Acta Neuropsychiatrica
An International Journal of Translational Neuropsychiatry

Acta Neuropsychiatrica 2012: 24: 255–265

DOI: 10.1111/j.1601-5215.2012.00683.x

ACTA NEUROPSYCHIATRICA

Review article

Epigenetic alterations related to early-life stressful events

Ventura-Junca, R, Herrera, LM. Epigenetic alterations related to early-life stressful events.

Objective: Early stress events severely impact brain and behaviour. From a neurobiological point of view early stress influences neuroanatomical structures and is associated with a dysregulation of the hypothalamic-pituitary-adrenal axis. The objective of this article is to review the epigenetic alterations implicated in brain adaptation to early stress events.
Method: A review of empirical research of epigenetic alterations associated to early stress events was performed.
Results: Neuroanatomic and epigenetic alterations have been observed after early stress events. Epigenetics alterations include DNA methylation, histones modifications and microRNA (miRNA) expression. The most studied is largely the former, affecting genes involved in neuroendocrine, neurotransmission and neuroplasticity regulation after early stress exposition. It includes glucocorticoid receptor, FK506-binding protein 5, arginine vasopressin, oestrogen receptor alpha, 5-hydroxy-tryptamine transporter and brain-derived neurotrophic factor.
Conclusion: Epigenetic regulation is critical in the interplay between nature and nurture. Alterations in the DNA methylation as well as histones modifications and miRNA expression patterns could explain abnormal behaviours secondary to early stress events.

Raúl Ventura-Junca[1,2], Luisa M. Herrera[2]

[1]School of Psychology, Universidad de los Andes, Santiago, Chile; and [2]Human Genetics Program, Faculty of Medicine, Institute of Biomedical Sciences, Universidad de Chile, Santiago, Chile

Keywords: behaviour; early stress; epigenetic; HPA; methylation

Luisa Herrera, Programa de Genética Humana, ICBM, Facultad de Medicina, Universidad de Chile, Independencia 1027, Independencia, Santiago, Chile.
Tel: 562 9786976;
Fax: 562 7373158;
E-mail: lherrera@med.uchile.cl

Accepted for publication July 12, 2012

Summations

- The exposure to stressful situations early in life is associated with an increased susceptibility to develop both physical and mental illnesses.
- Early stress has been consistently related to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis.
- Epigenetic alterations after early stress exposition include DNA methylation, histone modifications and miRNA expression changes.
- Alterations in methylation and expression levels of genes involved in the neuroendocrine system, serotonergic neurotransmission and neuroplasticity have been found secondary to early stress exposure.

Considerations

- To date, few studies relating epigenetic alterations after early stress exposition have been carried out in humans. Results from animal studies cannot be extrapolated to humans.
- It is possible that a larger number of genes modulates behaviour through epigenetic mechanisms.

Introduction

Early stressful life events (ESLE) have been related to physical and mental health disorders in adults (1,2). These adverse events during childhood include interpersonal losses, violence, neglect, parental divorce and sexual abuse, among others (3); domestic violence and parental divorce are the most common (3). The mental disorders associated with ESLE include depression, increased impulsivity and higher suicide risk. These disorders usually begin during childhood or adolescence, although many of them persist until adulthood (3–7). Additionally, other clinical consequences such as early menarche and sexual risk behaviours in adolescence have been related to preschool anomalous maternal care, such as harshness (8).

From the psychological point of view, the high prevalence of psychiatric disorders has been related to the fact that adverse childhood events are associated with poorer mental representation of self-concept, for example 'I'm not valuable', and with arbitrary negative inferences, such as 'I will be criticised' (4,9).

The prevalence of ESLE varies from one country to another, but it is estimated that at least half of the population has suffered one or more of these events in their early years. According to the World Health Organization (WHO) approximately 20% of women and 5–10% of men report being sexually abused in childhood, while 25–50% of all children report being physically abused (10). Also, many children have suffered emotional abuse (sometimes referred to as psychological abuse) and neglect.

