Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Behavioral Sciences

# Early life exposure to obesogenic diets and learning and memory dysfunction

Emily E Noble and Scott E Kanoski

Obesogenic dietary factors, such as simple sugars and saturated fatty acids, have been linked to memory impairments and hippocampal dysfunction. Recent evidence suggests that the brain may be particularly vulnerable to the effects of obesogenic diets during early life periods of rapid growth, maturation, and brain development. Investigations utilizing rodent models indicate that early life exposure to 'high fat diets' (40–65% kcal derived from fat) or simple sugars (sucrose or high fructose corn syrup) can impair hippocampus-dependent learning and memory processes. In some cases, these deficits occur independent of obesity and metabolic derangement and can persist into adulthood despite dietary intervention. Various neurobiological mechanisms have been identified that may link early life consumption of obesogenic dietary factors with hippocampal dysfunction, including increased neuroinflammation and reduced neurotrophin-mediated regulation of neurogenesis and synaptic plasticity. Age, duration of exposure, and dietary composition are key variables contributing to the interaction between early life diet and cognitive dysfunction, however, more research is needed to unravel the precise crucial windows of development and causal dietary factors.

**Address**
Department of Biological Sciences, Human and Evolutionary Biology Section, University of Southern California, Los Angeles, CA, USA

Corresponding author: Kanoski, Scott E (kanoski@usc.edu)

**Current Opinion in Behavioral Sciences** 2016, **9**:7–14

This review comes from a themed issue on **Diet, behavior and brain function**

Edited by **Dana M Small** and **Susanne E la Fleur**

http://dx.doi.org/10.1016/j.cobeha.2015.11.014



## Introduction

A bourgeoning body of research highlights the negative impact of 'obesogenic diets' on the brain and cognitive function. The hippocampus, a brain region most famously associated with learning and memory function and more recently with food intake control [1–5], is highly susceptible to the deleterious effects of consuming foods high in saturated fatty acids and simple sugars [6,7]. While previous reviews have discussed the impact of consuming obesogenic diets on hippocampal dysfunction and memory ability more generally [8–15], these reviews did not highlight age or period of life as a crucial variable. Herein we review literature, primarily from animal models, suggesting that the negative impact of obesogenic dietary factors on cognitive function is exacerbated during critical periods of development (prenatal, juvenile, and adolescence) (Tables 1 and 2). We also highlight various neurobiological mechanisms linking early life dietary factors with hippocampal dysfunction.

## Perinatal period: obesogenic diets and memory function

The theory that adult susceptibility to disease states is programmed during early development, also termed 'fetal programming' [16], has given momentum to investigations of how the perinatal environment, in particular maternal nutrition, affects the cognitive health of the offspring. Human epidemiological studies have reported an association between maternal obesity and poor cognitive performance of the child [17–20]. However, few studies dissociate the effects of obesity and metabolic dysfunction from the effects of maternal obesogenic diets per se on cognitive outcomes in human children. Several carefully controlled rodent studies discussed below, however, have attempted to bridge this gap.

Consuming a 'high fat diet' (HFD) containing 40–65% kcal from fat and abundant simple sugars to enhance palatability (typically half of the total carbohydrate source derived from sucrose), is a commonly used obesity model in rodents. Evidence suggests that maternal consumption of such a HFD beginning before mating and ending just before weaning caused hippocampal-dependent spatial learning deficits in offspring at 4 weeks of age, however, these deficits were no longer present when animals were tested later during adulthood [21,22,23•]. Similarly, perinatal HFD exposure had no effect on fear conditioning performance when animals were tested during adulthood after having been fed a standard chow diet post-weaning [24]. Thus, the detrimental effects of maternal HFD on cognitive performance are seemingly more pronounced during early life, at least when offspring are weaned on a healthy diet. In fact, one study reported that spatial learning and memory function are improved in the adult male progeny of dams that were fed a 60% HFD [25]. Collectively these data suggest that under some conditions prenatal and perinatal exposure to a HFD does not

**Table 1**

**Effects of perinatal obesogenic diet consumption on hippocampal-dependent learning and memory. Only articles containing hippocampal-dependent cognitive tasks were included. M: male, F: female, SD: Sprague Dawley, RD: Research Diets, PND: post-natal day, MWM: Morris Water Maze, HFD: high-fat diet, TFD: trans-fat diet, CD: control diet, TBI: traumatic brain injury.**

