Early-life sugar consumption has long-term negative effects on memory function in male rats

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Objectives: Added dietary sugars contribute substantially to the diet of children and adolescents in the USA, and recent evidence suggests that consuming sugar-sweetened beverages (SSBs) during early life has deleterious effects on hippocampal-dependent memory function. Here, we test whether the effects of early-life sugar consumption on hippocampal function persist into adulthood when access to sugar is restricted to the juvenile/adolescent phase of development.

Methods: Male rats were given *ad libitum* access to an 11% weight-by-volume sugar solution (made with high fructose corn syrup-55) throughout the adolescent phase of development (post-natal day (PN) 26–56). The control group received a second bottle of water instead, and both groups received *ad libitum* standard laboratory chow and water access throughout the study. At PN 56 sugar solutions were removed and at PN 175 rats were subjected to behavioral testing for hippocampal-dependent episodic contextual memory in the novel object in context (NOIC) task, for anxiety-like behavior in the Zero maze, and were given an intraperitoneal glucose tolerance test.

Results: Early-life exposure to SSBs conferred long-lasting impairments in hippocampal-dependent memory function later in life- yet had no effect on body weight, anxiety-like behavior, or glucose tolerance. A second experiment demonstrated that NOIC performance was impaired at PN 175 even when SSB access was limited to 2 hours daily from PN 26–56.

Discussion: Our data suggest that even modest SSB consumption throughout early life may have long-term negative consequences on memory function during adulthood.
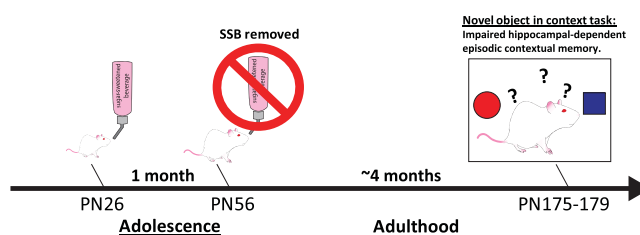
Introduction

Consuming a 'Western Diet', high in saturated fat and added sugars, has deleterious effects on neurocognitive function,[1–15] particularly for memory processes that rely on the integrity of the hippocampus.[4,16,17] However, relatively little is known regarding how the individual components of a Western diet impact cognitive heath. For example, a surfeit of added sugars (sugars added during food processing or preparation) contributes substantially to the modern food supply in the USA and in other Westernized countries. While several lines of research are actively investigating the metabolic consequences of excessive sugar consumption (for review see[18,19]), the impact of added sugars (independent of elevated dietary fat and obesity) on cognitive function is less well understood.

In the USA, children are the highest sugar consumers of any age group, with ~16% of their total

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daily caloric intake from added sugars.[20,21] This is particularly concerning given that the juvenile/adolescent period is a highly susceptible period for the onset of metabolic deficits, resulting from excessive sugar intake,[22] and new evidence suggests that this period of development is also a vulnerable time for sugar-related neurocognitive deficits.[3,23,24] According to the 2005–2008 NHANES report, sugar-sweetened beverages (SSBs) are the source of over 40% of added sugar intake among youth.[20] Given that the number of children aged 6–11 consuming SSBs has risen since the 1980s, and the kcal contribution of SSBs to the diet of juveniles rose by 60% between 1989 and 2008,[25] understanding the long-term impacts of SSB consumption on cognitive function later in life is increasingly critical.

Our lab and others have recently reported (using rodent models) that the juvenile/adolescent stage of development is a vulnerable period in which consuming dietary sugars negatively impacts the hippocampus,[3,23,24] a brain region essential for learning and memory function that has more recently been linked with learned and rewarding aspects of feeding behavior.[26] In rats, *ad libitum* access to an 11% high fructose corn syrup solution (HFCS-55) beginning during the juvenile period of development (immediately post weaning) but not beginning during early adulthood impairs hippocampal-dependent spatial memory in the Barnes maze task and increases neuroinflammation in the hippocampus.[3] It has also been reported that intermittent access to a 10% sucrose solution (2 hours daily access) during the juvenile/adolescent period impairs hippocampal-dependent spatial learning and memory in the Morris water maze,[23] as well as hippocampal-dependent object-in-place task.[24] Relatively little is understood, however, as to whether these early-life SSB-associated memory deficits can be reversed with dietary or other behavioral intervention. Therefore, using a rat model of juvenile/adolescent SSB consumption, we investigated whether impairments in hippocampal-dependent memory function due to early-life SSB access persist well into adulthood, even after a long-term (~4.5 months) dietary intervention in which sugar is no longer available. In our previous report, juvenile/adolescent SSB access was associated hippocampal-dependent memory deficits, concomitant with impaired glucose tolerance when tested towards immediately following the juvenile/adolescent period (PN 60–70). Thus, in the present study we also administered an intraperitoneal glucose tolerance test (IP GTT) shortly after behavioral testing in adulthood (PN 175) to examine whether dietary intervention (SSB removal) can attenuate deficits in glucose metabolism associated with early-life sugar consumption. Secondary outcome measures included testing for anxiety-like behavior (Zero maze), energy intake, and body weight.

Methods

Experimental design
All experiments were performed in accordance with the approval of the Animal Care and Use Committee at the University of Southern California.

