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The three-hit concept of vulnerability and resilience: Toward understanding adaptation to early-life adversity outcome

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Summary Stressful experiences during early-life can modulate the genetic programming of specific brain circuits underlying emotional and cognitive aspects of behavioral adaptation to stressful experiences later in life. Although this programming effect exerted by experience-related factors is an important determinant of mental health, its outcome depends on cognitive inputs and hence the valence an individual assigns to a given environmental context. From this perspective we will highlight, with studies in rodents, non-human primates and humans, the three-hit concept of vulnerability and resilience to stress-related mental disorders, which is based on gene—environment interactions during critical phases of perinatal and juvenile brain development. The three-hit (i.e., hit-1: genetic predisposition, hit-2: early-life environment, and hit-3: later-life environment) concept accommodates the cumulative stress hypothesis

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Genetic predisposition;
Early life environment;
Later life environment

stating that in a given context vulnerability is enhanced when failure to cope with adversity accumulates. Alternatively, the concept also points to the individual's predictive adaptive capacity, which underlies the stress inoculation and match/mismatch hypotheses. The latter hypotheses propose that the experience of relatively mild early-life adversity prepares for the future and promotes resilience to similar challenges in later-life; when a mismatch occurs between early and later-life experience, coping is compromised and vulnerability is enhanced. The three-hit concept is fundamental for understanding how individuals can either be prepared for coping with life to come and remain resilient or are unable to do so and succumb to a stress-related mental disorder, under seemingly identical circumstances.

1. Introduction

It is well-documented that during critical periods of brain development stressful experiences can modulate the functioning of specific circuits that underlie adult emotional and cognitive functioning, and behavior (Taylor, 2010). These effects exerted by stress are mediated by the autonomic nervous system and the hypothalamus—pituitary—adrenal (HPA)-axis. Hence, decades of research have been devoted to understand how the mediators of these systems such as adrenaline and other biogenic amines, neuropeptides and hormones can modulate brain function and behavior for life (Maras and Baram, 2012). These programming effects induced by the stress mediators suggest enduring changes in the transcriptome underlying DNA methylation and chromatin modifications. In fact, recent research has revealed that the mediators and their receptors of the HPA-axis themselves are prime targets of epigenetic modification. This includes corticotrophin releasing hormones (CRH), vasopressin and their receptors, and also the receptors for circulating adrenal corticoids in the limbic-cortical circuitry (Murgatroyd and Spengler, 2012). Although rapid progress has been made in unraveling this epigenetic mechanism induced by early experience, it is still unresolved how this modulation of programming by the environment precisely occurs (Franklin et al., 2012).

Here we focus on the HPA-axis and its glucocorticoid endproducts, i.e., cortisol and corticosterone in human and non-human primates and only corticosterone in rodents, collectively called CORT. These hormones coordinate and synchronize daytime and sleep-related events, regulate the organism's response to stress and facilitate adaptation (de Kloet et al., 2005). We ask the question how CORT action during stress can change from a protective into a harmful signal by focusing on the environmental programming effects powered by the hormone.

To address this question this review reflects the content of the Presidential Symposium held under the title ''Resilience and vulnerability: adaptations to early-life adversity outcome'' at the 42nd ISPNE Conference in the New York Academy of Sciences. Thus we first briefly discuss, for rodents, monkeys and humans, the development of the pup's/infant's HPA-axis at perinatal life when they are particularly susceptible to environmental influences. We briefly review rodent (Daskalakis et al., 2011a) and non-human primate (Parker et al., 2006) animal models, that are appropriate to exploit gene—environment interactions at these critical periods in the perspective of later-life outcome. We focus on a mechanism involving excitatory neurotransmission and stress mediators (Champagne et al., 2008; Bagot et al., 2012a). Next this analysis is projected to the human situation. We conclude with the presentation of the three-hit concept of vulnerability and resilience. This concept unifies the currently dominant viewpoints that have precipitated as the cumulative stress hypothesis, and the stress inoculation and match/mismatch hypotheses.

2. Early-life stress in animal models

Mother-pup interactions during the first postnatal period have been studied the last 60 years in rodents and in non-human primates to evaluate the significance of early-life experiences for individual differences in adult neuroendocrine activity, emotional responses, cognitive performance and behavior. Some researchers studied the impact of experimental early-life manipulations such as neonatal handling and maternal separation (Levine, 2005), and others examined the outcome of naturally occurring variations of maternal care (Meaney, 2001). Also significant progress has been made with studies using monkeys exposed to moderate postnatal stressors (Parker et al., 2006).

2.1. Stress hypo-responsive period (SHRP) and the short-term effects of maternal absence

The SHRP is a developmental period, from postnatal days (*pnd*) 1—10 in mice and *pnd* 3—14 in rats, in which the elevation of CORT is attenuated after exposure to mild stressors, that otherwise trigger a profound response in the adult animals (Schapiro et al., 1962; Sapolsky and Meaney, 1986; Levine, 2001; Schmidt et al., 2003a). The human HPA-axis development is in concordance with that of rats (even though rats are prematurely born) since the axis is not yet fully developed at birth and CORT secretion manifests a comparable SHRP during postnatal months 6—12. During this period human babies are dependent on their caregivers for normal development, and adverse experiences in this period can have a long-lasting impact (Gunnar and Quevedo, 2007).

There are phylogenic differences, however, in HPA-axis development between rodents and primates. Detailed studies with the New World monkeys, the marmosets, have shown basal hyperactivity of the HPA-axis in neonates, but without an apparent circadian rhythmicity. From infancy to adulthood the pattern of stress responsiveness remains similar. Hence in view of its neonatal hypercorticism the marmoset is an interesting animal model to study the outcome of

early manipulations of the stress system under a high steroid titer as compared to rodents, humans and other non-human primates (Pryce et al., 2002).

For the neonate's hypo-responsiveness to stressors a lot of factors have been implicated like: adrenal inhibition/insensitivity (Stanton et al., 1988; Chatelain et al., 1989; Walker, 1995; Okimoto et al., 2002), enhanced glucocorticoid receptor (GR) mediated negative feedback (Walker et al., 1986; van Oers et al., 1998a; Schmidt et al., 2005), inhibition of the brain renin-angiotensin system (Muret et al., 1992; Liebl et al., 2009), CRHR1 and CRHR2 receptors functions (Eghbal-Ahmadi et al., 1998; Schmidt et al., 2003b, 2006a; Fenoglio et al., 2005), central α_2 adrenoreceptor control of pituitary adrenocorticotropic hormone (ACTH) release (Grino et al., 1994) and central action of metabolic factors (Proulx et al., 2001; Salzmann et al., 2004; Schmidt et al., 2006b, 2008) as well as immaturity of the hypothalamus-pituitary connection (Suchecki et al., 1993). Yet, the most proximal cause for the transient hypo-responsiveness to stress is a strongly reduced responsiveness of the adrenals to ACTH (Rosenfeld et al., 1991; Okimoto et al., 2002). In fact, during the SHRP, the central stress response after a challenge does not translate into adrenal corticosterone secretion.

