Brain, Behavior, & Immunity - Health 3 (2020) 100043

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Full Length Article

Therapeutic efficacy of environmental enrichment on behavioral, endocrine, and synaptic alterations in an animal model of maternal immune activation

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ARTICLE INFO

Keywords:
Environmental enrichment
Social housing
Maternal immune activation
Fetal programming
Corticosterone
Glucocorticoid receptor
Amygdala
Synaptic plasticity
Sex difference
Experience
Inflammation
Memory

ABSTRACT

Maternal immune activation (MIA) has been identified as a significant risk factor for several neurodevelopmental disorders. We have previously demonstrated that postpubertal environmental enrichment (EE) rescues and promotes resiliency against MIA in male rats. Importantly, EE protocols have demonstrated clinical relevancy in human rehabilitation settings. Applying some of the elements of these EE protocols (e.g. social, physical, cognitive stimulation) to animal models of health and disease allows for the exploration of the mechanisms that underlie their success. Here, using a MIA model, we further investigate the rehabilitative potential of complex environments with a focus on female animals. Additionally, we expand upon some of our previous work by exploring genetic markers of synaptic plasticity and stress throughout several brain regions of both sexes. In the current study, standard housed female Sprague-Dawley rats were challenged with either the inflammatory endotoxin lipopolysaccharide (LPS; 100 μg/kg) or saline (equivolume) on gestational day 15. On postnatal day 50, male and female offspring were randomized into one of three conditions that differed in terms of cage size, number of cage mates (social stimulation) and enrichment materials. Spatial discrimination ability and social behavior were assessed six weeks later. Similar to our previously published work in males, our results revealed that a single LPS injection during mid gestation disrupted spatial discrimination ability in female rats. Postpubertal EE rescued this disruption. On the endocrine level, EE dampened elevations in plasma corticosterone that followed MIA, which may mediate EE's rehabilitative effects in female offspring. Within the prefrontal cortex, hippocampus, amygdala, and hypothalamus, MIA and EE altered the mRNA expression of several genes associated with resiliency and synaptic plasticity in both sexes. Overall, our findings provide further evidence that EE may serve as a therapeutic intervention for MIA-induced behavioral and cognitive deficits. Moreover, we identify some sexually dimorphic molecular mechanisms that may underlie these impairments and their rescue.

1. Introduction

Evidence from epidemiological studies has shown that exposure to inflammatory insults during pregnancy is a risk factor for the later life emergence of psychiatric disorders in offspring (Babulas et al., 2006; Sørensen et al., 2008). In preclinical research, several animal models have been developed to mimic the adverse effects of maternal immune activation (MIA; Estes and McAllister, 2016; Kentner et al., 2019; Knuesel et al., 2014). One of the most commonly used approaches is to challenge pregnant rats with the bacterial endotoxin lipopolysaccharide (LPS), a component of the outer membrane of Gram-negative bacteria that mimics bacterial infections by binding to toll-like receptor 4 (Hao et al., 2010; Elovitz et al., 2011). Studies using the LPS-induced MIA model have revealed links between prenatal infection and abnormalities in behavioral and neurological phenotypes, mirroring symptoms of neurodevelopment disorders such as schizophrenia, depression and autism (Boksa, 2010; Harvey and Boksa, 2012). Furthermore, studies using rodent MIA models have identified inflammatory responses in the maternal compartment, as well as the changes in cytokines in the placenta, as possible mediators of prenatal infection-induced changes in offspring brain function (Oskvig et al., 2012; Parker-Athill and Tan, 2010; Smith et al., 2007; Núñez Estevez et al., 2020).

Despite the wide application of MIA in animal research, the majority of published studies mainly used male subjects, and the detrimental effects of gestational infection on behavior, cognition and neurophysiology have been relatively unattended in females (Boksa, 2010; Rana et al.,

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https://doi.org/10.1016/j.bbih.2020.100043
Received 31 December 2019; Received in revised form 27 January 2020; Accepted 28 January 2020
Available online 30 January 2020

2012; Coiro and Pollak, 2019). Sex differences in pathophysiology exist in a broad range of neurodevelopmental disorders such as autism, depression and schizophrenia (Aleman et al., 2003; Beery and Zucker, 2011; Flor-Henry, 1990; Wald and Wu, 2010), and findings in females are particularly valuable for discovering potential intervention strategies and improving the efficacy of therapeutic endpoints.

Many MIA-associated psychiatric disorders (e.g. schizophrenia) show a progression of phenotypic abnormalities which fully develop during late adolescence or early adulthood (Ozawa et al., 2006; Piontkewitz et al., 2011; Zuckerman et al., 2003). This late adolescent onset provides a critical window for intervening and protecting against the manifestation of these deficits. Among the potential therapeutic intervention strategies, environmental enrichment (EE) is a non-invasive and non-pharmacological therapy characterized by exposure to novel environments with rich social, motor, cognitive and sensory stimulation. Compelling evidence has shown that exposure to an enriched environment can enhance brain plasticity (e.g., increased dendritic branching, synaptogenesis, etc.; Kolb et al., 1998; Van Praag et al., 2000), the turnover of several neurotransmitters (Escorihuela et al., 1995), as well as improvement in cognitive functions (Williams et al., 2001). Such work in the animal laboratory provides insight into the underlying biological mechanisms that may dictate the success of EE in clinical settings. Indeed, EE has been used with humans in clinical rehabilitation research and has been shown to reverse behavioral and cognitive impairments associated with stroke, cerebral palsy and autism (Janssen et al., 2014; Morgan et al., 2014; Rosbergen et al., 2017; Woo et al., 2015). Combined, this evidence raises the potential utility of EE as a rehabilitative intervention for psychiatric disorders associated with prenatal infections.

Using an LPS MIA model in rats, it has been demonstrated that EE prevents against 1) elevations in hippocampal corticosterone level, 2) decreased hippocampal glucocorticoid receptor (GR) expression, and 3) reduced social contact in juvenile males (Connors et al., 2014). In other work, EE has been shown to rescue impairments in spatial memory, as measured by the object-in-place test (Kentner et al., 2016), and reductions in offspring body weight (Bakos et al., 2004) following MIA. Again, some of this work is limited in their conclusions by evaluating only male animals (Bakos et al., 2004; Kentner et al., 2016). Moreover, phenotypic discrepancies between the sexes following EE housing suggest that male and females may respond to the same EE protocol differently (Kentner et al., 2018; Connors et al., 2015).

