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Synaptic proteome perturbations after maternal immune activation: Identification of embryonic and adult hippocampal changes

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ABSTRACT

Background: Maternal immune activation (MIA) triggers neurobiological changes in offspring, potentially reshaping the molecular synaptic landscape, with the hippocampus being particularly vulnerable. However, critical details regarding developmental timing of these changes and whether they differ between males and females remain unclear.

Methods: We induced MIA in *C57BL/6J* mice on gestational day nine using the viral mimetic poly(I:C) and performed mass spectrometry-based proteomic analyses on hippocampal synaptoneurosomes of embryonic (E18) and adult (20 ± 1 weeks) MIA offspring.

Results: In the embryonic synaptoneurosomes, MIA led to lipid, polysaccharide, and glycoprotein metabolism pathway disruptions. In the adult synaptic proteome, we observed a dynamic shift toward transmembrane trafficking, intracellular signalling cascades, including cell death and growth, and cytoskeletal organisation. In adults, many associated pathways overlapped between males and females. However, we found distinct sex-specific enrichment of dopaminergic and glutamatergic pathways. We identified 50 proteins altered by MIA in both embryonic and adult samples (28 with the same directionality), mainly involved in presynaptic structure and synaptic vesicle function. We probed human phenome-wide association study data in the cognitive and psychiatric domains, and 49 of the 50 genes encoding these proteins were significantly associated with the investigated phenotypes.

Conclusions: Our data emphasise the dynamic effects of viral-like MIA on developing and mature hippocampi and provide novel targets for study following prenatal immune challenges. The 22 proteins that changed directionality from the embryonic to adult hippocampus, suggestive of compensatory over-adaptions, are particularly attractive for future investigations.

1. Introduction

A viral infection during pregnancy is an established risk factor for neurodevelopmental psychiatric disorders (NPDs), including schizophrenia (SCZ), autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD), in the offspring (Estes and McAllister, 2015; Han et al., 2021; Meyer, 2019). Consistently, maternal infections during pregnancy lead to structural, developmental, and social deficits in offspring (Estes and McAllister, 2016; Hall et al., 2023; Meyer, 2019). Animal and cell models of maternal immune activation (MIA), mimicking infection during pregnancy, have been developed to elucidate the risk of NPD-relevant behavioural, functional, morphological,

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and molecular deficits in the offspring (Brown and Meyer, 2018; Estes and McAllister, 2016; Mueller et al., 2021).

Hippocampal dysfunction has been implicated in multiple behavioural aberrations observed in mental disorders, e.g. ASD and SCZ, including social and spatial memory deficits, novelty response and cognitive impairments (Banker et al., 2021; Gomez-Ocadiz et al., 2022; Ito et al., 2010; Lieberman et al., 2018). Neuroinflammation, especially during gestation, has deleterious effects on hippocampus (HPC) morphology, neurogenesis, and function (Couch et al., 2021; Dusedau et al., 2021; Guma et al., 2022; Kim et al., 2016), particularly at the synaptic level (Andoh et al., 2019; Chugh et al., 2013; de Bartolomeis et al., 2022). Such developmental disruptions play a central role in NPD susceptibility (de Bartolomeis et al., 2022; Estes and McAllister, 2016) as shown in both human (Guilmatre et al., 2009; Schork et al., 2019; Trubetskoy et al., 2022) and rodent (Andoh et al., 2019; Block et al., 2022; Cizeron et al., 2020; Coiro et al., 2015) studies. Substantial effects of MIA on the HPC have been found in transcriptomic studies in adolescent non-human primates, highlighting synaptic signalling and myelination changes (Page et al., 2021).

Transcriptional analyses in rodent whole embryos or embryonic brains following MIA have previously demonstrated alterations in expression profiles of RNA editing genes, interneuron migration, oxidative stress, neuronal development, neuroprotection, and neuroinflammatory processes, though these studies did not examine (Baines et al., 2020; Garbett et al., 2012; Oskvig et al., 2012) or identify (Tsivion-Visbord et al., 2020) sex differences. Importantly, late foetal cortical transcriptome analyses revealed sex-dependent, post-transcriptional aberrations after mid-gestational polyinosinic:polycytidylic acid [poly(I:C)]-evoked MIA (Kalish et al., 2021). Transcriptomic studies in adult male frontal cortex (Amodeo et al., 2019; Mueller et al., 2021; Richetto et al., 2017), nucleus accumbens (Richetto et al., 2017), and amygdala (Mueller et al., 2021; Weber-Stadlbauer et al., 2017) following MIA at different gestational time-points, highlighted neuronal signalling pathway alterations as a common denominator, in addition to changes in myelin and oxidative phosphorylation; among other more subtle region-specific effects. One study combining male and female adolescent mice found transcriptomic alteration in dorsal and ventral HPC and anterior cingulate cortex after early gestational MIA, disrupting signalling pathways involved in apoptosis, embryo- and synaptogenesis (Guma et al., 2021). Inflammatory chemokine receptor *Cx3cr1* knockout mice with poly(I:C)-induced MIA revealed sex-specific effects on HPC microglia, and adult HPC transcriptomics showed changes in mitochondrial metabolism, apoptosis, and reduced expression of gamma-aminobutyric acid (GABA) signalling genes in females (Carrier et al., 2024). Recent studies implementing single-cell RNA sequencing and chromatin accessibility assays largely focused on the role of microglia and other neuroimmune cells in MIA-linked outcomes, comparing the neuroglial profiles of newborn and adult brains, as well as embryonic cell cultures (Hayes et al., 2022; Matcovitch-Natan et al., 2016). Another study in male mice, concentrating on HPC glutamatergic neurons, provided *in vitro* and *ex vivo* evidence that embryonic HPC synaptogenesis plays a role in MIA-induced aberrations (Mirabella et al., 2021).

Importantly, sex-specific reports on gene expression and behavioural changes after MIA are increasing in number, in line with recent developments across preclinical studies (Shansky and Murphy, 2021). So far, available studies have examined either hypothesis-derived genes and pathways (Herrero et al., 2022; Lombardo et al., 2018; Nakamura et al., 2022; Purves-Tyson et al., 2021; Richetto et al., 2014; Zhang et al., 2020), or cell- or region-specific RNA transcripts, as described above. Importantly, RNA and protein levels often do not correlate fully (Floriou-Servou et al., 2018). The brain, specifically, exhibits many distinct protein expression profiles not detectable at the RNA level, including for neurotransmission-relevant vesicle transport genes (Jiang et al., 2020). To the best of our knowledge, MIA-evoked changes at the functional proteomic level have not been assessed at separate ages in a sex-specific manner in the hippocampus.

Recently, transcriptomic and proteomic studies in male and, increasingly, in female MIA offspring, have begun to elucidate the effects of MIA on the brain. However, data-driven investigations of how MIA affects the brain on the synaptic proteome level are still missing. To build upon previous findings and address some of the knowledge gaps, we investigated and compared the proteomic alterations in embryonic (E18) and adult (20 ± 1 weeks) hippocampal synaptoneurosomes of male and female mouse offspring after early poly(I:C)-induced MIA. Importantly, we aimed to determine early versus late synaptoneurosomal proteins that could provide targets for future studies or interventions after prenatal infection.

2. Materials and methods

2.1. Animals and Maternal Immune Activation (MIA)

2.1.1. Mice

All experiments were performed with wild-type *C57BL/6JRj* mice (Janvier Labs, or in-house bred F1 offspring). All experiments were conducted in accordance with national legislation (*TierSchG, TierSchVersV*) and the EU Council Directive *86/609/EEC* and were approved by the Regierungspräsidium Darmstadt (*AZ: FK/1101*).

2.1.2. Mating and MIA procedure

C57Bl/6JRj females aged 12 ± 2 weeks were mated overnight with males in a 2:1 female-to-male ratio, separated in the morning, and left undisturbed for a week. Observation of a viscous vaginal mucous on E7, together with maternal weight on E9 (Heyne et al., 2015) were indicative of pregnancy, eliminated false negatives and decreased false positives (Fig. S1A–D).

MIA was induced on E9 according to Meyer et al. (2005) by intravenous administration of poly(I:C) solution at 2.5 or 5 mg/kg (Sigma-Aldrich) or equivalent volumes (5 ml/kg) of phosphate-buffered saline (PBS) as a vehicle control. All offspring (n = 4–6 litters/group, 29 surviving litters over three cohorts) were used for behavioural or molecular analyses (Table 1). For more details see the Supplementary MIA Checklist according to reporting guidelines (Kentner et al., 2019), Supplementary Methods, Fig. 1.