Cohort 1
Twenty-four male Sprague Dawley rats (Envigo, Placentia, CA, USA; post-natal day (PN) 26; 50–70 g) were housed individually in standard conditions with a 12:12 light/dark cycle and were divided into two groups based on their *ad libitum* access to: (1) 11% weight-by-volume (w/v) HFCS-55 solution diluted in reverse osmosis-filtered water (HFCS-*ad lib*; $n = 12$) or (2) or an extra bottle of water (water; $n = 12$). For the sugar group, the 11% w/v concentration of total sugar was chosen to be comparable to the amount of sugar in SSBs typically consumed by humans and also based on our prior data.[3] In addition to the test solutions, all rats were given *ad libitum* access to Lab Diet 5001 (PMI Nutrition International, Brentwood, MO; 29.8% kcal from protein, 13.4% kcal from fat, 56.7% kcal from carbohydrate) and water. Food intake, solution intake, and body weights were monitored thrice weekly from PN 26–56, with additional recordings taken prior to behavioral testing. At PN 56 sugar solutions were removed and animals had access to water and chow only for the remainder of the study (Fig. 1A). At PN 175, rats underwent novel object in context (NOIC) testing, to measure hippocampal-dependent episodic contextual memory (described in detail below). Following NOIC testing, at PN 180, rodents underwent anxiety testing in the Zero maze. At PN 185 an IP GTT was performed in order to measure glucose disposal as an estimated measure of insulin sensitivity.

Cohort 2
Twenty-two juvenile, male Sprague Dawley rats (Envigo; PN 26; 50–70 g) were housed individually in the standard conditions with a 12:12 light/dark cycle similar to Cohort 1. Rats were classified into two groups based on 2-hour daily exposure to solution feeding of: (1) 11% w/v HFCS 55 solution (HFCS 2 hours; $n = 11$) or (2) water only (water; $n = 11$). The control group was given a second water bottle. The second water bottle and the SSB were given to the rats 4 hours into the light cycle and removed 2 hours later. The timing of scheduled SSB feeding was chosen to be similar to prior publications where intermittent SSB access conferred hippocampal-dependent memory impairments.[24] In addition to the test solutions, rats were given *ad libitum* access to Lab Diet 5001 (PMI Nutrition International, Brentwood, MO; 29.8% kcal from protein, 13.4% kcal from fat, and 56.7% kcal from carbohydrate)

and water throughout the study. Food intake, solution intake, and body weights were monitored thrice weekly from PN 26–56, with additional recordings taken prior to behavioral testing. At PN 56 sugar solutions were removed and animals had access to water only for the remainder of the study (Fig. 1B). At PN 175, rats underwent NOIC testing, to measure hippocampal-dependent episodic contextual memory, which is described in detail below. Zero maze testing and IP GTT were not examined in Cohort 2 based on the results from Cohort 1 (described below).

IP glucose tolerance test

Animals were food restricted 24 hours prior to IP GTT. Immediately prior to the test, baseline blood glucose readings were obtained from tail tip and recorded by a blood glucose meter (One touch Ultra2, LifeScan, Inc., Milpitas, CA). Each animal was then IP injected with dextrose solution (0.923 g/ml by body weight) and blood glucose readings were obtained at 30, 60, 90, and 120 min after IP injections, as previously described.[3]

Zero maze

To test for potential anxiety effects associated with SSB consumption, rats underwent testing in a Zero maze. The Zero maze is an elevated circular track (63.5 cm fall height, 116.8 cm outside diameter), divided into four equal length sections. Two sections were open with 3 cm high curbs, whereas the two other closed sections contained 17.5 cm high walls. Animals were placed in the maze for 5 minutes while the experimenter records the total time spent in open sections (defined as the head and front two paws in open arms) as previously described.[3]

