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High Energy Diets Prevent the Enhancing Effects of Emotional Arousal on Memory

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Over the past five decades, *per capita* caloric intake has increased by approximately 28% in the United States. Excessive intake of calories from fats and sugars (high energy diets; HEDs) negatively impacts hippocampal-dependent memory. These deleterious effects of HEDs on hippocampal function involve HED-induced decreases in neuronal growth factors, neurogenesis, and synaptic plasticity. Given that HEDs also alter responses to emotional arousal, the present experiment determined whether the effects of HEDs on memory depend on the emotional arousal produced by the memory task during encoding. Rats were fed a high fat/sugar cafeteria-style diet for 4 weeks and then tested in a low or high emotional arousal version of a spatial object place recognition task. The results demonstrated that the HED prevented the memory-enhancing effects of emotional arousal. Thus, altered responses to emotional arousal likely contribute to HED-induced memory impairments, particularly in stressful memory tasks such as the spatial water maze.

Keywords: spatial object place recognition, sucrose, fat, sugar emotional arousal

Over the past five decades, *per capita* caloric intake has increased by approximately 28% in the United States (USDA, 2011). These increases in caloric intake are due in large part to a disproportionate intake of energy from saturated fats and refined carbohydrates (Grotto & Zied, 2010; Hu et al., 1999; Iqbal et al., 2008). Extensive evidence demonstrates that excessive intake of fat and sugar impairs hippocampal-dependent memory. More specifically, HEDs impair hippocampal-dependent spatial water maze memory (Darling, Ross, Bartness, & Parent, 2013; Pathan, Gaikwad, Viswanad, & Ramarao, 2008; Pintana, Apaijai, Pratchayasakul, Chattipakorn, & Chattipakorn, 2012; Ross, Bartness, Mielke, & Parent, 2009; Ross, Bruggeman, Kasumu, Mielke, & Parent, 2012; Stranahan et al., 2008), spatial learning and memory in the radial arm maze (Greenwood & Winocur, 1990; Valladolid-Acebes et al., 2011), novel place memory (Kosari, Badoer, Nguyen, Killcross, & Jenkins, 2012), spontaneous alternation (McNay et al., 2010), and variable-interval delayed alternation (Greenwood & Winocur, 1990). These detrimental effects of high energy diets (HED) on memory likely involve HED-induced alterations in hippocampal brain derived neurotrophic factor (Molteni, Barnard, Ying, Roberts, & Gomez-Pinilla, 2002; Stranahan et al., 2008), long-term potentiation (Stranahan et al., 2008), and neurogenesis (Lindqvist et al., 2006; van der Borght et al., 2011).

A limitation of previous studies testing the effects of HEDs on hippocampal-dependent memory is that the diets contained the fat and/or sugars in a single pellet and nutritional alternatives were not available. Therefore, the investigator, rather than the rodent, determined the macronutrient composition of the calories consumed. Consequently, the physiological relevance of these diets to human voluntary food intake is questionable. To address these concerns, we recently reported that rats exposed to a high-energy cafeteria-style diet containing choices of lard, sucrose, and standard chow (Pecoraro, Reyes, Gomez, Bhargava, & Dallman, 2004) voluntarily consume more calories than rats fed standard chow and develop hippocampal-dependent memory deficits in the spatial water maze (Darling et al., 2013). These deficits manifest as early as 4 weeks after consumption of the cafeteria diet (Darling, unpublished observations).

It is possible that the memory-impairing effects of HEDs also involve alterations in the ability of emotional arousal to enhance memory. It is well established that emotional arousal during encoding modulates memory consolidation in an inverted U manner (Baldi & Bucherelli, 2005; Gold & Korol, 2012; Joels, 2006; Sandi & Pinelo-Nava, 2007). This memory-modulating influence of emotional arousal is mediated in large part by the stress hormones epinephrine and corticosterone (Gold & Van Buskirk, 1975; Gold, van Buskirk, & Haycock, 1977; Joels, 2006; Jurado-Berbel, Costa-Miserachs, Torras-Garcia, Coll-Andreu, & Portell-Cortes, 2010; Roozendaal & McGaugh, 2011; Sandi, Loscertales, & Guaza, 1997). The findings of many studies suggest that rodents fed HEDs have altered stress hormone responses. For instance, rodents fed high fat or high glucose diets have increased epinephrine secretion (Kaufman, Li, Peterson, & Gilardy, 1993) and rodents fed high fat diets also have increased basal (Cano et al., 2008; Tannenbaum et al., 1997) and stress-induced (Kamara, Eskay, & Castonguay, 1998; Legendre & Harris, 2006; Tannenbaum et al., 1997) corti-

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costerone concentrations. In contrast, rats with a history of sucrose ingestion (either alone or with fat) or voluntary consumption of fat have decreased stress-induced corticosterone release (Christiansen, Dekloet, Ulrich-Lai, & Herman, 2011; Kinzig, Hargrave, & Honors, 2008; la Fleur, Houshyar, Roy, & Dallman, 2005; Ulrich-Lai et al., 2010; Ulrich-Lai, Ostrander, & Herman, 2011; Ulrich-Lai et al., 2007).

