Disrupted Circadian Rhythm as a Common Player in Developmental Models of Neuropsychiatric Disorders

Eva M. Marco, Elena Velarde, Ricardo Llorente and Giovanni Laviola

Abstract The environment in which individuals develop and mature is critical for their physiological and psychological outcome; in particular, the intrauterine environment has reached far more clinical relevance given its potential influence on shaping brain function and thus mental health. Gestational stress and/or maternal infection during pregnancy has been related with an increased incidence of neuropsychiatric disorders, including depression and schizophrenia. In this framework, the use of animal models has allowed a formal and deep investigation of causal determinants. Despite disruption of circadian clocks often represents a hallmark of several neuropsychiatric disorders, the relationship between disruption of brain development and the circadian system has been scarcely investigated. Nowadays, there is an increasing amount of studies suggesting a link between circadian system malfunction, early-life insults and the appearance of neuropsychiatric diseases at adulthood. Here, we briefly review evidence from clinical literature and animal models suggesting that the exposure to prenatal insults, i.e. severe gestational stress or maternal immune activation, changes the foetal hormonal milieu increasing the circulating levels of both glucocorticoids and pro-inflammatory cytokines. These two biological events have been reported to affect genes expression in experimental models and critically interfere with brain development triggering and/or exacerbating behavioural anomalies in the offspring. Herein, we highlight the importance

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to unravel the individual components of the body circadian system that might also be altered by prenatal insults and that may be causally associated with the disruption of neural and endocrine developmental programming.

Keywords Early-life stress · Prenatal · Immune activation · Animal models · Clock genes

Contents

Despite genetics are critical for neuropsychiatric disorders' vulnerability, an increasing body of clinical and experimental evidence attests to the relevance of the environment during the developmental period. The time immediately before and after birth is a highly sensitive period characterized by a rapid and continuous neural maturation. During this prenatal and early postnatal period, the brain is particularly susceptible to insults and increasing literature gives support to the impact environmental changes have in the adult individual. Actually, there is now compelling evidence that exposure to suboptimal environments during perinatal life alters brain development and increases the risk for suffering several neuropsychiatric disorders, including schizophrenia, mood and anxiety disorders (Cirulli et al. 2009; Marco et al. 2011). In this regard, experimental animal models do represent an essential and valuable tool to investigate the causal relationship between a given environmental manipulation during development and the observation of persistent neurobehavioral anomalies reminiscent in the model of those frequently observed in mental health problems. Herein, we will briefly review current literature on animal models based upon in utero environmental challenges—prenatal insults—that have been extensively used in the investigation of neuropsychiatric disorders with a neurodevelopmental origin. In particular, we will first focus on models dealing with, i.e. maternal infection or severe stress conditions during gestation. Then, we

will consider how disruption of circadian sleep cycle and expression/function of clock genes are generated as a function of severe environmental insults during gestation. Despite the time of birth and early postnatal period are also time windows of enhanced sensitivity to environmental changes, analysing the diversity of animal models that consider perinatal and postnatal insults remains far beyond the scope of the present manuscript (for reviews on animal models of early-life stress consult (Cirulli et al. 2009; Laviola et al. 2009; Marco et al. 2011, 2015).

1 Changes in the Prenatal Environment to Model Neuropsychiatric Disorders

1.1 Brief Notes on the Maternal Immune Activation (MIA) Model

Maternal infection during pregnancy has consistently been associated with increased risk of developing symptoms related to schizophrenia in the offspring (Boksa 2010; Brown 2006; Brown and Susser 2002; Meyer and Feldon 2009; Patterson 2007). Epidemiological studies have mostly investigated an association between maternal immune activation and schizophrenia, while some other neuropsychiatric disorders have been disregarded. Maternal infection has also been suggested to play a role in the pathogenesis of autism spectrum disorders (ASD) (Hyman et al. 2006), although more epidemiology is needed here. Failed support for the hypothesis that prenatal exposure to a viral infection might be associated with risk of subsequent depression has derived from a human study with over 6000 subjects (Pang et al. 2009). However, more recently, a systematic analysis of the literature explored the potential association between depression, metabolic syndrome, inflammation and hypothalamic–pituitary–adrenal (HPA) axis; although the study did not achieve clear conclusions the importance of the immune system function, possibly through the release of cytokines, to induce and/or maintain depressive symptoms became of critical biological relevance (Martinac et al. 2014). Therefore, a role for prenatal activation of the immune system in depression should not be completely disregarded.

Several rodent models that mimic prenatal infection of bacterial or viral origin have been developed and a multitude of infectious agents have been tested, i.e. influenza, poliovirus, rubella, measles, varicella–zoster, retrovirus and several bacterial agents such as bacterial endotoxin lipopolysaccharide (LPS) or viral mimic polyinosinic: polycytidylic acid (poly I:C). In general, animal models of maternal immune activation have demonstrated alterations in behaviours relevant to both schizophrenia and depression [see recent reviews (Boksa 2010; Meyer and Feldon 2009; Samsom and Wong 2015)]. In this framework, changes in the prepulse inhibition of startle response (PPI), a measure of sensorimotor gating that reflects the ability of an organism to attain information and process it correctly,

have been reported. Loss of normal PPI is widely accepted as an endophenotype of schizophrenia with high translational validity since it can be assessed in both human subjects and animal models. Exposure to LPS during prenatal life has been reported to induce a deficit in PPI. Interestingly, the alteration emerges at "puberty" and seems to persist throughout adult life in male rats (Borrell et al. 2002; Fortier et al. 2007; Romero et al. 2010; Wischhof et al. 2015). With respect to sex-related vulnerability, however, a similar PPI impairment was only found at adolescence (not persisting in adulthood) in prenatally LPS-treated females (Wischhof et al. 2015). Worth mentioning, the administration of antipsychotics, i.e. haloperidol, successfully reversed the PPI impairment induced by prenatal LPS administration, thus providing pharmacological validity to this animal model of schizophrenia (Borrell et al. 2002; Romero et al. 2007). In contrast, other studies have reported no effects of gestational LPS on PPI response at adulthood, although an enhanced acoustic startle response was observed (Fortier et al. 2004). Maternal LPS administration also induced a marked increase in amphetamine-induced hyperactivity, compared to the offspring from control dams (Fortier et al. 2004), and more recently, locomotor hyperactivity has been reported following prenatal LPS administration in both male and female rats offspring (Wischhof et al. 2015).

