chamber was equipped with a liquid-dipper (ENV–202 M, Med Associates) located at the bottom middle of the right-side chamber wall. The dipper consisted of an arm with a small well (0.05 cc) at the end that could be lowered into a trough of sucrose solution (20% by volume) and then raised so the well protruded up into a recessed liquid food cup. Delivery of sucrose solution served as the appetitive reinforcer. An infrared photo beam was projected across the inside of the food cup. Interruption of the beam by the rat's nose entering the receptacle was recorded as a nose poke.

Each chamber was equipped with two 3.5-cm wide retractable levers (ENV-112CM, Med Associates), located on the metal wall of the chamber 8 cm to the left and right of the food cup, respectively, and 6.5 cm above the grid floor. Each lever could be independently programmed to retract from or extend 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.

Each chamber was equipped with two LED lights. Both were located on the right-side chamber wall, 6 cm below the ceiling. One was 8 cm above the right lever, and the other was 8 cm above the left lever. A schematic of the layout of the lights, levers, and drinking receptacle is shown on the left side of Fig. 1.

An echo Magnetic Resonance Image (MRI) 4-in-1 was located in a small room. The machine was connected to a QNMR system that measures body fat, lean mass, fluids and total water in live mass in rats weighing 10–1000 g.

2.4. Procedure

Fig. 2 provides a timeline of all experimental procedures. All rats initially were provided the CON diet which they consumed during all phases of behavioral training except for the Vigilance task (see below).

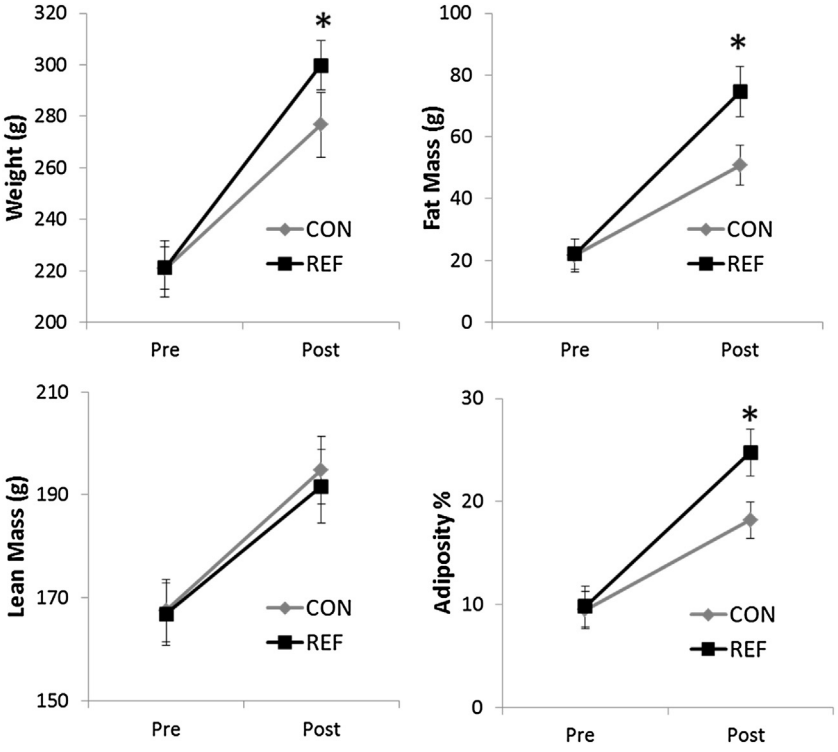

Fig. 3. Mean (& 95% CI) change in weight (top left) fat mass (top right), lean mass (bottom left), and adiposity (bottom right) in the CON and REF rats before and 2 months following consumption of the respective diets. Prior to the REF diet, all rats were on the CON diet.

2.4.1. Magazine training

The levers were retracted during this stage of training. In a single 60-min session, sucrose was delivered every 20 ± 15 s to train rats to approach and drink from the food cup.

2.4.2. Lever-press shaping

During this phase, rats were trained to approach and press the operant levers to gain access to sucrose solution. During each 60-min session, each lever was inserted into the chamber one at a time for a 5-min period on an alternating schedule, such as the left lever available for the first five minutes of the session, followed by the retraction of the left lever and extension of the right lever for the next five minutes, followed by the left lever again, etc. Lever press shaping was conducted on a continuous reinforcement schedule (CRF) in which each lever press was followed by delivery of sucrose solution. Additionally, sucrose was delivered every time a lever was inserted into the chamber (every 5 min), noncontingent on lever pressing. Sucrose was delivered by lowering the dipper into the trough of sucrose solution and raising it back into the food cup. Rats were required to press each lever a minimum of 25 times during two consecutive 60-min sessions to advance to the next stage of training. Failure to meet this criterion resulted in additional shaping sessions until criterion was met.

