Impact of early exposure to a cafeteria diet on prefrontal cortex monoamines and novel object recognition in adolescent rats

E. Moreton[1], P. Baron[1], S. Tiplady[1], S. McCall[1], B. Clifford[2], S. C. Langley-Evans[3], K. C.F. Fone[4], J.P. Voigt[1*]

[1] School of Veterinary Medicine and Science, [3]School of Biosciences, University of Nottingham, Sutton Bonington, Loughborough LE12 5RD, UK

[2] UCLA, MRL 3230/3240, 675 Charles E Young Drive South, Los Angeles CA 90095

[4] School of Life Sciences, Queen's Medical Centre, Nottingham, NG7 2UH, UK

*corresponding author

Accepted manuscript

Abstract

The prefrontal cortex (PFC) undergoes protracted postnatal development such that its structure and behavioural function may be profoundly altered by environmental factors. Here we investigate the effect of lactational dietary manipulations on novel object recognition (NOR) learning and PFC monoamine neurotransmitter metabolism in early adolescent rats. To this end, Wistar rat dams were fed a high caloric cafeteria diet (CD) during lactation and resultant 24-26 day old offspring exposed to NOR testing and simultaneous PFC dopamine and serotonin metabolism measurement. In the second NOR choice trial where one familiar and one novel object were presented controls explored the novel preferentially to the familiar object both after a 5 min ($P<0.001$) or 30 min ($P<0.05$) inter-trial intervals (ITI). By contrast, offspring from dams fed on lactational CD failed to show any significant preference for the novel object at either time point. Compared with chow fed controls, their average exploration ratio of the novel object was lower after the 5 min ITI ($P<0.05$). Following a 60 minute ITI, neither CD nor control offspring showed a preference for the novel object. PFC dopamine metabolism was significantly reduced in the CD group ($P<0.001$), whereas serotonin metabolism was increased ($P<0.001$). These results suggest that an obesogenic lactational diet can have a detrimental impact on cognition in adolescent offspring associated with aberrant PFC serotonin and dopamine metabolism.

Keywords: lactation; Western diet; brain; memory

1. Introduction

The prefrontal cortex (PFC) in the mammalian brain is involved in executive control including a variety of complex behaviours such as learning and memory, and also in coding of palatability [1-3] 2017. In the human brain, and in rodents, the PFC undergoes a protracted postnatal development which has been suggested to last until postnatal day 60 in rats [4], and until the third decade of life in humans [5]. Therefore the PFC is particularly susceptible to early-life environmental factors which can result in either positive or detrimental consequences in the adult [6-10].

Links between hyper-energetic diets during adolescence and PFC-dependent memory and other behaviours are well-established and include deficits in working memory and behavioural flexibility. Furthermore diet-induced alterations in PFC dopaminergic signalling may underlie diet-induced cognitive deficits [11, 12], review). However, less is known about dietary impacts on PFC during the early postnatal age. In rats, the lactational period is particular sensitive to dietary manipulations that programme changes in offspring behaviour at adulthood [13-16]. Rats fed on a lactational hyper-energetic cafeteria diet show decreased behavioural satiety, decreased anxiety and sex-dependent effects on object recognition memory when tested in adult age [13-15]. Although behavioural changes already manifest in young adolescence, where offspring from overfed dams show increased exploratory activity in the open field [17], it remains unknown if a hyper-energetic, high caloric lactational diet (CD) impacts on adolescent memory. In a novel object recognition (NOR) task, rodents show innate preference for a familiar over a novel object reflected by increased directed exploration of the novel object regarded as an index of visual recognition memory [18]. This paradigm was selected because of pharmacological sensitivity to drugs that modify dopaminergic activity, and established recognition of the translational relevance to visual learning and memory deficits seen in human CNS developmental disorders such as schizophrenia [19, 20]. Intact NOR requires an optimal functioning dopaminergic system in the PFC, as local stimulation of dopamine D1 and antagonism of dopamine D2 or D3 receptors modify NOR memory in the rat [21-23]. Other studies evidenced the role of the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) in this behavioural task [24-28] and both the dopaminergic and serotonergic functions in the brain can be altered by diet [29]. 5-HT and dopamine (DA) also impact on the development of the PFC, and they are interlinked during development [30, 31]. However, it remains to be investigated if an obesogenic diet influences the early postnatal development of these two neurotransmitter systems in the PFC.

In the context of human obesity, early dietary exposure to obesogenic diets could pose a risk to mental and cognitive development in adolescence. During adolescence, the human brain is particularly

sensitive to adverse environmental impacts as PFC-mediated behavioural control has not matured yet [32-34]. Effects of a lactational CD on memory in early adolescence has not yet been reported in rodents. To study dietary effects on brain neurotransmitter and learning, we exposed lactating dams to a highly palatable cafeteria diet and tested the offspring post-weaning in an NOR task; a type of recognition learning that develops early in rats, being established before weaning [35]. In a second part of the experiment, conducted in parallel, we measured brain regional levels of the neurotransmitters 5-HT, DA and their major metabolites in the PFC of the offspring. We hypothesized an impaired NOR performance in offspring from CD–fed dams and also aberrant DA and 5-HT metabolism in the PFC.

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. Rats were given sawdust as a cage substrate, paper strips for nesting and a cardboard tube for enrichment. Standard laboratory chow (Teklad Global 18% Protein Rodent Diet Harlan, UK) and water (filtered tap water) were available at *ad libitum*. The rats were maintained under a 12 hour light dark cycle (with 1 hour dusk and 1 hour dawn, lights on at 07:30 hours), 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 diets

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 [36]. 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. Weight loss due to evaporation was measured in triplicate samples of each individual food item placed in empty cages. 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 [36]. 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 (Fig. 1).

2.3 Behavioural testing

Novel object recognition (NOR) testing

Behavioural testing occurred in 24 to 26 days old offspring. Two randomly selected pups of each sex from each litter were used for testing; N= 9-12/dietary group/test condition, being in total, 62 offspring. Each individual was only tested once. Testing was undertaken in constant dim light (4 lux) between 08:30 and 13:30h. Only one male/female was used from each litter for each trial to avoid within-litter effects.

The methodology used in the present study was modified from Wright et al. [15]. Briefly, rats were habituated to the test arena (54cm × 38cm × 40cm) in the absence of any objects for one hour the day before testing. On the day of testing, animals received an additional 3-minute habituation session and were returned to the home-cage for 1 min, before being placed into the observation arena for the training trial (familiarisation) with two identical objects for 3 min. In three independent experiments, each animal was then returned to the observation arena for 3 minutes for the test trial (choice trial) with one of the two objects replaced by a similar but novel object present either after a 5, 30 or 60 min inter-trial-interval (ITI). The remaining object from the familiarisation trail was left untouched (familiar object). The experiment assessed three retention intervals, but in independent experiments. Individual rats were only tested once, and only for a single retention interval each.

The objects were 150ml water-filled plastic bottles with three horizontal strips of either white (W) or black (B) 1.2 cm wide masking tape being randomly assigned for each animal during the training schedule. The objects were positioned 13 cm from the length side and 11 cm from the width side of the arena in opposite corners. Arena and objects were cleaned with 70% ethanol between experiments to eliminate olfactory cues.

For both trials, object exploration was defined as sniffing the object from a distance of under 1.5 cm or touching the object with the forepaws or nose. Behaviour was analysed using Ethovision XT7

(Noldus, Netherlands). 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 novel object divided by the total object exploration time during the test trial (t novel/ (t novel + t familiar) [37, 38] .

2.4 Brain neurotransmitter content and metabolism

For monoamine neurotransmitter determination, rats exposed to lactational CD and their controls were culled on post-natal day 26. In total, 24 offspring were used for neurotransmitter analyses. To exclude any possible interference, these rats did not undergo behavioural testing. To eliminate circadian effects, culling occurred at the same time of day as the behavioural experiments were performed. Immediately after culling, brains were removed and placed upon a glass plate mounted on an ice-filled container. The PFC was dissected and placed in liquid nitrogen before being stored at a freezer at −80 °C prior to analysis.