Important cognitive deficits have also been reported following maternal immune activation. LPS injection to pregnant mice induced an enhancement in recognition memory, a deficit in associative learning and memory but no alterations in spatial memory as measured in the Morris water maze (MWM) (Golan et al. 2005). Impaired object recognition memory has been recently reported in both sexes following prenatal LPS administration, although males appeared to be more severely affected (Wischhof et al. 2015). Similarly, poly I:C administration to near-term mouse dams led to an impairment in reversal learning in the adult offspring (Meyer et al. 2006b). Notwithstanding, a deficit in the reversal phase is indicative of perseverative behaviour, also implicated in schizophrenia, autism, obsessive compulsive disorders, and addictive behaviour (Ridley 1994). Thus, prenatal poly I:C administration has been associated with the exhibition this symptom of altered mental health, i.e. perseverative behaviour. Prenatal poly I:C administration also reduced sucrose preference, indicative of anhedonia, but only if pregnant dams lost weight following MIA (Missault et al. 2014). Taken together, MIA has been related to psychotic symptoms, cognitive impairments and depression-like responses [consult (Meyer et al. 2009; Samsom and Wong 2015) for an extended review]. Different factors associated with the maternal infection process, including the time of maternal immune challenge (Meyer et al. 2006a, b) also seem to be critical for the behavioural outcome in offspring: whether or not dams displayed a febrile response (Lowe et al. 2008) and/or a loss in body weight (Missault et al. 2014) in response to the infectious agent have been identified as factors that should be taken into account when employing animal models of maternal immune activation.

1.2 Prenatal Restraint Stress (PRS)

In general, in both clinical reports and rodent studies, gestational stress has been related with an increased incidence of anxiety, depression and attention deficits in the offspring, together with major neurobehavioral disturbances relevant to ASD and schizophrenia (Beydoun and Saftlas 2008; Talge et al. 2007; Weinstock 2008). However, severe stress during gestation not only positively affects the probability to suffer from several neuropsychiatric disorders, but seems also to facilitate the onset of these disorders as well as potentiate comorbidity problems (Mill and Petronis 2008; Mittal et al. 2008; Rice et al. 2007).

Experimental research has employed different animal models of gestational stress, including altered maternal nutrition (Budge et al. 2007; MacLaughlin and McMillen 2007), administration of glucocorticoid hormones (Catalani et al. 2011; Macri et al. 2011), and obstetric complications mimicking reduced placental perfusion such as episodes of neonatal hypoxia (Boksa 2004; Laviola et al. 2004a). Among the available animal models of gestational stress, we have explored the consequences of exposure to intermittent restraint which also includes an important psychological component in the rat. In particular, we focused on the consequences in the offspring of exposure of pregnant dams to physical restrain immobilization during the last week of gestation.

A prominent reduction in social play behaviour has been reported as a consequence of prenatal restraint stress in adolescent male rats, which came in the absence of changes in environment exploration (Morley-Fletcher et al. 2003b); indeed, our observations confirmed other studies reporting impairments in affiliative behaviour as well as a reduced amount of age-typical rough-and-tumble play in the PRS offspring (Koenig et al. 2005; Lee et al. 2007; Ward and Stehm 1991). The offspring of stressed dams, as both adolescents and adults, has been reported to exhibit increased anxiety levels. In particular, an increased latency to approach a novel object in an open field (Laviola et al. 2004b), as well as increased anxiety-like responses in the elevated plus maze (EPM) (Darnaudery and Maccari 2008; Zuena et al. 2008). Depressive-like responses have also been observed following PRS since an increase in immobility time was registered in the forced swim test, a behavioural paradigm extensively used to validate the effectiveness and potency of antidepressant drugs (Morley-Fletcher et al. 2003a). Learning and attention deficits are also common in the offspring of PRS rats: impairments in spatial learning in the MWM were observed in PRS male rats (Lemaire et al. 2000), as well as impaired recognition memory and altered working memory (Maccari et al. 2003); notably, sex differences have been described with cognitive deficits being more evident in female PRS rats than in males (Zuena et al. 2008). Taken together, PRS seems to increase anxiety levels, induce a depressive-like phenotype and impair cognitive function in the offspring.

Further, profound disruption of circadian rhythmicity of several physiological responses, i.e. heart rate, body temperature, and physical activity (Mastorci et al. 2009), has been reported in rodent models following maternal exposure to prenatal

intermittent restraint. Long-term consequences of PRS significantly depend on the sex of the offspring, on the behavioural parameter being considered, and most importantly on the intensity and timing of the maternal stress [see (Darnaudery and Maccari 2008; Weinstock 2008) for review]. Great efforts have been devoted to understand the underlying mechanisms of the deleterious outcomes observed in the offspring of stressed pregnancies (Darnaudery and Maccari 2008; Maccari et al. 2003; Weinstock 2002, 2008); however, research in this field is still needed.

2 Relevance of the Circadian Rhythms in Neuropsychiatric Disorders

Alterations in circadian rhythm have a profound impact on the physical and psychological homeostasis of an individual (Atcheson and Tyler 1975). Indeed, a disruption of circadian clocks has been found in several neuropsychiatric disorders such as depression, post-traumatic stress disorder, mania and schizophrenia [(Agorastos et al. 2014; Mendlewicz 2009; Novakova et al. 2015) for a review, see (Karatsoreos 2014)]. The neurobehavioral deficits, such as changes in mood, affect or cognitive impairments, derived from altered circadian patterns have long been established. For instance, animal models relevant for jet-lag syndrome have provided evidence for negative long-lasting effects on hippocampal neurogenesis, deficient performance in hippocampal-dependent learning and memory and underlying depression as a consequence of altered circadian conditions (Gibson et al. 2010). However, it is yet to be determined if the alterations of the circadian system observed in neuropsychiatric disorders are mere symptoms or contributing factors.