2.2. Behavioural experiments

Offspring (n = 83, 40 males, 43 females; 5 ± 1 litters/treatment; see also Table 1, Supplementary Methods), were behaviourally phenotyped in order of increasing aversiveness, starting at 14 ± 1 weeks of age (Fig. 1A; Fig. S2). Locomotion, anxiety- and depressive-like behaviours, sensorimotor gating, sociability, and memory were assessed as adapted from previously published experimental designs (Candemir et al., 2023; Freudenberg et al., 2021; O'Leary et al., 2022). See Supplementary Methods for details.

2.3. Proteomics and bioinformatics

2.3.1. Tissue and synaptoneurosome preparation

Adult (20 ± 1 weeks) and embryonic (E18) HPC were extracted and stored liquid-free at –80 °C. Tail clippings were used to determine the embryonic sex by KAPA PCR assay (KAPA2G Fast HotStart Genotyping Mix, Roche) as described elsewhere (Clapcote and Roder, 2005). For synaptoneurosome preparation, a filtration method (Hollingsworth et al., 1985) was used, similar to previous descriptions (Chang et al., 2012); see Supplementary Methods for details. Four replicates each from the control and poly(I:C) groups were used for HPC proteomic analyses (embryos: 2 M, 2F/treatment pooled from 7 to 8 females and 8 males across 5 ± 1 litters [see Table 1]; adult samples: 2 M, 2F/treatment from different litters, replicates represent individual mice; see also Table 1, Supplementary Methods).

Table 1
Mouse numbers according to experimental design, sex, and dosage of poly(I:C) challenge on embryonic day E9 (*Ctrl*: control, PBS injected, *Low*: 2.5 mg/kg poly(I:C), *High*: 5 mg/kg poly(I:C), intravenous injection). Females (*F*) in the pregnancies category correspond to injected dams and males (*M*) to respective sires. Additional information can be found in the Supplementary MIA Reporting Guidelines Checklist.

Experimental Cohorts	MIA PROCEDURE				MIA OFFSPRING					
	Number of mated mice		Number of pregnancies		Number of litters *(average size ± SEM)*[2]			Number of tested mice *(F / M)*[2]		
	F	M	F	M	Ctrl	Low	High	Ctrl	Low	High
Adult behaviour & proteomics	64	22	44	18	5 *(7.4 ± 0.2)*	6 *(6.2 ± 0.5)*	4 *(3.4 ± 0.8)*	35 *(17/18)*	33[1] *(18/15)*	15 *(8/7)*
Embryonal proteomics	28	10	22	9	6 *(5.7 ± 1.4)*	4 *(8.5 ± 0.6)*	4 *(7.5 ± 0.3)*	30 *(14/16)*	32 *(16/16)*	30 *(14/16)*
TOTAL	124		93		29			175		

[1] Low concentration mice used only for phenotyping, the rest of adults for both behaviour and proteomics.
[2] See Data Availability for full details on litter sizes and sex.

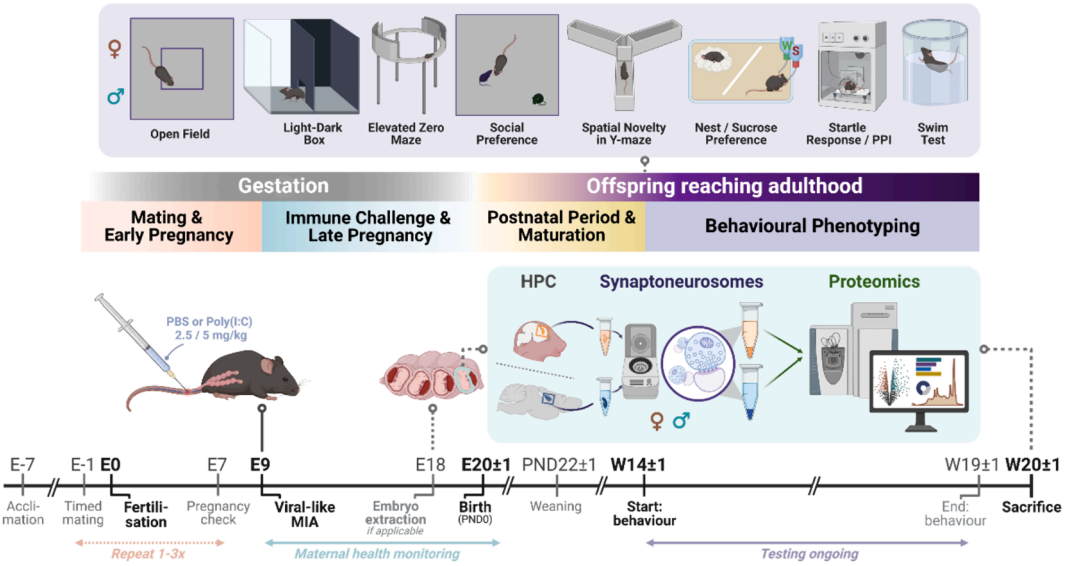

Fig. 1. Timeline and summary of experimental design. Maternal immune activation (MIA) was induced by an intravenous administration of 2.5 or 5 mg/kg poly(I:C) in *C57BL/6JRj* mice on embryonic day E9. An equivalent vehicle injection of 5 ml/kg phosphate-buffered saline (PBS) was used for controls. Male and female offspring (50 ± 4.5 % for each group) were either extracted before birth (E18, n = 92) for proteomic analysis in hippocampal (HPC) synaptoneurosomes (n = 4/treatment, pooled) or allowed to reach adulthood. The adult offspring (n = 83) was behaviourally tested for psychiatrically relevant endophenotypes (see also Fig. S2). After a recovery period following the end of testing, mouse brains were collected and synaptoneurosomal proteomics were performed in the HPC (n = 4/treatment). For more information on experimental procedure and animal numbers, see Table 1, Fig. S1-2, Supplementary Methods, and Supplementary MIA Checklist.

2.3.2. Protein digestion and mass spectrometry analysis

Mass spectrometry analysis was performed at the Biocenter Finland-supported Turku Proteomics Facility, University of Turku and Åbo Akademi University. Briefly, 25 or 50 µg of protein from embryos and adults, respectively, were digested and subjected to filter-aided sample preparation, FASP (Wisniewski et al., 2009). Samples were analysed via liquid chromatography with tandem mass spectrometry (LC-MS/MS, details in Supplementary Methods).

2.3.3. Protein Identification, differential abundance, and clustering analyses

Direct data-independent acquisition (DIA) approach was used to identify proteins and label-free abundance quantifications were performed with the MaxLFQ algorithm, using Spectronaut (v18.0.2, Biognosys) software (see Supplementary Methods for more). The candidate protein lists were cleaned by removing histones and keratins considered impurities (n = 24/4,744 in adult, 29/7,723 in embryonic list). The biologically relevant thresholds were set to 20 % absolute difference (fold-change, FC<0.8, FC>1.2) and multiple testing-corrected significance value of $q < 0.1$. The heat map and hierarchical clustering of the differentially MIA-regulated proteins common to the adult and embryonic datasets were generated using the *pheatmap* R package, where colour scale represents *log2*(FC).

2.3.4. Enrichment and network analyses

Significant proteins were compared between groups using InteractiVenn (Heberle et al., 2015). Functional enrichment was assessed using WebGestalt (v2019; *https://www.webgestalt.org/*) in organism *Mus musculus* (Liao et al., 2019). Enrichment of the full detected protein datasets in the protein-coding genome and immunoblotting of pre- and postsynaptic markers (see Supplementary Methods for details) confirmed the validity of the synaptoneurosome preparation (Table S6, Fig. S4). SynGO (v1.2; *https://www.syngoportal.org/*) was utilised to assess MIA-induced changes in synaptic proteins (Koopmans et al., 2019). Protein network analysis was performed with STRING (v12.0; *https://string-db.org/*) and functional network enrichment was assessed using the cleaned embryonic and adult background protein list as reference (Szklarczyk et al., 2023). More details provided in Supplementary Methods.

2.3.5. Phenome-wide association study (PheWAS) analysis

PheWAS was performed for all genes corresponding to proteins

common to the adult and embryonic datasets (n = 50), using the genome-wide association study (GWAS) ATLAS (v20191115; *https://atlas.ctglab.nl*) database (Watanabe et al., 2019). Associations of the genes and a total of 399 GWAS-acquired traits across two relevant domains (Psychiatric, n = 321; Cognitive, n = 78; full list in Table S1) were probed and significant correlations were identified ($p < 0.05$).

