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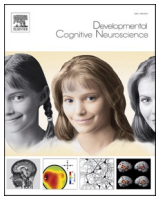

Maternal dietary patterns are associated with susceptibility to a depressive-like phenotype in rat offspring

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ABSTRACT

Environmental factors such as maternal diet, determine the pathologies that appear early in life and can persist in adulthood. Maternally modified diets provided through pregnancy and lactation increase the predisposition of offspring to the development of many diseases, including obesity, diabetes, and neurodevelopmental and mental disorders such as depression. Fetal and early postnatal development are sensitive periods in the offspring's life in which maternal nutrition influences epigenetic modifications, which results in changes in gene expression and affects molecular phenotype. This study aimed to evaluate the impact of maternal modified types of diet, including a high-fat diet (HFD), high-carbohydrate diet (HCD) and mixed diet (MD) during pregnancy and lactation on phenotypic changes in rat offspring with respect to anhedonia, depressive- and anxiety-like behavior, memory impairment, and gene expression profile in the frontal cortex. Behavioral results indicate that maternal HFD provokes depressive-like behavior and molecular findings showed that HFD leads to persistent transcriptomics alterations. Moreover, a HFD significantly influences the expression of neuronal markers specific to excitatory and inhibitory cortical neurons. Collectively, these experiments highlight the complexity of the impact of maternal modified diet during fetal programming. Undoubtedly, maternal HFD affects brain development and our findings suggest that nutrition exerts significant changes in brain function that may be associated with depression.

1. Introduction

The developmental origins of health and disease (DOHaD) theory postulates that exposure to environmental influences during critical periods of development and growth may have significant consequences on the offspring's health (Barker et al., 1993; Barker, 2007). The disturbances not only occur in children at an early stage of development but can remain latent for many years and manifest themselves in adulthood (Chavatte-Palmer et al., 2016; Parlee and MacDougald, 2014). One of the main long-lasting factors affecting offspring health is maternal lifestyle before conception. In particular, maternal nutrition and dietary behavior during pregnancy and lactation periods are important (Günther et al., 2019; Panchenko et al., 2019; Souto et al., 2020).

The growing occurrence of overweight and obesity is a worldwide health problem appearing in both sexes at every age (Mendes-da-Silva et al., 2014). The epidemic of obesity and metabolic diseases is related to eating habits based on meals high in calories and a high intake of fat and sugar (Kopp, 2019; Medina-Remón et al., 2018). In fact, overweight is a preexisting condition in 40 % of women who become pregnant (Bocarsly et al., 2012). Equally important, overweight pregnant women chose more unhealthy products of low quality compared to women with a normal body mass index (BMI) (Bocarsly et al., 2012; Laraia et al., 2007; Shin et al., 2016), and their unfavorable eating habits persist after childbirth (Moran et al., 2013).

Epidemiological and experimental data from recent years indicate that, through pregnancy and lactation, maternal modified diets (e.g.,

Abbreviations: ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; DOHaD, developmental origins of health and disease; EXT, excitatory neurons; EZM, elevated zero maze; FST, forced swimming test; GABA, gamma-aminobutyric acid; HCD, high-carbohydrate diet; HFD, high-fat diet; MAPK, mitogen-activated protein kinases; mPFCx, medial prefrontal cortex; MD, mixed diet; NGS, Next Generation Sequencing; NOR, novel object recognition; PND, postnatal day; PV, parvalbumin; SD, standard diet; SST, somatostatin; VIP, vasoactive intestinal polypeptide.

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high-caloric, rich in fat, sugar, or protein) increase offspring's predisposition to the development of diseases such as obesity, metabolic syndrome, and diabetes. Moreover, the lack of a properly balanced diet and obesity during pregnancy and lactation can lead to morphological, molecular, and functional changes in the offspring's brain, predisposing the offspring to the occurrence of behavioral disorders and mental diseases (de la Garza et al., 2019; Faa et al., 2014; Gawlińska et al., 2020; Gawliński et al., 2020a, 2020b; Sullivan et al., 2015). For example, maternal overnutrition and consumption of a diet rich in fat are associated with an increased risk of mental and neurodevelopmental disorders including depression (Gawlińska et al., 2019), attention-deficit hyperactivity disorder (ADHD) (Buss et al., 2012; Chen et al., 2014; Rodriguez et al., 2008), autism spectrum disorder (ASD) (Getz et al., 2016; Krakowiak et al., 2012; Reynolds et al., 2014) and schizophrenia in adulthood (Jones et al., 1998; Schaefer et al., 2000).

The frontal cortex is a brain region considered to be a significant center of cognitive function and behavior regulation and this area is associated with the pathogenesis of several mental disorders (e.g., depression) (Liu et al., 2017; Millan et al., 2016). Fetal and early postnatal development are sensitive periods in offspring life to maternal nutrition, which influences the epigenetic profile, resulting in changes in gene expression and affects the molecular phenotype (Li, 2018). Animal studies provide evidence that maternal nutrition, metabolic conditions, and stress are important in the development of the neural circuitry that regulates behavior, resulting in a persistent impact on the offspring's behavior (Kowalczyk et al., 2019; Song et al., 2017; Souto et al., 2020; Thompson et al., 2017). However, how modified maternal nutrition could influence brain development and function remains unknown.

In light of the above information, the main goal of this study was to evaluate the impact of maternal modified types of diet, including high-fat diet (HFD), high-carbohydrate diet (HCD, rich in sucrose) and mixed diet (MD, rich in carbohydrate and fat) during pregnancy and lactation on phenotypic changes in offspring with reference to anhedonia, depressive- and anxiety-like behavior and memory impairment. According to the assumption that obesity is associated with an increase in the consumption of unhealthy meals rich in carbohydrates and fats, these diets were selected in this study based on modern eating habits.

To investigate the effects that maternal diets exert on brain function, we analyzed offspring frontal cortex transcriptomes. Overall, we aimed to investigate the complex relationship between maternal diet and offspring mental health. To this aim, we investigated the influence of modified macronutrient supply during prenatal and preweaning periods on depressive-like behavior and frontal cortex gene expression in rats.

2. Methods and materials

2.1. Animals and diets

All experiments were performed in accordance with the EU Directive 2010/63/EU with the approval of the Ethical Committee at the Maj Institute of Pharmacology Polish Academy of Sciences.

Wistar rats from Charles River (Germany) were housed in standard cages in an animal colony room maintained at 22 ± 2 °C and 55 ± 10 % humidity under a 12 h light-dark cycle (lights on at 6.00 a.m.). Animals had free access to water and food. Virgin female rats (200–240 g), after the acclimatization period and during the proestrus phase (smears from females were assessed to determine the estrous cycle phase), were mated with males. The pregnancy was confirmed by examining vaginal smears for the presence of sperm. Then, pregnant females were individually housed and randomly assigned to four groups: standard diet – (SD; 65 % carbohydrate, 13 % fat, 22 % protein, 3.4 kcal/g; VRF1; Special Diets Services, UK) or modified diets purchased from Altromin (Germany): high-fat – (HFD; 24 % carbohydrate, 60 % fat, 16 % protein, 5.31 kcal/g; C1057 mod.), high-carbohydrate – (HCD; 70 % carbohydrate: rich in sucrose – 40 %, 12 % fat, 18 % protein, 3.77 kcal/g; C1010) or mixed - (MD; 56 % carbohydrate, 28 % fat, 16 % protein, 3.90 kcal/g; C1011). Dams were fed these diets *ad libitum* during pregnancy (21 days) and lactation (21 days). The modified maternal diets used in this study did not affect the litter size or birth weight of offspring (Gawliński et al., 2020a). Litter sizes were normalized to 9–12 pups with a sex ratio as close to 1:1 as possible.