In the case of depressive syndrome, this dual role of the circadian system is even more pronounced. On the one hand, patients with major depression exhibit direct disturbances of the circadian system, including changes in daily mood variation, brain activity, core body temperature, hormone secretion, sleep–wake cycle, motor activity and seasonal mood variation (Monteleone et al. 2011). On the other hand, disruption of the circadian system has been linked to the pathophysiology of depression, as it has been shown in transgenic mice for clock and clock-controlled genes (Mukherjee et al. 2010; Roybal et al. 2007). Moreover, in clinical studies, single-nucleotide polymorphisms in CLOCK, BMAL1, PER3 genes or in the circadian regulator glycogen synthase-kinase-3β (GSK-3β) have been related to sensitivity to antidepressant treatment (Benedetti et al. 2005; Serretti et al. 2003), increased recurrent rate of affective episodes (Benedetti et al. 2003), development of bipolar disorder (Nievergelt et al. 2006) and risk for seasonal affective disorder (Partonen et al. 2007). A more recent study also delves into the role of the circadian system in the pathophysiology of depression. By using a validated mouse model of depression, i.e. exposure to chronic mild stress, authors provide support for an association between mice depressive-like phenotype and a desynchronization of the core components of the molecular clock within the amygdala. Actually, the

rhythmicity exhibited by the basolateral amygdala of control mice was completely abolished in anhedonic mice, thus suggesting that the observed disruption in normal daily oscillations might be a consequence of the illness (Savalli et al. 2014).

2.1 *Circadian Rhythms: Brief Note on Neuroanatomy and Molecular Machinery*

All organisms have the ability to adapt to their environment by anticipating periodic changes such as the alternation of light and dark periods. This is possible due to the existence of an endogenous circadian system that works as a clock that can be synchronized by environmental cues, setting a period of around 24 h (thus the name circadian). In mammals, this system consists of a hierarchical structure, where the central or master clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus, which controls a network of peripheral clocks in every tissue (Hastings et al. 2007). This master clock—SCN—is mainly entrained to the light/dark cycle, receiving the light information directly from the retinohypothalamic tract and driving an output of metabolic (i.e. glucose homeostasis, gene expression) and hormonal rhythms (i.e. melatonin, cortisol/corticosterone) that keep the rest of the body oscillators in synchrony (Hastings et al. 2007; Iuvone et al. 2005). However, these peripheral clocks can be entrained by external cues different from the light/dark cycle and therefore remain functional without the control of the SCN. The strongest cue that can entrain peripheral clocks without affecting the phase of the SCN is food (in terms of feeding schedule and/or caloric consumption) despite other clocks related to the reward system have also been described for methamphetamine (Honma and Honma 2009; Mendoza 2007).

The molecular machinery responsible for circadian rhythm generation can be found in every single body cell and consists of transcriptional–translational feedback loops that involve a highly conserved set of "clock genes". In mammals, these loops are formed by the so-called positive elements, CLOCK and BMAL1, which heterodimerize and enhance the transcription of the negative components *Period* (*Per1*, *Per2* and *Per3*) and *Cryptochrome* (*Cry1* and *Cry2*) genes. The PER and CRY proteins form complexes that inhibit their own transcription by binding to the CLOCK:BMAL1 complex blocking its function. This negative loop allows a daily rhythm in expression of *Per* and *Cry* transcripts and their protein products (Iuvone et al. 2005; Okamura et al. 2002).

2.2 *The Circadian System During the Perinatal Period*

Considering that a hypothalamic structure—SCN—is central for the circadian system functioning, it seems plausible that an aberrant development of the related

hypothalamic circuitries may lead to a malfunctioning of this master clock as well as of extra-SCN non-photic oscillators. Accordingly, it seems reasonable to deep into the importance of an appropriate development of the circadian system during early stages and also to investigate the possible consequences of circadian rhythm disruption during the prenatal time window that might be related to the emergence of neuropsychiatric disorders later in life. It is well known that the SCN is fully formed and innervated by mid-gestation in humans and rhesus monkeys, and it presents oscillations in utero. Indeed, clear-cut circadian rhythms of heart rate, respiratory movements, foetal movements and hormones are already displayed by the foetus (Davis and Reppert 2001; Seron-Ferre et al. 2007; Weirnert 2005). In contrast, these rhythms seem to appear at a postnatal age in rodents; neurogenesis of SCN is completely close to birth, by gestational day (GD) 17 (Davis and Reppert 2001), although there are evidences of foetal rhythms in metabolic activity (Davis and Gorski 1985), vasopressin mRNA levels (Reppert and Uhl 1987) and spontaneous neural activity (Shibata and Moore 1987). However, in every mammalian specie, foetal circadian system depends on maternal signals (core body temperature, metabolic cues and hormonal milieu) that allow the immature offspring to synchronize to the external environment (Seron-Ferre et al. 2007). Thus, from a molecular perspective, the morphological development of the SCN parallels the gradual development of molecular clock robustness as shown by an increase in the clock gene expression rhythm amplitudes from no rhythmicity at GD 19 to highly developed rhythms at postnatal day (PND) 10 (Houdek and Sumova 2014). In rats, an analysis of clock gene transcripts at GD 19 showed that no rhythmic expression could be detected for *Per2* and *Bmal1* although some other genes related to cellular activity showed rhythmic, thus providing evidence for the maternal circadian system to drive these oscillations (Houdek and Sumova 2014). Likewise, a study in which pregnant dams were exposed to a 6-h delay of the dark period and then released into constant darkness at different stages of the foetal development showed that the expression of clock genes *Per1* and *Per2* in the SCN of newborn pups was shifted differently, according to the day the mother was housed in constant darkness (El-Hennamy et al. 2008). Besides, give that rat pups are blind until PND 15, studies with rats highlight the relevance of non-photic entrainment during perinatal stages. In this regard, it has been shown that keeping pregnant rats under a scheduled feeding regime—that is, food availability for a limited period of time without caloric restriction—is able to phase advance the expression of several clock genes at birth (PND 0), with less pronounced effects at PND 10 when maternal feeding schedules are not as important as nursing time for the offspring (Olejnikova et al. 2015). Therefore, after birth, maternal care becomes crucial for the generation and maintenance of pup's circadian rhythms, as the mother will nurse and take care of the pups until weaning. During lactation, nocturnal animals will provide nursing and maternal care during the light phase, shifting the clocks of the pups opposite to adults. Meanwhile, the SCN becomes a light-driven oscillator and peripheral clocks are entrained by competing signals from the SCN and the feeding regime (Polidarova et al. 2014).

