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How age, sex and genotype shape the stress response

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ABSTRACT

Exposure to chronic stress is a leading pre-disposing factor for several neuropsychiatric disorders as it often leads to maladaptive responses. The response to stressful events is heterogeneous, underpinning a wide spectrum of distinct changes amongst stress-exposed individuals'. Several factors can underlie a different perception to stressors and the setting of distinct coping strategies that will lead to individual differences on the susceptibility/resistance to stress. Beyond the factors related to the stressor itself, such as intensity, duration or predictability, there are factors intrinsic to the individuals that are relevant to shape the stress response, such as age, sex and genetics. In this review, we examine the contribution of such intrinsic factors to the modulation of the stress response based on experimental rodent models of response to stress and discuss to what extent that knowledge can be potentially translated to humans.

Contents

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1. Introduction

A stressor is by definition a stimulus that triggers a stress response. This stress response is generated when our brain perceives something as a potential threat. Perception to stress is dependent on a combination of factors intrinsic to the stressful stimulus (e.g. duration and intensity) and intrinsic to the individual. This perception varies across individuals, being the same stimulus relatively innocuous for some and a potential threat for others. Such individuals' variation is based on objective factors (e.g. age, sex, genetics) but also on subjective factors like stored memories that influence sensory inputs and respective processing; in this review, we discuss the relevance of these objective factors.

After processing a certain stimulus as a potential threat, the sympathetic nervous system is activated leading to the production of cathecolamines, adrenalin and noradrenaline, that trigger several physical outcomes to prepare the body to respond to that threat - the “fight or flight” response, as coined by Walter Cannon (Cannon, 1915). Increased heart rate, vasoconstriction and increased expenditure of energy reserves are some of the examples of this sympathetic stress-response (Jansen et al., 1995). Stress is however, also embodied by the hypothalamic-pituitary-adrenal (HPA) axis response, that by primarily activating the hypothalamus and the pituitary, triggers the adrenal production of glucocorticoids (McEwen, 2005). Glucocorticoids (cortisol in humans and corticosterone in rodents), in turn, impact several systems in an attempt to cope with the stressor and reinstate homeostasis, the so-called resistance phase of Selye's general adaptation theory (Selye, 1950).

Similarly to what happens with stressor perception, the ability to cope with a stressor is also dependent on individual factors such as genetics (de Kloet et al., 2005), age and sex (Bale and Epperson, 2015), but also on the aspects of the stressor itself, such as intensity, unpredictability and duration. The response to an acute stressful stimulus is for the most part beneficial and is primarily an evolutionary mechanism; in fact, it is a set of events, orchestrated by the brain, in order to adapt to that environmental challenge. If a stressor persists in time, or if it is too intense, the ability to cope with it can deteriorate and eventually become exhausted. Exhaustion can take form either through neuropsychiatric manifestations or other somatic complaints, the so-called maladaptive response to stress (Sousa and Almeida, 2012), that is the focus of this review.

In this review, we first center on how the stress response varies across the individual's lifespan, and the animal models that have been used to elucidate this subject. Then, we discuss how factors related to sex can influence stress response, by analyzing studies that report sex differences on the outcome of stress exposure, and also the influence of hormonal variability in shaping that response. Finally, we also compare the stress effects on different rodent strains, highlighting the impact of the genetic component on the stress response shaping. Emphasis is given on how the insights from experimental models can potentially be translated into humans.

2. The effect of age in the stress response

2.1. Stress exposure during the prenatal period

The origin of many health problems and susceptibility to disease can be traced back to the uterine life. Fetal development is a period highly sensitive to environmental factors as cells are proliferating and differentiating rapidly, in a delicate and precisely orchestrated process, to give rise to complex systems. Therefore, disturbances by stress can lead to erroneous developing steps that can either manifest immediately in the postnatal period (activational effects) or later in life (programming effects), increasing the susceptibility to certain disorders during adulthood (Seckl and Meaney, 2004). These alterations can disclose either directly or through interaction with other triggers in life.

During the prenatal period, the focus of the research on the impact of stress has been largely on the fetal exposure to glucocorticoids via the placenta, either by maternal exposure to stressors or by the administration of glucocorticoids.

2.1.1. Glucocorticoid metabolism across the placenta

Glucocorticoids are important to fetal development and are associated with organ maturation that is critical for extra-uterine life. The association of glucocorticoids with rapid tissue maturation has been particularly important for infants at risk of preterm birth. The administration of glucocorticoids is a widely used approach to induce rapid surfactant production in the lung and thereby improve neonatal viability. Excessive glucocorticoids, however, negatively interfere with fetal growth and maturation pattern, and imprint alterations that can persist throughout life. A protective barrier of the placenta to excessive fetal exposure to either maternal or exogenous glucocorticoids operates through the action of the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD) that metabolizes glucocorticoids to inactive 11-keto forms. The protective role of placental 11β-hydroxysteroid activity has been revealed, amongst others, by a study showing that the offspring from pregnant rats with reduced 11β-HSD activity display changes associated with increased exposure to glucocorticoids, like low birth weight and hypertension (Edwards et al., 1993). However, when glucocorticoids exceed a certain limit, such as in prolonged stress exposure during maternity or glucocorticoid therapy, the available 11β-HSD saturates and loses its efficiency. In addition, some synthetic glucocorticoids, such as dexamethasone, have low affinity for 11β-HSD, and therefore readily cross the placenta (Seckl and Holmes, 2007).

Rodent models of prenatal stress exposure are mainly based on fetal exposure to excessive levels of glucocorticoids. This can be modeled by: 1) excessive maternal glucocorticoids production, such as in the case of maternal exposure to chronic stress paradigms (Leuner et al., 2014; O'Mahony et al., 2006); 2) exogenous administration of glucocorticoids, such as dexamethasone, to pregnant rodents (Borges et al., 2013a, Borges, et al., 2013b; Soares-Cunha et al., 2014); or 3) breaching the fetoplacental barrier to maternal glucocorticoids, by carbenoxolone inhibition of 11β-HSD (Welberg et al., 2000) or using knock-out rodent models that do not express 11β-HSD (Holmes et al., 2006).