After weaning, offspring at postnatal day (PND) 22 were separated according to sex, housed 5 per cage, and switched to SD. Male and female offspring were used in this study. Ten animals per group were used in each behavioral test (subset I-III) and NGS analyses (subset IV). For each set of experiments, to reduce "litter effects" (Festing, 2006) animals for each group were selected from 3 to 4 different dams. The scheme of the performed experiments is illustrated in Fig. 1.

2.2. Behavioral tests

2.2.1. Locomotor activity

As described previously by Frankowska et al. (Frankowska et al., 2007) spontaneous locomotor activity was performed and recorded for the individual animals from subsets I and III twice at PNDs 28 and 63 in OptoVarimex cages (Columbus Instruments, USA) linked online to an IBM-compatible PC. Locomotor activity was defined as horizontal activity and presented as the distance traveled in centimeters during 5- and 30-min trials.

2.2.2. Elevated zero maze

Anxiety-like behavior was assessed in the zero-maze test consisting of a black annular platform (105 cm in diameter, 10 cm wide) elevated to 65 cm above the ground level, divided equally into four quadrants: two opposing 'open' quadrants without walls (1 cm lip) and two opposing 'closed' quadrants (27 cm high). The apparatus was illuminated by dim white light (30−50 lux). Twice at PNDs 30 and 65 rats from subset I were placed on a closed quadrant of the maze, and a 5-min test was recorded. Behavioral measures comprised the time spent in the open areas, the frequency of head dips over the edge of the platform when the animal was located in either the open or the end of the closed quadrants, and the frequency of stretch-attend postures from closed to open quadrants (Frankowska et al., 2007).

2.2.3. Forced swimming test

As described previously by Frankowska et al. (Frankowska et al., 2007) twice at PNDs 33 and 68, rats from subset I were individually placed in a cylinder (50 cm × 23 cm) with water to a depth of 30 cm (25 ± 1 °C) for a 15-min pretest. Then, rats were removed from the water and dried using towels. Next, rats returned to their home cages. The cylinders were emptied and cleaned between tests. Twenty-four hours after the pretest, the rats were retested under the same conditions for 5 min, and the immobility, swimming, and climbing were measured and recorded by a digital camera and then analyzed.

2.2.4. Sucrose preference test

The sucrose preference test assesses the reluctance to drink sweetened water – anhedonia. To conduct a two-bottle sucrose preference test, separate cohorts (subset II) of rats twice at PNDs 27 and 62 were individually placed in cages with free access to food and water. The position of the bottle with water was changed from the left to the right side to induce seeking behaviors in the animals. After 4 days, the animals were given access to two bottles of water, and intake was monitored for 2 days. Next, the animals were given access to two preweighed bottles (one with tap water and the second with a 1% sucrose solution) for 48 h. The bottles were weighed again after 24 h, and then the position was switched. After 48 h, the sucrose solution was replaced with water, and water consumption was measured. Sucrose and water consumption were calculated as milliliters of sucrose solution (or water) consumed per kilogram of animal body weight per day (ml/kg/day). Sucrose preference was calculated according to the formula:

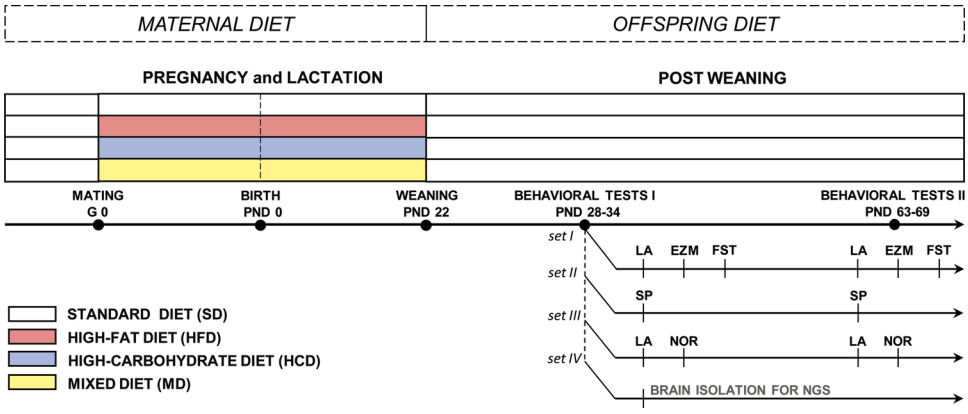

Fig. 1. Experimental design and timeline. Dams were fed a standard diet (SD) or one of the three modified diets: high-fat (HFD), high-carbohydrate (HCD) or mixed diet (MD, rich in carbohydrate and fat) during pregnancy and lactation (from gestational day (G) 0 to postnatal day (PND) 21). Adolescent and young adult male and female offspring (sets I-III) were assessed for behavioral tests. Moreover, at PND 28 the frontal cortex was isolated for gene expression profiling. *EZM – elevated zero maze test; FST – forced swimming test; LA – locomotor activity; NGS – next generation sequencing; NOR – novel object recognition test; SP – sucrose preference test.*

% Preference = [(sucrose intake/total intake: sucrose + water) × 100].

2.2.5. Novel object recognition

On the day of the experiment, individual rats from separate cohorts (subset III), twice at PNDs 30 and 64 were placed in an empty plastic box (57 cm × 35 cm × 30 cm) to explore the open-field area for 10 min (*habituation phase*). On the next day, novel objects were placed in two opposite corners with the center of the object 12 cm apart from the corner. First, a rat was placed in the middle of the arena and presented with two identical objects, A_1 and A_2, for 5 min [A + A] (*familiarization phase)*. After a 1-h interval in the home cage, the rats were again placed in the same plastic box as earlier and presented with two objects, the old familiar A_1, and a new object B for 5 min [A + B] (*recognition phase I*). After 24 h, rats were placed in the box and presented two objects, familiar A_1 and novel object C [A + C] (*recognition phase II*). Object exploration was defined as the rat sniffing or touching the object with its nose and/or forepaws. The measured parameters were calculated as the recognition index (RI) and the differences in exploration time (T) between familiar (F) and novel (N) objects: [$RI = T_N/(T_N+T_F)$]. The following objects were used during the adolescent period: a black metal can (A_I), white glass cone (B_I), and orange glass cone (C_I); in adulthood, the following objects were used: orange metal can (A_{II}), violet glass/plastic cone (B_{II}) and yellow plastic cube (C_{II}). The objects were cleaned with 10 % ethanol before being placed with each rat in each session.