The evidence reviewed above indicates that emotional arousal is altered in rats fed a HED. As a result, the present experiment tested whether the effects of a HED on memory depend on the emotional arousal produced by the memory task during encoding. Rats were fed a cafeteria-style lard/sucrose diet for 4 weeks and then trained and tested in a hippocampal-dependent spatial object place recognition memory task (Mumby, Gaskin, Glenn, Schramek, & Lehmann, 2002). Previous research indicates that extensively habituating rats to the testing apparatus prior to exposing them to the objects decreases novelty-induced arousal during training (Okuda, Roozendaal, & McGaugh, 2004; Roozendaal, Okuda, Van der Zee, & McGaugh, 2006). Therefore, withholding or providing habituation to the apparatus prior to training creates two groups of rats that differ in their degree of novelty-induced emotional arousal during training. Novelty-induced arousal increases plasma concentrations of epinephrine (Feenstra, Botterblom, & Mastenbroek, 2000; Ihalainen, Riekkinen, & Feenstra, 1999; McQuade, Creton, & Stanford, 1999) and corticosterone (De Boer, Koopmans, Slangen, & van der Gugten, 1990; Emmert & Herman, 1999; Handa et al., 1994). The likelihood that habituation decreases novelty-induced emotional arousal is strongly supported by the finding that object recognition training increases noradrenergic activity in the basolateral amygdala in nonhabituated rats and, more importantly, that prior habitation to the apparatus significantly diminishes this effect (Roozendaal et al., 2006). Similarly, habituation to the apparatus also reduces the ability of posttraining systemic administration of corticosterone to increase noradrenergic activity in the basolateral amygdala and prevents the enhancing effects of corticosterone on object recognition memory (Okuda et al., 2004; Roozendaal et al., 2006). In the present experiment we manipulated habituation to create low and high arousal versions of the same spatial object place recognition memory task. This permitted the analysis of the interaction between the effects of the HED and emotional arousal on memory while keeping most other experimental parameters constant, such as performance requirements, motivation, handling, testing apparatus, and lighting.

Method

Animals

Male Sprague–Dawley rats (Charles River, Wilmington, MA), aged 53 days, were weighed upon arrival and housed individually on a 12 h light cycle (lights on at 7:00 a.m.). All procedures involving rats were approved by the Georgia State University Institutional Animal Care and Use Committee and are in accordance with PHS guidelines.

Diets

The rats were fed standard chow (3.01 kcal/g; LabDiet 5001, Purina Mills, Gray Summit, MO) for 1 week after their arrival. On the seventh day, they were weighed, matched on percent change in body mass, and assigned to either the control or high energy diet (HED) group. The HED consisted of a bottle of tap water, a bottle of 32% sucrose solution (1.13 kcal/g), standard rat chow, and a glass petri dish containing animal lard (9.0 kcal/g; Armour, Omaha, NE; Pecoraro et al., 2004). The control diet consisted of two bottles of tap water and standard rat chow, and an empty glass petri dish was placed in the cage. Both the control and HED rats were fed ad libitum and all rats were handled twice weekly.

Measuring food intake and body mass in rats can be stressful because of the wire bottom cages and lack of bedding needed to collect food spillage and because of the extensive handling involved in measuring body mass regularly. As a result, body mass and food intake were measured in a separate group of rats. To measure food intake, pellets in each hopper and dried spillage from the bottom of each cage were weighed and then subtracted from the amount placed in the hopper the previous day. In a similar manner, lard dishes and water bottles were weighed individually, and then subtracted from the weight of the dish or bottle from the previous day. Rats were weighed daily and were fed their respective diets for the entire experiment.