Novel object in context task

NOIC measures episodic contextual memory by investigating the capacity to identify the novelty of a familiar object placed in a context in which it has not previously been paired. Procedures were adapted from prior reports.[27,28] Briefly, rats are habituated for 5-minute sessions to two distinct contexts on subsequent days (with the habituation order counterbalanced by group): Context 1 is a semi-transparent box (15 in W × x24 in L × 12 in H) with orange stripes and Context 2 is a grey opaque box (17 in W × 17 in L × 16 in H) (Context identify assignments counterbalanced by group). Day 1 of NOIC begins with each animal being placed in Context 1 containing two distinct objects placed in opposite corners: a 500-ml jar filled with blue water (Object A) and a square glass container (Object B) (object identify assignments counterbalanced by group). On day 2 of NOIC, animals are placed in Context 2 with duplicates of Object A. On NOIC day 3, rats are placed in Context 2 with Objects A and Object B (which is not novel per se, but its placement is novel to Context 2). Sessions are 5-minute long and are video recorded. The time spent investigating each object is recorded from the video recordings by an experimenter who is blinded to the treatment groups. Exploration is defined as sniffing or touching the object with the nose or forepaws. The task is scored by calculating the time spent exploring Object B divided by the time spent exploring both Objects A and B combined, which is the novelty or 'discrimination index' [Exploration of Object B/ (Exploration of Object A + Object B)]. Rats with intact hippocampi will preferentially investigate Object B given that Object B is a familiar object yet is now presented in a novel context for that Object, whereas hippocampal
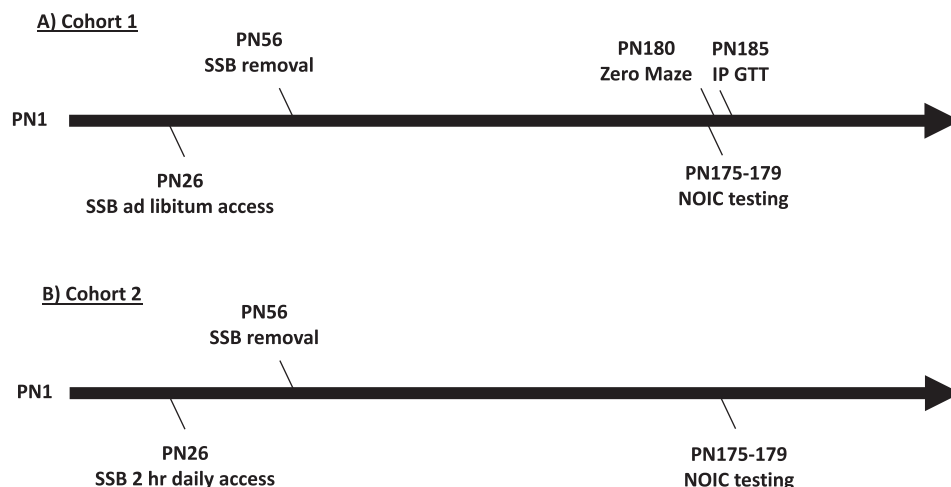

Figure 1   Timeline of experiments. A timeline of experiments for rats given either *ad libitum* (A) or 2-hour intermittent access (B) of 11% w/v HFCS-55 solution (SSB) from PN 26 to PN 56. Rats in (A) underwent NOIC testing from PN 175–179 and Zero maze testing at PN 180. IP GTT was administered at PN 185. Rats in (B) underwent NOIC at PN 175–179.

inactivation impairs the preferential investigation of Object B in Context 2.[27]

Statistics

Data are presented as means ± SEM. For analytic comparisons of body weight, total food intake, and chow intake, groups were compared using two-way mixed ANOVA with time as a within subjects factor and sugar as a between subjects factor. Data were analyzed in the Prism software (GraphPad, Inc., version 7.0). When significant differences were detected, the Sidak *post hoc* test for multiple comparisons was used. Area under the curve (AUC) for the IP GTT testing was also calculated using Prism. All other statistical analyses were performed using Student's two-tailed unpaired *t*-tests in excel software (Microsoft, Inc., version 15.26). For all analyses, statistical significance was set at $P < 0.05$.

Results

Metabolic measures in juvenile/adolescent rats fed ad libitum sugar solution

Ad libitum consumption of SSBs during the entire juvenile and adolescent phase of development did not result in significant differences in body weight during the access period (Fig. 2A). There was a significant interaction (time × group) for total kcal intake ($F_{(12, 264)} = 3.75$; $P < 0.0001$) with a main effects of time ($F_{(12, 264)} = 188.9$; $P < 0.0001$) but not group ($F_{(1, 22)} = 3.49$; $P =$ n.s.) (Fig. 2B). *Post hoc* analyses revealed that animals consuming SSBs consumed fewer calories than the control group toward the end of the treatment period, on days 24 and 27. The lack of difference in caloric intake until the end of the treatment period was due to compensatory reductions in chow intake (Fig. 2C), for which there was also a significant interaction (time × group; $F_{(12, 264)} = 10.51$; $P < 0.0001$) with main effects of time ($F_{(12, 264)} = 113.60$; $P < 0.0001$) and group ($F_{(1, 22)} = 73.14$; $P < 0.0001$) (Fig. 2C). Chow intake was significantly lower in the SSB treatment group than in the control group for the entire treatment period, with the exception of the first day of access to the treatment solutions. Intake of sugar solution steadily increased throughout the treatment period, with a mean kcal intake of 22.02 ± 1.94 on day 30 of access compared with 7.53 ± 0.80 on day 1 (Fig. 2D; Student's paired *t*-test; $P < 0.0001$). On average, animals given *ad libitum* access to the SSB consumed 24.36 ± 2.23% of their daily energy intake from SSBs. In the IP GTT, both groups showed a normal return to baseline in plasma glucose levels within 2 hours post injection, and comparisons of the AUC for the GTT revealed that there were no significant differences in glucose tolerance resulting from SSB intake (Fig. 2E and F).

Behavioral measures in adult rats exposed to SSBs ad libitum during the juvenile/adolescent phase of development

No significant group differences were observed in anxiety-like behavior in the Zero maze test (Fig. 3A). There were also no differences in body weight between the groups on PN 175 just prior to NOIC testing (Fig. 3B). Results from the NOIC task revealed that, while there was no baseline preference for one object over the other on day 1 of the task (Fig. 3C), rats exposed to SSBs during the juvenile/adolescent phase of development were significantly impaired in hippocampal-dependent episodic contextual memory at PN 179, as evidenced by a reduced discrimination index and a significantly lower shift from baseline discrimination index relative to controls (0.21 ± 0.06 (SSB group) vs. 0.08 ± 0.04 (water group), $P = 0.01$; Fig. 3D–E). It is important to note that there were no differences in total object exploration time (investigating either object) on day 1 of the task between the SSB group and controls, indicating that there were no group differences in novelty exploration (data not shown).

