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Preclinical animal models of mental illnesses to translate findings from the bench to the bedside: molecular brain mechanisms and peripheral biomarkers --Manuscript Draft--

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Abstract:	<p>Background: Animal models are useful preclinical tools for studying the pathogenesis of mental disorders and the effectiveness of their treatment. While it is not possible to mimic all symptoms occurring in humans, it is however possible to investigate the behavioral, physiological and neuroanatomical alterations relevant for these complex disorders in controlled conditions and in genetically homogeneous populations. Stressful and infection-related exposures represent the most employed environmental risk factors able to trigger or to unmask a psychopathological phenotype in animals. Indeed, when occurring during sensitive periods of brain maturation, including pre, postnatal life and adolescence, they can affect the offspring's neurodevelopmental trajectories, increasing the risk for mental disorders. Not all stressed or immune challenged animals, however, develop behavioral alterations and preclinical animal models can explain differences between vulnerable or resilient phenotypes.</p> <p>Methods: Our review focuses on different paradigms of stress (prenatal stress, maternal separation, social isolation and social defeat stress) and immune challenges (immune activation in pregnancy) and investigates the subsequent alterations in several biological and behavioral domains at different time points of animals' life. It also discusses the "double-hit" hypothesis where an initial early adverse event can prime the response to a second negative challenge.</p> <p>Results: Stress and infections early in life induce the activation of the hypothalamic-pituitary-adrenal (HPA) axis, alter the levels of neurotransmitters, neurotrophins and pro-inflammatory cytokines and affect the functions of microglia and oxidative stress.</p> <p>Conclusions: Animal models allow shedding light on the pathophysiology of human mental illnesses and discovering novel molecular drug targets for personalized treatments.</p>
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Brescia, December 7th 2021

Dear Editor-in-chief

E. Vieta, MD, PhD

Please find enclosed a review entitled *“Preclinical animal models of mental illnesses to translate findings from the bench to the bedside: molecular brain mechanisms and peripheral biomarkers”* by Nadia Cattane, Anthony C. Vernon, Alessandra Borsini, Catia Scassellati, Dominique Endres, Lucile Capuron, Ryad Tamouza, Michael Eriksen Benros, Juan C. Leza, Carmine M. Pariante, Marco A. Riva, European College of Neuropsychopharmacology (ECNP) ImmunoNeuroPsychiatry Thematic Working Group and Annamaria Cattaneo.

This Review is indeed part of the collaboration among the members of the Immuno-NeuroPsychiatry ECNP Network <https://www.ecnp.eu/research-innovation/ECNP-networks/List-ECNP-Networks/Immuno-NeuroPsychiatry>

This review focuses on the potential utility of animal models in dissecting the mechanisms associated with the pathogenesis of mental disorders and with the effectiveness of their therapeutic treatments.

It is well known that stressful and infection-related exposures represent the most employed environmental risk factors able to trigger or to unmask a psychopathological phenotype in animal models. Indeed, when occurring during sensitive periods of brain maturation, including pre, postnatal life and adolescence, they can affect the offspring's neurodevelopmental trajectories, increasing the risk for mental disorders. However, not all stressed or immune challenged animals develop behavioral alterations, as some of them maintain a resilient phenotype.

In this context, preclinical animal models can be useful also to explain differences underlying the development of vulnerable or resilient phenotypes.

In our review, we have discussed the different paradigms of stress (prenatal stress, maternal separation, social isolation and social defeat stress) and immune challenges (immune activation in pregnancy) that have been used so far to investigate alterations in biological systems and behavioral domains as consequence of such exposures. We have also discussed the “double-hit” hypothesis, where an initial adverse event early in life can prime the response to a second negative challenge.

Among the most robust results discussed in our review, stress and infections early in life have been shown to induce the activation of the hypothalamic-pituitary-adrenal (HPA) axis, to alter the levels of



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neurotransmitters and neurotrophins, to increase the production of pro-inflammatory cytokines and to affect the functions of microglia and oxidative stress. However, since a considerable variability in the results has been reported, we have also discussed the potential underlying causes of such differences, including the paradigm used or the nature of the exposure (i.e., type of stress, duration, time in gestation). In addition, our data suggest that most of the experimental approaches performed to characterize the effects of stress and immune challenges early in life have been conducted in adult male animals and only a limited number of studies have included in their analyses both male and female offspring assessed at different time points during life span. Therefore, future preclinical studies should be based on longitudinal analyses to identify the temporal onset of psychiatric-related dysfunctions and should investigate sex-specific differences induced by stressful exposure or infection-related events.

In conclusions, in our review we have underlined the utility of preclinical animal models in translating findings in humans and in setting the basis for future gene-environment interaction studies, aiming to discover new molecular drug targets and to test novel personalized treatments in the field of psychiatric disorders.

We therefore truly believe that our review represents an important step in the field of mental disorders, and we would be glad if you could consider the manuscript for publication in *European Neuropsychopharmacology*.

All co-authors reviewed the manuscript; they all agree with its contents and declare no financial interest. We also certify that the submission is an original work, and it is not under review at any other journal.

Thanking you in advance for your kind attention,

Sincerely

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TITLE: Preclinical animal models of mental illnesses to translate findings from the bench to the bedside: molecular brain mechanisms and peripheral biomarkers

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ABSTRACT

Background: Animal models are useful preclinical tools for studying the pathogenesis of mental disorders and the effectiveness of their treatment. While it is not possible to mimic all symptoms occurring in humans, it is however possible to investigate the behavioral, physiological and neuroanatomical alterations relevant for these complex disorders in controlled conditions and in genetically homogeneous populations. Stressful and infection-related exposures represent the most employed environmental risk factors able to trigger or to unmask a psychopathological phenotype in animals. Indeed, when occurring during sensitive periods of brain maturation, including pre, postnatal life and adolescence, they can affect the offspring's neurodevelopmental trajectories, increasing the risk for mental disorders. Not all stressed or immune challenged animals, however, develop behavioral alterations and preclinical animal models can explain differences between vulnerable or resilient phenotypes.

Methods: Our review focuses on different paradigms of stress (prenatal stress, maternal separation, social isolation and social defeat stress) and immune challenges (immune activation in pregnancy) and investigates the subsequent alterations in several biological and behavioral domains at different time points of animals' life. It also discusses the "double-hit" hypothesis where an initial early adverse event can prime the response to a second negative challenge.

Results: Stress and infections early in life induce the activation of the hypothalamic-pituitary-adrenal (HPA) axis, alter the levels of neurotransmitters, neurotrophins and pro-inflammatory cytokines and affect the functions of microglia and oxidative stress.

Conclusions: Animal models allow shedding light on the pathophysiology of human mental illnesses and discovering novel molecular drug targets for personalized treatments.

Keywords: animal models; psychiatric disorders; stress; maternal immune activation; behavioral outcomes

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1. The usefulness of animal models in the field of psychiatric disorders.

During the last years great advances have been made regarding the understanding of the biological and psychological mechanisms associated with psychiatric disorders and the description of brain circuits involved in abnormal information processing (Kaiser and Feng, 2015). This progress has been made possible in part with animal models, which have allowed the identification of deregulated candidate neural circuits, neurophysiological systems and molecular targets.

Preclinical animal models can be defined as non-human living organisms used to study different human biological or pathological processes (Hau, 2008). Their use assumes that the acquisition of functional mechanisms obtained from animal models can provide useful information on brain mechanisms occurring also in humans. In more detail, an animal model of pathology represents the simplified version of a real situation, shaped to study all the aspects that characterize the onset and course of the disease itself, but also to develop more targeted and effective therapeutic interventions (van der Worp et al., 2010). The main features of the pathology should be reproduced, albeit with some limitations, and therefore, any factors that cause the onset of the disease in humans, as well as the underlying biological mechanisms, must be recreated, including symptoms and clinical manifestations. In addition, the drug treatment used in therapy should be equally effective as in humans.

Interestingly, animal models have widely demonstrated their usefulness for studying psychiatric disorders (Donaldson and Hen, 2015; Kaiser and Feng, 2015). Although it is not possible to reproduce a psychiatric condition in its all complexity, specific behavioral, physiological and neuroanatomical phenotypes of psychiatric disorders can be investigated in animal models under controlled conditions, with stress or infections among the most employed environmental factors able to trigger or to unmask a possible psychopathological phenotype.

The goal is not to fully mimic human psychiatric conditions or specific features of the illness in animal models, rather to achieve a better understanding of the biological mechanisms that underlie the pathogenesis of the disorder and translatable them to humans. For example, in the context of stress, defined as *a definable trigger of the presentation of psychiatric disorders in vulnerable individuals* (Bale et al., 2019), the goal of preclinical stress research should be: i) to achieve a better understanding of the biology of stress and its deregulation that will shed light on the pathophysiology of mental illnesses risk and resilience, and ii) to provide sophisticated

behavioral models for discovering new molecular drug targets and for testing novel treatments (Bale et al., 2019).

As mentioned, animal models cannot be used to fully recreate the condition of a mental disorder in humans. Indeed, from a preclinical point of view, it is difficult to reproduce in rodents several symptoms of depression, such as guilt or suicidal thoughts (Krishnan and Nestler, 2008). In addition, in clinical terms, the biological causes and mechanisms downstream of the disease have not been fully clarified yet. Therefore, also the often-used terminology of “*an animal model of a neuropsychiatric disease*” is not appropriate and should be replaced with “*an animal model useful for the study of a neuropsychiatric condition*” (Bale et al., 2019).

Despite all these limitations, animal models are extremely useful for studying certain aspects of psychiatric disorders that have not been fully investigated yet and allow evaluating and monitoring the possible effectiveness of therapeutic treatments and interventions.

To achieve successful animal models, including those for psychiatric disorders, several criteria must be taken into account:

- FACE VALIDITY

The model is able to reproduce the anatomical, biochemical, neuropathological or behavioral characteristics of a human pathology: symptoms and specific behavioral endpoints resulting from experimental manipulations in the animal model are similar to those observed in humans. For example, since many patients affected by depression exhibit anhedonia (Buckner et al., 2008), it should be essential to include this feature in the behavioral assessment carried out in rodents. The model should also recapitulate the biological alterations found in the clinical condition, which are represented, for example, by changes in some peripheral biomarkers, such as altered levels of cortisol or corticosterone in humans or rodents, respectively. The face validity criteria however may be difficult to reach, because differences between patients’ subgroups may be greater not only in terms of biological processes that are affected, but also in terms of changes observed in a specific system (Planchez et al., 2019). In addition, while in humans pharmacological response occurs only after chronic (several weeks to months) administration of drugs, in animal models, improvements in behavioral changes are usually elicited by an acute administration of the same drugs but with a higher concentration to show similar effects on smaller samples. This suggests that the mechanisms by which many drugs alter behaviors in animal models are distinct from their therapeutic effects in humans (Bale et al., 2019).

- CONSTRUCT VALIDITY

The mechanisms underlying the phenotype observed in animal models should be the same as those underlying the human pathological phenotype: this means that the etiological processes that lead to human disease should be recreated in the animal model. In other words, construct validity means that the model has a strong theoretical rationale in terms of causative or triggering factors (i.e. vulnerability genes and/or environmental factors) associated with a given psychiatric disorder (Planchez et al., 2019). For instance, models based on chronic stress exposure have construct validity because they are characterized by changes in behaviors that do have parallels with symptoms of human depression, including behaviors related to the hedonic or reward-seeking state of experimental animals, such as in sucrose preference, female urine sniffing, or social interaction tests (Bale et al., 2019).

- PREDICTIVE VALIDITY

The model allows to extrapolate information about the effects of a given manipulation from one organism to another: for example, depending on how the animal model responds to a drug treatment, we can predict the effects of this treatment in humans (Shanks et al., 2009). This means that if a drug is effective in psychiatric patients under certain conditions, it should act in the same way also in the animal model.

Based on these objective criteria, animal models represent a fertile ground to investigate potential mechanisms underlying mental illnesses in humans (Davis et al., 2018). In addition, animals can be used to investigate the importance of the timing of the stress exposure and the different effect of stress in terms of resilience or vulnerability. Indeed animals can be exposed to various paradigms of stress at different temporal windows, prenatally (e.g. Prenatal Stress (PNS) paradigm) or early postnatally (e.g. Chronic Mild Stress (CMS), or Social Isolation (SI)) and animals can be then behaviourally assessed to evaluate the development of a vulnerable phenotype. Details about different paradigms of stress and behavioural tests will be mentioned and summarized in the following paragraphs of this review.