| Study | Subjects | Diets | Exposure | Test design | Task | Outcome |
|---|---|---|---|---|---|---|
| Bilbo *et al*., 2010 [25] | M and F SD rats | RD D12492 60% kcal fat, RD D06061202 60% kcal TFD or RD D12450B 10% kcal fat (control) | Gestation-weaning (PND 21) | Behavior at PND 85–95 | MWM | Early life consumption of HFD or TFD caused spatial learning impairments during adulthood despite switching to chow at weaning |
| Can *et al*., 2012 [28] | M SD rats | 65% kcal from fat versus 10% kcal from fat (control) | Gestation- (PND 119) | Behavior measured in adulthood | MWM | HFD impaired spatial learning |
| Kuang *et al*., 2014 [27] | M SD rats | 20% sucrose solution + chow or water + chow (control) | Gestational day 1–21 | Behavior at 1 and 2 months old | MWM | Impaired spatial learning in offspring of high sucrose-fed dams, especially at 1 mo |
| Lepinay *et al*., 2015 [23] | M Wistar rats | HFD (39% kcal from fat) with omega 6:omega 3 fatty acid ratio of 39 or control diet (12% kcal from fat) with omega 6:omega 3 ratio of 5 | Gestation-weaning (PND 21) or Gestation-5 months old | Behavior at 5 months | MWM | Perinatal HFD or exposure from weaning through adulthood had no effect on memory, however animals fed HFD during the perinatal period and post weaning had impaired spatial memory |
| Mychasiuk *et al*., 2015 [30] | M and F SD rats | HFD (60% kcal from fat) + 20% sucrose solution, standard chow and water (control) or caloric restriction on standard chow | Dams exposed 3 weeks before mating Gestation-PND 47 | At PND 30 animals were given mild TBI or sham injury. Behavioral testing PND 35–45 | MWM, Novel Context Mismatch | F offspring on HFD were impaired in novel context mismatch. TBI impaired performance in the novel context mismatch in both standard chow ad libitum and HFD groups, but not in calorically restricted animals |
| Page *et al*., 2014 [26] | M SD rats | RD D12451 45% kcal from fat versus control chow 10% kcal from fat D12451B | Dams exposed 4 weeks before mating Gestation-PND 21 or Gestation-PND 118 | Behavioral testing during adulthood (PND 110–118) | MWM | Both HFD–HFD and HFD–CD animals were impaired in spatial learning compared with CD–CD and CD–HFD |
| Peleg-Raibstein *et al*., 2012 [24] | M and F C57BL/6N mice | HFD (60% kcal from fat) versus standard chow (control) | Dams exposed 3 weeks before mating Gestation-weaning (PND 21) | Behavioral testing after PND 90 | Pavlovian Fear Conditioning | There were no differences in fear conditioning between offspring from HFD-fed and offspring from chow-fed dams |
| Tozuka *et al*., 2010 [21] | M C57BL/6N mice | HFD Clea Japan (57% kcal from fat) versus CE-2 Clea Japan chow (control) | Gestation–lactation d16 | Behavioral testing at PND 28 and PND 77 | Barnes Maze | Impaired spatial learning in adolescent but not adult mice |
| White *et al*., 2009 [22] | M Long Evans rats | RD D12492 60% kcal fat or RD D12450B 10% kcal fat control | Dams exposed 4 weeks before mating Gestation-weaning (PND 21) At 8 weeks old, put back on one of the perinatal diets for 9 weeks | Behavioral analyses were performed during adulthood (19.5 weeks old) | MWM | HFD–HFD animals were impaired in spatial memory retention, but HFD–CD, CD–CD and CD–HFD showed no difference in performance |

impair hippocampal-dependent learning and memory, whereas in other cases HFD-induced memory deficits may be overcome by switching the pups to standard chow at weaning.

In contrast to these findings, other reports indicate that pre-weaning HFD exposure confers cognitive deficits that persist into adulthood, even when the animals were fed a standard chow diet post-weaning. For example,

**Table 2**

**Effects of juvenile/adolescent obesogenic diet consumption on hippocampal-dependent learning and memory. Only articles containing hippocampal-dependent cognitive tasks were included. M: male, F: female, SD: Sprague Dawley, RD: Research Diets, PND: post-natal day, MWM: Morris Water Maze, HFD: high-fat diet, TFD: trans-fat diet, CD: control diet, HFCS-55: high fructose corn syrup 55, SFA: high saturated fatty acid diet.**

| Study | Subjects | Diets | Exposure/age | Test design | Task | Outcome |
|---|---|---|---|---|---|---|
| Hsu *et al*., 2015 [43] | M SD rats | Low-fat chow + either 11% sucrose solution of 11% high fructose corn syrup (HFCS-55) or water (control) | Adolescents: PND 30–60 Adults: PND 60–90 Diet exposure continued through behavioral testing | Behavioral testing beginning at PND 60 (adolescents) or PND 90 (adults) | Barnes Maze | HFCS-55 significantly impaired spatial learning and memory when consumed during juvenile/adolescence but not during adulthood |
| Kendig *et al*., 2013 [44] | M Wistar rats | Standard chow + either 10% sucrose solution or saccharin solution (control) | Adolescents: PND 28–56 Adults: PND 63–91 Intermittent access to sweet solutions (2 h/day) | Behavioral testing on PND 61 (adolescents) or PND 96 (adults) | MWM | Intermittent sucrose consumption spatial learning and memory in both adult and adolescent groups |
| Reichelt *et al*., 2015 [45] | M SD rats | Standard chow + either 10% sucrose solution or water (control) | PND 28–56 Intermittent access to sweet solutions (2 h/day) | Behavioral testing from PND 62 to 92 | Object in Place test | Sucrose exposed rats had impaired performance |
| Boitard *et al*., 2012 [41] | M C57BL6/J mice | RD D12451 HFD (45% kcal from fat) versus A04 SAFE chow (10% kcal from fat) | Juvenile-adult: PND 21–98 Adult: PND 84–161 | Behavioral testing at PND 98 (juvenile/adult) or PND 161 (adult) | Two-stage Radial Maze | HFD abolished relational memory flexibility in juveniles but not adults |
| Boitard *et al*., 2014 [40] | M Wistar rats | Research diets D12451 HFD (45% kcal from fat) versus A04 SAFE chow (10% kcal from fat) | Juvenile: PND 21–133 Adult: PND 84–196 | Behavioral testing after 1, 2 and 3 months diet exposure | MWM | Juvenile HFD consumption impaired spatial memory |
| Kaczmarczyk *et al*., 2013 [46] | M C57BL/6J mice | RD D12492 60% kcal fat or RD D12450B 10% kcal fat control | PND 21–28 or PND 21–42 | Behavioral testing at PND 28 or PND 42 | Y Maze | One week of HFD impaired spontaneous alternation. At 3 weeks there was no effect of diet on task performance |
| Valladolid-Acebes *et al*., 2013 [42] | M C57BL/6J mice | RD D12451 (45% kcal from fat) versus standard chow | Adolescent: PND 35–91 or Adult: PND 56–112 | Either 8 weeks of diet or 8 weeks of diet followed by 5 weeks of food restriction before behavioral testing | Novel Object Location Recognition | Adolescents, but not adults, on HFD had impaired learning performance, which persisted after 5 weeks of caloric restriction |
| Nyaradi *et al*., 2014 [38] | Humans | 'Western' versus 'Healthy' dietary pattern | Adolescence (14–17 years old) | FFQ 14 years of age, cognitive testing at 17. Data adjusted for energy intake, gender, income, maternal education, paternal presence | Groton Maze Learning Task, Detection Task | 'Western' diet consumption was associated with more errors in Groton Maze and longer detection time |
| Baym *et al*., 2014 [39] | Humans | Saturated fat (SFA), refined sugar, omega 3 fatty acids | 7–9 years old | Cross-sectional | Relational memory and item memory tasks | SFA intake associated with impaired performance in both tasks |