2.4. Statistical analyses

Behavioural data were analysed with PRISM (v9.5.1, GraphPad) using two-way ANOVA (variables: sex, treatment, and their interaction) with repeated measures where appropriate, followed by Tukey's *post-hoc* tests when significant. Additionally, data within each sex were assessed for normality and homogeneity of variances and appropriate tests (Kruskal-Wallis or Brown-Forsythe/Welch's ANOVA and the respective Dunn's and Dunnett's post-hoc tests; see Data Availability). Three-way repeated-measure ANOVA for startle-related tests was performed with Jamovi (v2.2, open-source, Greenhouse-Geissner correction when sphericity violated). ANOVA tables including effect sizes can be found in the Data Availability section.

To test for potential litter effects, data were analysed by linear mixed model with SPSS Statistics (IBM, v29.0). However, in all cases (with the exception of line crossing in the elevated zero maze), the random effect (i.e., litter) did not significantly influence the data (see Data Availability) and thus, incorporation of litter effects were not considered further. To assess potential clustering of behavioural data, two-step cluster analysis was performed with SPSS Statistics.

Proteomic results were analysed for differential abundance in Spectronaut using unpaired *t*-tests with the Storey-Tibshirani multiple-testing correction (q-values, significance $q < 0.1$). The full statistical analyses of proteomic data can be found in the shared data (see Data Availability); male and female proteomic comparisons presented here concern MIA effects stratified by sex for each timepoint. Enrichment significance of differentially MIA-regulated proteins was calculated with the pertinent online software (overrepresentation (ORA)/SynGO analyses: Fisher's exact test, Benjamini-Hochberg (B-H)-corrected). Significant gene-trait associations in the PheWAS analyses were Bonferroni-corrected. Correlation analysis of social preference and protein abundance was performed using Pearson's correlation coefficient for normally distributed data (except MT1, non-normal: Spearman correlation). Statistical significance for behavioural and pathway analyses was accepted for $p < 0.05$ and $q < 0.05$. All values are presented as mean ±

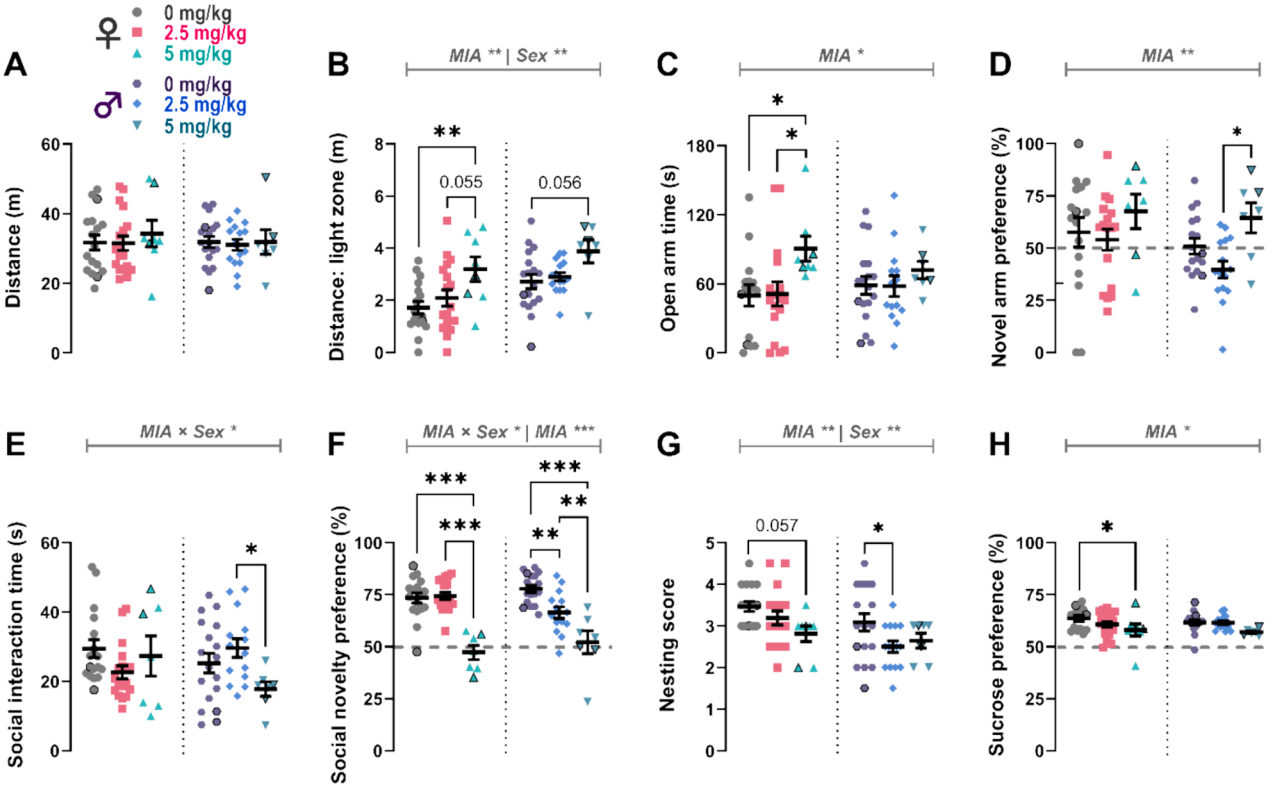

Fig. 2. Early maternal immune activation (MIA) alters relevant behavioural endophenotypes in adult male and female mice. A, No differences in locomotion were observed in an open field test (two-way ANOVA, $p > 0.66$). B, Males and females of the 5 mg/kg MIA-exposed group displayed hyperactivity in the brightly-lit compartment of the light–dark box (two-way ANOVA, MIA: $p = 0.001$, Sex: $p = 0.007$). C, The stronger prenatal immune challenge (5 mg/kg) increased the time spent in the open arm of an elevated zero maze – a measure of reduced anxiety-like behaviour, more robustly in females (two-way ANOVA, MIA: $p = 0.035$). D, Different dosage of the prenatal poly(I:C) treatment had divergent impact on the spatial novelty response in a Y-maze, stronger in male offspring (two-way ANOVA, $p = 0.004$). E, When presented with a sex-matched novel conspecific, the time experimental mice spent socially interacting was impacted by MIA in a sex-specific manner, with poly(I:C) dose differentially affecting males only (two-way ANOVA, MIA×Sex: $p = 0.026$; social interaction = interaction duration by the experimental mouse alone). F, Pronounced deficits in social preference toward a novel mouse compared to the previous familiar conspecific were present in offspring of the 5 mg/kg MIA group for both sexes, while only the males of the 2.5 mg/kg group displayed social memory or preference deficits (two-way ANOVA, MIA×Sex: $p = 0.018$, MIA: $p < 0.001$). G, Both treatment and sex affected nesting score (two-way ANOVA, MIA: $p = 0.007$, Sex: $p = 0.009$), wherein female offspring of 5 mg/kg poly(I:C)-challenged dams and male offspring from the 2.5 mg/kg group displayed a significant decrease of nest building quality in a two-day nesting test, indicative of self-neglect. H, The 5 mg/kg poly(I:C)-treated group exhibited an anhedonia-like decrease in sucrose preference, which was more pronounced in the female offspring (two-way ANOVA, MIA: $p = 0.016$). Grey dashed lines denote chance levels in choice tests. Tested offspring numbers by poly(I:C) treatment dose: *0 mg/kg*, n = 15–17 F, 15–18 M; *2.5 mg/kg*, n = 17–18 F, 14–15 M; *5 mg/kg*: n = 7–8 F, 6–7 M (see Supplementary Method for more). Significance denoted as follows: ANOVA main effects (grey) and Tukey *post-hoc* (black) – *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Mice used for proteomic study are denoted with black symbol borders. All data presented as mean ± SEM.

standard error of the mean (S.E.M.), unless stated otherwise.