2. Neurodevelopment as a key temporal window for the vulnerability of psychiatric illnesses

Neurodevelopment is a sensitive temporal window in which the individual experience has a strong influence on the development of a specific phenotype. This adaptive developmental plasticity often changes across the

lifespan and can be further affected especially during those temporal windows where the individual is particularly sensitive (Fawcett and Frankenhuis, 2015). According to this theory, prenatal, postnatal period and puberty/adolescence represent critical temporal windows of development that coincide with key brain maturational processes (Kane and Ismail, 2017). Indeed, major neuronal reorganization that implies anatomical and functional brain development occur during these periods (Anders et al., 2015). Of note, disruption of these processes by several factors, including psychosocial, stressful but also immunological hits or infections, during these sensitive periods can have short, but also long-term effects on various aspects of physical and mental health (Mariotti, 2015). For instance, higher glucocorticoids (GCs) levels that result from exposures to environmental stressors have been suggested to have deleterious effects on brain structure and function, especially when the exposure occurs during sensitive periods of life that involve increased neural development (Anacker et al., 2013a; Anacker et al., 2013b; Provencal et al., 2020). Similarly, an increased inflammatory response can lead to the same negative and harmful effects on brain maturation and development (Lopizzo et al., 2021; Mazzelli et al., 2020).

Several psychiatric disorders, such as schizophrenia and depression, are thought to have their origins early in (pre- and postnatal) life (Kim et al., 2015). Indeed, the mean age of onset of most psychiatric disorders is typically during adolescence or early adulthood and, nowadays, it is well accepted that brain regions involved in cognition and stress reactivity, such as the hippocampus or the prefrontal cortex (PFC), are still undergoing maturation during these periods (Kozareva et al., 2019; Schroeder et al., 2018). Thus, aberrant development during these critical temporal windows may underlie an enhanced vulnerability of developing primary psychiatric syndromes, and hence, the need to understand the role of environmental factors, mainly in terms of stressful exposure or infection-related events, during these sensitive periods of development should be a priority.

In this context, preclinical animal models represent a very useful tool to isolate and examine specific types of stressors at specific time points of neurodevelopment, while minimizing genetic differences and environmental factors (Nestler and Hyman, 2010). Indeed, rodent models represent a genetically homogeneous population, and they can be followed across their lifespan in a reasonable timetable. Thus, all critical periods of neurodevelopment can be longitudinally tested and monitored and/or long-term molecular and behavioral alterations induced by the negative effects of early life adverse events into adulthood can be analyzed.

Moreover, this may help to understand how stress or infections in sensitive periods of life can shape trajectories of brain development and function, in a short but also in a long-term way, and whether these alterations can be sex specific. In addition, rodents can be grown up in controlled and standardized conditions, which allow to minimize experimental variability (Franklin and Ericsson, 2017), such as the potential impact of different laboratory caging systems (Mueller et al., 2018).

Recent preclinical research has also focused the attention on the “double-hit” effect exerted by an initial adverse event early in life in priming the response to a second negative challenge occurring later on (e.g. in adolescence or adulthood).

Finally, animal models exposed to stress or immune challenges during neurodevelopment may offer important knowledge about the possibility to develop preventive strategies for stress-related psychiatric disorders in humans. This highlights the importance of animal studies relevant to mental health disorders as a necessary and invaluable aspect of biomedical research in drug discovery, development and validation (Bale et al., 2019).

3. Neurodevelopmental animal models to test behavioral outcomes and translational relevance

As previously mentioned, adverse events during sensitive periods of life are known to increase the risk for psychiatric disorders later on (Carr et al., 2013; Dube et al., 2003). However, it is important to note that the effects of an adverse environment on the offspring’s health are variable. Indeed, while some of the stress-exposed offspring develop mental disorders, a substantial portion of them does not. Hence, there may be a considerable degree of resilience to adverse and negative situations experienced early in life, which determines the extent to which offspring are protected from developing long-lasting abnormalities in brain functions and behavior (Mueller et al., 2021). Understanding how an adverse early life environment contributes to the development of altered molecular mechanisms and behavioral alterations, may help to understand the mechanisms underlying psychopathology, but also to explain differences between vulnerable and resilient phenotypes.

In the last decades, different paradigms have been developed and used to induce molecular but also behavioral alterations during neurodevelopment in animal models, trying to resemble those observed in patients with psychiatric disorders. Moreover, these paradigms have been also thought to mimic the double hit hypothesis allowing to assess whether offspring who may appear resilient after a first adverse event early in life (for

example to prenatal immune challenge), could be primed and still respond adversely to a second hit, for example to chronic stress or social isolation exposure (*See Figure 1*).

In the following paragraphs, several paradigms of stress or prenatal infections as well as behavioral tests and outcomes will be described, with a specific focus on the three main critical neurodevelopmental time points, represented by prenatal, postnatal life and adolescence, which are all characterized by an intense maturation of brain structure (*See Figure 1*). Behavioral tests in rodents encompass the open-field, elevated plus maze, forced swim, sucrose preference, Y-maze, object recognition, and Morris water maze tests allowing the evaluation of different behavioral domains like the locomotor activity, anxiety-like symptoms, depressive-like symptoms, working memory, recognition memory, spatial memory, and learning performance.

3.1 Early life stress models

3.1.1 Gestation: Prenatal stress or maternal immune activation

According to a growing body of evidence, an exposure to stress or infection during gestation can cause molecular and functional alterations, associated with an enhanced risk of developing behavioral deficits and emotional problems in the newborns. Animal models have proven to be key tools for investigating the effects of maternal stress or infections during pregnancy, because the timing and intensity of stimulus exposure can be precisely controlled (Gonzalez-Ochoa et al., 2018; Weber-Stadlbauer and Meyer, 2019).

Prenatal stress (PNS) in rodents is a well-characterized paradigm of stress early in life, which usually consists in the exposure of pregnant dams to a stress paradigm (i.e. restraint stress or forced swim stress or overcrowding or exposure to bright light and food deprivation) during the last week of gestation (Richetto and Riva, 2014). Several lines of evidence from preclinical models indicate the presence of long-lasting consequences of PNS exposure, which include alterations at molecular and behavioral levels in adult offspring, such as a reduced activity in the open field test, a reduced social preference and an enhanced anxiety-like behavior in the elevated plus maze and light–dark box tests (Grigoryan and Segal, 2013; Laloux et al., 2012; Marrocco et al., 2012). In addition, it has been shown that PNS exposure produces long-lasting alterations in cognitive functions (Nazeri et al., 2015; Zhang et al., 2017), in terms of impaired working (Cattaneo et al., 2019) and spatial memory (Barzegar et al., 2015).

Not only PNS, but also maternal infections during pregnancy can lead to disruptions in the fetal environment, which may negatively influence the offspring's physiological brain and behavioral development (Schwendener et al., 2009). Experimental investigations in rodent models of prenatal immune challenge have indeed demonstrated the cause-effect relationship between *in utero* exposure to infection and the higher risk of the offspring's brain dysfunctions (Meyer et al., 2009; Ronovsky et al., 2016). At the same time, recent studies have suggested that ~ 50% of the offspring exposed to maternal infections show a vulnerable phenotype, because they develop overt dysfunctions in social behavior, sensorimotor gating, and working memory, whereas the other half is more resilient and largely indistinguishable from control offspring in terms of behavioral performance (Estes et al., 2020; Mueller et al., 2021).

To date, the most widely used animal model of prenatal infection, also called maternal immune activation (MIA), is based on the administration to pregnant dams of immunogenic substances, such as lipopolysaccharide (LPS) or polyriboninosinic–polyribocytidilic acid (PolyI:C), which mimic bacterial and viral maternal infections respectively (Giovanoli et al., 2013; Meyer et al., 2005). Epidemiological studies also suggest that infection with the influenza virus during pregnancy increases the risk of developing psychiatric disorders, including schizophrenia or acute psychoses in adult offspring (Kepinska et al., 2020). In preclinical animal models, maternal administration of LPS or PolyI:C during pregnancy is considered a valuable experimental tool to study the effects of fetal brain inflammation on the subsequent brain development, but also to explore the influence of gestational immune challenge on postpartum maternal behavior (Lins et al., 2018; Meyer et al., 2009).

LPS is an inherent cell wall component of gram-negative bacteria, which is mainly recognized by the pathogen recognition receptor transmembrane protein toll-like receptor (TLR) 4, whereas PolyI:C is a synthetic analog of double-stranded RNA that efficiently stimulates an immune response via TLR3 activation (Meyer, 2014). The administration of both LPS or PolyI:C to pregnant dams acutely enhances the levels of pro-inflammatory cytokines in the mother's blood, placenta, amniotic fluid and fetus and can cause microglia activation and induction of the pro-inflammatory transcription factors in the fetal and neonatal brain (Meyer, 2014; Meyer et al., 2005; Saadani-Makki et al., 2008). Although their effect is mainly acute, the consequences of such exposure can persist over time up to adulthood, often resulting in a vast array of molecular and neurochemical abnormalities and in behavioral deficits, mainly affecting sensorimotor gating, selective attention, social and

exploratory behavior, working memory and cognitive flexibility (Estes and McAllister, 2016; Meyer, 2014). Interestingly, MIA can negatively affect brain and behavioral functions across multiple generations, suggesting that transgenerational transmission of psychiatric diseases susceptibility can occur following early life exposure to different prenatal environmental challenges (Weber-Stadlbauer et al., 2017).

Converging findings from such experimental approaches suggest that prenatal infections can act as a *neurodevelopmental disease primer* that is likely relevant for a number of chronic mental illnesses (Meyer, 2014). Nevertheless, there is also a substantial degree of resilience to MIA, which determines the extent to which offspring are protected from developing neurodevelopmental sequelae (Meyer, 2019). Several factors, including high maternal levels of vitamin D, iron, zinc, omega-3 fatty acids, and choline, have been suggested promoting resilience to MIA (Meyer, 2019). By contrast, among various factors acting at prenatal or postnatal stages of life that can promote vulnerability to MIA, there are maternal hypoferrremia and anemia, gestational diabetes mellitus, maternal stress, dysbiosis of the maternal gut microbiota, peripubertal exposure to psychological trauma, and chronic cannabis use during periadolescence (Meyer, 2019). In addition, although human epidemiological studies about the intensity of MIA and the gestational timing of exposure are insufficient, the current assumption is that MIA at high intensity, namely the magnitude of maternal inflammation, and occurring in the first half of pregnancy has a more extensive impact on the offspring's mental and physical health compared with milder forms of MIA and with exposure in the second half of pregnancy, respectively (Meyer, 2019). In a recent epidemiological study in humans, Lydholm and collaborators have looked at maternal infections before, during and after pregnancy and have suggested that the risk for mental disorders is only slightly increased during pregnancy for infections overall (Lydholm et al., 2019). However, if the exposure is severe enough, specific infections or brain-reactive antibodies transferred during pregnancy might increase the risk for the development of psychiatric conditions in the exposed offspring (Coutinho et al., 2017).

During pregnancy the mother and the offspring are biologically bonded with each other, and therefore the exposure of the mother to PNS or infections can directly affect the fetus. As an example, recent data in pre-clinical models have identified that PNS causes a reduction in the levels of the placental enzyme 11-beta-hydroxysteroid dehydrogenase type 2 (11 β -HSD-2), which converts corticosterone into a less active form, thus changing the tight regulation of the materno-fetal glucocorticoid transfer (Wyrwoll and Holmes, 2012) and

exposing the fetus to higher corticosterone levels (Chapman, 2013). Similarly, several studies have postulated that maternal infections during pregnancy can lead to the exposure of the fetus to high levels of pro-inflammatory cytokines, resulting in subsequent alterations on the offspring's behavior and cognitive functions (Boulanger-Bertolus et al., 2018; Ratnayake et al., 2013). Indeed, cytokines have important consequences on the fetal brain development, since its physiological trajectory requires a specific balance of constitutively expressed cytokines in the maternal and fetal environment. This balance is normally tightly controlled, but, in case of maternal infection, the excessively produced maternal cytokines can cross the placenta, have access to the fetal compartment and stimulate the *de novo* synthesis of cytokines in the fetal brain, with deleterious consequences (Cattane et al., 2020). As an example, in the prospective longitudinally study conducted by Rasmussen and collaborators, an inverse association between maternal Interleukin (IL)-6 concentration during pregnancy and the offspring's non-verbal fluid intelligence performance in early childhood was found (Rasmussen et al., 2019). These data confirm the damaging role of inflammation during the intrauterine period of life and highlight that maternal health conditions can influence the child cognitive abilities during development (Rasmussen et al., 2019). Moreover, a recent study has suggested that the exposure of human neural progenitor cells to Interferon gamma (IFN- γ) leads to morphological and transcriptomic changes that overlap with those observed in neurodevelopmental disorders, such as schizophrenia and autism, at the cellular and molecular level (Warre-Cornish et al., 2020).