Neuroanatomy and early-life stressful experiences

Consistent with previous clinical data, neuroanatomical studies have described that early stress is associated with alterations of some brain regions, such as the hippocampus and prefrontal cortex (PFC) among others. The hippocampus is involved in learning, memory and negative feedback of stress hormone secretions (11). It has connections with the amygdale and PFC, regions involved in emotions and cognition; thus alteration in these neurocircuits could account for the symptoms observed in mood and anxiety disorders (11). Reductions in the hippocampal volume have been observed in patients with major depressive disorder and post-traumatic stress disorder (PTSD), especially in adults with history of ESLE (12–14), and in personality disorders with history of child abuse (15). This hippocampal reduction is due to chronic stimulation of the hippocampal glucocorticoid receptors (GR) by circulating glucocorticoids (GC) (16). Chronic stress reduces hippocampal dendritic branching (17–19). Similarly, chronic stress also reduces medial PFC dendritic branching (17–19). In the amygdale the effect is opposite, with increased dendritic branching resulting in stimulus hyperreactivity (20,21). These changes may generate abnormal neurocircuitry, contributing to the development of mood and anxiety disorders. Also, a loss of the asymmetry of the hippocampus – the left side is normally larger than the right one – has been observed in individuals with PTSD (22). The size of the hippocampus correlates with the level of self-esteem and the internal locus of control, i.e. the ability to control events that occur to a person. Accordingly, the cortisol response to a stressor is lower at higher levels of self-esteem and internal locus of control (23). On the other hand, prolonged use of steroids has also been associated with hippocampal reduction (24). Finally, some studies have shown changes in total brain volume in patients with early trauma and PTSD; this effect is more pronounced in women (25).

Early stress effects on the HPA axis activity

The HPA axis displays a circadian rhythm that controls the secretion of adrenal corticoids. This system is activated by internal and external stimuli such as physical and psychological stressors (26). The activity of the HPA axis begins with the secretion of corticotropin-releasing hormone (CRH) from CRHergic neurons, located in the paraventricular nucleus (PVN) of the hypothalamus. Arginine vasopressin (AVP), also secreted by PVN, acts synergistically with CRH to stimulate the secretion of adrenocorticotropin (ACTH) from the pituitary (27,28). The activity of these neurons is regulated by excitatory afferents from the amygdale and inhibitory from the hippocampus (11). ACTH, in turn, stimulates the adrenal cortex to synthesise and secrete GC, the key mediator of the stress response. GC exerts its effects on a wide variety of physiological processes for adaptation to stress; activation of the sympathetic system, deactivation of the parasympathetic, adjustments of metabolism and regulation of the immune response. Finally, the activation of the HPA axis is normally counteracted by negative feedback regulation of the GC at the hypothalamic, pituitary and hippocampal levels (29,30). CRH, along with AVP, mediates the HPA axis regulation in response to acute and chronic stress. Alterations of normal HPA axis functioning have been observed in some mental disorders such as PTSD and depression, especially when there are histories of ESLE (31–34), with an altered synthesis and release of GC (35). Intriguingly, patients with PTSD exhibit alterations in the HPA axis, with both increased (36) and reduced cortisol levels compared to control groups (37). Also, depressed patients

https://doi.org/10.1111/j.1601-5215.2012.00683.x Published online by Cambridge University Press

exhibit higher basal plasma levels of cortisol than healthy controls, most of whom normalise cortisol rhythm after antidepressant treatment (38). Accordingly, experiments of early exposure to stress carried out in rhesus monkeys showed augmented cortisol responses to mild stressors in adulthood (39). This effect is explained by a reduction in the hippocampal expression of GR (40). Moreover, studies performed with the dexamethasone (DEX)/CRH test, a sensitive evaluation test for HPA axis hyperactivity, showed increased responsiveness in depressed patients with a history of stressful life events compared to controls (32). In animal models, mineralocorticoid receptors (MR) and GR expression levels and functioning have been observed to be altered under stress (41), affecting neurobiology and behaviour. For instance, stress during early development in marmoset monkeys leads to long-term reduction in MR and GR levels, which is associated to stress-related behaviour in adults (42,43). The hippocampal volume reduction described above is mediated by the sustained GC levels and is associated with a reduction in adhesion molecules. This affects the functionality of the synapse and neural architecture, leading to neuronal loss and consequently to hippocampal atrophy (29). This evidence supports the central role of HPA axis dysregulation in developing some mental disorders and their relation with ESLE.

