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Different Patterns of Memory Impairments Accompany Short- and Longer-Term Maintenance on a High-Energy Diet

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Intake of diets high in saturated fat and simple carbohydrates is associated with cognitive impairments in both humans and rodents. Here we report that feeding rats this type of high-energy (HE) diet has different effects on different types of learning and memory processes. Rats were first trained to solve spatial and nonspatial reference (RM) and working (WM) memory problems in a radial maze paradigm. Memory retention was assessed following six durations of free access to an HE or standard chow control diet ranging from 72-hr to 90 days. The results showed that performance on spatial RM and WM was impaired following only 72-hr on the HE diet and that the magnitude of the spatial RM and WM retention deficits were stable across all tests. On the other hand, stable deficits in nonspatial RM and WM emerged only after 30 days on the HE diet. The results suggest that the processes underlying spatial memory may be especially sensitive to disruption following intake of HE diets.

Keywords: high-fat diet, learning, radial maze, hippocampus, rat

The normal diet of many people in Western cultures contains high amounts of saturated fats and refined carbohydrates (Zhou et al., 2003). In recent years, evidence has accumulated that links excessive intake of such high-energy (HE) diets with the development of cognitive impairments. In humans, consumption of HE diets has been associated with increased incidence of Alzheimer's disease (e.g., Berrino, 2002; Grant, Campbell, Itzhaki, & Savory, 2002; Pasinetti & Eberstein, 2008) and with milder forms of cognitive dysfunction (e.g., Eskelinen et al., 2008; Morris, Evans, Bienias, Tangney, & Wilson, 2004). In rats, HE diet-induced impairments have been reported in spatial learning and memory tasks (Goldbart et al., 2006; Jurdak, Lichtenstein, & Kanarek, 2008; Molteni, Barnard, Ying, Roberts, & Gomez-Pinilla, 2002; Molteni et al., 2004; Wu, Molteni, Ying, & Gomez-Pinilla, 2003), operant rule-learning (Greenwood & Winocur, 1990; Greenwood & Winocur, 1996; Greenwood & Winocur, 2001; Winocur & Greenwood, 1999) and Pavlovian discrimination reversal learning (e.g., Kanoski, Meisel, Mullins, & Davidson, 2007).

The present research had three goals. First, we set out to confirm and extend previous reports that intake of HE diets is accompanied by impaired memory retention. We trained rats in a radial maze using a design (e.g., M'Harzi & Jarrard, 1992) that permitted us to compare retention performance on spatial and nonspatial forms of both reference and working memory. Previously, Jarrard, Davidson, and Bowring (2004) reported that rats with selective lesions of the hippocampus showed deficits in reference memory (RM), which involves remembering the location of baited arms across trials when the location of those arms is associated with extramaze, or spatial cues. In contrast, RM was not impaired for these rats when the arms were associated with nonspatial cues (i.e., cues that were presented within the maze). The same hippocampal-lesioned rats exhibited impaired working memory (WM) in both the spatial and nonspatial versions of the task, as indexed by their increased tendency to return to arms of the maze that they had already visited within a trial. In the present study we assessed whether intake of an HE diet would produce a similar profile of spatial and nonspatial RM and WM memory impairments.

Second, we assessed the effects of duration of ad libitum exposure to HE diets, at intervals ranging from 3 to 90 days, on performance in the radial arm maze. This allowed us to (a) compare the time course for the emergence of impairments in memory performance, and (b) assess changes in the magnitude of specific memory deficits with increasing exposure to the HE diet.

Third, previous studies maintained rats on HE diets for 30 days or more before the beginning of testing. Under these conditions, rats given HE diets often weigh more than controls that are fed standard, low-fat, laboratory chow, making it difficult to separate the effects of the HE diet from the effects of elevated body weight on memory retention. Accordingly, we examined whether or not the emergence of memory deficits by rats maintained on an HE diet were manifested prior to, or subsequent to, the emergence of significant differences in body weight compared to controls. This goal is also relevant to recent suggestions that impairments in learning and memory processes might be a causal factor, rather than only an effect, of excess body weight gain (Davidson, Kanoski, Walls, & Jarrard, 2005).