Interestingly, several studies have suggested that cognitive and emotional dysfunctions observed in the offspring could be induced by disrupted postpartum maternal behavior of pregnant dams exposed to PNS or MIA during pregnancy (Korosi and Baram, 2009; Patin et al., 2002; Schwendener et al., 2009; Smith et al., 2004). It is well known that both PNS and immunological stimulation are associated with the activation of several stress response systems in the mother, including the Hypothalamic–Pituitary–Adrenal (HPA) axis (Perani and Slattery, 2014; Silverman et al., 2005). Hence, changes in postnatal maternal factors and care resulting from PNS or immunological challenges during pregnancy may expose the pups to an adverse rearing environment and thereby confer additional risk in the offspring.

In this regard, Schwendener and collaborators exposed pregnant mice during late gestation to PolyI:C (or sham treatment), and offspring born to PolyI:C- and sham-treated dams were simultaneously cross-fostered to surrogate rearing mothers, which had either experienced inflammatory or vehicle treatment during pregnancy.

The authors found that MIA during pregnancy leads to altered postpartum maternal behavior in the form of reduced licking/grooming (LG) of pups and increased nest building activity. These alterations in maternal behavior were paralleled by postnatal development of abnormal fear-related behavior in the offspring. Interestingly, the adoption of neonates by PolyI:C-challenged surrogate rearing mothers led to enhanced conditioned fear in the periadolescent and adult offspring. These results suggest that being raised by gestationally immune-challenged surrogate mothers increases the vulnerability for specific forms of fear-related behavioral pathology in later life, and that this association may be mediated by deficits in postpartum maternal care (Schwendener et al., 2009).

Longitudinal Magnetic Resonance Imaging (MRI) studies in rodents have also suggested that prenatal exposure to MIA leads to structural brain changes in late adolescence/early adulthood. Indeed, exposure to MIA resulted in a decreased volume of several regions such as. cortex, hippocampus, amygdala, striatum, nucleus accumbens and the lateral ventricles, whereas, the volumes of the thalamus, ventral mesencephalon, brain stem and major white matter tracts were found larger, when compared to controls. These volumetric changes were maximal between PNDs 50 and 100 with no differences between the groups thereafter. This suggest that the effects of MIA on brain structure may occur early in life and that these features do not show further progression (Crum et al., 2017). MRI investigations have also suggested a delay in the normal process of mouse brain maturation induced by MIA, showing that the major postnatal changes are represented by cortical thinning through adolescence to early adulthood which likely reflects abnormalities in myelination functionality and stability (Richetto et al., 2017).

Similarly, the *in vivo* longitudinal study performed by Piontkewitz and collaborators (Piontkewitz et al., 2011) has provided that PolyI:C offspring had smaller volumes of the hippocampus, striatum and prefrontal cortex, and larger ventricular volume. This prenatal PolyI:C-induced insult to the fetal brain, which leads to aberrant temporolimbic and frontocortical neurodevelopment, evolves during adolescence/young adulthood, interacts with earlier striatal abnormality as well as other maturational processes, and leads to the emergence of behavioral negative outcomes (Piontkewitz et al., 2011).

3.1.2 Early postnatal stress

For an infant, the interaction with the parents is an essential relationship that can drive the development of its nervous system, brain circuitries and therefore also behavior (Tierney and Nelson, 2009). Disrupting this interaction can result in abnormal brain development, growth, and behavior (Bath et al., 2016; Korosi and Baram, 2009). In rodents, as in other mammals, the early postnatal environment is strongly determined by interactions of pups with the mother. Although during the postnatal period the mother and the offspring are not biologically bonded with each other, as in the womb, postpartum period involves social-environmental factors, mainly represented by a lack of maternal care, which can negatively influence the pups' behavioral outcomes.

Several preclinical studies have clearly demonstrated that repeated maternal separation (MS) (for 3 or 6 hours) during the first 2-3 weeks of postnatal life have long-term consequences on endocrine, behavioral and brain development later in life, suggesting that postnatal MS dramatically interrupts the newborn's brain development and affect also several behavioral of exposed animals, increases the risk for neuropsychiatric diseases including anxiety and depression, assessed through behavioral tests including the forced swim test, open field test, elevated plus-maze test, and splash test (Amini-Khoei et al., 2019).

One of the first study focusing on the post-partum period was performed by Weaver and collaborators and suggested that rats receiving less mothering behavior including licking/grooming (LG) and arched backed nursing in their early postnatal life show an enhanced neuroendocrine response to acute stress in adulthood (Weaver et al., 2004), a greater fear-like behavior, and an increased depressive-like behavior in the forced swim test as compared to offspring from high-LG mothers (Weaver et al., 2005). In addition, MS in rats has been associated with stress hyperactivity, anxious behavior, anhedonia, increased ethanol consumption, and increased in the HPA axis activity (Pascual and Zamora-Leon, 2007). Accordingly, animal models of disrupted mother-pup interactions in the early postnatal period have provided valuable insights into the effects of MS on behavior, with a prominent role for the HPA axis. Deprivation of maternal care leads to an increase in circulating corticosterone and HPA axis activity in a period where HPA axis activity should be physiologically low (Maniam et al., 2014). Corticosterone overexposure caused by a lack of maternal care for 24h or repeatedly for 3h per day in the 2 postnatal weeks after delivery is known to alter HPA axis functionality and stress reactivity later in life and to cause deficits in cognitive and emotional behavior (Kentrop et al., 2018).

Interestingly, Parent and colleagues (Parent et al., 2017) have suggested that adult offspring born to mothers that naturally change maternal LG show an increase in the innate immune response following an exposure to an LPS challenge (Parent et al., 2017). According to the authors' point of view, on one side offspring from low-LG mothers appear programmed to grow up in an environment with greater risk of threat, including greater exposure to infections. The increased elicitation of the immune response in low-LG offspring may aid them in overcoming infectious pathogens with greater facility than high-LG offspring. On the other side, the over-activation of the innate immune system observed in the offspring from low-LG mothers may induce the development of inflammation-based pathologies, such as depression, in adulthood as compared to offspring from high-LG mothers (Parent et al., 2017).

Recently, a positive correlation between the amount of maternal care received during the first weeks of life and the amount of social play behavior in adolescent male but not female rats has been observed (van Hasselt et al., 2012), indicating that maternal care plays a key role in the development of adolescent social behavior. Indeed, Kentrop and collaborators investigated the effects of early maternal deprivation (24h on postnatal day (PND) 3) on rats' social competence in adolescence and adulthood. In addition, they examined the effects of a complex rearing environment (from PND 26 onward) on these same measures, and they analyzed the interactive effects of these two manipulations. The authors found that adolescent maternally deprived males, but not females, showed a decreased total amount of social play behavior after 24h of maternal deprivation as compared to non-deprived animals. In adulthood, social interest was not affected, but both male and female rats deprived of maternal care early in life showed impaired social discrimination (Kentrop et al., 2018).

Other studies have suggested that MS can determine alterations in animals' sociability. Indeed, social interest was reduced in male but not female rats after 12h of maternal deprivation on PND 9 and 11 (Takase et al., 2012), whereas 24h of maternal deprivation on PND 9 did not affect male or female rodents' social exploration (Zamberletti et al., 2012).

Interestingly, social discrimination or preference for social novelty, such as for example the ability to discriminate between a familiar and unfamiliar conspecific, were impaired after daily MS in male rats (Lukas et al., 2011), but unaffected in male mice (Zoicas and Neumann, 2016).

Recent studies have also suggested that MS may disturb the development and the composition of the intestinal microbiota (O'Mahony et al., 2017). For instance, through the evaluation of the bowel (colon) tissue, Amini-

Khoei and collaborators observed that MS led to histopathologic changes in the colon and was able to change the microbiota composition in the bowel (Amini-Khoei et al., 2019).

3.2 Stress paradigms during adolescence

Adolescence represents a critical neurobehavioral and developmental period wherein the maturing nervous system is sensitive to stress-related psychosocial events (Manz et al., 2018). Indeed, this phase of life is usually accompanied by a number of external stressors (pressure to perform, partnership, clarification of career aspirations, etc.). Biologically, this is a period characterized by physiological, behavioral and neurobiological transition that prepares the animal for adult life (Cotella et al., 2020). In mammalian species, this transition includes increases in peer influences, sexual competition, novelty-seeking and risk-taking behaviors, all necessary skills to survive without parental caregiving (Brenhouse and Andersen, 2011; Spear, 2000). In parallel, a continuous neural maturation process occurs in the form of synaptic pruning and sprouting, reorganization of innervating neurotransmitter systems, myelination of nerve fibers and cell proliferation (Brenhouse and Andersen, 2011; Eiland and Romeo, 2013; Lee and Gorzalka, 2012). Because of all these neuroanatomical rearrangements, adolescence can be considered a particularly sensitive developmental period (Leussis and Andersen, 2008; Musliner et al., 2021; Paus et al., 2008). Adolescence is indeed the period where the first symptoms related to psychiatric disorders can become manifested (Paus et al., 2008). In addition, exacerbation of symptoms related to the attention deficit hyperactivity disorder (ADHD), autistic symptomatology or the onset of other comorbidities also occur during this time.

Although often used interchangeably, puberty and adolescence do not refer to the same process. The term puberty refers to the maturation of the reproductive system, whereas the term adolescence refers to the development of the social and cognitive behavior along with the maturation of the reproductive system (Kane and Ismail, 2017). According to several studies, one generally accepted developmental timeline in rodents (mice and rats) suggests that adolescence has three stages: early adolescence (PNDs 21-34), mid-adolescence (PNDs 34-46) and late adolescence (PNDs 49-59). Adulthood is usually considered to extend onwards of PND 60 (Lupien et al., 2009).

As previously mentioned, adolescence represents a dynamic and critical period of brain maturation (Crum et al., 2017) and, for this reason, it is particularly vulnerable to stress. In support to this hypothesis, several studies

have suggested that stress mainly targets specific brain areas including the PFC, a late maturing brain structure (Gogtay et al., 2004), whose brain circuits are “under construction” during adolescence. Indeed, exposure to repeated stress in adolescent rodent models reduces the total length and number of branches of dendrites in the PFC of adult rats, alters dendritic spine morphology and causes myelin-related alterations in this brain area (Garrett and Wellman, 2009; Radley et al., 2008; Shansky and Morrison, 2009; Shaw et al., 2020).

Besides the early prenatal and postnatal period, adolescence is gaining interest as a sensitive period in which environmental factors can impact brain development (Fuhrmann et al., 2015). The idea of adolescence as a critical window during development may explain the permanent effects on behavioral and neurochemical regulation observed in adult animal models undergoing social-environmental stress in adolescence. The structural changes observed in the brain of adolescent individuals are extremely important for social, emotional (Burnett et al., 2009; Burnett and Blakemore, 2009; Smetana et al., 2006) and cognitive functions (Chen et al., 2018; Luna et al., 2010) and are necessary to make a subject as an independent adult in a social context. Indeed, adolescents must often face changes in socio-environmental context and must manage repeated conflicts with novel situations and emotions.

The excess of glucocorticoids (GCs) production that occurs in response to stress during adolescence induces long-term changes in the brain, such as changes in glucocorticoid receptors (GRs), neuronal density and structural changes (de Lima et al., 2017). Animals exposed to stressful events during adolescence present higher circulating levels of corticosterone that persist into adulthood (Bazak et al., 2009).

Although for all these reasons adolescence is considered a vulnerable stage, several studies have suggested that this critical period of life may also represent an opportunity. Stressful situations in adolescence, indeed, can not only be related to the development of a future psychiatric disorder, but can also be associated with greater behavioral flexibility in response to different environmental and social contexts in the future (Romeo, 2015). Although it is well recognized that stress-related vulnerability increases during adolescence, not all the exposed adolescents develop negative outcome upon exposures to stressful experiences as many adolescents show resilience to stress-induced dysfunctions (Romeo, 2015).