Prolonged ($\geq$8 h) maternal absence (i.e., maternal separation; MS), implemented within the SHRP, causes neonatal rodents to emerge from the SHRP and to display elevated basal and stress-induced levels of CORT (Stanton et al., 1988). These observations showed that a central mechanism required to elicit an endocrine response following stress can be effective already early in development (Walker et al., 1986, 1990, 1991; van Oers et al., 1998a). Various components of the dam's behavior (mostly feeding and tactile stimulation) seem capable of inhibiting or dampening the MS-induced responsiveness of the HPA-axis, but do so at different levels. Feeding during maternal absence acts as an inhibitory factor to the neonate's basal and stress-induced adrenal activity (Stanton et al., 1988; Stanton and Levine, 1990; Suchecki et al., 1993; van Oers et al., 1998b; Schmidt et al., 2002, 2006b), and stroking (e.g., 45 s every 8 h) can inhibit the activation of pituitary ACTH release as well as of excitability of the limbic and hypothalamic brain areas over the 24 h period (Suchecki et al., 1993; van Oers et al., 1998b; Zhang et al., 2002).

Short MS for periods of 3 min to 3 h are insufficient to increase basal CORT-secretion. If repeated daily, this MS procedure is capable to induce sensitization of the CORT stress-response in parallel with adrenal growth (D'Amato et al., 1992; Huot et al., 2002; Knuth and Etgen, 2005; Levine et al., 1991; McCormick et al., 1998; Schmidt et al., 2004; Vazquez and Akil, 1992). Extension of MS to periods beyond 3 h causes increased basal and stress-induced CORT levels. If the 8h-MS procedure was repeated the next day this rise in basal CORT is abolished, however. The explanation of this habituation or adaptation of the pup's HPA-axis to the experience of repeated MS is probably psychological. Apparently, already after one episode of maternal absence the pup has learned to predict the return of the mother if it is exposed to MS the next day, a phenomenon that occurs irrespective of genotype or species. Single MS causes, however, also increased adrenal sensitivity to heterotypic stressors and exogenous ACTH (Levine et al., 1991; Rosenfeld et al., 1992; Okimoto et al., 2002). Furthermore, we show that even though basal levels of ACTH and CORT remain low if separations are repeated, the pups stay on alert and retain the ability to respond to stressors with increases in ACTH and CORT levels (Enthoven et al., 2008; Daskalakis et al., 2011a) (Fig. 1).

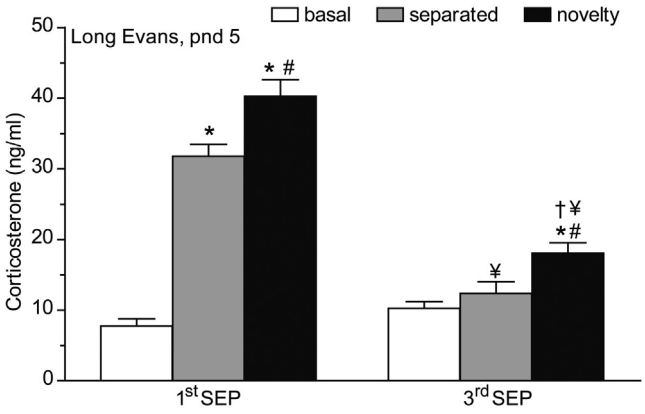

Figure 1 The newborn rat's stress system readily habituates to repeated and prolonged maternal separation, while continuing to respond to stressors. Corticosterone (ng/ml) blood plasma levels measured on postnatal day (pnd) 5 at basal conditions ("basal"; white bars), after 8 h of maternal separation ("separated"; gray bars) or 8 h of maternal separation with an additional 30 min of exposure to novelty ("novelty"; black bars). First separation rat pups ("1st SEP") had no previous history of treatments. Third separation rat pups ("3rd SEP") were exposed to 8 h of maternal separation on *pnd* 3 and 4. For the experiment, Long Evans litters were used. Data represented mean $\pm$ SEM. Significance level was set at $p < 0.05$. * vs. basal, # vs. separated levels of the same treatment group, † vs. basal of 1st HOME SEP, ¥ vs. correspondent value of 1st HOME SEP. $n = 14–16$ per time point of each treatment group.
Adapted from Daskalakis et al. (2011a).

We studied post-MS stress sensitivity using two different MS-conditions, in which the rat pups were either with their siblings together in the home cage (HOME-SEP) or isolated and housed individually for 8 h in a novel cage (NOVEL-SEP). Our studies showed that habituation of basal CORT secretion to repeated-MS occurs irrespective of the home or novel context (Daskalakis et al., 2011a). However, the two separation procedures demonstrated a different response to a subsequent 30 min novelty stressor. Rat pups separated in a novel environment adapt and do therefore not respond to the novelty stressor, while the repeated "home separation" animals do. The adrenal ACTH receptor (MCR2) varies in parallel with these changes in adrenal responsiveness; the home separation group displayed increased MCR2 expression (Daskalakis et al., 2011a).

It is well established in squirrel monkeys that brief maternal separations elicit increases in plasma cortisol levels in infants (Mendoza et al., 1978; Levine et al., 1989). These separations evoke also species-typical distress peep-calls and locomotor agitation. Recovery of baseline measures is achieved after each social reunion (Coe et al., 1983; Stanton and Levine, 1985; Hennessy, 1986). The neuroendocrine responses are fairly resistant to habituation, as they have

been shown to persist after as many as 80 intermittent maternal separations (Hennessy, 1986). The social environment has been shown to be an important mediator of the magnitude of this adrenocortical activation (Levine, 2000). Infants removed from both their mother and home cage and then housed in a novel environment exhibit larger cortisol increases as compared to infants whose mothers were removed, but which remained in the familiar home cage surrounded by known cage-mates. The increase in cortisol was larger when the infants were housed in isolation rather than with familiar conspecifics, and a further increase was noted when housed with non-familiar conspecific (Levine and Wiener, 1988).