2.2.6. Statistical analysis

Statistical analysis of behavioral test results was performed with R software v3.4. All data are expressed as the mean ± SEM. The analysis was performed with a three-way repeated measures analysis of variance (ANOVA, diet × sex × age). In post hoc analysis each group was compared to the SD group. Pairwise t-tests with Bonferroni correction for multiple comparisons were performed for both sexes (overall diet effect) and for each sex separately (sex-specific diet effect). Adjusted $p < 0.05$ was considered statistically significant. For clarity and due to the diet-focused nature of the manuscript mainly the diet effects from three-way ANOVA and post hoc comparisons with the SD group are reported in the main text and figures. The full results of the behavioral data statistical analysis are reported in the Supplemental Table S1.

2.3. Molecular analysis

2.3.1. Tissue collection and RNA sequencing

The separate cohorts (subset IV) of experiment-naïve male and female offspring were sacrificed through decapitation at PND 28. The frontal cortex was dissected according to The Rat Brain Atlas (Paxinos and Watson, 1998) and immediately frozen on dry ice and stored at -80 °C until RNA isolation. RNA was isolated following the manufacturer's protocol and further purified using the RNA Mini Kit (A&A Biotechnology, Poland). The total RNA concentration was measured using an ND-1000 Spectrometer (NanoDrop Technologies Inc., USA). The quality of RNA was determined by using an RNA 6000 Nano LabChip Kit and an Agilent Bioanalyzer 2100 (Agilent, USA). Based on the RNA integrity number (RIN > 7.5) values, samples from 10 animals from each group were chosen for RNA sequencing (80 samples total). RNA sequencing was performed as an external service by Novogene (Hong Kong). A total amount of 1 μg of RNA per sample was used as input material for the RNA sample preparations. mRNA from eukaryotic organisms was enriched using oligo(dT) beads. Subsequently, sequencing libraries were generated using the NEBNext Ultra II Directional RNA Library Prep Kit for Illumina (NEB, USA) following the manufacturer's recommendations. Complete cDNA libraries of 250–300 bp in length acquired from samples were subjected to sequencing on an Illumina system (PE150, 20 M reads per sample). The raw reads were submitted to Sequence Read Archive (SRA) under the PRJNA669556 BioProject.

2.3.2. Bioinformatic analysis

All samples were checked for quality with fastQC v0.11.8 and aligned to a rat reference genome (rn6 from Ensembl database) with hisat2 2.1.0. The Cufflinks v2.2.1 package and GTF from the Ensembl gene database were used to quantify (cuffquant) and normalize (cuffnorm) transcripts to FPKMs (fragments per kilobase of transcript per million fragments mapped). All statistical analyses were performed with R software v3.4. The statistical significance of differential gene expression was tested using two-way ANOVA (diet × sex) on log2(1 + FPKM) values with false discovery rate (FDR) adjustment. For post hoc analysis, on genes that passed the 5%. FDR threshold, pairwise t-tests with Bonferroni correction for the number of performed tests per gene were conducted (each dietary group was compared to SD – three t-tests per gene). Adjusted p values and FDR values < 0.05 were considered statistically significant. To select the top genes custom filtering was applied as follows: p value of diet effect from ANOVA < 0.01, standard deviation to mean ratio of log2(FPKM + 1) in each group < 0.1, minimum 10 samples with log2(FPKM + 1) > 7.

To investigate functional changes induced by different diets, the top selected genes were checked against the Gene Ontology and KEGG pathway databases (Accessed via Chen et al., 2013 terms: GO Biological Process 2018 and KEGG 2019 Human). Two lists of genes were separately submitted: The 'UP' gene list consisted of genes that were upregulated by maternal HFD and the 'DOWN' gene list consisted of genes that were downregulated by maternal HFD. For analysis of affected cell types, the top 500 markers of each cortical neuronal subtype were investigated (excitatory, somatostatin (SST), parvalbumin (PV) and vasoactive intestine polypeptide (VIP) neurons) (http://research-pub.gene.com/NeuronSubtypeTranscriptomes/#). Each set of markers was filtered to FDR diet < 5%. and for post hoc vs standard diet significance

$p < 0.05$. Markers that fulfilled the condition of p.diet and post hoc significance were also tested for the direction of regulation by each diet. The results of all analyses are available in Supplemental Table S2. All of the code used in the projects is available in the projects github repository (https://github.com/ippas/ifpan-kinga-dieta).

3. Results

3.1. Influence of maternal diet on locomotor activity in offspring

First, we assessed spontaneous locomotor activity in male and female offspring at PNDs 28 and 63. The activity, recorded for 5 and 30 min, did not differ between any of the diet groups (Supplemental Table S3).

3.2. Influence of maternal diet on the anxiety-related phenotype of adolescent and adult offspring

To evaluate the anxiety-related phenotype, an elevated zero maze test was performed (Fig. 2). Three-way ANOVA showed a significant effect of maternal diet on the time spent in open quadrants ($F_{(3,143)} = 13.351$, $p < 0.001$), the number of entries into open areas ($F_{(3,143)} = 14.531$, $p < 0.001$), head dips ($F_{(3,143)} = 5.456$, $p < 0.01$) and stretch-attend postures ($F_{(3,143)} = 10.153$, $p < 0.001$) in offspring. In adolescence and adulthood, post hoc analysis showed that maternal HFD increased the number of entries into open areas ($p < 0.05$ and $p < 0.01$, respectively) in offspring from HFD group. At PND 65, female offspring exposed to maternal HFD were characterized by an increased time spent in open quadrants ($p < 0.01$) and the number of entries into open area ($p < 0.001$), and decreased the number of stretch-attend postures ($p < 0.05$) compared to female control rats (Fig. 2B).

3.3. Influence of maternal diet on offspring memory

In the novel object recognition test analysis performed in adolescent and young adult rats showed an effect of maternal diet on the recognition index evaluated in the first hour after familiarization ($F_{(3,143)} = 8.396$, $p < 0.001$) and after 24 h ($F_{(3,143)} = 3.040$, $p < 0.05$) (Fig. 3). Maternal HFD decreased the recognition index in adolescent ($p < 0.05$) and young adult ($p < 0.001$) females assessed 1 h after the familiarization phase, while in recognition phase II, we observed significant increased in time exploring the new object ($p < 0.01$) in young adult offspring exposed to maternal HCD (Fig. 3B).

3.4. Influence of maternal diet on the depression-related phenotype of adolescent and adult offspring

The effects of modified maternal diets on depressive-like behavior in the male and female offspring evaluated in the FST at PNDs 34 and 69 are shown in Fig. 4. In offspring three-way ANOVA indicated a significant effect of diet on time of immobility ($F_{(3,143)} = 8.369$, $p < 0.001$), swimming ($F_{(3,143)} = 13.675$, $p < 0.001$) and climbing ($F_{(3,143)} = 12.994$, $p < 0.001$). Adolescent offspring from the HFD group showed significantly increased time of immobility ($p < 0.05$) and swimming ($p < 0.001$), and decreased time spent climbing ($p < 0.01$). In turn, maternal MD (also enriched in fat) increased the time of immobility ($p < 0.01$) and decreased swimming time ($p < 0.05$). Analyzing sex-specific effects between the examined groups, we showed that maternal HFD increased immobility time ($p < 0.05$) in adolescent females. Moreover, the maternal MD increased immobility ($p < 0.05$) and reduced swimming time ($p < 0.001$), while exposure to the maternal HCD decreased swimming time ($p < 0.01$) in females at PND 34. In adolescent males, we observed a reduced time of climbing ($p < 0.05$) and increased time of swimming ($p < 0.001$) in the HFD group (Fig. 4A).