Metabolic measures in juvenile/adolescent rats fed sugar solutions for 2 hours daily

Similar to the *ad libitum* access group, consumption of SSBs for a restricted period of 2 hours/day during the entire juvenile/adolescent phase of development did not result in significant differences in body weight gain (Fig. 4A), nor were there significant group differences in total kcals consumed (Fig. 4B). There was a significant interaction for chow intake (time × group; $F_{(29, 580)} = 2.06$; $P = 0.001$) with main effects of time ($F_{(29, 580)} = 71.85$; $P < 0.0001$) but not group on kcal intake from chow (Fig. 4C). Intake of sugar solution steadily increased throughout the treatment period, with a mean kcal intake of 5.18 ± 0.55 on day 30 of access compared with 2.06 ± 0.26 on day 1 (Fig. 4D; Student's paired *t*-test; $P < 0.0001$) Over the treatment period, rats given 2 hours of SSB access a day consumed an average of 5.03 ± 0.43% of their kcal from the SSB.

NOIC behavioral testing in adult rats exposed to SSBs for 2 hours daily during the juvenile/adolescent phase of development

There were no differences in body weight between the groups at the time of NOIC testing, which was from PN 175–179 after ~4.5 months without access to SSBs (Fig. 5A). Results from the NOIC task revealed that while there was no baseline preference for one object over the other on day 1 of the task (Fig. 5B), rats exposed to SSBs for 2 hours daily during the adolescent phase of development were significantly impaired in hippocampal-dependent episodic
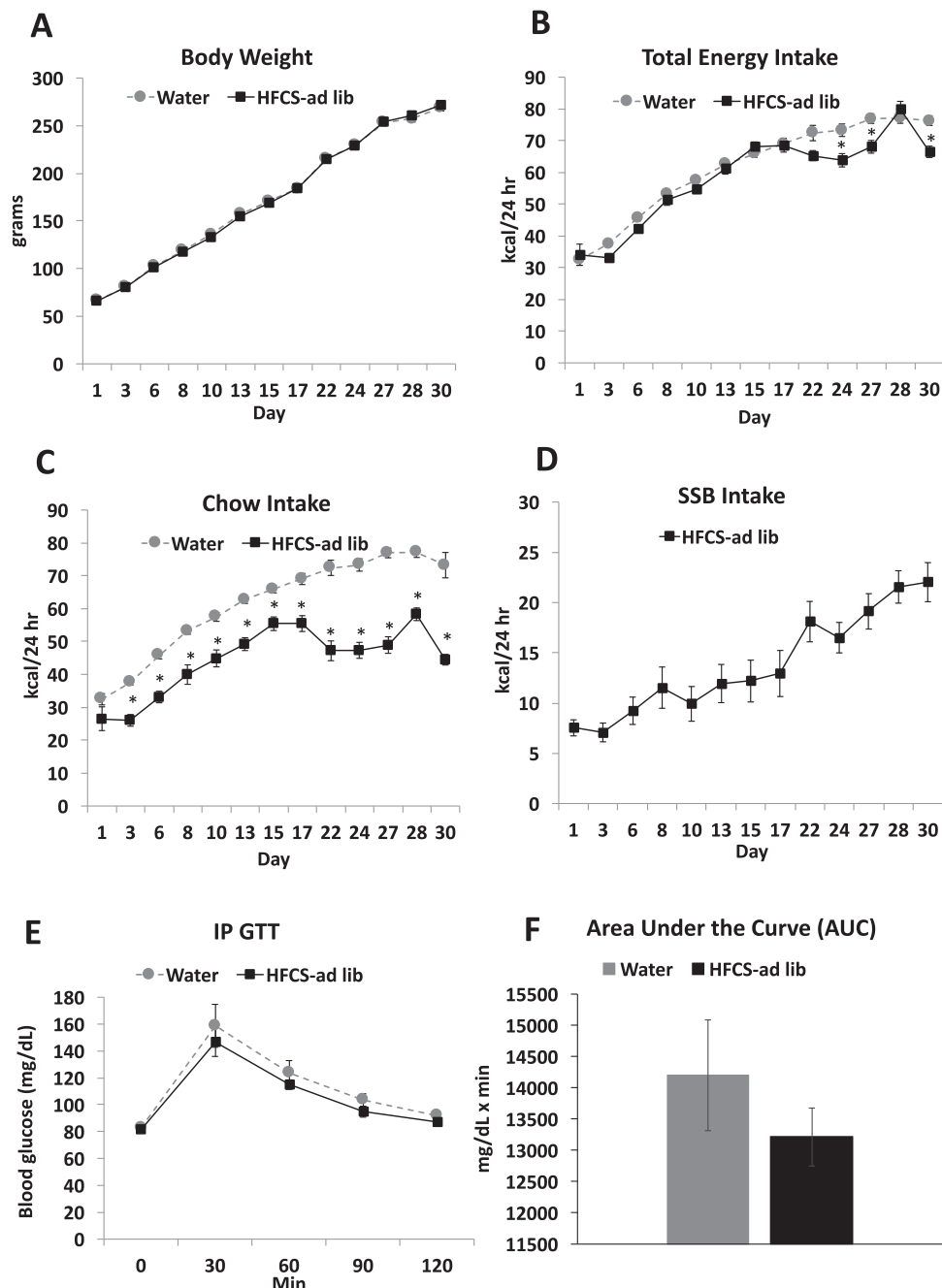
Figure 2   Metabolic measures and dietary intakes in juvenile/adolescent rats fed *ad libitum* sugar solution. Body weights (A), total kcal intake (chow + sugar solutions; B), chow intake (C) and sugar intake (D) for animals who received *ad libitum* access to 11% w/v HFCS-55 (HFCS-ad lib) or a second water bottle for the control group (control). Results from an IP GTT (D and E) showed no differences between the two treatment groups. Data are means ± SEM; $n = 12$/group, *$P < 0.05$. SSB: sugar-sweetened beverages.