In the current study, we use a rodent MIA model to examine the beneficial effects of EE in female rats. The offspring of dams exposed to either prenatal LPS or saline were evaluated in both an object-in-place task and the social interaction test. Impaired performance in these behavioral tests are thought to be reflective of clinical symptoms in MIA-associated neurodevelopmental disorders, such as schizophrenia and autism (Howland et al., 2012; Patterson, 2011; Rajagopal et al., 2014). Also, early adverse life events like MIA have important programming effects on the hypothalamic-pituitary-adrenal (HPA) axis (Kapoor and Matthews, 2005), in addition to brain synaptic development (Coiro et al., 2015; Pendyala et al., 2017). Hence, we investigated the potential endocrine and molecular mechanisms that may underlie the beneficial effects of EE by analyzing plasma corticosterone and mRNA expression of neural markers associated with the HPA axis and synaptic plasticity. To do so, we extended some of our previous work in males (Kentner et al., 2016) to female animals by measuring brain-derived neurotrophic factor (BDNF) and tyrosine receptor kinase B (TrkB) as previous work has shown EE to increase BDNF, a cognate ligand for TrkB, which modulates hippocampal neuroplasticity (Falkenberg et al., 1992).

Moreover, we expanded upon both the original male data set (Kentner et al., 2016) and the current female study by measuring mRNA expression of GR and FK506 binding protein 5 (Fkbp5), a co-chaperone component of the GR heterocomplex involved in modulating GR sensitivity (Binder, 2009). Dysregulation of the glutamate signaling pathway has also been implicated in the neuropathology of schizophrenia (Howes et al., 2015; Hu et al., 2015; Plaitakis et al., 1982). We therefore investigated mRNA expression of two primary subclasses of glutamate transporters: the excitatory amino acid transporter (EAAT) family and vesicular glutamate transporter (VGLUT), two subunits of ionotropic glutamate receptors: The a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) Type Subunit 1 (Gria A1) and 1, N-methyl-d-aspartate 2B (NR2B), and postsynaptic density protein 95 (PSD95), which is enriched at postsynaptic sites of excitatory synapses. The expression of PSD95 has previously been shown to be reduced following prenatal immune activation (Giovanoli et al., 2016). We focused our neuroanatomical investigations on prefrontal cortex (PFC), hippocampus, amygdala, and hypothalamus because they are implicated in modulating a series of behaviors and cognitive abilities that may contribute to the neuropathology of the MIA-associated disorders, for instance, integrating information related to object placement and object recognition (Barker et al., 2007; Barker and Warburton, 2011), memory consolidation (Roozendaal, 2000), sensorimotor gating (Lipska, 2004) and social behaviors (O'Connell and Hofmann, 2011).

2. Materials and methods

2.1. Animals and gestational treatment

Pregnant Sprague-Dawley rats at gestational day (G)12 (Charles River, Wilmington, MA) were immediately pair-housed in standard cages and maintained at 20 °C on a 12 h light/dark cycle (0700–1900 light) with ad libitum access to food and water. Animal procedures were conducted in accordance with the Association for Assessment and Accreditation of Laboratory Animal Care with protocols approved by the MCPHS University Institutional Animal Care and Use Committee. A flow chart of study procedures is presented in Fig. 1. We also include a methods reporting table (Supplementary Table 1), as recommended by a recent paper to improve reporting of MIA models (Kentner et al., 2019).

On the morning of G15 (between 9:00 and 10:00 h), pregnant dams were separated into individual clean cages and randomly assigned to receive an injection of 100 μg/kg LPS (*Escherichia coli*, serotype 026:B6; L-3755, Sigma, St. Louis, MO) in pyrogen-free saline, or an equivalent volume of pyrogen-free saline (control) intraperitoneally between 11:30 and 12:30 a.m.

Day of birth was designated as postnatal day (P)1. On P3 litters were culled to 10 pups, with balanced sex ratios. Data from the female animals are the main focus of the current study. While we present some extensions to their neurophysiological data (see Supplementary Table 2), behavioral results from the male siblings were featured in previous work (see Kentner et al., 2016). On P22, all pups were weaned and pair-housed in clean standard cages. Each cage contained one LPS and one saline-treated animal. On P50, offspring were randomly assigned to fresh cages and cage mates in one of three housing conditions: a) standard housing (SD), where same sex animals were reared in a standard sized cage (26 × 48 × 20 cm) with only a tube, Nylabone and Nestlets©, b) communal nesting (CN) where four same-sex animals were reared in a larger style one-level cage (50 × 40 × 21 cm) with a tube, Nylabone and Nestlets©, and c) EE where four animals of the same sex lived in a large multi-level cage (91.5 × 64 × 159 cm; Critter Nation, Muncie IN) with novel toys and ramps, in addition to a tube, Nylabone and Nestlets©. Toys and tubes were changed twice a week to maintain the novelty of the EE condition. For the female data, there were n = 8 saline and n = 8 LPS litters for each of the three housing conditions.

2.2. Offspring behavior

Animals' spatial working memory and social behavior were assessed six weeks after being placed into either SD, CN or EE housing. To habituate to the testing environment, all females freely explored a black open field arena (40 cm × 40 cm × 28 cm) for 10 min/day three times

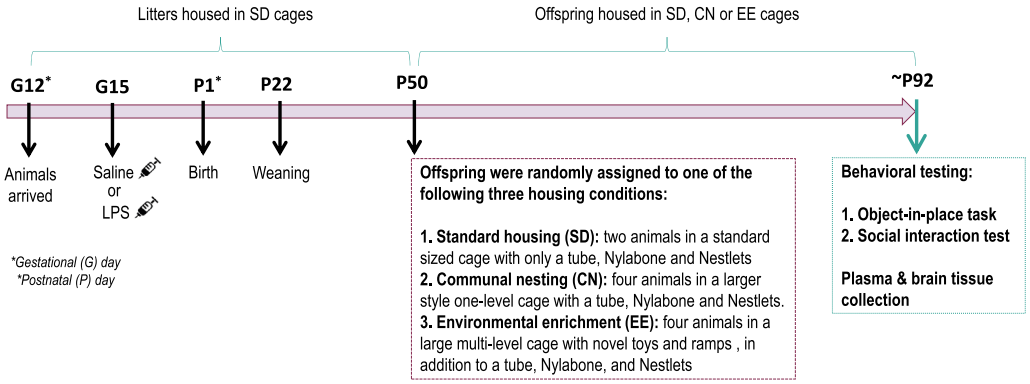

Fig. 1. Flow chart of experiment procedures.

before the testing. The order of social behavior and spatial memory testing were counterbalanced. All behaviors were video recorded and manually scored using the software ODLog™ 2.0 (http://www.macropodsoftware.com/) by blinded observers.