progeny born from dams that were fed a HFD (45% kcal from fat) performed worse in the hippocampal-dependent Morris Water Maze (MWM) spatial learning task during adulthood relative to offspring born from dams on standard chow. Moreover, animals that were switched to standard chow at weaning were equally impaired in learning the learning task compared to animals weaned on the HFD [26••]. One possible explanation for the discrepancies between this study and those discussed above is the percentage of fat and sugar in the diet. The study reporting MWM deficits despite the animals being weaned on chow (Page *et al.* [26••]) utilized a HFD with 45% kcal from fat, whereas others reporting conflicting 'recovery of function' results (e.g., [21,22,24,25]) utilized a 60% HFD. Notably, these diets not only differ in the % kcal from fat, but also in the % kcal from sugar. The 45% HFD used by Page *et al.* contains a considerably higher proportion of kcal from sugar compared with the 60% HFD used by others (17% vs 7%) [22,25]. Thus, it is possible that the combined impact of high sugar and fat in the diet is greater than the impact of fat alone. Alternatively, perinatal exposure to sugar may have a more detrimental effect on adult memory function than perinatal exposure to fat. Consistent with this notion, one study demonstrated that maternal consumption of a 20% sucrose sweetened solution from gestational day 1 to day 21 produced impairments in spatial learning performance of juvenile and adolescent offspring [27•], however, the effects of perinatal sucrose exposure in adult offspring was not tested.

Some studies have extended feeding of an obesogenic diet beyond the perinatal period to study the impact of perinatal through childhood and/or early adulthood consumption of an obesogenic diet on learning and memory function. For example, progeny of dams maintained on a HFD (60–65% kcal from fat) who were also fed the HFD for over 2 months post-weaning exhibited impaired performance in the MWM [22,28]. Another study examining the effects of a HFD (39% kcal from fat) reported that when the diet was confined exclusively to either the prenatal or postnatal phase, HFD-feeding had no effect on spatial memory in the MWM during adulthood relative to controls. However, when the HFD was fed throughout both prenatal and postnatal development, as well as post-weaning, the offspring had deficits in spatial learning capabilities during adulthood [23•]. Similar findings were reported using the Novel Context Mismatch task, which is a hippocampus-dependent memory task that presumably measures contextual episodic memory [29]. Juvenile rats born of dams that had been exposed to a combined HFD/high sucrose diet (60% kcal from fat/20% sucrose in the drinking water) that were maintained on the diet post-weaning had impaired performance in the Novel Context Mismatch task [30•]. Overall the literature suggests that consumption of obesogenic diets during the perinatal period and throughout juvenile/adolescent phase of development impairs hippocampal dependent learning and memory. There are various unresolved discrepancies, however, regarding the long-term impact to the offspring following maternal consumption of obesogenic dietary factors during the perinatal period. For example, the extent that maternal obesity plays a role independent of prenatal offspring diet exposure is an important unresolved question. One additional area for further study is to investigate the importance of the fat:sugar ratio in the diet, as in some cases it appears that a higher % kcal from sugar may preclude the benefits of being weaned on a healthy diet.

## Juvenile and adolescent period

It is crucial to understand how consumption of obesogenic foods impacts the brain during childhood, as the juvenile/adolescent period of development is one of rapid growth and maturation and is a particularly critical period for hippocampal development [31–35]. Although little is known thus far on the impact of childhood metabolic and dietary factors on cognition in human populations, a link between childhood obesity and impaired performance on tasks involving executive function and attention has been identified [36,37]. Notably, a recent prospective epidemiological study showed that consumption of a 'Western' dietary pattern during early adolescence is associated with poor cognitive performance during late adolescence, specifically on visual spatial learning and long-term memory tasks [38•]. In addition, saturated fatty acid intake in children is associated with reduced performance in hippocampal-dependent relational and item memory tasks independent of body mass index [39•].