In order to address this topic, several paradigms can be applied by manipulating the way in which the adolescent animals are housed, either by providing an impoverished environment (isolation or rearing), or a more complex, socially and/or physically enriched environment. Stress models during adolescence can also

vary according to the duration and the types of stressors (e.g., physical, social, predation). As indicated by the studies of Romeo and collaborators (Romeo, 2010a, b; Romeo et al., 2006; Romeo and McEwen, 2006), the neuroendocrine response to acute stress (30 min of restraint stress in both the light and the dark phases) in early adolescent prepubertal rats (28 days old) differs from that in adult animals (77 days old). Specifically, although pre- and post-stress behaviors were similarly affected by the stressor in the light phase in prepubertal and adult males, during the dark phase, restraint stress suppressed play behavior in the prepubertal males, and increased their time spent resting together (huddling), while these behaviors were unaffected by stress in adulthood (Romeo, 2010b; Romeo et al., 2006).

While Romeo and colleagues focused on the effects associated with acute stress responses in adolescent animals, Avital and Richter-Levin mainly focused on the long-term effects of early adolescent or juvenile stress on the response to various stressors in adulthood. They performed studies in juvenile rats exposing them to the elevated platform test once a day (PNDs 27–29) and they observed that this juvenile stress impaired adult stress coping strategies in various paradigms such as the elevated plus maze, the acoustic startle response and the novelty exploration (Avital and Richter-Levin, 2005). Similarly, Tzanoulinou and colleagues have developed a model where rats are exposed to stressful experiences during the peripubertal period (childhood and puberty) leading to alterations in several behavioral domains during adulthood, including the presence of a decreased sociability, increased anxiety and aggression. The protocol consists of exposing rats to fearful experiences (that is, exposure to an elevated platform and to a synthetic fox odor) using an unpredictable schedule on 7 specific days, across PNDs 28–42, to cover the equivalent of childhood (PNDs 28–30) and puberty (PNDs 34, 36, 40 and 42) in rats. By using this protocol, the authors investigate whether the exposure of a repetitive peripubertal stress during either childhood/prepuberty (PNDs 28-30) or during the male puberty period (PNDs 40, 42) would lead to similar effects or no alterations in adulthood. They found that the full extent of the peripubertal stress protocol was required for the observed behavioral and neurobiological effects because exposure corresponding only to the period of rat childhood/prepuberty or male puberty alone was insufficient to elicit the same effects. These findings suggest peripuberty as a period in which stress can lead in adult animals to an altered response to a further stress exposure with the manifestation of latent vulnerable phenotype (Tzanoulinou et al., 2014).

McCormick and colleagues performed experiments applying a chronic social stress paradigm in adolescent rats. The social stress was applied by a regimen of daily social isolation (SI) for 1 hour (between day 30 and 45) followed by pair housing with an unfamiliar partner that had been exposed to the same protocol of social instability. The authors found that chronic social stress enhances adult anxiety on an elevated plus-maze test although this effect was rather mild (McCormick et al., 2008). Similarly, other studies have suggested that chronic social stress in adolescent mice is able to impair spatial memory in comparison with non-stressed controls (Sterlemann et al., 2010).

Not only chronic social stress, but also social deprivation during adolescence leads to changes in brain morphology and behavior (Buwalda et al., 2011). In social animals, as rodents are, deprivation of social contacts can, depending on the timing, lastingly affect the development of normal social behavior which results in alterations in neurochemistry and neuroplasticity (Fei et al., 2019; Fone and Porkess, 2008; Mumtaz et al., 2018).

While SI in experimental animals may model social exclusion from peer groups in adolescents, which can be considered as a part of peer victimization behavior, social defeat may mirror more the aspect of physical abuse and social subordination in bullying, well-known problems in adolescence. In laboratory animal models, social subordination is mimicked by the resident–intruder paradigm. Briefly, in this paradigm, experimental male animals are introduced into the territory of an aggressive male conspecific after which the intruder is rapidly investigated, attacked and defeated by the resident (Chen et al., 2015). In adult male rats, social defeat stress produces strong and long-lasting behavioral and physiological responses that are accompanied by substantial changes in brain neurochemistry (Pulliam et al., 2010). Notably, defeated animals develop depressive-like symptoms, exaggerated stress responses, and increased preferences for alcohol and other drugs of abuse (Bjorkqvist, 2001; Cruz et al., 2011; Yan et al., 2010). While a growing body of literature is available on the effects of adolescent social defeat stress paradigm on the adult brain and behavior, only a few studies have addressed how this paradigm affects the adolescent animal (Burke et al., 2016; Burke and Miczek, 2015; Buwalda et al., 2011). To understand early developmental mechanisms contributing to the isolation syndrome during adolescence and their modification following gestational MIA exposure, Goh and colleagues used a dual-hit neurodevelopmental rat model which combined gestational administration of PolyI:C with post-weaning isolation of resulting offspring to mirror adolescent social adversity (Goh et al., 2020). Interestingly,

instead of exacerbating the well-characterized isolation syndrome, gestational MIA exposure protected against a spectrum of isolation-induced behavioral and brain regional changes. Thus, isolation-reared rats exhibited locomotor hyperactivity, impaired associative memory and reversal learning, elevated hippocampal and frontal cortical cytokine levels, and increased mammalian target of rapamycin (mTOR) activation in the PFC, which were not evident in isolated and previously exposed to gestational MIA animals. Remarkably, hippocampal oxytocin, which can protect against stress, was higher in adolescent PolyI:C-exposed and isolated rats, suggesting that oxytocinergic system could explain the observed resilience to isolation (Goh et al., 2020).

4. Molecular signatures associated with neurodevelopmental animal models

4.1 Prenatal stress

4.1.1 Central alterations

One brain structure that is crucially involved in both learning and memory and in the neuroendocrine regulation of stress hormones is the hippocampus. In this region, exposure to PNS has been associated with a reduction in synaptic density (Hayashi et al., 1998), reduced number of neurons (Bock et al., 2015) and of granule cells (Lemaire et al., 2000), decreased 60% cell proliferation (Kawamura et al., 2006), and deficits in neurogenesis (Lemaire et al., 2006). These changes reduce learning and memory ability in the exposed offspring. A study demonstrated that this paradigm affects also hippocampal metabolic profiles: a different content in alanine, aspartate and glutamate metabolism pathways was observed (Akimoto et al., 2019). The effects of PNS on neurogenesis, glutamate neurotransmission and Long Term Potentiation (LTP) in the hippocampus were also investigated in adult offspring (Fujioka et al., 2006; Maccari et al., 2014). Data revealed that the presence of more severe impairments in hippocampal morphology depend on the intensity of the paradigm: whether PNS is mild (short-lasting: i.e., 30 min, once daily, between gestation days 15–17) or whether it is long-lasting (i.e., 240 min, once daily, between gestation days 15–17), respectively (Fujioka et al., 2006).

4.1.2 Stress-related mechanisms

The HPA axis is a physiological system that is critical in mediating the relationship between exposures to stress early in life and the offspring's developmental outcomes. This evolutionarily conserved system underlies the stress response across vertebrate species and is important for homeostasis. Glucocorticoids (GCs), the end

products of HPA-axis activation, are produced by the adrenal glands in response to adrenocorticotrophic hormone (ACTH) secretion in the pituitary gland. Predator- and ecologically-induced stressors have been found to modify GCs levels, which in turn directly influence important factors, such as brain maturation rate and body size. Activation of the hippocampus inhibits this endocrine cascade, whereas activation of the amygdala enhances the HPA response. In this manner, GCs sensitive brain regions refine challenges to homeostasis and adaptive responses to stress. The expression of glucocorticoid receptors (GRs) is also brain specific and it shows the most pronounced expression in the hippocampus (McEwen et al., 1992) and in the PFC (Gold, 2015).

It has been reported that PNS can lead to hyperactivity of the HPA axis in rats, which may then affect immune responses. Different studies agreed on the evidence that daily PNS over the last week of gestation can lead to elevated basal and activated corticosteroid responses in offspring (Brunton and Russell, 2010; Green et al., 2011; Matthews, 2000; McGowan and Matthews, 2018; Smythe et al., 1994; St-Cyr and McGowan, 2018), with effects that are species-, sex-, and age-specific and depend on the timing as well as the duration of exposure (McGowan and Matthews, 2018).

Although this compelling evidence, there is a considerable variability in the results because they are highly dependent on the nature of the exposure (type of stress, duration, time in gestation), the timing of assessment (prepubertal, peripubertal, adult, aged), the sex of the offspring, and the time of the reproductive cycle when testing females was undertaken (Weinstock, 2011).

4.1.3 Neuroinflammation

The immune system responds to stressors and communicates with the Central Nervous System (CNS) through several mechanisms, including the inflammatory cytokine signalling. It has been demonstrated that PNS modifies neuroinflammation-related processes. Indeed, this paradigm induces a basal pro-inflammatory status (IL-1 β ; Tumor Necrosis Factor alpha (TNF α)) in the hippocampal formation during adulthood that subsequently results in an enhanced activation of microglia in the form of higher proportion of ionized calcium-binding adapter molecule 1 (Iba-1)-immunoreactive cells and astrocytes in response to a further pro-inflammatory insult (Diz-Chaves et al., 2013; Diz-Chaves et al., 2012). Moreover, LPS induced a significant increase in mRNA levels of *IL-6*, *TNF- α* and *interferon γ -inducible protein 10 (IP10)* genes in the hippocampus

of PNS mice compared to non-stressed animals; in contrast, LPS induced similar increases in expression of IL1 β and toll-like receptor 4 (Tlr4) both in PNS and non-PNS animals (Diz-Chaves et al., 2013; Diz-Chaves et al., 2012). Similarly, microglia and maternal IL-6 may be involved in the effects of PNS (Gumusoglu et al., 2017). Microglia are myeloid cells, which provide the main form of adaptive immune response in the CNS (Mondelli et al., 2017). These cells modulate neuronal function not only during an inflammatory response, but also during developmental synaptic formation, pruning, elimination (Paolicelli et al., 2011) and plasticity in a healthy brain (Parkhurst et al., 2013). In addition, they are able to rapidly respond to even minor changes in the brain (Lawson et al., 1990). Microglia monitor the functional state of synapses, influence neuroplastic changes by remodelling extracellular spaces and eliminating synaptic elements by phagocytosis (Brown and Neher, 2014).

Increasing evidence has supported the role of activated microglia in the development of psychiatric disorders. However, although no association have been found with specific diagnostic categories, microglial activation might be the consequence of an excessive exposure to stress and might play a role in the identification of more severe or treatment-resistant patients, or as a target for novel pharmacological interventions, or both (Mondelli et al., 2017). Iba-1 is a well-known microglia related marker widely used to assess and monitor microglia activation as it is specifically expressed by both reactive and quiescent microglial cells (Frick et al., 2013). Recently, Bennett and colleagues have identified the transmembrane protein 119 (Tmem119), a cell-surface protein of unknown function, as a highly expressed microglia-specific marker in both animals and humans. Interestingly, by using antibodies against Tmem119, the authors observed that microglia mature by the second postnatal week of life in mice (Bennett et al., 2016).

When occurring early in life, stress can induce different microglial responses that may have two main consequences. First, interfering with microglial phagocytic activity and neuronal–microglial signalling can disrupt neural circuits' developmental trajectories and alter behavior. Proof of concept for this was provided by Zhan and colleagues who observed that mice lacking the chemokine receptor Cx3cr1 exhibited a transient reduction of microglia during the early postnatal period and a consequent deficit in synaptic pruning. These alterations were also associated with weak synaptic transmission, decreased functional brain connectivity, deficits in social interaction and increased repetitive-behavior phenotypes. According to the authors, all these findings support the hypothesis that a primary deficit in microglia can induce long-term changes in gross brain

wiring and behavior, contributing to the development of neurodevelopmental and neuropsychiatric disorders (Zhan et al., 2014).

Second, aberrant functionality of maturing microglial cells can alter their developmental programs, with long-lasting consequences for their reactivity. Indeed, stress exposure early in life can “prime” microglia to be more responsive to subsequent challenges later in life, leaving a permanent memory of the stressful experience with only partially known consequences in adulthood (Catale et al., 2020). A meta-analysis of studies (Calcia et al., 2016) confirms that PNS exposure reliably leads to a microglial response in hippocampus and PFC regions, with significant increases in Iba-1 activity. These studies support the ‘two-hit’ hypothesis, where an initial adverse event early in life primes microglia, leading to an exaggerated response of the microglia to a second inflammatory stimulus following initial stimulation (Frank et al., 2007; Giovanoli et al., 2013; Hickie et al., 2009).