Spatial Object Place Recognition

After 3 weeks of feeding, the rats were brought to the testing suite and handled for 1 min twice a day for 7 days. For the low emotional arousal manipulation, half of the rats from each diet group were habituated to the apparatus for 3 min immediately after each of the 14 handling sessions (Okuda et al., 2004; Roozendaal et al., 2006). The apparatus was a white Plexiglas box (60 cm $\times$ 70 cm $\times$ 70 cm) with a layer of corncob bedding. Rats in the high emotional arousal group were not habituated to the spatial object place recognition box during this time. Instead, they were returned to their home cages immediately after each handling session (Okuda et al., 2004; Roozendaal et al., 2006). For the training session, two identical soda cans were placed toward the center of the box 16 cm from the sides of the box and 22 cm from each other. Each rat was placed into the box facing the wall, equidistant from each soda can. Rats in both arousal conditions were given 5 min to explore the spatial object place recognition box and the cans. After each trial, the sides of the box were cleaned with 70% alcohol and the bedding was stirred. The bedding was replaced every five trials.

For the memory test 24 h later, one of the soda cans was moved to the corner of the box, 10 cm from each side of the box and 34 cm from the other can. Rats were placed in the box in the same location as in training and allowed to explore for 1 min. Previous findings indicate that, on the retention test, control rats given this kind of training will spend more time exploring the object in the novel location than the nonmoved object, suggesting that they remember the placement of the objects from the previous day (Choi et al., 2011; Ennaceur & Meliani, 1992; Mumby et al., 2002). By contrast, rats with hippocampal lesions explore both objects comparably (Mumby et al., 2002; Oliveira, Hawk, Abel, & Havekes, 2010).

A camera mounted to the ceiling above the spatial object place recognition box recorded the behavioral sessions. Time spent investigating the objects during training and testing were measured using real-time ethological recording and analysis software (Hindsight for MS-DOS, version 1.5, programmed by Scott Weiss,

United Kingdom). One HED rat was eliminated from the analyses because he explored the objects for less than 10 sec during training. Three control rats and two HED rats were also eliminated because they displayed an object bias during training (exploring one object three times more than the other). A final total of 27 control rats and 26 HED rats were included in the analyses. A discrimination index was calculated for the retention data by subtracting the amount of time spent investigating the nonmoved object from the time spent investigating the moved object and then dividing this value by the total investigation time. Data were stored and analyzed using Microsoft Excel, Version 5.0 and Statistical Package for the Social Sciences (SPSS), Version 18.0.

Statistical Analysis

Univariate analysis of variance (ANOVA) was performed on object exploration during training and discrimination scores on the retention test, with "diet" and "habituation" as factors. Tukey post hoc tests were used to analyze significant main effects. In order to examine emotional arousal-induced modulation of memory, it was necessary to ensure that there was memory to be modulated. To do so, a median division of the average discrimination score for rats in each of the four groups was used to divide rats in each group into those had good discrimination (i.e., top 50%; $n = 14$ control and 14 HED rats) and those that had poor discrimination (i.e., bottom 50%; $n = 13$ control and 12 HED rats; Epp, Spritzer, & Galea, 2007). Differences between groups were considered statistically significant if $p < .05$.

Results

The HED significantly increased percent change in body mass, $t(106) = -2.35$, $p = .02$; see Figure 1A, and caloric consumption, $t(106) = -24.83$, $p = .00$; see Figure 1B. All rats offered the HED consumed more calories from sucrose and lard than from chow. In addition, the HED rats consumed fewer calories from chow than did control diet rats, $t(106) = 40.40$, $p = .00$; see Figure 1B.

The results from training were similar for rats with good or poor discrimination scores. Specifically, prior habituation to the apparatus affected the amount of time rats spent investigating objects during training, good discriminators: $F(1, 24) = 35.40$, $p = .00$; poor discriminators: $F(1, 21) = 27.35$, $p = .00$; see Figure 2. Rats previously habituated to the apparatus spent more time exploring the objects than did nonhabituated rats, good discriminators: $t(26) = 6.15$, $p = .00$; poor discriminators: $t(23) = 5.48$, $p = .00$. Diet did not affect object investigation, good discriminators: $F(1, 24) = .11$, $p = .74$; poor discriminators: $F(1, 21) = .20$, $p = .89$, nor did it interact with the effects of prior habituation during training, good discriminators: $F(1, 24) = .21$, $p = .65$; poor discriminators: $F(1, 21) = .00$, $p = .99$.

As expected, the pattern of findings on the retention test 24 h later differed between the rats with good and poor discrimination scores. In rats with good discrimination scores, withholding habituation enhanced memory in a diet-dependent manner, $F(1, 24) = 7.85$, $p = .01$; see Figure 3A. Specifically, withholding habituation enhanced memory in control rats but not in the HED rats. That is, control diet-nonhabituated rats had higher discrimination index scores than did control diet-habituated rats, HED-habituated rats, and HED-nonhabituated rats (all $p = .00$). The discrimination index scores of HED-nonhabituated rats did not differ from those of HED-habituated rats ($p = .99$). Although the HED prevented the enhancing effects of withholding habituation on memory, it did not impair memory in the rats with good discrimination scores. The discrimination index scores of control diet-habituated rats did not differ from those of HED-habituated rats ($p = .48$) and HED-nonhabituated rats ($p = .65$).