2.4.3. Lever-light contingency training

During each 60-min session, each lever was inserted into the chamber for 5-min periods on an alternating schedule. The light above the inserted lever was illuminated coincident with lever insertion. During the presentation of the light, pressing the lever below resulted in termination of the light and delivery of sucrose solution. Each sucrose delivery was followed by a 10-s intertrial interval (ITI). Following the ITI, the light was presented again. A single lever press during each light presentation was reinforced, while lever presses during the ITI had no consequence. This procedure continued for 5 min, after which the lever was retracted, the light terminated, the other lever was extended, and the other light was presented. Rats were required to press each lever a minimum of 25 times during a 60-min session to advance to the next stage of training.

2.4.4. Two-choice visual discrimination task

During this stage of training, a trial was initiated by the rat placing its nose into the food cup, whereupon the left and right levers were simultaneously inserted into the chamber, and the light located above one of the levers (randomly determined) was illuminated. The light remained on until the rat made a choice (pressing the right or left lever) or until 60 s had elapsed, whichever came first. If 60 s had elapsed without a lever press, the light was extinguished, the levers were removed, and the next trial began when the rat again placed its nose in the food cup. During a trial, a single press (CRF) of the lever under the light (correct choice) resulted in retraction of the levers, termination of the light, and delivery of sucrose, followed by an ITI. During this and all subsequent stages of the procedure, sucrose was only available for a 10-s period following delivery. A single press of the lever under the unilluminated bulb (incorrect choice) resulted in the retraction of the levers, termination of the light, the end of the trial without reinforcement, and the start of the ITI. Each ITI was set to a minimum of 10-s in duration. This required that the rat not place its nose into the food cup for 10 continuous seconds. If the rat placed its nose into the food cup prior to the elapsing of the 10-s ITI, the ITI clock was reset to zero and the ITI interval restarted. After this response-withholding criterion was met, the next trial commenced when the rat placed its nose into the food cup. Each session contained an equal number of trials with the left and right bulb illuminated. The order of left and right light illumination trials was randomly determined in four blocks of 20 trials, each block containing 10 left-light and 10 right-light trials. Daily sessions for this and the following stage of training lasted until 80 trials or 60 min had been reached, whichever came

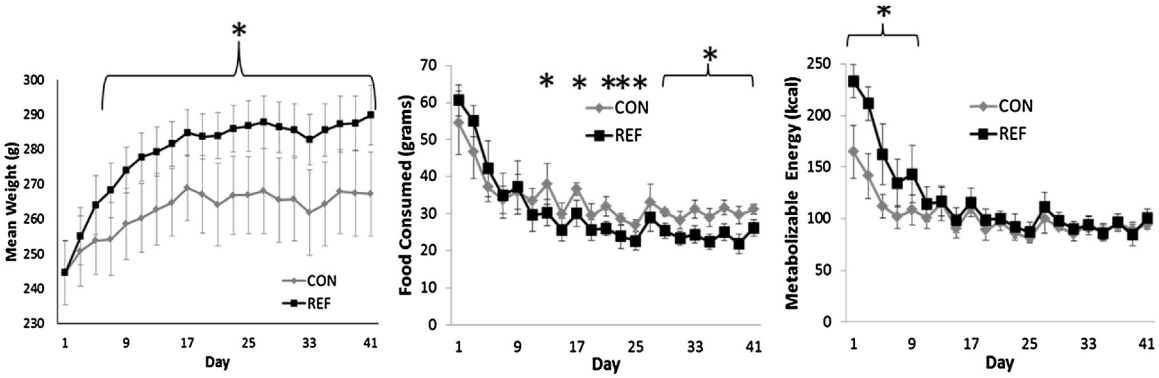

Fig. 4. Mean (& 95% CI) weight (left), food consumption (middle), and metabolizable energy consumption (right) during the first 41 days after initiation of free-feeding and placement on diet (CON and REF).

first. Each rat was trained on this procedure until a criterion of 80% correct on 2 consecutive sessions was reached.

2.4.5. Introduction of diets and body composition analyses

Once all rats had reached criterion performance on the two-choice visual discrimination training procedure, their body compositions were analyzed using an echo MRI. Following the echo MRI, half of the rats were placed on unrestricted feeding of the REF diet. The remaining rats were placed on unrestricted feeding of the CON diet. After 41 days of ad lib feeding on their respective diets, all rats received a second echo MRI scan to determine body composition changes related to diet. Following this second scan, rats were placed on a food restriction schedule for 20 days to prepare them for behavioral testing on the Vigilance task.