In addition, an exposure to early life stress results in the activation of the sympathetic nervous system, which affects the regulation of the innate immune system. Of particular interest is the bone marrow, which is densely innervated by the sympathetic nervous system. In pathological conditions, the activation of this system in response to stress leads to the production of noradrenaline, which subsequently triggers the release of monocytes into circulation. Then, these cells migrate to the CNS and, through the secretion of specific cytokines and chemokines, enter the brain parenchyma. The infiltrating pro-inflammatory monocytes lead to further sustained activation of neural stress circuits, resulting in the emergence of abnormal behaviors. In parallel, early life stress may also influence the development and function of central microglia. Hence, any disruption of this process following stress exposure early in life may result in the abnormal neural circuit development, which, by itself, may predispose an individual to psychopathology in later life (Mondelli and Vernon, 2019). Although these data are promising, there is a paucity of studies about the sympathetic nervous system activation in PNS models.

4.1.4 Neuroplasticity

Neurotrophic factors (NTFs), along with cytokines, play an important role in supporting brain equilibrium in stressogenic situations and are central to many aspects of the CNS functions. These systems regulate the development, maintenance, and survival as well as the death of neurons and glial cells. A vast amount of

evidence indicates that alterations in the levels of NTFs as well as of their receptors can modify normal neuronal function and even lead to neuronal damage (Poyhonen et al., 2019).

Brain Derived Neurotrophic Factor (BDNF) plays a critical role during neuronal development and undergoes changes due to PNS exposure. Interestingly, recent evidence suggests that both typical and fast-acting antidepressants directly bind to tyrosine kinase receptor 2 (TRKB), the BDNF receptor. By increasing BDNF signaling, this mechanism can contribute to the efficacy of antidepressants (Casarotto et al., 2021).

A recent systematic literature search (Badihian et al., 2020) has reviewed 2132 studies with 43 found to meet the inclusion criteria. Decreased or unchanged BDNF total mRNA and BDNF mature protein (mBDNF), with hypermethylation of the coding exons were the most reported changes. The results also indicate that hippocampus and PFC are the most vulnerable regions, showing long-lasting and persistent transcriptional and epigenetics changes of BDNF following PNS exposure. However, also in this case, stress paradigm, sex of the fetus, strain specificity and the day of sacrifice were found to significantly affect the results.

Significant decrease in the activity and expression in the hippocampus of tissue plasminogen activator (tPA), a key serine protease involved in the extracellular conversion of pro-BDNF to mBDNF was observed in PNS (Yeh et al., 2012). The working group around van den Hove and colleagues showed that in newborn Fischer 344 rats, PNS resulted in an approximately 50% decrease in brain cell proliferation just after birth in both sexes with a concomitant increase in caspase-3-like activity accompanied by a decrease of BDNF protein levels in the hippocampus (Van den Hove et al., 2006). Moreover, alterations in *Glycogen synthase kinase 3 beta (GSK-3 β)* expression (Van den Hove et al., 2013) with consequent inhibition in mRNA and protein levels of *sonic hedgehog (SHH)*, *β -catenin*, *Notch* and *BDNF* genes (Fatima et al., 2019) were observed in PNS rats. Finally, also reelin that mediates neural plasticity is decreased in PNS rodents (Weinstock, 2017).

4.1.5 Neurotransmitter dysfunctions

It is known that Glutamate (Glu) is the most important excitatory neurotransmitter in the CNS and is involved in important physiological and pathological processes such as synaptic plasticity, emotion, and cognition (Popoli et al., 2011). The hyperactivity of the HPA axis observed in PNS rodents causes an increase in the accumulation of corticosterone, which results in an increased release of Glu in the hippocampus and PFC, and consequently affecting the synaptic plasticity, leading to electrophysiological excitation-inhibition imbalance,

producing neuronal toxicity and degeneration, impairing learning and memory ability and leading to behavioral alterations in offspring (Weinstock, 2017; Zhang et al., 2013b).

Furthermore, dysregulated Glu receptors observed in PNS can also mediate learning and memory ability and hippocampal LTP (Berger et al., 2002; Holloway et al., 2013; Morley-Fletcher et al., 2011; Wang et al., 2018; Weinstock, 2017). Promoter methylation of *metabotropic glutamate receptor 1 (mGluR1)* and *metabotropic Glutamate Receptor 5 (mGluR5)* genes was observed in PNS in a sex-specific manner (Lin et al., 2018). PNS increases the serotonin receptor 5-HT_{2A} in PFC (Holloway et al., 2013) and leads to alterations in serotonin transmission (Weinstock, 2017). Long-lasting effects on dopamine (DA) in limbic areas of the brains of adult offspring were also observed (Berger et al., 2002). Finally, this paradigm increases the *GABAA receptor α5 subunit* gene expression in hippocampus (Nejatbakhsh et al., 2018).

A significant down-regulation of hippocampal presynaptic voltage-gated Ca²⁺ type P/Q and several K⁺ channels that regulate the neuron membrane potential has been also reported in 23-day-old female rats whose mothers were stressed from gestational days 17–21 (Bogoch et al., 2007), suggesting a potential decrease in the excitability of newly formed synapses induced by PNS.

4.1.6 Oxidative Stress

Several studies have reported that stress can mediate alterations in the antioxidant enzymes, reactive oxygen species (ROS) and glutathione (GSH) levels in several brain regions especially the hippocampus and the PCF (Duman and Voleti, 2012). In this regard, Fatima and colleagues showed that PNS can modify the levels of several factors involved in the oxidative stress process: for example, GSH levels were found reduced whereas Superoxide dismutase (SOD) and catalase (CAT) were elevated both in the PFC and in hippocampus of PNS rats (Fatima et al., 2019).

To understand the negative effects of PNS on the offspring's learning and memory behavioral deficits, Li and collaborators have recently analyzed the hippocampal protein profiles of offspring whose mothers were exposed to PNS, in terms of chronic fear stress during pregnancy, compared to control animals (Li et al., 2020). They found 158 differentially modulated proteins mainly involved in the oxidative phosphorylation pathway, as demonstrated by GO classification and pathway enrichment analysis. According to the authors, this could negatively influence the ability to remember and learn (Li et al., 2020).

4.2 Maternal immune activation (MIA)

4.2.1 Central alterations

Several studies reviewed by Bergdolt and Dunaevsky, 2019 (Bergdolt and Dunaevsky, 2019) have suggested a reduction in the brain volume mediated by loss of neurons caused by MIA (Crum et al., 2017; Guma et al., 2019). Moreover, reduced dendritic branching and dendritic spine density have been observed following MIA exposure (Coiro et al., 2015). Altered innervation of dendritic spines in the cortex and the cerebellum has been shown, whereas reduced synaptic transmission has been observed in the cortex and hippocampus. In addition to synaptic impairment, neurons in the hippocampus show altered membrane properties that result in reduced excitability. In adult offspring exposed to PolyI:C *in utero*, patches of cortical disorganization were observed throughout the cortex, however most of the patches were located in the primary somatosensory cortex, secondary motor cortex, and temporal association cortex (Bergdolt and Dunaevsky, 2019; Shin Yim et al., 2017). However, not all studies have found these effects induced by MIA either (Crum et al., 2017; Mueller et al., 2021).

MIA may also impair migration of pyramidal neurons. Reduced production of the glycoprotein reelin, involved in the migration of both embryonic-born and adult-born neurons was observed in the neonatal, developing and adult brain of MIA-exposed offspring (Bergdolt and Dunaevsky, 2019). Abnormalities in cortical neurons have been already reported two days (E14.5) after MIA induction with PolyI:C, or four days (E18.5) after MIA induction with LPS. These abnormalities were characterized by loss of neurons expressing special AT-rich sequence-binding protein 2 (SATB2) and later by disorganized expression of the layer-specific neuronal markers SATB2 and T-brain-1 (TBR1) (Bergdolt and Dunaevsky, 2019).

Finally, sensorimotor gating was reported to be impaired in male and female offspring of mothers treated with LPS between gestation day 15 and 19, with more severe effects in male mice (Romero et al., 2010).

Of note, prenatal immune challenges, including MIA or microglia deficit, has been shown to induce reduced functional GABAergic transmission from a specific population of interneurons expressing parvalbumin (PV) in both the prefrontal and the somatosensory cortices of rodents' adult offspring. A recent work by Thion and collaborators has suggested that transient early macrophage depletion and MIA have a biphasic impact on PV interneurons wiring onto their excitatory target neurons in the barrel cortex. In adults, both challenges reduced

the inhibitory drive from PV interneurons, whereas in juveniles, an unexpected, profound miswiring and hyperconnectivity of PV interneurons preceded this hypo-inhibition. These findings highlight that inhibitory GABAergic networks have several waves of adaptation to an initial embryonic immune perturbation, which can be drastically distinct in juveniles and adults. Moreover, they underline the importance of examining the full developmental trajectory of inhibitory circuits that may lead to pathological brain wiring (Thion et al., 2019).

4.2.2 Stress-related mechanisms

Several studies have demonstrated disruptive effects of MIA on several aspects of hippocampal anatomy and functioning, including decreased levels of glucocorticoid receptors (Bergdolt and Dunaevsky, 2019; Connors et al., 2014). Recently, Zhao and colleagues have demonstrated that the disruptive effects of MIA on social behaviors are associated with HPA axis dysregulation in the ventral hippocampus. Indeed, they have showed that PolyI:C male mice had delayed recovery of plasma corticosterone in response to a novel social encounter. Interestingly, environmental enrichment was able to rescue MIA-impaired social behaviors (Zhao et al., 2021). In addition, male offspring mice born to LPS-treated dams exhibited a more pronounced release of corticosterone in response to an acute restraint stress (Zager et al., 2014).

4.2.3 Neuroinflammation

Altered cytokine levels may both contribute to and are the result of epigenetic alterations in MIA offspring. Central to the mechanism of MIA is the induction of long-lasting changes in expression of immune molecules known to regulate neural connectivity and function in the offspring. Indeed, the levels of numerous cytokines are altered throughout development and into adulthood in the brain of MIA-exposed offspring in a region and age-specific manner, and can be detected in the maternal serum, placenta, amniotic fluid, and fetal brain (Bergdolt and Dunaevsky, 2019; Choi et al., 2016; Garay et al., 2013; Meyer et al., 2008).

As reviewed in Bergdolt and Dunaevsky, 2019, two specific maternal cytokines seem to be critical in mediating the behavioral abnormalities in MIA-exposed offspring: IL-6 and IL-17a that mediate the activation of Th17 cells (Bergdolt and Dunaevsky, 2019). In maternal serum, IL-6 can cross the placental barrier during mid-pregnancy and in the fetal circulation, it can exert positive feedback causing a prolonged inflammatory

response in the offspring. IL-6, in addition to IL-17, is reported to increase in response to MIA in the fetal as well as the postnatal brain. In fact, IL-6 can promote Th17 cell differentiation, leading to IL-17 production that, in turn, results in disorganized lamination of the fetal brain. On the other side, these elevated IL-6 levels can induce the expression of cytokine signalling 3 (SOCS3), that suppresses the physiological Leukemia Inhibitor Factor (LIF) signal relay pathway related to corticogenesis. Another hypothesis that has been proposed is that elevated IL-6 levels in maternal serum suppress the expression of important fetal brain development growth factors, such as growth hormone (GH), insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP3), in the placenta resulting in changes in fetal brain development. Other maternal cytokines that are increased in the periphery following infections during pregnancy include TNF- α , IL-10, IL-1 β , IL-4, and interferon beta (IFN- β) (Ashdown et al., 2006; Ballendine et al., 2015; Choi et al., 2016; Giovanoli et al., 2013; Giovanoli et al., 2015; Money et al., 2018; Wu et al., 2015). Similarly, many cytokines are also dysregulated in the serum of MIA-exposed offspring throughout development (IL-2, IL-5, and IL-6) (Bergdolt and Dunaevsky, 2019). In addition, alterations in brain cytokines (IL6, IFN, IL-1 β , TNF- α) have been detected during development of MIA-exposed offspring (Bergdolt and Dunaevsky, 2019). Recently, Mueller and collaborators observed that ~ 40% of MIA-exposed isogenic mouse offspring displayed an elevated production of innate inflammatory cytokines such as IL-1 β , IL-6, and TNF- α at adulthood, whereas the remaining portion of exposed offspring was comparable with controls in terms of plasma cytokine profiles. The first subgroup also showed significant impairments in social approach behavior and sensorimotor gating, whereas MIA-exposed offspring with a low inflammatory cytokine status did not. Taken together, these results highlight the existence of vulnerable or resilient subgroups of MIA-exposed offspring that show specific inflammatory profiles even under conditions of genetic homogeneity (Mueller et al., 2021).