For sample preparation tissue was weighed and placed in a perchloric acid working solution (0.05% PCA, 0.02% sodium metabisulphate, 0.01% EDTA). Tissue was homogenized using a sonic probe (Soniprobe 150, output 20, 20–30 s). Each sample was then placed in 1.5 ml centrifuge tube and centrifuged at 17,500 g in a Harrier 18/80 centrifuge) at 4 °C for 20 min. Supernatant was removed and filtered through 0.45 µm PVDF 4 mm syringe filters immediately before analysis by chromatography as detailed below.

High performance liquid chromatography with electrochemical detection was used to measure 5-HT and its major metabolite 5-hydroxyindolacetic acid (5-HIAA), DA and the two major dopamine metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) as described previously (Rodsiri et al., 2010). Samples were analysed using a CuO4 detector connected to a VT-03 cell with a glassy carbon working electrode operated at a potential difference of +0.7 V vs. Ag/AgCl. (Antec, Netherlands), a PU980 pump (Jasco Pump PVT. Ltd., India), a Rheodyne injection valve (7125 injection valve; IDEX Corp., USA), a 4.6 mm × 150 mm Sphereclone, 5 µm ODS(2) column (Phenomenex, UK) with a Chromjet integrator (Newport Spectra-Physics Ltd., UK). The mobile phase consisted of 0.05 M KH2PO4, 0.1 mM EDTA, 0.32 mM octane sulfonic acid and 13% methanol, adjusted to pH 2.8–3 with orthophosphoric acid which was run at a flow rate of 1 ml/min. Calibration standards of DA, DOPAC, HVA, 5-HT and 5-HIAA were run three times daily before, midway and after running brain samples. All chemicals and standards were obtained from Sigma (Poole, UK).

2.5 Statistics

Student's *t*-test was used to analyse all nutritional data. The statistical unit for macronutrient intake was the dam**.** The statistical unit for the neurochemical and behavioural analyses was the litter.

DA, DOPAC, HVA, 5-HT and 5-HIAA concentrations were analysed using a two-way independent measures ANOVA (diet × sex) with post-hoc Tukey-test, or, when sphericity was not assumed, Games–Howell test. To investigate if diet or sex impact on exploratory behaviour during the familiarisation trial and thus introducing a bias for NOR testing, object exploration across the three ITI was subjected to Two-Way ANOVA (diet, sex).

NOR testing was powered to detect a difference of 20% for the time spent in exploration between groups, based upon σ=0.11 (determined from published studies) and an α-value of 0.05 at 80% power. 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 [37]. Sex was not seen as a differential factor in NOR in agreement with evidence from previous studies [39, 40]. Object discrimination task data has often a small effect size and thus ANOVA would be insufficiently powered [35]. In addition, it is thought that different memory mechanisms underlie the separate time intervals [41, 42] and for these reasons data at all ITIs were analysed independently. Consequently, no offspring NOR data was analysed using an ANOVA and no between group comparison were made.

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

3. Results

3.1 Macronutrient and energy intake in dams during lactation

Fat ($t=18.45$, $P<0.0001$) and sugar ($t=15.7$, $P<0.0001$) intake were significantly increased in lactating CD-fed dams (Tab. 1) which led to a higher total energy intake in these dams ($t=3.9$, $P<0.001$). The overall protein intake was reduced by 27% ($t=5.13$, $P<0.0001$). Despite the increased sugar intake, CD-fed dams consumed less carbohydrates in total ($t=3.8$, $P<0.001$) (Tab. 1).

3.2. Novel object recognition

No effects of diet (F (1, 66) =0.02, P=0.12) or sex (F (1, 66) =0.55, P=0.46) on the time exploring the objects could be observed during the familiarisation trial when rats were first exposed to the two identical objects (Table 2).

During the choice trial, controls explored the novel preferentially over the familiar object after both the shorter 5 min (t=4.56, df=11, P<0.001) or 30 min (t=0.0129, df =10, P<0.05) ITI. By contrast, offspring from dams fed on the lactational cafeteria diet did not show any significant preference for the novel object at any of these time points. Compared with offspring on a lactational chow, their average discrimination ratio of the novel object was lower after the 5 min ITI (t=2.348, df = 20, P<0.05). Following a 60 minute ITI, neither of the two groups showed a preference for the novel object (Fig. 2).

3.3 Effects of diet on DA and 5-HT in the prefrontal cortex

Feeding a lactational cafeteria diet changed prefrontal DA and 5-HT metabolism. There was a main effect of treatment as dopamine was significantly reduced (F (1, 20) = 4.87, P=0.0392) and so were its two metabolites DOPAC (F (1, 20) = 10.24, P=0.0045) and HVA (F (1, 19) = 45.54, P<0.0001) in CD offspring. It needs to be mentioned though, that in 8 out of 12 rats in the cafeteria diet group (but in not in controls) HVA was below the detection limit. Therefore the ratio of DOPAC (instead of DOPAC and HVA) to DA was utilised [43] as an indicator of DA metabolism. This ratio was significantly reduced in the CD group (F (1, 20) = 32.89, P<0.0001). None of the measured parameters were affected by sex (P>0.05) (Fig. 3).

Whereas 5-HT in the PFC was not affected by diet (P>0.05), the 5-HT metabolite 5-HIAA was increased following lactational exposure to CD (F (1, 20) = 11.93, P<0.01). For this parameter, there was also an interaction with sex (F (1, 19) = 35.5 P<0.0001) such that the 5-HIAA content was higher in female CD offspring (P < 0.01). 5-HT metabolism as expressed by the 5-HIAA/5-HT ratio (F (1, 20) = 21.29, P<0.001) was increased in the cafeteria group with no significant interaction between diet and sex (Fig. 4).

4. Discussion

Feeding a cafeteria diet during lactation led to maternal overconsumption of fat and sugars (though not total carbohydrates) and thus increased energy intake. The carbohydrate content of chow is high (mostly starch), but with low sugar, whereas a CD item can have less total carbohydrates (compared to chow) but more sugar. Therefore, despite the overconsumption of sugars, total carbohydrate intake

in CD fed dams can be marginally reduced. This intake pattern, alongside a slight but significant reduced protein intake, is consistent throughout studies in our laboratory [36, 44-46] and does not lead to increased bodyweight in offspring at the time of weaning [14, 17, 44]. Feeding such a CD affects a variety of behaviours irrespective of whether the diet was fed either during early postnatal development or in adult age. Behaviours affected by CD include anxiety and exploration, memory and feeding behaviour itself [13-15, 47-51]. In the current study, offspring from dams fed on chow during lactation were able to discriminate between a familiar and novel object following both shorter 5 minute and 30 minute ITIs, indicating that the presentation of the familiar object had remained intact in their memory for at least up to 30 minutes following training. This appears to be in line with results from earlier rodent studies that have demonstrated evidence for NOR in weanlings and adolescent rats after a short ITI [35, 52]. No indication of object discrimination was found following a 60 minutes ITI. In contrast to chow fed controls, object memory was impaired in 25 days old offspring from dams that have been exposed to the cafeteria diet during lactation even at 5 and 30 minutes it is suggesting the diet may have caused a premature forgetting of object recognition. Our sampling data shows that this memory impairment is not due to changes in exploratory motivation during the sampling phase of the task, since exploration of both objects is identical for both groups, as expected [53].

The observed memory impairment is a significant finding because the rodent brain is still under development during the postnatal period, and sensitive periods in memory in adolescence have been reported [4, 54-58] . Of note, early life social isolation has been robustly shown to impair a similar NOR protocol compared to group-housed littermate controls; an effect that can be reversed by dopamine D3 and 5-HT6 antagonists consistent with the involvement of developmental modifications in these neurotransmitters [22, 24, 59]. Consequently, environmental, including nutritional, challenges during this time could have effects on the developing brain and behaviour lasting into adulthood. Among all these factors, maternal behaviour seems to play a fundamental role [60], and maternal behaviours as grooming, nursing and licking increase when dams are fed a hyper-energetic diet [61, 62]. Although not investigated in the current study, we found increased licking and grooming of the pups when lactating dams were fed a cafeteria diet [17] . Together these findings suggest an effect of diet on maternal behaviour and subsequently on offspring behaviour.