2.1.2. Effects of prenatal stress exposure

Prenatal stress exposure negatively impacts both the pregnant dam and the offspring. For instance, the exposure of pregnant dams to stress is associated with increased susceptibility to develop postpartum depressive-like behavior, which can impact on maternal care to the pups (O'Mahony et al., 2006). However, most studies focus on the offspring. The immediate association of stress exposure during pregnancy and the consequences to the fetus comes from studies that associate stress exposure to pregnant women with prematurity (Lilliecreutz et al., 2016) or low birth weight (Rondo et al., 2003). However, prenatal stress can also induce serious long-term effects on adult pathophysiology, the so-called "glucocorticoid programming". For instance, prenatal glucocorticoids exposure leads to metabolic dysfunction in the adulthood, such as hypertension, hyperinsulinemia and hyperglycemia, but also to hyperactivity of the HPA axis, brain alterations and associated behavior (Seckl and Holmes, 2007). In animal models, rats born from dams prenatally exposed to stress, present in the adulthood lower responsiveness to glucocorticoids and low expression of mineralocorticoid receptors (MR) in the hippocampus, impairing the HPA axis negative feedback loop (Barbazanges et al., 1996). In addition, glucocorticoid exposure during the prenatal period also leads to alterations on affective and emotional behaviors in the adulthood (Borges et al., 2013a, Borges, et al., 2013b; Oliveira, et al., 2006; Roque et al., 2011). For instance, prenatal exposure to synthetic glucocorticoids results in hyperanxiety, increased fear and hyperactivity to negative stimuli, which correlates with an increased mesopontine cholinergic activity (Borges et al., 2013b; Oliveira, et al., 2006). Moreover, prenatal exposure to glucocorticoids leads to deficits in motivational drive by interfering with the mesocorticolimbic dopaminergic circuitry, leading to a reduction in the attribution of the incentive salience to cues, in a dopamine-D2/D3-dependent manner (Soares-Cunha et al., 2014).

In addition to studies using rodents, prenatal stress exposure has also been addressed using non-human primates. These studies demonstrate that prenatal dexamethasone administration impairs proliferation of new neurons but not neuronal differentiation (Tauber et al., 2006). However, prenatal dexamethasone administration does not impair neurogenesis at the long-term in non-human primates (Tauber et al., 2008).

Finally, it is important to note that while the animal model based on the administration of synthetic glucocorticoid (e.g. dexamethasone) is very useful, it lacks the complexity given by other molecules that also participate in the stress response. In addition, synthetic dexamethasone or corticosterone (such as the one produced upon stress exposure) presents different affinity to corticosteroid receptors. While corticosterone has higher affinity for MR, dexamethasone is a glucocorticoid receptors (GR) agonist (Reul and de Kloet, 1985). This differential affinity may have important implications into the stress response, since it is known that the balance between MR and GR receptors activation regulates HPA activity (including the negative feedback loop) and behavior (De Kloet et al., 1998; Harris et al., 2013). Therefore, the choice of the animal model should have into consideration the mechanistic aspects.

2.1.3. Sex differences in the effects of prenatal stress

Prenatal stress has been shown to impact differently in males and females and these differences have also been shown to depend on the animal model used (Weinstock, 2011). Prenatal stress, such as daily restraining for 30 min during the last week of gestation (Zagron and Weinstock, 2006), or by maternal exposure to variable stressors (Nishio et al., 2001), results in cognitive deficits in the water maze tasks but only in the male, not in the female offspring (Nishio et al., 2001; Zagron and Weinstock, 2006). Prenatally stressed males exhibit impairments on learning-induced neurogenesis (Lemaire et al., 2000), and reduced hippocampal long-term potentiation (LTP), together with increased long-term depression (LTD) (Yang et al., 2006), which potentially correlates with the alterations reported on cognitive behavior. Prenatally stressed females, on the other hand, are more susceptible to a dysfunctional emotional behavior exhibiting an increase in anxiety and depressive-like behaviors (Nishio et al., 2001; Weinstock, 2007; Zagron and Weinstock, 2006). Furthermore, prenatally stressed females exhibit a reduction in the number of hippocampal granule cells (Schmitz et al., 2002). These sex differences are likely to illustrate some relevant interactions with sex-related factors (most obvious hormones) and stress-related factors that impact on very specific periods of neurodevelopment. This is certainly, a topic that needs further attention from researchers in the field.

2.1.4. Studies of prenatal stress in humans

Several clinical studies suggest an association between maternal exposure to different stressors during pregnancy and an increased susceptibility of the child to develop emotional and cognitive disorders, such as attention deficits, anxiety and language delays (Talge et al., 2007). Besides maternal stress exposure, the administration of glucocorticoids during pregnancy is also a source of programming effects to the progeny. Glucocorticoid therapy during pregnancy is not uncommon, and has been widely used to treat inflammatory disorders of pregnant women (asthma or systemic lupus), for congenital problems of the fetus (adrenal or lung malformations) or to accelerate lung development in the case of premature birth risk (Lunghi et al., 2010). Administration of corticosteroids to pregnant women results in low birth weight (Nyirenda et al., 1998; Reinisch et al., 1978) that has a perfect parallel on animal experimental models. Furthermore, gestational exposure to betamethasone (week 24–35) has been associated with brain morphological alterations in children with age 6 to 10, namely in a thinning of the rostral anterior cingulate cortex (Davis et al., 2013). The same study showed an association between these alterations and dysfunctional affective behaviors (Davis et al., 2013). The interesting parallel between these observations in humans and the results obtained with animal studies strongly suggest that the use of rodents is of relevance to elucidate the molecular mechanisms underlying the short and long-term effects of prenatal stress exposure.

2.2. Stress exposure during the early postnatal period

After birth, the brain continues to develop following a combination of genetically driven processes and environmental inputs (Jernigan et al., 2011). Neuronal circuits are actively being refined through dendritic and axonal growth, synaptic stabilization and pruning (Hua and Smith, 2004; Jernigan et al., 2011). As such, this period is particularly sensitive to environmental challenges, such as stress stimuli, that can disorganize specific circuits and lead to permanent changes in brain morphology and function (Lee et al.,

2015).