The above findings suggest that in the newborn familiar signals can buffer against stress-induced HPA-axis activation and that rodents and monkeys respond comparably in this respect. The question is whether this type of buffering occurs in human neonates or infants. The studies by Gunnar and Cheatham (2003) suggest that the quality of care of children and the degree of attachment are capable to attenuate stress-induced cortisol secretion suggesting the existence of a SHRP (Gunnar and Cheatham, 2003). Childers's attachment security and cortisol-reactivity depend on both genetic factors and the early environment (Bakermans-Kranenburg and van Ijzendoorn, 2007; Ouellet-Morin et al., 2008). Interestingly, infants in transition to day-care, which is an unfamiliar setting, show higher cortisol response to the daily MS in comparison with infants that stay at home and show the first signs of habituation after more than a week (Ahnert et al., 2004).

2.2. Long-term effects of early-life manipulations

Adversity of the maternal environment, either experimentally induced or naturally occurring, can predict alterations in social behavior, susceptibility to drugs of abuse, learning & memory processes and sensorimotor gating of the adult offspring (Liu et al., 1997, 2000; Ellenbroek et al., 1998; Ellenbroek and Cools, 2000; Plotsky et al., 2005; Zhang et al., 2005; Veenema et al., 2006; Parent and Meaney, 2008; van der Veen et al., 2008; Veenema and Neumann, 2009; Oomen et al., 2010; Lukas et al., 2011). Originally, maternal behavior per se was proposed to mediate the effect of early-life experience (Meaney, 2001). However, the exclusivity of the role of maternal behavior was questioned, since the pup's environmental input appears to be equally important (Macri et al., 2004; Macri and Wurbel, 2006; Tang et al., 2006).

Early handling (*EH*; i.e., brief MS of 3—15 min the first 2 or 3 weeks of life) results in increased maternal care in the reunion periods and across the day (Liu et al., 1997; Pryce et al., 2001; Macri et al., 2004; Claessens et al., 2012) and can lead to better coping with stressful situations later in life (Levine, 1957; DeNelsky and Denenberg, 1967; Meaney and Aitken, 1985). Handled offspring exhibiting good performance in cognitive tasks, show reduced anxiety and display a lower endocrine response to a mild stressor in comparison with non-handled rats (Levine, 1967; Meaney and Aitken, 1985; Meerlo et al., 1999; Kosten et al., 2012). Interestingly, apart from maternal care, the individual components of the early-handling procedure (i.e., maternal absence, novelty exposure, tactile stimulation) also contribute to the observed phenotype (Tang, 2001; Daskalakis et al., 2009b). Taken together, the early handing experiments demonstrated that exposure to a mild predictable stressor early in life can be beneficial (Macri and Wurbel, 2006; Claessens et al., 2011). This finding was replicated in other species (non-human primates; *see below*) and served as the basis for the stress-inoculation theory (Parker and Maestripieri, 2011).

MS (i.e., prolonged MS of typically 3—8 h daily during the first two or three weeks of life): Maternally separated pups, as compared to handled individuals or controls (animal facility reared), display as adults increased stress-responsiveness, enhanced emotional reactivity and impaired cognitive performance. MS also results in enhanced acoustic startle, and lower prepulse or latent inhibition. The MS outcome is a function of strain and gender of the animals, the frequency and duration of the separation as well as the pup's age, time point within the light cycle and ambient temperature at the moment the separation occurs (Lehmann and Feldon, 2000; Claessens et al., 2011; Kosten et al., 2012).

The environmental context such as the housing in groups or in isolation, inside the home cage or in a novel environment, is important (Lehmann and Feldon, 2000; Ruedi-Bettschen et al., 2004). We found that HOME-SEP animals maintain a remarkably enhanced stress-induced CORT response throughout life. The enhancement of their CORT response occurs in the face of attenuated stress-induced ACTH-release indicating a profound adrenal hyper-responsiveness. The endocrine phenotype of the NOVEL-SEP offspring also persisted into adulthood as judged from its enhanced stress-induced amygdala c-Fos activation and ACTH-release (Daskalakis et al., 2009a; Daskalakis, 2011).

In Table 1, the long-term effects of the NOVEL and HOME-SEP MS paradigms on a wide spectrum of behavioral endophenotypes are summarized. Our data suggest that the social and environmental context in which the adverse early-life experience took place is an important determinant of the long-term outcome of early-life adversity. HOME-SEP rats have behavioral deficits mainly in the cognitive domain (↓ working and emotional memory vs. non-separated controls); NOVEL-SEP rats display behavioral alterations in all domains (↑stereotypy, ↓gating, ↑emotional memory, and ↓ social interaction vs. non-separated controls) (Daskalakis et al., 2009a,

Table 1 Long-term behavioral outcome of maternal separation depends on context.

Behavioral endophenotypes	HOME SEP	NOVEL SEP
Stereotypy	No change	↑
Sensorimotor gating	No change	↓
Working memory	↓	No change
Emotional memory	↓	↑
Social interaction	No change	↓

Note: Repeatedly separated pups were exposed to 8h-maternal separation on postnatal day 3, 4 and 5 in a home (HOME-SEP; home separated) or novel context (NOVEL-SEP; novel separated) and tested in the behavioral tasks post-weaning. Rats, non-separated as pups (no history of postnatal treatments) served as controls. Based on data from Daskalakis et al. (2009a, 2012) and Daskalakis (2011).

2012; Daskalakis, 2011). Apart from its scientific relevance, the difference in the long-term outcome of the two paradigms asks for standardization of methodology in animal studies of early-life adversity. In human studies, early-life history is also increasingly implicated. Very often these studies classify the participants according to the presence or absence of early-life adversity based on self-report, but only to a limited extent the desired contextual information is provided.

2.2.1. Naturally occurring variations in maternal care

In the absence of any experimental manipulations, there is a considerable variation in maternal care in the rat (Champagne et al., 2003). The frequency with which a dam licks/grooms her pups (LG) is a stable behavioral trait and is normally distributed across dams (Champagne et al., 2003). Pup LG is a major source of tactile stimulation for the neonatal rat that regulates several physiological systems of the neonate (Bagot and Meaney, 2010). There is considerable evidence, mainly from studies using Long Evans rats, for a sustained effect of maternal care on the behavioral and endocrine responses to stress in the offspring. Maternal LG frequency correlates with hippocampus-dependent learning in adulthood. Offspring of High LG mothers more rapidly acquires the location of a hidden platform in the Morris water maze (Liu et al., 2000) and also shows enhanced memory in an object recognition task (Bredy et al., 2003). Low LG offspring displays potentiated acoustic startle responses and deficits in prepulse inhibition (Zhang et al., 2005).