2.4.6. Vigilance task

The Vigilance task began 2 months after the rats had been placed on their respective diets (REF and CON), and after completion of the second echo MRI body scan. The Vigilance task procedure was a variation of two-choice visual discrimination training procedure, with the addition of two modifications. First, variable delays between the start of the trial and the onset of the light were introduced. The interval between trial onset (with both levers inserted at the start of each trial) and cue light onset (or stimulus-onset asynchrony; SOA) was varied with values of 0, 3, 6, and 12 s. The delay for each trial was selected according to a pseudorandom schedule, in three blocks of 24 trials (for a total of 72 trials per session). Each 24-trial block contained 6 each of 0-s, 3-s, 6-s, and 12-s delay trials, three with the left cue-light and three with the right cue-light for each delay. Thus, each trial was initiated by the rat placing its nose into the food cup (once the 10-s minimum ITI criterion had been met). Once the trial initiated, both levers were extended into the chamber. One of the lights was then presented following one of the four delays. A second change that was made in this procedure was that the duration of light illumination was fixed at 1 s. A *Correct response* consisted of pressing the lever underneath the illuminated light. Correct responses made within 6 s of light onset (i.e., during the light presentation, or during the 5-s period following light termination) were reinforced (i.e., a limited hold schedule of reinforcement was in effect). If the correct lever was not pressed within this 6-s period, the trial would end without reinforcement, with the levers being retracted, and the start of the ITI. Each incorrect trial was scored as one of three types of error. 1) A *Premature response* was recorded if the rat pressed a lever prior to light onset. Such responses were considered incorrect and a measure of impulsivity. 2) A *Choice error* was recorded when the incorrect lever was pressed within the 6-s window following light onset. 3) An *Omission error* was recorded if the rat failed to press a lever within 6 s following light onset. Such errors were considered indicative of lapses in attention. Training continued until accuracy and error rates stabilized, which took 35 sessions.

2.4.7. Body scans

Each rat received two echo MRI body scans. The first scan was taken on the day prior to placing half of the rats on the REF diet, and the second scan was taken 41 days after the first scan was taken. For each scan, all 32 rats were transported from the Psychology Department vivarium to the room at CHS housing the echo MRI machine. Each rat was scanned one at a time. The procedure for scanning a rat involved removing the rat from the transport cage and placing it in a long transparent acrylic tube with an opening at one end. Once the rat was placed, nose first, inside the tube, a plunger with a bung that fit snug against the inside of the tube was inserted. The plunger was slowly and gently pushed forward, forcing the rat towards the front of the tube where it was held secure so that it could not turn around inside the tube during the scan. Once the rat was secured, the tube was gently inserted into a circular opening in the echo MRI machine. Once the tube was all the way in place, the scan was started by the press of a button. About a minute later, the completion of the scan was signaled by an auditory alert. The tube was removed from the machine and the rat was retrieved from the tube and placed back in the transport cage. The process repeated again with each rat until all 32 rats had been scanned. Each scan took about 2 min to complete. Body composition data from the scans were stored in a single electronic file containing all the data coded by each subject for later analysis.

3. Results

3.1. Weight and body composition

The first echo MRI showed that all rats had a similar body weight and composition prior to the REF rats being placed on the refined diet (Fig. 3). After two months on their respective diets, a second echo MRI scan revealed that both groups of rats increased in weight, fat mass, lean mass, and% adiposity. These observations were supported by 2-way repeated-measures analysis of variance (rm-ANOVA) conducted on each measure with diet (CON and REF) and time (Pre and Post) as factors. There were main effects of time for weight, $F(1, 30) = 418.21$, $p < 0.001$, $\eta p^2 = 0.93$, fat mass, $F(1, 30) = 189.35$, $p < 0.001$, $\eta p^2 = 0.86$, lean mass, $F(1, 30) = 258.85$, $p < 0.001$, $\eta p^2 = 0.90$, and adiposity, $F(1, 30) = 143.20$, $p < 0.001$, $\eta p^2 = 0.83$. There were also main effects of diet on fat mass, $F(1, 30) = 12.18$, $p = 0.002$, $\eta p^2 = 0.29$, and adiposity, $F(1, 30) = 11.17$, $p = 0.002$, $\eta p^2 = 0.27$. Critically, there was an interaction between diet and time for increase in weight, $F(1, 30) = 12.02$,