Several recent studies using highly controlled animal models have revealed that juvenile and adolescent obesogenic dietary factors negatively impact hippocampal function. Boitard *et al.*, observed that in juvenile but not adult rats, HFD (45% kcal from fat) consumption impaired spatial memory retention and spatial reversal learning [40•]. The same group reported that mice fed HFD for 11 weeks post weaning (a period spanning the entire juvenile adolescent period and ~7 weeks into young adulthood) demonstrated impaired relational memory flexibility assessed in a two-stage radial arm maze concurrent spatial discrimination task, whereas adults exposed to the diet beginning at 12 weeks and for a similar amount of time were not impaired [41]. On a similar diet, juvenile/adolescent mice (5 weeks old) were impaired in the hippocampal dependent Novel Location Recognition task, whereas mice that were given the diet at 8 weeks old were not impaired [42••]. Collectively these studies strongly suggest that the juvenile/adolescent brain is particularly vulnerable to the effects of obesogenic dietary factors.

Consistent with perinatal and adult exposure studies, the hippocampus appears to be a particularly susceptible brain region to the negative effects of dietary sugars consumed during the juvenile and adolescent period, even in the absence of elevated fat intake. For example, Hsu, Kanoski and colleagues recently reported in rats that juvenile and adolescent, but not adult, *ad libitum* consumption of an 11% high fructose corn syrup (HFCS-55) solution for 30 days impaired hippocampal-dependent spatial learning and memory retention [43••]. Kendig *et al.* utilized an intermittent access model of 10% sucrose solution for 28 days and observed that both juvenile/adolescent and young adult exposure to the intermittent sucrose impaired learning and memory in the MWM [44•]. Using a similar paradigm of intermittent sucrose access, a recent study exposed rats to 10% sucrose for 2 hours a day during the juvenile and adolescent period. Results revealed sucrose-associated deficits in object-in-place task, which tests hippocampal-dependent episodic contextual memory. In this study access to the diet ended at the end of the adolescent period and the testing was performed during adulthood 5-weeks after the last sucrose treatment [45•].

The question as to whether obesity as a consequence of the obesogenic diet, or rather, components of the diet itself are driving the deficits in hippocampal dependent cognitive function is a crucial one that is not easily addressed with many experimental designs. In one of the aforementioned studies, however, Valladolid Acebes and colleagues conclude that caloric intake was not driving the impairment, since the controls and HFD animals consumed similar total kcal amounts. Rather, the authors argue that the effect is likely due to dietary composition [42••]. In support of this notion, they found that cognitive performance remained impaired after a 5-week dietary restriction (restricted to 70% of their ad libitum total kcal of the HFD) period following 8 weeks of ad libitum HFD (45% kcal from fat) consumption. In further support of the idea that dietary factors rather than obesity or excess adipose tissue is causing the effects, short-term (1 week) HFD feeding (60% kcal from fat) significantly impaired spatial memory in the spatial-cued Y-maze before the onset of weight gain or impaired glucose metabolism in juvenile mice [46]. Moreover, Hsu *et al.*, found that despite similar caloric intake and levels of body weight gain, animals that consumed an 11% HFCS-55 solution during the juvenile and adolescent period performed worse in the spatial Barnes Maze task relative to controls [43••], however, the HFCS group showed moderate glucose intolerance relative to controls. Taken together these data strongly suggest that dietary factors contribute to the memory impairments in some cases independent of excessive caloric intake, weight gain, or full-blown metabolic derangements. Future studies are warranted to understand which specific dietary factors (e.g., monosaccharide ratios, fatty acid profiles, fat to sugar ratio) are causally related to early life obesogenic diet-induced cognitive deficits.

## Neurobiological mechanisms

### Inflammation/cytokines

Obesity promotes a form of chronic low-grade inflammation (for review see [47]). Elevated levels of proinflammatory cytokines in the brain are directly linked with impaired hippocampal-dependent memory [48,49] and the offspring hippocampus is particularly susceptible to maternal inflammation [50]. Perinatal and juvenile exposure to a chow diet supplemented with saturated fat, cholesterol, and sugar, produced elevations in expression of the cytokines TNF-alpha and IL-6, with concurrent morphological changes in the hippocampal CA-1 region [51]. Similar to effects observed following prenatal LPS injections which promote acute inflammation [52], hippocampal pyramidal cells were smaller in pups born from dams fed the fat, cholesterol, and sugar-enriched diet [51]. Maternal saturated fat consumption is also associated with increased expression of the proinflammatory cytokine, IL-1β at P20 and during adulthood, as well as increased microglia expression in the CA1, CA3 and dentate gyrus of the hippocampus [25]. Hsu *et al.* reported elevated levels of IL-1β and IL-6 in the dorsal hippocampus of rats fed 11% HFCS-55 solution during the juvenile and adolescent period, however, no significant cytokine elevations were observed either in adult rats fed 11% sucrose or HFCS-55 solutions, or in juvenile/adolescent animals fed the sucrose solution. These findings are notable with regard to the relationship between neuroinflammation and hippocampal function, as only the juvenile/adolescent rats fed HFCS-55 had pronounced spatial memory deficits [43••]. Conversely, in a study showing impairments in long-term memory after juvenile HFD consumption, no differences were observed in expression of the inflammatory cytokines TNFα and IL-1β in untreated animals; however, there was an exaggerated increase in expression of both of these two cytokines following an LPS immune challenge [40•], suggesting that the dietary manipulation did indeed increase neuroinflammatory signaling pathways relative to controls.