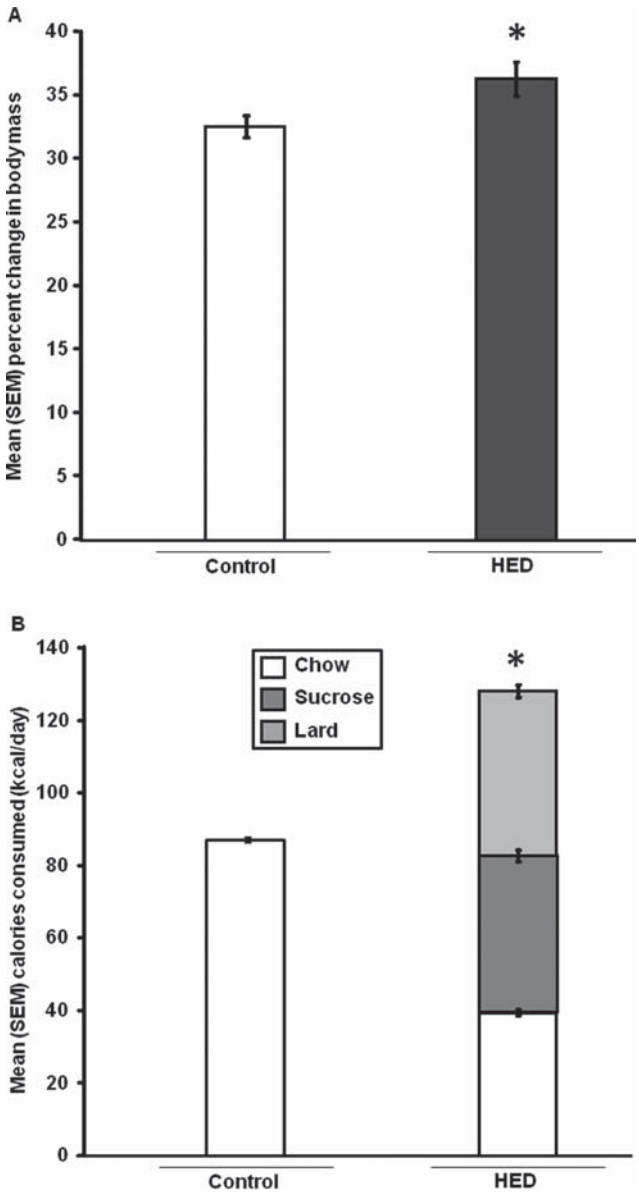

Figure 1. The effects of consumption of a high energy diet (HED) on mean (+/− SEM) (A) percent change in body mass and (B) caloric intake; * $p < .05$ versus control.

In contrast to the effects of withholding habituation in the good discriminators, withholding habituation did not enhance memory in the control or HED group in the poor discriminators, main effect: $F(1, 21) = .09$, $p = .76$; interaction: $F(1, 21) = 3.90$, $p = .06$; see Figure 3B. Also, unlike the good discriminators, the HED significantly decreased discrimination scores in poor discriminators,