In young adult animals post hoc analysis also showed the importance of the dietary effect and increased the immobility time ($p < 0.01$), as well as reduced time of swimming ($p < 0.001$) and climbing ($p < 0.05$) in offspring exposed to maternal HFD. Moreover, the maternal HCD and MD reduced swimming time ($p < 0.001$ and $p < 0.01$, respectively) in offspring at PND 69. Analysis of sex-specific effects showed that

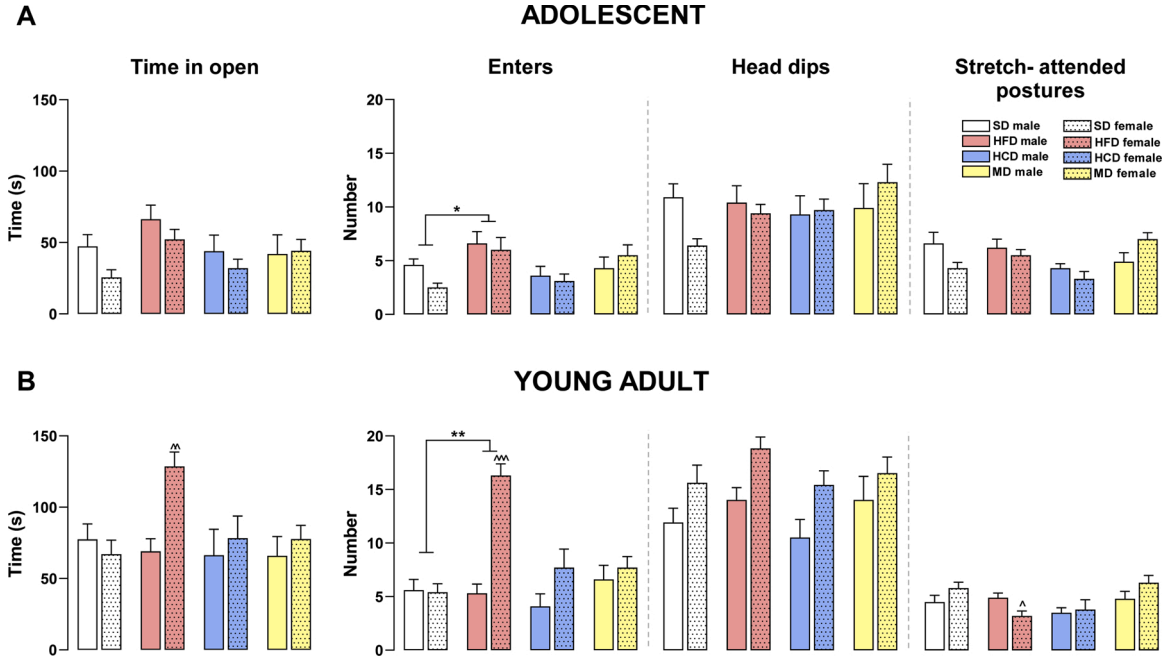

Fig. 2. Maternal high-fat diet (HFD) reduced anxiety-like behavior in offspring. The effects of maternal HFD, high-carbohydrate (HCD) and mixed diet (MD) during pregnancy and lactation on anxiety-like behavior were examined in the elevated zero maze (time spent in open areas and number of entries into open areas, number of head dips and stretch-attend postures) in male and female offspring (A – at postnatal day (PND) 30; B – at PND 65). N = 10 rats/group. Data were analyzed by three-way ANOVA, and post hoc analysis was performed with pairwise t-tests with Bonferroni correction for multiple comparisons. $*p < 0.05$, $**p < 0.01$ versus standard diet (SD); $\hat{}p < 0.05$, $\hat{}\hat{}p < 0.01$, $\hat{}\hat{}\hat{}p < 0.001$ versus controls of the same sex.

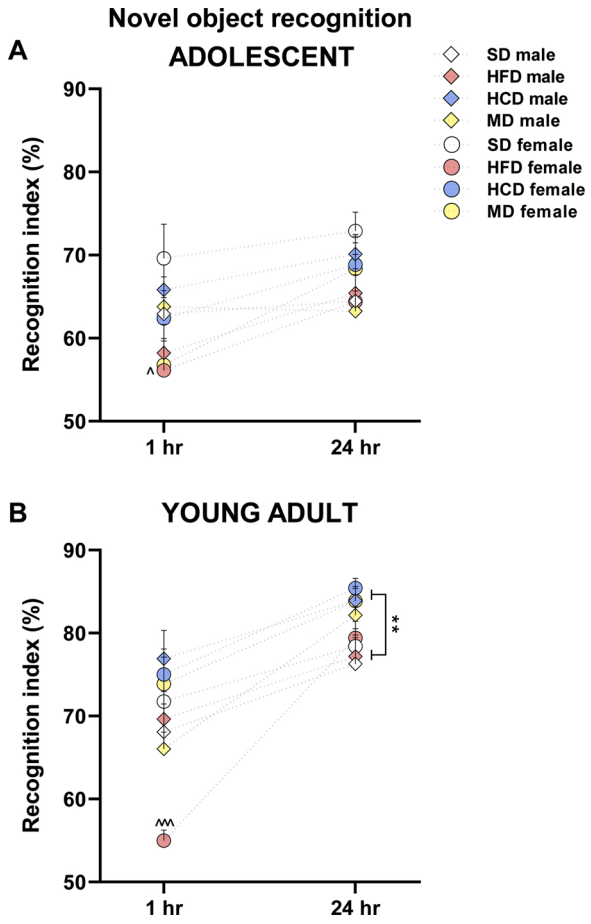

Fig. 3. Maternal high-fat diet (HFD) disturbed nonspatial memory in offspring. The effects of maternal HFD, high-carbohydrate (HCD) and mixed diet (MD) during pregnancy and lactation on recognition memory were examined in the novel object recognition test 1 h after the familiarization phase or 24 h after the familiarization phase in male and female offspring (A – at postnatal day (PND) 31; B – at PND 65). N = 10 rats/group. Data were analyzed by three-way ANOVA, and post hoc analysis was performed with pairwise t-tests with Bonferroni correction for multiple comparisons. $^{**}p < 0.01$ versus standard diet (SD); $^{\wedge}p < 0.05$, $^{\wedge\wedge}p < 0.001$ versus controls of the same sex.

maternal HFD evokes prolong immobility time ($p < 0.05$) in females and decreased time of swimming in males ($p < 0.01$) and females ($p < 0.001$). We also observed a reduced time of swimming in young adult males from HCD group ($p < 0.001$) and females from MD group ($p < 0.01$) (Fig. 4B).