Consistent with enhanced hippocampal-dependent learning and memory, long-term potentiation (LTP) in the hippocampal DG and CA1 areas of High LG offspring is increased compared to Low LG offspring (Bredy et al., 2003; Champagne et al., 2008; Bagot et al., 2009). The high LG offspring, moreover, displays increased spine densities and enhanced dendritic arborization (Champagne et al., 2008; Bagot et al., 2009). Although under low stress conditions the High LG offspring shows enhanced hippocampal-dependent learning and corresponding hippocampal plasticity compared to Low LG offspring, when the High LG animals are exposed to stress or high corticosterone, both measures become compromised (Champagne et al., 2008) (see also Section 2.6).

The large variation in maternal care used by this paradigm can be interpreted as variation in maternal strategies and maternal investment, evoked by environmental adversity. In other words, maternal care would be a response to environmental demands and pups' distress, and its evolutionary goal would be to preserve the fitness of the offspring (Beery and Francis, 2011). Whatever the evolutionary significance might be, the combined exposure to care, moderate environmental challenges and corticosteroids seem to prepare the pup for life to come.

2.2.2. Nesting conditions

Standard nesting conditions may represent an impoverished environment (Levine, 2005; Macri and Wurbel, 2006). Enrichment of the nesting conditions is a way to manipulate maternal care behavior and the pup's development in a naturalistic way. Two environmental enrichment paradigms studied are the communal nesting (CN) (Branchi, 2009) and the double mothering paradigm (D'Amato et al., 2011). In the former, three females breed and keep pups together, and share care-giving behavior in a single nest from birth to weaning. In the latter, pups are raised by two dams (one or two are lactating; i.e., Lactating/Non-Lactating or Lactating/Lactating).

In both paradigms pups are provided with high levels of maternal care compared to mice reared in standard laboratory conditions, but yet the phenotype is diverging (Branchi, 2009; D'Amato et al., 2011). Paradoxically, CN mice display increased anxiety-related behavior and normal cognitive performance, but enhanced social competences and resilience to social stress (D'Andrea et al., 2007; Branchi, 2009; Branchi et al., 2010). Moreover, this effect depends on interaction with both the peers and the mother (Branchi et al., 2013a). Also, in later-life the vulnerability to psychosocial stressors rather than to physical stressors is attenuated in response to this type of early social enrichment (Branchi et al., 2013b). Mice experiencing double mothering do not differ in their emotional or stress-hormone profile from mice reared by their mothers alone, but do exhibit enhanced cognitive performance (D'Amato et al., 2011).

Opposite effects on maternal care levels (i.e., reduced levels) are achieved by the limited nesting material model where mothers are provided with reduced nesting and bedding material from *pnd* 2—9 of their litter. This manipulation results in inconsistent and fragmented maternal care (Ivy et al., 2008), producing a continuously stressful environment for the offspring that is reflected in high basal CORT levels of the pups and long-lasting HPA-axis hyperactivity and cognitive impairment in hippocampal-dependent cognitive tasks (Rice et al., 2008).

2.2.3. Beyond maternal mediation

The maternal mediation hypothesis might not be the sole mechanism explaining the effects of early-life stress. Instead it is proposed that the combination of the extent of environmental adversity and the maternal repertoire determines the lasting alterations of the offspring's HPA-axis response (Macri and Wurbel, 2006; Tang et al., 2011). The pup's stress reactivity is proposed to be a function of the additive effects of the environmental stress and maternal care responsivity to environmental stress, acting as two independent factors (Macri and Wurbel, 2006; Tang et al., 2011). Thus, as noted above enhanced maternal care occurs in response to either maternal perception of environmental stress and demands (Beery and Francis, 2011) or the stress signals produced by the neonate after periods away from the mother (Hofer, 1996; Macri and Wurbel, 2006).

2.3. Long-term effects in non-human primates

Although there is considerable evidence for the enduring effects of stressful early experiences on HPA-axis physiology in adult rodents, surprisingly few studies have examined the outcome of similar early-life stress in adult monkeys. The vast majority of early stress paradigms in monkeys have focused on effects that persist only into late infancy. Nevertheless, data are available from several primate paradigms which have examined the persistent effects of early-life stress on HPA-axis physiology into adolescence and early adulthood. Some of these models are reviewed briefly below.

A primate model of early-life adversity similar to the rodent maternal separation paradigm is the parental deprivation model in common marmosets. This model is unique, because it involves both parents. Common marmoset social ecology is characterized by monogamous breeding pairs and intensive biparental care of young (Pryce, 1996). Infants are in constant (i.e., 24 h a day) contact with their parents throughout the first 2—3 weeks of life (Ingram, 1977; Pryce, 1993). To examine the consequences of early stressful experience, Pryce and colleagues exposed marmoset infants to daily parental separations on *pnds* 2—28 (Dettling et al., 2002). Each infant is exposed to a total of 9 h of social deprivation each week, with each session being variable in duration (30—120 min per session) and time of day, a feature implemented to increase stressor unpredictability. Control infants are briefly handled on their parents' backs daily during *pnds* 2—28. No baseline or stress-induced HPA-axis physiology data are available from this model, but repeated parental separations in monkeys have been shown to induce mild reductions in mineralocorticoid receptor (MR) and GR gene expression in the hippocampus (in CA 1—2 subfield) in late adolescence. These effects are specific to the hippocampus, as no differences in MR or GR gene expression were observed in the prefrontal cortex, other cortical areas, or the hypothalamus (Arabadzisz et al., 2010).

A different developmental outcome occurred in another New World monkey, the squirrel monkey, by using a brief intermittent maternal separation paradigm. This paradigm has been termed the "stress inoculation" protocol. Various separation protocols have been used. We summarize here the results of rearing experiments that occurred between 17 and 27 weeks of age for the offspring, a developmental period during which young monkeys are becoming independent from their mothers (Boinski and Fragaszy, 1989). In 1 h sessions of maternal separation which occurred every week for 10 weeks, the monkeys were maintained in a room different from their colony room, while the control monkeys remained in their home cages (Parker et al., 2004). The stress-inoculated monkeys were less anxious than the non-inoculated controls as appeared from a number of behavioral tests including increased food intake, decreased clinging to the mother and increased exploratory behavior. The stress-inoculated monkeys also displayed reduced stress-induced ACTH and cortisol responses as compared to controls. The findings are robust and replicated in other independent cohorts using slightly different stress inoculation protocols (Lyons et al., 1999, 2000; Levine and Mody, 2003).