### Neurotrophic factors: neurogenesis and synaptic plasticity

Neurogenesis and synaptic plasticity are purported to be essential for hippocampal-dependent learning and memory, and these functions rely on neurotrophic factors such as brain derived neurotrophic factor (BDNF) (for review see [15]). Tozuka *et al.* observed that hippocampal BDNF was reduced and dendritic arborization was impaired during the juvenile/adolescent phase in offspring born from dams fed a HFD (57% kcal from fat). BDNF levels were not different from controls in adulthood, however, which is consistent with previously discussed behavioral outcomes showing HFD-associated impaired spatial learning during adolescence, but not adulthood [21]. Page and colleagues reported that hippocampal BDNF and activity-regulated cytoskeleton associated protein (ARC), whose expression is necessary for late phase learning and

memory consolidation [53,54], were significantly reduced in the adult offspring of HFD-fed dams compared with those of chow-fed dams, irrespective of whether they were weaned on chow or HFD (45% kcal from fat). These findings corresponded to impaired spatial memory performance during adulthood in the offspring of HFD-fed dams [26••]. Together these data suggest that HFD consumption during the perinatal period reduces hippocampal BDNF expression in the offspring (particularly when HDF is maintained post weaning), which may negatively impact neurogenesis and synaptic plasticity in hippocampal neurons.

Insulin and insulin-like growth factor-1 (IGF-1) are important regulators of CNS development. Similar to neurotrophins, IGF-1 and insulin signaling promotes both neurogenesis and synaptogenesis in the dentage gyrus via dendritic sprouting, stem cell activation, cell growth signaling, synaptic maintenance, cell repair and neuroprotection [55–60]. The hippocampus is densely populated with insulin receptor and IGF-1R, and their activity has been linked with hippocampal-dependent memory function [61,62]. Impaired IR and/or IGF-1R signaling may be one mechanism through which early life consumption of obesogenic dietary factors leads to hippocampal dysfunction. For example, when confined only to the gestational period, maternal consumption of a 20% sucrose sweetened beverage impairs spatial learning concurrent with reduced expression of IGF-1, and downstream signaling molecules phosphoinositide 3 kinase (PI3K), and phosphorylated protein kinase B (pAKT) in the hippocampus of juvenile offspring [27•]. Insulin receptor expression was reduced in the hippocampus of adult rats that were exposed to HFD (39% kcal from fat) before weaning, both in animals weaned on chow and on HFD. However, only those weaned on HFD demonstrated sustained memory impairments in the MWM [23•]. These data indicate that impairments in insulin and IGF-1 receptor signaling pathways represent one potential mechanism through which early life exposure to obesogenic diets impairs hippocampal function.

Like insulin, the adipokine leptin has a role in facilitating synaptic plasticity [63,64]. For example, in the hippocampal CA1 region leptin increases AMPA receptor trafficking at synapses [65], which is required for synaptic plasticity [66]. Furthermore, rodents who have a deficient leptin receptor function have cognitive deficits [48,67], and peripheral [63] and intra-hippocampal [68] leptin injections enhance hippocampal-dependent spatial learning and memory performance. Valladolid-Acebes *et al.* reported that there was a specific resistance of the PI3K/Akt pathway in LepRb-expressing neurons in the hippocampus of juvenile, but not adult rodents fed a HFD (45% kcal from fat), which corresponded to impaired hippocampal-dependent cognitive function [69].

Since the discovery of adult neurogenesis, evidence has mounted to support that adult born neurons contribute significantly to hippocampal-dependent learning and memory function (for review see [70]). Animals fed HFD (65% kcal from fat) during both the perinatal and post-weaning phase have a significantly reduced number of neurons in the pyramidal layer of CA1-3 of the hippocampus [28], which may be related to HFD-induced reductions in neurogenesis. Similarly offspring born from dams that were fed an obesogenic HFD (46% kcal from fat) before pregnancy and up until weaning had markers of impaired neurogenesis, Notch 1 (which suppresses neuronal differentiation) and Hes5 (which negatively regulates neurogenesis), at PND 28 [71,72]. These data are corroborated by a recent study showing that the Notch/Hes5 signaling pathway is significantly increased in neural stem cells of offspring from dams fed a HFD (35% kcal from fat) during pregnancy [73]. Another study showed that progeny of HFD-fed dams had elevated markers of cell proliferation in hippocampal and cortical subventricular zones, but reduced markers in the dentate gyrus, which the authors hypothesized represents a form of developmental delay [74]. Similar to animals exposed to HFD during the perinatal period, neurogenesis is also impaired in mice fed HFD during the juvenile/adolescent period, but not during adulthood [41]. However, the impact of dietary factors during juvenile/adolescence on neurogenesis is an area that has thus far received little attention.