2.2.1. Object-in-place

The object-in-place task was conducted in the black open field arena with four novel objects located in each of the four corners. During the first trial of a two-step procedure, a female rat was placed into the center of the field and allowed to explore the enclosure/objects for 5 min. One hour later, the focal rat was returned to the arena to engage in the second trial (5 min). During this second trial, the four objects had been replaced with identical copies and the positions of two objects exchanged. Based on the time spent exploring each object, we calculated a discrimination ratio ([(total time exploring moved objects − total time exploring permanent objects)/(total time exploring both objects)]; Connors et al., 2014; Howland et al., 2012). A higher discrimination ratio indicates a better ability to recognize the moved objects from the familiar permanent objects; in another words, a better spatial working memory.

2.2.2. Social interaction

The social interaction procedure was performed as previously described (Connors et al., 2014; Kentner et al., 2016) and each trial lasted 10 min, during which the focal female was put in the open field arena with another age-matched novel female. We evaluated animals on the frequency and duration of social contacts, which included the following behaviors: allogrooming, mounting/crawling, approaching/following, biting, and converted into a composite score (Connors et al., 2014; Kentner et al., 2016).

2.3. Tissue collection and analysis

After completion of the behavioral tests, animals were anesthetized with a mixture of Ketamine/Xylazine (40–80 mg/kg, i.p/5–10 mg/kg, i.p). Blood was collected via cardiac puncture and placed into an ethylenediaminetetraacetic acid (EDTA)-coated microtainer tube (Becton Dickson, Franklin Lakes New Jersey). Blood samples were centrifuged at 1000 relative centrifugal force (rcf) for 10 min for plasma separation for Enzyme-linked immunosorbent assay (ELISA). Animals were perfused intracardially with a phosphate buffer solution and whole amygdala, hypothalamus, hippocampus and prefrontal cortex were dissected. All samples were frozen on dry ice and stored at −75 °C until processing.

2.3.1. ELISA assay

Corticosterone ELISA was performed to analyze plasma samples using a kit purchased from Enzo Life Sciences (#ADI-900-097, Farmingdale, NY). We followed the small sample assay protocol recommended by the manufacturer and ran each sample in duplicate. The minimum detectable concentration was 26.99 pg/ml, and the intra- and inter-assay coefficients of variation were 6.6% and 7.8%, respectively.

2.3.2. RT-PCR

Genes of interest were analyzed as described previously (Kentner et al., 2016; Kentner et al., 2018). Briefly, total RNA was extracted from frozen tissue using RNeasy (Qiagen) and resuspended in RNase-free water. Isolated RNA concentration was quantified on a spectrophotometer (Synergy™ HT, Biotek). According to the manufacturer's protocol, total RNA was reverse transcribed to cDNA with the transcriptor first strand cDNA synthesis kit (Roche) and the final cDNA solution was stored at −20 °C for analysis. Quantitative real-time PCR with Taqman Fast Advanced Mastermix (ThermoFisher Scientific) was used to measure the expression of *Fkbp5* (Rn01768371_m1), *Eaat1* (*Slc1a3*; Rn01402419_g1), *Eaat2* (*Slc1a2*; Rn00691548_m1), *Eaat3* (*Slc1a1*; Rn00564705_m1), *Vglut1* (*Slc17a7*; Rn01462431_m1), *AMPA* (*Gria1*;Rn06323759_m1), *Nr2b* (*Grin2b*; Rn00680474_m1), *PSD95* (Rn00571479_m1), *Bdnf* (Rn00560868_m1), and *TrkB* (*Ntrk2*; Rn01441749_m1). All reactions were analyzed in triplicate using optical 96-well plates (Applied Biosystems StepOnePlus Real-Time PCR System). We used the standard curve method to calculate the relative gene expression levels based on the cycle number at threshold (C_T value; Kentner et al., 2016; Kentner et al., 2018). Glyceraldehyde-3-phosphate dehydrogenase (*Gapdh*; Rn99999916_s1) was used as a housekeeping gene as it is not affected by prenatal LPS treatment (Núñez Estevez et al., 2020). Gene expression was normalized in relation to *Gapdh* and data presented as mean expression relative to SD-saline treated controls.

2.4. Statistical analysis

The Shapiro-Wilk test was used to test assumptions of normality. Kruskal-Wallis tests (expressed as X^2) were employed to evaluate significantly skewed data. Except for the case of the object-in-place test, two-way ANOVAs were conducted to analyze the interaction between drug treatment (Saline vs LPS) and housing condition (SD, CN and EE) for normally distributed data. With respect to parametric data, LSD post hocs were applied unless there were fewer than three levels in which case pairwise t-tests were utilized. The False Discovery Rate (FDR) was applied to correct for multiple testing in the gene expression experiments. Discrimination ratio, in the object-in-place test, was assessed using one-sample t-tests, where '0' was used as a comparison value, corresponding to a lack of discrimination between novel and familiar objects. All tests used a significance level of $p = 0.05$ and were two-tailed. Analyses were conducted using SPSS version 21.0 software (IBM, Armonk, NY) and data expressed as mean ± SEM. The partial eta-squared (η_p^2) is also reported as an index of effect size for the ANOVAs (the range of values being 0.02 = small effect, 0.13 = moderate effect, 0.26 = large effect; Miles and Shevlin, 2001).

3. Results

3.1. Behavioral tests

3.1.1. Object-in-place

Object-in-place associative recognition memory has been shown to be impaired in patients with schizophrenia (Burglen et al., 2004) and such an impairment was rescued by EE in our previous study using a male rodent MIA model (Kentner et al., 2016). For all saline treated females, the discrimination ratio was significantly larger than "0" for SD (t_7 = 6.683, p = 0.0001), CN (t_7 = 3.438, p = 0.011) and EE (t_7 = 12.695, p = 0.0001), suggesting intact memory for previously viewed objects in these groups (Fig. 2A). LPS disrupted the spatial memory in both the SD (t_7 = 0.972, p = 0.363) and CN (t_7 = 0.586, p = 0.576) groups, which was reflected by the non-significant difference between the discrimination ratio and "0" (Fig. 2A). This disruption was rescued in LPS-treated females housed in EE, for which the discrimination ratio was significantly higher than "0" (t_7 = 2.621, p = 0.034; Fig. 2A).

3.1.2. Social behavior

Disrupted social interactions and communication are core symptoms of MIA-associated psychiatric disorders (Knuesel et al., 2014). For the duration of time spent in social contact, the two-way ANOVA did not reveal either a significant interaction or a main effect of drug treatment (p > 0.05; Fig. 2B). However, there was a significant main effect of housing condition ($F_{2,\ 42}$ = 9.113, p = 0.001, η_p^2 = 0.303; Fig. 2B). LSD post hocs demonstrated that female rats housed in CN (p = 0.0001) and EE (p = 0.020) spent longer durations of time in contact compared to SD animals. In parallel, Kruskal-Wallis tests revealed that CN and EE housing promoted increased frequencies of social contact (CN vs. SD, χ^2 = 11.510, p = 0.001; EE vs. SD, χ^2 = 15.966, p = 0.001; Fig. 2C).