Epigenetic mechanisms of gene expression regulation

The mechanisms of epigenetic regulation are of particular interest in the study of interaction between genetic backgrounds and environmental conditions, as they provide the means by which the latter factor may affect gene expression. Epigenetics refers to heritable and functionally important modifications of chromatin that affect phenotypes without alterations in the DNA sequence (44). Epigenetic mechanisms include DNA methylation, histone modifications, chromatin remodelling and regulation by non-coding RNA (ncRNA), all of which influence chromatin structure and gene expression.

DNA methylation consists of the addition of a methyl group to position 5 of some cytosine nucleotides, predominantly at the CpG dinucleotides. This contributes to chromatin condensation and consequently to gene transcription inhibition (45). DNA methylation is a modification heritable through mitosis and stable over time, although they can change when cells differentiate or are under environmental influences. The enzymes responsible for catalysing the methylations are a family of DNA methyl-transferases (DNMT) (46,47). Conversely, no enzymes responsible for DNA demethylation have been described yet, although it is known that there is active demethylation (48). Once the DNA is methylated the chromatin silencing occurs by alteration of the structure of nucleosomes, interference by the methyl group in the binding of transcription factor or by recruiting proteins that bind methylated cytosines, such as methyl cytosine-binding domain proteins (MECP2, MBD1, MBD2, MBD3 and MBD4) and proteins of the Kaiso family (46). These proteins in turn recruit the enzymatic machinery necessary to establish silent chromatin, such as histone deacetylases (49).

On the other hand, the epigenetic regulation by histone modifications consists in differential covalent modifications of histones, including acetylation, methylation, phosphorylation, ubiquitination, sumoylation, ADP-ribosylation and biotinylation. Acetylation and methylation are the most studied (50). These changes are 'written' or 'erased' by histone-modifying enzymes, such as histone acetyltransferases (HAT), that acetylate lysine residues of histones; histone kinases that phosphorylate serine, threonine and tyrosine; and histone methyl transferases (50). Combinations of histone modifications and the positions of these modifications determine different accessibilities for transcription factors to the DNA and consequently define the gene expression profiles. This is currently known as the histone code hypothesis (51). The histone modifications participate in the gene expression regulation through two main mechanisms: by controlling the chromatin structure and therefore the accessibility to the DNA, and by the binding of effector molecules (50). For instance, it has been postulated that acetylation reduces the strength of the interaction between the DNA and the histones, through the reduction of positive charges of the lysines. This would loosen up chromatin conformation and therefore facilitates the access of the transcriptional machinery. On the other hand, many proteins that bind to chromatin by recognising modified histones have been identified, including proteins that promote chromatin condensation (HP1, heterochromatin protein 1) and chromatin remodelling complexes (50,52).

These histone modifications occur in concert with DNA methylation either activating or repressing the chromatin (reviewed in 47). For instance, the methyl cytosine-binding protein, MeCP2, binds to methylated cytosines and in turn recruits HDACs that collaborate in the chromatin inactivation by histone deacetylation.