## Conclusions and thoughts on future directions

Perinatal exposure to obesogenic diets may confer deficits in hippocampal-dependent memory that can, in some cases, persist despite switching to a healthy diet at weaning. The juvenile/adolescent period is a particularly vulnerable time for diet-induced impairments in hippocampal function, and recent evidence suggests that sugar may be as potent (or more) as HFD in its deleterious effects on memory. Mechanistic rodent studies suggest that obesogenic dietary factors can impair hippocampal function independent of obesity and metabolic derangement, and therefore further research into neurobiological mechanisms of diet, metabolic, and cognitive interactions should carefully consider nuances of the dietary composition. Due to recent reports suggesting that diet alters neurotrophic factors in the hippocampus via epigenetic mechanisms [75], future studies that consider whether dietary interventions impart long-lasting epigenetic changes to genes crucial for learning and memory function will be highly relevant.

## Conflict of interest statement

Nothing declared.

## Acknowledgements

We acknowledge our research support from the NIH: DK097147, DK102478, and DK104897 (S.E.K.).

## References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest


1. Kanoski SE, Grill HJ: **Hippocampus contributions to food intake control: mnemonic, neuroanatomical, and endocrine mechanisms**. *Biol Psychiatry* 2015. Epub ahead of print.
2. Davidson TL *et al.*: **Contributions of the hippocampus and medial prefrontal cortex to energy and body weight regulation**. *Hippocampus* 2009, **19**:235-252.
3. Davidson TL *et al.*: **A potential role for the hippocampus in energy intake and body weight regulation**. *Curr Opin Pharmacol* 2007, **7**:613-616.
4. Parent MB, Darling JN, Henderson YO: **Remembering to eat: hippocampal regulation of meal onset**. *Am J Physiol Regul Integr Comp Physiol* 2014, **306**:R701-R713.
5. Petrovich GD: **Forebrain networks and the control of feeding by environmental learned cues**. *Physiol Behav* 2013, **121**:10-18.
6. Davidson TL *et al.*: **The effects of a high-energy diet on hippocampal-dependent discrimination performance and blood–brain barrier integrity differ for diet-induced obese and diet-resistant rats**. *Physiol Behav* 2012, **107**:26-33.
7. Kanoski SE *et al.*: **The effects of a high-energy diet on hippocampal function and blood–brain barrier integrity in the rat**. *J Alzheimers Dis* 2010, **21**:207-219.
8. Kanoski SE, Davidson TL: **Western diet consumption and cognitive impairment: links to hippocampal dysfunction and obesity**. *Physiol Behav* 2011, **103**:59-68.
9. Cordner ZA, Tamashiro KL: **Effects of high-fat diet exposure on learning & memory**. *Physiol Behav* 2015, **152(Pt B)**:363-371.
10. Monti JM, Baym CL, Cohen NJ: **Identifying and characterizing the effects of nutrition on hippocampal memory**. *Adv Nutr* 2014, **5**:337S-343S.
11. Zainuddin MS, Thuret S: **Nutrition, adult hippocampal neurogenesis and mental health**. *Br Med Bull* 2012, **103**:89-114.
12. Stranahan AM, Mattson MP: **Impact of energy intake and expenditure on neuronal plasticity**. *Neuromol Med* 2008, **10**:209-218.
13. Francis H, Stevenson R: **The longer-term impacts of Western diet on human cognition and the brain**. *Appetite* 2013, **63**:119-128.
14. Morris MJ *et al.*: **Why is obesity such a problem in the 21st century? The intersection of palatable food, cues and reward pathways, stress, and cognition**. *Neurosci Biobehav Rev* 2014. Epub ahead of print.
15. Noble EE *et al.*: **The lighter side of BDNF**. *Am J Physiol Regul Integr Comp Physiol* 2011, **300**:R1053-R1069.
16. Barker DJ: **The fetal and infant origins of adult disease**. *BMJ* 1990, **301**:1111.
17. Tanda R *et al.*: **The impact of prepregnancy obesity on children's cognitive test scores**. *Matern Child Health J* 2013, **17**:222-229.
18. Hinkle SN *et al.*: **Associations between maternal prepregnancy body mass index and child neurodevelopment at 2 years of age**. *Int J Obes (Lond)* 2012, **36**:1312-1319.
19. Neggers YH *et al.*: **Maternal prepregnancy body mass index and psychomotor development in children**. *Acta Obstet Gynecol Scand* 2003, **82**:235-240.
20. Casas M *et al.*: **Maternal pre-pregnancy overweight and obesity, and child neuropsychological development: two Southern European birth cohort studies**. *Int J Epidemiol* 2013, **42**:506-517.
21. Tozuka Y *et al.*: **Maternal obesity impairs hippocampal BDNF production and spatial learning performance in young mouse offspring**. *Neurochem Int* 2010, **57**:235-247.
22. White CL *et al.*: **Effects of high fat diet on Morris maze performance, oxidative stress, and inflammation in rats: contributions of maternal diet**. *Neurobiol Dis* 2009, **35**:3-13.
23. • Lepinay AL *et al.*: **Perinatal high-fat diet increases hippocampal vulnerability to the adverse effects of subsequent high-fat feeding**. *Psychoneuroendocrinology* 2015, **53**:82-93.

Animals fed HFD during the perinatal period and post weaning had impaired spatial memory associated with reduced neurogenesis and plasticity markers.

24. Peleg-Raibstein D, Luca E, Wolfrum C: **Maternal high-fat diet in mice programs emotional behavior in adulthood**. *Behav Brain Res* 2012, **233**:398-404.
25. Bilbo SD, Tsang V: **Enduring consequences of maternal obesity for brain inflammation and behavior of offspring**. *FASEB J* 2010, **24**:2104-2115.
26. •• Page KC, Jones EK, Anday EK: **Maternal and postweaning high-fat diets disturb hippocampal gene expression, learning, and memory function**. *Am J Physiol Regul Integr Comp Physiol* 2014, **306**:R527-R537.

