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Early postnatal exposure to a cafeteria diet interferes with recency and spatial memory, but not open field habituation in adolescent rats

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Early postnatal exposure to a cafeteria diet interferes with recency and spatial memory, but not open field habituation in adolescent rats

Running title: Early postnatal exposure to a cafeteria diet

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Abstract

The cafeteria diet (CD), an experimental diet that mimics the obesogenic Western diet, can impair memory in adult rats. However, the suckling period is also particularly susceptible to diet-induced behavioural modification. Here, following exposure to CD feeding during lactation, 24-26 day old offspring were tested to determine maternal dietary effects on either open field habituation, object location (OL) learning or on recency learning. Whereas no impact on habituation learning could be demonstrated, both OL and recency memory were impaired. In controls (C), OL memory was shown both after a 5 min ($P<0.05$) or 60 min ($P<0.001$) inter-trial interval (ITI). After the 60 min ITI, the difference between C and CD was significant ($P<0.05$). Learning did not occur in the CD group at any time point and was not observed after the 24hr ITI in in either group. Whereas control rats demonstrated intact recency memory ($P<0.00001$), no learning occurred in the CD group. Both groups differed significantly in their exploration ratios ($P<0.01$). This study suggests a detrimental effect of exposure to an unhealthy Western diet during lactation, on cognitive functions in adolescent rats. These results could have implications for human cognition in the context of obesity epidemic.

KEYWORDS

Western diet, rodents, memory, lactation,

1 INTRODUCTION

The cafeteria diet is an experimental diet that had been developed to model Western nutritional habits and their pathophysiological consequences in rodents (Rothwell & Stock, 1979; Sclafani & Springer, 1976). Although the composition of this diet is not strictly defined, it usually comprises high-calorie, highly palatable human food items. In rodents, this diet leads to hyperphagia and subsequently to increased energy intake based on overconsumption of fat and sugar. In comparison with high fat diets, cafeteria diet better mimics pathophysiological aspects of human obesity, which is the product of excessive energy intake due to unrestricted dietary choices and inadequate physical activity (Sampey et al., 2011).

Human obesity is also being linked to cognitive dysfunctions (Contu & Hawkes, 2017; Francis & Stevenson, 2013; Morris, Beilharz, Maniam, Reichelt, & Westbrook, 2015; Pedditzi, Peters, & Beckett, 2016; Reichelt, Stoeckel, Reagan, Winstanley, & Page, 2018; Stevenson et al., 2020; Yeomans, 2017), and even a short four day exposure to a high fat-high sugar breakfast can interfere with human memory (Attuquayefio, Stevenson, Oaten, & Francis, 2017). In this context, experimental studies demonstrated that cafeteria feeding has detrimental effects in a variety of rodent memory tests (Andre, Dinel, Ferreira, Laye, & Castanon, 2014; Beilharz, Kaakoush, Maniam, & Morris, 2018; Beilharz, Maniam, & Morris, 2014; Bondan, Cardoso, Martins, & Otton, 2019; Darling, Ross, Bartness, & Parent, 2013; Ferreira, Castro, Andrade, Dulce Madeira, & Cardoso, 2018; Kendig, Westbrook, & Morris, 2019; Kosari, Badoer, Nguyen, Killcross, & Jenkins, 2012; Lewis, Singh, & Youssef, 2019; Reichelt, Gibson, Abbott, & Hare, 2019; Reichelt, Loughman, et al., 2018; Tran & Westbrook, 2018, Abbott, Arnott, Westbrook, & Tran 2019). Whereas many of these studies have been conducted in adult rats, fewer studies specifically addressed memory effects of a cafeteria diet in adolescent rats (Reichelt et al., 2019; Reichelt, Loughman, et al., 2018, Noble & Kanoski, 2016). Of particular interest is a literature which demonstrates that exposure to a hypercaloric diet during early postnatal development impacts upon later behaviour and memory (DeCapo, Thompson, Dunn, & Sullivan, 2019; Moreton et al., 2019; Wright, Langley-Evans, & Voigt, 2011; Wright, Fone, Langley-Evans, & Voigt, 2011; Wright, King, Davey, Langley-Evans, & Voigt, 2014).

In rodents, exposure to cafeteria diet during lactation leads to changes in object discrimination memory in adult age (Alamy & Bengelloun, 2012). This suggests that postnatally developing structures and functions of the offspring's central nervous system are susceptible to challenges associated with hyper-energetic diets. One brain region that undergoes a protracted postnatal development, both in humans and rodents, is the

prefrontal cortex (PFC) (Callaghan & Tottenham, 2016; Kolb et al., 2012; Petanjek et al., 2011) which renders this brain region susceptible to environmental challenges including malnutrition (Reichelt, 2016). In a previous study, we demonstrated that exposure to cafeteria diet during suckling changes PFC dopamine and serotonin neurotransmitter mechanism while also interfering with novel object recognition during adolescence (Moreton et al., 2019). The PFC is also involved in in recency memory in rats (Barker, Bird, Alexander, & Warburton, 2007; Hannesson, Vacca, Howland, & Phillips, 2004; Nelson, Cooper, Thur, Marsden, & Cassaday, 2011), and a cafeteria diet interferes with recency memory in adult rats (Tran & Westbrook, 2018).