Another important event linked to the prenatal exposure to MIA is the activation of microglia resulting in further down-stream activation of a wide array of cytokines, growth factors, and free radicals. (Hadar et al., 2017; Juckel et al., 2011; Li et al., 2014; Mattei et al., 2014; Mattei et al., 2017; Van den Eynde et al., 2014; Wu et al., 2018; Zhu et al., 2014). However, the role and activation of microglia following MIA exposure are still unclear and several studies have pointed out the chicken-or-egg problem. Indeed, while microglia could be the first cells to sense the maternally-induced fetal pro-inflammatory cytokines, leading to abnormal changes during CNS development and to behavioral disturbances, cytokines could directly alter neuro- and

gliogenesis and network formation, to which microglia subsequently react (Notter et al., 2018; Smolders et al., 2019).

To understand the putative relationship between neuroinflammatory alterations in schizophrenia and 18-kDa translocator protein (TSPO), a transmembrane protein that is located mainly in the outer mitochondrial membrane, Notter and colleagues implemented a translational approach that combined investigations in MIA-exposed mice with imaging studies in patients with recent-onset schizophrenia. Interestingly, their findings challenged the widely accepted assumption that increased TSPO expression in schizophrenia generally mirrors central inflammation and altered microglia activity. Similarly, two meta-analyses actually show that TSPO is not increased (Marques et al., 2019; Plaven-Sigra et al., 2018).

Indeed, the MIA-based neurodevelopmental disruption model shows that increased levels of inflammatory cytokines can emerge concomitantly with a downregulation - rather than upregulation - of TSPO. Moreover, the downregulation of prefrontal TSPO in the MIA model was not associated with overt signs of microglial anomalies nor was there an association between microglia morphology and TSPO expression in this neurodevelopmental animal model relevant to schizophrenia. Hence, according to the authors' findings, decreased TSPO expression levels do not necessarily suggest a reduced inflammation (and vice versa), implying furthermore that ongoing inflammatory processes are not always mirrored by increased TSPO signals. Therefore, without the concomitant assessment of additional inflammatory markers such as cytokines, interpreting 'neuroinflammation' only on the basis of TSPO signals can readily lead to wrong conclusions (Notter et al., 2018).

Although available data are contrasting, the effects of MIA on microglia are long-acting and may contribute to the elevated levels of inflammatory mediators with neurotoxic effects into adulthood (Dheen et al., 2007). When there is an increase in the number of microglia, there is often an increase in the number of amoeboid microglia, indicative of activated microglia (Juckel et al., 2011). Astrocytes, the most abundant glial cells, are involved, together with microglia, in brain immune activation (de Souza et al., 2015). Conversely, under inflammatory conditions, they enter a state of astrogliosis, which is characterized by functional, structural, and genetic changes. Astrogliosis has been observed to varying degrees in animal models of MIA with several groups observing an increase in the expression of common astrocyte markers such as glial fibrillary acidic

protein (GFAP) and S100 β in the brain and CSF of MIA-exposed offspring when MIA is induced by LPS (Cai et al., 2000; de Souza et al., 2015; Hao et al., 2010; O'Loughlin et al., 2017; Rousset et al., 2006).

The cytokines in MIA can also regulate the expression of other classes of immune molecules on neurons, including major histocompatibility complex I (MHC-I) molecules. In the immune system, MHC-I levels are controlled by cytokines as an important early step in the immune response. In the healthy brain, MHC-I has been found on neurons where it negatively regulates synapse formation and synaptic plasticity required for activity-dependent synaptic pruning (Tetrushvily et al., 2016). MIA causes a dramatic change in MHC-I levels in the offspring's brains and the resulting increase in MHC-I at birth is required for the dramatic MIA-induced deficit in the ability of newborn neurons to form synapses (Antonson et al., 2019; McAllister, 2014). MHC-I also plays a key role in axon pathfinding at growth cones (Shatz, 2009). Indeed, a recent work has suggested that treatment with IFN- γ , an activator of the innate cellular antiviral signalling, of neural progenitor cells (NPCs) from human induced pluripotent stem cells (hiPSCs) leads to increased neurite outgrowth. Moreover, genes of the MHC-I complex were among the top differentially expressed in both neural progenitors and mature neurons following IFN- γ exposure, highlighting a potential mechanism through which antiviral signalling could contribute to intrinsic neuronal phenotypes in neurodevelopmental disorders (Warre-Cornish et al., 2020).

4.2.4 Neuroplasticity

Different studies supported that MIA can cause a decrease in BDNF, nerve growth factor (NGF) ((Giovanoli et al., 2015; Han et al., 2017; Schaafsma et al., 2017), GSK-3 β and protein kinase B (AKT) levels (Bitanhirwe et al., 2010; Willi et al., 2013). Consistent with the reduction in the structural unit of synapses, there is a reduction in the expression of presynaptic (cerebellin-1, bassoon, and synaptophysin) and post synaptic proteins (Glutamate receptor delta 2 (GluR δ 2), PSD-95, SynGAP) in the cerebellum and hippocampus of MIA-exposed offspring (Giovanoli et al., 2015; Pendyala et al., 2017). The decrease in BDNF expression levels and signalling activity contribute to the reduced expression of other synaptic proteins, such as synaptophysin, that are downstream targets of BDNF signalling. In the case of GluR δ 2 expression on Purkinje cells, the proportion of spines in which GluR δ 2 is expressed is lower in MIA-exposed offspring compared to controls (Pendyala et al., 2017). These findings support that synaptic functions are impaired by MIA.

A recent work on rodent models has indicated that MIA can cause epigenetic deregulation in the offspring's brains (Nemoda and Szyf, 2017). Indeed, injections of PolyI:C to pregnant mice caused a decrease in DNA methylation levels of cytosine-phosphate-guanine (CpG) islands associated with *MECP2* and *LINE-1* genes within the hypothalamus, whereas it provoked hypermethylation at the promotor of *glutamic acid decarboxylase (GAD) 1* and *GAD2* genes in the PFC of MIA-exposed newborns. By using genome-wide DNA methylation profiles in PFCs obtained from postnatally MIA-exposed offspring (Basil et al., 2019), a recent study has found changes in DNA methylation levels of genes relevant to the Wnt signalling and neural development, as well as of genes involved in the GABAergic system. These changes were associated with the timing of MIA. Moreover, a direct interaction between MIA and epigenetic regulation of fetal brain development/ via IL-6-mediated activation of DNA methyltransferase 1 has been reported (Pujol Lopez et al., 2016).

4.2.5 Neurotransmitter dysfunctions

In line with the altered neuronal function described above, components of neurotransmitter systems (neurotransmitters, receptors, and transporters) are dysregulated in MIA-exposed offspring. As reviewed in Bergdolt and Dunaevsky, 2019, affected systems include the glutamatergic, dopaminergic, GABAergic, serotonergic and cholinergic systems (Bergdolt and Dunaevsky, 2019).

4.2.6 Oxidative Stress

The developing fetus relies on placental transfer of maternal nutrients including oxygen and glucose. Carpentier and colleagues showed a reduced oxygen supply to the mouse fetal brain following maternal LPS administration on gestational day 12.5 (Carpentier et al., 2011). Similarly, through a whole genome microarray analysis of the fetal brain, Oskvig and collaborators observed an up-regulation of genes associated with cellular stress, hypoxia, and pro-apoptosis in offspring born to LPS-treated dams. According to the authors, this suggests a plausible scenario whereby maternal LPS results in fetal oxygen deprivation leading to a transient threat to cell viability (Oskvig et al., 2012).

4.3 Early postnatal stress paradigm

4.3.1 Central alterations

Different studies have shown that early postnatal stress (EPS) suppresses the developmental trajectory of hippocampal pyramidal neurons (Liao et al., 2014; Liu et al., 2016; Wang et al., 2012; Yang et al., 2015). For instance, Wang and colleagues have demonstrated that EPS impairs hippocampus-dependent spatial learning and memory in adult mice (Wang et al., 2012) whereas corticotropin-releasing hormone (CRH)/ corticotropin-releasing hormone receptor 1 (CRHR1) system plays a crucial role in modulating and programming these cognitive functions as consequence of early life stress. Moreover, EPS mice showed dendritic spine loss with decreased hippocampal nectin-3 levels, a protein necessary for postnatal hippocampal development of memory functions and structural integrity (Liu et al., 2019; Wang et al., 2013). In the dentate gyrus, granule neurons show a looser packing density and an altered morphology after EPS exposure (Fabricius et al., 2008; Oomen et al., 2011; Wang and Gondre-Lewis, 2013). Long-term changes in the density of astroglia in the brain regions involved in stress responses (Leventopoulos et al., 2007), a reduced hippocampal mossy fiber density (Huot et al., 2002) have been also reported following maternal separation (MS).

The transcriptional repressor REST has an important role in the developmental switch of synaptic N-methyl-D-aspartate receptors (NMDARs). Maternal deprivation impaired REST activation and acquisition of the mature NMDAR phenotype (Rodenas-Ruano et al., 2012) and altered the hippocampal structural plasticity in a sex-dependent manner (Oomen et al., 2009).

4.3.2 Stress-related mechanisms

Many studies have shown that daily repeated MS can regulate the HPA axis and affect subsequent brain functions and behavior during adulthood. In studies examining the corticosterone and c-Fos expression levels, it has been suggested that repeated EPS may affect neuronal function in region- and temporal-specific manners (Nishi et al., 2014). Moreover, a 24h MS paradigm in 11-day-old rat pups can lead to an increase of ACTH and corticosterone (Rajan et al., 2019; van Oers et al., 1998) and a decrease in the expression of GRs and mineralocorticoid receptors (MRs) mRNA levels in the hippocampus (van Oers et al., 1998). This has been also shown in maternally separated mice on PND 9 (Schmidt et al., 2002). An influence of EPS on brain neurosteroid systems (5α -reduced/ 3α -hydroxylated metabolites of progesterone, testosterone and deoxycorticosterone) has been proposed (Brunton, 2015).

Pioneering studies on epigenetic alterations in GR promoter in response to variations in maternal care were first shown by Weaver and colleagues. They reported increased methylation of the 5' exon17 GR promoter and decreased H3K9 acetylation both associated with reduction in GR mRNA levels in the hippocampus of pups raised by low licking grooming arched-back nursing (LG-ABN) dams (Weaver et al., 2004). Extended studies have shown that increased CpG sites methylation in the low LG-ABN pups reduced the binding of the transcription factor Nerve Growth Factor Inducible protein A (NGFI-A) to GR exon 17 promoter and reduced recruitment of CREB binding protein (CBP), subsequently reducing the levels of GR mRNA levels in the hippocampus (Weaver et al., 2007). These changes were observed both at PND 6 (early) and PND 90 (adulthood) suggesting the long-lasting nature of the epigenetic mark. In contrast, Daniels and colleagues reported no differences in the methylation status of exon 17 GR promoter in MS rats compared to controls on PND 21 (Daniels et al., 2009). The conflicting results could be due to differences in the early stress model (maternal care vs MS) and strain (Long-Evans vs Sprague Dawley) which may exert different effects on the epigenetic signature of the GR. Other studies have also reported epigenetic alterations in the GR promoter using different EPS models of rat/mouse strains (Kember et al., 2012; McGowan et al., 2011).

Chen and colleagues reported hypomethylation of the CRH promoter in the paraventricular nucleus (PVN) of maternally deprived Sprague Dawley rats on PND 61. This was associated with an increased phosphoCREB binding to the CRH cAMP response element (CRE), critical in the regulation of transcription of CRH (Chen et al., 2012). Similarly, Wang and colleagues reported increased H3 acetylation and hypomethylation of the CRH promoter region in the hippocampal CA1 region of rats exposed to postnatal MS (Wang et al., 2014). Franklin and colleagues reported hypomethylation of the CRH receptor 2 (CRHR2) in MS-exposed male C57/BL6 mice at 3–8 months of age. In addition, the authors provided evidence that behavioural alterations induced by MS can be in part transmitted to the subsequent generations; indeed they showed that MS affects DNA methylation in the germline of stressed male mice, with either increased or decreased methylation levels depending on the locus (Franklin et al., 2010).