3.2. Plasma corticosterone

Elevated levels of glucocorticoids have been shown to impair working and reference memory (Kamphuis et al., 2003; Yaka et al., 2007; Pascuan et al., 2017; Stylianakis et al., 2018). Two-way ANOVA revealed a significant interaction between drug treatment and housing condition for female animals ($F_{2,\ 36}$ = 5.621, p = 0.008, η_p^2 = 0.238; Fig. 3A). Further, post hocs showed that SD-LPS females had higher levels of plasma corticosterone than SD-Saline females (t_{12} = 2.649, p = 0.021). There were no significant differences between saline and LPS animals housed in either CN or EE conditions (p > 0.05; Fig. 3A). Moreover, female EE-LPS animals had significantly lower plasma corticosterone levels compared to SD-LPS animals (t_{12} = −2.751, p = 0.018), suggesting that the complex environmental condition reversed the detrimental effects of MIA on the HPA axis. There were no significant effects of prenatal treatment or housing on male rats (p > 0.05; Fig. 2B).

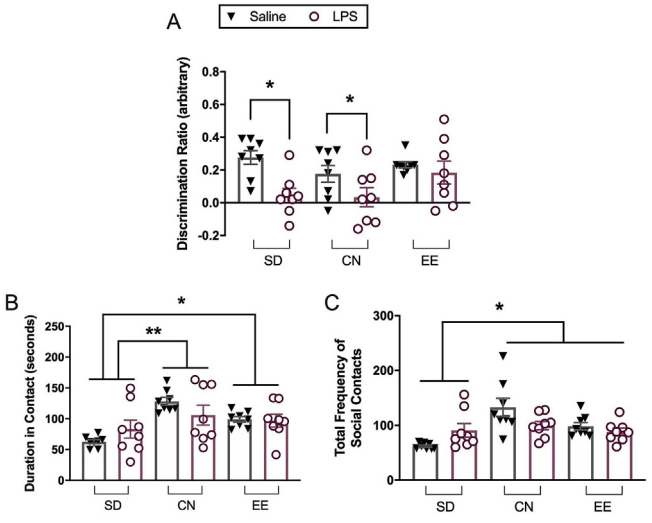

Fig. 2. Effects of maternal immune activation (MIA) on female offspring behavior. (A) MIA decreased spatial discrimination ability in an object-in-place task and environmental enrichment rescued this effect. Both (B) duration in social contact and (C) and total frequency of social contacts were elevated by six weeks of postpubertal housing in environmental complexity. Saline = solid black triangles, LPS = open maroon circles. Data represent mean expression (±SEM); *p < 0.05, **p < 0.01, n = 8 litters for each group.

3.3. qPCR results

We previously examined the expression of several markers of plasticity in male rats and revealed that EE reversed the effect of MIA on hippocampal *Bdnf*, prefrontal *TrkB* and prefrontal *Eaat2* mRNA (Kentner et al., 2016). In the current study, we extended this examination to females. Additionally, we measured mRNA expression of *Vglut1*, *Nr2b*, *Gria1* and *Psd-95*, as well as indicators of chronic stress (*Gr* and *Fkbp5*) throughout critical brain regions of both male and female animals.

3.3.1. Extending the evaluation of synaptic plasticity markers in male offspring

Prenatal LPS challenge was associated with significantly reduced levels of *Eaat1* ($F_{1,42}$ = 46.831, p = 0.0001, η_p^2 = 0.527; Fig. 4A), *Eaat3* ($F_{1,42}$ = 14.995, p = 0.001, η_p^2 = 0.263; Fig. 4B), *Psd-95* ($F_{1,42}$ = 7.540, p = 0.009, η_p^2 = 0.152; Fig. 4C), *Gria1* (χ^2 = 7.296, p = 0.007; Fig. 4D) and *TrkB* (χ^2 = 10.48, p = 0.001; Fig. 4E) in the amygdalae of male offspring. No further main effects of MIA were revealed for the expression of other markers of synaptic plasticity in the amygdala or hypothalamus (p > 0.05; refer to Supplementary Table 2).

3.3.2. Altered markers of synaptic plasticity in female offspring

In the amygdala, prenatal LPS was significantly associated with downregulated levels of *Eaat1* ($F_{1,41}$ = 17.003, p < 0.01, η_p^2 = 0.293; Fig. 5A), *Vglut1* ($F_{1,41}$ = 8.800, p = 0.005, η_p^2 = 0.177; Fig. 5B) and *Gria1* ($F_{1,41}$ = 8.171, p = 0.007, η_p^2 = 0.166; Fig. 5C), compared to saline treated female offspring. For the levels of *Eaat2* in the amygdala, two-way ANOVA revealed a significant interaction between drug treatment and housing condition ($F_{2,\ 41}$ = 4.116, p = 0.023, η_p^2 = 0.167) in that SD-LPS animals had lower expression compared to SD-Saline animals (t_{14} = −4.708, p = 0.001; Fig. 5D). There were no significant differences in *Eaat2* amygdala level between prenatal LPS and saline animals housed in CN or EE (p > 0.05; Fig. 5D). A significant main effect of housing condition was also revealed for amygdala levels of *Eaat1* ($F_{2,\ 41}$ = 5.905, p = 0.006, η_p^2 = 0.224; Fig. 5A), *Vglut1* ($F_{2,\ 41}$ = 5.870, p = 0.006, η_p^2 = 0.223; Fig. 5B) and *Gria1* ($F_{2,\ 41}$ = 5.777, p = 0.006, η_p^2 = 0.220; Fig. 5C), compared to saline treated female offspring.

In female brains, two-way ANOVA did not reveal statistically significant effects for *bdnf* in the amygdala (p > 0.05; **refer to** Supplementary Table 3). However, *TrkB* in this region was significantly reduced following prenatal LPS treatment, compared to saline exposed animals (χ^2 = 15.873, p < 0.001; Fig. 5E). While *TrkB* in the amygdala was significantly higher in SD compared to CN housed females (χ^2 = 4.225, p = 0.04; Fig. 5E), environmental complexity was associated with elevated *Bdnf* levels in the hypothalamus (CN vs SD: χ^2 = 5.638, p = 0.018; EE vs SD: χ^2 = 7.658, p = 0.022; Supplementary Table 3). Interestingly, hypothalamic *Bdnf* in CN rats was significantly higher than EE (χ^2 = 5.638, p = 0.018; Supplementary Table 3), suggesting that the increased level of enrichment may not be as beneficial for females on some measures. Additional markers of synaptic plasticity in the prefrontal cortex, hippocampus, amygdala, and hypothalamus are provided in Supplementary Table 3.