No study has yet considered the impact of early postnatal dietary CD effects on recency memory. Considering the importance of the lactational period for behavioural and memory development (Moreton et al., 2019; Speight, Davey, McKenna, & Voigt, 2017; Wright et al., 2011a,b; Wright et al., 2014), we aimed to investigate the impact of CD exposure during this period on recency memory. This was to address the wider hypothesis that early postnatal overnutrition impacts on a range of memories. Thus we compared the effects of lactational exposure to a cafeteria diet on prefrontal cortex-dependent recency memory, hippocampus dependent object location memory (Ainge & Langston, 2012; Dix & Aggleton, 1999) and habituation (Rankin et al., 2009) learning in the open field (Leussis & Bolivar, 2006). We hypothesised a detrimental effect of the diet in all three models of memory.

2 METHODS

2.1 Experimental animals

Virgin female Wistar rats (n = 24; Charles River UK) were mated with male rats at 9 weeks of age. Dams were housed two per cage until they had reached the last four days of their gestation period when they were placed in individual cages. Standard laboratory chow (Teklad Global 18% Protein Rodent Diet Harlan, UK) and water (filtered tap water) were available ad libitum. The rats were maintained under a 12 h light dark cycle (with 1 h dusk and 1 h dawn, lights on at 07:30 h), between 20 and 22 degrees C° and at 55 + 10% relative humidity. Light intensity was 370 lx. At birth, litter size was adjusted to eight, 4 females and 4 males.

All experiments were performed with approval from the University of Nottingham Animal Welfare and Ethical Review Body (AWERB) and in accordance with the Animals (Scientific Procedures) Act, 1986 and ARRIVE guidelines.

2.2 Experimental diet

Following parturition, dams were randomly allocated to either standard laboratory chow diet (control) or the same chow diet in conjunction with a variety of highly palatable, energy-dense human foods (experimental cafeteria diet, CD). Food items consisted of shortbread, golden syrup cake, plain chocolate, pork pie, pâté, cocktail sausages, cheddar cheese, crisps, peanuts and strawberry jam. Of these items, four were provided in excess each day and placed in a bowl on the cage floor. At least one item was exchanged daily in order to maintain novelty and interest (Akyol, Langley-Evans, & McMullen, 2009). Food consumption of the dams was measured every other day during lactation. Energy intake (kJ) and macronutrient consumption (carbohydrates including sugar, fat and protein) were calculated from the manufacturers' data. The average daily percentage change in the weight of foods ranged from 0.0 to 6·2 % and corresponded to an average overestimation of energy intake by 2·51 % (7·5 kJ/d), which can be considered within an acceptable error of measurement (Akyol, Langley-Evans, & McMullen, 2009). Dam body weight was determined alongside food intake measures. On postnatal day 21, offspring were weaned from their dams and then housed in groups of four with littermates of the same sex. Weanlings were fed standard chow for the remainder of the study.

2.3 Behavioural testing

Behavioural testing occurred in 24 to 26 day old offspring. Two randomly selected pups, of each sex from each litter were used for testing; a total of 151 offspring were tested. The remaining offspring were not used in the current study. Testing was undertaken between 08:30 and 13:30h. Only one male/female were used from each litter for each trial to avoid within-litter effects. Experiments were independent, i.e. each individual was only tested in one of the experiments outlined below. Likewise, different offspring were allocated to the separate intervals in the object location test (2.3.2).

All testing took place in an arena measured 60 x 60 x 30 cm, with a grey floor insert and plastic walls. A camera was positioned over the centre of the arena and connected to a computer screen in an adjacent room. On three of the walls, visual cues were displayed. These visual cues were images of a black triangle, circle or square on a white background, placed in the centre of each wall. Behaviour was analysed using Ethovision XT 7 (Noldus, Netherlands). The room was dimly lit (8.0 lux) as dim lighting was used as a measure to reduce stress and anxiety (Voigt et al., 2005). The arena and the objects were cleaned with 70% ethanol solution between uses by different rats, to remove any olfactory cues.

2.3.1 Open field habituation

Each rat to be used was removed from its cage, and placed in the centre of the arena facing the wall with the circle image. Each animal was exposed twice for 10 minutes to the open field, 24 hours apart. Intersession habituation was determined using the behavioural parameters of locomotion (in cm) and rearing (frequency) (Wilson, Voigt, Bader, Marsden, & Fink, 1996). Locomotion was tracked automatically using Ethovision. Rearing was defined as raising both forepaws simultaneously and was tracked manually using the same software.