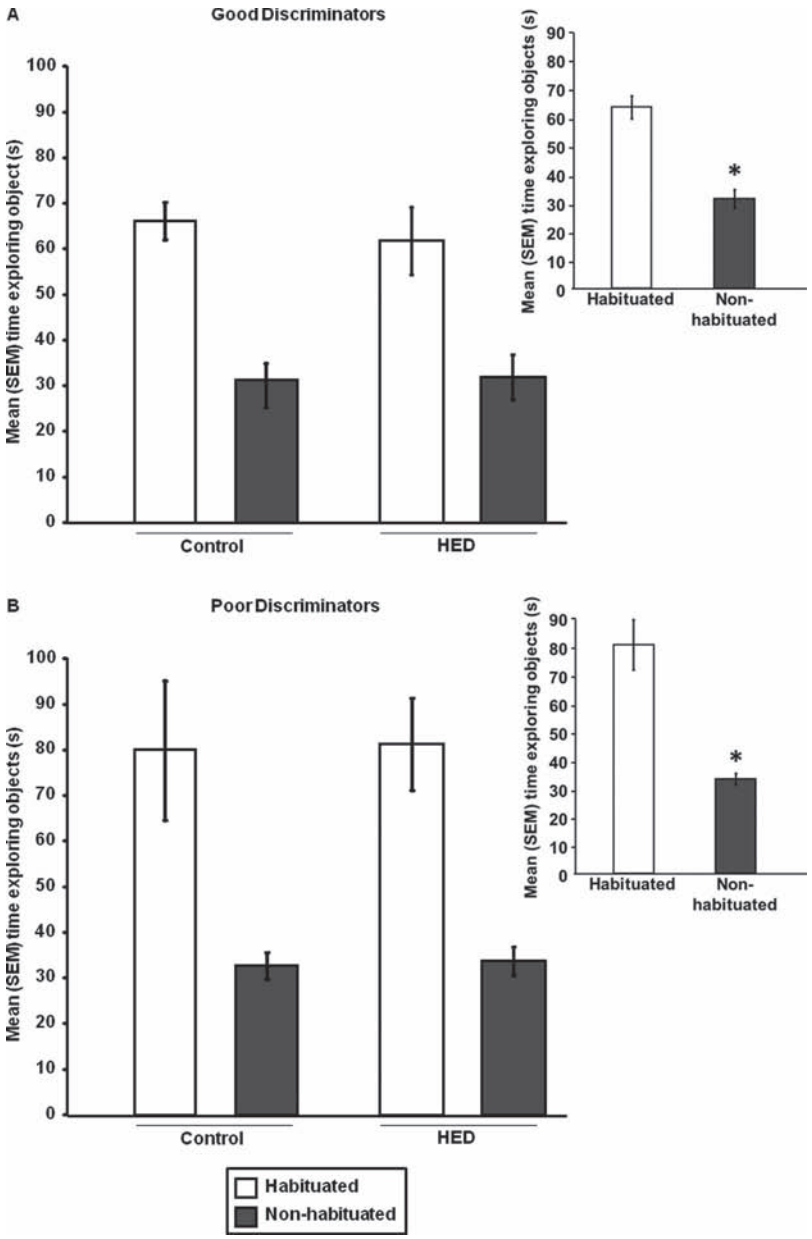

Figure 2. The effects of emotional arousal and/or consumption of a HED on mean (+/− SEM) time spent exploring objects during spatial object recognition training in (A) good discriminators and (B) poor discriminators; * $p < .05$ versus habituated. Inset depicts significant main effects.

$F(1, 21) = 7.46$, $p = .01$, such that HED rats had lower discrimination index scores than control diet rats, $t(23) = 2.69$, $p = .01$.

When all rats were analyzed collectively, the training data had the same pattern as when the rats were separated into good and poor discriminators (see Figure 4A). The retention data for all rats combined was similar to that observed in poor discriminators (see Figure 4B). That is, withholding habituation did not significantly enhance memory, $F(1, 49) = .38$, $p = .54$, did not interact with the effects of diet, $F(1, 49) = 2.91$, $p = .10$, and there was a significant main effect of diet, $F(1, 49) = 7.15$, $p = .01$, such that HED rats had lower discrimination index scores than control rats, $t(51) = 2.68$, $p = .01$.

The effects of the HED on the discrimination indices during the retention test were not likely due to an effect of the HED on the total amount of time spent exploring the objects on the retention test. Diet did not affect total object exploration on the retention test or interact with the effects of prior habituation in rats with good discrimination scores, diet: $F(1, 24) = 2.82$, $p = .11$; interaction: $F(1, 24) = .01$, $p = .94$, poor discrimination scores, diet: $F(1, 21) = .45$, $p = .51$; interaction: $F(1, 21) = .02$, $p = .88$, or when all the rats were combined, diet: $F(1, 49) = .80$, $p = .38$, interaction: $F(1, 49) = .01$, $p = .93$; data not shown. As expected, total object exploration time was increased in rats previously habituated to the apparatus compared with nonhabituated rats, poor discrim-