In the early postnatal period, considering the time since birth until weaning, a disturbed parent-pup interaction is a particularly important source of stress, inducing changes in the offspring that can manifest either immediately or later in life. This interaction can be affected by behavioral alterations of the mother (and therefore affect the quality of interactions with the baby) or can be artificially disrupted (such as in the case of exposure to stressors or through maternal separation).

2.2.1. Postnatal stress exposure and the critical period for HPA axis maturation

The timing for HPA axis maturation differs across species and is associated with brain development milestones. In animals that give birth to complete mature offspring (e.g. non-human primates and sheep), most of the HPA axis development occurs during fetal growth (Kapoor et al., 2006). However, rodents and humans, give birth to a still immature HPA axis, and so, the postnatal period is critical for its maturation (Kapoor et al., 2006). The peak of glucocorticoids production occurs during the last period of gestation (third week for rodents) (Dalle et al., 1978; Dupouy et al., 1975) and is thought to be crucial for fetal development. At postnatal day two, glucocorticoid levels drop to minimum levels and remain low until the end of the second week. During this period, the ability to respond to stressors by secreting glucocorticoids is reduced, the so-called stress hyporesponsive period (Schapiro et al., 1962). Although it seems counterintuitive that during the early postnatal period, in which the presence of stressors is highly probable, the adaptation mechanism to stress is quite limited, it is likely that it represents a protective strategy to favor optimal central nervous system (CNS) development in an environment low in glucocorticoids (Sapolsky and Meaney, 1986). Altering glucocorticoids levels either too high or very low levels is certainly deleterious for postnatal brain development. As so, the hyporesponsive period hampers the potential harmful effects of extreme variations of glucocorticoids levels. Curiously, during the first two postnatal weeks the half-life of circulating glucocorticoids is extended (three times higher than in the adult), which may represent a mechanism to sustain stable physiological levels (Sapolsky and Meaney, 1986).

2.2.2. Rodent models of postnatal stress exposure

Despite the fact that during the stress hyporesponsive period elevation in corticosterone by common stressors is reduced, there is still a response to stressors. This is particularly true for stressors involving disturbed maternal care, highlighting the central role of the quality of maternal care during this period (reviewed in (Lupien et al., 2009)). Improved maternal care in rodents, such as increased pup-licking events, grooming or archback nursing, has been associated with enhanced synaptogenesis and cognitive abilities of the offspring (Liu et al., 2000). In contrast, poor maternal care, such as increased unpredictable and fragmented behaviors, is associated with the development of anhedonia during adolescence (Molet et al., 2016). Models of postnatal stress are mostly based on maternal separation, which consist on temporarily separating the offspring from the lactating damn daily (usually 3–6 h per day), during the first two weeks of life. Although the behavioral outcomes reported with these models consistently reveal alterations in the offspring, some studies report that mice are resistant to 3 h maternal separation protocols (Savignac et al., 2011). Since mice might be naturally more stress resistant than rats (George et al., 2010; Harrison and Baune, 2014; Monteiro et al., 2015), a few adaptations to the rat models of stress during the early postnatal period could be done to render them applicable to mice; these include adding an early weaning at postnatal day 17 after maternal separation (George et al., 2010), or extending the separation time since it was shown that the main activation of the HPA axis occurs between 4 h and 8 h after separation from the dam (Schmidt et al., 2004). Importantly, these adaptations enable modeling maternal separation stress in mice similarly to rats, namely in terms of its consequences. Adaptations of maternal separation protocols for rats were also developed, such as adding 10 min of various stressors such as bright lights, noise, handling, low temperature and pain, aiming at modeling the neonatal stress of babies in the intensive care unit (Huppertz-Kessler et al., 2012).

Interestingly, there are also postnatal stress models that target poor maternal care. In a mouse model, first described by Rice and colleagues, maternal care disruption is based on limiting bedding and nesting material. This protocol results in acute and long-lasting effects of stress on the offspring (Rice et al., 2008). In 2014, Stamatakis developed a new paradigm of stressful early experience in which rat pups (between postnatal day 10–13) are trained in a T-maze apparatus where they can be rewarded with maternal contact, being the deprivation of this maternal contact used as aversive stimuli (Stamatakis et al., 2014). This paradigm has been shown to lead to increased levels of corticosterone and activation of the amygdala in the pups for which maternal contact is denied, and also to lead to behavioral alterations in the adulthood (Diamantopoulou et al., 2013; Stamatakis et al., 2014).

Certainly, different models have advantages and limitations and consequently the analysis of data generated by using distinct paradigms is of relevance to obtain a more comprehensive perspective of such topic in a complex period of neurodevelopment.

2.2.3. Effects of postnatal stress exposure

Maternal separation leads to a vast spectrum of changes in the offspring. For example, maternal separation affects hippocampal neurogenesis by decreasing cell proliferation and the production of immature neurons (Aisa et al., 2009; Mirescu et al., 2004), or by decreasing the production of molecules important for synaptic plasticity such as neural cell adhesion molecules (NCAM), brain-derived neurotrophic factor (BDNF) or synaptophysin in the hippocampus (Aisa et al., 2009). Maternally separated rats also present impaired acquisition in the Morris water maze, but interestingly LTP is intact, and, more importantly, in stressful situations, the LTP response is even facilitated and contextual learning enhanced (Oomen et al., 2010). Moreover, in another study, adult rats that went through maternal separation, when trained in an inescapable shock paradigm, performed better in consecutive trials where they were given the chance to escape to the shock (van der Doelen et al., 2013). These studies suggest that although postnatal stress can negatively program behavioral and morphological changes in the adult brain, it can also lead to adaptive programming, improving coping strategies when facing similar levels of stress in the adulthood, a trait that is transmitted through epigenetic mechanisms to next generations (Gapp et al., 2014).