2.3.2 Object location memory

Three proximal visual cues, black shapes (square, triangle and circle) on a white background were fixed to the centre point of three of the four walls. This was to facilitate spatial orientation in the arena, as the rats were able to see and use the cues, without physically touching them (Ainge & Langston, 2012; Dix & Aggleton, 1999). Clear plastic bottles, with three horizontal black strips, were used as objects for testing. They were filled with water and secured to the arena floor using blue tack. Two identical objects were placed 20 cm away from the corners of the arena. Placing the objects here gave the rat the ability to walk all the way around the object.

Each rat was briefly habituated to the empty arena for 3 minutes and then returned to the home cage. After 2 minutes, the rat was returned again to the arena for a 5 minute trial phase, in which two identical objects had been placed into the arena. All rats were placed into the centre of the arena facing the circle visual cue, regardless of object placement to ensure all rats started with the same spatial orientation in the arena. Exploration of the objects was defined by active pawing at, or sniffing of the objects, as well as rats having their nose directed towards the object, within a 1.5 cm distance. Climbing or rearing on the object were not recorded as object exploration. Contact time with the objects (s) was manually scored using Ethovision. After an inter-testing-interval (ITI) of either 5 minutes, 60 minutes or 24 hours, the rat re-entered the arena for a 5 minute test phase. During the ITI, the rat was returned to their home cage. In the test phase, one of the two objects was moved to another corner of the arena, whereas the other object which remained in the same familiar location. The distance between objects was kept the same throughout all trials. Between experiments the objects were placed in different corners, so that all corner combinations where used in order to remove any bias and counterbalance any corner preferences that the rats might develop. To quantify object preference, exploration times for each object from both trials were converted to an exploration ratio. This ratio represents the proportion of time spent exploring the object in the novel location divided by the total object exploration time during the test trial (t

novel/ (t novel + t familiar) (Dix & Aggleton, 1999; Jablonski, Schreiber, Westbrook, Brennan, & Stanton, 2013). If the rat showed a distinct preference for the object in the novel location (exploration ratio > 0.5), then a learning effect would be considered present.

2.3.3 Recency memory

Recency memory testing (Mitchell & Laiacona, 1998) took place in the same arena as under 2.3.1 and 2.3.2., and the objects the rats were exposed to were plastic bottles with either three black or white horizontal tape stripes around them (2 black striped bottles, 2 white striped bottles). The bottles were placed roughly 20 x 20cm from the walls of the arena. The order and position of these bottles were counterbalanced to control for location and colour bias.

Each rat was placed into the arena and exposed to the first pair of identical objects (e.g. black stripes) for 5 minutes while the incidence and length of object exploration was recorded using EthoVision. Contact with the objects was defined as active sniffing of the object within a radius of 1.5 cm and/or touching with the front paws and nose. Climbing or rearing on the object were not counted as exploration. After the first exposure, the rat was returned to its cage for 60 minutes, after which it was placed back in the arena and exposed to the second pair of identical objects (white stripes) for 5 minutes and the same behaviours were recorded. After this exposure, the rat was placed back in its cage for 15 minutes, before being placed in the arena for the test exposure. In this exposure, the rat is exposed to one object from each pair (one black, one white) and contact with the remote ('novel', black stripes in this example) and recent ('familiar', white stripes in this example) objects is recorded, as per the previous trials.

To quantify object preference during the exploration, times for each object from both trials were converted to an exploration ratio. This ratio represents the proportion of time spent exploring the remote ('novel') object divided by the total object exploration time during the test trial (t novel/(t novel + t familiar) (Dix & Aggleton, 1999; Jablonski et al., 2013; Mitchell & Laiacona, 1998). If the rat showed a distinct preference for the remote object (exploration ratio > 0.5), then a learning effect would be considered present.

2.4 Statistical analyses

The statistical unit for macronutrient intake was the dam. The statistical unit for the behavioural analyses was the litter.

Student's t-test was used to analyse all nutritional data.

For both object location and recency memory, object familiarisation was analysed by Two Way ANOVA (sex, diet) to exclude that these two factors impact on the exploration of object upon first exposure. Males and female offspring were then combined for subsequent analyses since sex differences in memory do not manifest before puberty (Cyrenne & Brown, 2011).

Intersession habituation was assessed based on locomotion (distance travelled) and frequency of rearing events. Both of these parameters were analysed independently using a Two-Way RM ANOVA (diet, trial). The effect of diet on body weight of the dam during lactation was analysed by a Two-Way RM ANOVA (diet, time).