Milk composition during lactation reflects dietary intake when exposed to CD [63]. Hence, a direct nutritional effect on the pups could possibly override subtle diet-induced positive changes in maternal behaviour. Milk consumption of pups peaks around postnatal day 15 whereas pups start feeding solid food around day 17 [64]. In the current study, pups were weaned on postnatal day 21, leaving not more than four days of direct CD intake. Given that milk consumption remains high at least to

postnatal day 19 [64], CD consumption by the pups would be minimal. Hence the observed effects are most likely mediated via maternal milk ingestion rather than a direct CD consumption.

In the current literature, there are mixed results from studies investigating the effects of hyper-energetic feeding on NOR. In contrast to the current findings, exposure of adult rats to a cafeteria diet for 20 days did not alter NOR [65, 66]. However, dietary effects on recognition memory have been demonstrated, when the exposure took place during lactation and the sensitivity of the lactational period could explain this discrepancy [13, 15]. Studies testing adult rats have also found impairments in NOR following feeding a high sucrose diet [67, 68], or a high fat (HF) diet [69]. On the other hand, adult rats fed a CD/HF diet presented with no deficits in NOR [65, 70]. It could be suggested that these conflicting results are attributable to the variations in macronutrient content between diets, or differences in experimental design, but also to the time point in postnatal development when the diet was fed.

Feeding a lactational CD had significant and reciprocal effects on PFC 5-HT and DA metabolism, the latter being decreased. In the current study, DA metabolism was expressed as DOPAC/DA ratio and the DA metabolite HVA was not accounted for. DOPAC is the major DA metabolite in rat brain whereas HVA dominates in primates. Although the DOPAC/DA ratios in the context of feeding have been reported in the past [43, 71], many rodent studies present the DOPAC+HVA/DA ratio. However, in the present study, HVA was reduced below detection level in some rats of the CD group, and could not be measured in the control group. This finding adds strong support to the interpretation of an overall reduced DA metabolism in CD fed rats and suggests a dramatic suppressive effect of exposure to the lactational diet on expression of enzymes involved in the metabolism of DA to DOPAC i.e. the monoamine oxidase-aldehyde dehydrogenase (MAO). However, a change in reuptake via DAT alterations cannot be excluded since DA needs to undergo reuptake to be metabolised by MAO. Exposure to high fat diets [72-76], but also cafeteria diets [77-80] affects DAT expression in hypothalamus and midbrain, but also dopamine D2 receptor expression. Both effects could be indicative of diet-induced changes in DA release. Of note, a three to four weeks exposure to a cafeteria diet enhances D2 receptor mediated autoinhibition thus causing deficits in DA signalling [80]. Alternatively, DA synthesis could be affected by an obesogenic diet. In mice, fed on a high fat diet, the expression of midbrain tyrosine hydroxylase (TH) was reduced [81], however increased in the hypothalamus [76]. TH is the rate limiting enzyme in DA synthesis, and a reduced activity could undelay the reduced DA concentrations as observed in the present study.

Albeit many of the aforementioned studies were conducted in adult animals, maternal exposure to HF diets also alters dopaminergic brain functions [75, 82] and the effect of a cafeteria diet can change fundamentally during development [77].

A study in adolescent rats found reduced prefrontal gene expression of the dopamine degrading enzymes MAO and catechol-O-methyltransferase (COMT) following exposure to a high fat and high sugar diet [83]. This study supports our finding that a hyper-energetic diet impacts on prefrontal cortical DA in adolescence. Although the study by Reichelt et al. [83] did not measure DA content or turnover, their data would rather predict increased PFC DA concentrations. This is would contradict our findings of a reduced DA activity, but due to differences in study design (e.g. age of animals, diet, and feeding procedure) conclusions cannot be drawn without further experimentation.

DA plays a role in short term memory across species, although conceptual questions of memory models require consideration [84]. The reduced DOPAC/DA ratio could be indicative of a diminished release or increased presynaptic DA uptake, although changes in metabolite/neurotransmitter ratio do not always translate into changes in release [85] and the neurochemical data provided here cannot easily be related to the observed dietary effects on memory. The functional significance of the observed alterations in post-mortem brain neurochemistry needs to be confirmed in further *in vivo* studies. However, pharmacological data demonstrates the involvement of DA receptors modulating NOR, suggesting a functional impact of the observed changes in the DA/DOPAC ratio. Thus, PFC D1 receptor activation and D2 receptor antagonism impair NOR, whereas D3 receptor blockade improves NOR [21, 86].

5-HT metabolism in PFC was increased in CD fed offspring and CD fed offspring showed impaired NOR in the current study. Thus, assuming a cafeteria diet – induced increase in serotonergic activity and impaired NOR would be in line with reports demonstrating that 5-HT6 , 5-HT7, postsynaptic 5-HT1A receptor antagonists as well as presynaptic 5-HT1A receptor agonists have positive effects on NOR [57, 87-91] . Although the serotonergic drugs were given systemically in these studies, evidence for an involvement PFC 5-HT in NOR exists [25, 26, 28]. However, based on focal lesions, an involvement of the PFC in NOR has been questioned [92], although the aforementioned pharmacological studies seem to contradict these earlier findings as they suggest an involvement of PFC DA and 5-HT in NOR (but see [93]). In addition, it is unknown if lesions to the PFC also affect NOR in very young rats. Lesion studies in adults established the perirhinal cortex as the main brain correlate of NOR [94, 95]. However lesions of the perirhinal cortex do not impair NOR when the inter-trial interval is short in [94]

and adolescent rats seem to remember the object only for a short period of time in the current study. In fact, short term memory of both, hippocampus-dependent spatial tasks and NOR are impaired following D1 antagonism in the prelimbic cortex, further suggesting an involvement of PFC in NOR [96]. Thus it is quite possible that under certain conditions (age/short inter-trial interval) the PFC also plays a role in NOR. It has also been suggested that PFC lesions do not impact on NOR, as this relatively simple form of learning could be processed in other brain regions as well [96]. Although the hippocampus does not seem to play a dominant role in NOR (but [97, 98]), hippocampal function is particularly sensitive to hyperenergetic diets [99, 100] and hippocampal lesions alter the functional maturation of the prefrontal cortex [101]. As the prefrontal cortex in young adolescent rats is still developing, one could hypothesize that changes in hippocampal function could contribute to the observed aberrations in 5-HT and DA metabolism. Thus, albeit indirectly, the hippocampus could possibly play a more prominent role in NOR when the brain is still developing. In addition, PFC functioning itself could be altered by diet [102-104]. Recently, a model of adolescent maturation of hippocampal and PFC circuity has been suggested. This model also proposes dopaminergic control over the developing PFC-hippocampal interactions [105].

Despite the fact that dopaminergic and serotonergic functions in the PFC are undergoing substantial postnatal development, and thus are subject to environmental factors [106], relatively little is known about the impact of diet on PFC functioning during early development. However, in the rat, a 5-HT sensitive period impact on PFC function has been established between postnatal day 2 and 11 [107]. The development of the dopaminergic innervation of the PFC lasts at least until postnatal day 60 which includes the lactational period. Both 5-HT and DA syntheses are influenced by diet [29]. However, it remains to be investigated if and how an obesogenic Western diet impacts on the postnatal development of these two neurotransmitter system in the PFC. The early postnatal period, i.e. the lactational period, in rodents has been related to the third semester of gestation in humans, but brain development in both humans and rodents is similar in that there is an increase in postnatal brain synaptogenesis [56]. In the rat, brain differentiation occurs mostly postpartum [58]. Given that PFC maturation in both rats and humans is incomplete until puberty, postnatal manipulations of diet might impact on brain development in both species.

Changes in rodent PFC functioning are seen as a potential model for human PFC development [11, 108] and the involvement of PFC 5-HT and DA has been suggested in related behavioural pathology. In humans, early environmental challenges can be detrimental to neurodevelopment and predispose to mental and behavioural disorders [32, 109]. Experimental and clinical neurobehavioural research is focussing on adolescence where about 50% of adult neuropsychiatric disorders emerge [7, 11, 110]

and where therapeutic invention could be beneficial [111]. Here we provide experimental evidence for a possible role of unhealthy diets in that context.

In conclusion, we demonstrate that lactational diet impacts on PFC neurochemistry and on the development of NOR behaviour in the early adolescent rat. It cannot be excluded that the early exposure to a cafeteria diet could possibly delay the development of this behaviour. Considering that psychiatric diseases are increasingly seen as developmental disorders, an early obesogenic diet could be a potentially under-investigated contributing factor.

