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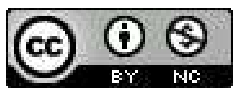

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Maternal immune activation exerts long-term effects on activity and sleep in male offspring mice

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Abstract

Exposure to infectious or non-infectious immune activation during early development is a serious risk factor for long-term behavioural dysfunctions. Mouse models of maternal immune activation (MIA) have increasingly been used to address neuronal and behavioural dysfunctions in response to prenatal infections. One commonly employed MIA model involves administering poly(I:C) (polyriboinosinic-polyribocytdilic acid), a synthetic analogue of double-stranded RNA, during gestation, which robustly induces an acute viral-like inflammatory response. Using electroencephalography (EEG) and infrared (IR) activity recordings, we explored alterations in sleep/wake, circadian and locomotor activity patterns on the adult male offspring of poly(I:C)-treated mothers. Our findings demonstrate that these offspring displayed reduced home cage activity during the (subjective) night under both light/dark or constant darkness conditions. In line with this finding, these mice exhibited an increase in non-rapid eye movement (NREM) sleep duration as well as an increase in sleep spindles density. Following sleep deprivation, poly(I:C)-exposed offspring extended NREM sleep duration and prolonged NREM sleep bouts during the dark phase as compared with non-exposed mice. Additionally, these mice exhibited a significant alteration in NREM sleep EEG spectral power under heightened sleep pressure. Together, our study highlights the lasting effects of infection and/or immune activation during pregnancy on circadian activity and sleep/wake patterns in the offspring.

KEYWORDS
activity, animal model, autism, circadian rhythms, cytokines, infection, inflammation, maternal immune activation (MIA), poly(I:C), schizophrenia, sleep, slow waves, spindles

Abbreviations: ANOVA, analysis of variance; ASD, autism spectrum disorder; CORT, corticosterone; DD, dark–dark; GD, gestational day; IL, interleukins; IFN-γ, interferon-gamma; i.v., intravenous; LD, light–dark; LDB, light–dark box; MIA, maternal immune activation; NREM, non-REM; PND, postnatal day; poly(I:C), polyriboinosinic-polyribocytidilic acid; REM, rapid eye movement; SCZ, schizophrenia; SD, sleep deprivation; TNF, tumour necrosis factor.

Weber-Stadlbauer and Leila Tarokh contributed equally.

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1 | INTRODUCTION

Epidemiological studies over the past decades have repeatedly implicated maternal immune activation (MIA) in the aetiology of neuropsychiatric illnesses, including schizophrenia (SCZ), autism spectrum disorder (ASD) and bipolar disorder (Brown & Derkits, 2010; Brown & Meyer, 2018; Estes & McAllister, 2016). As such, infectious or noninfectious MIA is an established environmental risk factor for psychiatric and neurological disorders with neurodevelopmental etiologies (Meyer, 2019). Concurrent with these epidemiological findings are animal models of MIA, which have identified a broad spectrum of behavioural, physiological and molecular alterations in offspring of MIA-exposed mothers (Careaga et al., 2017; Harvey & Boksa, 2012; Meyer, 2014; Meyer, Feldon, & Yee, 2009). The current consensus is that cytokine-associated inflammatory events, together with downstream pathophysiological effects such as oxidative stress and (temporary) macronutrient and micronutrient deficiency, are critical in mediating the adverse effects of MIA on the fetal system (Labouesse et al., 2015; Meyer, 2013; Meyer & Feldon, 2010). These post-acute pathological processes disrupt normal development of the central nervous system (Stolp et al., 2011; Vuillermot et al., 2010), change subsequent maturation of the central nervous system's micro- and macro-structures (Piontkewitz et al., 2011; Raymann et al., 2023; Richetto et al., 2014) and cumulate into long-term behavioural and cognitive disturbances (Harvey & Boksa, 2012; Kneeland & Fatemi, 2013; Meyer, 2014; Meyer & Feldon, 2010; Weber-Stadlbauer, 2017). While the majority of these models have been developed in rodent species, most notably rats and mice (Meyer, 2014), some have been extended to species that are evolutionarily and ethologically closer to humans, including rhesus monkeys (Bauman et al., 2014; Short et al., 2010; Weir et al., 2015; Willette et al., 2011). The use of animal models aims at complementing the epidemiological work by establishing causal relationships between MIA and pathological outcomes, identifying the underlying cellular and molecular mechanisms and exploring potential therapeutic interventions against MIA-induced neurodevelopmental abnormalities (Careaga et al., 2017; Estes & McAllister, 2016; Harvey & Boksa, 2012; Meyer, 2014; Meyer, Feldon, & Yee, 2009; Weber-Stadlbauer, 2017).

In contrast to the widely described behavioural and cognitive disturbances manifest in the offspring of gestationally infected mothers, the effects of MIA on (circadian) activity and sleep patterns are less clear. Sleep and circadian rhythms control a variety of physiological and behavioural processes—thus, disruptions in these systems have widespread and detrimental effects. In humans, neurodevelopmental disorders are frequently associated with comorbidities, including sleep disorders and altered activity patterns (e.g., Laskemoen et al., 2019; Missig et al., 2020). For example, there is evidence of disrupted sleep and alterations in circadian activity in individuals with psychiatric disorders, including but not limited to SCZ (e.g., Ferrarelli, 2021; Markovic et al., 2020), autism (e.g., Schwichtenberg et al., 2022), depression (e.g., Castiglione-Fontanellaz & Tarokh, 2024) and bipolar disorder (e.g., Scott et al., 2022). Moreover, the extent of sleep and circadian rhythm disruptions corresponds with the severity of symptoms experienced (Kawai et al., 2022; Korenic et al., 2020). Conversely, there is evidence that the association between sleep and mental health is bi-directional, with poor sleep being associated with worse mental health outcomes (e.g., Hertenstein et al., 2023). Hence, the investigation of sleep and circadian rhythmicity has gained increasing recognition over the last years in view of its potential importance on the aetiology and treatment of neurodevelopmental disorders.