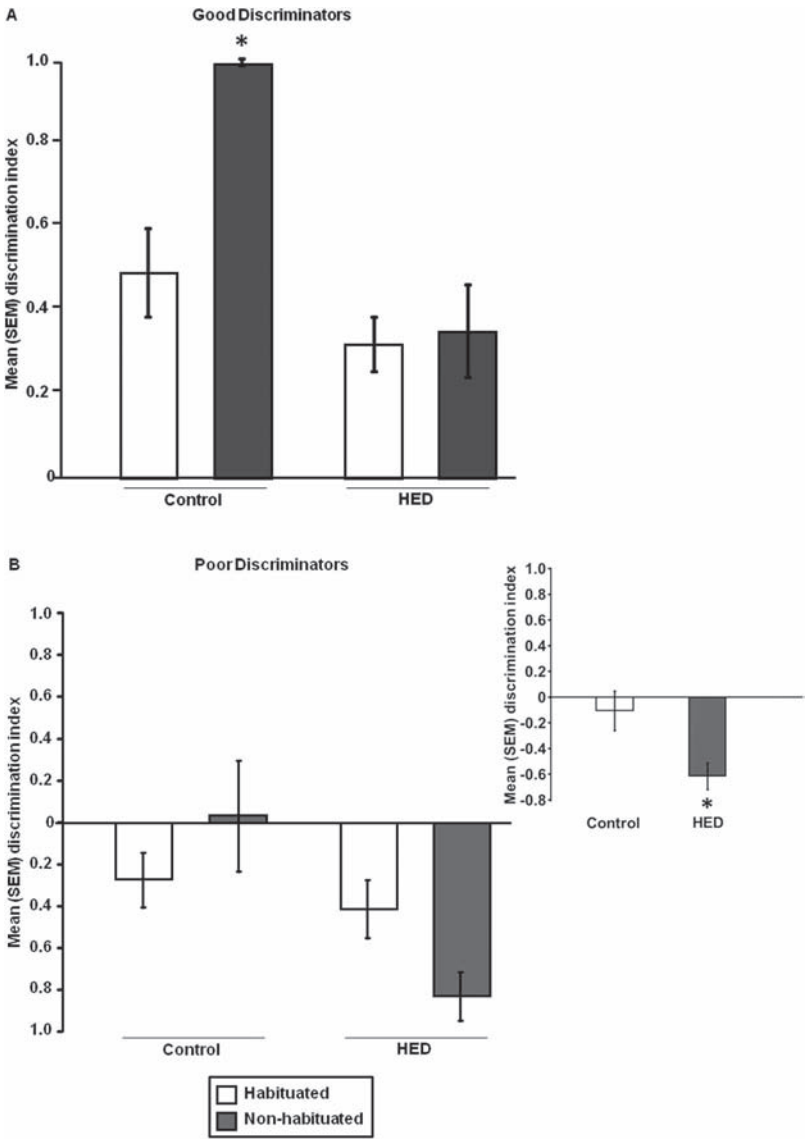

Figure 3. The effects of emotional arousal and/or consumption of a HED on mean (+/− SEM) discrimination index scores during the spatial object recognition memory testing (A) good discriminators; $^{*}p < .05$ versus all groups and (B) poor discriminators; $^{*}p < .05$ versus control. Inset depicts significant main effect.

ination: $F(1, 21) = 20.58$, $p = .00$; all rats combined: $F(1, 49) = 17.49$, $p = .00$, although this effect was not statistically significant in rats with good discrimination scores: $F(1, 24) = 3.41$, $p = .08$.

Discussion

To our knowledge, this is the first study to examine the interaction between the effects of a HED and emotional arousal on memory. Specifically, we tested the effects of voluntary consumption of a HED on memory in a low or high emotional arousal version of the same hippocampal-dependent object place recognition memory task. Emotional arousal was decreased in one group by habituating these rats extensively to the apparatus prior to training. The results demonstrate that the HED prevented the memory-enhancing effects of emotional arousal. Importantly, these effects cannot be explained by differences in exposure to the objects during training because the HED did not affect object investigation. Moreover, the fact that the objects were cleaned after each trial and the bedding replaced every five trials suggests that differences in olfactory processing did not contribute to the effects of the HED on memory.

The division of rats into poor and good discriminators revealed that the memory-enhancing effects of emotional arousal were only observed in rats with good discrimination scores. There was not a significant effect of emotional arousal when all rats were analyzed collectively, or when rats with poor discrimination scores were analyzed separately. These findings suggest that emotional arousal enhances memory most effectively when there are significant baseline levels of memory to enhance. Interestingly, the HED did