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Method

Subjects

The subjects were 16 naïve, male Sprague–Dawley rats (*Rattus norvegicus*; Harlan, Indianapolis, IN). The rats were 60 days old upon arrival, housed individually in stainless steel cages, and maintained on a 12-hr light/dark cycle. Body weights for each rat were recorded daily. All of the procedures for the care and treatment of the rats were approved by the Purdue Animal Care and Use Committee.

Diets

The HE diet was high in saturated fat (170*g*/kg lard, 40% kcal total fat) and glucose (220.5*g*/kg glucose) (Harlan, TD.04489), with a caloric density ≈ 4.55 kcal/g. A standard rodent chow (LabDiet, 5001) was used for the control diet (caloric density ≈ 3.0 kcal/g, 13% kcal fat). Both diets were powdered and nutritionally adequate. A pelleted version of the 5001 diet was used during training.

Apparatus

The radial maze (Lafayette Instruments) had eight arms (10 × 70 cm) that radiated from a central platform (34 cm diameter). Clear Plexiglas walls (20 × 30 cm) extended along each arm; approximately 2 in from the end of each arm was a food well that could not be seen from the central platform. For nonspatial trials, eight removable inserts, each with a distinct surface texture of different materials (rubber, wood, hardware, cloth, plastic, etc.), served as intramaze cues that covered the floor of each arm. No inserts were in the maze on the spatial trials. Extramaze cues (posters, shapes, etc.) for spatial trials were placed around the radius of the maze (within 1–2 m). The lights were on, and a 70-db white noise masked background noise for all trials. Forty-five-milligram sucrose pellets were used as food reinforcement throughout all procedures.

Design and Procedure

Training. Prior to training, the rats were habituated to the radial maze during five 3-min sessions across 5 days. For the first three of these five sessions, sucrose pellets were scattered around the maze. For the last two of these sessions, sucrose pellets were only placed at the end of each arm.

The rats were all maintained on standard pelleted chow for the training phase. They were food deprived throughout training to maintain 85% of an ad libitum body weight established after the first 2 weeks in the laboratory. All 16 rats received two spatial and two nonspatial trials in alternating order on each training day. The order of which type of trial was first (spatial vs. nonspatial) was alternated each training day. Training consisted of 80 spatial and 80 nonspatial trials across 40 training days. For spatial trials, arms #1–8 were assigned based on their spatial location in the room. Four of these eight arms were randomly assigned as rewarded prior to training (different for each rat); the other four were assigned as nonrewarded. No more than two adjacent arms could be assigned as rewarded. Reward designations were maintained throughout the entire experiment. Two sucrose pellets were placed in food wells at the end of rewarded arms; no food was placed in nonrewarded arms. For each trial, one rat was placed in the center platform and arm entries, defined as the rat's full body entering an arm, were recorded by an experimenter. Trials ended when any one of the following occurred: (1) all four correct arms were entered and the sucrose pellets were consumed from each baited arm, (2) 16 arm entries were recorded, or (3) 5 minutes elapsed. The rats were then returned to their cages until the next trial.

For nonspatial trials, each rat was presented with four removable inserts to be designated as rewarded and four designated as nonrewarded. Prior to each nonspatial trial, the inserts were randomly placed into each of the eight arms, with no more than two rewarded inserts placed in adjacent arms. For nonspatial trials, the spatial location of the arms was not informative about the reinforcer location, but rather the surface texture of the removable inserts. The criterion for ending a trial was the same as for spatial trials.

The number of RM and WM errors was recorded for both types of trials. RM errors were recorded whenever a rat entered a nonbaited arm, whereas WM errors were recorded whenever a rat reentered a baited arm after previously consuming the sucrose pellets from that arm on the same trial.