In the regulation of gene expression, different types of chromatin remodelling complexes collaborate by controlling the chromatin packaging in the eukaryotic cell nucleus and consequently the access to the DNA by regulatory proteins (53). The remodelling complexes are multiproteic structures

https://doi.org/10.1111/j.1601-5215.2012.00683.x Published online by Cambridge University Press

that alter the conformation of chromatin by mobilisation, removal or assembly of nucleosomes (52,54). The chromatin conformation alteration promotes or interferes with the interaction between DNA and transcriptional regulatory factors and determines the conformation of active or silent chromatin states (55). For chromatin remodelling, both energy (ATP) and changes in the composition of the nucleosome are required. The chromatin remodelling also occurs in concert with histone modifications. For instance, bromodomain-containing proteins (such as Brg and the BAF180 subunit of SWI/SNF) are recruited by acetylated histone residues and may be involved in chromatin relaxation at these sites favouring transcriptional activation (52).

Finally, ncRNA represent a group of non-translated RNAs, including microRNAs (miRNAs), small nucleolar RNAs (snoRNAs), small interfering RNAs (siRNAs) and PIWI-interacting RNAs. They are involved in gene expression control at different levels, ranging from the DNA methylation, chromatin remodelling, control of the stability of other RNAs and processing and translation of the mRNA (56). For instance, the long non-coding RNAs (lncRNAs) trigger epigenetic modifications that maintain specific states of inheritable chromatin (56). These lncRNAs act by coating regions of the chromatin and recruiting remodelling complexes, which in turn promote some histone modifications that establish gene repression-specific patterns (57–59). On the other hand, miRNAs (60) act by pairing with specific mRNA to whom they exhibit complementarity, and silence gene expression likely by induction of degradation or downregulating their translation (61). They participate in the regulation of gene expression of large networks and are very much involved in animal development, such as differentiation, maintenance and neuronal plasticity (62).

Epigenetic regulation in health and disease: histone modification and DNA methylation

As the epigenetic programming affects gene expression, epigenetic alterations may have significant consequences, affecting diverse human traits such as metabolic, immunological and behavioural traits (63). Furthermore, it has been shown that possession of genetic risk factors does not necessarily result in the development of a disorder, suggesting that environmental factors may also be involved (64). Therefore, something in addition to the DNA sequence such as epigenetic alterations may be responsible for the development of complex diseases, stressing the relevance of understanding the genome-environment interplay.

It has been described that some environmental effects on behaviour are mediated by epigenetic alterations (1,2). These effects could become more significant over a longer time span and greater frequency and magnitude of exposure to the external conditions (65–67). Moreover, earlier life events can have long-lasting effects on epigenetic programming (68–70) and some epigenetic alterations can last potentially during the whole life span or, outstandingly, be transmitted across generations (63,71–74).

During the last decade a growing number of articles exploring the relationship between ELSE, adult psychopathology and epigenetic alterations have been published (2–6,8,63,68,75–77). Although DNA methylation is the epigenetic alteration most investigated, histone modification and miRNA expression have also been explored. For instance, in a model of maternal separation, a reduction in mRNA expression of the Histone Deacetylases (HDAC) 1, 3, 7, 8 and 10, accompanied by increased acetylation in lysine 12 of histone H4 in the adult and adolescent forebrain neocortex was observed (78). Interestingly, the reversion of H4K12 acetylation worsened the abnormal emotive phenotype elicited by ELSE. This phenotype is characterised by increased anxiety and depressive-like behaviours. Conversely, the potentiation of histone modification improves the antidepressant action. This implies that histone regulation seems to be an adaptive strategy that allows the individual to better deal with ELSE, specifically maternal separation.

Additionally, it has been described that the expression levels of a number of miRNA is altered after early stress exposition – maternal separation during 180 min a day between day 2 to 14 – in the medial prefrontal cortex. This alteration is dependant of the transcriptional regulator REST-4 (77). For instance, the miRNAs 132 and 212 (miR132 and miR212) expression levels were augmented immediately after the stressful situation (day 14) and also in adulthood. These two miRNAs, miR132 and miR212, are involved in the modulation of synaptic plasticity (79).

In the same way, changes in the patterns of DNA methylation have been described after exposure to early stressors, triggering HPA axis dysregulation and neurochemical and neuroanatomical alterations (80). Thus epigenetic alterations in genes related to these functions may be potentially involved in the susceptibility to develop diseases.