3. Results

3.1. Adult MIA mice display deficits in neurodevelopmental psychiatric disorder (NPD)-related behaviours

We established an early-gestation MIA model by adapting previously published methods (Meyer et al., 2005), utilising the viral mimetic poly

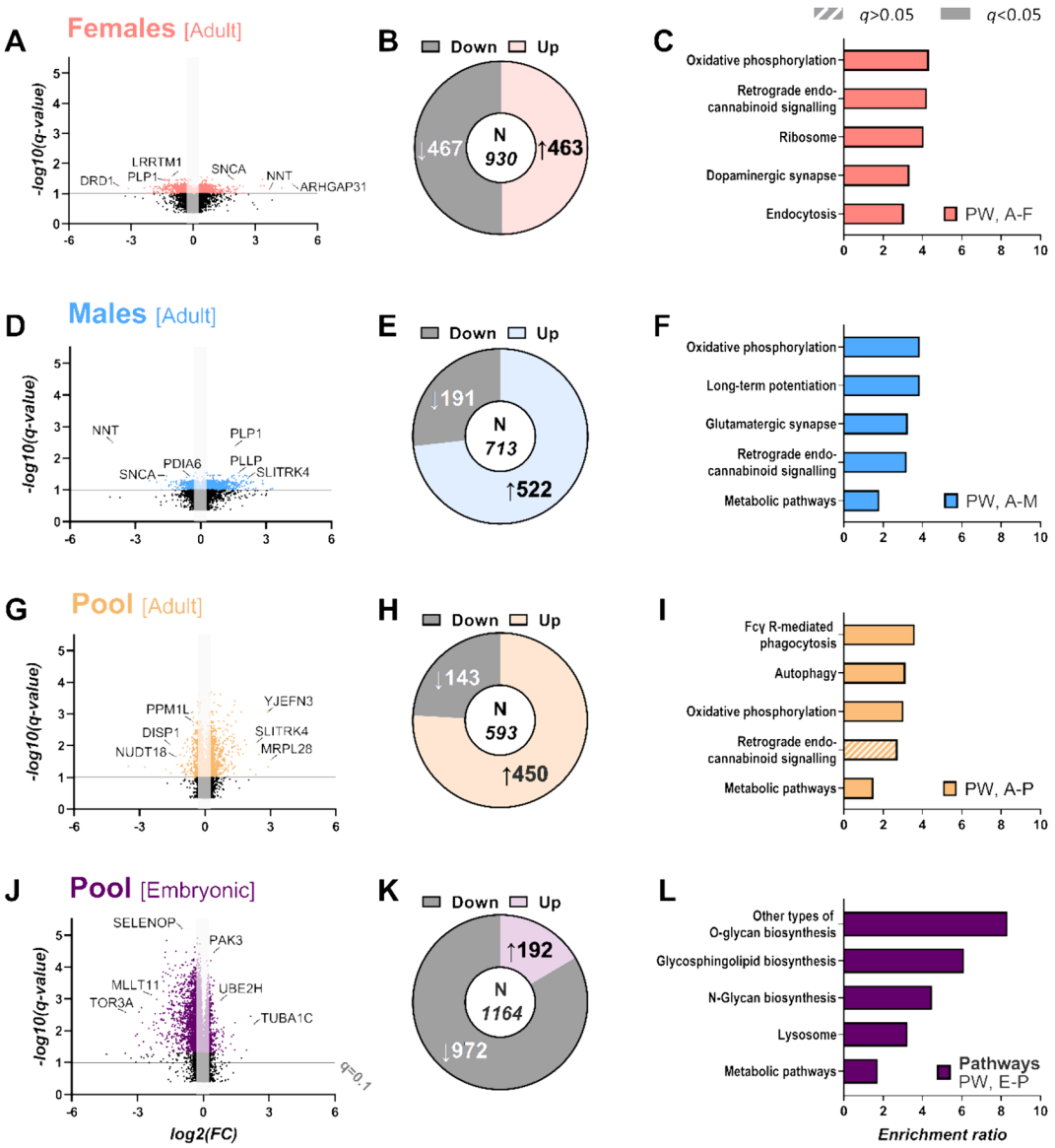

Fig. 3. Dynamic alterations of the embryonic and adult synaptic proteome follow maternal immune activation (MIA). Volcano plots of proteomic results from synaptoneurosomes of early MIA mice (poly(I:C), 5 mg/kg) and controls: A, adult females (AF); D, adult males (AM); G, adult pool (AP); J, embryonic pool (EP, E18: n = 16 M, 14 F each control and treated mice; 4 EP replicates per group, pooled from 7 to 8 mice each; adults: n = 2 M, 2 F each control and treated, 4 AP replicates per group). These show all detected proteins, based on the significance (q-value) and fold-change (FC) in hippocampi of MIA offspring when compared to controls. Selected proteins shown by name in the volcano plots exhibit a combination of high significance, FC, and biological relevance. Colour denotes significant changes ($q < 0.1$, multiple-corrected *t*-tests, *all volcano plots*), shaded boxes indicate minor changes in regulation (absolute FC below 0.2). Of those meaningfully altered synaptoneurosomal proteins, upregulation was observed in adults for nearly half in females (B) and most in males and pool (E, H), while the majority of changes in the embryonic pool were downregulations (K). The functional involvement of prenatal immune challenge-affected proteins in molecular pathways was investigated further for all groups (*right column*). The KEGG pathway (PW) enrichment ratios for MIA-altered proteins of adult females (C) and males (F) indicated partially sex-specific activation of distinct cellular responses to MIA immune challenge, such as overrepresentation of dopaminergic synapses and endocytosis in females, and glutamatergic synapses and metabolism in males. Enriched terms for the pooled adult samples mirrored some pathway categories from the male and female-specific analyses, including mitochondrial and general metabolism, and plasticity-regulating synaptic signalling (I). Here, more generalised effects of MIA manifested in the form of the pathogen response-related phagocytosis and cellular self-degradation. The dynamic nature of the synaptoneurosomal proteomic alterations following MIA is reflected in the embryonic data, which lacked significant sex differences. The affected proteins were involved in highly enriched cell membrane-building glycoprotein and lipid synthesis, as well as lysosomal pathways (L). See also Table S7 for underlying data on pathways and specific proteins. Significance threshold for pathway analysis, using Benjamini-Hochberg multiple-test corrected *p*-value (q), was set at p/q = 0.05 (Fisher's exact test, *all pathways*).

(I:C). Initial dose optimisation revealed 2.5 mg/kg (*low dose*) and 5 mg/kg (*high dose*) produced pronounced IL-6 activation in the mother (Fig. S1E).

To validate our model, we tested adult male and female MIA offspring for NPD-relevant behaviours (Fig. 2, Figs. S2–S3). High-dose offspring of both sexes exhibited reduced anxiety-like behaviours and increased distance travelled and time spent in open and brightly lit environments (Fig. 2B-C, Fig. S3B-C), while retaining normal locomotor function in the open field (Fig. 2A). The anxiolytic effect of the high-dose poly(I:C) treatment was more pronounced in females (Fig. 2B-C, Fig. S3B-C). However, no differences for the high-dose group were observed for centre time in the open field (Fig. S3A).

Additionally, the low- and high-dose offspring displayed divergent spatial novelty preference outcomes, with increased preference in the high-dose group, which was more pronounced in males (Fig. 2D). We found sex- and dose-dependent MIA effects on social interaction and social novelty preference during interaction with juvenile conspecifics (Fig. 2E-F). While social interaction was only reduced in high-dose male offspring, social novelty preference was significantly impaired in high-dose MIA males and females. Depressive- or self-neglect-like behaviours in high-dose offspring manifested as impaired nest building (Fig. 2G) and reduced sucrose preference (Fig. 2H) – both more pronounced in females. No changes were observed in the swim test (Fig. S3E). Overall, the acoustic startle reflex (ASR) remained intact after MIA (Fig. S3D). Simultaneously, subtle deficits in sensorimotor gating, i.e. pre-pulse inhibition (PPI) of the ASR, were observed in female MIA offspring (Fig. S3F).

Poly(I:C)-induced MIA has been described to result in dichotomous outcomes with resilient and non-resilient offspring (Lorusso et al., 2022; Mueller et al., 2021). Therefore, we performed two-step clustering analysis of our behavioural data (see Data Availability). We identified two clusters, which largely separated between controls (n = 24 in Cluster 1 and n = 5 in Cluster 2) and high-dose MIA offspring (n = 1 in Cluster 1 and n = 12 in Cluster 2), while low-dose MIA offspring was distributed across both clusters (n = 16 in Cluster 1 and n = 12 in Cluster 2), suggesting distribution into resilient and non-resilient groups in low-dose MIA offspring only.

Taken together, these findings substantiate the successful implementation of the MIA model in our laboratory and further expand on the effect on NPD-associated behaviours, revealing a subset of sex- and dose-specific poly(I:C) effects.