Testing. Following training, the rats were assigned to two diet groups (HE or C) that were matched on body weight and on WM and RM errors with both spatial and nonspatial cues over the last two training trials. Each group was given free access to their respective diets (HE or C); Group C was switched from pelleted to powdered standard chow (5001 formula) for the retention test phase. The rats were given retention tests when nondeprived at 3, 10, 18, 30, 60, and 90 days after the presentation of the respective HE and C diets. The procedures for the retention tests were the same as those used for training sessions. Half of the rats from each group received a spatial trial first (S, NS, S, NS), and the other half received a nonspatial trial first (NS, S, NS, S). The rats were also given two probe tests on Days 14 and 64 in which all food was removed for 24-hrs prior to the beginning of testing. The rats were returned to ad libitum feeding of their designated diet immediately after the conclusion of these two probe tests. The probe tests were conducted to assess the degree to which radial maze performance for rats given the HE and C test diets was differentially sensitive to shifts in level of food deprivation. Previous reports suggested that food deprivation may protect against or reverse spatial memory impairments (e.g., Beatty, Clouse, & Bierley, 1987).

Results

Training

As shown in the leftmost panels of Figure 1, the number of RM (top) and WM (bottom) errors with spatial and nonspatial cues exhibited by rats that were subsequently assigned to receive the HE and C diets during testing decreased across the 20, four-trial blocks of training. An overall analysis of variance (ANOVA) obtained a significant main effect of Block, $F(19, 266) = 73.81$, $p < .01$ and Error type, $F(1, 14) = 389.85$, $p < .01$, along with a significant Error type × Block interaction, $F(19, 266) = 50.47$, $p < .01$. No other main effects or interactions approached significance. Thus, the results showed that overall radial maze performance improved across blocks of training with more errors exhib-