Of notice, the temporal dynamics of such penhomena are of extreme importance (see for review (Sousa, 2016)). In the early postnatal period, this dynamic is certainly crucial, as revealed by data showing the distinct impact of the maternal separation period during early life. In fact, when comparing the outcomes of maternal separation during the complete period of the glucocorticoid hyporesponsiveness (postnatal days 2–15) to the outcomes of a partial period (postnatal days 7–20), data revealed that although both time windows lead to increased levels of corticosterone in the sera, only the maternal separation for postnatal day 2–15 leads to anxiety, depressive-like behavior and immunological alterations in adulthood (Roque et al., 2014).

There are also studies showing that the long-term effects of early-life experience, including stressful experiences, can also differ between sexes. For instance, Diamantopoulou and colleagues

demonstrated that male rats, but not female, postnatally exposed to a paradigm of expected reward through maternal contact in a T-maze, exhibit enhanced fear memory during adulthood (Diamantopoulou et al., 2013). Furthermore, male rats exposed postnatally to the denial of an expected reward of maternal contact (stressful stimuli) exhibit increased activation of the amygdala during adulthood, an effect not observed in females (Diamantopoulou et al., 2013). In a different study, Oomen and colleagues compared the impact of a single episode of maternal separation, performed on postnatal day 3, on hippocampal structural plasticity at postnatal day 21, and found opposite effects in males and female rats. While hippocampal neurogenesis was increased in males, a reduction was observed on females (Oomen et al., 2009), showing once again that the same stressful stimuli can lead to divergent outcomes in a sex-dependent manner.

2.2.4. Studies of postnatal/early life stress in humans

Several studies revealed that early life stress in humans, namely through the follow-up of infants from mothers with depression or neglected/abused infants, is associated with increased susceptibility to the effects of stress later in life and vulnerability to develop stress-related psychiatric disorders (Graham et al., 1999; Nugent et al., 2011) and cardiovascular diseases (Loria et al., 2014). Indeed, in a prospective longitudinal study, 38 participants (mean age 22 years) born from mothers that suffered from postpartum depression, showed increased stress reactivity, measured by increased cortisol levels, to a social-evaluative threat (Trier Social Stress Test) when compared to controls (Barry et al., 2015). Whether this result is aligned, or not, with rodent data is, as described above, disputable and clearly illustrates the complexity of the topic. Certainly, higher integrated research projects are needed to address this issue in humans; fortunately, the field seems to be moving in that direction by supporting such multimodal and longitudinal research efforts.

The serious long-term effects caused by maternal separation stress in rodent models, even during reduced daily periods (3 h per day), raised the concern on the importance of the mother-baby contact after birth. A standard medical practice in western countries is to place neonates sleeping alone shortly after birth to allow the mother to rest, what is a form of maternal separation. An interesting study compared the physiological response of neonates sleeping alone to that of the ones sleeping with skin-to-skin contact with theirs mothers. This study found that the first presented 176% increased autonomic activity and 86% decreased quiet sleep duration (Morgan et al., 2011) when compared with the latter. While these studies highlight how much we can learn about maternal separation using rodent models, the effects of early life stress in adult human behavior and susceptibility to neuropsychiatric disorders are controversial. There are at least two conflicting frameworks: on one side, the cumulative stress theory in which early life stress predisposes for increased stress reactivity (Power et al., 2013), and on the other, the adaptive programming, in which early life adversity prepares the individual to better cope when exposed to stress in adulthood (Chen and Miller, 2012). One possibility for a unifying theory is based on the fact that effects of stress follow a non-linear U-shaped curve as a function of stress intensity and latter performance, with exposure to low-to-moderate levels of stress increasing general performance (adaptation) and high levels of stress leading to worst performance (maladaptive) (Boyce and Ellis, 2005; Russo et al., 2012; Sapolsky, 2015). Experimental animal models may be useful to dissect the factors that could be on the origin of early-life stress-induced adaptation or maladaptation, since, as described before, they do exhibit behavioral and morphological outcomes that could fit either one or the other theory.

2.3. Stress exposure during adolescence

Adolescence is a vulnerable period for the onset of many stress-related psychopathologies such as anxiety, depression and eating disorders. Extrinsic factors, such as changes in lifestyle and behaviors are often accompanied by shifts in the nature and quantity of stressors encountered. In addition, this period heightened vulnerability to the effects of stress is also due to intrinsic factors that occur during puberty. Stress-responsive brain regions, such as fronto-cortical and limbic areas, are still maturating during puberty (Morrison et al., 2014). Moreover, close interactions between stress hormones and gonadal hormonal axes occur in adolescence (Marceau et al., 2015) and, as a consequence, many sex-differences on stress responses emerge in this period of life (Ver Hoeve et al., 2013).

2.3.1. Effects of stress exposure during adolescence

It is known that the susceptibility to stress differs between the pre-pubertal and the adult brain (Hamilton et al., 2014; Romeo and McEwen, 2006). Although adrenocorticotropin hormone (ACTH) and glucocorticoids levels remain similar to that of other periods, when exposed to stress, the amount and duration of glucocorticoids are heightened during puberty (McCormick et al., 2008; Romeo et al., 2014). Injections of ACTH to pre-pubertal rats lead to increased levels of circulating corticosterone when compared to that observed using the same procedure in adult rats (Romeo et al., 2014). Furthermore, adolescent male rats exhibit impairments in the HPA axis negative feedback loop response to an acute stress, failing to shut down corticosterone production even 90 min after stress cessation (McCormick et al., 2008). These studies suggest that puberty is another critical period for shaping the HPA axis responsiveness.

Behaviorally, the impact of stress in rodents seems to differ between adolescence and adulthood. Adolescent female rats when facing a resident female exhibit “play and avoidant behaviors”, which contrast with adult females that in the same context exhibit active and aggressive behaviors toward the resident female (Ver Hoeve et al., 2013). Moreover, the stress impact on anxiety seems to differ between adolescent and adult rats when submitted to social defeat stress: while adolescent female rats exhibit less anxiety in response to stress and males show no effect of stress, the same stress procedure in adults (both sexes) results in increased anxiety (McCormick et al., 2008). On the other hand, the programming effects of stress during puberty are quite similar to those observed in earlier periods of life, in that adolescent rats exposed to stress exhibit increased anxiety-like (Vidal et al., 2007) and depressive-like (Tsoory et al., 2007) behaviors in the adulthood.