For both object location and recency memory, one sample t-test was used to compare the discrimination ratio of each diet group with values above 0.5 indicating a preference for the novel object and hence a learning effect (Dix & Aggleton, 1999). The exploration ratios between the two diet groups were compared using a Student's t-test. In addition, it is thought that different memory mechanisms underlie the separate time intervals (Rosenzweig, Bennett, Colombo, Lee, & Serrano, 1993) and for these reasons object location data at all ITIs were analysed independently. Consequently, no object location data was analysed using an ANOVA and no between ITI comparisons were made. The use of exploration ratio as a parameter for measuring the learning effect, parallels with other spatial learning and recency memory studies (Nelson et al., 2011).

All figures were created and statistical analysis was performed using GraphPad Prism version 7 (GraphPad Software, USA). All values are shown as means + SEM. Differences between groups were considered significant if the P value < 0.05.

3 RESULTS

3.1 Macronutrient and energy intake in dams during lactation

Fat ($t=22.71$, $P<0.0001$) and sugar ($t=9.93$, $P<0.0001$) intakes were significantly increased in lactating CD-fed dams (Tab. 1) which led to a higher total energy intake in these dams ($t=7.54$, $P<0.0001$). The overall protein intake was reduced by 13% ($t=2.43$, $P<0.05$). Despite the increased sugar intake, CD-fed dams consumed less carbohydrates in total ($t=3.58$, $P<0.01$) (Tab. 1). Mean daily chow consumption as measured during lactation was reduced by 59 % in the CD-fed group (C: 59.52 ± 2.18 g; CD: 21.45 ± 2.84 g; $t=10.61$, $P<0.0001$). Although body weight increased in both groups during the lactational period ($F(10, 220) = 88.34$, $P<0.0001$), differences in macronutrient intake did not affect body weight ($F(1, 22) = 0.28$, $P=0.59$).

3.2 Open field habituation

When exposed to the open field arena, offspring from both cafeteria fed and chow fed dams explored the arena in a similar way. Both groups travelled a similar distance and showed similar numbers of rearing responses. Upon a second exposure, Two-WAY RM ANOVA revealed a decrease in the total distance travelled ($F(1,26)= 7.65$, $P<0.01$), and in the number of rearing responses ($F(1, 26) = 17.02$, $P<0.001$). As there was no effect of diet on either parameter, the observed decreases in locomotor activity and rearing suggest that habituation occurred similarly in both groups (Fig. 1).

3.2 Object location

No effects of diet or sex on the time exploring the objects could be observed in any of the three experiments during the 5 min sampling period (trial 1) (Tab. 2).

When exposed to the two objects 5 and 60 minutes later, but with one object in a novel location, offspring from the control group explored the object in the novel location for longer than the object that remained in the familiar location ($t=2.66$ $df=19$, $P<0.05$; $t=4.658$ $df=13$, $P<0.001$). No learning occurred in the cafeteria group though, and the cafeteria group had a lower exploration ratio compared to control at the 60 minutes test session ($t=2.686$ $df=24$, $P<0.05$). By contrast to open field habituation, no learning occurred in either of the two groups when tested 24hrs following the first exposure (Fig. 2).

3.3 Object recency

As shown before (3.2), there was no impact of sex or diet on object exploration during the first 5 minute exposure to the two objects (Tab. 3).

Fifteen minutes after exposure to the recent and the distant object, rats from chow-fed dams explored the distant object for longer than the more recent object ($t=6.99$ $df=13$, $P<0.0001$), whereas such a learning effect was not observed in the cafeteria group. Both groups differ significantly in their exploration ratios ($t=3.60$ $df=23$, $P<0.01$) (Fig. 3).

4 DISCUSSION

The macronutrient intake pattern as obtained in the present study is very similar to previous reports from our laboratory. Increased overall energy intake was due to increased consumption of fat and sugars and is accompanied by a light but significant reduction of protein intake (Akyol et al., 2009; Akyol, McMullen, & Langley-Evans, 2012; George et al., 2019; Speight et al., 2017; Wright et al., 2014). Hence it is safe to say that the macronutrient and energy intake as independent variables are similar across previous behavioural studies including the present one. As discussed previously (Moreton et al., 2019), any observed behavioural effects are most likely mediated via maternal milk consumption rather than active pre-weaning CD intake by the pups. Milk composition during lactation reflects dietary intake when animals are fed CD (Rolls et al., 1986). Milk consumption of pups peaks around postnatal day 15 whereas pups start feeding solid food around day 17 (Ostadalova & Babicky, 2012). Given that milk consumption remains high at least to postnatal day 19 (Ostadalova & Babicky, 2012), direct CD consumption by the pups would be minimal, as they were weaned on day 21. Hence the observed effects are most likely mediated via maternal milk ingestion rather than a direct CD consumption.