High fat diet exposure during the perinatal period impairs spatial learning and memory during adulthood and alters genes related to hippocampal plasticity.

27. • Kuang H *et al.*: **Hippocampal apoptosis involved in learning deficits in the offspring exposed to maternal high sucrose diets**. *J Nutr Biochem* 2014, **25**:985-990.

Offspring of Dams fed high sucrose had spatial memory deficits, especially at 1 month old.

28. Can OD *et al.*: **The effect of simvastatin treatment on behavioral parameters, cognitive performance, and hippocampal morphology in rats fed a standard or a high-fat diet**. *Behav Pharmacol* 2012, **23**:582-592.
29. O'Brien N *et al.*: **Enhanced context-dependency of object recognition in rats with hippocampal lesions**. *Behav Brain Res* 2006, **170**:156-162.
30. • Mychasiuk R *et al.*: **Dietary intake alters behavioral recovery and gene expression profiles in the brain of juvenile rats that have experienced a concussion**. *Front Behav Neurosci* 2015, **9**:17.

Female pups fed a high-fed diet had impaired memory in the novel context mismatch test. TBI impaired performance in the novel context mismatch in both standard chow *ad libitum* and high-fat diet fed, but not in calorically restricted animals.

31. Spear LP: **The adolescent brain and age-related behavioral manifestations**. *Neurosci Biobehav Rev* 2000, **24**:417-463.
32. Sherman LE *et al.*: **Development of the default mode and central executive networks across early adolescence: a longitudinal study**. *Dev Cogn Neurosci* 2014, **10**:148-159.
33. Casey BJ, Getz S, Galvan A: **The adolescent brain**. *Dev Rev* 2008, **28**:62-77.
34. Giedd JN *et al.*: **Brain development during childhood and adolescence: a longitudinal MRI study**. *Nat Neurosci* 1999, **2**:861-863.
35. Higuera-Matas A *et al.*: **Sex-specific disturbances of the glutamate/GABA balance in the hippocampus of adult rats subjected to adolescent cannabinoid exposure**. *Neuropharmacology* 2012, **62**:1975-1984.
36. Khan NA *et al.*: **Central adiposity is negatively associated with hippocampal-dependent relational memory among overweight and obese children**. *J Pediatr* 2015, **166** p. 302–308 e1.
37. Smith E *et al.*: **A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment**. *Obes Rev* 2011, **12**:740-755.
38. • Nyaradi A *et al.*: **Prospective associations between dietary patterns and cognitive performance during adolescence**. *J Child Psychol Psychiatry* 2014, **55**:1017-1024.

'Western' diet consumption was associated with more errors in Groton Maze and longer detection time in humans.

39. Baym CL *et al.*: **Dietary lipids are differentially associated with hippocampal-dependent relational memory in prepubescent children**. *Am J Clin Nutr* 2014, **99**:1026-1032.
Saturated fatty acid intake was associated with impaired performance in both relational and item memory tasks in humans.

40. Boitard C *et al.*: **Impairment of hippocampal-dependent memory induced by juvenile high-fat diet intake is associated with enhanced hippocampal inflammation in rats**. *Brain Behav Immun* 2014, **40**:9-17.
Juvenile, but not adult high-fat diet consumption impaired spatial memory and elevated inflammatory cytokines in rats.

41. Boitard C *et al.*: **Juvenile, but not adult exposure to high-fat diet impairs relational memory and hippocampal neurogenesis in mice**. *Hippocampus* 2012, **22**:2095-2100.

42. Valladolid-Acebes I *et al.*: **Spatial memory impairment and changes in hippocampal morphology are triggered by high-fat diets in adolescent mice Is there a role of leptin?** *Neurobiol Learn Membr* 2013, **106**:18-25.
Adolescent, but not adult mice on high fat diet had impaired learning performance, which persisted after 5 weeks of caloric restriction.

43. Hsu TM *et al.*: **Effects of sucrose and high fructose corn syrup consumption on spatial memory function and hippocampal neuroinflammation in adolescent rats**. *Hippocampus* 2015, **25**:227-239.
High fructose corn syrup-55 significantly impaired spatial learning and memory when consumed during juvenile/adolescence but not during adulthood. Memory impairments of animals on high fructose corn syrup were independent of changes in body weight, as animals compensated for caloric sugar consumption by reducing intake of chow. These results suggest that the brain is particularly vulnerable to the effects of high fructose corn syrup during the juvenile period.

44. Kendig MD *et al.*: **Chronic restricted access to 10% sucrose solution in adolescent and young adult rats impairs spatial memory and alters sensitivity to outcome devaluation**. *Physiol Behav* 2013, **120**:164-172.
Intermittent sucrose consumption spatial learning and memory in both adult and adolescent groups.

45. Reichelt AC *et al.*: **Impact of adolescent sucrose access on cognitive control, recognition memory, and parvalbumin immunoreactivity**. *Learn Membr* 2015, **22**:215-224.
Young rats exposed to intermittent (2 hours a day) sucrose had impaired performance in the object in place task.