A note to mention sex differences in the effects of pubertal stress exposure. Puberty comes along with the rise of the hypothalamus-pituitary-gonadal (HPG) axis responsiveness, and it is a critical phase for interactions between stress hormones and gonadal hormonal axes to occur. Such interactions might be critical to understand the relevance of sex in the etiopathogenesis of important neuropsychiatric disorders, such as depression. Indeed, depression is twice more prevalent in females than in males, and importantly, this sex difference is not evident during childhood, emerging with puberty (Wade et al., 2002). These facts highlight the importance of puberty for sex-differences on stress-reactivity (Andersen and Teicher, 2008; Wade et al., 2002). Moreover, when juvenile rats are submitted to stress, females and males show a different profile of adaptation, which continues to reflect later in adulthood (Horovitz et al., 2014). For example, juvenile stress reduces sacharinne preference only in females; however, pre-exposed male rats to juvenile stress present a higher sacharine preference loss when re-exposed to stress in adulthood. Furthermore, stressed

juvenile male rats, but not females, present deficits on avoidance learning (Horovitz et al., 2014). These studies reveal that sex differences in stress-related disorders in adulthood can be substantially modified, namely enhanced, by stress in puberty.

2.3.2. Studies of pubertal stress exposure in humans

The increased HPA axis responsiveness during puberty observed in rodents seems to exist also in humans. In fact, it was reported that individuals between 15 and 17 years of age display higher cortisol levels in response to stress than those in late childhood or earlier stages of adolescence (9–13 years old) (Gunnar et al., 2009). In addition, there is a significant interaction between HPA axis reactivity to a stressor during puberty and the onset of major depression (MDD); yet, this association is highly dependent on the level of pubertal development. A hyper-responsive HPA axis in girls exhibiting early pubertal development was associated with higher probability to develop MDD, whereas a late pubertal development in girls exhibiting a hypo-responsive HPA reactivity predicts MDD onset (Colich et al., 2015). Lastly, it is relevant to highlight that the exposure to stress during puberty can induce long-lasting changes in the expression of hormone receptors in the brain, and therefore impact on the behavioral responses regulated by hormones throughout life (Blaustein and Ismail, 2013).

2.4. Stress response in adulthood

The vast majority of the stress research focuses on its effects in the adult brain. Thus, it is not surprising that our knowledge of the impact of stress on the structure and function of the CNS is mostly based on data derived from adult subjects. Many reviews on this topic are available (Gold, 2015; McEwen et al., 2015; Sousa, 2016; Sousa and Almeida, 2012), and so herein we only provide a short summary of the main effects of stress in the structure and function of the adult brain.

2.4.1. Effects of chronic stress exposure in the adult brain

Several studies have shown that the adult brain under chronic stress exposure undergoes structural and functional changes that translate into behavioral dysfunction. Cognitive and emotional alterations correlate with neuroplastic events occurring in stress-responsive areas such as the hippocampus, amygdala and prefrontal cortex (PFC) (Chattarji et al., 2015), but not exclusively. Hippocampal dendritic atrophy was observed after chronic stress in CA3 (Watanabe et al., 1992) and CA1 (Sousa et al., 2000) pyramidal neurons, together with loss of synapses, and impaired LTP in this brain region (Diamond and Rose, 1994), which correlates with impairments in learning and memory in the Morris water maze (Sousa et al., 2000). Likewise, decreased synaptic plasticity was also reported in the PFC. For instance, it was shown that upon exposure to chronic stress the PFC suffers reorganization, with reduction on the total length and branch numbers of PFC neurons (Radley et al., 2004). The stress-induced neuronal atrophy supports the concept that chronic stress leads to a disconnection syndrome by ending synapses and impairing connections between brain regions (Sousa and Almeida, 2012). For instance, the PFC neuronal atrophy was shown to affect the hippocampal-PFC pathway, by reducing the LTP response that disrupts working memory and behavioral flexibility (Cerqueira et al., 2007) as well as attentional set-shifting (Liston et al., 2006). It may also underlie the loss of coherence observed between the ventral hippocampus and the medial PFC after chronic stress exposure (Oliveira et al., 2013). Another example of the impact of chronic stress on synaptic plasticity is that the dendritic atrophy seen in the medial PFC is also accompanied by atrophy on the associative striatum and hypertrophy of the sensorimotor striatum, which correlates with a shift between goal-direct to habit-based behaviors (Dias-Ferreira et al., 2009). The amygdala, in clear contrast, exhibits a stress-induced increase on synaptic phenomena. Neurons from the basolateral complex of the amygdala exhibit enhanced dendritic arborization and spine density in response to chronic stress (Mitra et al., 2005; Vyas et al., 2002). These neuroplastic enhancements in the amygdala have been associated with increased emotional behavior such as anxiety and fear (Vyas et al., 2002). Moreover, after chronic stress the orbitofrontal cortex, a brain region involved in decision-making, also exhibits hypertrophy and an increase on apical dendrites (Dias-Ferreira et al., 2009; Liston et al., 2006). In rats submitted to chronic mild stress (CMS) and exhibiting anhedonia, hypertrophy of medium spiny neurons and increased spine densities are observed in the core division of the nucleus accumbens (NAc) (Bessa et al., 2013); interestingly, in this brain region, the expression genes encoding for BDNF, NCAM and synapsin 1 is increased in rats submitted to CMS (Bessa et al., 2013). Noticeable, all the morphologic and genetic alterations induced by CMS in the NAc can be reverted with antidepressant treatment (Bessa et al., 2013). All those different functional and morphologic alterations observed in different brain regions upon stress highlight the complexity of the neuronal networks involved in the stress response.

2.4.2. Studies of the stress response during adulthood in humans

In humans, as observed in animal models, there seems to be an association between hippocampal atrophy and high levels of cortisol; in addition this also correlates with deficits in hippocampal-dependent learning tasks (Lupien et al., 1998). Moreover, the chronic stress biasing effect on decision-making is also observed in stressed individuals. Using functional imaging techniques, it was shown that chronic stress shifts activation from associative to sensorimotor circuits and this is accompanied by atrophy of the medial prefrontal cortex and caudate and hypertrophy of the putamina (Soares et al., 2012). Importantly, these volumetric changes are associated with an increased behavioral strategy towards habits and decreased sensitivity to changes in outcome value (Soares et al., 2012).