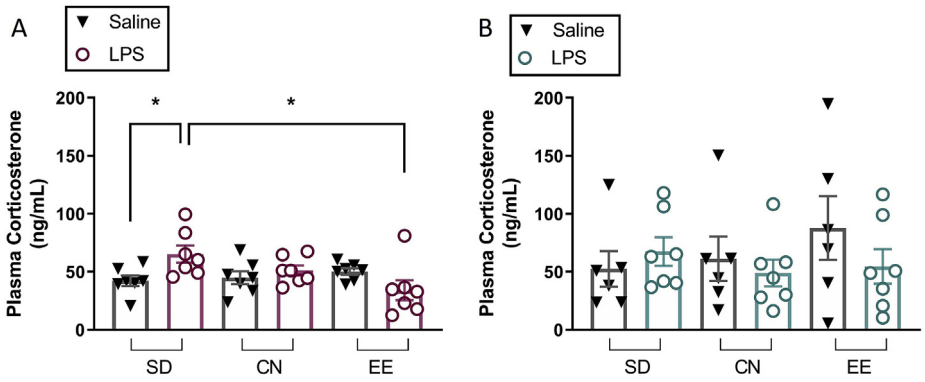

Fig. 3. The impact of maternal immune activation (MIA) on plasma corticosterone levels in A) female and B) male offspring housed in standard cages (SD), communal nesting (CN) or environmental enrichment (EE) for six weeks post-puberty. Saline = solid black triangles, LPS = open maroon or teal circles. Data represent mean expression (±SEM); *p < 0.05, n = 6–7 litters for each group.

3.3.3. Extending the evaluation of genetic stress markers in male offspring

The amygdala has been implicated in mediating effects of glucocorticoids on memory consolidation (for review see Roozendaal, 2000), therefore we investigated mRNA expression of *Gr* in this region. MIA male offspring expressed significantly lower *Gr* levels than saline treated ($\chi^2 = 7.408$, p = 0.006; Fig. 6A). There was also a significant interaction between MIA treatment and housing condition ($F_{2,41} = 10.463$, p = 0.0001, $\eta_p^2 = 0.338$) for the level of *Fkbp5* in hypothalamus. Further, independent t-test revealed that EE-LPS animals expressed significantly lower levels of *Fkbp5* than EE-saline ($t_{12} = -3.301$, p = 0.006; Fig. 6B). This suggests that enrichment promoted compensatory action against the stress associated with MIA. No significant effects of MIA were revealed for the expression of other genetic markers of stress in the amygdala or hypothalamus (p > 0.05; refer to Supplementary Table 2).

3.3.4. Altered indicators of stress in females

For the hypothalamic data, two-way ANOVA revealed a significant interaction between MIA and housing for the level of *Gr* ($F_{2,42} = 5.452$, p = 0.008, $\eta_p^2 = 0.206$; Fig. 7A). Specifically, an independent t-test showed that for the level of *Gr*, CN-LPS was significantly higher than CN-saline ($t_{14} = 2.448$, p = 0.028; Fig. 7A) and EE-LPS significantly lower than EE-saline ($t_{14} = -3.005$, p = 0.009; Fig. 7A). No further effects were detected for the levels of *Gr* or *Fkbp5* in the PFC, hippocampus, of hypothalamus (p > 0.05; Supplementary Table 3).

In the amygdala, LPS females expressed significantly lower *Gr* levels than saline treated offspring ($F_{1,41} = 4.440$, p = 0.041, $\eta_p^2 = 0.098$; Fig. 7B). A significant main effect of housing condition ($F_{2,41} = 9.096$, p = 0.001, $\eta_p^2 = 0.307$; Fig. 7A) was also revealed. Post hocs showed that SD females expressed significantly higher *Gr* levels than the CN (p = 0.034) and EE females (p = 0.0001), while no significant difference between CN and EE groups was observed (p > 0.05). In the amygdala, *Fkbp5* was significantly downregulated in LPS females, compared to saline-treated offspring ($F_{1,41} = 5.894$, p = 0.020, $\eta_p^2 = 0.126$; Fig. 7C). Two-way ANOVA also revealed a significant main effect of housing condition ($F_{2,41} = 4.262$, p = 0.021, $\eta_p^2 = 0.172$; Fig. 7C). Post hocs showed that EE females expressed significantly lower *Fkbp5* levels than SD (p = 0.010) and CN females (p = 0.024), while no significant difference between SD and CN groups was observed (p > 0.05).

4. Discussion

In the current study, we demonstrate that EE rescues behavioral deficits in the object-in-place task and dampens the elevation of plasma corticosterone that female MIA offspring display. Our results extend upon previous findings from our lab, showing that a single LPS injection during mid gestation disrupts spatial and object memory in male rats, and housing in EE mitigates this disruption (Kentner et al., 2016). We further demonstrate alterations in the mRNA expression of several synaptic neural markers in brain regions implicated in MIA-induced behavioral abnormalities. In particular, there was a downregulation of markers associated with HPA axis and glutamate signaling pathways in the amygdala, among other brain regions, following MIA in both males and females. Altogether, these data confirm previous work showing that MIA leads to chronic changes in behavioral expression and alterations in synaptic development (see Estes and McAllister, 2016; Knuesel et al., 2014), and that this extends to female animals as well. Moreover, our data suggest the potential of EE as an intervention for these MIA-induced deficits, in terms of both behavior and synaptic remodeling.

The disrupted object-in-place associations appear to be a consequence, at least in part, of alterations in the HPA axis of female MIA offspring. Prenatal exposure to LPS induces increased cytokine and glucocorticoid levels in the maternal circulation, in addition to the placenta and fetal brain (Cai et al., 2000; Gayle et al., 2004; Reul et al., 1994; Núñez Estevez et al., 2020). Together, these effects are thought to be involved in programing the HPA axis in rats and mice (Hava et al., 2006; Noorlander et al., 2006; Stojanoski et al., 2004, 2006). In the current study, MIA on GD15 was likely involved in the long-term impact on HPA activity in adult female animals. This notion stands in line with previous data showing elevated corticosterone levels and hyperactivity of the HPA axis in adult prenatally treated LPS offspring (Basta-Kaim et al., 2011; Reul et al., 1994; Zager et al., 2014). Although we did not observe such plasma corticosterone elevations in male animals, we have previously measured elevated corticosterone in male hippocampus following MIA (Connors et al., 2014), suggestive of targeted impairments in HPA-dysregulation. These discrepancies are perhaps dependent on the serotype/lot of LPS employed and other methodological factors such as dose and timing of prenatal challenge. New guideline recommendations for reporting this type of information may help to disentangle some of this literature.