However, both in foetal and postnatal stages, the main environmental factor controlling for the adequate development of the circadian system is the light–dark cycle. In studies with animals raised at different photoperiods, it has been shown that SCN photic sensitivity develops gradually, with clock genes like *Per1* or *Per2* being rhythmic from PND 10 but others like *Cry1* from PND 20 (Kovacikova et al. 2005). Before birth, foetuses do not receive light directly, but photic entrainment is set by maternal cues via melatonin secretion. This hormone is mainly produced by the pineal gland keeping a high-at-night secretion pattern that contributes to photic entrainment of physiological and behavioural processes. By contrast, glucocorticoids are produced in the adrenal glands controlled by the HPA axis and are also released in a rhythmic manner but opposite in phase to melatonin, peaking during the daytime. Brain structures controlling the secretion of these hormones, the pineal gland and the parvocellular neurosecretory cells of the hypothalamus, respectively, are under regulation of the SCN which maintains melatonin and glucocorticoids in opposite phases as direct outputs of the clock. Both hormones will affect the development of the circadian rhythms in pups. It has been shown that suppressing maternal melatonin rhythmic secretion by exposing animals to constant light at mid-gestation leads to intrauterine growth retardation, to an altered pattern of clock gene expression in foetal adrenal glands with suppression of glucocorticoid rhythm together with an altered response to corticotrophin-releasing hormone (ACTH) effects that were counteracted by melatonin injection during the subjective night (Mendez et al. 2012). Likewise, it has been shown that constant light during the last third of pregnancy in primates affected the entrainment of temperature rhythms in the newborns, which were re-synchronized with melatonin injections to the pregnant mothers highlighting the physiological importance of the maternal melatonin rhythm during pregnancy (Seron-Ferre et al. 2013).

2.3 *Disruption of Circadian Rhythms from Postnatal Periods to Adulthood*

Chronodisruption has been used in several ways in adult and gestational animal models, and it can be defined as an alteration of the normal 12-h light/12-h darkness (12L:12D) photoperiod. In humans, the most common circadian disruptors include environmental lighting (including both the exposure to low light during daytime or to electric light sources during night time), shift work (which implies the exposure to abnormal light cycles and the interference of work hours with sleep timing), jet lag from transmeridian travel (which requires the adaptation of body clocks to a new time zone), social jet lag (temporal differences between the endogenous clock and the social clock) and sleep disorders (Bedrosian et al. 2015 in press). Several animal models have been developed to study these conditions including long photoperiods (16L:8D, to mimic summer conditions), short photoperiods (8L:16D to mimic winter conditions), phase advances (i.e. 12L:12D photoperiod but lights

on 5 h earlier to mimic jet lag) or constant conditions (i.e. 24 h of light to mimic shift work). As a conclusion from those studies, darkness is needed for the normal development of the circadian system. This consideration is of special relevance for neonatal intensive care units (NICUs) as early newborn babies born with low weight are kept in facilities with artificial light conditions during 24 h rather than to the 24-h darkness they get inside the womb. The importance of the amount of light received during the perinatal stages became evident in studies performed with mice exposed to different seasonal photoperiods until weaning and then changed to the opposite seasonal photoperiod for four weeks; this study demonstrates that perinatal photoperiod has long-term effects on the rhythmicity of clock neurons and on animal behaviour. Perinatal seasonal lighting seems to imprint individual clock neurons. Thus, long-photoperiod-raised pups display low-amplitude rhythms of *Per1*, a free running period of behavioural activity and a stability of these conditions when season shifted. In contrast, short-photoperiod-exposed pups showed high-amplitude rhythms, and waveform changes when season light was changed (Ciarleglio et al. 2011a). A similar study has measured the ability to develop circadian rhythmicity under constant light in rats that received different quantity and quality of light during suckling. Normal circadian patterns under constant light, that is becoming arrhythmic, were only developed by those animals which received darkness during suckling, whereas the animals that were kept under light during suckling remained rhythmic with a stability dependent on light intensity received prior to weaning (Cambras et al. 2015). This imprinting of the circadian system by perinatal seasonal light has proven to have implications in the later development of neurobehavioral disorders. Early exposure to short photoperiods in rodents has been linked to an increase in depressive and anxiety-like behaviours (Pyter and Nelson 2006). In humans, light levels during the night may play an increasingly evident role in regulating behaviour and mood in adults (Bedrosian and Nelson 2013), and therefore, light conditions may play a yet unrecognized role in controlling physiological functions, sleep–wake cycles, alertness and cognitive functions in preterm and neonatal infants. For instance, the rate and severity of seasonal affective disorder are elevated in winter-born humans, as is the risk for developing schizophrenia or bipolar disorder (Castrogiovanni et al. 1998; Foster and Roenneberg 2008). Moreover, studies performed at the NICUs indicated continuous light as a stressful condition for preterm babies that could be related to later impaired academic performance, attention-deficit, general hyperactivity and psychiatric disorders at puberty (Perlman 2001).