Accordingly, inappropriate stress-induced activation of the infant primate HPA-axis does not necessarily lead to stress hyper-reactivity in adulthood, which is often considered a hallmark for psychopathology. Moreover, in view of the profound glucocorticoid resistance characteristic, the New World monkey's programming likely involves a mechanism distinct from that in the rodent (Parker et al., 2006).

2.4. Biological basis of early-life programming

Genetic variation in combination with external non-genetic factors has an effect on the regulation and expression of genes influencing protein functions. The biological basis of this is the epigenome. Epigenetics refers to the functionally relevant modifications of the genome that do not involve a change in nucleotide sequence. Such modifications include chemical marks that regulate the transcription of the genome (e.g., DNA-methylation, histone modifications and chromatin remodeling). There is now evidence that environmental events can directly modify the epigenetic state of the genome during sensitive developmental periods, but also — possibly to a lesser extent — in adulthood leading to changes in gene expression and neural function (Fagiolini et al., 2009). These studies define a biological interplay between environmental signals and the genome in the regulation of individual differences in behavior, cognition, and physiology. Some recent findings suggest the intriguing possibility that the epigenetic signature of the environment induced early in life or in adulthood may be transferred through generations (Franklin et al., 2010; Dietz et al., 2011; Rodgers et al., 2013), although the mechanism by which this may occur is unclear. Possible paths of transmission include environmental influences on gametes, gestational development, postnatal care and social context during development (Curley et al., 2009; Drake et al., 2011). Factors influencing environmentally induced transgenerational transmission of phenotypes can be the gender of the parent, the age of the parent at exposure, parental pathology or psychopathology induced by the exposure (Pembrey et al., 2006; Yehuda, 2011; Champagne, 2013).

The first example of epigenetic programming by early-life experience in the rodent was demonstrated in Long Evans rats by researchers in McGill University using the naturally occurring variations in the maternal care model. They proved that these variations in maternal care permanently affect the extent of hippocampal GR expression, through epigenetic changes occurring the first week of life. These changes involved DNA methylation changes in a GR promoter region (1_7 homolog of human 1F), where NGFI-A binds as transcription factor (Weaver et al., 2004). This lasting modulation of the GR has in turn consequences for HPA-axis activity later in life and reportedly appears linked to hyper-activity in case of the Low LG offspring and hypo-activity of the axis of the High LG offspring. This phenotype can be transmitted in a non-genomic way to the next generation (Liu et al., 1997; Francis et al., 1999). After this seminal example of epigenetic programming, more studies appeared using the various models of early-life adversity to study epigenetic programming of the HPA-axis including its afferent projections areas in hippocampus and prefrontal cortex. In Table 2, we summarize recent rodent literature on the topic. The last years the first monkey and human data on the topic appeared leading to more convergent conclusions on the interaction of early-life adversity with the glucocorticoid-related genes leading to epigenetic modifications observed in brain post-mortem and blood samples (Oberlander et al., 2008; McGowan et al., 2009; Perroud et al., 2011; Radtke et al., 2011; Provencal et al., 2012; Tyrka et al., 2012; Klengel et al., 2013).

Another recent development in the field was the evidence that these epigenetic marks of developmental programming can be modified in adulthood by stressful experiences. Chronic CORT exposure was able to decrease methylation in the intronic regions of the gene encoding FK506 binding protein 5 (FKBP5) in the brain and periphery. FKBP5 operates in an ultrashort negative feedback loop regulating of the GR responsiveness (Lee et al., 2010, 2011). Similarly, chronic, but not acute, restraint stress increased methylation of GR 1_7

Table 2 Evidence of epigenetic alterations of the HPA-axis in rodent models of early-life adversity.

Early-life stress paradigm	Species/strain	DNA methylation	References
Early handling (vs. non-handling)	Rat, Sprague Dawley	Hypothalamus: ↑*Crh*[a] gene promoter	Korosi et al. (2010) and McClelland et al. (2011)
Maternal separation (vs. non-handling or animal facility rearing)	Rat, Sprague Dawley	Hippocampus: not changed *Nr3c1* Exon 1_7 promoter	Daniels et al. (2009)
	Mouse, C57BL/6N	Parvocellular PVN: ↓*Avp* enhancer	Murgatroyd et al. (2009)
	Mouse, C57BL/6J	Hippocampus: ↑ *Avp* enhancer, not changed *Nr3c1* promoter, ↓ *Nr4a1* promoter	Kember et al. (2012)
	Mouse, DBA/2J	Hippocampus: ↑ *Avp* enhancer, ↑ *Nr3c1* promoter, not changed *Nr4a1* promoter	Kember et al. (2012)
Natural occurring variations of maternal care (low LG vs. high LG)	Rat, Long Evans	Hippocampus: ↑ *Nr3c1* Exon 1_7 promoter, ↑ *Pcdh* α, β, and γ gene families regulatory regions, ↑ *Grm1*	Weaver et al. (2004), Champagne et al. (2006), McGowan et al. (2011), Bagot et al. (2012b) and Suderman et al. (2012)
		MPOA: ↑*ER*α Exon 1b promoter	
Communal nesting (vs. standard nesting)	Mice, CD1	Hippocampus: Not changed *Bdnf* promoters 1, 4, 6 and 7 (but ↑ levels of the acetylated form of histone H3)	Branchi et al. (2011)
Limited access to nesting material (vs. non-handling)	Rat, Long Evans	PFC: ↑*Bdnf* (Exons 4 and 9 promoters)	Roth et al. (2009)

[a] *Abbreviations*: LG, licking & grooming; *Crh*, corticotropin-releasing hormone; *Nr3c1*, nuclear receptor subfamily 3, group C, member 1; i.e., glucocorticoid receptor; PVN, paraventricular nucleus of the hypothalamus; *Avp*, arginine vasopressin; *Nr4a1*, nuclear receptor subfamily 4, group A, member 1; i.e., Nerve Growth Factor IB; *Pcdh*, protocadherins; *Grm1*, glutamate receptor, metabotropic 1; MPOA, medial preoptic area of the hypothalamus; *ER*α, estrogen receptor α; PFC, prefrontal cortex; *Bdnf*, brain-derived neurotrophic factor.

promoter in the adrenal and pituitary (Witzmann et al., 2012).