contextual memory at PN 179, as evidenced by a reduced discrimination index and a significantly lower shift from baseline discrimination index relative to controls (0.17 ± 0.03 (SSB group) vs. 0.05 ± 0.03 (water group), $P = 0.009$; Fig. 5C–D).

Discussion

Results from the rodent experiments presented herein show that consumption SSBs during the juvenile/adolescent phase of development significantly impairs hippocampal-dependent episodic contextual memory when tested much later in life following an extended period (~4.5 months) without SSB access. These memory deficits persisted even when SSB access was intermittent/restricted to 2 hours per day, resulting in ~5% of total kcal from sugar consumption. Furthermore, memory impairments were observed independent of metabolic abnormalities such as body weight gain and glucose intolerance. These findings reveal that the juvenile/adolescent period is one of high vulnerability to long-lasting cognitive impairments, resulting from habitual sugar consumption.

In our previous report[3], 11% HFCS-55 access during the juvenile/adolescent period significantly
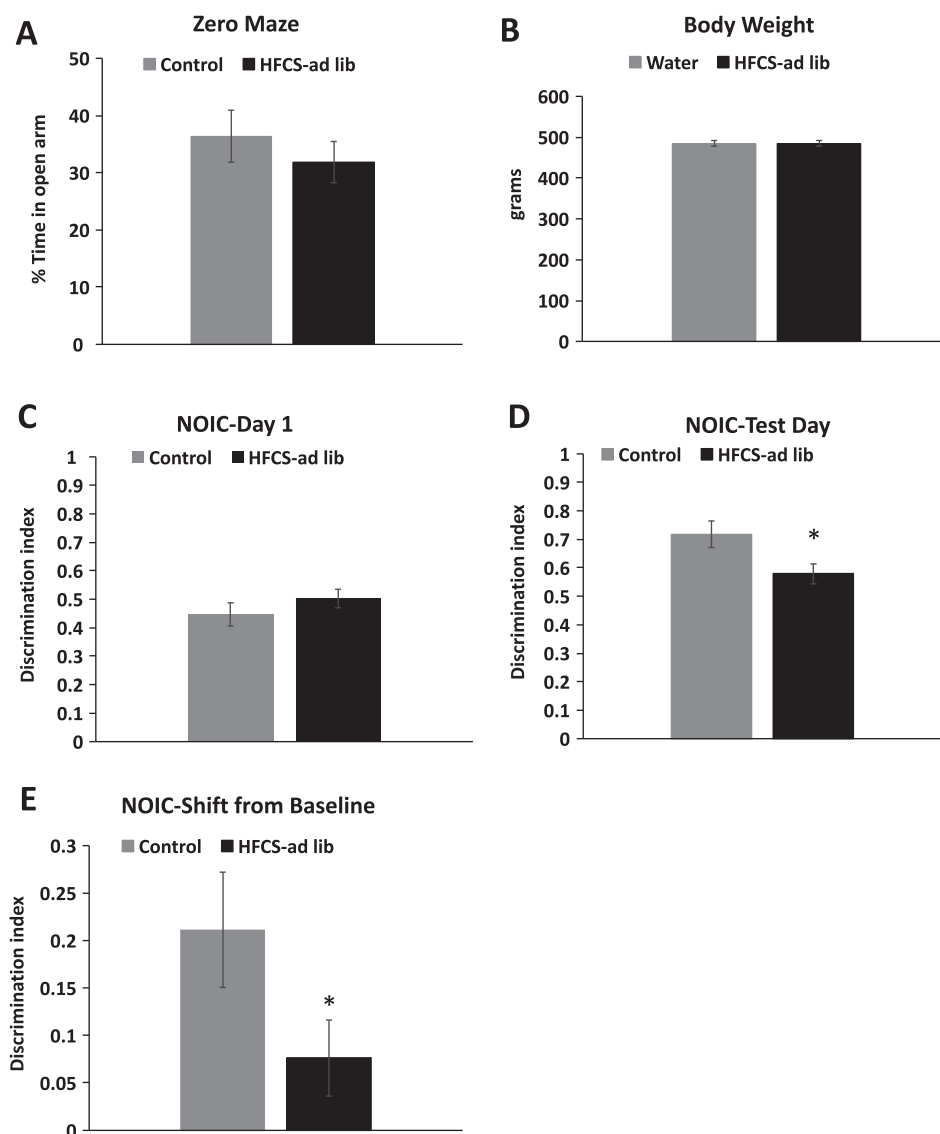
Figure 3 Behavioral measures in adult rats that were fed *ad libitum* sugar solutions during the juvenile/adolescent phase of development. Zero maze test for anxiety (A) body weight at PN 175 (B) Discrimination index results from day 1 and test day of NOIC testing (C and D), and results from NOIC calculated as the shift from baseline discrimination index (E) in HFCS-*ad lib* rats. Data are means ± SEM; *n* = 12/group, *P < 0.05.