Acknowledgement

This study was supported by grants A13848 and SD3513 (University of Nottingham).

References

[1] H. Eichenbaum, Prefrontal-hippocampal interactions in episodic memory, Nat. Rev. Neurosci. 18 (2017) 547-558.

[2] A. Jezzini, L. Mazzucato, G. La Camera, A. Fontanini, Processing of hedonic and chemosensory features of taste in medial prefrontal and insular networks, J. Neurosci. 33 (2013) 18966-18978.

[3] J.F. Morici, P. Bekinschtein, N.V. Weisstaub, Medial prefrontal cortex role in recognition memory in rodents, Behav. Brain Res. 292 (2015) 241-251.

[4] B. Kolb, R. Mychasiuk, A. Muhammad, Y. Li, D.O. Frost, R. Gibb, Experience and the developing prefrontal cortex, Proc. Natl. Acad. Sci. U S A 109 Suppl 2 (2012) 17186-17193.

[5] Z. Petanjek, M. Judas, G. Simic, M.R. Rasin, H.B. Uylings, P. Rakic, I. Kostovic, Extraordinary neoteny of synaptic spines in the human prefrontal cortex, Proc. Natl. Acad. Sci. U S A 108 (2011) 13281-13286.

[6] B.L. Callaghan, N. Tottenham, The Neuro-Environmental Loop of Plasticity: A Cross-Species Analysis of Parental Effects on Emotion Circuitry Development Following Typical and Adverse Caregiving, Neuropsychopharmacology 41 (2016) 163-176.

[7] L.D. Selemon, N. Zecevic, Schizophrenia: a tale of two critical periods for prefrontal cortical development, Transl. Psychiatry 5 (2015) e623.

[8] E. McCrory, S.A. De Brito, E. Viding, Research review: the neurobiology and genetics of maltreatment and adversity, J. Child. Psychol. Psychiatry 51 (2010) 1079-1095.

[9] C. Kieling, R.R. Goncalves, R. Tannock, F.X. Castellanos, Neurobiology of attention deficit hyperactivity disorder, Child Adolesc. Psychiatr. Clin. N. Am. 17 (2008) 285-307.

[10] N.J. Gamo, G. Lur, M.J. Higley, M. Wang, C.D. Paspalas, S. Vijayraghavan, Y. Yang, B.P. Ramos, K. Peng, A. Kata, L. Boven, F. Lin, L. Roman, D. Lee, A.F. Arnsten, Stress Impairs Prefrontal Cortical Function via D1 Dopamine Receptor Interactions With Hyperpolarization-Activated Cyclic Nucleotide-Gated Channels, Biol. Psychiatry 78 (2015) 860-870.

[11] A.C. Reichelt, Adolescent Maturational Transitions in the Prefrontal Cortex and Dopamine Signaling as a Risk Factor for the Development of Obesity and High Fat/High Sugar Diet Induced Cognitive Deficits, Front. Behav. Neurosci. 10 (2016) 189. eCollection 2016.

[12] A.C. Reichelt, L.E. Stoeckel, L.P. Reagan, C.A. Winstanley, K.A. Page, Dietary influences on cognition, Physiol. Behav. 192 (2018) 118-126.

[13] T. Wright, S.C. Langley-Evans, J.P. Voigt, The impact of maternal cafeteria diet on anxiety-related behaviour and exploration in the offspring, Physiol. Behav. 103 (2011) 164-172.

[14] T.M. Wright, K.C. Fone, S.C. Langley-Evans, J.P. Voigt, Exposure to maternal consumption of cafeteria diet during the lactation period programmes feeding behaviour in the rat, Int. J. Dev. Neurosci. 29 (2011) 785-793.

[15] T.M. Wright, M.V. King, W.G. Davey, S.C. Langley-Evans, J.P. Voigt, Impact of cafeteria feeding during lactation in the rat on novel object discrimination in the offspring, Br. J. Nutr. 112 (2014) 1933-1937.

[16] M. Alamy, W.A. Bengelloun, Malnutrition and brain development: an analysis of the effects of inadequate diet during different stages of life in rat, Neurosci. Biobehav. Rev. 36 (2012) 1463-1480.

[17] A. Speight, W.G. Davey, E. McKenna, J.W. Voigt, Exposure to a maternal cafeteria diet changes open-field behaviour in the developing offspring, Int. J. Dev. Neurosci. 57 (2017) 34-40.

[18] A. Ennaceur, J. Delacour, A new one-trial test for neurobiological studies of memory in rats. 1: Behavioral data, Behav. Brain Res. 31 (1988) 47-59.

[19] L. Lyon, L.M. Saksida, T.J. Bussey, Spontaneous object recognition and its relevance to schizophrenia: a review of findings from pharmacological, genetic, lesion and developmental rodent models, Psychopharmacology (Berl) 220 (2012) 647-672.

[20] L. Rajagopal, B.W. Massey, M. Huang, Y. Oyamada, H.Y. Meltzer, The novel object recognition test in rodents in relation to cognitive impairment in schizophrenia, Curr. Pharm. Des. 20 (2014) 5104-5114.

[21] D.J. Watson, F. Loiseau, M. Ingallinesi, M.J. Millan, C.A. Marsden, K.C. Fone, Selective blockade of dopamine D3 receptors enhances while D2 receptor antagonism impairs social novelty discrimination and novel object recognition in rats: a key role for the prefrontal cortex, Neuropsychopharmacology 37 (2012) 770-786.

[22] D.J.G. Watson, M.V. King, I. Gyertyan, B. Kiss, N. Adham, K.C.F. Fone, The dopamine D(3)-preferring D(2)/D(3) dopamine receptor partial agonist, cariprazine, reverses behavioural changes in a rat neurodevelopmental model for schizophrenia, Eur Neuropsychopharmacol 26 (2016) 208-224.

[23] M.A. Pezze, J.W. Dalley, T.W. Robbins, Remediation of attentional dysfunction in rats with lesions of the medial prefrontal cortex by intra-accumbens administration of the dopamine D(2/3) receptor antagonist sulpiride, Psychopharmacology 202 (2009) 307-313.

[24] J. Meffre, S. Chaumont-Dubel, C. Mannoury la Cour, F. Loiseau, D.J. Watson, A. Dekeyne, M. Seveno, J.M. Rivet, F. Gaven, P. Deleris, D. Herve, K.C. Fone, J. Bockaert, M.J. Millan, P. Marin, 5-HT(6) receptor recruitment of mTOR as a mechanism for perturbed cognition in schizophrenia, Embo. Mol. Med. 4 (2012) 1043-1056.

[25] G. Levallet, M. Hotte, M. Boulouard, F. Dauphin, Increased particulate phosphodiesterase 4 in the prefrontal cortex supports 5-HT4 receptor-induced improvement of object recognition memory in the rat, Psychopharmacology (Berl) 202 (2009) 125-319.

[26] P. Bekinschtein, M.C. Renner, M.C. Gonzalez, N. Weisstaub, Role of medial prefrontal cortex serotonin 2A receptors in the control of retrieval of recognition memory in rats, J. Neurosci. 33 (2013) 15716-15725.

[27] W.D. Hirst, T.O. Stean, D.C. Rogers, D. Sunter, P. Pugh, S.F. Moss, S.M. Bromidge, G. Riley, D.R. Smith, S. Bartlett, C.A. Heidbreder, A.R. Atkins, L.P. Lacroix, L.A. Dawson, A.G. Foley, C.M. Regan, N. Upton, SB-399885 is a potent, selective 5-HT6 receptor antagonist with cognitive enhancing properties in aged rat water maze and novel object recognition models, Eur. J. Pharmacol. 553 (2006) 109-119.

[28] J.F. Morici, L. Ciccia, G. Malleret, J.A. Gingrich, P. Bekinschtein, N.V. Weisstaub, Serotonin 2a Receptor and Serotonin 1a Receptor Interact Within the Medial Prefrontal Cortex During Recognition Memory in Mice, Front. Pharmacol. 6 (2015) 298. eCollection 2015.

[29] J.D. Fernstrom, Large neutral amino acids: dietary effects on brain neurochemistry and function, Amino Acids 45 (2013) 419-430.