Three-way ANOVA showed that exposure to modified maternal diets did not alter sucrose preference in offspring ($F_{(3,143)} = 2.659$, $p = 0.0506$); however, there was a significant interaction of diet × age ($F_{(3,143)} = 15.496$, $p < 0.001$). Post hoc analysis showed that the offspring exposed to HFD indicated decreased sucrose preference in adulthood ($p < 0.001$) (Fig. 5). Analysis of sex-specific effects showed that maternal HFD significantly decreased the preference for natural reward (sucrose) in young adult males ($p < 0.05$) and females ($p < 0.001$) (Fig. 5B). Maternal HCD and MD did not affect sucrose preference in offspring.

3.5. Effects of various maternal diets on gene expression in the cortices of offspring

Changes in gene expression in the brain caused by altered metabolism may affect distinct pathways. To conduct an unbiased analysis of gene expression in the frontal cortex of adolescent rats associated with maternal diet, we conducted next generation sequencing of mRNA (RNA-seq). Overall, the abundance of transcripts from 20,895 genes was estimated (Supplemental Table S2). Statistical analysis resulted in the selection of the 75 top differentially expressed genes affected by maternal diet (Fig. 6A). Post hoc analysis revealed that most of these transcripts were significantly affected by maternal HFD (HFD vs SD: 50/75 genes $p < 0.05$, post hoc *t*-test with Bonferroni correction) (adjusted FDR/p values for each gene are shown in Supplemental Table S2). The effects of maternal MD and HCD were drastically smaller (MD vs SD: 4/75 genes, HCD vs SD: 5/7 genes; $p < 0.05$, post hoc *t*-test with Bonferroni correction). Clustering of gene expression (based on Pearson distance) revealed two major clusters – genes upregulated in the HFD group (n = 30) and downregulated in the HFD group (n = 45) (Fig. 6A).

Detected clusters were further investigated to reveal their common pathways and targets. To this end GO and KEGG databases were used (for full results see Supplemental Table S2). For the genes upregulated in adolescent rats whose mothers were on HFD, 3 out of 6 of the top GO and KEGG terms included intracellular transport-related processes (cytoskeleton-dependent intracellular transport, synaptic vesicular transport and endocytosis). For the downregulated cluster, the top terms included basic cellular function aspects, such as cellular respiration and protein translation and degradation (Fig. 6B).

3.6. Influence of maternal diets on the expression of markers of cortical neuron types

An altered environment during the neurodevelopmental period may potentially affect the cellular composition of brain regions. To examine the changes in neuronal types present in the cortex of tested rats, an additional analysis of cell-type markers enriched in various neuronal subsets was conducted. We investigated 500 top-enriched genes from cortical excitatory neurons (EXT) and three canonical inhibitory cell types: PV, SST and VIP (Fig. 7 and Supplemental Table S2). Out of 500 markers, 39 EXT, 34 SST, 32 PV and 15 VIP marker genes were differentially expressed in our dataset (ANOVA *p* diet < 0.05), with the majority affected by maternal HFD. Overall, in rats of both sexes in the HFD group, there was a tendency for upregulation of markers related to the excitation of cortical circuits, namely, EXT and VIP. On the other hand, markers of cell types that inhibit EXT neurons (PV and SST) were typically downregulated, suggesting a possible change in the excitation-inhibition balance in rats from the HFD group (Fig. 7, see Supplemental Table S2 for details).

4. Discussion

Fetal exposure to maternal nutrition is associated with *in utero* programming and can result in later life metabolic outcomes and changes in different physiological, neurochemical developmental, and behavioral parameters in the offspring (Gimpfl et al., 2017). The main novelty of this study is the comprehensive assessment of offspring behavior combined with neuronal markers and a transcriptomic profile analysis approach in both male and female offspring exposed to different modified maternal types of nutrition during pregnancy and lactation. Through a series of behavioral tests carried out in adolescent and adulthood life, we evaluated a range of behaviors including anxiety- and depressive-like behavior, anhedonia, and memory impairment. In parallel, we conducted transcriptomic profiling within the frontal cortex with analysis of neuronal types. Overall, we have made a complex assessment of the offspring phenotype. Data from our study indicate that maternal HFD leads to the development of depressive-like behavior and that dietary manipulation leads to altered transcriptomes, including significantly influencing neuronal markers enriched in excitatory and inhibitory cortical neurons in offspring.

Recent preclinical evidence indicates that maternal HFD during pregnancy and lactation affects the behavioral programming of rat offspring, such as increasing depressive-like and aggressive-like behaviors (Gawlińska et al., 2019; Giriko et al., 2013). The results from the