In line with this notion, a variety of studies have explored sleep and circadian patterns in disease-relevant animal models, with the majority of studies focusing on genetic models (e.g., Wintler et al., 2020). These studies typically show a pattern of diminished and fragmented sleep in animal models of neurodevelopmental disorders such as SCZ and autism (Delorme et al., 2020). Thus far, only a very limited number of studies, however, have addressed sleep and circadian rhythms in the MIA model (Missig et al., 2018). One such study in male mice found that a viral infection during the perinatal period resulted in offspring with a slight increase in slow wave sleep duration that persisted into adulthood (12 weeks of age) compared with unexposed animals (Missig et al., 2018). Another study, which included male and female animals, found altered circadian locomotor activity rhythms in MIA male but not female mice as compared with unexposed animals (Delorme et al., 2021). In this study, male mice showed increased daytime activity in the 12:12 light–dark (LD) and dark–dark (DD) conditions.

In the current study, we investigated alterations in both sleep and circadian locomotor activity in a mouse model of MIA. The model is based on maternal administration of the viral mimetic poly(I:C; =polyriboinosinic-polyribocytidilic acid), which induces a cytokine-associated viral-like acute phase response in maternal and fetal compartments, including the fetal brain (; Mueller et al., 2019). Prenatal poly(I:C) treatment leads to multiple behavioural and cognitive disturbances in the offspring, many of which are associated with developmental psychiatric disorders such as SCZ and autism (Brown & Meyer, 2018; Estes & McAllister, 2016). The

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prenatal poly(I:C) exposure model thus offers a unique opportunity to identify possible long-term effects on sleep and circadian activity following prenatal exposure to an etiologically relevant risk factor. With the use of this model, we compared activity, circadian rhythmicity and sleep characteristics in MIA-exposed and control male offspring.

2 | MATERIALS AND METHODS

2.1 | Animals

C57BL6/N mice were used throughout the study. Female and male breeding mice were obtained from Charles River Laboratories (Sulzfeld, Germany) at the age of 10–12 weeks. The animal vivarium was a specific-pathogen-free (SPF) holding room, which was temperature- and humidity-controlled (21 ± 3°C, 50 ± 10%) and kept under a 12 h:12 h LD cycle with lights off at 08:00 PM. All animals had ad libitum access to the same food (Kliba 3436, Kaiseraugst, Switzerland) and water throughout the entire study. All procedures described in the present study have been previously approved by the Cantonal Veterinarian's Office of Zurich, and all efforts were made to minimize the number of animals used and their suffering.

2.2 | Breeding and maternal manipulations

Breeding began 2 weeks after the animals were acclimatized to our facility. To this end, female and male C57BL6/N mice were subjected to a timed-mating procedure as previously described (Mueller et al., 2021; Weber-Stadlbauer et al., 2017). Successful mating was verified by the presence of a vaginal plug, upon which dams were housed individually throughout gestation. The presence of a vaginal plug was referred to as gestational day (GD) 0.

Pregnant dams were randomly assigned to MIA or corresponding control treatment on the ninth gestational day (GD9). This was based on the frequent use in poly(I:C)-based mouse models (for GD9, see Meyer et al., 2005, 2006, 2008; Vuillermot et al., 2010; Giovanoli et al., 2013, 2016; Weber-Stadlbauer et al., 2017). MIA was induced through a single intravenous (i.v.) tail-vein injection of poly(I:C) solution, whereas animals assigned to control treatment (CON) received sterile, pyrogen-free 0.9% NaCl (B. Braun, Melsungen, Switzerland) vehicle solution only (Mueller et al., 2021). Poly(I:C) potassium salt was obtained from Sigma-Aldrich (Buchs, St. Gallen, Switzerland; lot #086M4045V) and was administered at a dose of 1 mg/kg.

A first cohort of 12 pregnant dams was used to determine maternal cytokines, chemokines and corticosterone (CORT) 1 h after poly(I:C) or vehicle treatment to assess immunopotency of the used lot (see Figure S1). A second cohort of 12 pregnant dams was then used to generate offspring for subsequent behavioural and sleep analyses. Immediately after poly(I:C) or vehicle administration, the dams were placed back in their home cages and left until they were sacrificed at the appropriate post-injection intervals (cohort 1) or undisturbed until 7 days after birth of the offspring (cohort 2), when home cage bedding, huts and nesting material were exchanged for the first time after the maternal manipulations.

2.3 | Determination of corticosterone, cytokines and chemokines in maternal plasma

Pregnant mice (cohort 1) were decapitated 1 h after vehicle or poly(I:C) administration, and trunk blood was collected into EDTA-containing tubes. The collected blood was kept on ice for 30 min before centrifugation (2000×g, 5 min) to collect plasma, the latter of which was stored at −20°C until further use.

Cytokine and chemokine protein levels in maternal plasma were quantified using a Meso-Scale Discovery (MSD) V-Plex electrochemiluminescence assay for mice as previously described (see Giovanoli et al., 2015; Notter et al., 2018). The assay allowed the simultaneous quantification of multiple cytokines and chemokines, including IL-1β, IL-2, IL-4, IL-6, IL-10, IL-15, IL-17α, IL-27p28, TNF-α, CXCL1, CXCL2 and MCP-1 and IFN-γ. V-plex 96-well plates coated with primary antibodies directed against the targeted cytokines and chemokines were treated with the corresponding detecting antibodies, which were prelabeled with SULFO-TAGTM (MSD, Rockville, Maryland, USA). The plates were read using the SECTOR PR 400 (MSD) imager and analysed using MSD's Discovery Workbench analyzer and software package. All assays were run in duplicates according to the manufacturer's instructions. The detection limits were 0.06 pg/ml for IL-1β, 0.12 pg/ml for IL-2, 0.04 pg/ml for IL-4, 0.50 pg/ml for IL-6, 0.26 pg/ml for IL-10, 0.08 pg/ml for IL-15, 0.04 pg/ml for IL-17α, 0.02 pg/ml for IL-27p28, 0.04 pg/ml for TNF-α, 0.18 pg/ml for CXCL1, 0.02 pg/ml for CXCL2, 0.39 pg/ml for MCP-1 and 0.05 pg/ml for IFN-γ.

CORT levels in maternal plasma were quantified using a DetectX® ELISA kit (K014-H1; Arbor Assays, LubioScience GmbH, Zurich, Switzerland) according to

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FIGURE 1 Schematic image of experiments. Pregnant dams were intravenously injected with poly(I:C) (1 mg/kg) on GD9. (a) Validation of inflammatory response in pregnant dams, 1 h post injection with poly(I:C). (b) A second cohort of pregnant dams, injected with either poly(I:C) or saline, delivered their litter naturally. Male offspring were tested in adulthood (postnatal day [PND] ≥ 70) for circadian locomotor activity, sleep/wake patterns and novelty-induced activity.

the manufacturer's instructions. The samples were run in duplicates and were read with an EPOCH 2 spectrophotometer (BioTek, Sursee, Switzerland). The detection limit of the assay was 16.9 pg/ml.