[30] F.M. Benes, J.B. Taylor, M.C. Cunningham, Convergence and plasticity of monoaminergic systems in the medial prefrontal cortex during the postnatal period: implications for the development of psychopathology, Cereb. Cortex 10 (2000) 1014-1027.

[31] M.G. Cunningham, C.M. Connor, K. Zhang, F.M. Benes, Diminished serotonergic innervation of adult medial prefrontal cortex after 6-OHDA lesions in the newborn rat, Brain Res. Dev. Brain Res. 157 (2005) 124-131.

[32] A. Diamond, Biological and social influences on cognitive control processes dependent on prefrontal cortex, Prog. Brain Res. 189 (2011) 319-339.

[33] L.P. Spear, The adolescent brain and age-related behavioral manifestations, Neurosci. Biobehav. Rev. 24 (2000) 417-463.

[34] L.P. Spear, Adolescent neurodevelopment, J. Adolesc. Health 52 Suppl 2 (2013) S7-13.

[35] S.R. Westbrook, L.E. Brennan, M.E. Stanton, Ontogeny of object versus location recognition in the rat: acquisition and retention effects, Dev. Psychobiol. 56 (2014) 1492-1506.

[36] A. Akyol, S.C. Langley-Evans, S. McMullen, Obesity induced by cafeteria feeding and pregnancy outcome in the rat, Br. J. Nutr. 102 (2009) 1601-1610.

[37] S.L. Dix, J.P. Aggleton, Extending the spontaneous preference test of recognition: evidence of object-location and object-context recognition, Behav. Brain Res. 99 (1999) 191-200.

[38] S.A. Jablonski, W.B. Schreiber, S.R. Westbrook, L.E. Brennan, M.E. Stanton, Determinants of novel object and location recognition during development, Behav. Brain Res. 256 (2013) 140-150.

[39] D.L. Cyrenne, G.R. Brown, Ontogeny of sex differences in response to novel objects from adolescence to adulthood in lister-hooded rats, Dev. Psychobiol. 53 (2011) 670-676.

[40] C.J. Heyser, J.S. Ferris, Object exploration in the developing rat: methodological considerations, Dev. Psychobiol. 55 (2013) 373-381.

[41] K.T. Cost, Z.N. Williams-Yee, J.N. Fustok, G.P. Dohanich, Sex differences in object-in-place memory of adult rats, Behav. Neurosci. 126 (2012) 457-464.

[42] M.R. Rosenzweig, E.L. Bennett, P.J. Colombo, D.W. Lee, P.A. Serrano, Short-term, intermediate-term, and long-term memories, Behav. Brain Res. 57 (1993) 193-198.

[43] K.J. Simansky, K.A. Bourbonais, G.P. Smith, Food-related stimuli increase the ratio of 3,4-dihydroxyphenylacetic acid to dopamine in the hypothalamus, Pharmacol. Biochem. Behav. 23 (1985) 253-258.

[44] A. Akyol, S. McMullen, S.C. Langley-Evans, Glucose intolerance associated with early-life exposure to maternal cafeteria feeding is dependent upon post-weaning diet, Br. J. Nutr. 107 (2012) 964-978.

[45] A. Speight, W.G. Davey, E. McKenna, J.-P.W. Voigt, Exposure to a maternal cafeteria diet changes open-field behaviour in the developing offspring, Int. J. . Dev. Neurosci. 57 (2017) 34-40.

[46] T. Wright, M. King, W. Davey, S.C. Langley-Evans, J.-P. Voigt, The impact of cafeteria feeding during lactation in the rat on novel object discrimination in the offspring, Br. J. Nutr. 112(12) (2014) 1933-1937.

[47] W. Warneke, S. Klaus, H. Fink, S.C. Langley-Evans, J.P. Voigt, The impact of cafeteria diet feeding on physiology and anxiety-related behaviour in male and female Sprague-Dawley rats of different ages, Pharmacol. Biochem. Behav. 116 (2014) 45-54.

[48] A. Ferreira, J.P. Castro, J.P. Andrade, M. Dulce Madeira, A. Cardoso, Cafeteria-diet effects on cognitive functions, anxiety, fear response and neurogenesis in the juvenile rat, Neurobiol. Learn. Mem. 155 (2018) 197-207.

[49] R.T.B. Pini, L.D.M. Ferreira do Vales, T.M. Braga Costa, S.S. Almeida, Effects of cafeteria diet and high fat diet intake on anxiety, learning and memory in adult male rats, Nutr. Neurosci. 20 (2017) 396-408.

[50] A.C. Reichelt, J. Maniam, R.F. Westbrook, M.J. Morris, Dietary-induced obesity disrupts trace fear conditioning and decreases hippocampal reelin expression, Brain Behav. Immun. 43 (2015) 68-75.

[51] J.F. Lalanza, A. Caimari, J.M. del Bas, D. Torregrosa, I. Cigarroa, M. Pallas, L. Capdevila, L. Arola, R.M. Escorihuela, Effects of a post-weaning cafeteria diet in young rats: metabolic syndrome, reduced activity and low anxiety-like behaviour, PLoS One 9 (2014) e85049.

[52] M.L. Reger, D.A. Hovda, C.C. Giza, Ontogeny of Rat Recognition Memory measured by the novel object recognition task, Dev. Psychobiol. 51 (2009) 672-678.

[53] S. Akkerman, A. Blokland, O. Reneerkens, N.P. van Goethem, E. Bollen, H.J. Gijselaers, C.K. Lieben, H.W. Steinbusch, J. Prickaerts, Object recognition testing: methodological considerations on exploration and discrimination measures, Behav. Brain Res. 232 (2012) 335-347.

[54] S.H. Albani, D.G. McHail, T.C. Dumas, Developmental studies of the hippocampus and hippocampal-dependent behaviors: insights from interdisciplinary studies and tips for new investigators, Neurosci. Biobehav. Rev. 43 (2014) 183-190.

[55] L.J. Chareyron, P.B. Lavenex, P. Lavenex, Postnatal development of the amygdala: a stereological study in rats, J. Comp. Neurol. 520 (2012) 3745-3763.

[56] B.D. Semple, K. Blomgren, K. Gimlin, D.M. Ferriero, L.J. Noble-Haeusslein, Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species, Prog. Neurobiol. 106-107 (2013) 1-16.

[57] M.V. King, A.J. Sleight, M.L. Woolley, I.A. Topham, C.A. Marsden, K.C. Fone, 5-HT6 receptor antagonists reverse delay-dependent deficits in novel object discrimination by enhancing consolidation--an effect sensitive to NMDA receptor antagonism, Neuropharmacology 47 (2004) 195-204.

[58] J.D. Stead, C. Neal, F. Meng, Y. Wang, S. Evans, D.M. Vazquez, S.J. Watson, H. Akil, Transcriptional profiling of the developing rat brain reveals that the most dramatic regional differentiation in gene expression occurs postpartum, J. Neurosci. 26 (2006) 345-353.

[59] D.J. Watson, C.A. Marsden, M.J. Millan, K.C. Fone, Blockade of dopamine D(3) but not D(2) receptors reverses the novel object discrimination impairment produced by post-weaning social isolation: implications for schizophrenia and its treatment, Int. J. Neuropsychopharmacol. 15 (2012) 471-84.

[60] C. Caldji, B. Tannenbaum, S. Sharma, D. Francis, P.M. Plotsky, M.J. Meaney, Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat, Proc. Natl. Acad. Sci. U S A 95 (1998) 5335-5340.

[61] R.H. Purcell, B. Sun, L.L. Pass, M.L. Power, T.H. Moran, K.L. Tamashiro, Maternal stress and high-fat diet effect on maternal behavior, milk composition, and pup ingestive behavior, Physiol. Behav. 104 (2011) 474-479.

[62] M. Bertino, Effects of high fat, protein supplemented diets on maternal behavior in rats, Physiol. Behav. 29 (1982) 999-1005.

[63] B.A. Rolls, M.I. Gurr, P.M. van Duijvenvoorde, B.J. Rolls, E.A. Rowe, Lactation in lean and obese rats: effect of cafeteria feeding and of dietary obesity on milk composition, Physiol. Behav. 38 (1986) 185-190.