3.2. Sex-specific alterations of the synaptic proteome in adult MIA offspring

To interrogate the molecular consequences of poly(I:C)-evoked MIA, we investigated the synaptoneurosomal proteome using mass spectrometry in the HPC of randomly-selected controls and high-dose MIA offspring, as it resulted in a more discernible behavioural phenotype. The functional relevance of the proteomic changes was investigated by enrichment analyses in the protein-coding genome and at the synapse, specifically. Of the 4,744 detected proteins, 593 were significantly altered ($p < 0.05$, $q < 0.1$, $|change| > 20$ %; n = 532 at $q < 0.05$, see Data Availability), 450 of which were upregulated (Fig. 3G-H, Table S2). Functionally enriched pathways included those involved in autophagy, receptor-mediated phagocytic response, cell growth and morphogenesis, mitochondrial function and metabolic regulation, cytoskeletal organisation, and plasticity-related signal transduction (Fig. 3I, Fig. S6A, Table S7). Closer inspection of synaptic mechanisms affected by MIA highlighted synapse organisation and transport, postsynaptic specialisation, and – central to neurotransmission – the synaptic vesicle membrane and trafficking (Fig. S5D, S5G).

Considering the role of sex in animal behaviour, as well as prevalence differences of NPDs, we wanted to further examine possible sex-dependent effects of MIA on the adult synaptic proteome. Indeed, 59.2 % of significantly up- or downregulated proteins in the adult pool were sex-specific (Fig. 3A, D, Fig. S5A, Table S2-3). Moreover, some of the proteins changed in both male and female MIA offspring (e.g., NNT, SNCA) were regulated in opposite directions, while other protein abundance differences were exclusive to either females or males (n = 546 and 406, respectively; Fig. 3A, 3D, Fig. S5A, Table S2). In females, about half of the significantly altered proteins (463 of 930 total changed proteins, $p < 0.05$, $q < 0.1$, $|change| > 20$ %; total n = 65 at $q < 0.05$) and in males a large majority (522 of 713 at $q < 0.1$; total n = 52 at $q < 0.05$, see Data Availability) were upregulated (Fig. 3B, E, Table S2-S3). Overrepresented molecular pathways in the females included actin cytoskeleton and synaptic organisation, synaptic vesicle and endocytic processes, and the ribosome (Fig. 3C, Fig. S6B, Table S7). In males, specifically, enriched pathways were involved in synaptic plasticity via long-term potentiation, multiple metabolic processes, gliogenesis, and myelination (Fig. 3F, Fig. S6C, Table S7). In both sexes, pathways related to retrograde endocannabinoid signalling, mitochondrial oxidative phosphorylation, and intracellular signalling via GTPases were affected by MIA (Fig. 3C, F, S5B-S5C). Importantly, prenatal MIA exposure caused enrichment of proteins associated with dopaminergic synapses in females and glutamatergic synapses in males (Fig. 3C, F). In line with previous studies (Atanasova et al., 2023), selected members of the HOMER and SHANK protein families were also affected by MIA (see Data Availability).

In summary, the differences in the HPC synaptic proteome of males and females might underlie some of the sex specificity of behavioural phenotypes.

3.3. MIA alters the prenatal synaptic proteome in a sex-independent manner

Next, we wanted to explore the role of MIA on synaptic neurodevelopment. Thus, the late embryonic (E18) HPC synaptoneurosomal proteome of MIA male and female offspring was probed for changes. Tissue extraction shortly before birth allowed for an examination at a time after astrocytes and oligodendrocytes have differentiated (La Manno et al., 2021), but before the perinatal excitatory-to-inhibitory GABA switch, which is affected by MIA (Corradini et al., 2018), is completed. Here, 1,164 proteins were significantly altered ($p < 0.05$, $q < 0.05$, $|change| > 20$ %) by high-dose MIA, 972 of which were downregulated (Fig. 3J-K, Table S4). Interestingly, HOMER3 (−8.3 %) and SHANK3 (−12 %) were slightly but significantly downregulated by MIA (see Data Availability). Synapse-level enrichment revealed nominal significance ($p < 0.05$) for pre- and postsynaptic structure and organisation, modulation of chemical transmission, and the synaptic vesicle cycle, though these associations did not pass the significance threshold after correction (Fig. S5E, S5H). Affected protein-coding genome pathways include lysosomes and mitochondria, as well as modifications related to proper biomembrane development and environmental stimuli response function, such as sialic acid, membrane lipid, and glycoprotein metabolism (Fig. 3L, Fig. S6D, Table S7).

Notably, no MIA-induced sex-specific differences in protein abundance crossed the significance threshold in the embryonic tissue except one (SSX2IP), in male vs female low-dose MIA offspring (see Data Availability for embryonic results by sex). This indicates that divergent effects on the male and female synaptic proteome occur later in life.

Investigating poly(I:C) dose-dependent effects on the embryonic proteome, we found that 501 proteins were significantly influenced ($p < 0.05$, $q < 0.05$, $|change| > 20$ %) in the low-dose MIA offspring, of which 438 were downregulated (Fig. S5C). Significantly affected pathways centred around the regulation of RNA metabolism and localisation, especially post-transcriptional processes like splicing, transport, and surveillance, indicating more transient synaptic responses to the low-dose immune challenge (Fig. S5F, S6E). The majority of the observed changes (54.3 %) comprised proteins different from those altered by a high-dose treatment compared to controls (Fig. S5B, Table S5). Indeed, when contrasting the synaptoneurosomal proteome composition

between the two poly(I:C) treatments directly, 1,222 proteins differed significantly, of which 692 were downregulated in the high-dose MIA-exposed offspring (Fig. S5B, S5I). Functional differences involved regulatory RNA processing and binding, membrane surface modification, synaptic structure and vesicle cycle, and axonal development (Fig. S6F). Of the differently abundant proteins overlapping between the high- and low-dose MIA group, 411 were not affected when either group was compared to controls, which might underlie some of the observable phenotypic divergences in low- versus high-dose MIA offspring.

Collectively, our results show significant modifications of the embryonic synaptic proteome during late embryonic development following early MIA, which are dose- but not sex-dependent.

3.4. Synaptoneurosomal changes associate with NPD-related phenotypes and synaptic signalling

Next, we wanted to explore the dynamic influence of early gestational MIA on the developing and mature synaptic proteome. While most of the identified proteomic changes in the HPC following high-dose poly (I:C) exposure were age-specific, 50 proteins discovered in the embryos were also found in the adult pool (Fig. 4A). Hierarchical clustering of these common proteins revealed four major clusters, namely two downregulated in adults and mostly in embryos (Cluster 1: n = 11 and Cluster 2: n = 1 protein), one decreased in embryos but increased in adults (Cluster 3: n = 19), and one upregulated at both ages (Cluster 4: n = 19 proteins; Fig. 4D). Synaptic-level analyses revealed enrichment in proteins of the presynapse and synaptic vesicle membrane in particular, and their functional role was tied to synaptic vesicle endocytosis and cycling (Fig. 4B-C).