2.4 | Infrared activity recordings

Offspring of poly(I:C)- or vehicle-treated mothers (cohort 2) were weaned on postnatal day (PND) 21 (see Figure 1). Male littermates were caged separately and maintained in groups of 2–5 animals per cage until adulthood. Mice were housed under normal light/dark cycles (12 h:12 h, lights off at 8 PM) for 2 weeks before starting the experiment to allow for adaptation to the experimental room. At PND70, one male offspring in each litter, of a total of 6 per group, was randomly assigned to testing in order to avoid potential confounds arising from litter effects (Meyer, Feldon, & Fatemi, 2009; Zorrilla, 1997). Animals were then individually housed in Macrolon cages (36 × 20 × 35 cm) to avoid social effects on circadian behaviour. After 3 days of adaptation, locomotor activity was recorded using infrared-wireless sensor placed on top of the cage (Actimetrics #ACT-557W). Infrared activity was continuously recorded for 7 days under regular 12 h light (≈200 lux)/12 h dark cycle. Data were collected and processed using ClockLab (Actimetrics # V 6.0.53 #434CA921). Activity was quantified as counts per minute and extracted as averages within 1-h bins. To obtain a robust activity profile for each mouse, the hourly activity was averaged across the 7 days. For activity measurements in DD condition, lights were switched off for 12 days. Instead, the room was illuminated with ≤.5-lux dim red light to satisfy legal requirements, and we refer to this condition as DD throughout the manuscript. The first 3 days under DD were considered as an adaptation period and not included in the analysis, and the hourly activity profile for each mouse was averaged across the remaining 9 days.

2.5 | Behavioural testing of offspring

Behavioural testing (see below) included tests for locomotor activity and innate anxiety in male offspring. The same testing order was always applied to each animal, with 3–4 test-free resting days being the two tests. Tests were performed during the animals' active phase, and the order of testing was counterbalanced across experimental groups.

2.6 | Light–dark box (LDB) test

The LDB test was conducted using 4 identical Multi-Conditioning boxes (Multi Conditioning System, TSE,

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Germany). Each box contained a dark (1 lux) and a bright (100 lux) compartment, which were separated from each other by a dark plexiglass wall, within which there was an electrically controlled door. Each mouse was placed in the dark compartment to start the test. After a 5-s acclimatization period, the door automatically opened, allowing the animals free access to both the dark and bright compartments for 5 min. The measurements collected from this test included time spent in bright compartment (%) and total distance moved (cm).

2.7 | Open field test

The test was conducted using four identical open field arenas (40 × 40 × 35-cm high) made of white plastic as described in detail before (Meyer et al., 2005). They were located in a testing room under dim diffused lighting (approximately 35 lux as measured in the centre of the arenas). A digital camera was mounted directly above the four arenas. Images were captured at a rate of 5 Hz and transmitted to a PC running the Ethovision (Noldus, Wageningen, the Netherlands) tracking system to record locomotor activity indexed by the distance moved in the entire open field arena. To start a trial, the animals were placed into the centre of the open field arena and allowed to explore freely for 15 min. At the end of this period, the animals were removed from the apparatus and returned to their home cage.

2.8 | Surgery

Male mice were implanted with gold-plated intracranial EEG screws (0.9-mm diameter). Five EEG screws were implanted per mouse: 3 screws for EEG recordings and 2 for fixation purposes. The EEG screws were positioned as following: 1 screw in the right parietal lobe (Bregma −1.8, −1.8), 1 screw in the right frontal lobe (Bregma −1.5, 1.2) and above the cerebellum as a reference. Two golden wires were bilaterally inserted in the neck muscle for EMG recording. Electrodes and EMG wires were connected to stainless steel wires (0.07-mm thickness) soldered to a fine cable. All electrodes were fixed to the skull via dental cement. The mice were single housed and connected to a 360° rotatory custom-made swivel that allows free movements during the whole recovery and recordings periods. Mice were allowed at least 7 days before being placed in isolated chambers for EEG recordings.

2.9 | EEG recordings

Male mice were habituated to the isolated recording chambers for 3 days prior to the start of recording for habituation. Signal acquisition parameters were set using SignalExpress NI 2015 controlled via LABVIEW. The signals were amplified with amplification factor of ≈2000, analogue band-pass filtered (high pass filter: −3 dB at 0.016 Hz; low pass filter: −3 dB at 128 Hz), sampled at 10,240 Hz, then decimated and stored with 512-Hz resolution (ElGrawani et al., 2024). The recording always started at light onset ZT 0, and data were collected continuously for 4 days: two baseline days, one sleep deprivation (SD) day and 1 day of recovery. SD was done at the beginning of light onset for 4 h (ZT 0:ZT 4) using novel objects introduction and gentle handling to avoid stress (Deboer et al., 1994; Noya et al., 2019). The EEG and EMG signals were digitally band-pass filtered using MATLAB function 'cheby2' (between 0.1 and 48 Hz for EEG and 10 and 30 Hz for EMG), down-sampled and stored with 128-Hz resolution. The power spectral density was computed for 4-s epochs using p-welch estimate (0.25-Hz resolution bins with no overlap Hanning window). Adjacent 0.25 Hz bins were averaged and stored as 0.5-Hz bins for frequencies between 0.5–5 Hz and 1 Hz bins for frequencies between 5.25–25 Hz. Vigilance states (NREM, REM and wake) were automatically detected using the SPINDLE machine learning server (Miladinović et al., 2019), and raw traces were visually inspected for double confirmation. A representative example for raw EEG and EMG traces in different vigilance states is provided in Figure 4b. All analyses were done via custom-made scripts in MATLAB (MathWorks R2020b). Sleep spindles were detected and features extracted using a previously validated automated sleep spindle detection algorithm (Uygun et al., 2019).