One consequence of exposure to increased glucocorticoids during both fetal development and late adulthood is impairments in working and reference memory (Kamphuis et al., 2003; Yaka et al., 2007). Interestingly, the LPS-induced elevation of plasma corticosterone observed in females was accompanied by a decrease in the level of *Gr* in the amygdala. Activity of amygdala GR is thought to be involved in mediating effects of glucocorticoids on memory consolidation (for review see Roozendaal, 2000). Decreased amygdala *Gr* levels, coupled with elevated basal plasma corticosterone, in female animals may contribute to the disrupted consolidation of spatial memory observed here.

In female MIA offspring, EE may rescue the disrupted object-in-place performance via dampening of the LPS-induced HPA hyperactivity. This stands in line with previous data showing that EE inhibits the corticosterone elevation to an acute handling and leads to a more rapid extinction of corticosterone level in response to repeated handling, considered a stressor (Wright and Conrad, 2008). It should be noted that

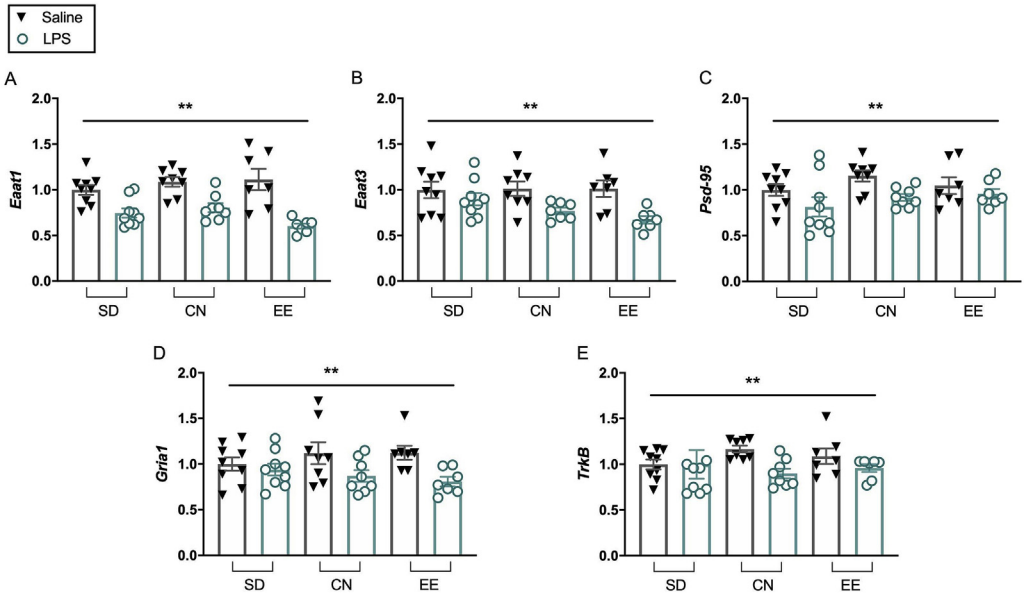

Fig. 4. The impact of prenatal LPS on the expression of synaptic plasticity mRNA markers in the amygdala of male offspring housed in standard cages (SD), communal nesting (CN) or environmental enrichment (EE) for six weeks post-puberty. A) *Eaat1*, B) *Eaat3*, C) *PSD-95*, D) *Gria1*, E) *TrkB*. Saline = solid black triangles, LPS = open teal circles. Data represent mean expression (±SEM) relative to SD-saline treated controls; **p < 0.01, n = 7–9 litters for each group.

data on changes in neuroendocrine status following EE is not consistent. Some studies report elevated corticosteroid secretion in mice and pigs (de Jong et al., 1998; Haemisch et al., 1994; Marashi et al., 2003), while others find no difference in basal corticosterone concentrations following EE (Pham et al., 1999; Schrijver et al., 2002). In the current study, EE alone did not change HPA activity, which is reflected by generally similar concentrations of corticosterone in animals treated with saline across all housing conditions. However, EE appears to contribute by dampening HPA axis hyperactivity, when primed by prenatal LPS injection, resulting in rescue of impairments in spatial discrimination memory.

Impairments in social interactions and communication are core symptoms of MIA-associated psychiatric disorders (e.g. schizophrenia and autism). Our lab's previous work (Connors et al., 2014), and those of others (Kirsten et al., 2010, 2012, 2013; Taylor et al., 2012) directly compared social behaviors of male and female rats treated with prenatal LPS, finding that females may be resilient to MIA with respect to the