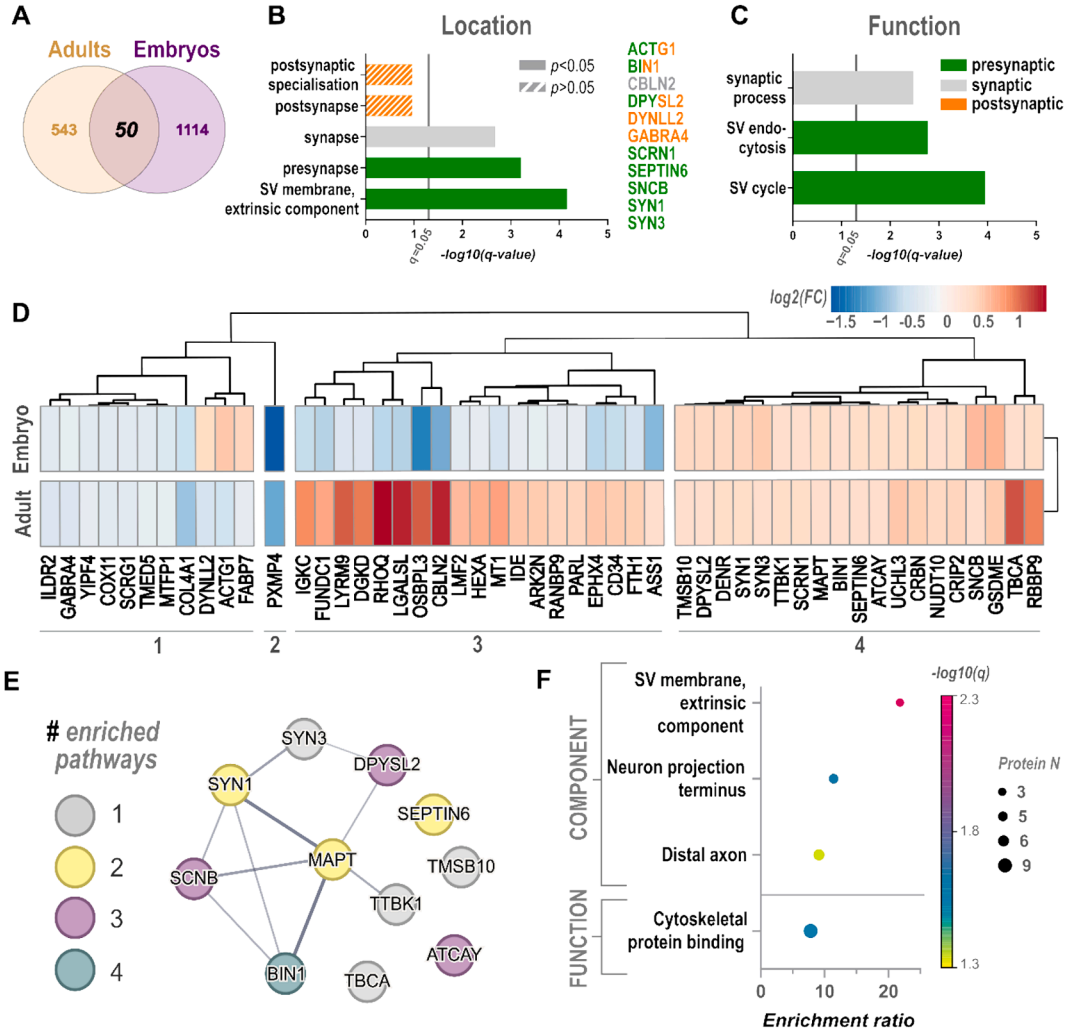

Fig. 4. Maternal immune activation (MIA)-induced protein changes shared in embryonic and adult hippocampal synaptoneurosomes involve neuronal signalling processes via the synaptic vesicle cycle and cytoskeletal dynamics. Long-term consequences of MIA were revealed by the overlap of proteins altered in synaptoneurosomes of both embryonic and adult hippocampi (A). The 50 overlapping proteins were enriched at the presynapse and the synaptic vesicle (SV) membrane (B). Functionally, these proteins are significantly involved in the SV cycle and endocytosis (C). Colours for the overrepresented proteins shown in B match those of the respective enriched term category (legend in C, *multiple colours = synaptic protein included in multiple functional terms*). Hierarchical clustering of the respective average fold-change (FC) revealed four clusters (D), namely downregulated in adults (Cluster 1, n = 11 proteins; Cluster 2, n = 1 stronger downregulation), downregulated in embryos and upregulated in adults (Cluster 3, n = 19), and persistently upregulated in both (Cluster 4, n = 19 / *Embryos*: n = 2 M, 2 F each control and treated mice pooled from 7 to 8 mice/condition; *Adults*: n = 2 M, 2 F each control and treated; 4 replicates per group at both ages). Cluster 4 formed a highly significant interaction network ($p = 6.48 \times 10^{-08}$ for embryos, $p = 6.28 \times 10^{-05}$ for adults) of proteins (E). Pathway enrichment underscored the involvement of this subnetwork's embryonic brain-enriched common proteins in synaptic signalling via SV composition, the neurite terminus and distal axon, and cytoskeletal dynamics (F). Additionally, the extrinsic component of SV membrane term was significantly overrepresented in the adult dataset (*Enrichment ratio: 19.2, n = 3 proteins, −log10(q) = 1.62*). Significance was set at $q < 0.05$ for all tests (Benjamini-Hochberg multiple-test corrected *p*-value).

Interrogation of protein–protein-interactions revealed a network of significantly interconnected proteins in the persistently upregulated cluster of 19 proteins (i.e., Cluster 4; interaction enrichment $p = 6.48 \times 10^{-8}$ in embryonic set, $p = 6.28 \times 10^{-5}$ in adult set; Fig. 4D-E). A subset of proteins (including BIN1, DPYSL2, SNCB, MAPT, SYN1) within this network was strongly represented in the identified functional pathways (Fig. 4E-F). Functional enrichment in the embryonic dataset highlighted cytoskeletal protein binding, while component enrichment confirmed the axonal terminus and the synaptic vesicle membrane as subcellular structures significantly converging with this upregulated protein cluster (Fig. 4E-F).

Furthermore, we examined the correlation between the measured adult social novelty preference and HPC abundance of the 19 proteins downregulated in embryos and upregulated in adults (Cluster 3), hinting at postnatal compensatory mechanisms (Fig. S7). All MIA-upregulated proteins were negatively correlated with the social task performance, and five of these proteins reached significance (CBLN2, DGKD, MT1, ARK2N, FTH1).

Finally, to investigate the extent of association between MIA-induced, long-term synaptic changes with NPDs, we analysed PheWAS data for the genes encoding the 50 proteins that overlapped between the embryonic and adult proteomes. All but one of these proteins (immunoglobulin kappa constant, IGKC) were significantly associated with psychiatric or cognitive traits (Table S8-S9). Apart from NPDs in a narrower sense, i.e. ADHD, ASD, SCZ, and bipolar disorder, the MIA-linked genes were associated with known comorbid conditions like conduct disorder, obsessive–compulsive disorder, post-traumatic stress disorder, substance use disorders, anxiety- and depression-related traits (Fig. 5, Table 2, Table S8). Memory, higher cognitive functions, and mild intellectual disability as well as temperament and personality traits were similarly among the significantly associated phenotypic categories (Table 2, Table S8-S9).

Taken together, our results indicate that a modest subset of synapse composition- and synaptic signalling pathway-enriched proteins, which are changed prenatally and in the adult HPC following MIA, might play a role in the increased risk of emergence of NPDs and related nervous system sequelae after a prenatal viral infection.

4. Discussion

Here, we revealed substantial HPC synaptoneurosomal proteome changes in embryonic and adult mouse offspring following a prenatal immune challenge. Interestingly, sex-specific findings were only observed in adult-, but not embryonic proteomes. Importantly, we identified 50 common proteins, some of which were up- or down-regulated by MIA at both ages, and an intriguing cluster comprising 19 proteins downregulated in embryos and upregulated in adulthood. PheWAS analysis revealed 49 of the 50 common proteins associated with NPD-related phenotypes, suggesting the identified proteins may represent targets for future translational MIA studies.

Our behavioural findings, validating the MIA model in our laboratory, suggest that male offspring are more susceptible to MIA exposure as previously shown (Block et al., 2022; Braun et al., 2019; Haida et al., 2019), with the behavioural consequences only observed in both sexes at the higher dose. Therefore, this dose (5 mg/kg) was selected to determine the early (embryonic) and late (adulthood) effects of MIA on alterations in the HPC synaptoneurosomal proteome. The adult samples were selected randomly across available litters from mice, for which data was available in all behavioural tests, to exclude bias, especially since targeted selection was intrinsically not possible for the embryonic samples, which were pooled across litters.

It should be noted that in our behavioural data larger within-group variability was only present in males in some selected measures of anxiety-like behaviour, social interaction, and nesting, suggesting robust induction of MIA in the mice tested in this study. Consistently, behavioural data from high-dose offspring clearly separated from controls and only low-dose offspring clustered into resilient and non-resilient mice, as described previously (Lorusso et al., 2022; Mueller et al., 2021); see Data Availability.