2.10 | Statistical analyses

All data were analysed using parametric analysis of variance (ANOVA) or unpaired Student's t test. Whenever appropriate, ANOVAs were followed by post hoc Fisher's exact test. For the main experimental conditions of interest (poly(I:C) vs. control), the entire data set of maternal cytokines and chemokines (comprising 12 variables) was analysed using unpaired Student's t tests. Home cage activity, sleep time course, sleep/wake bouts length and activity in the open field test were analysed with a mixed models (MM) two-way ANOVA with between subjects factor treatment (poly(I:C) vs. controls) and within subjects factor time bins. Power spectra in different vigilance states were analysed using MM ANOVA with between

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subjects factor treatment (poly(I:C) vs. controls) and within subjects factor frequency bins. All statistical analyses were performed using Prism (version 8.0; GraphPad Software, La Jolla, CA, USA). Statistical significance was defined as $*p < 0.05$, $**p < 0.01$ and $***p < 0.001$.

3 | RESULTS

3.1 | Circadian locomotor activity

Firstly, we confirmed that poly(I:C)-injected dams exhibited a significant elevation in blood plasma levels of CORT, as well as of IL-2, IL-6, IL-10, IL-15, IL-17α, IL-1β, IL-27p28, TNF-α, CXCL1, CXCL2 and MCP-1 (all $p < 0.001$), while the increase in IL-4 and IFN-γ was not significant ($0.07 \geq p > 0.05$; see Figure S1).

To assess whether MIA on GD9 would lead to altered daily activity rhythms in adult male offspring, we first compared home cage activity patterns in a regular 12 h/12 h LD cycle in control and poly(I:C)-exposed offspring. Both groups showed a robust entrainment, with most of the activity concentrated in the dark phase. Activity patterns featured 2 activity peaks separated by a period of reduced activity, known as a nadir or a siesta (Collins et al., 2020) (Figure 2a,b). Poly(I:C)-exposed animals displayed significantly reduced activity during the dark phase (Figure 2a–c). ANOVA of activity counts yielded a main effect of treatment ($F_{(1,10)} = 5.66$, $p < 0.05$) and a significant interaction between time and treatment ($F_{(23,230)} = 4.52$, $p < 0.05$), with the effect mainly being driven by reduced activity during the dark phase. Hence, to further dissect the effect of poly(I:C) exposure on light/dark home cage activity, data were split into light and dark phases. This analysis confirmed no difference in activity in MIA and control offspring during the light phase and a significant difference in the dark phase ($F_{(1,10)} = 8.62$, $p < 0.05$).

When comparing activity under constant conditions (i.e., in DD with constant dim red light ≤ 0.5 lux, see methods), we found a similar effect, with reduced activity in poly(I:C)-exposed animals as compared to control animals (Figure 2a,d,e). However, this effect was slightly blunted when compared with the LD cycle. In DD, repeated-measure ANOVA revealed a significant interaction between time and treatment ($F_{(23,230)} = 1.95$, $p < 0.05$). Subsequent post hoc comparisons revealed a significant reduction at ZT 17 and 18 ($p < 0.05$, Figure 2d). Furthermore, we observed a modest, yet statistically significant ($p < 0.05$), difference in the endogenous free running periods (≈7.5 min; Figure 2f). Together, these findings demonstrate that MIA reduces nighttime activity under LD and DD in male offspring.

3.2 | Locomotor activity and innate anxiety in the LDB and open field test

To assess whether MIA on GD9 would similarly affect experimentally induced locomotor activity and to assess intact locomotor functioning, we compared activity and innate anxiety parameters in the LDB test and the open field test. In contrast to home cage activity, poly(I:C)-exposed offspring displayed increased levels of activity, as indexed by total distance moved, in the LDB ($p < 0.05$, Figure 3a) and the open field (group effect $F_{(1,10)} = 5.65$, $p < 0.05$; Figure 3c,d). This effect, however, was not accompanied by changes in innate anxiety parameters, as indexed by similar levels of % time spent in the bright compartment of the LDB ($p > 0.05$; Figure 3b).

3.3 | EEG-based recordings of vigilance states under baseline conditions

In the next step, we assessed the effects of prenatal poly(I:C) exposure on adult sleep–wake patterns. To this end, mice were equipped with electrodes for EEG and EMG recordings (Figure 4a,b). Sleep/wake cycles in poly(I:C)-exposed offspring and control mice confirmed a robust distribution throughout the day where most of the sleep (≈60.16%) occurred in the light phase (Figure 4c). On average, mice slept 413.44 ± 7.7 min (mean ± SEM) in the light phase and 273.76 ± 12.59 min (mean ± SEM) in the dark phase. ANOVA analysis of sleep time-course showed a significant interaction between time and treatment ($F_{(7,56)} = 2.4$, $p < 0.05$), with the effect mainly being driven by increased sleep time in poly(I:C) mice between ZT9 and ZT21. Quantification of time spent in each vigilance states within these hours confirmed a significant increase in NREM sleep ($F_{(1,8)} = 5.96$, $p < 0.05$) and a decrease in wakefulness ($F_{(1,8)} = 9.28$, $p < 0.05$), whereas REM sleep did not show a significant group difference (Figure 4d). Sleep–wake bouts' length analysis showed no significant difference between the 2 groups (Figures 4e,f and S2A–D). Similarly, no significant group difference in the power spectral densities of different vigilance states was found in the baseline days (Figure 4g).

We further performed spindle analysis on frontal EEG signals during NREM sleep and observed that poly(I:C)-exposed mice showed more spindles in the light ($F_{(1,8)} = 5.48$; $p < 0.05$) and dark ($F_{(1,8)} = 7.4$;

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FIGURE 2 Assessment of locomotor home cage activity under both light–dark (LD) and dark–dark (DD, with constant dim red light ≤ 0.5 lux) conditions. (a) Representative actograms for the entire recording period of control (left) and maternal immune activation (MIA) mice (right). Note the reduced activity in MIA mice (red) compared with controls (grey) under both LD and DD conditions. Light is represented by a yellow bar. (b) Activity profile (1-h bins) in a regular 12 h/12 h LD cycle (mixed models [MM] two-way analysis of variance [ANOVA]). (c) Average of activity counts in light, dark or across the 24 h (unpaired Student's *t* test). (d) Activity profile (1-h bins) under DD condition (MM two-way ANOVA, followed by post-hoc Fisher's exact test). (e) Average of activity counts in the subjective light (i.e., circadian time 'CT' 0–12), dark (i.e., CT 12–24) or across the 24 h (unpaired Student's *t* test). (f) Average period length (unpaired Student's *t* test). $N = 6$, error bars represents mean ± SEM, * means $p < 0.05$.