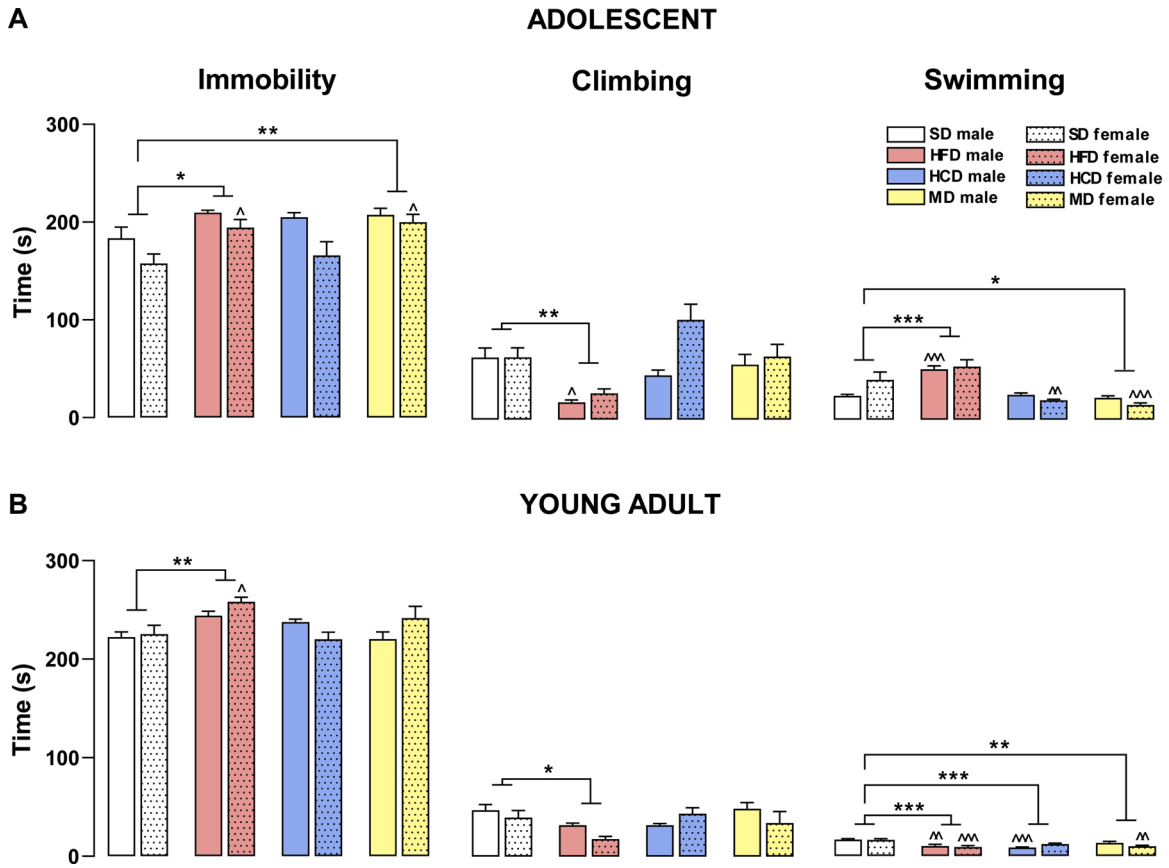

Fig. 4. Maternal high-fat (HFD) and mixed diet (MD) evoked depressive-like behavior in offspring. The effects of maternal HFD, high-carbohydrate diet (HCD) and MD during pregnancy and lactation on depressive-like behavior were examined in the forced swimming test in male and female offspring (A – at postnatal day (PND) 34; B – at PND 69). N = 10 rats/group. Data were analyzed by three-way ANOVA, post hoc analysis was performed with pairwise t-tests with Bonferroni correction for multiple comparisons. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ versus standard diet (SD); $\hat{}p < 0.05$, $\hat{}\hat{}p < 0.01$, $\hat{}\hat{}\hat{}p < 0.001$ versus controls of the same sex.

present study confirm the important role of maternal diet, particularly HFD, during gestation and lactation in offspring behavioral changes during a lifetime. First, we observed that both, adolescent and adult offspring exposed to a maternal HFD had significantly increased immobility time in the FST which suggests a depressive-like phenotype in those animals. Similar changes were noted at PND 34 in females whose mothers consumed a MD (rich in fat and sugars). Furthermore, despite the lack of exposure of the offspring to the HFD after the lactation period (change to SD after weaning), the adult offspring from HFD groups still maintained depressive-like behavior. These findings are consistent with our previous study (Gawlińska et al., 2019) as well as research in which depressive-like behavior was evaluated in male rats exposed to maternal HFD only during lactation (Giriko et al., 2013) or during pregnancy, lactation and 14 weeks post weaning (Can et al., 2012). At the same time, the studied diets did not induce changes in the spontaneous locomotor activity of the animals, which confirms the specificity of the results from the FST and other behavioral tests. Previous works in which a maternal diet high in fat was limited only to the last week of pregnancy and the lactation period also did not show any effects on the locomotor activity of the offspring (Giriko et al., 2013; Naef et al., 2008, 2011). Moreover, our research demonstrated the impact of maternal diets on anhedonia development, which is one of the widespread symptoms of depression, characterized by reduced ability or even an inability to feel pleasure (Cooper et al., 2018). In fact, our results of the sucrose preference test in adult – but not adolescent – rats showed that maternal HFD caused a significant reduction in the intake of a sweet solution, which indicates the development of anhedonia symptoms in these animals. Others observed similar behavioral changes in adult mice fed a HFD for 8 weeks, which indicates the role of direct and indirect HFD consumption on the development of depression symptoms (Hassan et al., 2018). Taken together, the results of the FST and the sucrose preference test indicate that an increase in depressive-like behavior develops in offspring with age after exposure to a maternal HFD. Clinical studies, due to their limitations, mainly indicate the role of maternal obesity in the increased risk of developing depression in offspring (Edlow, 2017; Marmorstein and Iacono, 2016).

Findings from our study also showed that HFD disrupts short-term memory functions but only in female offspring. We observed a decreased recognition index in the novel object paradigm, in adolescent females, and these changes persist to adulthood. Observations of other authors support the above results. It has been well documented that animals exposed to HFD show significant potentially pathological changes in the hippocampus, including reduced dendritic spines in CA1, which indicates disturbances in the process of learning and memory (Janthakhin et al., 2017; Underwood and Thompson, 2016). At the same time, it is worth noting that the increased (although statistically insignificant) recognition index in adult animals in 24 h test (compared to the results achieved by animals after 1 h) could result from the use of various items in recognition phase I and recognition phase II and the ease of their discriminated by rats (the object used for the test 24 h after the familiarization phase probably was more easily discriminated).

In the present study, we also demonstrated that maternal HFD limited to pregnancy and lactation reduces anxiety-like behavior in female – but not male – offspring as assessed in the EZM. Accordingly, a study conducted by Rincel et al. (2016) showed that maternal HFD has a protective effect on anxiety behavior resulting from stress separation from the mother. On the other hand, another study indicates that maternal HFD limited only to lactation does not affect anxiety-like

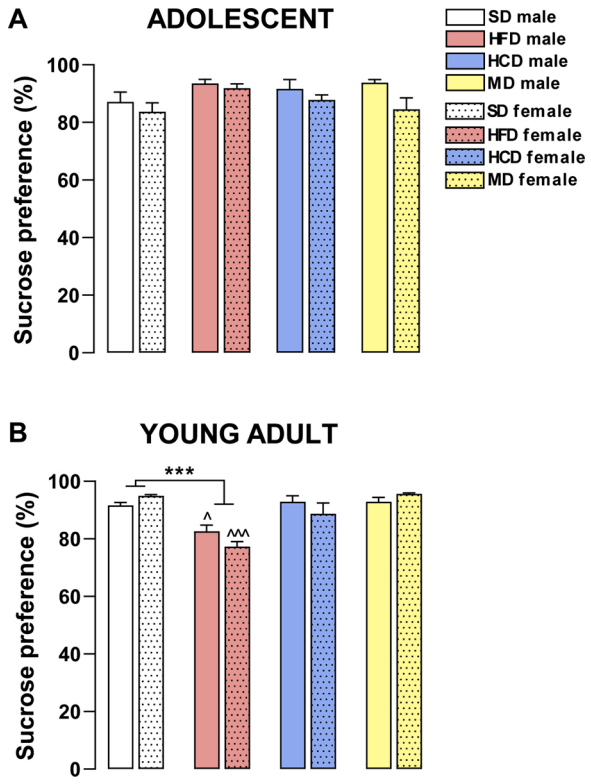

Fig. 5. Maternal high-fat diet (HFD) evoked anhedonia in offspring. The effects of maternal HFD, high-carbohydrate diet (HCD) and mixed diet (MD) during pregnancy and lactation on anhedonia were examined in the sucrose preference test in male and female offspring (A – at postnatal day (PND) 34; B – at PND 69). N = 10 rats/group. Data were analyzed by three-way ANOVA, and post hoc analysis was performed with pairwise t-tests with Bonferroni correction for multiple comparisons. ***$p <$ 0.001 versus standard diet (SD); ^$p <$ 0.05, ^^^$p <$ 0.001 versus controls of the same sex.

behaviors in the open field test in mice (Kang et al., 2014). Moreover, a study conducted by Winther et al. (2018) demonstrated increased anxiety-like behavior in adult rat offspring whose mothers consumed a diet rich in fats 8 weeks before pregnancy, which indicates that a high-fat maternal environment before conception, or permanent changes resulting from the mother's obesity, is important in the development of anxiety-like behavior.

Maternal nutritional compositions contribute to the establishment of epigenetic profiles *in utero*, which have a profound effect on individual susceptibility to certain diseases in offspring (Li, 2018). However, it is not well understood, how HFD may influence memory and the development of depressive and anxiety behavior in offspring. In our study, we demonstrated that dietary manipulation leads to an altered transcriptome in the frontal cortex of adolescent offspring. Among the assessed diets, the most influential factor changing transcript levels was the HFD.