The basis for this relationship between seasonal photoperiod imprinting and neurobehavioral disorders may lay, at least in part, in the link between circadian and serotonergic systems in the brain. The SCN is innervated by serotonin projections from the median raphe nucleus and also receives indirect information via neuropeptide-Y (NPY) input from the intergeniculate leaflet driven by the dorsal raphe (Deurveilher and Semba 2005). Serotonin regulates SCN response to light acting both presynaptically on retinal afferent terminals and postsynaptically on SCN neurons to inhibit retinal input to the central biological clock (Smith et al. 2001). Likewise, the dorsal raphe nuclei receive direct input from the circadian

visual system and indirect input from the SCN via the dorsomedial hypothalamic nuclei (Morin 2013). Besides, serotonergic raphe neurons express the elements of the molecular clock and rhythms in key serotonergic genes, as tryptophan hydrolase, and in serotonin secretion (Malek et al. 2007). Therefore, both systems are anatomically and genetically intertwined and together regulate affective behaviours, and any malfunction in their relationship might be associated with a range of mood disorders (Ciarleglio et al. 2011b). Recent studies have demonstrated that photoperiod received during perinatal period (both pre- and postnatal) imprints the serotonergic neurons of the dorsal raphe programming their firing rate, responsiveness to noradrenergic stimulation, intrinsic electrical properties, serotonin and norepinephrine content in the midbrain, and depression-/anxiety-related behaviour in a melatonin receptor 1 (MT1)-dependent manner, and these features remain later in life even after several subsequent photoperiod shifting (Green et al. 2015).

There is growing clinical evidence highlighting the importance of early-life photoperiod exposure in the development of a certain chronotype, referred to the phase of the endogenous sleep–wake cycle. The so-called *evening type* is normally born during spring and summer (long-photoperiod seasons), while the "*morning type*" is more frequently born during autumn and winter (short-photoperiod seasons) (Natale and Di Milia 2011; Takao et al. 2009; Tonetti et al. 2012). Such an association becomes more evident when seasonality is more clearly marked, like in residents of higher latitudes (Mongrain et al. 2006) or in rural areas with less amount of artificial light (Borisenkov et al. 2012). A person's chronotype influences the individual ability to adapt to circadian disruption and also to their future health and well-being. Moreover, chronotype and the amount of light received during childhood and adolescence may affect the susceptibility of a person to develop mood disorders later in life (Erren et al. 2012). Notwithstanding, puberty has been recently described as a period of increased sensitivity to light, in particular to evening light exposure. In the study, participants received 1 h of light prior to bedtime and the amounts of sleep as well as the melatonin salivary content were assessed. The suppression of melatonin shown by prepubertal participants was higher than the suppression observed among the more mature adolescents suggesting an increased sensitivity to evening light in early pubertal children (Crowley et al. 2015). The suppression in melatonin production seems to depend upon light intensity, and the study suggests that exposure to low light intensity, as that provided by the use of electronic devices as tablets or computers in the hour prior to sleep, may not only have short-term effects in adolescents' sleep quality but also long-term effects imprinting serotonergic and circadian systems as previously stated, thus increasing the risk for the development of mood disorders later in life.

2.4 Chronodisruption as a Perinatal Insult

In spite of the fact that the investigation of the relationship between brain developmental disruption and circadian system is a considerable novel topic, there is an

increasing amount of studies, both in animal models and humans, linking circadian system malfunctioning, early-life insults and the appearance of neuropsychiatric diseases at adulthood. Brain developmental disruption and circadian system seem to interact in a bidirectional way; not only exposure to a prenatal insult can provoke a misalignment in the biological rhythms of the offspring, but a disruption of the maternal circadian rhythm during gestation can also induce an aberrant development in neural circuitries that may render the offspring more vulnerable to undergo neuropsychiatric disorders later in life. Although this relationship between the circadian system and the development of neurobehavioral disorders has been described, not many studies have considered the use of chronodisruption as a perinatal insult. Conditions such as shift work are increasingly becoming frequent in modern society, and there is no exception for pregnant women. In a work developed by Roman and Karlsson (2013), authors recall that a technical problem at the animal facilities during their ongoing experiment led to seven days of constant light for a group of pregnant rats, from GD20 to PND 4; when these animals reached adulthood, a battery of behavioural tests was carried out, i.e. open field, object recognition and water maze. Animals exposed to constant light during the perinatal period showed intact recognition memory and no deficits in spatial learning or memory; however, these animals exhibited increased thigmotaxis in the open field and the water maze, less ambulatory behaviour in the open field, as well as lower exploration times in the object recognition test. Taken together, in this study, authors suggest an increased anxiety-like phenotype as a long-term effect of perinatal chronodisruption. This impact of light can be produced with dim light, mimicking the conditions of artificial light during the night for a pregnant woman. In this regard, pregnant mice were raised on either a 14L:10D photoperiod or a 14L:10dim-light condition. After weaning, the offspring was all maintained under constant darkness and at adulthood several behavioural and molecular measures were assessed. Mice early exposed to constant light (dim light) showed reduced growth rates, displayed an anxiety-like behaviour in the elevated plus maze and increased fear responses in the passive avoidance test (Borniger et al. 2014). Interestingly, other studies exposing pregnant rats to chronodisruption showed also impairment of hippocampal spatial memory in the adult offspring. Hippocampal clock gene rhythms in the foetuses from dams exposed to constant light were completely abolished and no detectable differences in plasma melatonin or corticosterone were reported although animals were reared under 12L:12D photoperiod. Notably, a significant deficit of spatial memory was also observed (Vilches et al. 2014). Considering the importance of light in current society, with artificial lights on almost all the time, further studies on the impact of shift work and social jet lag during gestation on mental health are needed. It is critical to better understand the impact of developmental chronodisruption on the adult circadian system, and its influence on the development of additional brain circuitries controlling for cognition, emotionality and energetic homeostasis. The investigation of a possible association between gestational circadian rhythm disruption and the risk for the development of neurobehavioral disorders during adulthood is of great clinical relevance.

3 Possible Molecular Players Involved in the Long-Term Consequences of Prenatal Insults on Behaviour and Circadian Rhythm Disruption

The interactions between central nervous system, endocrine and immune system are profuse and intricate (Bilbo and Schwarz 2012; Eskandari and Sternberg 2002) and initiate very early in life. The developing brain is exquisitely sensitive to both endogenous and exogenous signals. The prenatal insults here described include endocrine signals (glucocorticoids), immunological molecules (cytokines) and additional external factors comprised in the experimental procedures (injections, animal manipulation, etc.). All together are able to critically affect brain development so that the adult individual will exhibit abnormal emotional responses, cognitive deficits, and, possibly, an altered circadian activity (see previous sections). In this section, we will briefly delve into the particular contribution of glucocorticoids and cytokines to the hypothesized circadian rhythm disruption and the long-term behavioural outcomes.