$p < 0.05$) phase as compared with controls (Figure S2E). This increase in the number of detected spindles may be due to an increase in NREM sleep duration and/or frequency of spindle events. We demonstrated that poly(I:C)-exposed mice had higher sleep spindles density (i.e., number of spindles per minute of NREM sleep) in the light ($F_{(1,8)} = 5.95$; $p < 0.05$) and dark ($F_{(1,8)} = 10.67$; $p < 0.05$) phase as compared with controls (Figure 4i,j). Absolute sleep spindle amplitude did not differ between the two

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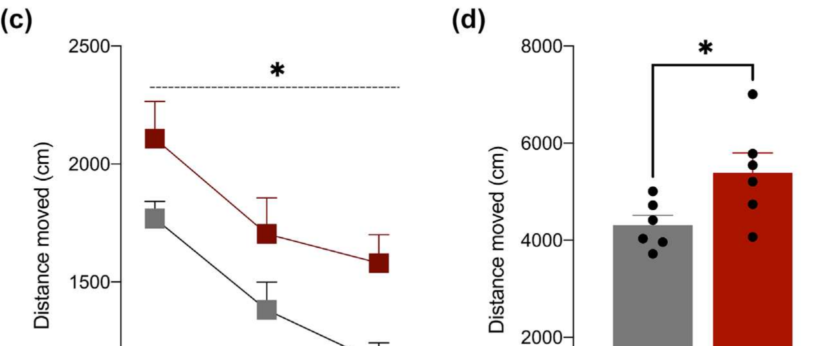

FIGURE 3 Innate anxiety and locomotor activity. (a,b) Locomotor activity in the light–dark box (LDB). (a) The total distance moved in the LDB (unpaired Student's *t* test). (b) Time spent in the bright compartment (unpaired Student's *t* test). (c,d) Locomotor activity in the open-field test as indexed by distance moved in 5-min bins. (c) The distance moved across 3-time bins (MM two-way ANOVA). (d) The average of the total distance moved (unpaired Student's *t* test). $N = 6$, error bars represents mean ± SEM, * means $p < 0.05$.

groups for either the light or the dark phase (Figure S2F); however, poly(I:C) mice had greater normalized sleep spindle amplitude in the light phase ($F_{(1,8)} = 5.12$; $p = 0.053$; Figure 4h). Peak spindle frequency and spindle duration did not differ between the two groups for either the light or the dark phase (Figure S2G,H).

3.4 | Assessment of sleep parameters under elevated sleep pressure

To investigate the effects of MIA on offspring tolerance to high sleep pressure, we subjected mice to 4 h of SD at light onset (ZT0–4). ANOVA analysis on the time-course of sleep following SD showed a significant group difference ($F_{(1,8)} = 5.83$, $p < 0.05$), with the effect mainly being driven by increased sleep time in poly(I:C) mice in the subsequent dark phase (Figure 5a). Following SD, time spent in each vigilance state during the remaining hours of the light phase (ZT4–12) showed no significant group difference. However, poly(I:C)-exposed mice exhibited a significant increase in NREM sleep and decrease in wakefulness during the subsequent dark phase, whereas REM sleep did not show a significant group difference (Figure 5b). In line with this, NREM sleep bouts were significantly longer in the dark phase but not in the light phase (Figure 5c,d). ANOVA analysis on the distribution of sleep bouts length during the dark phase revealed a significant interaction between NREM sleep bout duration and treatment ($F_{(7,56)} = 4.57$; $p < 0.05$), where the percentage of short bouts was decreased and compensated by increase in the longer bouts. No significant difference in the distribution of the length of wake and REM sleep bouts in either the light or dark phase was found (Figure S3A–D).

NREM sleep power spectral densities in response to SD showed a significant group difference in the recovery

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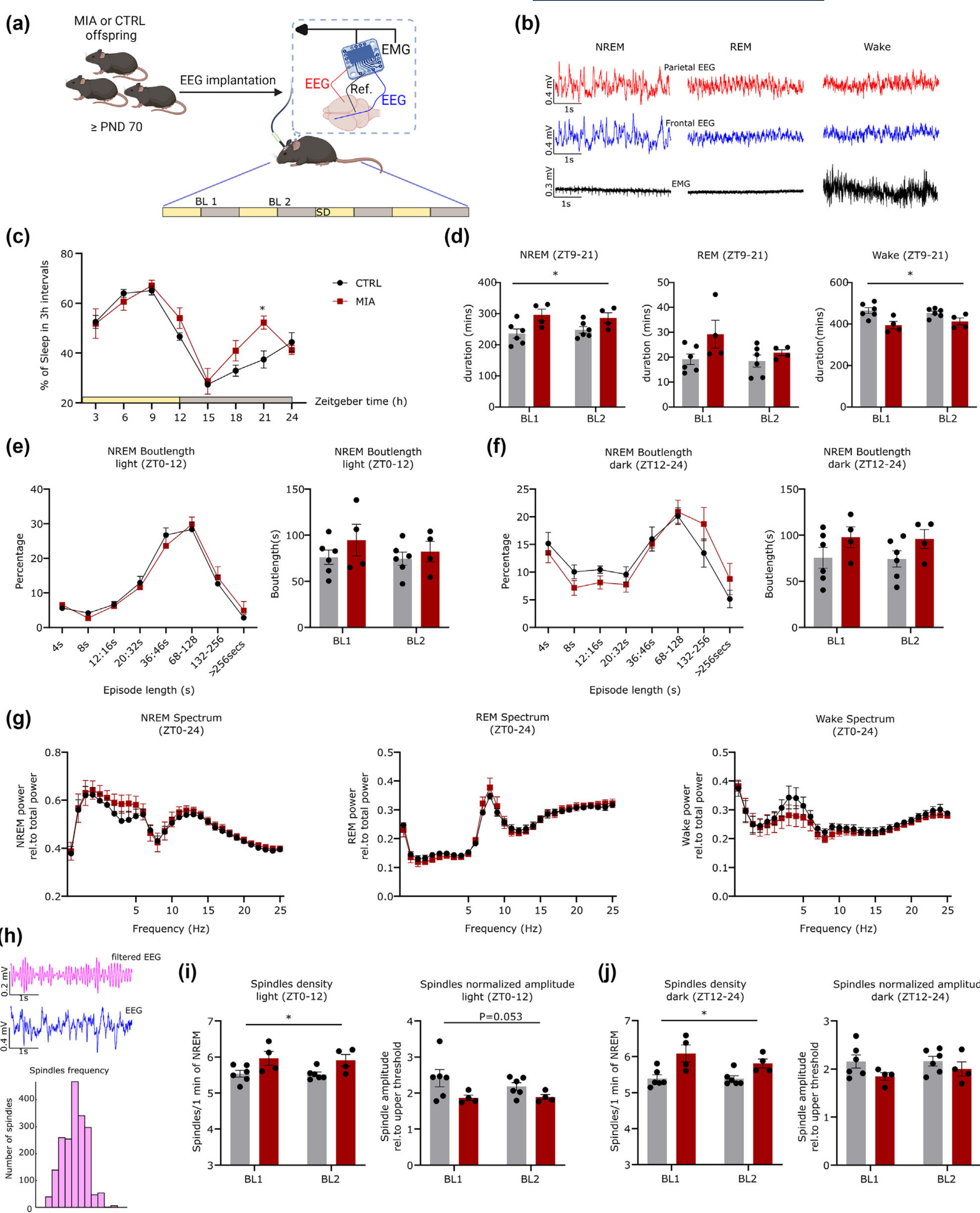