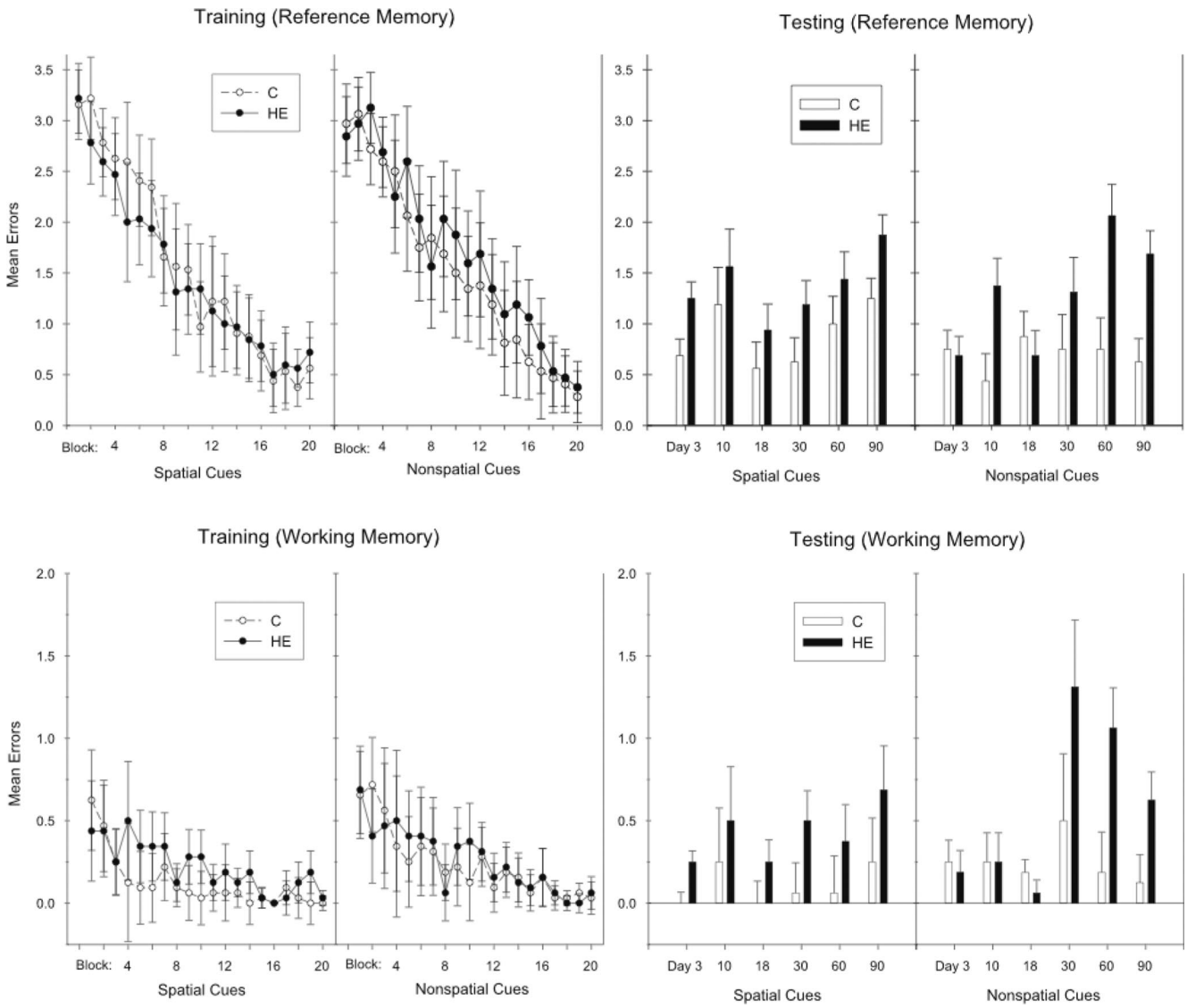

Figure 1. The average number of reference memory (RM; top) and working memory (WM; bottom) errors committed during training (left) (subsequent dietary assignment as dummy variable), and during each of six memory retention tests that occurred at intervals of ad libitum high-energy (HE) or control diet feeding ranging from 3 to 90 days (error bars represent *SEM*). The HE diet produced stable impairments in RM and WM based on spatial cues across the entire testing period, whereas impairments in RM and WM based on nonspatial cues were found consistently only after 30 days on the diet.

ited for RM compared to WM, and that these effects were substantially the same with both spatial and nonspatial cues for rats that were later assigned to receive HE and C diets during testing.

Testing

The rightmost panels of Figure 1 depict mean WM and RM errors when each diet group was tested with spatial and nonspatial cues at 3, 10, 18, 30, 60, and 90 days. The rats receiving 3 days of free access to the HE diet made more RM and WM errors with spatial cues compared to rats maintained on the C diet. In contrast, RM and WM errors based on nonspatial cues appeared to differ little as a function diet on the 3-day test. The data from the 3-day test were evaluated with an ANOVA that included with Diet, Cue, Error Type, and Trials as factors. This analysis yielded a significant main effect of Error type, $F(1, 14) = 45.10$, $p < .01$, which confirmed that the rats made more RM than WM errors, and a significant Diet x Cue interaction, $F(1, 14) = 4.76$, $p < .05$. When separate ANOVAs were conducted on the number of errors for each type of cue, the main effect of Diet was significant for spatial, $F(1, 14) = 10.66$, $p < .01$, but not for nonspatial cues, $F(1, 14) < 1$. Thus, following 3 days on the HE diet, rats showed more RM and WM errors with spatial cues, but not with nonspatial cues, compared to rats given the C diet.

We also analyzed RM and WM errors with spatial and nonspatial cues over all six ad libitum tests, with repeated measures for the variable Test day (1–6). The rightmost panels of Figure 1 show that rats given the HE diet tended to exhibit more RM and WM errors with both spatial and nonspatial cues than rats given the C diet, and that the magnitude of differences between the HE and C diets varied across test days. These impressions were confirmed by an overall ANOVA which obtained significant main effects of Diet, $F(1, 14) = 18.33$, $p < .01$, Test day, $F(5, 70) = 5.44$, $p < .01$, and a significant Diet × Test interaction, $F(5, 70) = 2.48$, $p < .05$. The data shown in the rightmost panels of Figure 1 also indicate that with spatial cues the HE diet was associated with more RM and WM errors that was the C diet across all test days. In contrast, with nonspatial cues the effect of the HE diet on RM and WM errors did not become apparent until the last three test days (30, 60, and 90 days) with the HE and C diets.