46. Kaczmarczyk MM *et al.*: **Methylphenidate prevents high-fat diet (HFD)-induced learning/memory impairment in juvenile mice**. *Psychoneuroendocrinology* 2013, **38**:1553-1564.

47. Hotamisligil GS: **Inflammation and metabolic disorders**. *Nature* 2006, **444**:860-867.

48. Dinel AL *et al.*: **Cognitive and emotional alterations are related to hippocampal inflammation in a mouse model of metabolic syndrome**. *PLoS One* 2011, **6**:e24325.

49. Pistell PJ *et al.*: **Cognitive impairment following high fat diet consumption is associated with brain inflammation**. *J Neuroimmunol* 2010, **219**:25-32.

50. Golan H *et al.*: **Involvement of tumor necrosis factor alpha in hippocampal development and function**. *Cereb Cortex* 2004, **14**:97-105.

51. Huang CF *et al.*: **Effect of prenatal exposure to LPS combined with pre- and post-natal high-fat diet on hippocampus in rat offspring**. *Neuroscience* 2015, **286**:364-370.

52. Golan HM *et al.*: **Specific neurodevelopmental damage in mice offspring following maternal inflammation during pregnancy**. *Neuropharmacology* 2005, **48**:903-917.

53. Guzowski JF *et al.*: **Inhibition of activity-dependent arc protein expression in the rat hippocampus impairs the maintenance of long-term potentiation and the consolidation of long-term memory**. *J Neurosci* 2000, **20**:3993-4001.

54. Plath N *et al.*: **Arc/Arg3.1 is essential for the consolidation of synaptic plasticity and memories**. *Neuron* 2006, **52**:437-444.

55. O'Kusky JR, Ye P, D'Ercole AJ: **Insulin-like growth factor-I promotes neurogenesis and synaptogenesis in the hippocampal dentate gyrus during postnatal development**. *J Neurosci* 2000, **20**:8435-8442.

56. Craft S, Watson GS: **Insulin and neurodegenerative disease: shared and specific mechanisms**. *Lancet Neurol* 2004, **3**:169-178.

57. Hoyer S: **Glucose metabolism and insulin receptor signal transduction in Alzheimer disease**. *Eur J Pharmacol* 2004, **490**:115-125.

58. Stockhorst U *et al.*: **Insulin and the CNS: effects on food intake, memory, and endocrine parameters and the role of intranasal insulin administration in humans**. *Physiol Behav* 2004, **83**:47-54.

59. Kleinridders A *et al.*: **Insulin action in brain regulates systemic metabolism and brain function**. *Diabetes* 2014, **63**:2232-2243.

60. Bedse G *et al.*: **Aberrant insulin signaling in Alzheimer's disease: current knowledge**. *Front Neurosci* 2015, **9**:p204.

61. Schioth HB *et al.*: **Brain insulin signaling and Alzheimer's disease: current evidence and future directions**. *Mol Neurobiol* 2012, **46**:4-10.

62. Cholerton B, Baker LD, Craft S: **Insulin, cognition, and dementia**. *Eur J Pharmacol* 2013, **719**:170-179.

63. Oomura Y *et al.*: **Leptin facilitates learning and memory performance and enhances hippocampal CA1 long-term potentiation and CaMK II phosphorylation in rats**. *Peptides* 2006, **27**:2738-2749.

64. Shanley LJ, Irving AJ, Harvey J: **Leptin enhances NMDA receptor function and modulates hippocampal synaptic plasticity**. *J Neurosci* 2001, **21**:pRC186.

65. Moult PR *et al.*: **Leptin regulates AMPA receptor trafficking via PTEN inhibition**. *J Neurosci* 2010, **30**:4088-4101.

66. Collingridge GL, Isaac JT, Wang YT: **Receptor trafficking and synaptic plasticity**. *Nat Rev Neurosci* 2004, **5**:952-962.

67. Li XL *et al.*: **Impairment of long-term potentiation and spatial memory in leptin receptor-deficient rodents**. *Neuroscience* 2002, **113**:607-615.

68. Farr SA, Banks WA, Morley JE: **Effects of leptin on memory processing**. *Peptides* 2006, **27**:1420-1425.

69. Valladolid-Acebes I *et al.*: **High-fat diets induce changes in hippocampal glutamate metabolism and neurotransmission**. *Am J Physiol Endocrinol Metab* 2012, **302**:E396-E402.

70. Deng W, Aimone JB, Gage FH: **New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory?** *Nat Rev Neurosci* 2010, **11**:339-350.

71. Mendes-da-Silva C *et al.*: **Maternal high-fat diet during pregnancy or lactation changes the somatic and neurological development of the offspring**. *Arq Neuropsiquiatr* 2014, **72**:136-144.

72. Shimojo H, Ohtsuka T, Kageyama R: **Dynamic expression of notch signaling genes in neural stem/progenitor cells**. *Front Neurosci* 2011, **5**:p78.

73. Yu M *et al.*: **Maternal high-fat diet affects Msi/Notch/Hes signaling in neural stem cells of offspring mice**. *J Nutr Biochem* 2014, **25**:227-231.

74. Niculescu MD, Lupu DS: **High fat diet-induced maternal obesity alters fetal hippocampal development**. *Int J Dev Neurosci* 2009, **27**:627-633.

75. Tyagi E *et al.*: **Interactive actions of Bdnf methylation and cell metabolism for building neural resilience under the influence of diet**. *Neurobiol Dis* 2015, **73**:307-318.