3.1 Glucocorticoids and the Hypothalamic–Pituitary–Adrenal (HPA) Axis

Dysfunctions in the HPA axis activity have been reported in many psychiatric disorders [e.g. (Jacobson 2014; Wingenfeld and Wolf 2011)]. The HPA axis and the autonomic nervous system are responsible for the elaborated multi-directional communication pathway designed to restore homeostasis upon a change in the environmental conditions, i.e. a stressful challenge. Both systems become activated to cope with adverse environmental situations that might be considered as physical and/or psychological challenge, e.g. low temperatures, undernutrition, inflammation, restraint immobilization. HPA actions are mediated by the glucocorticoids (cortisol/corticosterone) released from the adrenal glands act through their ubiquitously distributed intracellular receptors, glucocorticoid and mineralocorticoid receptors (GR and MR, respectively) (de Kloet et al. 2008). The importance of glucocorticoid receptors not only consists in their role in stress response, but also in their participation in processes related with synaptic plasticity and memory formation (Brinks et al. 2007; Oitzl et al. 1997). Both receptors are located in brain areas involved in emotion, learning and memory (de Kloet 2003). A balanced MR: GR activation in the limbic brain appears to be critical for the emotional and cognitive functioning required for optimal performance in a changing environment and thus beneficial for mental health (Oitzl et al. 2010). The development of HPA system is not uniform; different components of the system have different ontogenetic patterns. Actually, HPA axis circadian rhythmicity and feedback regulation in the rat are not yet fully developed until late in development (Levine 1994). Moreover, during brain development, the brain is highly sensitive to the effects of

glucocorticoids; therefore, maintaining glucocorticoid levels within a physiological range during the different stages of the nervous system development seems to be critical for a correct organization of brain. Worth noting, the existence of a time window during postnatal life (PND 4–14) of diminished circulating corticosterone levels and reduced adrenal sensitivity—the so-called stress hyporesponsive period, SHRP—that seems to be an adaptive mechanism to protect the brain developmental processes from the deleterious impact of heightened glucocorticoid levels during a critical time window (Levine 1994).

Early-life environmental factors seem to be critical for the development and functionality of the HPA axis (Karrow 2006; Levine 1994, 2000; Pryce et al. 2005). Indeed, a dysregulation of HPA activity has been consistently described in animal models of prenatal insults. Heightened stress during pregnancy increases plasma levels of glucocorticoids and ACTH in the mother and foetus and may consequently interfere with the required adaptive mechanisms triggering to a persistent dysregulation of the HPA axis (Laviola et al. 2004b; Lazinski et al. 2008; Mastorci et al. 2009; Morley-Fletcher et al. 2003b; Weinstock 2002). The offspring of PRS dams showed a prolonged corticosterone stress response together with a reduction in the hippocampal expression of both MR and GR. In animal studies, PRS-induced impairments in behaviour and HPA axis responsiveness are prevented by maternal adrenalectomy. However, maternal injection of corticosterone only reverses the increased anxiety and HPA alterations in the offspring (Weinstock 2008). Similar effects have been reported following MIA. Animals prenatally exposed to LPS showed, as adults, augmented corticosterone levels at baseline, a blunted stress response, as well as a decreased expression of MR and GR within the hippocampus (Basta-Kaim et al. 2011; Lin et al. 2012; Reul et al. 1994). Indeed, since hippocampal GR seems to participate in an inhibitory feedback mechanism, the decrease in the levels of GR in this structure might involve HPA axis hyperactivity. Remarkably, the reported HPA axis disturbances reported following gestational LPS administration were reversed by the chronic administration of antipsychotic drugs, clozapine and to a lesser extent chlorpromazine (Basta-Kaim et al. 2011). Notably, the reported changes in hippocampal glucocorticoid receptors (GR and MR) may not only affect HPA functioning, but also emotional processing and cognitive function; therefore, the cognitive deficits described in these animal models may rely, at least in part, on the changes in glucocorticoid receptor expression already described within the hippocampus. Circulating maternal glucocorticoid levels may constitute one of the critical factors mediating the foetal programming of neural circuitries involved in the control of emotion, cognition and stress response. Last but not least, an affection of the placental function as a consequence of prenatal stress cannot be discharged and may also be considered as a critical factor mediating some of the deleterious outcomes described in the offspring (O'Donnell et al. 2009). Taken together, an elevation in glucocorticoid levels within the foetus—with foetal, maternal or a placental origin—may serve as one hormonal pathway that could mediate the brain development disruption that in the long term may provoke the behavioural anomalies already described.

The activity of the HPA axis follows a circadian rhythm, with peak levels of glucocorticoids during the active phase (daytime in humans and night in nocturnal animals, such as rats or mice). The circadian rhythm of the HPA axis is characterized by a pulsatile release of glucocorticoids from the adrenal gland that results in rapid ultradian oscillations of hormone levels both in the blood and within target tissues, including the brain. This rhythm is under control of the central clock system, in particular the hypothalamic SCN, throughout synapses from the SCN to the hypothalamic PVN (see Sect. 2.1). However, this control also affects other structures of the HPA axis such as adrenal glands, due to the activation of the autonomic nervous system and/or to the presence of an adrenal peripheral clock. In animal studies, glucocorticoids have been reported to be able to phase shift many clock-related genes, such as *Per1* and *Per2*, in peripheral tissues such as liver, heart and kidney. The HPA axis also influences the circadian system. Glucocorticoids seem to be able to change the circadian expression of different molecules providing an adaptive mechanism through which respond to stressors. The stress system, through the HPA axis, communicates with the clock system; therefore, any uncoupling or dysregulation could potentially cause several disorders, such as metabolic, autoimmune, and mood disorders [for recent review consult: (Nicolaides et al. 2014; Spiga et al. 2011)].