Our data from frontal cortex RNA-seq showed increased expression of genes coding constituents of dopaminergic and glutamatergic synapses. Moreover, our results demonstrated upregulated expression of genes involved in the Wnt signaling pathway, axonogenesis, MAPK (mitogen-activated protein kinase) cascade, and vesicle-mediated transport in synapses. Disruption of gene expression involved in dopaminergic signaling contributes to many brain disorders, including depression, which has been confirmed by numerous clinical and preclinical studies (Belujon and Grace, 2017; Sanacora et al., 2012). Few studies focused on the issue between maternal HFD and dopaminergic neurotransmission highlight these relationships (Sullivan et al., 2015). In offspring, maternal exposure to a HFD, as well as a diet rich in carbohydrates, affects the dopaminergic system, changing, among others, the amount of dopamine and its metabolite (DOPAC) in the nucleus accumbens or altering the expression of dopamine D_1/D_2 receptors in the ventral tegmental area (Naef et al., 2008, 2011; Paradis et al., 2017; Sullivan et al., 2015). Furthermore, Wnt and its receptors are involved in signal transduction and play a key role in axis formation and neuronal development and are reported to play roles in the pathogenesis of stress-induced depression-like behaviors (Zhou et al., 2016). It is known that abnormal regulation of the Wnt signaling pathway is associated with a number of neurological disorders and is currently a target to mediate the antidepressant effect (Lee et al., 2019; Zhou et al., 2016). Interestingly, the MAPK and Wnt signaling pathways are together modulated by stress and have been previously implicated in major depressive disorder and treatment response in humans and animal models (Lopez et al., 2017).

The present data also showed that the maternal HFD significantly influenced genetic markers of excitatory and inhibitory (PV, VIP, and SST) cortical neurons of offspring. In our model, the vast majority of markers of excitatory neurons were significantly upregulated. In addition, markers of inhibitory GABAergic neurons were significantly downregulated. The exception is VIP-expressing interneurons whose markers were significantly upregulated by maternal HFD. One-third of all synapses in the central nervous system connect via GABAergic interneurons. Neurons expressing markers belong to the group of GABA interneurons, calcium-binding protein PV and SST, which constitute the majority of neocortical interneurons. Network dysfunction associated with altered brain levels of GABA has been identified in both animal and human studies on depression (Lener et al., 2017). Preclinical studies indicate that dysfunctions of the GABAergic system are associated with the pathophysiology of depression, and normalization of this system is associated with remission of depressive symptoms (Fogaça and Duman, 2019). An animal model based on maternal separation stress decreased the expression of $GABA_A$ receptors in the prefrontal cortex and evoked anxiety and depressive-like behaviors in adulthood rodents (Caldji et al., 2003; Fogaça and Duman, 2019). Findings suggest that depression and chronic stress are associated with an imbalance of excitation-inhibition, within the prefrontal cortex, generated by a deficit of inhibitory synaptic transmission onto principal glutamatergic signaling (Fogaça and Duman, 2019; Fuchs et al., 2017). Evidence from clinical studies indicated that GABA levels are reduced in patients with major depressive disorder in several cortical areas (Hasler et al., 2007). Moreover, SST-positive interneurons are implicated in depression due to the reduced expression of SST in the postmortem brain of patients (Guilloux et al., 2012) as well as in animal models of depression (Fogaça and Duman, 2019; Fuchs et al., 2017). Collectively, these studies highlight the complexity of dividing the GABAergic system into different interneuron subtypes to study the pathophysiology of depression.

To our knowledge, there is a lack of data in the literature regarding the effect of maternal HFD and neuronal markers in the frontal cortex in offspring. However, the current findings provide evidence of the involvement of maternal HFD in the proper morphological development of other brain regions. Thus, maternal HFD affects the medial prefrontal cortex (mPFCx; anteroposteriority from bregma: 3.72–2.52 mm) and leads to reduction spines in basal dendrites of pyramidal neurons of mPFCx layer II/III in adolescent animals (Rincel et al., 2018) or decreased spine density in the primary somatosensory cortex in offspring at PND 56 (Hatanaka et al., 2017). Therefore, it can be concluded that a diet rich in fat can also change the cortical structure, which is suggested by our results. We have demonstrated that a maternal HFD upregulates markers of excitatory neurons and downregulates inhibitory markers of PV and SST interneurons. There is still a lack of sufficient clinical data, but some observations also indicate a reduction in the level of PV and SST in the cortical brain regions in patients with major depressive disorder (a more robust decrease in SST expression in females) and in animal models of depression (chronic unpredictable stress) (Fogaça and Duman, 2019). Moreover, in the genetic model, mice lacking SST (SST-KO) were characterized by an anxiety/depressive-like