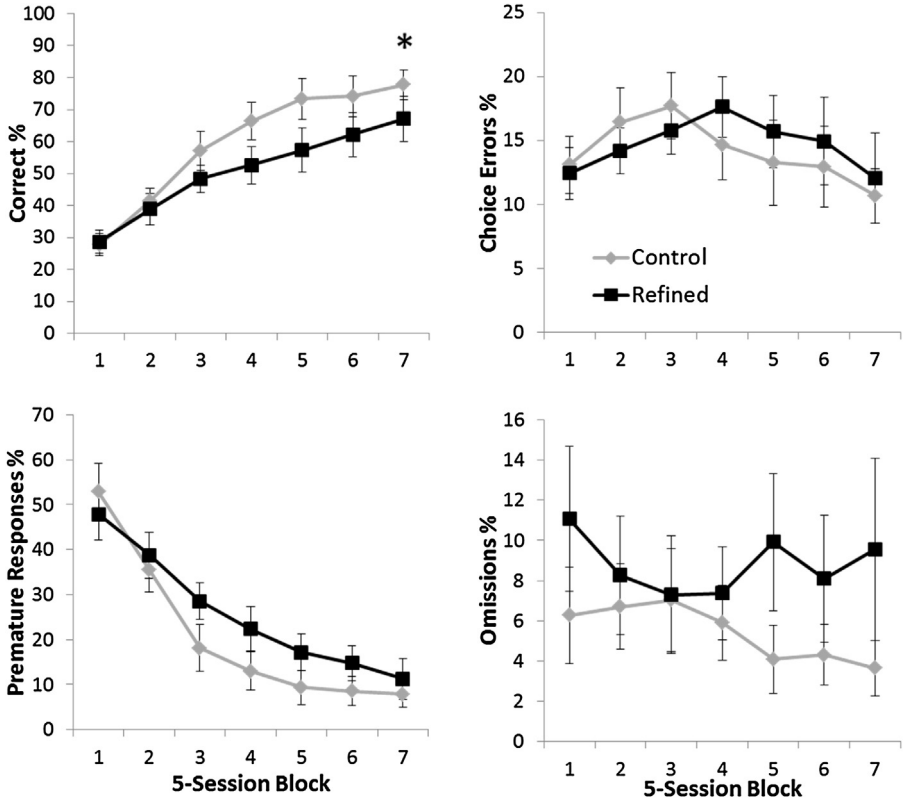

Fig. 5. Mean (& 95% CI) percent correct responses (top left), choice errors (top right), premature responses (bottom left), and omissions (bottom right) in rats on the REF and CON diets across 5-session blocks of training on the Vigilance task.

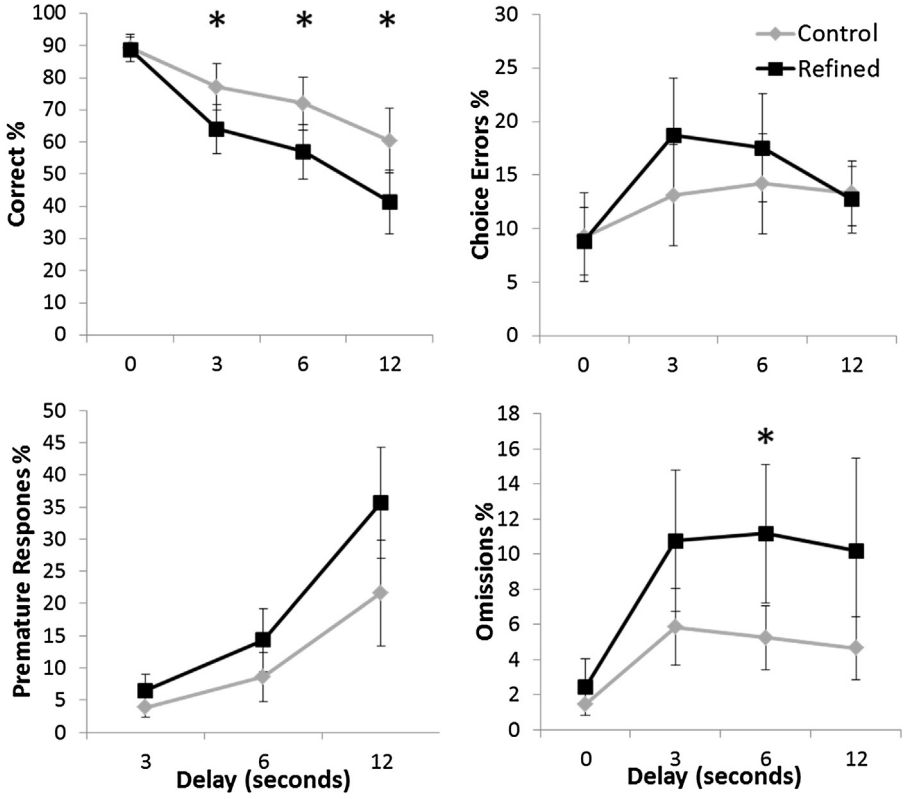

Fig. 6. Mean (& 95% CI) percentage of correct responses (top left), Choice errors (top right), Premature responses (bottom left), and Omissions (bottom right) in rats on the REF and CON diets as a function of light delay during the last 10 sessions of the Vigilance task.