Neural connections between the HPA axis and the circadian system are established early during brain development; thus, any environmental impact during a critical time frame could drive to a mismatch between these systems. In this regard, exposure to severe stress during gestation has been reported to alter the circadian system, and more particularly, the temporal functioning of the HPA axis (Koehl et al. 1999; Maccari et al. 2003; Maccari and Morley-Fletcher 2007). PRS induced higher levels of corticosterone secretion at the end of the light period in both males and females and hypercorticism over the entire diurnal cycle in females (Koehl et al. 1999). In addition, PRS induced a phase advance in the circadian rhythm of locomotor activity as well as an increase in the paradoxical sleep in adult rats (Maccari et al. 2003; Maccari and Morley-Fletcher 2007). These two behavioural effects might be mediated, at least in part, by the specific change in the temporal pattern of hippocampal GR expression induced by prenatal stress; PRS induced a reduction in hippocampal GR expression both at the beginning of the light period and at the end of the light period times at which total corticosterone levels are increased in PRS rats. Data from the prenatal immune activation model also demonstrated a disruption in the circadian system. Indeed, prenatal LPS administration (GD17) was reported to alter sleep architecture in mice by using continuous quantitative video/electroencephalogram/electromyogram analyses; changes that seem to be circadian cycle and activity state dependent (Adler et al. 2014). Further research is still needed to control for the consequences of prenatal insults on the temporal profile of the HPA functioning.

3.2 *Immune System Activation Through Inflammation and Cytokine Production*

Nowadays, extensive literature gives support to the fact that maternal infection during pregnancy is associated with increased risk of developing schizophrenia (Brown 2006; Meyer and Feldon 2009; Patterson 2007); however, the causal link underlying this observation is far from clear. The specific mechanisms by which maternal infection may lead to psychopathology include direct infection of the developing foetus and subsequent abnormal neural development, the generation of autoantibodies by the mother that subsequently react with foetal neural tissue and alterations in cytokine production, which may be an underlying component of all three mechanisms (Pearce 2001). Literature from animal models suggests a causal relationship between maternal immune activation and the altered behavioural traits observed in the adult offspring. Among the diversity of immunological events that can be triggered by infectious agents, the cytokine-associated inflammatory response may be of particular relevance. Cytokines are soluble bioactive mediators released by diverse immune cell types; these include interleukins (ILs), interferons, tumour necrosis factors (TNFs), chemokines and growth factors. Cytokines act within a complex network, either synergistically or antagonistically, and are generally associated with inflammation, immune activation and cell differentiation or death (Allan and Rothwell 2003). Cytokines can be produced by brain immune cells, also by neurons, and, more interestingly, cytokines can cross the blood–brain barrier. Thus, the central nervous system can be affected not only by cytokines produced within the brain, but also through the actions of mediators originating from the periphery (Lucas et al. 2006). Several studies have demonstrated an increase in pro-inflammatory cytokines in the adult offspring of dams exposed to gestational infection. In particular, prenatal LPS exposure induced an increase in chemokines and cytokines expression (Borrell et al. 2002). In the same line, the neonatal administration of pro-inflammatory cytokines (Samuelsson et al. 2006; Tohmi et al. 2004) or leukaemia inhibitory factors (Watanabe et al. 2004) to rats has been reported to induce behavioural changes, including cognitive deficits, together with neurobiological changes in specific brain regions such as the hippocampus. Following prenatal LPS administration, an unbalanced inflammatory reaction in the foetal environment that activates the foetal stress axis has also been suggested (Gayle et al. 2004). Remarkably, most of the cytokines altered by LPS administration have an important influence in different synaptic plasticity processes, and in learning and memory processes. Consequently, the increase in the expression of these cytokines may mediate, at least partially, the long-lasting cognitive deficits observed in this animal model (Bilbo and Schwarz 2012). In conclusion, the maternal immune response, possibly through the increase of pro-inflammatory cytokines, may represent one of the key events interfering with foetal brain development and maturation at critical time windows; the disruption of the balance between pro-inflammatory and anti-inflammatory cytokine during prenatal life may

trigger the debut of the behavioural anomalies already described as a consequence of prenatal immune activation and extensively related to neuropsychiatric disorders.

Severe stress condition during gestation has been reported to negatively affect the immune system and may possibly contribute to the maladaptive immune responses to stress that occur later in life. Exposure to psychosocial stress early in life—during early stages of pre- and postnatal life—seems to aggravate the effects of immunotoxicants or immune-mediated diseases in infants (Bellinger et al. 2008; Meerlo et al. 2008). In the long term, PRS produced important alterations in a number of peripheral and central immunological parameters, as previously described for several animal models (Coe et al. 2002; Gotz and Stefanski 2007; Llorente et al. 2002; Tuchscherer et al. 2002). Specifically, a decrease in blood cell populations devoted to immune competence, especially the $CD4^+$ T-lymphocytes and T4/T8 ratio were observed in response to PRS (Laviola et al. 2004b). PRS also produced an elevation in pro-inflammatory IL-1β concentration, both in the rats' spleen and frontal cortex (Laviola et al. 2004b). This increment in IL-1β production among the PRS offspring resembles human studies suggesting that stress and psychopathology can be indexed by a hypersecretion of pro-inflammatory cytokines, although other intervening variables have to be considered (Dabkowska and Rybakowski 1994; Elenkov and Chrousos 2002; Fan et al. 2007; Schiepers et al. 2005).

The immune system is also subjected to circadian rhythms. Most immune cells express circadian clock genes and present a wide array of genes expressed with a 24-h rhythm (Labrecque and Cermakian 2015). However, knowledge on the biological relevance of the immunological circadian clock is scarce, and few data are available regarding the ontogeny of the rhythmicity within this system. Cytokines have also a crucial role in brain maturation given their biological relevance in developmental processes such as neurogenesis, neuronal and glia cell migration, proliferation, differentiation, and synaptic maturation and pruning. The levels of several cytokines fluctuate during development based upon the neurodevelopmental processes occurring in the brain in a region-dependent manner; as an example, the content of IL-1β, TNFα or IL-6 seems to be higher during early phases of brain development than in adult brains (Bilbo and Schwarz 2012). Further research needs to focus on the ontogeny of the rhythmicity within the production of cytokines, and on its possible relationship with developmental events critical for brain maturation.