Cafeteria diet during lactation had no effect on body weight in the dam. This finding is in line with previous studies, both in lactating (Akyol et al., 2012) and non-lactating females of similar age (Warneke et al., 2014) Compensatory mechanisms, of which the induction of thermogenesis appears to be particularly important (Rothwell & Stock, 1979; Rothwell and Stock, 1980) can buffer some of the effects of cafeteria feeding in younger rats. Hyperenergetic diets can also reduce the expression of hypothalamic orexigenic signalling in young rats to counter the obesogenic effects of the diet (Archer et al., 2004). CD is more likely to increase body weight in adult rats (Sclafani & Gorman, 1977).

The manipulation of maternal diet during lactation, impaired novel object discrimination (recognition) learning in a study under similar experimental conditions (Moreton et al., 2019). In previous studies, demonstrating detrimental effects on spatial memory, rats have either been exposed to CD either after weaning (Ferreira et al., 2018) or in adult age (Beilharz et al., 2014; Kendig et al., 2019; Kosari et al., 2012; Pini, Ferreira do Vales, Braga Costa, & Almeida, 2017). Here we demonstrate for the first time a detrimental effect of lactational exposure to CD on object location memory. We also present the novel finding that exposure during suckling to a hyper-energetic highly palatable diet leads to impaired recency memory. Despite these effects on memory, there was no evidence that the diet had any effect on object exploration during the sample phase in either of the two tests, although object exploration in the sample phase is possibly not a decisive factor as shown for spatial memory (Ozawa, Yamada, & Ichitani, 2011).

Although the observed effects of maternal cafeteria feeding on spatial learning were generally in line with other studies, the lack of a learning effect following a 24 hour ITI, observed in this study, was in contrast to previous results (Westbrook et al., 2014). According to Westbrook, 26- and 31-day-old, but not 21-day-old rats retained the object location memory for a 24h ITI. Age differences could explain the discrepancy between the current and the aforementioned study. Our rats were between 24 and 26 days old, possibly just below the point where 24 h memory is fully developed. Strain differences are another factor to be considered, but the nature of the test can play a role as well (Kumar et al. 2019, Ennaceur et al., 2005). On a mechanistic level, it has been demonstrated that hippocampal mossy fibres are still growing and remodelling up to postnatal day 24 in rats (Holahan et al., 2007). These fibres are involved in spatial memory formation and their postnatal development and functional anatomy is strain dependent in rodents (Holahan et al., 2007; Crusio & Schwegler, 2005). Another study (Ainge & Langston, 2012), albeit using a model of associate spatial learning, revealed that spatial recognition does occur in 30-day-old rats, but not in 24-day-old rats. Of note that study used a short 1-2 minute ITI. One could speculate that our weak learning effect after a 5 minute ITI was rather in line with their finding, suggesting a rather late development of associative spatial learning. However, as this would contradict our finding after the 60 minute ITI, one could further speculate that different memories could be involved (Rosenzweig, Bennett, Colombo, Lee, & Serrano, 1993).

In contrast to spatial and recency memory, long-term habituation learning as studied during repeated exposure to the same open field arena was not affected by maternal diet. Habituation is a decreased response upon repeated exposure to the same stimulus or environment and occurs if the exposure has neither positive nor negative consequences (Rankin et al., 2009). Fully established 24 hour habituation of exploration has been demonstrated before in rats of this age (Parsons, Fagan, & Spear, 1973). The current results demonstrating established habituation learning in both the control and experimental group established are in line with this earlier finding. To explain the lack of dietary effects in this test, one could speculate that rats were ‘over-trained’ as a shorter than 10 minutes exposure could possibly reduce the strength of the memory formation, making it more susceptible to dietary challenge. This warrants further investigation including testing a range of intersession retention intervals, as adult rats have been shown to retain habituation over a period of 1 week (Richardson & Campbell, 1991). This latter finding suggests an alternative interpretation of our results in that habituation learning in the present paradigm is a robust and non-complex task which makes it less susceptible to the dietary manipulation.

Rats exposed to an open field arena as in the present study, are also exposed to distant spatial cues at the same time. Thus spatial long–term habituation requires a functioning

hippocampus (Riedel et al., 1999; Vianna et al., 2000). Consequently, as the dietary interference with hippocampal function is established (Kanoski & Davidson, 2011; Kanoski, Zhang, Zheng, & Davidson, 2010), dietary effects could have been expected. However, considering that brain regions involved in habituation learning are potentially more widespread (Yamaguchi & Knight, 1991), compensatory mechanisms could maintain functioning of long-term habituation in adolescent CD fed offspring. Hippocampus-dependent spatial memory has been shown to be particularly sensitive to unbalanced hyper-energetic diets (Noble & Kanoski, 2016). Of note, consumption of a Western diet reduces hippocampal volume, both in adults (Jacka, Cherbuin, Anstey, Sachdev, & Butterworth, 2015) and in obese children (Mestre et al., 2017). However, there is currently no evidence that developmental exposure to a cafeteria diet leads to impairment of spatial memory in humans.