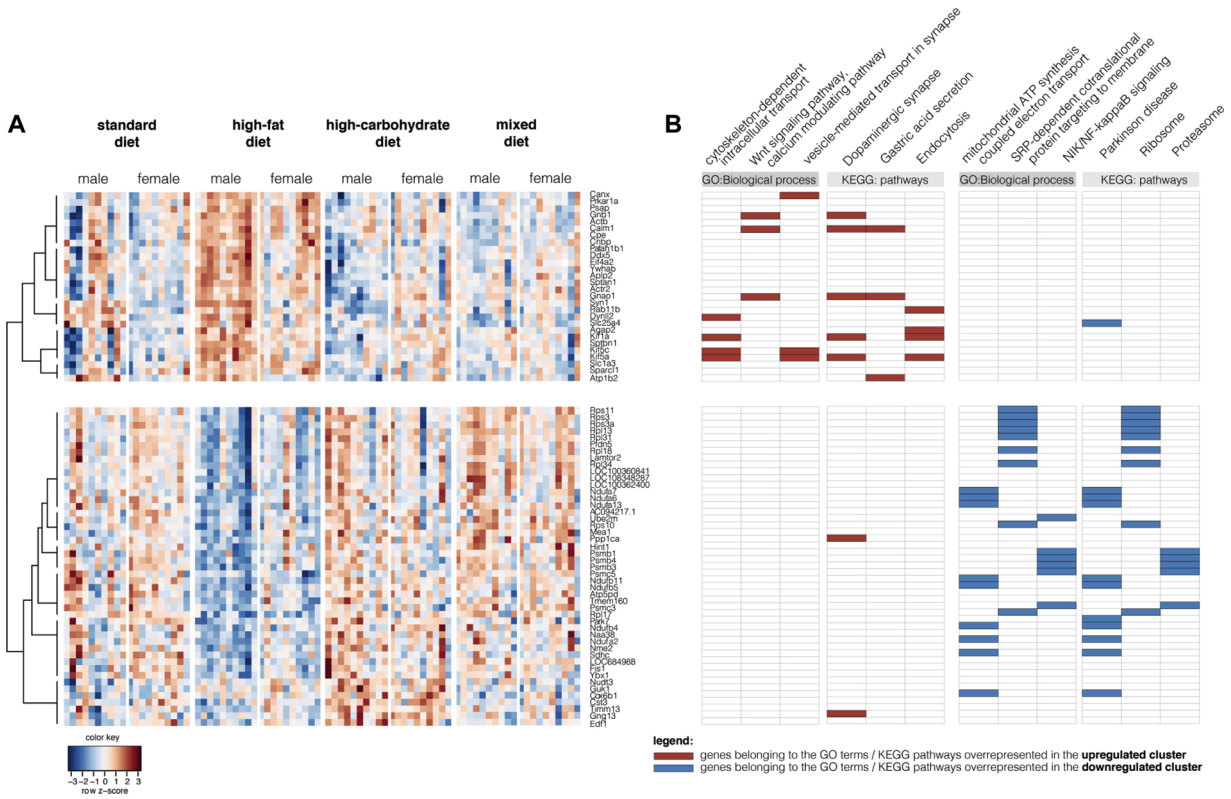

Fig. 6. Maternal diet influences gene expression in the frontal cortex of both male and female adolescent rats. (A) Heatmap of the gene expression of 75 selected DEGs. Clustering revealed two groups of genes: upregulated in the offspring of dams on a high-fat diet (HFD) and downregulated in the same group. (B) Lists of the top differentially expressed genes (DEGs) were investigated for overrepresented gene ontology (GO) and KEGG pathway terms. All results are presented in Supplemental Table S2. Here, the top unique (according to enrichment p-value) 3 terms for each database (GO, KEGG) and gene list (upregulated, downregulated) are shown. Genes that belong to GO/KEGG terms enriched in upregulated genes are marked with red rectangles (GO terms: GO:0030705, GO:0007223, GO:0099003). Genes that belong to GO/KEGG terms enriched in downregulated genes are marked with blue rectangles (GO terms: GO:0042775, GO:0006614, GO:0038061). If genes of the other cluster appear in a term they are also marked.

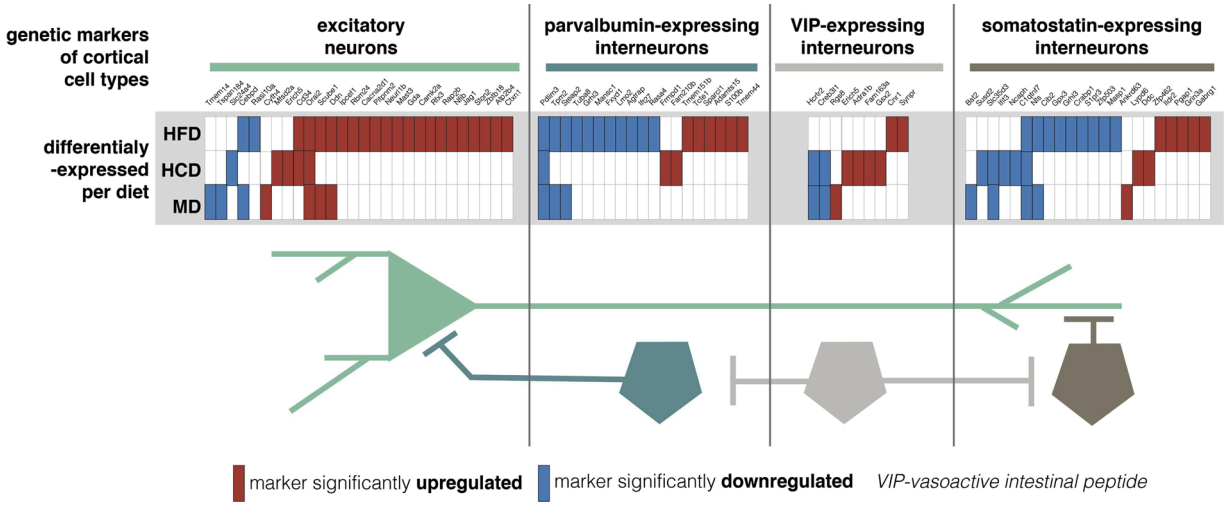

Fig. 7. Maternal diet influences neuronal markers specific to excitatory and inhibitory cortical neurons. Top-most part of the figure: For the panel of markers, lists of the top 500 genes significantly overexpressed in each cell type were filtered to contain only genes differentially expressed in our dataset (by diet). Three diets are shown (HFD – high-fat diet, HCD – high-carbohydrate diet, MD – mixed diet), and the direction of change in expression of each marker is in reference to the standard diet (up – red rectangle, down – blue rectangle, not significant – white rectangle). Schematic drawing shows the types of connections between the tested cell types in the cortex, with the soma of pyramidal excitatory neurons being inhibited by parvalbumin-expressing interneurons (PV), and the dendrites of excitatory cells being targeted by somatostatin-expressing interneurons (SST). Vasoactive intestinal polypeptide-expressing interneurons (VIPs) typically inhibit SST and PV cells (modified from: Fishell and Kepecs, 2020).

phenotype (Lin and Sibille, 2015).

Further studies should be conducted to precisely elucidate the mechanism of the maternal HFD effects on the frontal cortex gene expression changes and disturbance of behavior in offspring. Among the interesting areas through which maternal nutrition during pregnancy and lactation may affect the offspring's behavior could be brain inflammation which may contribute to long-term neurodegeneration and neuropathology (Hsu and Kanoski, 2014) as well as modulate brain areas through gut-brain interactions (Ahmadi et al., 2019; Buffington et al., 2016). Moreover, several potential limitations in the current literature and our own research affecting the interpretation of the results should be acknowledged. First, in current studies involving the effect of maternal diet on offspring, the scheme of the experiment mainly includes male offspring, which makes it difficult to compare results, though, our research also includes females, which is a novelty. Second, most of the studies focus on maternal HFD before pregnancy or maternal obesity. Third, there are many types of maternal HFD used by scientists, which differ in the amount and source of fat. Furthermore, lack of data from frontal cortex RNA-seq of adult offspring does not allow for complete elucidation of the molecular basis of behavioral disturbances affected by the modified maternal diet in adulthood. Therefore, further investigation in this field is needed. From a translational point of view, the mismatch between rodents and humans in terms of brain development should also be noted. Namely, exposure to external factors such as a modified diet during pregnancy in rats corresponds to the 1st and 2nd trimesters of a human pregnancy, and the early lactation period to the 3rd trimester (Clancy et al., 2007).

In conclusion, the present study consistently indicates that maternal HFD (compared to HCD and MD) is the most influential factor that promotes depressive-like behavior in offspring and significantly interferes with gene expression in the brain. Taken together, our study confirms the complexity and importance of fetal environmental programming by maternal nutrients and its lasting impact on offspring mental health.

Author contributions

M.F. conceived, designed, and coordinated the study and contributed to writing the manuscript. E.P. supervision and contributed to writing the manuscript. K.G. designed, and performed the study, analyzed the data, and wrote the manuscript. D.G. performed the study, analyzed the data, and contributed to writing the manuscript. M.B. and M.K. designed and analyzed NGS data, and contributed to writing the manuscript. M. Fr. performed the behavioral study. M.P. analyzed NGS data. All authors revised the manuscript and approved its final version.

Declaration of Competing Interest

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dcn.2020.100879.

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