3.3 Crosstalk Between Glucocorticoids and Cytokines

On the one hand, glucocorticoids play a modulatory role on the expression of numerous cytokines, adhesion molecules and other inflammatory molecules (Eskandari and Sternberg 2002). Classically glucocorticoids are considered as anti-inflammatory molecules, although some studies indicate that their immunomodulatory properties are tissue specific. Actually, stress has been considered to induce inflammation in the brain. Stress, depending of the age, nature,

intensity and length of the exposure, may activate the pro-inflammatory pathway that triggers the release of cytokines and promotes cell damage that may underlie some of the detrimental behavioural outcomes of stress exposure (Garcia-Bueno et al. 2008). On the other hand, interleukins such as IL-1, IL-1β and IL-6 induce the activation of the HPA axis, increasing the levels of glucocorticoids (Karrow 2006). The bidirectional influence between glucocorticoids and immune molecules may initiate at early stages of development, such as during foetal and neonatal developmental windows, as it might represent an adaptive feature that contributes to the survival of the offspring in its new environment. However, if the individual's environment is drastically changed such that neuroendocrine–immune programming becomes maladaptive, it may trigger or exacerbate certain diseases, including neuropsychiatric disorders (Karrow 2006). Further research is still needed to distinguish the temporal sequence of events triggered by prenatal insults, whether glucocorticoids induce pro-inflammatory release or *viceversa*, and to identify the critical time windows that may enable a modulation and/or regional and temporal restriction in brain damage by pharmacological or environmental interventions.

4 Conclusions and Future Remarks

The neurodevelopmental hypothesis suggests that the disruption of early brain development may increase the risk for the appearance of several neurobehavioural disorders later in life. Although genetics plays a clear crucial role, the maternal–foetal environment arises as a critical factor that needs to be taken into account. Neonatal neural programming seems to be highly sensitive to the content of glucocorticoids and to several immune signalling molecules, i.e. cytokines. Therefore, prenatal insults through the activation of the HPA axis and/or the release of pro-inflammatory cytokines may trigger a dysfunctional brain network and connectivity responsible for the emergence of behavioural symptoms that have been described in animal models of neuropsychiatric disorders.

The activity of the HPA axis and the immune system is subjected to circadian rhythms, and, in the recent years, a disruption of circadian clocks has been extensively described in several neuropsychiatric disorders. Moreover, optimal brain development has been related to intact synchrony between circadian and diurnal rhythms (Powell and LaSalle 2015). The role of altered expression and/or function of circadian genes in neuropsychiatric disorders is particularly compelling. Actually, gene mutations and single-nucleotide polymorphisms and haplotypes in several circadian genes have been recently associated with susceptibility to mood disorders (Mendlewicz 2009) (Fig. 1).

Changes in environmental contingencies have been shown to affect circadian rhythms. In particular, exposure to social stress—repeated social defeat—during the dark/active phase seems to induce long-lasting consequences for the functional output of the biological clock, i.e. general motor activity and core body temperature, effects that seem to depend, at least in part, on the clock genes *Per1* and *Per2*

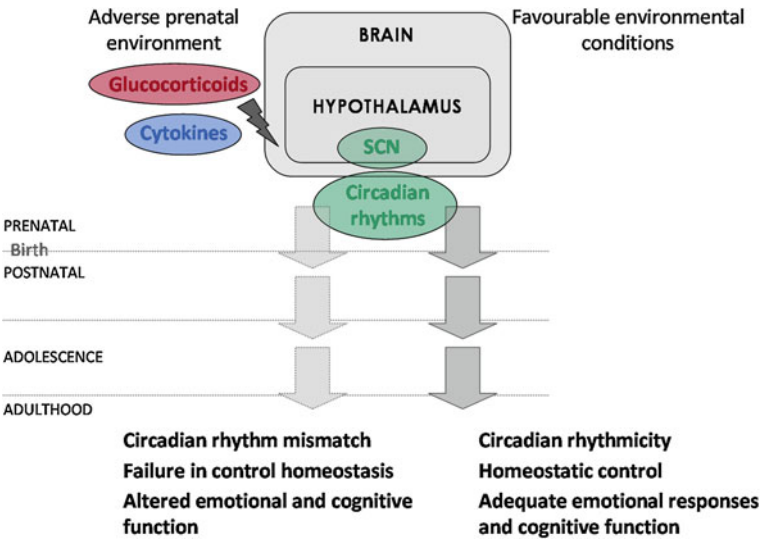

Fig. 1 Gestational stress and/or maternal infection during pregnancy has been related with an increased incidence of neuropsychiatric disorders, including depression and schizophrenia. It is of critical importance to unravel the individual components of the body circadian system that might also be altered by prenatal insults since they might be related with the disruption of neural and endocrine developmental programming

(Bartlang et al. 2015). If stress can affect the circadian system at adulthood, exposure to stress at critical developmental windows (gestation) may more critically affect the circadian clock. Whether clock genes are modified following exposure to prenatal stress deserves further investigation, as well as the analyses of similar changes in response to maternal immune activation.

Epigenetic regulation provides a mechanism for cells to integrate genetic programs with environmental signals in order to generate an adaptive and consistent output. DNA methylation is one epigenetic mechanism that entrains the circadian clock to a diurnal environment (Powell and LaSalle 2015) and has also been implicated in the pathophysiology of neurodevelopmental disorders including schizophrenia and ASD. Moreover, epigenetic changes have been described following maternal immune activation (Basil et al. 2014). Hence, epigenetic changes generated by prenatal insults have become an emergent and important target of investigation as a common molecular mechanism which may underlie changes in the circadian system, the HPA axis and the immune system.

Revealing a common pattern of circadian disruption in developmental models of neuropsychiatric disorders will open new avenues in the investigation of the biological bases of neuropsychiatric disorders as well as for the development of innovative strategies for therapy in mental health. In this framework, new antidepressants acting on melatonin receptors have been successfully developed. Interestingly, their efficacy seems to rely in the capacity to restore the internal clock

(Mendlewicz 2009) and the circadian homeostasis in rats exposed to PRS (Mairesse et al. 2013). Future application of additional strategies aimed at the manipulation of the circadian timing system via sleep deprivation, bright light or pharmacological therapy will become of great interest and further investigation in this field will be needed.

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