DNA methylation and dysregulation of the HPA axis

To reveal the mechanism involved in the HPA axis dysregulation, various animal models have been studied. For instance, in rhesus monkeys maternal abuse determines abusive parenting behaviour in the offspring. Strikingly, cross-fostering of infants

https://doi.org/10.1111/j.1601-5215.2012.00683.x Published online by Cambridge University Press

between abusive and non-abusive mothers reverses the effects in the offspring, supporting that this behaviour is mostly determined by the early environment (81). Weaver observed similar behaviour in rats. He reported that high-maternal care behaviour during the early postnatal period, consisting of licking, grooming and arched back nursing (LG-ABN), is transmitted to the next generation (75). In contrast, the offspring of low-care mothers exhibited fearful behaviour, high reactivity of the HPA axis and reproduced the same maternal behaviour in adulthood. Again, when the offspring of low- and high-care mothers were cross-fostered, the offspring replicate the adoptive mother's behaviour. These results are consistent with environmentally rather than genetically controlled behaviour. Weaver also showed that this programming of behaviour is determined during the first week of life, and depends on GR gene epigenetic modifications (82,83). The differences in rat behaviour mentioned above were produced by early hypermethylation of the GR gene (>80%), specifically in the exon 1_7 GR promoter region of the offspring of low maternal care mothers. The hypermethylation reduces GR mRNA levels in the hippocampus, preventing the proper negative feedback of the HPA axis (75,84). Accordingly, higher and sustained levels of corticosterone were observed, explaining the persistence of the low maternal care behaviour in the next generation. This methylation alteration, subsequent to low care, has critical and lasting effects on the stress responsiveness of offspring (73). On the contrary, in the high caring rats the offspring exhibited neither fearful behaviour nor alterations in HPA axis reactivity, and the GR exon 1_7 was rarely methylated (85). DNA methylation attracts proteins that bind methylated cytosines and HDAC which deacetylate histones, helping to keep the DNA tightly packed (86). Trichostatin A inhibits the histone deacetylation, which in turn favour the DNA demethylation. The trichostatin A treatment of mature low-care animals resulted in higher GR expression and reduced HPA response to stress, supporting that hypermethylation is the intermediary between maternal care and stress reactivity (75). This is in accordance with the GR reduction observed in marmoset monkeys after early stress (42,43). A reduction in the binding of the nerve growth factor inducible (NGFI)-A transcription factor to the GR promoter along with GR gene hypermethylation was observed in low-care rats (85). In humans, few similar studies have been carried out. However, in a postmortem study, the methylation levels in the GR gene were higher in subjects who died by suicide than in those who died in accident. Moreover, higher rates of methylation were present in individuals with a history of abuse/neglect, which is consistent with the results observed in animal models (87). Conversely, no changes in the methylation levels of exon 1_F, the human equivalent of the rat exon 1_7 GR promoter, were observed in a postmortem study carried out in subjects with history of depression but without history of abuse. However, a reduction in the transcript carrying the 1_F first alternative exon was observed, which could be explained by a reduction in NGFI-A transcription factor levels in the hippocampus (88). This data also suggest that as well as methylation, the NGF1A transcription factor could be related to the epigenetic regulation of GR.

Other epigenetic alterations have been observed in genes involved in stress response, neurotransmission and neuroplasticity, including FK506-binding protein 5 (FKBP5), arginine vasopressin (AVP), oestrogen receptor alpha (ERα), 5-hydroxy-tryptamine transporter (5HTT) and brain-derived neurotrophic factor (BDNF).