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FIGURE 4 Electroencephalography (EEG)-based recordings of vigilance states. (a) Schematic timeline for the experimental sequence to investigate the impact of maternal immune activation (MIA) on offspring sleep. (b) Representative raw EEG and EMG traces of a mouse in different vigilance states. (c) Time course of sleep represented as percentage of total time within 3-h bins, across the day (MM two-way ANOVA, followed by post-hoc Fisher's exact test). (D) the average of minutes that mice spent in the different vigilance states between ZT9–21 (MM two-way ANOVA). (e) (Left panel) NREM sleep bouts length distribution in the light phase (ns, MM two-way ANOVA). *Y*-axis shows the percentage of NREM sleep bouts that corresponds to the different bouts' length on the *x*-axis. (Right panel) the average NREM sleep bouts length in the light phase (ns, MM two-way ANOVA). (f) Identical analysis to E for NREM sleep in the dark phase (ns, MM ANOVA). (g) Power spectral densities in the different vigilance states in baseline days (ns, MM two-way ANOVA). (h–j) NREM sleep spindle analysis in baseline days. (h) Representative EEG filtered (pink) and raw (blue) traces from the same mouse shown in Panel B. (Bottom panel) histogram plot of the spectral frequency distribution of the detected spindles from the same mouse. *Y*-axis represents the number of spindles that had the spectral frequencies shown on the x-axis. (I) (left panel) the average of spindles density in the light phase. (Right panel) the average normalized spindles amplitudes in the light phase (MM ANOVA). (j) Identical to panel I for spindles in the dark phase (MM two-way ANOVA). $N = 6$ for control and $N = 4$ for MIA, error bars represent mean ± SEM, * means $p < 0.05$. For extended data: see Figure S2.

hours of the light ($F_{(1,8)} = 6.02$; $p < 0.05$) and the dark ($F_{(1,8)} = 5.58$; $p < 0.05$) phase whereas REM sleep and wake power spectra exhibited no significant group differences (Figure 5e,f). Furthermore, spindle analysis on the 2 h following SD revealed a significant increase in NREM sleep spindle density whereas spindle duration and normalized spindle amplitude were reduced in poly(I:C)-exposed mice compared with controls (Figure S3E). Peak spindle frequency, number of spindles and absolute spindle amplitude did not differ between the two groups (Figure S3E).

4 | DISCUSSION

In this study, we show that MIA during gestation results in persistent alterations in daily locomotor activity and sleep/wake profiles in adult male offspring. MIA is a well described risk factor for neurodevelopmental disorders such as autism and SCZ, with an infection in the first trimester increasing the risk of developing SCZ by approximately seven fold (Brown et al., 2004) and autism by about two-fold (Atladóttir et al., 2010; Lee et al., 2015). Disruptions in sleep and circadian rhythms are found in most adults with autism and SCZ and may arise from a genetic predisposition that is expressed in response to environmental exposure (e.g., MIA). With regard to circadian rhythms, a shift and/or blunting of circadian rhythmicity is observed in human adults as reflected in melatonin and activity profiles in both autism and SCZ (Tordjman et al., 2012; Wiggs & Stores, 2004; Wulff et al., 2012), among other neurodevelopmental disorders (Herrera & Tarokh, 2024).

Disruptions of the circadian system have also been reported in animal models based on genetic risk for SCZ (Delorme et al., 2020) and autism (Wintler et al., 2020). Two prior studies examined daily activity patterns in response to MIA. One study utilized running wheel measurements in 8-week-old MIA offspring mice and reported a sex-dependent increase in daytime wheel running activity—that is an increase in activity counts at the beginning and end of the (subjective) day under LD and/or DD conditions in male but not female mice (Delorme et al., 2021). Using wireless telemetry transmitters, another study by Missig and colleagues (Missig et al., 2018) have reported a significant increase in daytime locomotor activities under LD condition at 7 but not 12 weeks age. Concomitant with this, activity counts on the dark phase between ZT15–18 appears to be reduced in both studies, although statistical significance was not explicitly reported. In line with this, we used infrared sensors and observed that poly(I:C)-exposed mice have reduced home cage locomotor activity in the dark phase under regular LD and in the subjective dark phase under DD. Unlike the previous studies, we did not detect a significant difference in activity counts in the (subjective) light phase. This could be attributed to age difference of the tested mice, difference in the exact prenatal day when poly(I:C) was delivered, or to the methodologies used: running wheel activity counts reflect voluntary exercise behaviour, telemetry transmitters measure physiological data (such as heart rate, body temperature and activity), whereas infrared sensors capture passive activity profiles. We speculate that because there is very little activity during the light phase, the differences in activity only become apparent in the dark phase. We postulate that this pattern of diminished activity during the active phase is similar to what is observed in patients with psychiatric disorders, such as SCZ and depression (Fasmer et al., 2016; Todder et al., 2009). These patients show lower activity levels during the waking day than healthy age matched controls (Fasmer et al., 2016; Todder et al., 2009). In SCZ, an association between lower activity and diminished white matter integrity in the