A majority of, but not all (Nguyen et al., 2017; Pini et al., 2017), rodents studies suggests that CD feeding interferes with hippocampus mediated spatial learning (Beilharz et al., 2014; Ferreira et al., 2018; Kendig et al., 2019; Kosari et al., 2012; Tran & Westbrook 2015) but functioning of other brain structures can also be affected (Nguyen et al., 2017). Two different pathways have been described for underlying either object recognition memory or spatial and hippocampal memory although both require PFC, albeit different substructures of the PFC, functioning (Barker et al., 2007; Steckler, Drinkenburg, Sahgal, & Aggleton, 1998). Interestingly, recency memory has also been attributed directly to hippocampal function (Albasser, Amin, Lin, Iordanova, & Aggleton, 2012), but also PFC functioning (Mitchell & Laiacona, 1998; Nelson et al., 2011). Of note, hippocampal lesion at birth decreases PFC functioning with a behavioural readout of reduced performance in spatial and temporal memory tests in adolescence (Kruger et al., 2012) indicating functional connections between these two structures. As outlined above many studies that have examined the impact of cafeteria diets on memory used adult rats rather than younger animals in which the postnatal brain is still under development. The interaction between diet and memory could be different in young compared with adult rats. The prefrontal cortex is a brain structure that undergoes a protracted postnatal development (Kolb et al., 2012; Petanjek et al., 2011). Therefore the PFC is particularly susceptible to early-life environmental factors which can result in either positive or detrimental consequences in the adult (Callaghan & Tottenham, 2016; Kieling, Goncalves, Tannock, & Castellanos, 2008; McCrory, De Brito, & Viding, 2010; Selemon & Zecevic, 2015). A protracted development has not only been shown for the PFC alone but could also affect functional interactions with the hippocampus (Murty et al., 2016). Here we show for the first time that PFC and hippocampus dependent (Mitchell & Laiacona, 1998; Nelson et al., 2011) temporal memory is impaired due to exposure to cafeteria diet during suckling. However, other brain regions generally important in information processing like the subcortical thalamus are less studied regarding the impact of hyper-

energetic diets (Dumont & Aggleton, 2013; Li et al., 2019). Adding complexity to this, CD feeding alters not only a range of brain neurotransmitters and of behaviours, but also gut microbiota (Leigh, Kaakoush, Bertoldo, Westbrook, & Morris, 2020; Moreton et al., 2019; Reichelt, Loughman, et al., 2018; Wright et al., 2011). The latter could impact on neurodevelopmental processes and cognitive performance (Cowan, Dinan, & Cryan, 2020; Cryan et al., 2019).

Experimental studies, including the current one, provide accumulating evidence that obesogenic diets interfere with a range memory processes (Reichelt, Loughman, et al., 2018; Tran & Westbrook, 2018). This goes along with an increasing awareness that exposure to hyperenergetic and unbalanced diets relate to cognitive disturbances and psychiatric diseases later in later live as reviewed in (Adan et al., 2019; Francis & Stevenson, 2013; Reichelt, Stoeckel, et al., 2018). Notably, two randomised controlled trials demonstrated improvements in depressive patients when their diet was changed from a poor Western diet to a healthier diet. (Francis et al., 2019; Jacka et al., 2017). The finding that the impact of a poor quality diet is pronounced even when the exposure occurs during early development, is of particular significance.

In conclusion, we demonstrate here that exposure to a palatable, but unbalanced, hyper-energetic cafeteria diet during lactation impairs recency memory and object location memory in early adolescence, whereas the impact on spatial habituation learning warrants further investigation. These results further support the notion that dietary challenges during early postnatal development impact on learning in early adolescence. Experimental findings like this, in conjunction with an increasing number of human studies, suggest a detrimental effect of unhealthy Western diets on cognitive functions.

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Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

TABLE 1 Average daily energy and macronutrient intake in lactating dams

Diet	Energy (kJ/d)		Carbohydrate total (g/d)		Sucrose (g/d)		Fat (g/d)		Protein (g/d)	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Chow	786.20	20.49	26.79 (64.06)	0.70	2.12	0.05	3.76 (8.99)	0.10	11.27 (26.95)	0.29
Cafeteria	1001.00 ****	19.77	22.24 ** (50.29)	1.06	4.91 ****	0.27	11.99 **** (27.11)	0.35	9.99 * (22.59)	0.43

Data represent mean values from 12 dams/group as collected over 21 days of lactation. Percent of total macronutrient intake are given in brackets. Student's t-test.
*P<0.05, **P<0.01, ***P < 0.001. ****P < 0.0001 vs. chow fed controls.