4.3.3 Neuroinflammation

It has been demonstrated that MS potentiates the inflammatory response and the resulting HPA-axis activation, which may have detrimental effects if MS is prolonged or repeated (Zajdel et al., 2019). A differential cytokine

expression has been observed after MS: in hippocampal extracts, MS increased IL-1 β mRNA levels, while IL-6 and TNF- α did not change; in hypothalamic tissue, MS increased TNF- α and IL-6 mRNA, but not IL-1 β . Peripheral concentrations of IL-1 β were decreased, TNF- α expression levels were unchanged, whereas IL-6 mRNA levels increased in MS-exposed animals (Roque et al., 2016). Another study reported that MS resulted in significant down-regulation of the expression of 6 cytokine genes: *chemokine ligand 7*, *chemokine receptor 4*, *IL-10*, *IL-1 β* , *IL5 receptor alpha* and *integrin alpha* (Dimatelis et al., 2012). Moreover, MS attenuates the hippocampal IL-1 β protein and peripheral cytokine response (IL-1 β , TNF- α ; IL6) to LPS (Saavedra et al., 2017). Significant increases were detected in leptin, IL-1 α , and BDNF, while C-reactive protein (CRP) was significantly reduced in MS-exposed rats (Carboni et al., 2010). Kim and colleagues reported that compared with controls, plasma levels of corticosterone, IL-1 β , IL-6 and glial cell-derived neurotrophic factor (GDNF) were significantly increased in mice exposed to MS (Kim et al., 2017). Similarly, increased IL-1 β , IL-2, IL-6 and TNF- α levels were observed in both plasma and brain of MS-exposed offspring (Hohmann et al., 2017). In rats, MS on PND 9 caused increased hippocampal IL-1 β receptor in male offspring (Viviani et al., 2014) and an increase in IL-1 β mRNA levels in the hippocampus were observed in rats with a neonatal infection and an immune challenge in adults (Bilbo et al., 2008). Finally, maternal deprivation increased the levels of IL-10 in the hippocampus, and the levels of TNF- α in the hippocampus and in the cortex, whereas decreased hippocampal levels of BDNF in adult life (Pineiro et al., 2015).

Several studies have demonstrated that MS exposure has long lasting and permanent effects on microglia (Catale et al., 2020). In general, adult brains from MS mice do not present differences in the number of microglial cells but show region-specific modulation in the expression of activation markers and phagocytic activity and motility. Specifically, MS induces long-term increases in the expression of Iba-1 in the PFC, the dorsal striatum, the nucleus accumbens, and the CA3 subregion of the hippocampus. However, a decrease in Iba-1 expression was detected in the adult spinal cord from MS-exposed rats. In an *in vitro* assay, hippocampal microglia from adult MS-exposed mice showed an increased phagocytic activity (Delpech et al., 2016). Delpech and colleagues profiled the gene expression of hippocampal microglia in MS-exposed mice (brief daily separation model) immediately after the stress procedure, revealing perturbation of several genes, including an increased expression of genes involved in cell cycle regulation and apoptosis (e.g., *CSF1*,

CSF3R), microglial activation, and anti-inflammatory function, and a reduced expression of several pro-inflammatory genes (Delpech et al., 2016).

4.3.4 Neuroplasticity

A plethora of studies focused on neuroplastic findings have been reviewed by Stepanichev et al., 2014 (Stepanichev et al., 2014). In this review it has been indicated that early MS increased levels of neurotrophic factors (BDNF, NGF, NT-3) in both the dorsal and ventral hippocampi. Cerebellar BDNF and TrkB mRNA and protein levels were significantly increased in mother-deprived rats at PND 16. However, by PND 30, these parameters reached levels similar to controls. In contrast, the mRNA and protein levels of NGF, TrkA, p75 NTR, and Nogo receptor (NgR) were unchanged at both ages examined. The expression levels of *BDNF*, *TrkB*, *IGF-1*, and *type 1 IGF receptor (IGF-1R)* in Wistar rat pups separated from their mothers for 3h per day during PNDs 10 to 15 was enhanced on PNDs 16 and 20 and then returned to baseline levels on PND 30. MS (3 h per day from PNDs 2 through 14) in Sprague-Dawley rat pups increased plasma corticosterone release and elevated NGF levels in the hippocampus (Stepanichev et al., 2014). Kikusui and Mori revealed a higher HPA activity in mother separated pups to novelty stress. Neurochemically, the early-weaned male mice showed precocious myelination in the amygdala, increased corticosterone levels on PND 14, decreased BDNF protein levels in the hippocampus and PFC, and reduced BrdU immunoreactivity in the dentate gyrus. Marais and colleagues separated rat pups from their mothers for 3 h/day on PNDs 2-14. This caused significant changes in NGF and NT-3 levels in the dorsal and ventral hippocampus, increased basal corticosterone levels, and decreased ACTH levels in response to acute restraint stress. Separation from mothers down-regulated neurotrophins in the ventral hippocampus, possibly as an effect of higher corticosterone levels, and increased neurotrophin levels in the dorsal hippocampus may reflect compensatory mechanisms against cell death (Kikusui and Mori, 2009). Interestingly, MS induced epigenetic changes at the BDNF exon I promoter: the levels of BDNF protein, exon I mRNA, histone H3 acetylation, and DNMT1 and DNMT3a mRNA were altered in the MS group (Park et al., 2018). Zhang and colleagues reported hypermethylation of the *reelin* gene and a subsequent down-regulation of this gene mRNA levels in the hippocampus of Wistar rats exposed to MS from PNDs 2–15 compared to controls (Zhang et al., 2013a).

4.3.5 Neurotransmitter dysfunctions

In MS mice, three brain areas represented by frontal cortex, amygdala and hippocampus have been reported to show the main differential alterations in 5-HT and DA concentrations both in basal condition and when animals were challenged with an acute stressor in adulthood (Recamier-Carballo et al., 2017). In this regard, Ohta and collaborators demonstrated an imbalance between 5-HT and 5-hydroxyindoleacetic acid in midbrain raphe nuclei, the amygdala, the hippocampus, and the medial prefrontal cortex (mPFC) on MS-exposed rats at PNDs 7 and 14 (Ohta et al., 2014). Furthermore, real-time PCR (RT-PCR) showed an attenuation of mRNA levels of the serotonin 1A (5-HT_{1A}) receptor in the hippocampus and the mPFC and of the serotonin 2A (5-HT_{2A}) receptor only in the mPFC at PNDs 7 and 14. MS on PND 9 decreased the levels of the AMPA receptor GluA1 and GluA2 subunits, altered NMDA receptor subunits GluN2B to GluN2A ratio, and increased IL-1R interactions with GluN2B at the synapse of male hippocampal neurons (Viviani et al., 2014). This mechanism is part of a complex re-organization of the excitatory glutamatergic synapses. Hsu and colleagues reported two episodes of handling with MS during early postnatal development resulted in long-term changes in postsynaptic GABA receptor function and subunit expression in hippocampal dentate gyrus (Hsu et al., 2003). As reported by Jawahar and colleagues, several studies supported the role of EPNS-induced epigenetic modifications also in the serotonin transporter (5-HTT, SLC6A6) gene (Jawahar et al., 2015).

4.3.6 Oxidative stress

A reduction in nitric oxide (NO) levels was found in the hippocampus of MS-exposed offspring, whereas no alterations were observed in the activity of the antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase (Li et al., 2013). In another study, MS in association with early weaning has been found able to affect superoxide production and endothelial dysfunction in adult mice (Ho et al., 2016). Ghatebi and colleagues found that the level of malondialdehyde, a marker of oxidative stress, was significantly higher whereas the total antioxidant capacity level was lower in the MS-exposed group with respect to controls. Malondialdehyde is one of the final products of polyunsaturated fatty acids peroxidation in the cells. An increase in free radicals causes its overproduction.

Also, the activity of superoxide dismutase, glutathione peroxidase and catalase, derived from the MS-exposed animals, was significantly lower compared with those of the control group (Ghatebi et al., 2019). Moreover,

MS induces a phenotype with reduced endothelial NO synthase (NOS) buffering capacity leading to dysfunctional endothelial angiotensin II (AngII)-mediated signalling and sensitization to Ang II-induced vasoconstriction (Loria et al., 2011).

4.4 Adolescent models

4.4.1 Central alterations

Ion channels have an important role in the release of neurotransmitters and stimulate the post-synaptic neurons in CNS by increasing the intracellular concentration of Na⁺ and Ca²⁺ ions in pre-synaptic neurons. In socially isolated (SI) rats, alterations in the electrophysiological properties of some neurons have been observed, that means reduced action potential height and increased action potential threshold in hippocampal pyramidal neurons, short hyper-polarization and abnormal firing of pyramidal neurons in the PFC (Mumtaz et al., 2018). A number of studies reviewed by Mumtaz et al., 2018 reported that environmental or social stressors tend to decrease neurogenesis (Mumtaz et al., 2018). However, SI in rats for 15 days leads to an increased number of adult generated hippocampal cells expressing a neuronal phenotype. In adult *P. californicus* mice, SI increases adult cellular proliferation and cell survival in the hippocampus, confirming that SI should have particularly acute effects on neurogenesis in highly social species of mice.

A significant elevation in c-fos mRNA and protein levels is a useful and frequently used method to elucidate neural circuitry deregulated by a variety of psychological and physiological challenges. It has been reported that in the PFC, dorsal raphe nucleus, and ventral tegmental area, male isolation-reared mice show increased encounter-induced c-Fos expression (Ago et al., 2013). Encounter stimulation increased c-Fos expression in the nucleus accumbens shell of group- and isolation reared mice to a similar degree (Ago et al., 2013).

In SI, stress-induced brain immunoreactivity for c-Fos revealed the activation of the medial and basolateral amygdala, the hypothalamic PVN and hypothalamic attack area were involved in aggressive behavior towards an intruder (Mumtaz et al., 2018).

4.4.2 Stress-related mechanisms

Exposure to SI induces a variety of endocrinological changes including the activation of the HPA axis, culminating in the release of GCs, the production of catecholamines, the activation of the sympatho-

adrenomedullary system (Mumtaz et al., 2018). However, to date, the results on the directions of the alterations (increased or decreased) are controversial for HPA axis, GCs, ACTH, and corticosterone.

Moreover, different studies reviewed by Mumtaz and colleagues showed the significant involvement of oxytocin and vasopressin-dependent underlying mechanisms in SI (Mumtaz et al., 2018).

4.4.3 Neuroinflammation

A change in the function of inflammatory factors has been found to be a pathophysiological consequence of SI. As reviewed in Mumtaz et al., 2018, after contextual fear conditioning, SI for 1 or 3h causes an increase in IL-1 β protein levels in the cerebral cortex and hippocampus. In depression model of chronic mild SI, the decrease in the levels of IL-2, IL-4 and higher basal corticosterone levels was observed. In another study, SI leads to increased levels of TNF- α and IFN γ . Under chronic SI stress exposure, disruption of the HPA axis activity is the result of the overproduction of inflammatory cytokines, including IL-1 β (Mumtaz et al., 2018).

The study by Gong and collaborators showed that one day of brief SI at PND 14 was enough to increase microglial density in the hippocampus, likely by augmenting the proliferation of these cells. After 4 days of isolation (PNDs 14-17), cell number returned to control levels and microglia showed ongoing apoptotic processes. In adulthood, exposure to a week of brief SI (PNDs 14-21) induced a reduction in the number of microglial cells in the dentate gyrus. As a result of these findings, the authors suggested that brief SI during the third postnatal week triggers a complex process of activation and subsequent apoptosis of microglial cells, resulting in a significant loss of microglia in adults (Gong et al., 2018). Similarly, social defeat stress in adolescent mice provokes an early augmentation in PFC Iba-1 and a subsequent reduction in microglial Iba-1 expressing cells in adulthood (Zhang et al., 2019a; Zhang et al., 2019b).

4.4.4 Neuroplasticity

In the SI model, 6h of SI immediately after contextual fear conditioning impaired memory for context fear measured 48h later and decreased mRNA levels of neurotrophins especially BDNF in the dentate gyrus and the CA3 region of the hippocampus collected immediately after the isolation. A number of studies has reported that SI exerted multiple effects also on the serotonergic system as well as on BDNF chromatin remodelling, as SI reduced the transcription activity of the *BDNF* gene and of GCs (Mumtaz et al., 2018). It has been

evaluated that the effects of a prolonged corticosterone administration differ between adolescent and adult rats because hippocampal expression of BDNF was increased in adolescent animals, while it was decreased in the adult ones. In contrast, SI seems to decrease hippocampal BDNF irrespective of animals' age when they were isolated.