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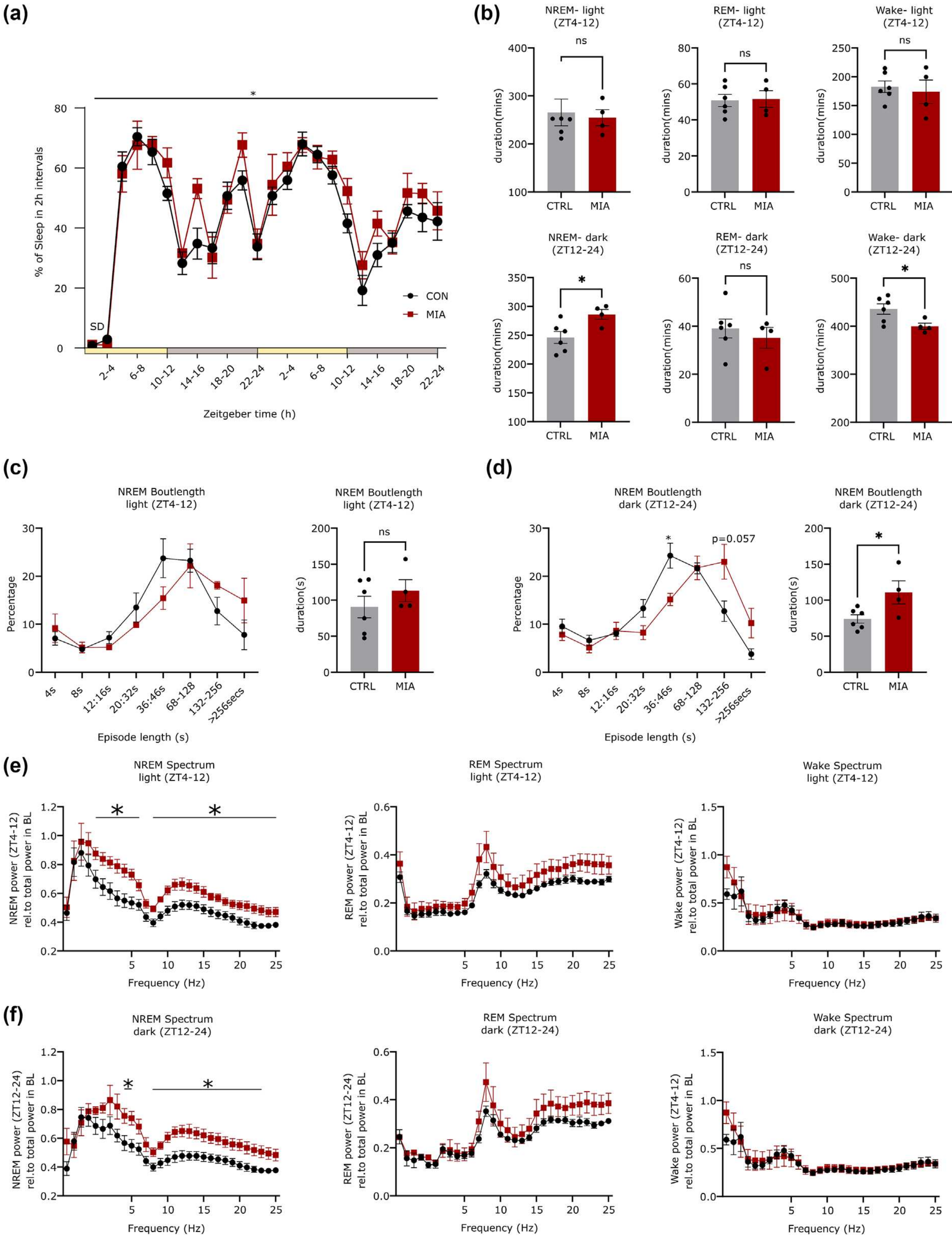

FIGURE 5 Legend on next page.

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FIGURE 5 Assessment of sleep parameters under elevated sleep pressure. (a) Time course of sleep represented as percentage of total time within 2-h bins, across 2 days (MM two-way ANOVA). (b) The average of minutes that mice spent in the different vigilance states in the light phase (top panel) and dark phase (bottom panel) following sleep deprivation (MM two-way ANOVA). (c) (Left panel) NREM sleep bouts' length distribution in the remaining light phase hours following sleep deprivation (ns, MM two-way ANOVA). (Right panel) the average NREM sleep bouts length in the same hours (ns, unpaired Student's *t* test). (d) Identical analysis to C for NREM sleep in the subsequent dark phase ($p < 0.05$, MM two-way ANOVA, followed by post hoc Fisher's exact test; unpaired Student's *t* test). (e) Power spectral densities in the different vigilance states of the remaining light phase hours following sleep deprivation (MM two-way ANOVA, followed by post hoc Fisher's exact test). (f) Identical to E for the subsequent dark phase. $N = 6$ for control and $N = 4$ for MIA, error bars represent mean ± SEM, * means $p < 0.05$. For extended data: see Figure S3.

supplementary motor area has been reported (Walther et al., 2011). MIA has been shown to impact cortical lamination (McEwan et al., 2023) and white matter volume (Kreitz et al., 2020) in mice. Therefore, the findings of reduced white matter integrity and its association with lower activity found in SCZ patients may in part be explained by MIA. Furthermore, in mice, poly(I:C) exposure has been shown to result in alterations in microglial morphology, which was then attenuated by environmental exposure to constant light suggesting interactions between circadian disruption and prenatal infection (Delorme et al., 2023).

Our interpretation that the reduced activity in the home cage is a manifestation of pathological brain processes is made more compelling by the novelty induced activity and the innate anxiety task during which poly(I:C) mice show more movement. The increased movement in the open field test was observed within the first minutes and persisted across the assay duration, indicating that poly(I:C) mice react more readily to new environmental stimuli and exhibit higher explorative behaviour tendency in novel environment. This finding mirrors what is seen in individuals with psychiatric disorders such as depression, ASD and SCZ that typically show higher stress reactivity (Myin-Germeys & van Os, 2007) in conjunction with reduced basal locomotor activity.