impaired hippocampal-dependent spatial memory when tested from PN 60–70, while having no effect on anxiety-like behavior in the Zero maze. Similar to this previous study, HFCS-55 had no effect on body weight during the access period (nor at the time of NOIC testing), nor was there an effect on Zero maze performance in the present study. The rationale for assessing Zero maze performance behavior is that the hippocampus, particularly the ventral subregion, is linked with anxiety-like behavior in rodents,[29] and potential group differences in anxiety can complicate interpretation of the NOIC data. The lack of group differences in Zero maze performance in the present study combined with group differences in NOIC (a dorsal hippocampal-dependent memory task[28] suggests the dorsal subregion may be more vulnerable than the ventral subregion to disruption by early-life SSB consumption. However, more research is required

to explore this possibility. Moreover, there is little consensus in the literature regarding the precise differentiation of function between the dorsal and ventral hippocampal subregions.[29–31]

One key difference between the present results and our previous report is that in our previous report, the HFCS-55-exposed rats demonstrated impairments in IP GTT relative to controls when tested at ~PN 70, whereas in our current report the *ad libitum* SSB group in the present study was impaired in hippocampal-dependent memory without concomitant IP GTT deficits at PN 185 (following an extended period without SSB access). Thus, dietary intervention (removal of SSB for ~4.5 months) appears to be effective in reversing impaired glucose tolerance (at least when measured with IP GTT), but is not effective in reversing hippocampal-dependent memory deficits. Collectively, these findings suggest that the
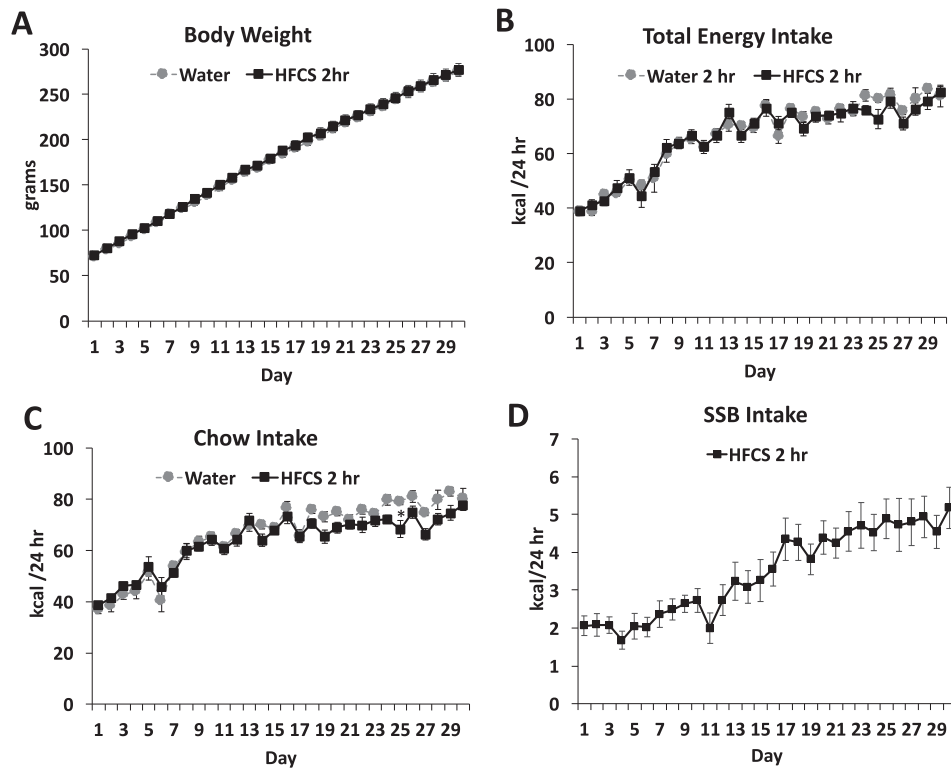
Figure 4   Metabolic measures and dietary intakes in juvenile/adolescent rats fed sugar solution with intermittent 2-hour daily access. Body weights (A), total kcal intake (chow + sugar solutions; B), chow intake (C) and sugar intake (D) for animals who received intermittent, 2-hour daily access to 11% w/v HFCS (2 hours) or a second water bottle for the control group (control). Data are means ± SEM; *n* = 11/group, *P < 0.05 SSB: sugar-sweetened beverages.

hippocampal dysfunction associated with early-life SSB consumption in rats is not easily reversible with dietary intervention, and is unlikely to be related to SSB effects on peripheral glucose metabolism.