Separate ANOVAs compared the effects of Diet on RM and WM errors with spatial and nonspatial cues, respectively. With spatial cues, this analysis yielded a significant main effect of Diet, $F(1, 14) = 10.03$, $p < .01$, but no significant interactions involving Diet and Test day. These results confirm that the HE diet was associated with more RM and WM errors compared to the C diet and that this effect did not vary across test days. A main effect of Error type, $F(1, 14) = 75.88$, $p < .01$, was also obtained, indicating that rats made more RM than WM errors, independent of Diet treatment. The same analysis with nonspatial cues also obtained a significant main effect of Diet, $F(1, 14) = 12.40$, $p < .01$, and Error type, $F(1, 14) = 32.30$, $p < .01$, but in this analysis the Diet × Test day interaction was also significant, $F(5, 70) = 3.20$, $p < .05$. An additional ANOVA evaluated this interaction by comparing the number of RM and WM errors over blocks of the first three (Days 3, 10, and 18) and the last three (Days 30, 60, and 90) days of testing. This analysis obtained a significant Diet × Test Block interaction, $F(1, 14) = 7.18$, $p < .05$. Newman–Keuls tests found that, with nonspatial cues, the HE diet was associated with more RM and WM errors than the C diet over the last block ($p < .05$), but not over the first block of three test days. These results indicate that the detrimental effect of the HE diet was present over all six ad libitum tests for spatial cues, whereas a longer duration of exposure to the HE diet was required to impair memory performance based on nonspatial cues.

Probe Tests Under 24-hr Food Deprivation

The effects of the HE and C diets on RM and WM with spatial and nonspatial cues were also examined on Days 14 and 64 when the rats had been food deprived for 24-hrs. Mean overall errors for rats given the HE diet and C diets were 0.36 and 0.44, *SEM* ± 0.08, respectively, on Day 14, and were 0.73 and 0.44, *SEM* ± 0.07 on Day 64. ANOVA revealed that the main effect of Diet was significant only on Day 64, $F(1, 14) = 7.33$, $p < .05$. Neither analysis yielded significant interactions involving Diet with Cue type or Error type. Thus, while differences between the two groups were not significant when the rats were tested under 24-hrs food deprivation after only 2 weeks of exposure to the HE diet, the detrimental effect of the HE diet was still apparent when testing under 24-hr food deprivation following a longer exposure to that diet.

Body Weight

The body weights at the end of training and at each memory retention test are presented in Table 1 for rats given the HE and C diets. An ANOVA revealed no significant differences for these diet conditions at the end of training, nor during the 3- and 10-day tests, (largest F for 3-day test, $F(1, 14) = 3.65$, $p = .077$). Thus, the HE diet was associated with impaired memory performance relative to the C diet on test days during which these diets produced no differences in body weight. However, beginning on Day 14 (a probe test day under 24-hr food deprivation) rats given the HE diet weighed significantly more than rats given the C diet on each test for the reminder of the study, all Fs$(1, 14) > 5.0$, all ps $< .05$. A significant Diet × Test day interaction was obtained across all tests, $F(7, 98) = 30.66$, $p < .01$, showing that body weight differences between the two groups became larger across time.

Discussion

Our results confirm previous findings by showing that rats maintained on an HE diet exhibit impaired memory retention performance. We also extended previous results in several ways. First, the present research showed that memory impairment emerges following as few as 72 hr on an HE diet. This deficit was exhibited for both RM and WM performance based on spatial cues, whereas performance based on nonspatial cues was spared. With increasing durations of exposure, rats maintained on the HE diet exhibited RM and WM deficits based on both the spatial and the nonspatial cues. Our results also showed that differences in memory performance for rats receiving the HE and C diets were not dependent on differences in body weight. For example, more errors based on spatial cues were committed following three days of ad libitum access to the HE relative to the C diet even though differences in body weight between the groups had not yet emerged.