$p = 0.002$, $\eta p^2 = 0.29$, fat mass, $F(1, 30) = 15.60$, $p < 0.001$, $\eta p^2 = 0.34$, and adiposity, $F(1, 30) = 10.02$, $p = 0.004$, $\eta p^2 = 0.25$, but not for lean mass, $F < 1.0$. Thus, the REF diet caused significantly greater weight gain and fat mass, but not lean mass. Planned comparisons revealed that, compared to CON rats, REF rats had greater weight, $F(1, 30) = 8.23$, $p = 0.007$, $\eta p^2 = 0.215$, fat mass, $F(1, 30) = 20.12$, $p < 0.001$, $\eta p^2 = 0.401$, and adiposity, $F(1, 30) = 19.65$, $p < 0.001$, $\eta p^2 = 0.396$, after two months on the REF diet.

Most of the difference in weight between dietary conditions accrued during the first 17 days after placement on their respective diets with *ad libitum* feeding (Fig. 4, left). This was supported by a Day x Diet interaction, $F(20, 280) = 4.30$, $p < 0.001$, $\eta p^2 = 0.24$. Differences in weight between diet conditions emerged on Day 4. All rats had been on a food-restriction schedule for initial training prior to placing half of the rats on the REF diet, thus, rats in both dietary conditions increased in weight as a result of free feeding, $F(20, 280) = 44.59$, $p < 0.001$, $\eta p^2 = 0.76$. The difference in accumulated weight was due to rats on the REF diet consuming a higher metabolizable energy content, $F(1, 14) = 11.65$, $p < 0.005$, $\eta p^2 = 0.45$ (Fig. 4, right), despite the fact that, overall, rats on the CON diet consumed more food by weight, especially after about Day 9 (Fig. 4, middle), $F(1, 14) = 5.92$, $p < 0.05$, $\eta p^2 = 0.30$. This is not surprising given that the energy density of the REF diet was higher, and therefore the initial equivalent amount of consumption during the first 9 days would constitute a higher energy intake for rats on the REF diet than on the CON diet (cf. right panel of Fig. 4). Energy consumption was greater in Group REF than in Group CON for the first 9 days of free feed, but energy consumption by rats on the REF diet dropped thereafter to match that of rats on the CON diet. Food consumption by weight was greater in Group CON than in Group REF on Days 13, 17, 21–25, and 29–41, $ps < 0.05$.

3.2. Vigilance task acquisition

All rats quickly acquired magazine training (1 day), lever press shaping (5 days), lever-light contingency training (6 days), and 2CVDP training ($M = 25.90$ days, 95% CI [23.38, 28.43]). Fig. 5 shows accuracy and error rates across the 35 sessions of Vigilance training. Given prior training on the no-delay 2CVDP, introduction of delays reduced accuracy to about 25% for both diet groups. To assess the impact of diet on training, we performed a number of rm-ANOVA, separately for percent correct responding and the three error types, with diet (CON, REF) and 5-Session Block as factors. Accuracy increased ($F(6, 132) = 121.80$, $p < 0.001$, $\eta p^2 = 0.85$) and premature responses decreased ($F(6, 132) = 104.54$, $p < 0.001$, $\eta p^2 = 0.83$) across block. There was also a main effect of block on choice errors ($F(6, 132) = 5.05$, $p < 0.001$, $\eta p^2 = 0.19$). We found a main effect of diet on percent correct ($F(1, 22) = 5.39$, $p = 0.023$, $\eta p^2 = 0.20$), with better performance by CON than REF rats. Finally, diet X block interactions for percent correct ($F(6, 132) = 5.22$, $p < 0.001$, $\eta p^2 = 0.19$) and premature responses ($F(6, 132) = 4.48$, $p < 0.001$, $\eta p^2 = 0.17$) revealed that accuracy reached asymptotic levels faster for rats on the CON compared to the REF diet due to a faster increase in accuracy and decrease in premature responses. We also found a diet X block interaction for omissions ($F(6, 132) = 2.78$, $p = 0.014$, $\eta p^2 = 0.11$). By block 7, accuracy was higher for CON rats ($M = 77.76$, 95% CI [73.15, 82.36]) than REF rats ($M = 67.12$, 95% CI [60.10, 74.15]), $F(1, 22) = 4.85$, $p = 0.038$.