The juvenile/adolescent period of development is one of rapid growth and maturation and is a particularly critical period for hippocampal development.[32–36] The hippocampus is highly susceptible to the deleterious effects of obesogenic dietary factors,[2,6–8] as several recent studies have revealed that juvenile and adolescent obesogenic dietary factors such as palatable high-fat/high-sugar diets (HFDs) negatively impact hippocampal function. For example, juvenile/adolescent mice fed an HFD (45% kcal from fat) beginning at 5 weeks old showed impairments in the hippocampal-dependent novel location recognition task, whereas mice that were given the diet at 8 weeks old were not impaired.[37] Similarly, in juvenile but not adult rats, consumption of an HFD (45% kcal from fat) significantly impaired hippocampal-dependent spatial memory retention and spatial reversal learning,[38] and mice fed an HFD for 11 weeks post weaning (a period spanning the entire juvenile adolescent period and ∼7 weeks into young adulthood) were impaired in hippocampal-dependent relational memory flexibility assessed in a two-stage radial arm maze concurrent spatial discrimination task, whereas adults exposed to the diet for a similar amount of time were not impaired.[39] The reproducibility of these outcomes using several different hippocampal-dependent memory tasks strongly suggests the capacity for dietary and metabolic factors to negatively impact hippocampal function when exposure to these factors occurs during early life. A recent study showed that early-life exposure to an HFD in mice in sufficient quantities as to induce diet-induced obesity and insulin resistance during the juvenile/adolescent phase of development had long-lasting negative implications for hippocampal function that were not reversible by switching animals to a low-fat diet during adulthood. Interestingly, however, the dietary intervention reversed the effects of the HFD on body weight and glucose metabolism.[40] Our data isolate one component of the HFD (added sugars) that is sufficient on its own to promote similar deleterious effects on hippocampal function, even following extended dietary intervention. We also note that the prefrontal cortex (PFC) is another brain region that appears to be vulnerable to obesogenic dietary factors when consumed during early-life periods. For example, Reichelt *et al.*[24] observed deficits in a PFC-dependent rodent Stroop task in rats given intermittent (2 hours daily) access to sucrose during adolescence. In addition, Labouesse *et al.*[41] demonstrated that mice given a high-fat diet during adolescence were impaired in a PFC-dependent cognitive flexibility task, whereas no impairments were
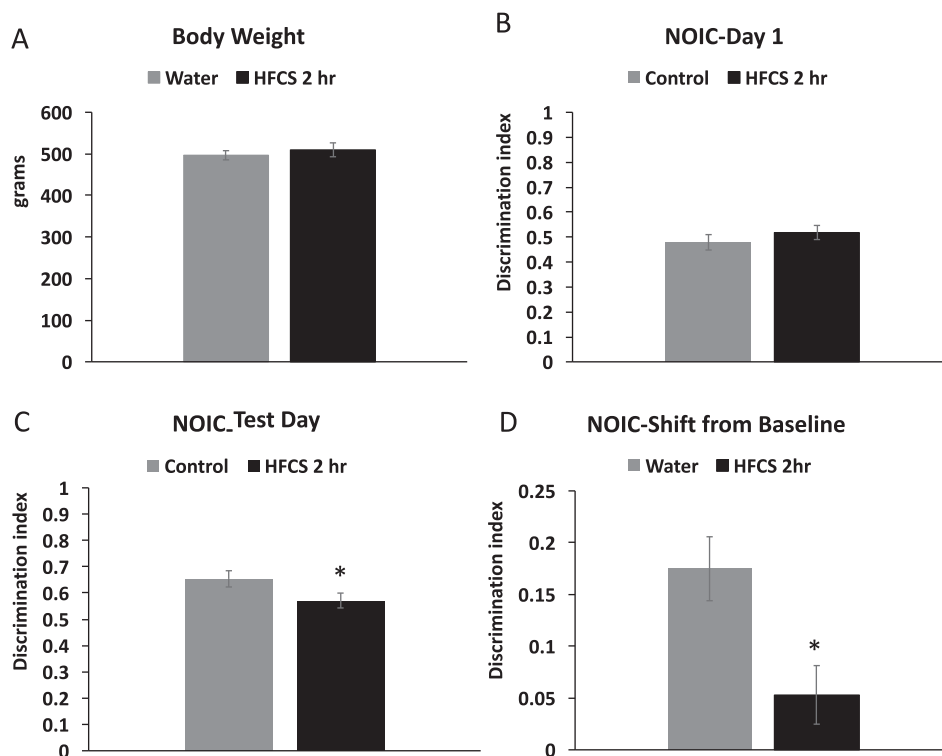
Figure 5   NOIC in adult rats that were given intermittent sugar solution access for 2 hours daily during the juvenile/adolescent phase of development. Body weight at PN 175. (A) Discrimination index results from day 1 and test day of NOIC testing (B and C), and results from NOIC calculated as the shift from baseline discrimination index (D) in rats given 2 hours daily access to a solution of 11% w/v HFCS solution (2 hours) or a second water bottle for the control group (control). Data are means ± SEM; $n = 12$/group, *$P < 0.05$.

observed when the high-fat diet was given during adulthood at PN 70.