2.5. Early-life stress and the development of fear aversion-learning

Besides the epigenetic modifications in the HPA-axis by early-life stress, recent findings suggest the involvement of amygdala-dependent fear-learning in early-life programming and ask for experiments on the epigenetic alterations within the amygdala subnuclei (Davidson and McEwen, 2012). Rat pups are dependent on maternal care for survival and, undergo under the age of *pnd* 10, a sensitive period of facilitated preference-learning to maternal odor. During this period, pups show an attenuated learning of fear. The absence of fear aversion-learning is crucial for forming dam-pup attachments (Sullivan and Holman, 2010). After *pnd* 10 (post-sensitive period), just a short-term maternal absence allows odor aversion-learning (Moriceau and Sullivan, 2006). Elevation of CORT levels is crucial for transition to aversion. CORT needs to activate the amygdala to prematurely trigger aversion to noxious stimuli (Moriceau et al., 2006).

In our studies the MS paradigm was combined with the ontogeny of the amygdala-dependent fear aversion-learning. Briefly, pups were at an age (*pnd* 3—5 during the SHRP) that permitted formation of memories only during long-term absence of the dam. After being separated from their mothers for the first time, pups experienced high amounts of CORT that permits priming of the amygdala. Yet, the outcome is profoundly diverging as a function of the MS-context. At *pnd* 5, HOME-SEP pups responded to a mild novelty stressor with an enhanced CORT response, since in this condition their adrenal cortex was primed for hyper-responsiveness. In contrast, NOVEL-SEP pups displayed enhanced amygdala c-Fos expression and increased ACTH-release in response to the same stressor, while they did not show a peripheral adrenocortical stress-response (Daskalakis et al., 2009a, 2011a; Daskalakis, 2011). In the NOVEL-SEP offspring, the relatively enhanced amygdala c-Fos activation and ACTH-release persisted into adulthood and were paralleled by higher retention of the freezing response (Daskalakis et al., 2009a, 2011a; Daskalakis, 2011), in agreement with studies linking early-life stressful experience with the adult fear-response through long-lasting changes in amygdala processing (Sevelinges et al., 2007, 2008).

Taken together, these findings suggest a modulation in programming of amygdala function through early-life stress, as previously reported in other stress-regulated brain regions. Amygdala programming seems to be context-specific, since the interaction of maternal absence with early-life context predicts the adult outcome rather than the maternal absence per se.

2.6. Maternal care and glucocorticoid regulation of hippocampal plasticity

In addition to effects on learning and memory, maternal care influences stress reactivity and HPA-axis. High levels of LG early in life associate with decreased stress responsivity in adulthood. Compared to the adult offspring of Low LG mothers, offspring of High LG mothers have lower plasma levels of ACTH and CORT both during and following the termination of acute restraint stress (Liu et al., 1997). Up-regulation of hippocampal GR expression in offspring of High LG mothers, in part, appears associated with enhanced negative feedback control (Liu et al., 1997; Francis et al., 1999; Weaver et al., 2004). Hippocampal control of stress-induced HPA-axis activity is mediated by stimulation of GR by CORT during stress-induced CORT elevations, although the outcome is disinhibitory rather than inhibitory raising the possibility of implication of other feedback sites as well (De Kloet et al., 1998; Furay et al., 2008). The central role of the hippocampus as target and regulator of the HPA-axis suggests that alterations of HPA-axis activity should have wide ranging consequences for hippocampal learning and plasticity. Indeed, brief CORT treatment suppresses LTP in the hippocampal CA1 (Champagne et al., 2008) and DG (Bagot et al., 2009) of High LG offspring. However, CORT facilitates LTP in Low LG offspring. Stress also enhances hippocampus-dependent learning in Low LG offspring in contextual fear-conditioning (Bagot et al., 2009). Thus the maternal effect on stress responsivity influences hippocampus-dependent learning and synaptic plasticity. The interaction between maternal care and CORT effects on hippocampal function may be mediated through effects on NMDA receptor function.

Although maternal care might be expected to differentially affect CORT-regulation of NMDAR function, the direction of such an effect is difficult to predict based on previous findings. Since High LG offspring are less stress responsive than Low LG offspring, one might expect CORT to exert a stronger impact on NMDAR in Low LG offspring. Alternatively, since High LG offspring express higher levels of GR in the hippocampus, and GR activation is necessary for CORT-induced enhancement of NMDAR function (Tse et al., 2011), CORT may more potently regulate NMDAR function in High LG offspring. In fact, the stress-level CORT (100 nM) significantly enhances NMDAR function in High LG offspring and increases the normalized NMDAR-fEPSP. In contrast, CORT treatment does not alter NMDAR-fEPSPs in Low LG offspring.

The mechanism underlying the loss of CORT-regulation of NMDAR in Low LG offspring is unclear. Since NMDAR function is maintained at a high and possibly saturated level in Low LG offspring in basal conditions, the capacity for further enhancement of NMDAR function after CORT treatment could be limited. Interestingly, the time-course of CORT-induced enhancement of NMDAR function (within 20 min) suggests that a classical genomic action requiring cytoplasmic corticosteroid receptors is not involved. Indeed a BSA-CORT conjugate replicates the effect of CORT, implicating the involvement of a membrane-bound corticosteroid receptor. Thus, similar to non-genomic effects of CORT in facilitating AMPAR (Karst et al., 2005) and LTP formation (Wiegert et al., 2006), CORT-induced facilitation of synaptic NMDAR in the adult hippocampus of High LG offspring is likely mediated by non-genomic mechanisms.

2.6.1. Functional implications

Offspring of Low LG rats is largely insensitive to the acute effects of CORT on NMDAR function. In contrast, in offspring of High LG mothers, CORT increases postsynaptic NMDAR current (Bagot et al., 2012a). This differential sensitivity is consistent with the maternal effect on HPA-axis negative feedback sensitivity (Liu et al., 1997). Thus, as a consequence of reduced glucocorticoid sensitivity, Low LG offspring is exposed to more sustained elevations of CORT; yet the acute effects of CORT exposure, at least in terms of NMDAR function, are attenuated. Altered HPA-axis negative feedback sensitivity is in part a consequence of epigenetic effects of maternal care on hippocampal GR expression. Maternal effects on sensitivity to rapid effects of CORT are likely independent of classical GR expression. Membrane-bound corticosteroid receptors might also be differentially regulated in High and Low LG offspring.