[64] I. Ostadalova, A. Babicky, Periodization of the Early Postnatal Development in the Rat With Particular Attention to the Weaning Period, Physiol. Res. 61 (2012) S1-S7.

[65] J.E. Beilharz, J. Maniam, M.J. Morris, Short exposure to a diet rich in both fat and sugar or sugar alone impairs place, but not object recognition memory in rats, Brain Behav. Immun. 37 (2014) 134-141.

[66] D.M.D. Tran, R.F. Westbrook, Dietary effects on object recognition: The impact of high-fat high-sugar diets on recollection and familiarity-based memory, J. Exp. Psychol. Anim. Learn. Cogn. 44 (2018) 217-228.

[67] H. Francis, R. Stevenson, The longer-term impacts of Western diet on human cognition and the brain, Appetite 63 (2013) 119-128.

[68] N. Jurdak, R.B. Kanarek, Sucrose-induced obesity impairs novel object recognition learning in young rats, Physiol. Behav. 96 (2009) 1-5.

[69] M.M. Kaczmarczyk, A.S. Machaj, G.S. Chiu, M.A. Lawson, S.J. Gainey, J.M. York, D.D. Meling, S.A. Martin, K.A. Kwakwa, A.F. Newman, J.A. Woods, K.W. Kelley, Y. Wang, M.J. Miller, G.G. Freund, Methylphenidate prevents high-fat diet (HFD)-induced learning/memory impairment in juvenile mice, Psychoneuroendocrinology 38 (2013) 1553-1564.

[70] S. Kosari, E. Badoer, J.C. Nguyen, A.S. Killcross, T.A. Jenkins, Effect of western and high fat diets on memory and cholinergic measures in the rat, Behav. Brain. Res. 235 (2012) 98-103.

[71] T.G. Heffner, J.A. Hartman, L.S. Seiden, Feeding increases dopamine metabolism in the rat brain, Science 208 (1980) 1168-1170.

[72] K.T. Jones, C. Woods, J. Zhen, T. Antonio, K.D. Carr, M.E. Reith, Effects of diet and insulin on dopamine transporter activity and expression in rat caudate-putamen, nucleus accumbens, and midbrain, J. Neurochem. 140 (2017) 728-740.

[73] R.L. Barry, N.E. Byun, J.M. Williams, M.A. Siuta, M.N. Tantawy, N.K. Speed, C. Saunders, A. Galli, K.D. Niswender, M.J. Avison, Brief exposure to obesogenic diet disrupts brain dopamine networks, PLoS One 13 (2018) e0191299.

[74] V. Narayanaswami, A.C. Thompson, L.A. Cassis, M.T. Bardo, L.P. Dwoskin, Diet-induced obesity: dopamine transporter function, impulsivity and motivation, Int. J. Obes. (Lond) 37 (2013) 1095-1103.

[75] L. Naef, L. Moquin, G. Dal Bo, B. Giros, A. Gratton, C.D. Walker, Maternal high-fat intake alters presynaptic regulation of dopamine in the nucleus accumbens and increases motivation for fat rewards in the offspring, Neuroscience 176 (2011) 225-236.

[76] A.K. Lee, M. Mojtahed-Jaberi, T. Kyriakou, E.A. Astarloa, M. Arno, N.J. Marshall, S.D. Brain, S.D. O'Dell, Effect of high-fat feeding on expression of genes controlling availability of dopamine in mouse hypothalamus, Nutrition 26 (2010) 411-422.

[77] Z.Y. Ong, B.S. Muhlhausler, Maternal "junk-food" feeding of rat dams alters food choices and development of the mesolimbic reward pathway in the offspring, FASEB J 25 (2011) 2167-2179.

[78] Y. Gautier, I. Luneau, N. Coquery, P. Meurice, C.H. Malbert, S. Guerin, B. Kemp, J.E. Bolhuis, C. Clouard, I. Le Huerou-Luron, S. Blat, D. Val-Laillet, Maternal Western diet during gestation and lactation modifies adult offspring's cognitive and hedonic brain processes, behavior, and metabolism in Yucatan minipigs, FASEB J. (2018) fj201701541.

[79] S.H. Robertson, E.B. Rasmussen, Effects of a cafeteria diet on delay discounting in adolescent and adult rats: Alterations on dopaminergic sensitivity, J. Psychopharmacol. 31 (2017) 1419-1429.

[80] J.B. Cook, L.M. Hendrickson, G.M. Garwood, K.M. Toungate, C.V. Nania, H. Morikawa, Junk food diet-induced obesity increases D2 receptor autoinhibition in the ventral tegmental area and reduces ethanol drinking, PLoS One 12 (2017) e0183685.

[81] Y. Jang, M.J. Lee, J. Han, S.J. Kim, I. Ryu, X. Ju, M.J. Ryu, W. Chung, E. Oh, G.R. Kweon, J.Y. Heo, A High-fat Diet Induces a Loss of Midbrain Dopaminergic Neuronal Function That Underlies Motor Abnormalities, Exp. Neurobiol. 26 (2017) 104-112.

[82] S. Barrand, T.M. Crowley, R.J. Wood-Bradley, K.A. De Jong, J.A. Armitage, Impact of maternal high fat diet on hypothalamic transcriptome in neonatal Sprague Dawley rats, PLoS One 12 (2017) e0189492.

[83] A.C. Reichelt, A. Loughman, A. Bernard, M. Raipuria, K.N. Abbott, J. Dachtler, T.T.H. Van, R.J. Moore, An intermittent hypercaloric diet alters gut microbiota, prefrontal cortical gene expression and social behaviours in rats, Nutr. Neurosci. (2018) 1-15. [Epub ahead of print]

[84] M.V. Puig, J. Rose, R. Schmidt, N. Freund, Dopamine modulation of learning and memory in the prefrontal cortex: insights from studies in primates, rodents, and birds, Front. Neural Circuits 8 (2014) eCollection 2014.

[85] J.W. Commissiong, Monoamine metabolites: their relationship and lack of relationship to monoaminergic neuronal activity, Biochem. Pharmacol. 34 (1985) 1127- 1131.

[86] M.A. Pezze, H.J. Marshall, K.C. Fone, H.J. Cassaday, Dopamine D1 receptor stimulation modulates the formation and retrieval of novel object recognition memory: Role of the prelimbic cortex, Eur. Neuropsychopharmacol. 25 (2015) 2145-2156.

[87] J. Arnt, B. Bang-Andersen, B. Grayson, F.P. Bymaster, M.P. Cohen, N.W. DeLapp, B. Giethlen, M. Kreilgaard, D.L. McKinzie, J.C. Neill, D.L. Nelson, S.M. Nielsen, M.N. Poulsen, J.M. Schaus, L.M. Witten, Lu AE58054, a 5-HT6 antagonist, reverses cognitive impairment induced by subchronic phencyclidine in a novel object recognition test in rats, Int. J. Neuropsychopharmacol. 13 (2010) 1021-1033.

[88] M. Horiguchi, M. Huang, H.Y. Meltzer, The role of 5-hydroxytryptamine 7 receptors in the phencyclidine-induced novel object recognition deficit in rats, J. Pharmacol. Exp. Ther. 338 (2011) 605-614.

[89] M. Horiguchi, H.Y. Meltzer, The role of 5-HT1A receptors in phencyclidine (PCP)-induced novel object recognition (NOR) deficit in rats, Psychopharmacology 221 (2012) 205-215.

[90] M.V. King, C.H. Spicer, A.J. Sleight, C.A. Marsden, K.C. Fone, Impact of regional 5-HT depletion on the cognitive enhancing effects of a typical 5-ht(6) receptor antagonist, Ro 04-6790, in the Novel Object Discrimination task, Psychopharmacology 202 (2009) 111-123.

[91] M.V. King, C.A. Marsden, K.C. Fone, A role for the 5-HT(1A), 5-HT4 and 5-HT6 receptors in learning and memory, Trends Pharmacol. Sci. 29 (2008) 482-492.

[92] A. Ennaceur, N. Neave, J.P. Aggleton, Spontaneous object recognition and object location memory in rats: the effects of lesions in the cingulate cortices, the medial prefrontal cortex, the cingulum bundle and the fornix, Exp. Brain Res. 113 (1997) 509-519.