3.3. Vigilance task delay analysis

We pooled data over the last 10 sessions of training during which performance had reached a stable asymptote (Fig. 6). Correct responses were equally high (about 90%) for both CON and REF rats at the 0-s delay. A Bayes Factor (BF) = 33.56 showed strong support for the Null hypothesis that the two conditions did not differ in accuracy on no-delay trials (http://cognitivegenetic.rutgers.edu/ptn/). Likewise, both groups had equally low percentages of Choice errors (BF = 28.80) and Omission errors (BF = 251.54) at the 0-s delay. This is important in that it establishes that there was equivalently strong stimulus control by the light for both diet groups, and that the rats on the REF diet were equally motivated and capable of responding as were rats on the CON diet. That is, performance variables at the zero-delay were equated across dietary conditions. Thus, differences in performance at increasing delays cannot be interpreted as resulting from differences in motivation or capability in engaging in the basic task (Ward et al., 2012). Rather, they would suggest deficits in sustained attention and behavioral control, both necessary to respond to an unpredictably-timed brief external event (i.e., vigilance).

As delays increased accuracy declined and errors tended to increase in both groups, $F(3, 87) = 95.32$, $p < 0.001$, $\eta p^2 = 0.77$. Accuracy declined more steeply for REF than CON rats, $F(3, 87) = 6.01$, $p < 0.001$, $\eta p^2 = 0.17$, with significant differences in accuracy at the 3-s ($F(1, 29) = 5.88$, $p = 0.022$), 6-s ($F(1, 29) = 6.18$, $p = 0.019$), and 12-s ($F(1, 29) = 6.90$, $p = 0.019$) delays. This was largely due to greater increases in premature responses, $F(1, 29) = 4.67$, $p = 0.039$, $\eta p^2 = 0.14$, and omissions, $F(1, 29) = 5.62$, p=0.025, $\eta p^2 = 0.15$ in rats consuming a REF compared to a CON diet. There was a main effect of delay on choice errors, $F(3, 87) = 8.71$, $p < 0.001$, $\eta p^2 = 0.23$. While choice errors were nominally higher in the REF than CON rats at the 3-s and 6-s delays, these differences were not significant, $p = 0.136$ and $p > 0.250$, respectively. We assessed correlations between adiposity and performance measures, but none of the correlations were significant. Thus, it appears that while diet itself had a main effect on both adiposity and some of the behavioral measures of vigilance and behavioral control, adiposity did not appear to be a strong direct causal factor affecting performance.

4. Discussion

Rats consuming a REF diet consisting of refined and purified ingredients became obese and showed impairments (relative to rats consuming a CON diet) in vigilance in detecting the brief presentation of a light. The increasing difference between the dietary groups in the percentage of premature responses suggests that rats consuming the REF diet were more impulsive than rats consuming the CON diet. The higher percentage of omission trials shown by rats on the REF diet compared to the CON diet at all non-zero delays suggests that REF rats also had greater lapses in attention, reflecting a difficulty in maintaining focused and sustained attention. Nevertheless, the similarity in choice errors between the two groups suggests that when the rats on the REF diet were attending to the task, they were able to perform as accurately as did rats on the CON diet. Rats consuming a CON diet consisting of ingredients derived largely from unrefined, whole-food sources, however, remained comparatively lean, and showed better performance on the vigilance task than did rats consuming the REF diet.

REF diet animals exhibited more omissions. This could reflect one of two things. First, it might reflect an altered motivation following exposure to the high-sugar REF diet. Could it be that the food restriction imposed on subjects for conducting the Vigilance task was less effective in REF animals? They had more white adipose tissue and therefore may have had greater energy reserves. Greater amounts of white adipose tissue, however, is often accompanied by leptin resistance (Spiegelman and Flier, 2001; Münzberg et al., 2004). Leptin resistance impairs the monitoring of energy reserves stored in adipocytes, and thus impairs access to energy reserves stored in fat tissue. Also, as shown in Fig. 4, after the first week on the diet, REF rats were consuming the same number of calories as

were CON rats. This remained the case throughout and following completion of the study. Thus, it is unlikely that food restriction had different effects on motivation in the two dietary conditions given that rats in each condition were consuming the same number of calories daily while on ad lib feeding. This conclusion that motivation was similar between diet groups was also supported by the equal and high accuracy and equal and very low level of omissions on the 0-delay trials.