2.5. The impact of stress exposure in aging

Exposure to different stressors throughout life can have an impact in the aging process. In fact, the way individuals' age can be highly influenced by major life events and stressors of daily life and their interaction with other modulating factors. Several hypotheses have been put forward to explain the relation between aging and the response to stress; one of the most well-known is the so-called “glucocorticoid cascade hypothesis of aging” (Sapolsky et al., 1986). In line with this hypothesis, although immobilization stress increase corticosterone secretion in a similar profile in aged and young animals, aged rats cannot re-establish their levels at least for the subsequent 4 h, showing impairments in the negative feedback control of the HPA axis (Sapolsky et al., 1983). Nowadays the glucocorticoid cascade hypothesis has been strengthened by the causal relationship established between longevity genes expression (e.g. sirtuin-1) or shorter telomeres and response to chronic stress (Sanchez-Hidalgo et al., 2016; Zhang et al., 2014) and, with modifications that have been clearly incorporated in the aging clinical algorhythms and even on aging predictive models.

2.5.1. Challenges on studying the effects of chronic stress in aged rodents

Although rodents physiologically age in a different manner than humans, studying animal models is of great importance to understand aging-related diseases. The evolution of genetic engineering in mice allowed the generation of rodent models of

neurodegenerative disorders crucial to understand such aging-related disorders. Importantly, such models have enabled the study of the impact of stress in the etiology of these disorders (Yuan et al., 2011). Aging-related changes observed in aged rodents mimic hallmarks of the effect of chronic stress in humans such as cognitive decline, immune system dysregulation and decreased synaptic plasticity in stress-related regions (Barrientos et al., 2012). However, there are some practical issues when studying the effects of stress on aging animals. With aging, there is increasing sensorial loss, such as sight or olfaction, which can interfere with stress perception (Tikhonova et al., 2015; Zeng and Yang, 2015). Likewise, it is important to adequate the intensity and nature of the stressors (as well as the stress read-out behavioral tests) when studying chronic stress in aged rodents (Prusky et al., 2000). The lack of standardization across studies brings limitations to the analysis of stress effects in aging. For instance, the use of different endpoints across studies, combined with the lack of a necropsy report, can render an aging study incomplete (Santulli et al., 2015; Treuting et al., 2016). Similarly, the use of different paradigms of chronic stress render inter-study consistency even more difficult to achieve (Allard and Duan, 2011). These are some of the critical challenges for the field in the near future; hopefully, more multi-centric collaborative research efforts may allow for the overcome of such critical obstacles.

3. The effect of sex in the stress response

The prevalence of neuropsychiatric disorders is higher in women (WHO, 2012). This and other sources of evidence created an incentive coming from national funding agencies, such as the National Institute of Health, for the inclusion of groups of females or for the justification of the choice of the sex of the animals in pre-clinical research (Clayton and Collins, 2014). Since stress is a precipitating factor for neuropsychiatric disorders, such as depression, it is important to unravel the basis of the dimorphic response to stress. Throughout the years, several authors have described sex differences in behavior, neuroendocrine, neuron morphology, immune, and neurochemical systems in response to different stress protocols (acute, repeated or chronic).

In this section, we approach the fundamental sex differences in stress response by discussing the dimorphism that underlies it and by reviewing the impact of hormonal variability in the stress response.

3.1. Dimorphism in the stress response

The brain of males and females shows anatomic differences that can impact on the stress response, in both fast and slow phases of the response. For instance, females have bigger locus coeruleus, the brain region that produces noradrenaline (Pinos et al., 2001), an important initiator of the arousal in the fast phase of the stress response (Bangasser and Valentino, 2012). On the other hand, the brain has also been described to have a dimorphic expression of GR (Kitraki et al., 2004), with potential impact in the HPA axis negative feedback loop. These sex differences are likely to underlie the higher levels of glucocorticoids observed in females compared to males in response to acute and repeated stress (Seale et al., 2004a).

3.1.1. Sex differences in the neuroendocrine response

The HPA axis can modulate the HPG axis and vice-versa (Toufexis et al., 2014). Males and females differ at the level of the reproductive axis (or HPG) and therefore animals from each sex can perceive stress differently and develop distinct coping mechanisms (Wingfield and Sapolsky, 2003). The bi-directional influence between the HPA and HPG axis starts centrally, in the hypothalamus. The secretion of corticotrophin-releasing factor (CRF) inhibits the HPG through CRF1 and 2 (Li et al., 2006) and, on the other hand, estrogen response elements are present at the *CRF* gene (Vamvakopoulos and Chrousos, 1993). Evidences of different levels of CRF expression in the paraventricular nucleus were reported along the estrous cycle, which also suggests that the HPG can influence the outcome of the HPA response (Bohler et al., 1990).

At the level of the anterior pituitary, where ACTH secretion takes place, physiological replacement with estrogens at pro-estrus levels has been shown to increase ACTH and therefore glucocorticoid levels after restraint stress. Higher levels of ACTH were also observed at the peak (not basal levels) in cycling rat females in pro-estrus compared to estrous and di-estrus (Viau and Meaney, 1991). A distinct sensitization of the anterior pituitary to exogenous female hormones reveals estrogens to display an exacerbation effect, opposite to progesterone, in response to acute stress. In males, testosterone was observed to decrease ACTH and glucocorticoid levels after stress (Viau and Meaney, 1996), revealing an inhibitory effect over the anterior pituitary that is reverted by gonadectomy of male rats (Seale et al., 2004b). Briefly, during a stress response, the body activates processes essential for survival mechanisms and therefore inhibits the non-surviving (such as reproduction) in a non-sex dependency. Consequently, glucocorticoids inhibit the production of gonadotropin hormone-releasing hormone (GnRH) by hypothalamic neurons by blocking the expression of *GnRH gene* (Chandran et al., 1994; Oakley et al., 2009). In the pituitary, gonadotrophins' secretion is repressed (Sakakura et al., 1975) and finally the gonadal function is blocked (Sapolsky, 1985). Summarizing, chronic dysregulation of the HPA axis can inhibit the release of GnRH, pituitary luteinizing hormone and ovarian estrogens and progesterone (Chrousos, 1993). The hippocampus is richly endowedwith GR, which play an important role in shutting down the stress response (the HPA axis negative feedback loop); interestingly, also here a dimorphic expression of sex hormone receptors can be observed (McEwen et al., 1995; Weiland et al., 1997) and both adrenal and gonadal hormones have been shown to rearrange hippocampus plasticity (McEwen, 2010; McEwen et al., 1995).