[93] A.J. Nelson, M.T. Cooper, K.E. Thur, C.A. Marsden, H.J. Cassaday, The effect of catecholaminergic depletion within the prelimbic and infralimbic medial prefrontal cortex on recognition memory for recency, location, and objects, Behav. Neurosci. 125 (2011) 396-403.

[94] E. Dere, J.P. Huston, M.A. De Souza Silva, The pharmacology, neuroanatomy and neurogenetics of one-trial object recognition in rodents, Neurosc.i Biobehav. Rev. 31 (2007) 673-704.

[95] G.R. Barker, F. Bird, V. Alexander, E.C. Warburton, Recognition memory for objects, place, and temporal order: a disconnection analysis of the role of the medial prefrontal cortex and perirhinal cortex, J. Neurosci. 27 (2007) 2948-2957.

[96] B. Clausen, T.R. Schachtman, L.T. Mark, M. Reinholdt, G.R. Christoffersen, Impairments of exploration and memory after systemic or prelimbic D1-receptor antagonism in rats, Behav. Brain Res. 223 (2011) 241-54.

[97] R.E. Clark, S.M. Zola, L.R. Squire, Impaired recognition memory in rats after damage to the hippocampus, J. Neurosci. 20 (2000) 8853-8860.

[98] E.R. Wood, D.G. Mumby, J.P. Pinel, A.G. Phillips, Impaired object recognition memory in rats following ischemia-induced damage to the hippocampus, Behav. Neurosci. 107(1) (1993) 51-62.

[99] T.L. Davidson, A. Monnot, A.U. Neal, A.A. Martin, J.J. Horton, W. Zheng, 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. 107 (2012) 26-33.

[100] S.E. Kanoski, T.L. Davidson, Western diet consumption and cognitive impairment: links to hippocampal dysfunction and obesity, Physiol. Behav. 103 (2011) 59-68.

[101] H.S. Kruger, M.D. Brockmann, J. Salamon, H. Ittrich, I.L. Hanganu-Opatz, Neonatal hippocampal lesion alters the functional maturation of the prefrontal cortex and the early cognitive development in pre-juvenile rats, Neurobiol. Learn. Mem. 97 (2012) 470-481.

[102] S.E. Kanoski, R.L. Meisel, A.J. Mullins, T.L. Davidson, The effects of energy-rich diets on discrimination reversal learning and on BDNF in the hippocampus and prefrontal cortex of the rat, Behav. Brain Res. 182 (2007) 57-66.

[103] Z. Vucetic, J.L. Carlin, K. Totoki, T.M. Reyes, Epigenetic dysregulation of the dopamine system in diet-induced obesity, J. Neurochem. 120 (2012) 891-898.

[104] J. Carlin, T.E. Hill-Smith, I. Lucki, T.M. Reyes, Reversal of dopamine system dysfunction in response to high-fat diet, Obesity (2013) 2513-2521.

[105] V.P. Murty, F. Calabro, B. Luna, The role of experience in adolescent cognitive development: Integration of executive, memory, and mesolimbic systems, Neurosci. Biobehav. Rev. 70 (2016) 46-58.

[106] L.J. Kepser, J.R. Homberg, The neurodevelopmental effects of serotonin: a behavioural perspective, Behav. Brain. Res. 277 (2015) 3-13.

[107] T.J. Rebello, Q. Yu, N.M. Goodfellow, M.K. Caffrey Cagliostro, A. Teissier, E. Morelli, E.Y. Demireva, A. Chemiakine, G.B. Rosoklija, A.J. Dwork, E.K. Lambe, J.A. Gingrich, M.S. Ansorge, Postnatal day 2 to 11 constitutes a 5-HT-sensitive period impacting adult mPFC function, J. Neurosci. 34 (2014) 12379-12393.

[108] A. Caballero, R. Granberg, K.Y. Tseng, Mechanisms contributing to prefrontal cortex maturation during adolescence, Neurosci. Biobehav. Rev. 70 (2016) 4-12.

[109] A. Diamond, Evidence for the importance of dopamine for prefrontal cortex functions early in life, Philos. Trans. R. Soc. Lond. B. Biol. Sci. 351 (1996) 1483-1493.

[110] M.L. Belfer, Child and adolescent mental disorders: the magnitude of the problem across the globe, J. Child Psychol. Psychiatry 49 (2008) 226-236.

[111] L.L. Davidson, E.L. Grigorenko, M.J. Boivin, E. Rapa, A. Stein, A focus on adolescence to reduce neurological, mental health and substance-use disability, Nature 527 (2015) S161-166.

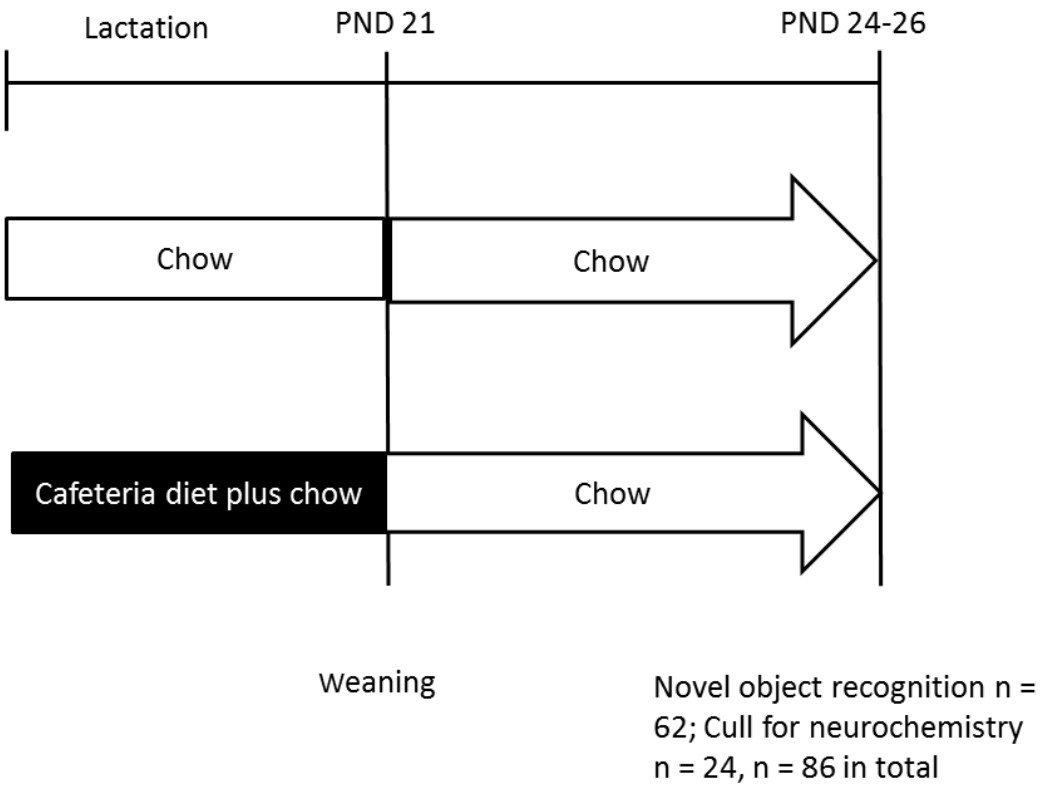

Fig. 1 Timeline of experimental procedures. PND = postnatal day.

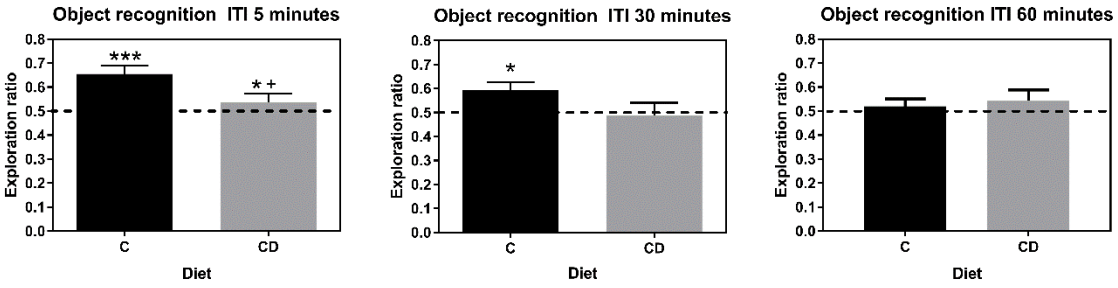

Fig. 2 Impact of lactational cafeteria diet (CD) on novel object recognition in 24-26 day old weaner rats. Control dams were fed on show (C). Values over 0.5 represent learning. In controls, learning occurred both after a 5 min (***) or 30 min (*) inter-trial interval (ITI). Learning occurred also in the CD group after 5 minutes (*), but was impaired when compared to control (+). Offspring from CD fed dams did not show memory after 30 min and no group showed memory after 60 min either. ***P<0.001; * P<0.05; One-sample t-test. +P<0.05 Student's *t*-test. N = 9-12 / group; 62 in total.