Unrestricted access to the HE diet was accompanied by impairments in RM and WM with spatial cues that were relatively stable across all test days. In contrast, consistent retention deficits in nonspatial WM and RM were observed only after 30 days on the HE diet. This pattern of results suggests that the detrimental effects

Table 1
Average Body Weights in Grams (±SEM) for the High-Energy (HE) and Control (C) Groups at the End of Training and at Each of the Memory Retention Tests in Experiment 2

Test	Number of days on diets	Average body weights (g)		
		C	HE	*SEM*
	0	258.0	258.8	2.10
1	3	314.6	306.9	2.85
2	10	358.6	366.8	4.54
3	14	342.6	365.8	4.96*†
4	18	370.0	385.1	4.75*
5	30	397.1	416.8	5.93*
6	60	429.3	465.9	6.41*
7	64	401.4	446.6	5.31*†
8	90	450.0	496.4	6.56*

* Significant body weight differences ($p < .05$).
† 24-hr food deprived.

of access to the HE diet on spatial memory reaches a stable asymptote very rapidly, whereas the manifestation of nonspatial RM and WM memory deficits requires longer duration exposure to HE diet.

The results we obtained do not seem consistent with the idea that the HE diet influenced performance based primarily on motivational mechanisms. For example, 3-day ad libitum exposure to HE diet was accompanied by increased errors with spatial but not with nonspatial cues. It is difficult to explain how this type of selective effect could be based on either a general increase or decline in a motivational factor, such as decreased hunger, arousal, or reduction in reward value. We also found that the magnitude of memory impairment increased with nonspatial but not with spatial cues after longer-term exposure to the HE diet. This selective change in performance with nonspatial cues also seems inconsistent with the operation of a nonspecific (e.g., motivational) process. This is not to say that memory performance is independent of motivational factors. Our findings provided evidence that, both early and later in testing, differences in radial maze performance between HE-fed and chow-fed rats were abolished (Day 14) or reduced (Day 64) following a 24-hr period of food deprivation compared to food satiation. However, in our view, the overall pattern of errors we observed made it difficult to account for our findings by appealing solely to motivational processes.

Our findings suggest that the effects of consuming HE diets on retention of spatial and nonspatial information differ depending on the duration of exposure. Impaired retention based on spatial information appeared following as few as 3 days, and remained quite stable over the entire 90-day course of exposure to the HE diet. In contrast, exposure periods of greater than 30 days were required for rats given the HE diet to show stable deficits in retention of nonspatial information relative to chow-fed controls. These findings support the view that rats rely on multiple memory systems (e.g., Kim & Baxter, 2001; Poldrack & Packard, 2003) that can be influenced differentially by dietary manipulations. For example, retention of spatial information in the radial maze is not defined by the memory of a single item or event, but by the representation of a complex set of cues and relationships among cues that form the experimental context. On the other hand, the retention of nonspatial information may have required our rats to form associations between intramaze cues specific to each arm and the sucrose pellet reward (e.g., Rosenbaum, Winocur, & Moscovitch, 2001; Winocur, Moscovitch, Caruana, & Binns, 2005). Viewed this way, our results suggest that intake of the HE diet had the initial effect of impairing this type of context-dependent memory, whereas associative, or context-free memory processes were spared.

It is also possible that the effects of HE diets on performance with spatial cues reflected an impairment in the inhibition of competing memories. Davidson and Jarrard (2004) suggested that because irrelevant, as well as relevant, spatial cues can be observed from each of the baited arms of the radial maze, it is conceivable that any number of these cues could become associated with reward, especially early in training. Accordingly, solving radial maze problems based on spatial cues may depend, in part, on learning to inhibit responding to extramaze stimuli that are inaccurate markers for the location of the baited arms.

In contrast, when performance is based on responding to nonspatial cues, memory inhibition may play a smaller role because when the relevant cues are located within the arms of the maze, the number of irrelevant cues that are available to be associated with each baited arm is more limited. This may make performance based on nonspatial cues less dependent on the ability to inhibit responding to irrelevant cues. Thus, by interfering with memory inhibition, shorter-term HE diet consumption might impair performance more with spatial compared to nonspatial cues. Other analyses also suggest that deficits in spatial memory retention involves more than a loss of spatial information (Clark, Broadbent, & Squire, 2007). There is also evidence that consuming HE diets can impair the ability of rats to inhibit responding to previously rewarded nonspatial stimuli (Kanoski et al., 2007). However, these findings were obtained with Pavlovian discrimination problems and conditions of access to the HE diet that were quite different from the radial maze problems and diet exposure conditions used in the present experiment.