TABLE 2 Exploration time of the two objects during training (sampling period)

Intertrial interval	Diet	Exploration time (s) during familiarisation Male offspring		n	Exploration time (s) during familiarisation Female offspring		n
		Mean	SEM		Mean	SEM	
5 min	C	52	8.1	9	50	3.2	11
	CD	52	3.6	10	61	4.2	9
60 min	C	38	6.0	7	40	3.3	7
	CD	40	3.0	6	38	2.5	6
24 h	C	52	7.3	6	46	7.0	8
	CD	55	7.0	9	53	3.4	10

Familiarisation data for each of the three time points have been analysed separately. No significant effects of sex and diet have been observed. Sex: 5 min: $F(1, 35) = 1.18$, $P=0.28$; 60 min: $F(1, 22) = 0.01$, $P=0.92$; 24 h: $F(1, 29) = 0.36$, $P=0.55$. Diet: 5 min: $F(1, 35) = 0.67$, $P=0.42$; 60 min: $F(1, 22) = 0.01$, $P=0.92$; 24 h: $F(1, 29) = 0.75$, $P=0.39$. Two-Way ANOVA (diet, sex).

TABLE 3 Exploration times of the two objects during first exposure in the recency test

Diet	Exploration time (s) first exposure Male offspring		n	Exploration time (s) first exposure Female offspring		n
	Mean	SEM		Mean	SEM	
C	36.2	2.9	7	44.6	2.9	7
CD	46.4	6.4	6	44.4	7.9	5

No significant effects of sex (F (1, 21) = 0.41, P=0.5299) and diet (F (1, 21) = 1.009, P=0.33) have been observed. Two-Way ANOVA (diet, sex).

LEGENDS

FIGURE 1 Impact of lactational cafeteria diet (CD) on open field habituation in 24-26 day old weaner rats. Control (C) dams were fed on show. Both groups travelled a shorter distance (A) (*** $P < 0.001$) and showed significantly reduced rearing (B) (** $P < 0.01$) upon a second exposure (effect of time) to the open field arena. Left columns of each pair represent the first exposure to the open field, right columns the second exposure 24 hrs later. No effects of diet on either rearing ($F(1, 26) = 1.41$, $P= 0.24$) or locomotion ($F(1, 26) = 1.07$,$P=0.31$) were observed. Mean ± SEM. Two-Way RM ANOVA (time, diet). N = 16 (C) and 12 (CD).

FIGURE 2 Impact of lactational cafeteria diet (CD) on object location memory in 24-26 day old weaner rats. Values over 0.5 (dotted line) represent memory. In controls (C), memory occurred both after a 5 min (* $P<0.05$) or 60 min (*** $P<0.001$) inter-trial interval (ITI). After the 60 min interval, the difference between C and CD was significant (+ $P < 0.05$). Memory did not occur in the CD group at any time point 5 min ($t=1.10$, $df=18$, $P = 0.28$), 60 min ($t=1.34$, $df=11$, $P = 0.21$ and 24 h ($t=1.27$, $df=13$, $P = 0.22$) and was not observed after 24hrs in the CD group either ($t=0.94$, $df=18$, $P = 0.36$). *One-sample t-test. + Student's t-test. N: 5 min C=20 CD=19; 60 min: C=14, CD=12; 24 h: C=14, CD=19.

FIGURE 3 Impact of lactational cafeteria diet (CD) on recency memory in 24-26 day old weaner rats. Values over 0.5 represent learning. Controls (C; n = 14) explore the distant object longer than the more recent object, whereas such a learning effect is not observed in the cafeteria group (CD; n =11; $t=1.55$, $df=10$, $P = 0.15$). Both groups differ significantly in their exploration ratios. ****$P<0.0001$. One-sample t-test. +$P<0.05$. Student's t-test.

TABLE 1 Average daily energy and macronutrient intake in lactating dams

Diet	Energy (kJ/d)		Carbohydrate total (g/d)		Sucrose (g/d)		Fat (g/d)		Protein (g/d)	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Chow	786.20	20.49	26.79 (64.06)	0.70	2.12	0.05	3.76 (8.99)	0.10	11.27 (26.95)	0.29
Cafeteria	1001.00 ****	19.77	22.24 ** (50.29)	1.06	4.91 ****	0.27	11.99 **** (27.11)	0.35	9.99 * (22.59)	0.43

Data represent mean values from 12 dams/group as collected over 21 days of lactation. Percent of total macronutrient intake are given in brackets. Student's t-test.
*P<0.05, **P<0.01, ***P < 0.001. ****P < 0.0001 vs. chow fed controls.