Early growth response transcription factor genes (Egr-1-Egr-4) and synaptic activity-inducible immediate early genes regulate some aspects of synaptic plasticity-related cognitive performance. Among Egr family, Egr-1 is an important molecule for triggering activity-dependent modifications in the visual cortex and a useful marker of sensory input and for memory consolidation. The SI stress down-regulates the expression of Egr-1 in an isolation-period dependent manner in the cerebral cortex but not in the striatum whereas, Egr-2, -3 and -4 protein levels were not affected by SI stress. It has been reported that down-regulation of Egr-1 mRNA levels in the frontal cortex is occurred as early as 7 days after starting SI housing. This led to similar behavioral changes induced by SI, such as impaired prepulse inhibition, enhanced aggressiveness, and reduced susceptibility to pentobarbital anaesthesia. Neurochemical changes associated with down-regulation of Egr-1 mRNA levels in the frontal cortex included down-regulation of type I 5-reductase, a key enzyme involved in neurosteroid synthesis, which is responsible for major behavioral changes induced by SI. Moreover, SI causes epigenetic changes in neurodevelopmental disorder-related protein levels, and in rat hippocampal neurons, Egr-1 was also increased by epigenetic regulation.

4.4.5 Neurotransmitter dysfunctions

In several regions of the CNS, SI alters the level of neurotransmitters as well as their receptor sensitivity (Mumtaz et al., 2018). A number of studies has shown that interruption or impairment in neurotransmitter systems play a major role in the development of neuronal disorders in socially isolated rodents. In particular, SI alters the levels of DA, 5-HT, GABA, Glu, nitrenergic system and adrenaline as well as leads to alterations in the sensitivity of NMDA and AMPA receptors. Other systems are involved and altered: opioid pathway, cannabinoid system, and nitrenergic system (NO, neurotransmitters and second messenger molecules).

4.4.6 Oxidative stress

A change in the function of oxidative and nitrosative stress-mediated mitochondrial dysfunction are involved as a pathophysiological consequence of SI (Mumtaz et al., 2018). A study reported that SI rearing for 8 weeks decreased the activities of antioxidant enzymes catalase, glutathione peroxidase, superoxide dismutase, and the total antioxidant capacity, but increased the levels of hydrogen peroxide, in certain brain regions, and in particular of PFC and hippocampus (Shao et al., 2015). Moreover, post-weaning SI-mediated impairment in antioxidant defence mechanisms results in oxidative stress. This is mediated by the down-regulation of peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1 α), a master regulator of mitochondrial energy metabolism and antioxidation, in the NMDAR-deleted PV-positive interneurons (Jiang et al., 2013).

5. Conclusive remarks and future perspectives

In the field of psychiatric disorders, preclinical animal models have been proving to be extremely important in the identification of causative mechanisms as well as in drug discovery, development and validation. They have allowed the possibility of achieving a greater understanding of the mammalian brain and how its functionality can be disrupted as consequence of stressful exposures or infection-related events in sensitive periods of life. Most importantly, they can enable novel and powerful translational approaches in humans. Indeed, a pharmaceutical company would not move forward with a clinical trial for a molecule that was only validated in a cellular model without efficacious data from laboratory animal models.

Our review, mainly focused on biological alterations and behavioral negative outcomes induced by different paradigms of stress (prenatal stress, maternal separation, social isolation and social defeat stress) and immune challenges (maternal immune activation), whose negative effects have been assessed during different sensitive periods of animals' life, including gestation, postnatal life and adolescence, shows a considerable variability in the results. This may depend on the paradigm used or on the nature of the exposure (i.e., type of stress, duration, time in gestation). However, most of the studies taken into consideration suggest that stress and infections early in life impair synaptic plasticity, induce deficits in neurogenesis levels and activate the HPA axis, culminating in a chronic release of GCs, such as corticosterone in rodents. Moreover, they alter the levels of neurotransmitters, including the glutamatergic, dopaminergic, GABAergic, serotonergic, cholinergic and nitrergic systems, and those of neurotrophins, above all BDNF. Stress or infection-related events in sensitive periods of life are also able to increase the production of pro-inflammatory cytokines, to enhance the activation

of microglia and to affect the functionality of oxidative stress, through the modification of antioxidant levels (see Table 1).

Interestingly, our findings suggest that most of the available studies in preclinical animal models are mainly focused on the biological systems disrupted by early life stress in the perinatal period rather than in adolescence (see Table 1). This may be explained by the fact that adolescence is recently emerging as a critical period of vulnerability for psychiatric disorders.

Data reported in our review also suggest that, so far, most of the experimental approaches performed to characterize the effects of stress and immune challenges early in life have been only conducted once animals reach adulthood. Likewise, only a limited number of studies have included male and female offspring in their analyses. Therefore, future preclinical studies should be based on longitudinal analyses to identify the temporal onset of psychiatric-related dysfunctions and should investigate sex-specific differences induced by stressful exposure or infection-related events.

Similarly, the transgenerational effect of stress and/or infections early in life represents an interesting topic, which needs to be better elucidated by further studies in preclinical animal models.

In addition, most of the already available studies in animal models are not designed to establish the cause-effect relationship among exposures to adverse events, molecular alterations and behavioral changes. Exploring such relationships in future studies will be pivotal, as they may open new avenues for novel therapeutic targets in psychiatric disorders.

Finally, animal models will be useful to study the effects associated with exposures to two adverse challenges, occurring in two different sensitive periods of life, to investigate whether the first adverse hit can increase the animal's vulnerability to a second negative challenge. This approach will be of great utility to study molecular signatures associated with vulnerable or resilient phenotypes.

To sum up, preclinical animal models offer the possibility to translate findings in humans and to set the basis for future gene-environment interaction studies, aiming to discover new molecular drug targets and to test novel personalized treatments in the field of psychiatric disorders.

Figure 1: From the bench to the bedside. Focus on: i) the three main critical neurodevelopmental periods, represented by prenatal, postnatal life and adolescence, which are all characterized by an intense maturation of brain structures, and ii) the different paradigm of stress (prenatal stress, maternal separation, social isolation and social defeat stress) and immune challenges (maternal immune activation) performed in the previously mentioned periods of enhanced vulnerability.

Flash represents the “double-hit” effect exerted by a first negative event early in life (1st hit) in priming the response to a subsequent second adverse challenge (2nd hit).

Table 1: Summary of biological systems and molecular signatures, stress-related mechanisms, neuroinflammation, neuroplasticity, neurotransmission and oxidative stress, influenced by early life stressful and adverse events in sensitive periods of animal's life (represented by perinatal period and adolescence).

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Contributors

N.C. collected information, elaborated ideas and wrote the first draft of the paper. A.C.V., A.B., C.S., D.E., L.C., R.T., M.E.B., J.C.L., C.M.P. and M.A.R. contributed on specific parts of the manuscript and provided an overall critical reading. A.C. supervised the preparation of the manuscript and provided the last revised version.

Conflict of interest

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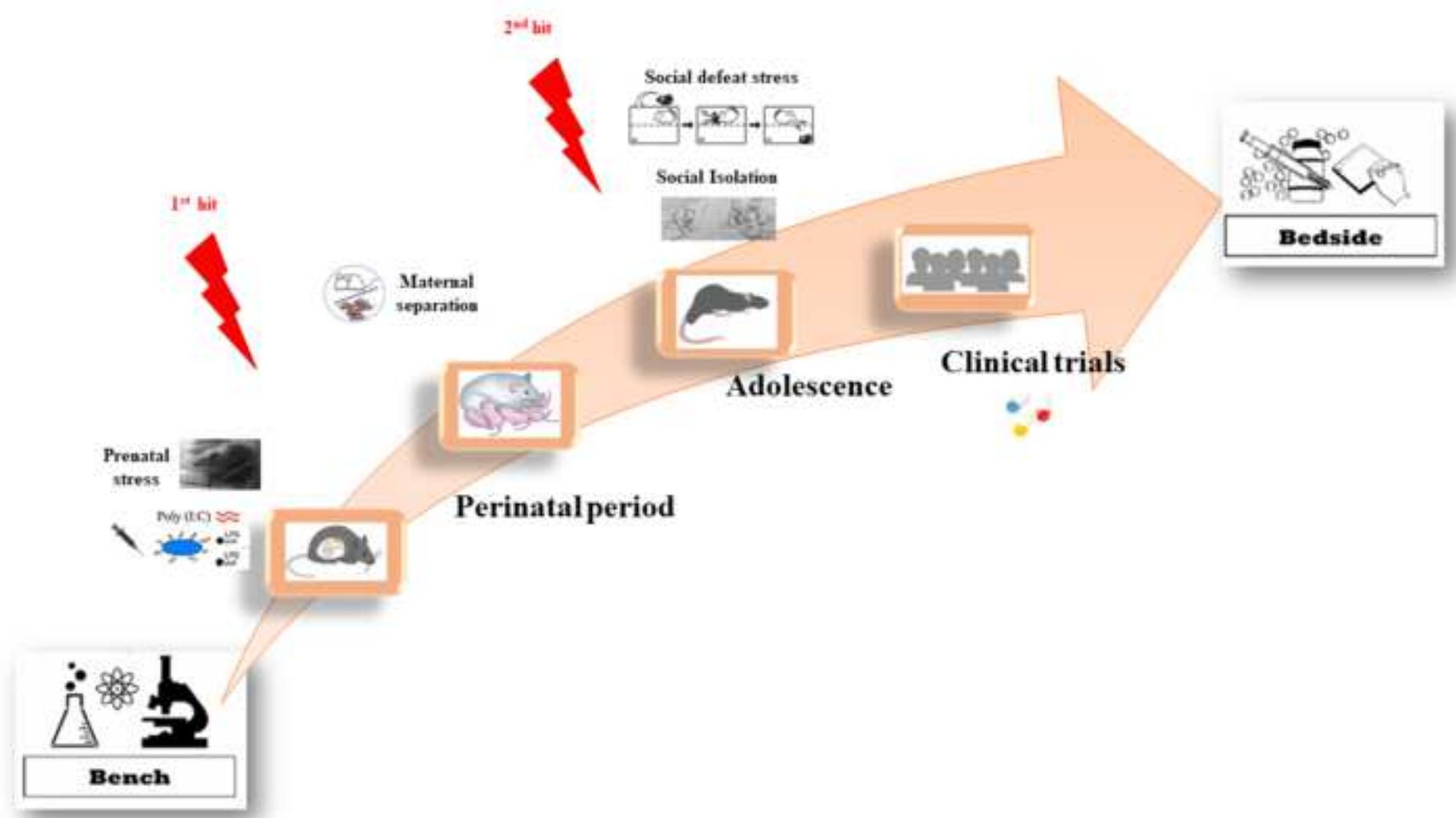
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		PERINATAL PERIOD			ADOLESCENCE	
		PRENATAL STRESS	MATERNAL IMMUNE ACTIVATION	MATERNAL SEPARATION	SOCIAL ISOLATION	SOCIAL DEFEAT STRESS
CENTRAL ALTERATIONS	Reduction in synaptic density and plasticity	✓	✓	✓		
	Reduction in the brain volume		✓			
	Reduction of the total length and number of dendrites	✓	✓	✓		
	Impairment in neuronal migration		✓			
	Impairment in the sensorimotor gating		✓			
	Deficits in neurogenesis	✓			✓	
STRESS-RELATED MECHANISMS	Hyperactivity of the HPA axis	✓	✓	✓	✓	✓
	Higher circulating levels of corticosterone	✓	✓	✓	✓	
NEUROINFLAMMATION	Enhanced levels of pro-inflammatory cytokines	✓	✓	✓	✓	
	Activation of microglia	✓	✓	✓	✓	✓
	Activation of the sympathetic nervous system	✓				
NEUROPLASTICITY	Alterations in neurotrophic factors levels	✓	✓	✓	✓	

NEUROTRANSMISSION	Neurotransmitters dysfunctions	✓	✓	✓	✓	
OXIDATIVE STRESS	Alterations in the antioxidant levels	✓	✓	✓	✓	



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Contributors

N.C. collected information, elaborated ideas and wrote the first draft of the paper. A.C.V., A.B., C.S., D.E., L.C., R.T., M.E.B., J.C.L., C.M.P. and M.A.R. contributed on specific parts of the manuscript and provided an overall critical reading. A.C. supervised the preparation of the manuscript and provided the last revised version.

Conflict of interest

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