Concomitant with the reduced activity in the dark phase, adult offspring born to poly(I:C)-exposed mothers exhibited a significant increase in sleep duration between ZT9–21. This increase in sleep duration was primarily driven by an increase in NREM sleep. To the best of our knowledge, only one prior study has addressed the long-term changes in sleep–wake patterns in MIA mouse model (Missig et al., 2018). In this study, the authors delivered poly(I:C) infection at embryonic Day 12.5 and observed a slight increase in NREM sleep. In a subset of mice, another poly(I:C) was delivered at post-natal day 9 resulting in a more evident increase in NREM sleep, even when mice were tested at 12-week age. Together these findings are in line with our results and suggest that prenatal MIA has a long-lasting impact on sleep. The exact mechanism of how such a prenatal immune challenge alters sleep during adulthood remains unknown. One potential explanation is that MIA not only causes a temporary surge in pro-inflammatory cytokines within the foetal brain but is also associated with enduring alterations in brain cytokine levels that continue into adulthood (Garay et al., 2013). At PND 60, MIA offspring exhibits higher levels of IL-1α, IL-6, IL-9 and IL-10 in the frontal cortex, along with increased IL-10 and IFNγ in the cingulate cortex compared with control mice. The sleep promoting effect of cytokines is well-established across multiple species including mice, rats, rabbits and monkeys (reviewed in Krueger et al., 2001). Hence, we propose that alterations in sleep patterns observed in adult MIA offspring could be linked to cytokine levels in their brain. However, further research is needed to validate this hypothesis.

In line with the reduced daily/circadian locomotor activities and the increased sleep duration in MIA offspring mice, a meta-analysis in SCZ-remitted individuals noted prolonged overall sleep duration and time spent in bed, alongside reduced motor activities (Meyer et al., 2020). Conversely, contrary to our findings, another meta-analysis found reduced total sleep time in untreated SCZ patients (Chouinard et al., 2004). The difference in sleep phenotype between SCZ patients and MIA mice might stem from the difference in genetic background, epigenome modification and transcriptome landscape between the two species (Lin et al., 2014). We note, that genomic responses to acute inflammatory stress in mice models appear to poorly mimic human inflammatory diseases (Seok et al., 2013). Future studies should disentangle how genetic and environmental factors interplay to shape sleep patterns in neuropsychiatric disorders.

With regard to sleep neurophysiology, no differences were found at baseline between the poly(I:C)-exposed and control mice in the power spectrum for NREM and REM sleep. However, with the use of an established spindle detection algorithm (Uygun et al., 2019), we found that poly(I:C)-exposed mice showed higher spindle density in both the light and dark phase. This contrasts with data in humans that show diminished sleep spindle

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density in neurodevelopmental disorders such as ASD (Farmer et al., 2018) and SCZ (Ferrarelli, 2024) (Ang et al., 2018). Sleep spindles are thought to play a role in the consolidation and maintenance of sleep, and therefore, the increased incidence of spindles coupled with the longer sleep duration in poly(I:C) mice may result in increased sleep propensity. On the other hand, normalized spindle amplitude is diminished in the poly(I:C)-exposed mice, an effect that might likely be driven by the slight increase in the delta band (see NREM spectrum in Figure 4g) and may not hold functional relevance.

When subjected to SD, poly(I:C)-exposed mice exhibited more sleep in the recovery dark phase as compared with control mice, indicating alteration in homeostatic response to elevated sleep pressure. It could be argued that this increase in dark phase sleep was also observed under baseline conditions and therefore reflects a general increased sleep need in poly(I:C)-exposed mice rather than higher accumulation of sleep pressure during the SD challenge per se. However, this increase in NREM sleep following SD was, unlike baseline, accompanied by longer NREM sleep bouts. Furthermore, NREM sleep power spectrum following SD showed a greater increase of slow waves power (SWA; higher delta: 2.5–4.5 Hz)—a reliable marker for sleep pressure—among other frequency bands (Hubbard et al., 2020). Given that SD involved introducing novel objects into the home cage, and poly(I:C)-exposed mice showed increased activity in both the novelty-induced activity test and the novel environment of the LDB test, it is plausible that the longer sleep bouts length and changes in power spectrum following SD could be attributed to the increased activity of these mice during SD period. Future research should address the hypothesis that the methodology used to induce SD in mice may interact with poly(I:C) status to impact sleep.

We acknowledge several other limitations in our study. First, additional investigations will be required to investigate the underlying molecular mechanisms translating prenatal immune activation into long-term alterations in sleep and activity. Exploring whether the activity and sleep changes are unique to MIA or indicative of broader impairments affecting other bodily functions would offer valuable insights into the overall impact of MIA. Future studies should also examine whether MIA impacts the phase-shift response to a pulse of light. A second limitation of our study is that we did not include female mice; hence, it remains unexplored whether MIA induced similar effects on sleep and activity in males and females. An extension of our investigations to the female sex also appears crucial in view of the fact that prenatal immune activation can lead to distinct phenotypes in males and females (Haida et al., 2019). Furthermore, in humans, the prevalence of neuropsychiatric disorders often varies by sex, highlighting the importance of examining sex differences in the context of environmental risk factors for neuropsychiatric disorders.

Despite these limitations, we conclude that exposure to prenatal MIAs results in lasting changes in sleep and circadian rhythms in adult male offspring mice. Our findings add to understanding the mechanisms governing sleep and circadian rhythm disruptions in neurodevelopmental disorders and highlight how environmental factors early in life may precipitate long-term changes. Prenatal poly(I:C) administration in mice is currently one of the most widely used models in developmental brain research and has applicability to various neurodevelopmental disorders, especially to those with inflammatory etiologies (Estes & McAllister, 2016; Meyer, 2014). Therefore, our findings appear relevant to developmental brain disorders independently of existing diagnostic classifications and may help advance the understanding of the role of sleep and circadian alterations in these disorders.

AUTHOR CONTRIBUTIONS

Waleed ElGrawani: Formal analysis; investigation; project administration; writing—original draft; writing—review and editing. **Flavia S. Mueller**: Data curation; formal analysis; investigation. **Sina M. Schalbetter**: Data curation. **Steven A. Brown**: Conceptualisation; supervision. **Ulrike Weber-Stadlbauer**: Data curation; formal analysis; conceptualization; project administration; supervision; writing—original draft; writing—review and editing. **Leila Tarokh**: Conceptualization; project administration; supervision; writing—original draft; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

LT serves as a consultant for F. Hoffmann-La Roche Ltd., which is unrelated to this study.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

EEG and IR data have been deposited to https://doi.org/10.5281/zenodo.10555224. Other raw data can be made available upon request.

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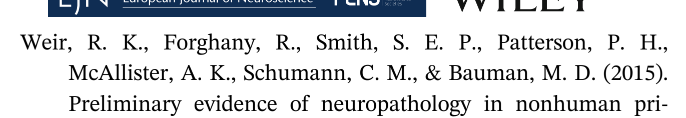

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