Several studies showed that exogenous replacement of estrogens leads to an enhanced response of the HPA axis while testosterone leads to an inhibition (Lund et al., 2004; Viau et al., 2005). Interestingly, testicular-secreted testosterone that enters the brain is converted into estrogen (aromatization hypothesis) (Roselli et al., 2009) and it regulates several processes such as memory, cognition and mood (Gillies and McArthur, 2010). Progesterone, on the other hand, has sedative and anxiolytic effects (Gulinello et al., 2003).

3.1.2. Sex differences in the behavioral response to stress

Biobehavioral studies of rodents exposed to stress have described the sympathetic response to a stressor as a “fight or flight” conflict, due to the release of noradrenaline and adrenaline. Controversial evidences suggest that most males adopt an aggressive or fleeing behavior, while females evolved to a “tend-or-befriend” response (Taylor et al., 2000). Studies allege that oxytocin released during childbirth labor and lactation, program the response to stress to act in favor of the progeny safety, by promoting a calm and protective (tending) response or to social or seek for help (befriending) response (Carter et al., 2001). These differences might contribute to the distinct behavioral responses to an aggressive male resident intruder (social defeat protocol); in fact, since females do not show such an obvious fight or flight response to stress, this influence the study of this response in this sex (Jacobson-Pick et al., 2013).

At the behavior level response, acute uncontrolled stress has been shown to enhance associative learning and induce learned

helplessness in males, but the opposite in females (Wood and Shors, 1998). Depressive-like behavior evaluated through the re-exposure to the forced swim test (FST) showed that males increase the immobilization time, corticosterone level and serotonergic inputs to the limbic system revealing an adaptive response to uncontrollable acute stress. However, females increase significantly the immobility time compared to males, which indicates higher levels of behavioral despair, suggestive of a depressive-like phenotype that is not followed by coping serotonergic inputs (Drossopoulou et al., 2004). It should be highlighted that this is not observed when different controllable and uncontrollable acute stress paradigms are applied (Dalla et al., 2008; Dalla and Shors, 2009), that might even show opposite differences between the two sexes (Dalla et al., 2010).

Regarding chronic stress, the disruption of both HPA and HPG axis in both sexes reveals less inter-sex variability than acute stress exposure (Baker et al., 2006; Dalla et al., 2005). As any rodent model, chronic stress models have strengths and limitations that need to be accounted for the correct interpretation of the data. The choice of the inaccurate stress model (as well as the behavioral assessment) can lead to misinterpretation of resilience, adaptation or recovery mechanisms. As an example, Kokras, et al. described the latency to immobility on the FST to be different in females from males (Dalla et al., 2010; Kokras et al., 2009); thus, the tools used to assess it in males may not be completely transversal to females (Kokras et al., 2016).

3.2. Female response to stress across lifespan

The natural hormonal variations occurring across lifespan in females is accompanied by differences in the stress response. The adult female before pregnancy (nulliparous) has been shown to adapt differently to stress when compared with dams and multiparous females (Rima et al., 2009). The hormonal environment experienced through pregnancy and post-partum are known to change hormonal receptors in the brain, hippocampal neurogenesis and spatial memory (Barha et al., 2015), in such a way that it re-formats the brain to be better prepared to cope with stressors. Indeed, multiparous females increase exploration time and reduce corticosterone levels compared to nulliparous females in a cued-contextual fear conditioning paradigm (Rima et al., 2009). Studies comparing the vulnerability of nulliparous and dams when stressed and treated with antidepressants also reveal that pregnancy confers stress resilience (Workman et al., 2016).

A good example of the interaction of the HPA and HPG axes is the etiology of post-partum depression, which can develop up to 4 weeks after birth and has an incidence of around 15% of all pregnancies (First, 2013). Although one of the main risk factors is depression history for the women (First, 2013), changes in the HPA axis might also play a triggering role. For example, fluctuations in the HPA axis during pregnancy are hypothesized to play a part in the etiology of post-partum depression (Glynn et al., 2013), which fits with the observation that after reaching a peak in the third trimester there is a significant drop in CRF and cortisol levels 5 days after birth (with the total expel of the placenta) (Hendrick et al., 1998).

With the advance of menopause, a dysregulation of the HPA occurs, which results in increased cortisol production (Seeman et al., 1997; Woods et al., 2006). Mimicking the natural steps of menopause in animal models is a challenge; as a consequence, most studies use artificial menopause manipulations, such as ovariectomy or through the administration of toxins that induce accelerated ovarian failure (Diaz Brinton, 2012). Despite their limitations, both models have been very useful to study the effects of chronic stress in this phase of life (Takuma et al., 2007). Nevertheless, due to great variations in the age time window when the procedures are performed, it is difficult to separate the effects of sex hormones from the ones of menopause itself.

4. The effect of genotype in the stress response

Like humans, rodents also use distinct stress coping strategies that determine their degree of resilience or susceptibility to stress. One of the most consistent observations is the fact that the genetic background of rodents plays a crucial role in the resilience/susceptibility to stress. In this section, we address the impact of different genetic backgrounds of mice and rats in the response to stress.