The FK506-binding protein 5 (FKBP5) is a co-chaperone that modulates the activity of GC, making it especially important in stress-response regulation. The relevance of FKBP5 in the development of mental disorders including mood disorders and PTSD with child abuse has been acknowledged through several genetic association studies (89–91). Indeed, FKBP5 genetic polymorphisms have been associated with suicide risk (92,93), insecure-resistant attachment (94) and behavioural traits known as higher harm avoidance in women and less cooperativeness in men (95). Some of the genetic variations have been also related to altered sensitivity to cortisol and to FKBP5 protein expression, affecting the HPA axis response (96). Similarly, mice lacking the FKBP5 coding gene are less vulnerable to the adverse effects of 3 weeks of chronic social defeat stress, probably due to an increased GR sensitivity increasing the feedback regulation of HPA (96). On the contrary, mice exposed to high doses of corticosterone exhibited reduced methylation levels in two CpG islands of intron 1 of the FKBP5 gene in both hippocampus and hypothalamus, with elevation in FKBP5 expression (97). Thus, FKBP5 protein interferes with GR activity mediating corticosterone action over the feedback regulation of HPA. This data suggest that epigenetic regulation of this gene could be involved in the behavioural stress response.

Similarly, epigenetic regulation in response to early environmental influences of the arginine vasopressin gene – the modulator of CRH actions over HPA axis – has been described. An early-life stress model in mice (periodic infant-mother separation during early postnatal life) exhibited a reduction in the methylation levels of the AVP enhancer in the PVN (98). This is important, since ACTH secretion by the pituitary is synergistically

https://doi.org/10.1111/j.1601-5215.2012.00683.x Published online by Cambridge University Press

regulated by the CRH and AVP neuropeptides (27,28). This reduction in methylation correlates with sustained AVP expression and augmented HPA axis activity, prompting the long-lasting endocrine and behavioural alterations observed until adulthood (98). In addition, early-life stress model in mice has shown behavioural alterations such as reduced stress-coping ability and memory deficits, and features frequently observed in depression and PTSD (99,100). Accordingly, treatment with SSR149415, antagonist of the AVPV1b receptor, reversed the mice's increased stress responses and impaired memory, indicating that the augmented AVP level is responsible, at least in part, for the early-life stress phenotype (98).

Oestrogen receptor

Oestrogens, through the coordination of the neuroendocrine system, exert diverse actions on sexual development, sexual behaviour and reproduction. In addition, in the brain they contribute to other functions such as learning, memory and emotions, and also have neurotrophic and neuroprotective properties. These oestrogen actions are mediated by two intracellular receptors; alpha (ERα) and beta (ERβ) (101). These receptors are expressed in different tissues including several brain regions. The ERα is expressed only in the ventromedial nucleus of the hypothalamus and subfornix, whereas ERβ is widely expressed in the brain. They are co-expressed in the arcuate nucleus and hippocampus, but in the latter the levels of ERβ are higher (102). In animal studies it has been shown that agonists of ERα are anxiogenic, while ERβ agonists are anxiolytic (102). On the other hand, it has been suggested that oestrogen may regulate the HPA axis through the control of CRH expression (103). The clinical importance of oestrogens in stress response has been evaluated in the study of differences in response to stress by gender. For instance, women in the follicular phase or women who use contraceptives have lower levels of free cortisol under stress compared with men or with women in the luteal phase (104,105).

As previously described, rats exposed to low-care rearing reproduce the mother's conduct in terms of mothering, early menarche and sexual behaviour. At the molecular level, an increased methylation of the ERα gene in the low-care rats leads to a reduction in the oxytocin receptor levels. As a consequence during adulthood a reduction in responsiveness to oxytocin released in the postpartum has been described, altering mothering behaviour (106). This methylation is due to the low caring behaviours in the mother, expressed as less licking and arching back nursing for breast feeding (106).

5-Hydroxy-tryptamine transporter

5HTT mediates the reuptake of serotonin (5HT) into the presynaptic cell, terminating the action of this neurotransmitter. It is inhibited by various antidepressants with a consequent increase of 5HT in the synaptic cleft. Many associated studies have related this gene to several mental disorders including anxiety, depression and suicide risk, particularly in individuals with ESLE (107–112).