While some of the behavioural changes common in poly(I:C)-

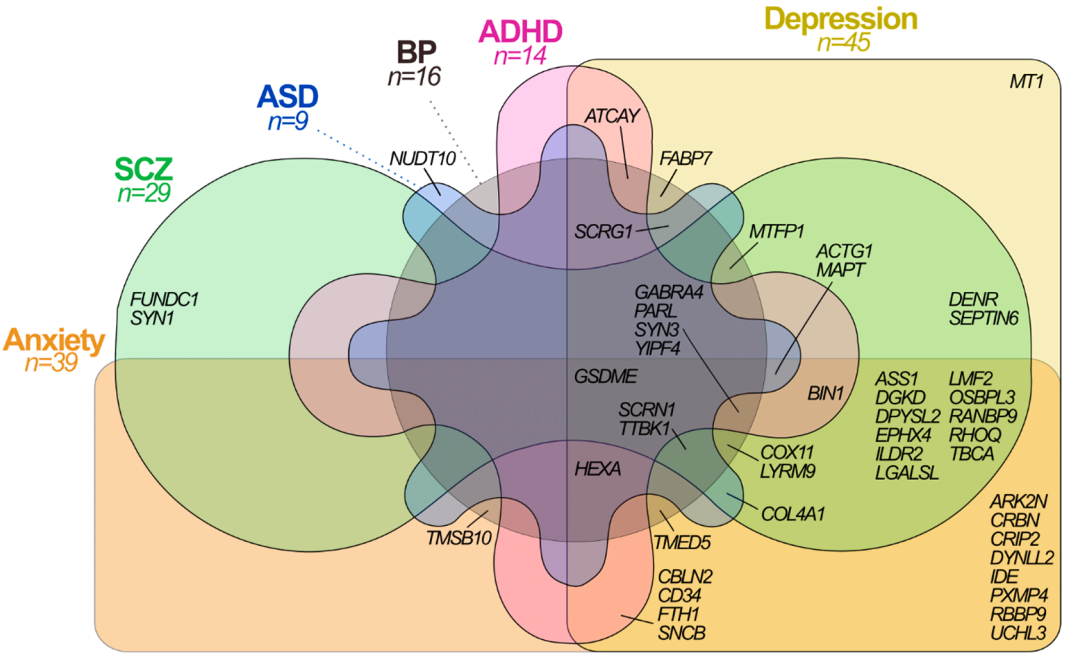

Fig. 5. Proteins altered in embryonic and adult MIA hippocampal synaptoneurosomes correspond to genes significantly associated with neurodevelopmental psychiatric disorders (NPDs) and comorbid phenotypes. Genes exhibiting pleiotropic effects and correlated with most of the six interrogated psychiatric conditions were GSDME (alias DFNA5, n = 6) and ACTG1, GABRA4, HEXA, MAPT, PARL, SCRN1, SYN3, TTBK1, YIPF4 (n = 5) – a multitude of which play a role in neuronal cell fate, inflammatory response, and signal transmission. Additional information on the Phenome-Wide Association Study (PheWAS) results can be found in Table 2 and Supplementary Tables S1, S8-S9. Significance threshold for gene-trait associations in GWAS atlas database: $p < 0.05$, Bonferroni-corrected. ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; BP, bipolar disorder; SCZ, schizophrenia.

Table 2
Phenome-wide association study (PheWAS) of genes, encoding proteins significantly changed in both embryonic and adult hippocampal synaptoneurosomes of maternal immune activation offspring.[1]

Condition or Function	Significantly correlated genes PheWAS analysis summary
ADHD	*ACTG1, BIN1, CBLN2, CD34, FABP7, FTH1, GABRA4, GSDME, HEXA, MAPT, PARL, SNCB, SYN3*
CD	*FTH1, PARL, SEPTIN6*
Anxiety* | Neuroticism	*ACTG1, ARK2N, ASS1, BIN1, CBLN2, CD34, COL4A1, COX11, CRBN, CRIP2, DGKD, DPYSL2, DYNLL2, EPHX4, FTH1, GABRA4, GSDME, HEXA, IDE, ILDR2, LGALSL, LMF2, LYRM9, MAPT, OSBPL3, PARL, PXMP4, RANBP9, RBBP9, RHOQ, SCRN1, SNCB, SYN3, TBCA, TMED5, TMSB10, TTBK1, UCHL3, YIPF4*
ASD	*ACTG1, COL4A1, GSDME, HEXA, MAPT, NUDT10, SCRG1, SCRN1, TTBK1*
BP	*ATCAY, COX11, FABP7, GABRA4, GSDME, HEXA, LYRM9, MTFP1, PARL, SCRG1, SCRN1, SYN3, TMED5, TMSB10, TTBK1, YIPF4*
Depressive Disorders**	*ACTG1, ARK2N, ASS1, ATCAY, BIN1, CBLN2, CD34, COL4A1, COX11, CRBN, CRIP2, DENR, DGKD, DPYSL2, DYNLL2, EPHX4, FABP7, FTH1, GABRA4, GSDME, HEXA, IDE, ILDR2, LGALSL, LMF2, LYRM9, MAPT, MT1, MTFP1, OSBPL3, PARL, PXMP4, RANBP9, RBBP9, RHOQ, SCRG1, SCRN1, SEPTIN6, SNCB, SYN3, TBCA, TMED5, TTBK1, UCHL3, YIPF4*
Memory | Cognition***	*ACTG1, ARK2N, ASS1, ATCAY, BIN1, CBLN2, CD34, CRBN, CRIP2, DENR, DPYSL2, DYNLL2, FABP7, FTH1, FUNDC1, GABRA4, GSDME, HEXA, IDE, ILDR2, LGALSL, LMF2, LYRM9, MAPT, MT1, MTFP1, OSBPL3, PARL, PXMP4, RANBP9, RBBP9, RHOQ, SCRG1, SCRN1, SEPTIN6, SNCB, SYN3, TBCA, TMED5, TMSB10, TTBK1, UCHL3, YIPF4*
OCD	*FTH1, PARL, SEPTIN6*
PTSD	*CBLN2, MAPT, OSBPL3, RANBP9*
SCZ | SCZ vs BP	*ACTG1, ASS1, BIN1, COL4A1[$], COX11, DENR[#], DGKD[#], DPYSL2, EPHX4[$], FUNDC1[#], GABRA4[$], GSDME[&], ILDR2, LGALSL[#,&], LMF2[#], LYRM9[&], MAPT, MTFP1, OSBPL3, PARL, RANBP9, RHOQ[#], SCRN1, SEPTIN6[&], SYN1[#], SYN3[&], TBCA[$], TTBK1[&], YIPF4[$]*

[1]For visual representation of the directionality of changes in our age-specific datasets, see Fig. 4D. Full lists of significantly associated disorders and traits for each gene, including statistics and sample sizes, can be found in Tables S8-9. *Anxiety includes traits containing "Anxiety", "Anxious", Neuroticism comprises "Neuroticism" and "Worry". **Depressive Disorders includes "Depressive Episode", "Recurrent Depressive Disorder", and "Bipolar Affective Disorder/Depressive Episode" subchapters, as well as "Depressive Symptoms" and "Depressive Affect" traits, ***Memory comprises "Memory Functions" and "Dementia in Alzheimer's Disease" subchapters, Cognition corresponds to "Higher-Level Cognitive Functions", "Mild Mental Retardation" (*updated to Mild Intellectual Disability in text*), "Attention Functions", and "Mental Functions of Language". [#]SCZ only, [$]SCZ vs BP only, [&]incl. Psychiatric Genomics Consortium (PGC) cross-disorder. *ADHD*, Attention Deficit Hyperactivity Disorder; *CD*, conduct disorder; *ASD*, Autism Spectrum Disorder; *BP*, Bipolar Disorder; *OCD*, Obsessive Compulsive Disorder; *NPD*, Neurodevelopmental Psychiatric Disorder; *PTSD*, Posttraumatic Stress Disorder; *SCZ*, Schizophrenia.

induced MIA were not observed (e.g., reduced sensorimotor gating in males) or tested (e.g., cognitive flexibility), we showed several previously described (Solek et al., 2018) behavioural deficits in sociability, novelty response, and sucrose preference. Additionally, we observed less-described aberrations in nest building quality and context-specific hyperactivity (see Fig. 2, Fig. S3). This is in keeping with the extensively studied heterogeneity of MIA designs and outcomes (Kentner et al., 2019; Mueller et al., 2018; Mueller et al., 2019) and the lack of disorder specificity of psychiatric animal models and tests (i.e., they can be translated to more than just one diagnostic entity), as previously discussed by us (Freudenberg et al., 2021) and others (e.g., Kalueff et al., 2015). Moreover, these findings are in line with proposed trans-diagnostic and dimensional approaches (e.g., Cuthbert and Insel, 2013; Krueger and Eaton, 2015), and the common genetic and neurobiological underpinnings described for mental disorders (e.g., Lee et al., 2019; Opel et al., 2020).