TABLE 2 Exploration time of the two objects during training (sampling period)

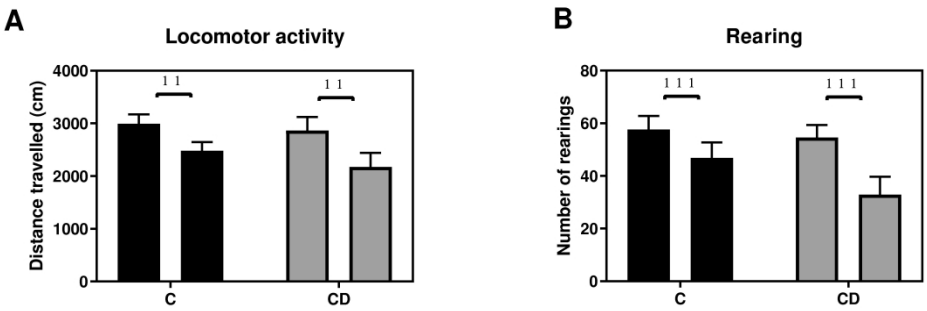
Intertrial interval	Diet	Exploration time (s) during familiarisation Male offspring		n	Exploration time (s) during familiarisation Female offspring		n
		Mean	SEM		Mean	SEM	
5 min	C	52	8.1	9	50	3.2	11
	CD	52	3.6	10	61	4.2	9
60 min	C	38	6.0	7	40	3.3	7
	CD	40	3.0	6	38	2.5	6
24 h	C	52	7.3	6	46	7.0	8
	CD	55	7.0	9	53	3.4	10

Familiarisation data for each of the three time points have been analysed separately. No significant effects of sex and diet have been observed. Sex: 5 min: $F(1, 35) = 1.18$, $P=0.28$; 60 min: $F(1, 22) = 0.01$, $P=0.92$; 24 h: $F(1, 29) = 0.36$, $P=0.55$. Diet: 5 min: $F(1, 35) = 0.67$, $P=0.42$; 60 min: $F(1, 22) = 0.01$, $P=0.92$; 24 h: $F(1, 29) = 0.75$, $P=0.39$. Two-Way ANOVA (diet, sex).

TABLE 3 Exploration times of the two objects during first exposure in the recency test

Diet	Exploration time (s) first exposure Male offspring		n	Exploration time (s) first exposure Female offspring		n
	Mean	SEM		Mean	SEM	
C	36.2	2.9	7	44.6	2.9	7
CD	46.4	6.4	6	44.4	7.9	5

No significant effects of sex ($F(1, 21) = 0.41$, $P=0.5299$) and diet ($F(1, 21) = 1.009$, $P=0.33$) have been observed. Two-Way ANOVA (diet, sex).



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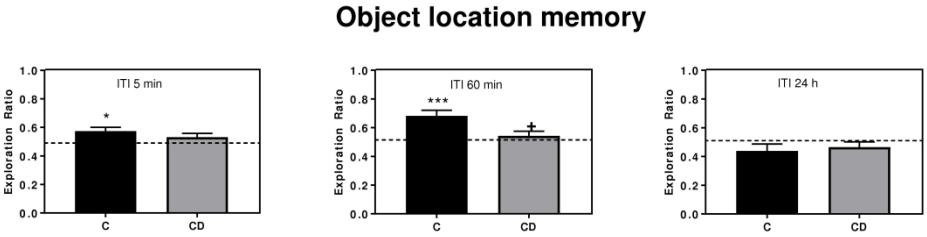

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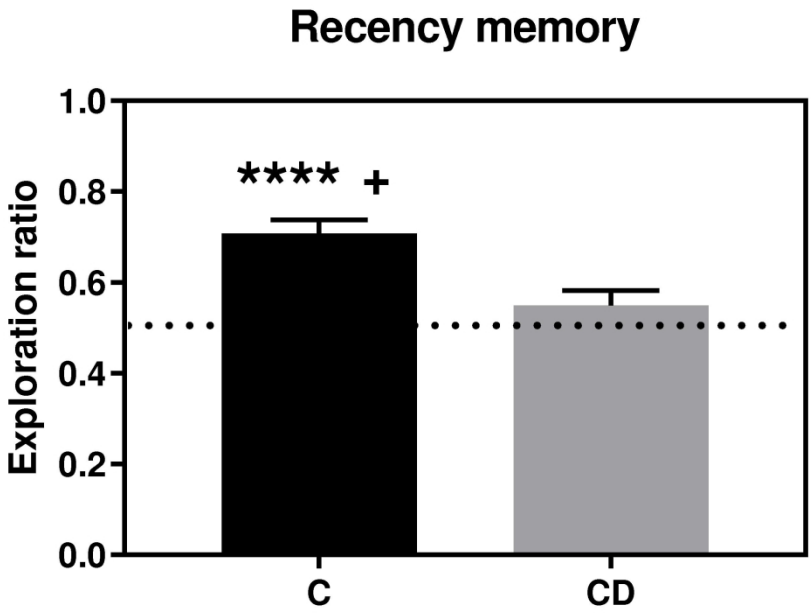

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