Accordingly, studies carried out in lymphoblast cells have shown epigenetic alterations in the 5HTT gene. Specifically, a CpG island located in an alternative first exon is regulated by methylation, generating reduced mRNA levels when it is methylated (113). Moreover, environmental trauma modulates the effects of genetic polymorphisms through alterations of methylation levels in the transporter. Thus in patients, high methylation levels have been related to the severity of unresolved trauma (114). In agreement, secure attachment ameliorates the effect of the genetic polymorphisms in relation to self regulation in human infants at 25, 38 and 52 months of age (115). Additionally, early exposure to maternal depression is related to alterations of epigenetic programming in the umbilical cord leukocytes of newborn infants and consequently affects HPA stress reactivity three months after birth (116,117). The latter evidence supports a transgenerational maternal effect in the epigenetic signatures, and supports the possibility of detection of epigenetic alterations in peripheral blood.

Neuroplasticity, BDNF and epigenetic alterations

The neurotrophin BDNF performs multiple functions in the central nervous system, from neuroplasticity to regulating mood, behaviour and stress response (118). BDNF has been associated with mental illnesses such as depression and anxiety disorder, among others (119,120). For instance, low serum BDNF levels have been observed in depressive patients without pharmacological treatment, which correlated with the severity of depression (121). Accordingly, antidepressant treatment increases serum BDNF levels of depressed patients (122). In animal models, the rise of corticoids induced by stress leads to a loss of cognitive abilities and to a reduction of the apical dendrites of pyramidal neurons of the CA3 region of the hippocampus, an effect related to reduction of BDNF expression (123–125). Interestingly, BDNF knockdown mice in the dorsal dentate gyrus exhibit depressive-like behaviours (126) and BDNF overexpression in the hippocampus elevates the resilience to stress (127). BDNF, like other neurotrophic factors, increases neuronal survival through negative regulation of

https://doi.org/10.1111/j.1601-5215.2012.00683.x Published online by Cambridge University Press

apoptotic cascades (128,129). These actions are exerted in part by regulation of the expression of BDNF itself (130).

Early stress (abuse and neglect) has been related to alterations in the BDNF gene methylation levels in animal models. For instance, rats exposed to abusive caregivers during the first 7 days of life (30 min daily) exhibited reductions in BDNF levels, with elevated methylation levels in PFC. Moreover, this change has been reported to be transmitted to the next generation (131,132). Also, in a fear, learning model changes in hippocampal pattern of methylation of the BDNF gene have been observed (133). This alteration correlates with different mRNA levels. This evidence supports the importance of the methylation of the BDNF gene in normal and altered functioning of this system. Similar results have been observed in response to environmental influences such as early social experiences, with reduced and long-lasting hippocampus and PFC mRNA and protein levels (131,134–136).

Conclusions

Early environmental conditions configure the epigenetic state adapted to the context. For instance, differences in maternal care of LG-ABN rats depend on environmental circumstances. In the face of danger the low-caring mothers 'prepare' their kin to a harsh environment through epigenetic alterations, shaping their brain and other organs to achieve more adaptive behaviours such as defensive and reproductive strategies to survive. As a result of this adaptive situation, offspring tend to be more promiscuous, favouring larger progeny. Also, the offspring show less explorative behaviour and greater resistance to infections and starving (137). These features result in improved fitness under adverse conditions. By extension, it may be hypothesised that in humans the emotional architecture is an adaptation to the closer context that includes parents-infant attachment style, family group constitution, socioeconomic status, political conditions, etc. that interact with genetic predispositions. This genetic and environmental interaction programs a profile of adjusted responses to the demands of the environment. Consequently, impulsivity or an elevated startle reaction may be an adaptive strategy developed in a dangerous context such as a dysfunctional family (aggressive, abusive, violent, etc.). However, this behaviour could be maladaptive in a safe context where children do not feel in danger. Accordingly, indiscriminate attachment behaviour in foster care children could also be considered as an adaptive strategy, where children crave for protection (138). In biological terms, it can be hypothesised that this behaviour may be epigenetically controlled.