Glutamate receptors are gaining increased attention as therapeutic targets in depression research. The glutamatergic hypothesis of depression implicates NMDAR hyperfunction in the pathophysiology of the disorder (Pittenger et al., 2007; Skolnick et al., 2009). Expression of NMDARs is bidirectionally regulated by antidepressants and chronic-stress. Clinically, the NMDAR-antagonist ketamine alleviates symptoms of treatment-resistant depression after a single acute treatment (Berman et al., 2000; Zarate et al., 2006). NMDAR-antagonists also produce rapid antidepressant-like responses and reverse some of the behavioral and physiological consequences of chronic stress in rodent models of depression (Autry et al., 2011; Li et al., 2011). Moreover, chronic stress induces certain depression-like behaviors and sustained increases in NMDAR/AMPAR ratio in hippocampal neurons (Kole et al., 2002). This is similar to the basal profile observed in Low LG offspring. Low LG offspring exhibits phenotypes associated with vulnerability for depression, such as reduced glucocorticoid negative-feedback sensitivity and increased HPA-axis responses to stress as well as increased fearfulness (Liu et al., 1997; Caldji et al., 1998; Weaver et al., 2004) and increased immobility in the forced swim test (Weaver et al., 2005).

In conclusion, studies of Low LG offspring may have utility in uncovering endophenotypes that predict an increased risk for depression in humans. We suggest that variations in early-life environments might, in part, influence the risk for depression through effects on NMDAR function.

3. Gene—environment interaction studies in the human: Examples from the GR/MR genetic variation

There is convincing evidence that (traumatic) stress, especially during early-life, is a major risk factor for the development of almost all psychiatric disorders, including post-traumatic stress disorder (Bremner et al., 1993), major depressive disorder (Heim et al., 2008), and schizophrenia (van Os et al., 2010). However, despite decades of research, it is currently unknown which combination of stressful life events are the most etiologically relevant to predict the development of psychopathology and how stressful events interact at different periods of life.

In the literature, several hypotheses exist to explain the effect of variable outcomes after (repeated) exposure to traumatic events. Methodological limitations in the current literature preclude firm conclusions on the validity of these models for human psychopathology. For example, human studies generally have a retrospective methodological design. Also, the simultaneous retrospective assessment of adversity is subject to recall bias and cannot determine any causality or disentangle the temporal course of stressful experiences across the life span. Importantly, across studies, diverse phenomena have been defined to represent 'stress', ranging from prenatal adverse events, maternal psychopathology, infections during pregnancy, childhood abuse and neglect, a specific life event, and chronic perceived stress due to daily hassles. These events represent different aspects of stress but do not necessarily measure the same construct. A good example of the methodological issues surrounding stress assessment methods is the moderating effect of the serotonin transporter gene polymorphism (5-HTTLPR) on the relationship between stressful life events and depression (Caspi et al., 2010).

Another important factor in the assessment of adversity is the possibility that certain time windows of vulnerability exist in which traumatic and/or stressful experiences disproportionately affect at-risk individuals. Obviously, it is also of great importance to take personality characteristics, prior psychiatric symptoms, and coping mechanisms into account. Especially the role of personality traits is of importance in light of the existence of dependent stressful life events, i.e., events that are directly related to an individual's own behavior (Kendler et al., 1999).

Considerable inter-individual differences exist in outcomes after (repeated) adversity, and many individuals do not develop psychopathology (Southwick and Charney, 2012). The leading hypothesis is that stress exposure only affects individuals with a susceptible genetic background. Therefore, an individual's history of adversity should be interpreted in light of genetic predisposition. While multiple genetic factors are thought to be involved, the HPA-axis is pivotal in shaping dynamic stress reactivity. Indeed, exposure to adverse events across the life span has been commonly associated with abnormal basal and stress-induced HPA-axis activity, even though the developmental course of such changes has not yet been elucidated.

Several clinical gene—environment studies have shown that genetic variation in the HPA-axis moderates the long-term effects of stress, conferring either an adaptive advantage or a risk for psychiatric disorders. Corticosteroids bind to both GR and MR, regulating gene transcription and triggering a cascade of cellular and network changes in the brain underlying physiological and behavioral adaptations. Several gene—environment studies have been published on the GR (van Rossum et al., 2006; Bet et al., 2009), including a pivotal role for the GR-complex chaperone FKBP5 (Binder et al., 2008; Klengel et al., 2013). In contrast, the role of the MR has received less attention. MR play a critical role in stress appraisal (Oitzl and de Kloet, 1992), not only via the (classical) slow genomic pathway but also—as recently revealed - through rapid non-genomic effects which require elevated hormone levels (Karst et al., 2010). Since MR are closely involved in stress appraisal, several studies have put the MR rs5522/rs2070951 haplotype forward as a prominent and plausible player in stress research (Klok et al., 2011a, 2011b). Moreover, several seminal studies have shown that genetic variation in the CRHR1 receptor is involved in the subsequent development of depression (Bradley et al., 2008; Polanczyk et al., 2009) (see Binder and Nemeroff, 2010, for review).

To our knowledge, no studies have been published on the interaction between adversity across the entire life span and genetic variation in the HPA-axis. However, investigating biologically plausible genetic variation in HPA-axis activity may enhance our understanding of the large variation in outcomes after accumulating acute and chronic adversity. An important advantage of a comprehensive and integrated assessment of adversity across the life span is that the causal relation between proximal and more distal adverse events as well as their interaction may be studied. Also, multiple assessments across various stress domains may increase the validity and reliability of the impact of stress exposure compared to a single assessment.

Thus, we believe that assessment of an individual's life time adversity history should receive special consideration in future clinical studies. Such studies may eventually elucidate to what extent the accumulation of stress is context-dependent or whether cumulative stress exposure has negative long-term consequences in the context of both psychiatric and somatic disorders. Instead of focusing on a single stress domain, a comprehensive measure of stressful experiences in conjunction with the genetic background may lead to a fundamentally new way of understanding the variable outcomes after (repeated) traumatic stress. The study of individual developmental trajectories which are uniquely shaped by the environment may ultimately lead to the identification who is and who is not at risk for psychiatric disorders. In conclusion, individuals with a particular genetic variation in the HPA-axis may be associated with certain specific developmental trajectories in terms of psychopathology in response to accumulating environmental stress.

4. The three-hit concept of resilience and vulnerability

The previous sections did highlight that adversity is often found associated with psychopathology. Accordingly, in studies on the cumulative stress model (the ''classic'' diathesis-stress model) it is postulated that if the accumulation of stressors across the life span exceeds a certain threshold, the development of psychopathology is enhanced in at-risk individuals (McEwen, 1998). Alternatively, in an evolutionary perspective, early-life experience could induce (epigenetic) changes underlying predictive adaptive responses (Gluckman et al., 2009). In this view plasticity evolved to match an organism to its predicted environment. Hence, a mismatch between the phenotypic outcome of adaptive plasticity and the ability to cope with the current environmental experience is thought to increase the risk of disease (i.e., developmental match/mismatch hypothesis).