Our proteomic pathway analyses implicated lipid, polysaccharide, and glycoprotein metabolism pathway disruptions in the embryonic synaptoneurosomes following high-dose MIA, which may contribute to the lasting NPD-pertinent sequelae, as previously reported (Schneider et al., 2017). Further changes in mitochondrial organisation and the lysosome, as well as impaired glycan and glycosphingolipid metabolism, which are important for cell signalling and myelination, were observed (Hannun and Obeid, 2008). Moreover, MIA induced changes in proteins involved in post-translational modifications by glycans and sialic acid, which affect membrane bio-properties and proteins controlling the secretory pathway, intercellular interactions, and developmental timing (Hayes and Melrose, 2018; Lee et al., 2020; Li and Ding, 2019). Interestingly, a study of the transcriptome of stimulated microglia in adulthood following early-gestational poly(I:C) treatment found enrichment of fatty acid metabolic and protein localisation pathways in offspring (Hayes et al., 2022).

In embryonic synaptoneurosomes we discovered novel dose-dependent alterations of synaptic protein composition with the lower dose influencing alternative splicing and RNA metabolism, constituting more transient changes. These may be of importance for follow-up adult studies, given that male offspring showed more behavioural consequences to the weaker immune challenge. Our findings are largely in keeping with previous studies highlighting pathway enrichment for cellular and immune responses, transmembrane signalling, and axon guidance (Baines et al., 2020; Oskvig et al., 2012), networks of neuronal development and metabolic/energy processes (Tsivion-Visbord et al., 2020), and cytoplasmatic translation (Kalish et al., 2021).

In line with, and building upon, previous findings in MIA models (Amodeo et al., 2019; Farrelly et al., 2015; Guo et al., 2018; Gyorffy et al., 2016; Lombardo et al., 2018; Mirabella et al., 2021; Mueller et al., 2021; Richetto et al., 2014; Richetto et al., 2017; Weber-Stadlbauer et al., 2017; Woods et al., 2021), we found that MIA changes in adult HPC synaptoneurosomes had shifted to divergent transmembrane and cytoskeletal trafficking, energy metabolism, cell fate-governing signals and processes, and plasticity-related endocannabinoid signalling. It should be noted that the presented analysis provides information about the MIA effects on molecular composition and inferred functionality of the HPC synapse. Nevertheless, it has been shown that HPC pyramidal neurons from adult MIA offspring have altered synaptic properties, i.e. less frequent and higher amplitude miniature excitatory postsynaptic currents (Ito et al., 2010), and MIA affects spine morphology and density (Pekala et al., 2021).

The proteins altered by high-dose MIA in both the embryonic and adult pool were enriched for those of the presynaptic terminal and synaptic vesicle, consistent with previous studies (Coiro et al., 2015; Gyorffy et al., 2016; Hayes et al., 2022; Ito et al., 2010; Oh-Nishi et al., 2010). Importantly, they also showed significant association with multiple psychiatric disorders (see Table 2, Fig. 5 for details), underscoring the non-disorder-specific nature of the MIA model as described above and proposed previously (Brown and Meyer, 2018), and contain a cluster of persistently upregulated proteins that are enriched in a functional network. These proteins, including BIN1, DPYSL2, SNCB, MAPT, SYN1, are involved in synaptic plasticity, cognition, and neuro-inflammatory, -degenerative, and -developmental conditions (Biundo et al., 2018; De Rossi et al., 2020; Desprez et al., 2023; Maphis et al., 2015; Mohaupt et al., 2022; Parenti et al., 2022; Pham et al., 2016; Sudwarts et al., 2022). Furthermore, correlation of the Cluster 3 proteins downregulated in embryonic and upregulated in adult HPC synaptoneurosomes and social behaviour suggest MIA-induced functional alternations. Indeed, many of these – CBLN2 (Seigneur and Sudhof, 2018; Tao et al., 2018), DGKD (Barber and Raben, 2020; Lu et al., 2020), MT1 (Mamdani et al., 2022; West et al., 2008), FTH1 (Mazare et al., 2020; Otero-Garcia et al., 2022), RANBP9 (Kootbodien et al., 2023; Wang et al., 2014) – are implicated in neuronal function, synaptic transmission, and neuropsychiatric deficits.

Finally, our study suggests that significant sex-specific, synaptic-level MIA effects emerge later in life, possibly following known influences such as chromatin remodelling, environmental and hormonal regulation (Gegenhuber et al., 2022; McCarthy et al., 2017), which add to the available data regarding MIA-induced changes in the brain (Herrero et al., 2022; Kalish et al., 2021; Nakamura et al., 2022; Tsivion-Visbord et al., 2020). Importantly, enrichment in divergent, psychiatrically-relevant signalling pathways – namely, dopaminergic (Dunlop and Nemeroff, 2007; Hasbi et al., 2020) in female and glutamatergic (Javitt, 2004; Mohn et al., 1999) in male MIA offspring – might further underlie differences in behavioural outcomes, such as the observed more pronounced depressive-like behaviours in females and social interaction deficits in males. Similar MIA effects have been consistently observed in both glutamatergic (Amodeo et al., 2019; Block et al., 2022; de Bartolomeis et al., 2022; Mirabella et al., 2021; Nakamura et al., 2022) and dopaminergic (Basil et al., 2014; Hayes et al., 2022; Luchicchi et al., 2016) signalling, even across multiple generations (Weber-Stadlbauer et al., 2017; Weber-Stadlbauer et al., 2021).

For statistical analysis of our proteomic data, we used a more inclusive significance threshold (i.e., $q < 0.1$). A more stringent threshold of 0.05 did not affect the outcome of the embryonic analysis and only mildly affected the adult pool data (532 vs 593 significantly changed proteins for $q < 0.05$ vs $q < 0.1$), supporting the robustness of these data. However, the number of detected proteins significantly dropped with the more stringent q-value threshold in the sex-specific analyses in both females (from 713 to 52) and males (from 930 to 65), possibly caused by the limited sample size. However, it should be noted that a more inclusive threshold of $q < 0.1$ has been used in previous studies, yielding robust results (Abbas et al., 2021; Navajas et al., 2022; Thuy-Boun et al., 2022).

In conclusion, we observed dynamic alterations at the HPC synapse that were age-specific and varied by sex or immunostimulant dose in the adult and embryonic brain, respectively. The more abundant protein alterations in embryonic HPC might be based on the temporal proximity to MIA induction, whereas the long-term affected proteins in adults could represent more permanent effects of MIA. Importantly, we discovered a smaller, but highly relevant subset of MIA-induced embryonic proteome changes that remain affected into adulthood, which could represent targets for future translational studies. Furthermore, these proteins might be probed for identification of potential targets for tailored treatments, for example via screening/connectivity mapping (e.g., CLUE: *https://clue.io/*, PHAROS: *https://pharos.nih.gov/*, or the Open Targets Platform: *https://platform.opentargets.org/)* or by functional screening in gain- and loss-of-function experiments. Thus, our findings, together with previous transcriptomic research into changes caused by poly(I:C)-evoked MIA, allow an advanced understanding of the functional molecular effects of prenatal immune challenges on the brain across the lifespan.

CRediT authorship contribution statement

Anna Y. Yotova: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Li-Li Li:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis. **Aet O'Leary:** Writing – review & editing, Visualization, Formal analysis, Conceptualization. **Irmgard Tegeder:** Writing – review & editing, Resources, Conceptualization. **Andreas Reif:** Writing – review & editing, Resources, Project administration, Funding acquisition, Conceptualization. **Michael J. Courtney:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **David A. Slattery:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Andreas Reif has received honoraria for lectures and/or advisory board activity from Janssen, Boehringer Ingelheim, COMPASS, SAGE/Biogen, LivaNova, Medice, Shire/Takeda, MSD and cyclerion and received grant support from Medice and Janssen. None of these relationships are directly related to the study reported herein. All other authors report no financial relationships with commercial interests.

Data availability

The mass-spectrometry proteomics data have been deposited to the ProteomeXChange Consortium via the PRIDE partner repository (PMID: 34723319) with the dataset identifier PXD043094. Synaptic proteome analysis files are available on Figshare (licence CC-BY 4.0) with the following DataCite DOIs: *https://doi.org/10.6084/m9.figshare.22581628* for embryonic dataset analyses, *https://doi.org/10.6084/m9.figshare.22581766* for adult dataset analyses. Full behavioural data, including information on litters and animal numbers, and extensive statistical analyses are available under *https://doi.org/10.6084/m9.figshare.26076451*. Full immunoblots for synaptoneurosomal extraction validation can be accessed here: *https://doi.org/10.6084/m9.figshare.26187023*. Previous versions of this work have been made available as a preprint (*https://doi.org/10.21203/rs.3.rs-3100753/v1)* and as part of a doctoral thesis (AYY, *https://doi.org/10.21248/gups.85791)*. All other data supporting this study's findings is presented either in the main text or supplementary tables, figures, and files.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2024.07.040.

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