The second interpretation of greater omissions in rats on the REF diet is in terms of an impairment in maintaining sustained intention. If the REF diet or the obesity phenotype it causes affect areas of the brain, such as the PFC, responsible for attentional processes, then attention itself could become dysregulated. We discuss the mechanisms of the effects of the REF diet on cognition further below.

We intentionally chose diets that differed in many factors as a result of the CON diet consisting of ingredients derived from whole foods and the REF diet built from highly refined and purified ingredients. This was done for purposes of ecological validity, with the intent to mimic the large differences between a primarily whole-foods versus refined-foods diet as consumed by humans in real world settings. Consuming a REF diet by humans is associated with obesity and poor mental health and cognition. What factor or factors that differed between the two diets caused the differences in adiposity, attention, and behavioral control in our study? Although the CON and REF diets were similar in macronutrient content, they differed in the degree of refinement and purification of the ingredients that constituted the two diets. The CON diet contributed proteins, fats, and carbohydrates from less processed sources, such as ground seeds and animal matter. The REF diet, however, was derived from refined and purified ingredients that had been isolated from the original foods in which they are found. Protein, for example, consisted of casein which is derived from dairy. Fats were derived from industrially rendered soybean oil and industrially rendered lard (porcine belly fat). Carbohydrate was primarily from sucrose, corn starch, and some maltodextrin. The differences in the sucrose content made the REF diet much sweeter than the CON diet. Higher sweetness could be a basis for increased caloric intake of the REF compared to the CON diet during the initial week after being placed on the REF diet, which led to higher adiposity. It's possible that the higher sugar content of the REF diet led to hyperglycemia or changes in insulin sensitivity compared to the low-sugar CON diet. High-sugar diets have been linked to cognitive impairments in human and nonhuman animals (Hsu et al., 2015; Jurdak and Kanarek, 2009; Ross et al., 2009; Lowette et al., 2015; Ye et al., 2011). This could be the basis for the behavioral differences between rats fed REF and CON diets in our study. Future research could discern whether disturbance of glucoregulation is a contributor to these cognitive impairments.

The two diets also differ in regards to how processed and refined are the fats and proteins, thus further manipulations of each macronutrient independently of the rest is necessary to make specific claims about their causal role in our effects. Given that natural human diets that run the gamut from low carb to low fat are healthy (Lindeberg, 2010), we hypothesize that it is the degree of refinement and not macronutrient ratio that determines whether a diet is healthy or contributes to disease. The degree of refinement is the major difference between the two diets used in this study, and so this is what caused the differences in adiposity and cognition in our rats. We next consider the biological mechanisms of the effect of diet on sustained attention and behavioral control.

Impairments in sustained attention and behavioral control are both symptoms of ADHD. To what degree has diet been implicated in these symptoms? While early studies found equivocal evidence for a role of diet in the manifestation or treatment of ADHD, more recent studies have uncovered specific dietary factors that are involved in ADHD symptoms (Schnoll et al., 2003; Stevenson et al., 2014). Diets that eliminate allergenic foods or highly processed foods have led to improvements in behavioral and cognitive symptoms of ADHD (Pelsser et al., 2011; Arnold et al., 2013). More promising work has revealed the role of polyunsaturated fats, in particular n3 fatty acids (FA, e.g., alpha linolenic acid). Deficiencies in n3-FA are associated with worsening symptoms (Hawkey and Nigg, 2014) while n3-FA supplementation has resulted in marked improvements in ADHD symptoms (Hawkey and Nigg, 2014; Millichap and Yee, 2012). One study in particular (Vaisman et al., 2008) found that supplementing n3-FA improved performance on a visual sustained attention task in children with inattention. Treatment with multi-nutrients (vitamins and minerals) has also shown to reduce ADHD symptoms (Rucklidge et al., 2014; Rucklidge and Kaplan, 2014). These intriguing findings suggest that various differences between the CON and REF diets used in our study may be contributing to the cognitive deficiencies shown in rats on the REF diet, such as insufficient n3-FA, the large amount of sugar, and a micronutrient deficient in the REF diet.