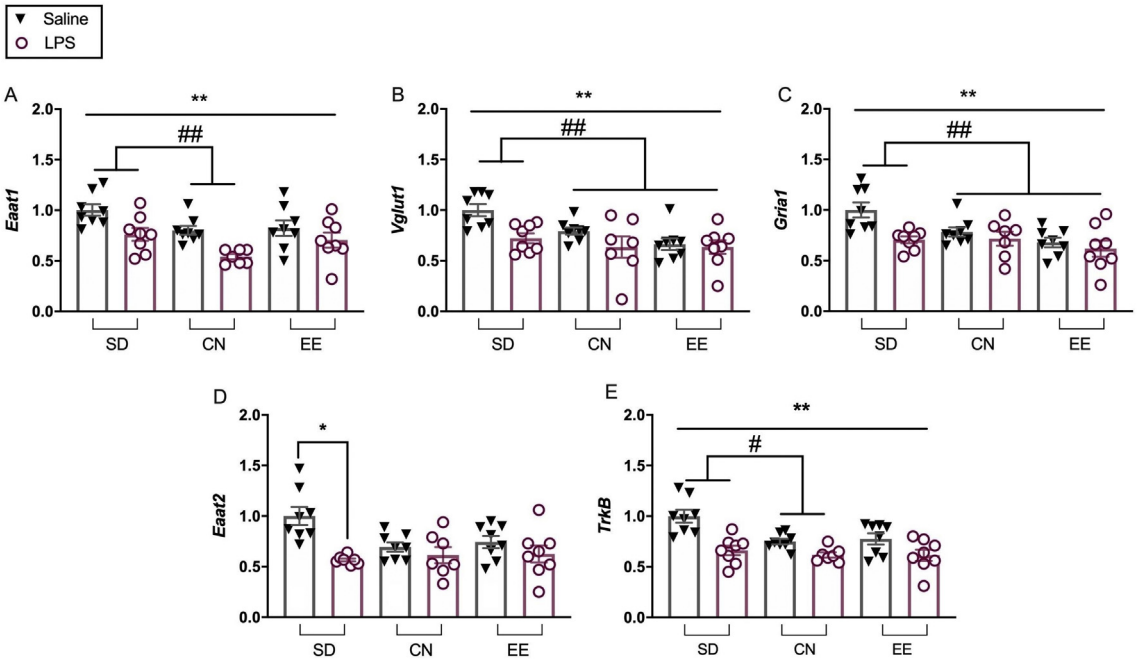

Fig. 5. The impact of prenatal LPS on the expression of synaptic plasticity mRNA markers in the amygdala of female offspring housed in standard cages (SD), communal nesting (CN) or environmental enrichment (EE) for six weeks post-puberty. A) *Eaat1*, B) *Vglut1*, C) *Gria1*, D) *Eaat2*, E) *TrkB*. Saline = solid black triangles, LPS = open maroon circles. Data represent mean expression (±SEM) relative to SD-saline treated controls; *p < 0.05; **p < 0.01, LPS vs Saline; # < 0.05; ## < 0.01, effect of housing; n = 8 litters for each group.

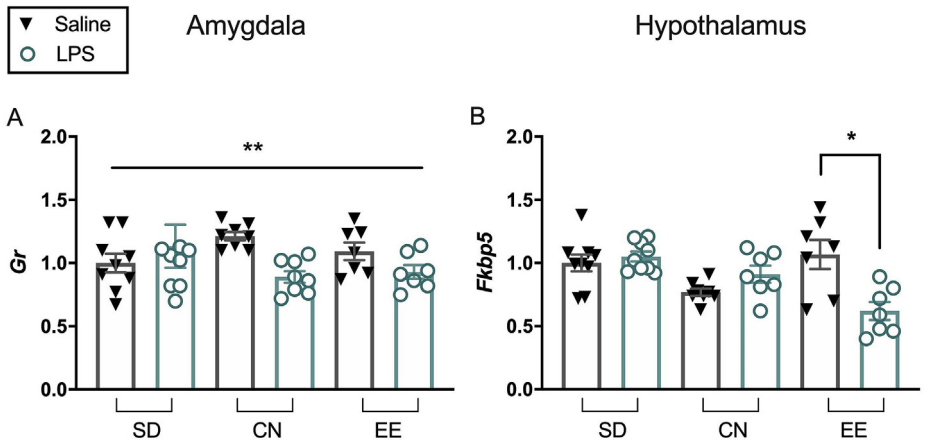

Fig. 6. The impact of prenatal LPS on the expression of mRNA markers of stress in male offspring housed in standard cages (SD), communal nesting (CN) or environmental enrichment (EE) for six weeks post-puberty. Saline = solid black triangles, LPS = open teal circles. A) *Gr* in the amygdala and B) hypothalamic *Fkbp5*. Data represent mean expression (±SEM) relative to SD-saline treated controls; *p < 0.05, **p < 0.01, LPS vs Saline; n = 7–9 litters for each group.

disruption in social interactions. Our current results provide further evidence for this observation and support the view that increased environmental complexity promotes social behaviors (Connors et al., 2014; Kentner et al., 2018).

Contrary to findings in rats, a study using mice found modest social impairments in female, but not male offspring challenged prenatally with LPS (Xuan and Hampson, 2014). A key methodological difference was that in this work MIA and 'healthy' social stimulus mice were prevented from direct physical interaction. This was done by isolating the stimulus mice in wire cups during the social test. In many studies using rats, MIA and stimulus rats freely interact in an open field and a composite social score calculated based on a series of behaviors (e.g. sniffing, following, crawling under/over, and mounting). Differences in experimental design may account for the discrepancy observed between these studies. Indeed, using a similar design to Xuan and Hampson's mouse study (2014), we have shown that female rats prenatally treated with LPS have disruptions in social discrimination, although not social preference. The former impairment was prevented by life-long housing in EE (Núñez Estevez et al., 2020).

From an evolutionary perspective, the difference in sensitivity to MIA-induced social impairments may be accounted by the varied parental investment made by the two sexes. Males are subjected to higher reproductive competition and group housing of male rodents may be considered stressful for subordinate animals (Hurst et al., 1996). In comparison, females are less sensitive to social instability (Brown and Grunberg, 1995). Communal nesting has been reported for some species of female rats and mice, in both the wild and in the laboratory (Hayes, 2000; Schultz and Lore, 1993; Connors et al., 2015; Curley et al., 2009). In general, it may be that female rodents are more resilient to the effects of MIA on some social behaviors, given their different social and reproductive roles.

Synaptic proteins are important markers of membrane fusion, exocytosis, and the recycling of synaptic vesicles (Béïque and Andrade, 2003; Derkach et al., 2007; Leal et al., 2014; Yoshii and Constantine-Paton, 2010). Disruptions in these proteins are reported to underlie the neuropathology of psychiatric disorders (Eastwood, 2004; Ebrahimi-Fakhari and Sahin, 2015). In the current study, we found decreased mRNA expression of several genes associated with glutamate signaling pathways and synaptic plasticity (e.g. *Eaats*, *Psd-95*, *Gria1*, *TrkB*), particularly in the amygdala. This suggests that disturbances to this region may be involved in mediating the effects of MIA.

Previous MIA studies have primarily focused on the developing hippocampus, cortex, and mid-brain, while findings on changes in the amygdala are relatively limited (Knuesel et al., 2014). Of the work that has been done, it is clear this region is sensitive to the effects of prenatal inflammatory challenges. For example, MIA led to the upregulation of several inflammatory markers in the amygdala, both prenatally and in adulthood (O'Loughlin et al., 2017). Prenatal inflammatory challenge is associated with decreased amygdalar volume (Crum et al., 2017) and systemic neuroinflammation resulted in increased neuronal activity within this region. The latter of which was correlated with increases in innate fear and anxiety responses (De La Mora et al., 2006; Engler et al., 2011; Frankland et al., 1997). A previous study in male C57BL/6J mice also demonstrated that glutamatergic projections from medial PFC to basal lateral amygdala are altered following MIA (Li et al., 2018). Adding another layer to these previous findings, our current results show that MIA disrupts amygdalae mRNA expression of several markers associated with synaptic plasticity and resiliency against early-life stressors, which may further give rise to the pathogenesis of neurodevelopmental disorders such as schizophrenia (Purcell et al., 2001; Sheldon and Robinson, 2007).