While sugar is often a component of the palatable obesogenic HFDs used for research purposes, until recently few studies investigated the effects of dietary sugar per se on hippocampal function. Jurdak and Kanarek[42] reported that free access to a 32% sucrose solution in adult rats produced body weight gain and impaired novel object recognition relative to controls. Hsu et al.,[3] reported that juvenile and adolescent, but not adult, *ad libitum* consumption of an 11% HFCS-55 solution for 30 days impaired hippocampal-dependent spatial learning and memory retention in rats. However, no effect of juvenile/adolescent HFCS-55 access was observed in a hippocampal *independent* response learning task of comparable difficulty that was performed under similar conditions and using similar motivational tactics but did not require the utilization of spatial cues.[3] Using a separate spatial learning and memory task (the Morris water maze) and an intermittent access (2 hours daily) model of 10% sucrose solution for 28 days, Kendig et al.[23] observed that both juvenile/adolescent and young adult exposure to the intermittent sucrose impaired hippocampus-dependent spatial learning and memory. Our current finding that early-life access to 11% HFCS solution for just 2 hours/day impairs hippocampal-

dependent episodic contextual memory is in agreement with this study, as well as another recent study from Reichelt et al.,[24] where rats were exposed to 10% sucrose for 2 hours a day during the juvenile and adolescent period and showed an impaired memory capacity in an object-in-place task, which tests hippocampal-dependent episodic contextual memory. In this study the sucrose treatment stopped at PN 56 and rats were tested at PN 92, 5-weeks after the last sucrose treatment when the animals are in early adulthood.[24] Our results extend these findings and show, remarkably, that impairments persist for 4.5 months after removing SSB access at the end of the adolescent period, suggesting that the damage imparted by early-life HFCS SSB exposure is not reversible by withdrawing sugar access alone. One limitation of our current findings is the use of only one hippocampal-dependent memory task. However, the notion that early-life sugar consumption produces hippocampal deficits is further supported by the aforementioned studies[23,24] that utilized different hippocampal-dependent tasks, as well as our previous findings that early-life sugar consumption impairs hippocampal-dependent spatial memory in the Barnes maze task.[3] Future research will be needed to determine whether early-life sugar consumption confers long-lasting impairments in hippocampal-dependent spatial memory.

While obesity and elevated BMI are associated with cognitive deficits,[43,44] our data suggest that weight gain is not necessary for sugar-induced cognitive deficits caused by early-life sugar consumption. Similarly, while obesity per se is associated with reduced hippocampal volume[45] and impaired hippocampal function,[46–48] evidence shows that dietary factors can negatively impact hippocampal function independent of obesity. For example, hippocampal-dependent spatial memory impairments have been reported in rats following Western diet consumption even before the onset of diet-induced obesity or weight gain.[49,50] Similar to Western diets, high fructose diets can also impair hippocampal-dependent learning and memory in rodents independent of obesity.[3,7,51–54] Our data corroborate and extend the work of others[3,13] in showing that neither weight gain nor peripheral glucose intolerance is a necessary component of sugar-induced cognitive deficits.

The neurobiological mechanisms underlying long-lasting hippocampal-dependent memory deficits, resulting from early-life sugar consumption are poorly understood. One possibility is that the long-term dietary sugar 'programming' of behavioral deficits involves changes in the brain epigenome. Indeed, a recent study reported in mice that high-fat diet-induced obesity altered DNA methylation in memory-associated genes in the hippocampus, including Sirtuin 1 and reelin, and these effects were functionally relevant to high-fat diet-related memory deficits in a hippocampal-dependent object location memory task.[55] Another possibility is that early-life habitual sugar consumption produces long-lasting changes in the gut microbiome (the collective genome of microbes residing in the gastrointestinal tract) that contribute to negative cognitive outcomes. Several recent findings are consistent with this possibility. For example, depleted gut microbiota during early adolescence in mice impairs novel object recognition and hippocampal-dependent social transmission of food preference, and colonization with commensal microbiota from a replete host normalizes these cognitive abnormalities.[56] In addition, microbiome transplantation in mice consuming a healthy chow from donor mice fed a high-fat diet recapitulated high-fat diet-associated deficits in exploratory and stereotypical behaviors.[57] Finally, we recently reported that *ad libitum* access to an 11% w/v sugar solution during the juvenile and adolescent period (modeling the approach in Cohort 1 in the present paper) significantly altered gut bacteria relative to controls at every phylogenetic level, with significant group effects in ~33% of gut bacteria at the family level.[58] Follow-up research is warranted to investigate whether long-lasting memory deficits resulting from early-life consumption of obesogenic dietary factors are related to changes in the brain epigenome and/or gut microbiome.

Conclusions

Results from this study suggest that consumption of an 11% HFCS solution during early life (childhood and adolescence) may confer long-lasting impairments in memory function independent of changes in body weight or aberrant glucose metabolism. Specifically, we found that early-life consumption of SSBs in rats impaired contextual episodic memory, a mnemonic processes that relies on the integrity of the hippocampus.[27] Strikingly, the impairments lasted well into late adulthood, even after SSB access was completely removed from the diet, and even when SSB access during the juvenile/adolescent period was restricted to 2 hours per day. These findings suggest that the mechanisms altering hippocampal function are not easily reversible by simply removing sugars from the diet. These results further suggest that young people may be at risk for long-term negative cognitive consequences from consuming SSBs, however, as we utilized a rodent model of SSB consumption during early life, further studies are necessary to infer whether these results are translatable to humans.

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