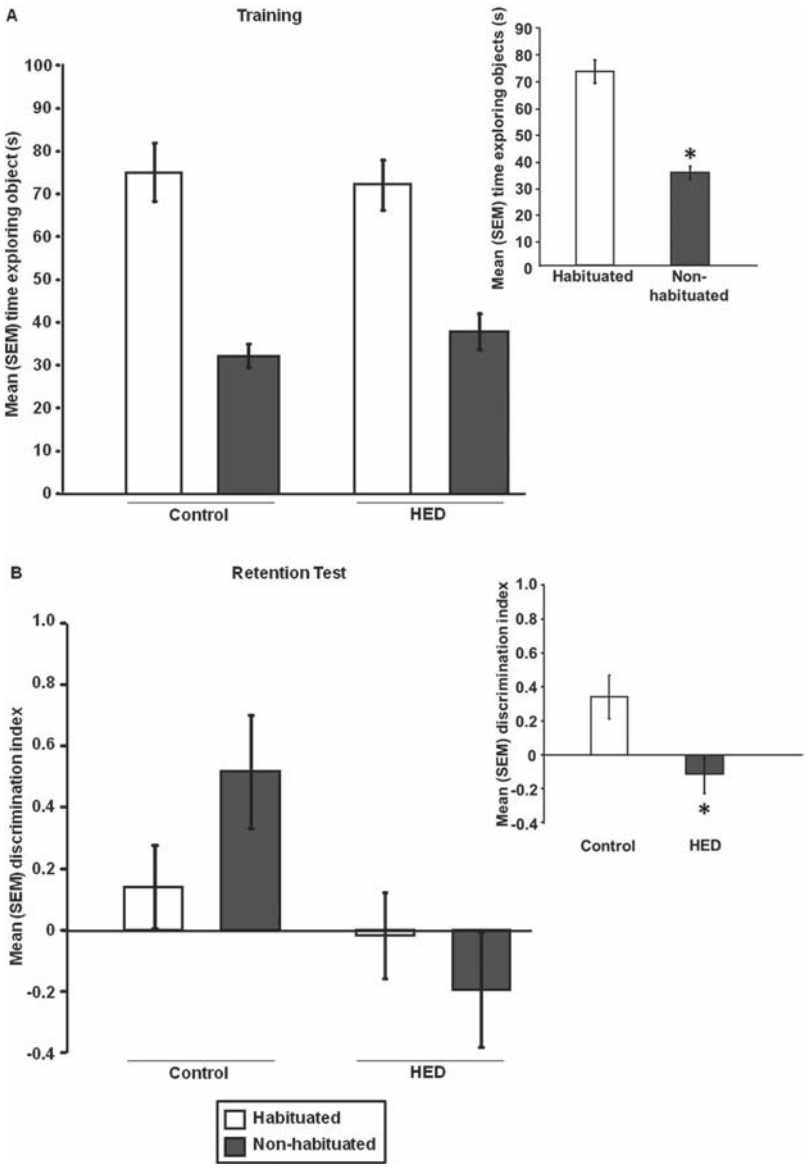

Figure 4. Spatial object recognition results for all rats. The effects of emotional arousal and/or consumption of a HED on mean (+/− SEM) (A) time spent exploring objects during spatial object recognition training; * $p < .05$ versus habituated and (B) discrimination index scores during the spatial object recognition memory test; * $p < .05$ versus control. Inset depicts significant main effects.

significantly decrease discrimination scores in the poor discriminators and when all rats were analyzed collectively. This decrease does not likely reflect a memory deficit, however, because the HED rats did not explore the two objects randomly on the retention test that is, the discrimination index was not close to zero. Rather, these HED rats had discrimination indices that were quite lower than zero, indicating that they spent more time exploring the nonmoved item than the moved one. It is not clear why the HED rats preferred the nonmoved object. As noted earlier, the objects were wiped after each trial and the bedding replaced after every five trials, suggesting that olfactory cues were not a factor. This nonrandom exploration of the two objects in the HED rats could indicate that the HED increased perseverance or altered a process such as stress or anxiety that decreased their preference for exploring novel objects or locations.

It is likely that the HED prevented the memory enhancing of emotional arousal through a mechanism that involved HED-induced alterations in stress hormone release. Corticosterone and epinephrine influence memory in an inverted U dose-dependent manner (Gold & Van Buskirk, 1975; Gold et al., 1977; Joels, 2006; Okuda et al., 2004), and placing rats in a novel environment significantly increases plasma concentrations of both hormones (De Boer et al., 1990). The present results suggest that the stress hormone responses in the rats fed the cafeteria-style diet were not within the range that enhanced memory. The present results do not reveal, however, whether the rats in the present study had dimin-

ished (Christiansen et al., 2011; Kinzig et al., 2008; la Fleur et al., 2005; Ulrich-Lai et al., 2010; Ulrich-Lai et al., 2011; Ulrich-Lai et al., 2007) or potentiated (Cano et al., 2008; Kamara et al., 1998; Kaufman et al., 1993; Legendre & Harris, 2006; Tannenbaum et al., 1997) stress hormone responses.