A major differentiating factor between the cumulative stress model and the match/mismatch model is the possible adaptive value of experienced early-life adversity. Whereas the cumulative model asserts that the extent of cumulative adversity does generally not have any advantageous effect

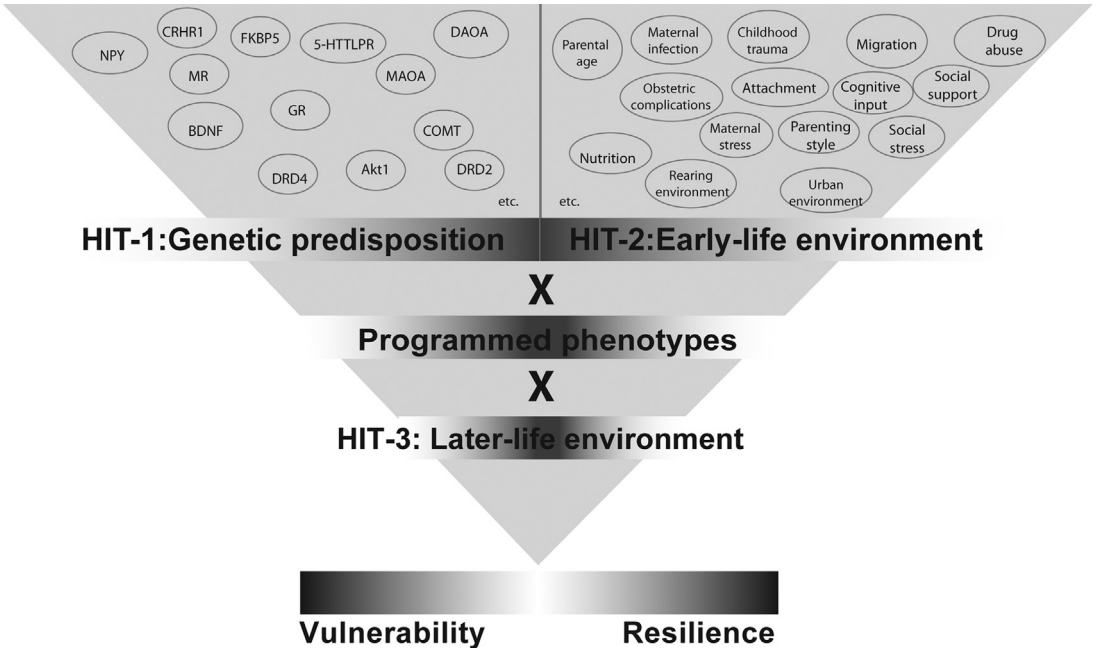

Figure 2 The three-hit concept of vulnerability and resilience. Multi-genic inputs (hit-1) interact with early-life environmental inputs and experience-related factors (hit-2), programming phenotypes with differential susceptibility to later-life challenges (hit-3). Depending on the interaction of "programmed phenotypes" with later-life environment vulnerability or resilience may precipitate. *Abbreviations*: *5-HTTLPR*, serotonin-transporter-linked polymorphic region; *Akt1*, RAC-alpha serine/threonine-protein kinase; *BDNF*, brain-derived neurotrophic factor; *COMT*, catechol-*O*-methyltransferase; CRHR1, corticotropin releasing hormone receptor 1; *DAOA*, D-amino acid oxidase activator; *DRD2*, dopamine receptor D_2; *DRD4*, dopamine receptor D_4; *FKBP5*, FK506 binding protein 5; *GR*, glucocorticoid receptor; *MAOA*, monoamine oxidase A; *MR*, mineralocorticoid receptor; *NPY*, neuropeptide Y.

but progressively increases disease risk, the mismatch model explicitly assumes that adverse events during development may constitute a possible source of adaptation for certain individuals. In this context, exposure to a challenging, but still moderate stressful environment which promotes active coping ("stress inoculation") should be distinguished from severe physical and sexual abuse. Early exposure to severe stress in childhood increases the incidence of mood and anxiety disorders in adulthood. Moderate early stress exposure results in subsequent resilience rather than enhanced vulnerability.

Consistent with this view is also the differential susceptibility to environmental influence ("for-better-and-for-worse") model, which assumes that genetic susceptibility should be contextually interpreted: vulnerability in one environment may actually constitute an adaptive benefit in another environment (Belsky and Beaver, 2011). Individuals with reactive (to the environment) alleles are expected to display heightened susceptibility to environmental influences for better or worse. Hence in a stressful environment these reactive alleles will increase on the one hand the risk for disease in an adverse context, but also increase sensitivity to beneficial effects of the environment on the other hand. Individuals with less reactive alleles will be less susceptible to environmental influence (Belsky, 1997; Boyce and Ellis, 2005; Bakermans-Kranenburg and van Ijzendoorn, 2007; Belsky et al., 2007, 2009; Ellis et al., 2011).

Attempts to reconcile the different models were proposed from the perspective of individual differences in programming sensitivity (Nederhof and Schmidt, 2012), which is most likely defined by the interaction of genetic predisposition and early-life environment. For gathering experimental evidence supporting this concept's face, predictive and construct validity, the three-hit concept of vulnerability and resilience offers a testable framework. This concept is depicted in Fig. 2 and can be formulated as follows: the interaction of genetic factors (hit-1) with early-life environmental factors (hit-2), as reflected in altered endocrine regulations and epigenetic modifications, programs during brain development gene expression patterns relevant for an evolving phenotype. A certain programmed phenotype when exposed to a later-life environment (hit-3) mental functions may become compromised and a higher risk of psychiatric symptoms may arise (vulnerability), but when exposed to another type of environment the same individual is expected to be resistant to mental dysfunction (resilience).

This contribution on adaptation to early-life adversity outcome documents progress at the verge of a new era, where complex interactions of genes with the environment will be tested in animals carrying inducible, brain site-specific or even brain cell-specific, gene modifications. Natural variation in genetic make-up can be also be used for this purpose, as is the case for the apomorphine-susceptible (APO-SUS) rat line (Ellenbroek et al., 2000; Ellenbroek and Cools, 2002; Daskalakis, 2011; Daskalakis et al., 2011b). These studies suggest that in the APO-SUS rat line, selected for enhanced dopamine responsiveness, a severe behavioral disruption precipitates upon a combined exposure to early-life adversity and peri-pubertal social isolation that allows discriminating between gene—environment conditions

programming resilience vs. vulnerability. CORT, and the HPA-axis, are in the driver's seat playing a key role in early programming effects, and are important determinants of the functional and structural plasticity underlying the adaptations to early-life adversity. These findings underscore the amazing plasticity of the brain; after all as the late Seymour Levine used to say "*nothing is written in stone*".

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