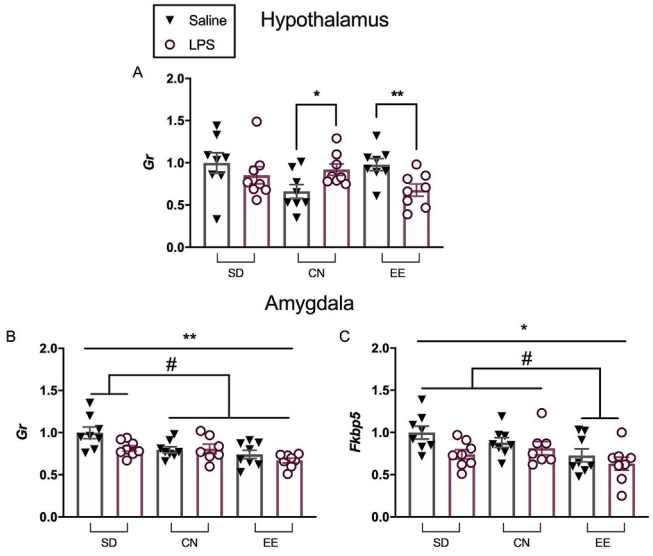

Fig. 7. The impact of prenatal LPS on the expression of mRNA markers of stress in female offspring housed in standard cages (SD), communal nesting (CN) or environmental enrichment (EE) for six weeks post-puberty. A) hypothalamic *Gr*, and amygdala levels of B) *Gr* and C) *Fkbp5*. Saline = solid black triangles, LPS = open maroon circles. Data represent mean expression (±SEM) relative to SD-saline treated controls; *p < 0.05, **p < 0.01, LPS vs Saline; # < 0.05; ## < 0.01, effect of housing; n = 8 litters for each group.

AMPA receptors are involved in regulating fast excitatory neurotransmission and the induction of synaptic plasticity (Derkach et al., 2007); blockade of these receptors in the perirhinal cortices has been shown to inhibit both encoding and retrieval of object-in-place memory (Barker and Warburton, 2008; Winters and Bussey, 2005). Deletion of *Gria1* severely impaired spatial working memory (Sanderson et al., 2010; Schmitt et al., 2005). Therefore, the downregulated *Gria1* observed in the current study may also contribute to impaired performance in this task. Moreover, there is accumulating evidence for altered BDNF–TrkB signaling in the etiology of schizophrenia (review see Pandya et al., 2013). Overall, our data provide additional evidence for a synaptic pathology in MIA-associated disorders, in terms of a downregulation of these synaptic genes.

Although prenatal LPS downregulated genetic markers of synaptic plasticity, increasing environment complexity also decreased the expression of some of these genes (e.g. *Eaat1, Vglut1, Gria1 and TrkB*). This may raise the question of whether animals housed in EE are exposed to chronic stress. In male rats, housing in EE has resulted in higher levels of plasma corticosterone, and enhanced responses to buspirone challenge by inducing larger adrenals and a corticosterone surge (Moncek et al., 2004). However, it is unlikely that EE exposure in the current study resulted in chronic stress because neither EE nor CN conditions were associated with elevated plasma corticosterone. This is consistent with our previous findings showing that basal hippocampal and plasma corticosterone have not been affected by EE (Connors et al., 2015; Kentner et al., 2018; MacRae et al., 2015).

Importantly, observed changes in synaptic markers following environmental complexity was not homogeneous across all the brain regions sampled, and was sex specific. Indeed, in the present study we observed EE to be associated with upregulated expression of hypothalamic *Bdnf* in female rats while our previous work demonstrated elevated levels of *Bdnf* in the hippocampus of males (Kentner et al., 2016). These results are consistent with previous findings of sex differences in the EE-altered expression of *Bdnf* in the hypothalamus (Bakos et al., 2009) and hippocampus (Chourbaji et al., 2012). Similar to other interventions, for example pharmacological treatments, it is likely that the benefits of EE are not perfect and impart widespread and differential effects across the brain. The benefits are also likely to be context, endpoint, and sex dependent.

The current results, coupled with our previous findings in males, suggest that while aspects of their behavioral phenotype were similar (e.g. disrupted spatial discrimination), the consequences of MIA and the rehabilitative effects of EE may be mediated via different mechanisms between the two sexes. Compared to what we observed here in females, our lab's previous work in males has shown prenatal LPS to disrupt the expression of prefrontal *Eaat2* in addition to *Bdnf* and *TrkB* receptor genes in hippocampus and PFC respectively; EE mitigated each of these neural changes (Kentner et al., 2016). In the current study, our data show that only in the amygdala, prenatal LPS downregulated *Eaat2* in SD, but not CN and EE females. In comparison, the results extending the evaluation of synaptic plasticity markers in male offspring, showed that in the amygdala, prenatal LPS downregulated *Eaat2* in CN and EE, but not in SD males. This suggests that male and female rats may show varied responses to MIA and environmental complexity at the cellular level. As another example, we demonstrated that EE is associated with upregulated levels of hippocampal corticotropin releasing hormone receptor 2 in males, but no such effect occurred in female rats (Kentner et al., 2018). Behaviorally, CN protected against the disrupted object-in-place memory in males (Kentner et al., 2016) but did not rescue it in females. Instead, female animals relied on a more complex environment to rescue their detriments in terms of both spatial discrimination ability and elevated HPA activity. Combined, these findings contribute to a growing literature identifying sexually dimorphic effects following both MIA and EE housing.

5. Conclusions

The current study demonstrates that MIA evoked disturbances in behavior, endocrine status, and neural markers of synaptic plasticity and stress in female offspring. We show that gestational LPS induces alterations in the expression of genes critical to synaptic transmission and plasticity, which may facilitate or even drive the subsequent development of cognitive impairments observed following MIA (reviewed in Boksa, 2010; Harvey and Boksa, 2012; Meyer and Feldon, 2010; Reisinger et al., 2015). EE may serve as an intervention to rescue these deficits through dampening the activity of the HPA axis. Importantly, EE also affected several markers of plasticity throughout the brain. Given the translational use of this intervention with humans (Janssen et al., 2014; Morgan et al., 2014; Rosbergen et al., 2017; Woo et al., 2015), our laboratory findings may contribute to the identification of molecular mechanisms that underlie the therapeutic success of enriched settings in clinical populations for both sexes.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This project was funded by the National Institute of Mental Health under Award Number R15MH114035 (to ACK) and MCPHS Center for Undergraduate Research Mini-Grants (to MP & RCR). The authors would like to extend their thanks to Antoine Khoury and Molly MacRae for technical assistance. The authors would also like to thank the MCPHS University School of Pharmacy and School of Arts & Sciences for their continual support. The content is solely the responsibility of the authors and does not necessarily represent the official views of any of the financial supporters.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2020.100043.

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