Obesity and metabolic syndrome are associated with alterations in sympathetic nervous system activation and diminished neural responsiveness to sympathetic activity (Grassi, Arenare, Quarti-Trevano, Seravalle, & Mancia, 2009; Straznicky, Lambert, & Lambert, 2010). Given that emotional modulation of memory is mediated via noradrenergic activity in the brain (Roozendaal & McGaugh, 2011), it is also possible that HEDs prevent emotional modulation of memory via a direct effect on brain norepinephrine levels. Also, it is conceivable that the HED impaired emotional modulation of memory through a process that involves alterations in food-related signals released in the gut. For instance, eating high fat foods induces the release of the fat-satiety factor oleoylethanolamide (OEA), which influences memory via effects on central noradrenergic activity (Campolongo et al., 2009). Additional research is needed to address these possibilities and to determine whether differences at the time of consolidation and/or retrieval mediate these effects of HEDs on memory.

As noted in the beginning of the article, previous research indicates that habituation to the apparatus prior to exposure to the objects during training decreases novelty-induced emotional arousal (Okuda et al., 2004; Roozendaal et al., 2006). This manipulation permits the manipulation of arousal while keeping most other experimental parameters constant, such as performance requirements, motivation, handling, testing apparatus, and lighting. The low and high emotional arousal groups did differ, though, in terms of their degree of familiarity with the training context. It is highly unlikely, however, that this difference contributed to the improved memory in the group that was not habituated to the apparatus. Memory of the placement of the objects should be easier to form in a chamber that is familiar compared with one that is novel. That is, if context familiarity influenced memory in this task, then multiple exposures to the context in the low arousal group should have produced the opposite effect (i.e., enhanced memory).

An additional strength of the present experiment was the use of a cafeteria-style lard/sucrose diet that offered rats high-energy nutrients in the context of healthy choices and allowed the rats to determine the amount of calories consumed. Previous research investigating the effects of HEDs on memory has employed diets in which the nutrients were all presented in one pellet (Greenwood & Winocur, 1990, 1996, 2001; Ross et al., 2009; Ross et al., 2012). Compared with these pelleted diets, the cafeteria-style high-energy diet has more relevance to human consumption patterns. We recently reported that rats fed this cafeteria diet are impaired in the hippocampal-dependent version of the spatial water maze (Darling et al., 2013). The findings from that study also demonstrate that the memory deficits are observed in rats that take in more of their calories from lard than sugar (Darling et al., 2013). Importantly, our data suggest that HED-induced memory deficits are related to elevated liver lipids but not increased body mass. This is based on our collective findings showing that both fructose-feeding and elevated consumption of lard and sucrose elevate liver lipids and impair hippocampal-dependent memory, but fructose-feeding does not significantly increase body mass (Ackerman et al., 2005; Bursac et al., 2012; Karsenty et al., 2012; Kelley, Allan, & Azhar, 2004; Park, Ahn, Huh, McGregor, & Choi, 2013; Ross et al., 2009; Ross et al., 2012). It is also likely that the effects of the HED in the present experiment are also associated with diet-induced insulin resistance (Brandt, De Bock, Richter, & Hespel, 2010; Harris & Apolzan, 2012; Panchal et al., 2011; Sampey et al., 2011; Stranahan et al., 2008).

The present findings have significant implications for the interpretation of previous research that has tested the effects of HEDs on memory in stressful memory tasks such as the water maze (Darling et al., 2013; Pathan et al., 2008; Ross et al., 2009; Ross et al., 2012; Stranahan et al., 2008). Swimming is an intense stressor for rats that causes large increases in plasma epinephrine and corticosterone concentrations (Mabry, Gold, & McCarty, 1995; McFadden et al., 2011). Thus, in studies testing the effects of HEDs on water maze memory, there were essentially only high emotional arousal control and HED animals. If one looks at the high emotional arousal control and HED rats in the rats with good discrimination scores in our study in isolation, rather than in the context of the low emotional arousal groups, it appears that the HED rats are impaired. The inclusion of the low emotional arousal group in the present study allowed us to discover that the HEDs prevented the memory-enhancing effects of emotional arousal. Indeed, it is possible that HED prevention of emotional modulation of memory accounts for HED-induced memory deficits observed in emotionally arousing memory tasks, such as the water maze.

In summary, the present findings are the first to show that a HED prevents the memory-enhancing effects of emotional arousal. The results of the current experiments add to the growing body of literature demonstrating that HEDs are harmful to cognition and suggest that altered responses to emotional arousal contribute to impaired cognition in obese individuals (Galioto et al., 2012; Gunstad, Paul, Cohen, Tate, & Gordon, 2006; Gunstad et al., 2007).

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