It is also important to note that our finding of a deficit in memory retention with spatial compared to nonspatial cues suggests that short-term exposure to the HE diet may have had a selective disruptive effect on hippocampal functioning. In an earlier radial maze study that used a design and procedure similar to the present experiments, Jarrard, Davidson, and Bowring (2004) reported that compared to sham- and nonlesioned controls, rats with neurotoxic lesions of the complete hippocampus also exhibited larger RM and WM retention deficits with spatial than with nonspatial cues. That study also found that lesioned rats were impaired relative to controls in WM with nonspatial cues—a finding that was attributed to a deficit in inhibitory learning. However, it should not be surprising that the effects of complete destruction of the hippocampus might be of greater magnitude than those produced by a dietary manipulation.

Our finding that WM performance with nonspatial cues was impaired following more extended exposure to HE diet may be attributable, in part, to more complete disruption of hippocampal functioning. For example, Broadbent, Squire, and Clark (2004), reported that impaired spatial memory resulted from damage to confined to the dorsal hippocampus that comprised 30% to 50% of total hippocampal volume bilaterally, and that magnitude of the impairment remained relatively constant as the amount damage increased from 50% to 100% of total volume. In contrast, object recognition, a type of nonspatial memory, was not impaired until at least 75% of the total volume of the hippocampus had been destroyed. We found that spatial memory deficits emerged quickly and were quite stable from 3 to 90 days on the HE diet whereas nonspatial memory deficits were not exhibited until more than 30 days on that diet. It is conceivable that the temporal pattern of impairment we observed reflects dysfunction originating in the dorsal hippocampus and encompassing a greater volume of the hippocampus with increasing days of exposure to the HE diet.

In contrast to WM, Jarrard et al. (2004) reported that RM based on nonspatial cues is not impaired in rats with complete hippocampal lesions. When considered with our present finding of RM deficits with nonspatial cues, this suggests that extended exposure to the HE diet may also have deleterious effects on the functioning of extrahippocampal structures. Previous reports (e.g., Greenwood & Winocur, 1990, 1996; Kanoski et al., 2007) provided evidence that intake of diets high in saturated fat may alter learning and memory functions that involve not only the hippocampus, but also the prefrontal cortex (PFC). Moreover, features of our present

experimental designs may have made radial maze performance especially susceptible to changes in PFC function. For example, mice with impaired prefrontal cortex function were reported to be less able to switch from using extramaze to intramaze cues (and vice versa) in a modified Morris water maze task (Hyde, Stavnezer, Bimonte, Sherman, & Denenberg, 2002). In the present study, our rats were tested with spatial trials followed by nonspatial trials, and vice versa. Thus, impaired performance following extended exposure to HE diet may have been based, in part, on reduction in prefrontocortical-dependent switching from spatial stimuli to nonspatial stimuli.

Our findings may also have implications for understanding the control of energy regulation. Recent reports have linked the intake of HE diets in humans to both obesity and the development later in life of Alzheimer's disease and other cognitive dementias (e.g., Whitmer et al., 2008). One interpretation of this relationship is that cognitive dysfunction is one of the many negative health consequences of excess body weight gain. By showing that rats given an HE diet exhibit cognitive impairment prior to the emergence of increased body weight gain, our present results also suggest the possibility that diet-induced cognitive impairments could contribute to obesity. Recent reports from our laboratory showed that neurotoxic lesions of the complete hippocampus are accompanied by increased food intake and body weight gain (Davidson et al., 2009; Davidson et al., 2005). It may be that excessive intake of HE diets also contributes to body weight gain and obesity by interfering with hippocampal-dependent controls of energy regulation (Davidson, Kanoski, Schier, Clegg, & Benoit, 2007; Davidson et al., 2005).

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