What brain mechanisms are affected by the REF diet to cause dysfunction in sustained attention and behavioral control? The frontal cortical regions, especially prefrontal cortex, have long been known to be involved in executive function, including working memory, sustained attention, and behavioral inhibition. Through its connections to most other areas of the brain, especially the basal ganglia, hippocampus, other cortical regions, and thalamus, the frontal system is involved in regulating behavioral decision making. Frontal circuit involvement in attention, specifically, is modulated by cholinergic signaling in both rats and humans (Demeter et al., 2008). Cholinergic deficiencies during early in life lead to developmental dysfunctions in sustained attention in mice (Mohler et al., 2001; Meck and Williams, 2003). Treatment with a nicotinic acetylcholine receptor (nAChR) agonist mitigates the deterioration of sustained attention induced by a distractor, suggesting that second-long increases in cholinergic activity (aka 'transients') mediate the detection of cues and that nAChR agonists augment such transients (Howe et al., 2010; Sarter et al., 2009). Transients mediate shifts from a state of perceptual attention, or monitoring for cues, to cue-evoked activation in both rats and humans (Howe et al., 2013). In humans, vulnerability to distraction induced experimentally and in real life settings is related to a genetic polymorphism in the cholinergic system (Berry et al., 2014). Enhancement of cognitive control in sustained attention tasks in rats involves mesolimbic activation of cholinergic projections to the PFC (St Peters et al., 2011). Thus, very short-term (seconds) changes in cholinergic modulation are triggered by sensory input cues and facilitate cue detection and attentional performance. It has been proposed that cholinergic induction of evoked intrinsic, persistent spiking mechanisms in frontal cortex serve to maintain sensory input and planned responses (Hasselmo and Sarter, 2011). We found that long-term consumption of a REF diet by rats resulted in impairments in sustained attention and self-control. Given the literature showing that these capacities are governed by the frontal cholinergic system, we hypothesize that a REF diet induces changes that dysregulate this system. If so, this raises important implications for diets consisting largely of processed and refined ingredients to cause similar dysregulation of attention and behavioral control in people. Given the long-term disruption of these cognitive processes in the face of dietary deficiencies early in development, children may be particularly vulnerable to the cognitive impairments induced by consuming a refined foods diet. Future work should be undertaken to test this hypothesis.

With the rapid increase over the past few decades of the amount of refined convenience foods consumed by the typical American and people in other industrialized nations (Powell et al., 2012), especially at younger ages (Poti and Popkin, 2011), it is critical

that we carefully evaluate what effects this might be having on not only physical health, but also mental health and cognition. We've already discussed the implications for attention and behavioral control, and for ADHD. Epidemiological research is starting to illuminate the links between diet-related disorders, such as obesity and inflammation, and development of other metal health problems as well, such as Major Depressive Disorder (MDD) in children (Byrne et al., 2015). Obesity early in life (e.g., at 3 years of age) is also a strong predictor of poor academic and cognitive performance a few years later (e.g., 5 years of age; (Martin et al., 2016)). Likewise, the consumption of processed and refined complementary foods during weaning in infants is negatively related to total, verbal, and performance IQ by the age of 8 years (Golley et al., 2013). Chronic low-grade inflammation may be a critical factor mediating the inverse relationship between obesity and fluid intelligence (Spyridaki et al., 2014). Identifying the environmental causes of these emerging relationships will allow us to address those causes through behavior and policy changes.

Together with motivational impairments (Blaisdell et al., 2014), our results suggest that consumption of a diet made up primarily of highly processed and refined ingredients leads to impairments in cognition. Nevertheless, it is still unclear as to the precise causal model underlying the relationship between REF diet consumption, obesity, and cognitive impairments. It could be that REF diets are a common cause of both obesity and cognitive impairments, each being an independent effect. On the other hand, it could be the case that a causal chain of REF diet causing obesity which in turn causes cognitive impairments, such as through the various metabolic and neural pathways discussed above, could best explain these relationships. It is likely that cognitive impairments are caused in part both directly by the diet and by the obesogenic metabolic state that itself is caused by diet. The more we learn about diet and physiology, the clearer it becomes that the relationships between diet, microbiome, metabolism, the endocrine system, and the nervous system are incredibly complex and complicated. More research is thus needed to untangle precise causal mechanisms (Waldmann et al., 2008).

While there is a growing literature investigating the causal role of processed and refined foods on many aspects of learning and cognition, including memory and impulsivity, using animal models (typically rodents), to our knowledge ours is the first study identifying a (direct or mediated) causal role of diet on sustained attention. This research raises many questions, some of which we addressed above. What are the mechanisms of the effects of refined diets on cognition? Which refined ingredients cause the effects (protein, carb, fat, all or only some of them)? Alternatively, what does the refined diet lack, such as essential fatty acids and micronutrients, which may be contributing to cognitive impairments? Given the association of consumption of diets with refined ingredients and mental health issues and cognitive impairments, it is important to understand how these diets produce their effects and how they can be avoided or remedied through proper nutrition.

Conflict of interest

None of the authors have conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.beproc.2017.03.007.

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