4.1. The impact of mouse genotype on stress response

Distinct mouse strains have been shown to present different responses to stress, which clearly indicates that genetic background impacts on the behavioral response [(Anisman et al., 2001; Anisman and Zacharko, 1992; Miller et al., 2010) and extensively reviewed in (Crawley et al., 1997; Jacobson and Cryan, 2007; Millstein and Holmes, 2007)]. Acute stress typically induces an obvious anxiety-like behavior and HPA axis activation in some strains, such as BALB/cJ and DBA/2J, but less in others such as C57BL/6J (Belzung and Griebel, 2001; Jacobson and Cryan, 2007; Miller et al., 2010). Even using slightly different protocols of chronic stress (with distinct types and duration of stressors) it is quite consistent that mice from the Balb/c strain are among the most susceptible to stress whereas C57BL/6 mice are the most resistant. Thus, we focus this section mainly in this two mouse strains since they represent very interesting animal models to study stress related disorders and are the two strains more widely used. After exposure to stress, Balb/c mice present a more pronounced anxious-like behavior when compared with C57BL/6 mice. Those behavioral alterations were observed in different behavioral paradigms (Anisman and Matheson, 2005; Belzung and Griebel, 2001). After stress, Balb/c mice also present a more evident depressive-like behavior compared to C57BL/6 mice (Ducottet and Belzung, 2005; Griffiths et al., 1992; Mineur et al., 2003; Shanks and Anisman, 1988; Zacharko and Anisman, 1991). In accordance with the behavioral alterations observed, HPA axis activation is more pronounced in Balb/c mice upon stress than in C57BL/6 (Anisman et al., 1998; Shanks et al., 1990). Also in line with this pattern of susceptibility, Balb/c mice submitted to stress display greater changes in noradrenaline levels when compared with C57BL/6 mice (Shanks et al., 1994); interestingly, the noradrenergic system of Balb/c also presents a slower adaptation to chronic unpredictable stress, comparing to the one of C57BL/6 (Shanks et al., 1994). Moreover, a comparative hippocampal gene expression study on the effects of chronic unpredictable mild stress on BALB/cJ and C57BL/6J mice revealed that BALB/cJ animals present more alterations in genes with higher probability of association to stress response. The several candidate genes and gene networks identified are associated with inflammation and neurogenesis (Malki et al., 2015).

The comparison between mouse strains also revealed that the innate predisposition of Balb/c strain to be more susceptible to stress, when compared with C57BL/6, is also associated with epigenetic markers in the brain (Franklin et al., 2012; Uchida et al., 2011).

An interplay between the genetic background and microbiota in the response to stress has also been suggested (Rabot et al., 2016; Rea et al., 2016). In fact, the more anxiety-prone Balb/c germ free (GF) mice, when inoculated with microbiota from anxiety-resistant Swiss mice, showed a decreased anxious-like behavior.

Accordingly, the transfer of microbiota from Balb/c mice to Swiss GF mice also increases their anxious-like behavior phenotype (Bercik et al., 2011). The mechanisms underlying these interactions remain to be deciphered.

4.2. The impact of rat genotype on stress response

The study of the different rat strains demonstrated that the heterogeneity of the responses to stress is very complex, even though few papers compare several rat strains using the same stress protocol. For example, F344 and Lewis rats, both inbred strains, do not differ very much in baseline HPA axis activity. However, Lewis rats show a blunted HPA axis response to a variety of stressors while F344 present a strong HPA axis response (Ellenbroek et al., 2005). Interestingly the stress response in those animals seems also to be modulated by gut microbiota. F344 rats (genetically more susceptible to stress) present an exacerbated neuroendocrine and behavioral response to stress in the absence of gut microbiota (Crumeyrolle-Arias et al., 2014).

Studies using the forced swim test (FST) also revealed that different inbred rat strains present distinct behavior phenotypes. The F344, Lewis and SHR present lower immobility time in the FST when compared to Brown Norway and to Wistar Kyoto (the most immobile rat strain) (Gomez et al., 1996). In fact, several authors showed that Wistar Kyoto rats exhibit a pronounced pro-depressive phenotype including behavioral despair, social avoidance and anhedonia (Nam et al., 2014; Solberg et al., 2004), as well as enhanced physiological responses to repeated stress (Morilak et al., 2005). Another rat strain that is widely used to study depression is the Flinders sensitive line (FSL) (reviewed in Overstreet and Wegener, (2013)). Originally this rat strain was created to study the cholinergic system. However, the selective breeding program of the original animals resulted in two different strains: one that is super-sensitive to cholinergic agonist (FSL rats) and other, the Flinders resistant line (FRL), that resembles control Sprague Dawley rats. Interestingly, the FSL rat when subjected to CMS shows increased anhedonia compared with FRL, and present several similarities with depression in humans (Ayensu et al., 1995; Overstreet and Wegener, 2013; Pucilowski et al., 1993). Taken into account the origin of the FSL strain it was proposed as a genetic model of depression.

Interestingly most of the stress-response behavioral research in rats is performed in outbred strains. For example, after CMS, Lister hooded and Wistar rats (outbred strains) present decreased sucrose preference when compared with Sprague Dawley (also outbred) (Marona-Lewicka and Nichols, 1997). A similar protocol demonstrated that chronic stress induces an increased immobility in the FST of the Long Evans strain when compared with Sprague Dawley (Bielajew et al., 2003). Such differences in the stress response are certainly of relevance when studying this topic and it would be of great interest to promote global studies using similar stress protocols, in different strains, to ascertain for the importance of the rat genotype in the distinct outcomes.

5. Conclusions

The origin of individual differences in the stress response is a long-held question still puzzling the stress research field. The stress response, as a process orchestrated by the brain, varies across the lifespan. The early exposure to stressful events can trigger immediate changes, or re-shape the way the brain reacts to stress in the adulthood towards maladaptive responses. In addition, maladaptive responses can also be triggered by exposure to stress later in life, particularly chronic stress, which increases the susceptibility to psychiatric disease. Adaptive or maladaptive responses to chronic stress depend also on other intrinsic factors like sex and genetics or extrinsic factors (e.g. the nature of the stressors or the microbiota among several others). Remarkably, the study of such interdependent factors, rather than an obstacle, might constitute a valuable opportunity to dissect the mechanisms underlying stress-related disorders.

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