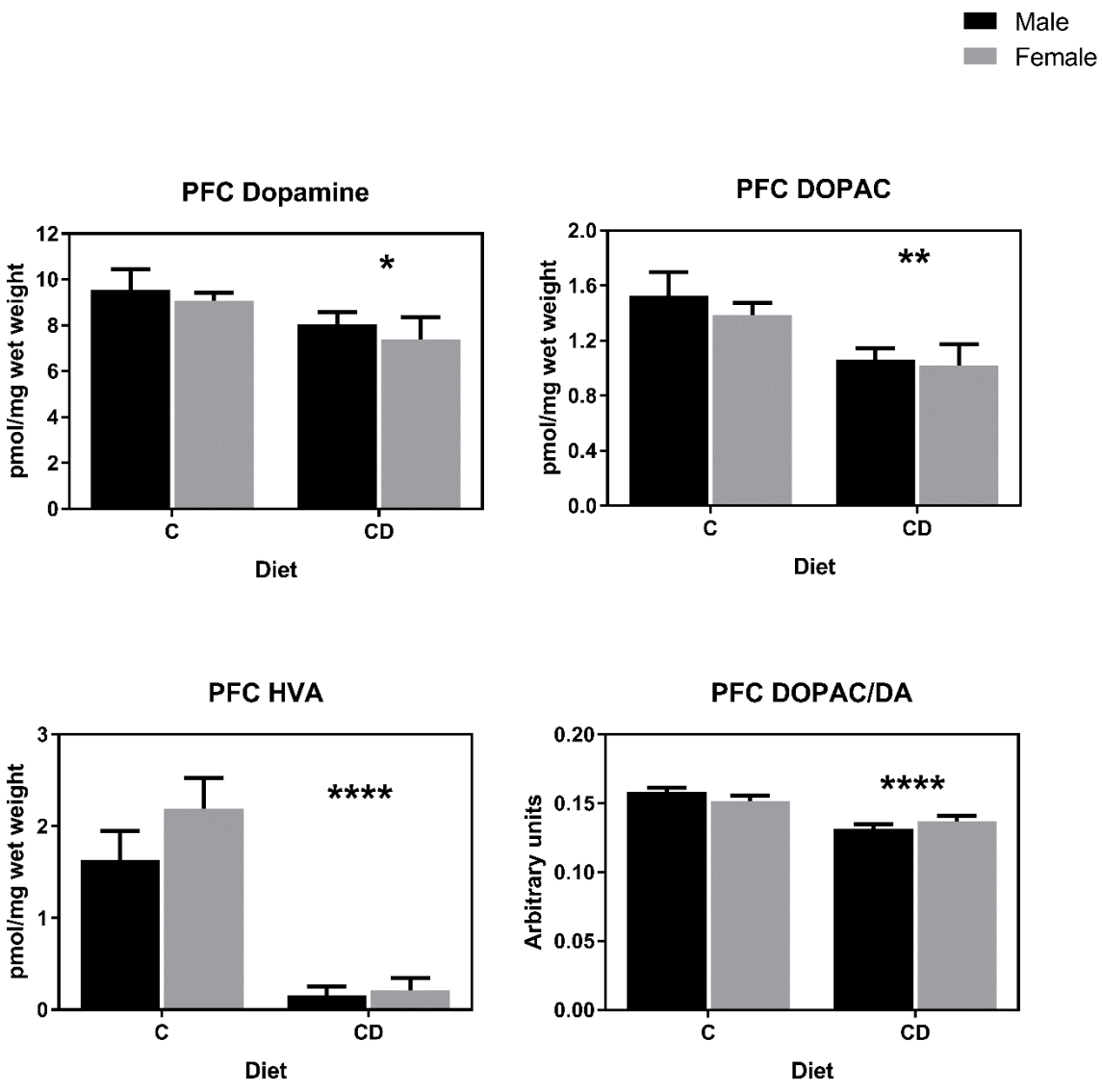

Fig. 3 Impact of lactational cafeteria diet (CD) on PFC dopamine (DA), homovanillic acid (HVA), 3, 4-Dihydroxyphenylacetic acid (DOPAC) and DOPAC/DA ratio (turnover) in 24-26 day old weaner rats. Control dams were fed on show (C). All parameters were reduced in offspring from dams fed on CD during lactation. *P<0.05, **P<0.01, ****P<0.0001. Two-way ANOVA (diet × sex) with post-hoc Tukey-test. N = 6 / group; 24 in total.

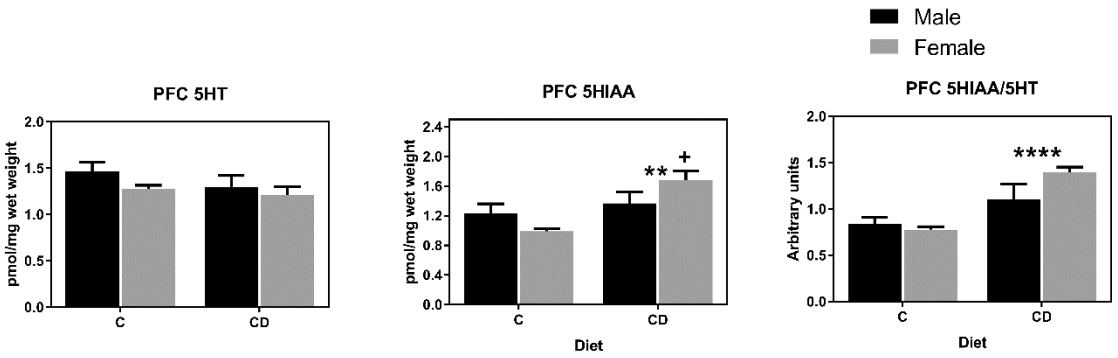

Fig. 4 Impact of lactational cafeteria diet (CD) on PFC serotonin (5-HT), 5-Hydroxyindoleacetic acid (5-HIAA) and 5-HIAA/5-HT ratio (turnover) in 24-26 day old weaner rats. Control dams were fed on show (C). 5-HIAA and turnover were both increased in offspring from dams fed on CD during lactation. **P<0.01, ****P<0.0001. Two-way ANOVA (diet × sex) with post-hoc Tukey-test. + P < 0.05 N = 6 / group; 24 in total.

Table 1

Average daily energy and macronutrient intake in lactating dams

Diet	Energy intake (kJ/d)		Carbohydrate Sucrose (g/d)		Fat (g/d)		Protein (g/d)	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Chow	755.9	34.92	25.75 2.02	1.14 0.09	3.60	0.16	10.8	0.48
Cafeteria	950.1***	35.38	20.13*** 5.96 ****	0.94 0.23	12.33****	0.44	7.95****	0.27

Data represent mean values from 12 dams/group as collected over 21 days of lactation. Student's t-test. ***P < 0.0001. ****P < 0.00001 vs. chow fed controls.

Table 2 Exploration time of the two identical objects during familiarisation

Intertrial interval (min)	Diet	Exploration time (s) during familiarisation Male offspring		Exploration time (s) during familiarisation Female offspring	
		Mean	SEM	Mean	SEM
5	C	88.8	12.5	97.5	9.9
	CD	93.6	8.9	115.7	13.3
30	C	86.8	16.4	125.9	29.9
	CD	101.3	16.7	99.2	9.5
60	C	79.6	13.6	71.8	4.4
	CD	81.9	10.9	75.1	9.6

Familiarisation data for each of the three experimental situations have been analysed separately. No significant effects of sex and diet have been observed.

Two-Way ANOVA (diet, sex). N=4-5 / group; 62 in total.