Epigenetic alteration is an excellent mechanism for controlling this behaviour, because it is a mechanism that could regulate gene expression and could be affected by the environment. Also it has been shown that it may be heritable across generations, although in absence of the stimuli the epigenetic alterations fade over generations (139).

Acknowledgements

This research was supported by grant FAI-7, 2011, Universidad de los Andes, Chile and Fondecyt 1090219. We also thank Dr. Lafayette Eaton for revising the English. The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

1. Ramiro LS, Madrid BJ, Brown DW. Adverse childhood experiences (ACE) and health-risk behaviors among adults in a developing country setting. Child Abuse Negl 2010;**34**:842–855.
2. Van Der Vegt EJ, Tieman W, Van Der Ende J, Ferdinand RF, Verhulst FC, Tiemeier H. Impact of early childhood adversities on adult psychiatric disorders: a study of international adoptees. Soc Psychiatry Psychiatr Epidemiol 2009;**44**:724–731.
3. Mclaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM, Kessler RC. Childhood adversities and adult psychopathology in the National Comorbidity Survey Replication (NCS-R) III: associations with functional impairment related to DSM-IV disorders. Psychol Med 2010;**40**:847–859.
4. Alloy LB, Abramson LY, Smith JM, Gibb BE, Neeren AM. Role of parenting and maltreatment histories in unipolar and bipolar mood disorders: mediation by cognitive vulnerability to depression. Clin Child Fam Psychol Rev 2006;**9**:23–64.
5. Kessler RC, Davis CG, Kendler KS. Childhood adversity and adult psychiatric disorder in the US National Comorbidity Survey. Psychol Med 1997;**27**:1101–1119.
6. Afifi TO, Mather A, Boman J et al. Childhood adversity and personality disorders: Results from a nationally representative population-based study. J Psychiatr Res 2011;**45**:814–822.
7. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;**62**:593–602.
8. Belsky J, Steinberg L, Houts RM, Halpern-Felsher BL. The development of reproductive strategy in females: early maternal harshness → earlier menarche → increased sexual risk taking. Dev Psychol 2010;**46**:120–128.
9. Beck AT. The evolution of the cognitive model of depression and its neurobiological correlates. Am J Psychiatry 2008;**165**:969–977.
10. WHO. Child Maltreatment. World Health Organization Fact Sheet No. 150, 2010.
11. Herman JP, Ostrander MM, Mueller NK, Figueiredo H. Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. Prog Neuropsychopharmacol Biol Psychiatry 2005;**29**:1201–1213.

12. Penza KM, Heim C, Nemeroff CB. Neurobiological effects of childhood abuse: implications for the pathophysiology of depression and anxiety. Arch Womens Ment Health 2003;**6**:15–22.
13. Jackowski A, Perera TD, Abdallah CG et al. Early-life stress, corpus callosum development, hippocampal volumetrics, and anxious behavior in male nonhuman primates. Psychiatry Res 2011;**192**:37–44.
14. Vythilingam M, Heim C, Newport J et al. Childhood trauma associated with smaller hippocampal volume in women with major depression. Am J Psychiatry 2002;**159**:2072–2080.
15. Driessen M, Herrmann J, Stahl K et al. Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. Arch Gen Psychiatry 2000;**57**:1115–1122.
16. Mirescu C, Gould E. Stress and adult neurogenesis. Hippocampus 2006;**16**:233–238.
17. Mcewen BS. Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. Metabolism 2005;**54**:20–23.
18. Liston C, Miller MM, Goldwater DS et al. Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. J Neurosci 2006;**26**:7870–7874.
19. Radley JJ, Sisti HM, Hao J et al. Chronic behavioral stress induces apical dendritic reorganization in pyramidal neurons of the medial prefrontal cortex. Neuroscience 2004;**125**:1–6.
20. Mitra R, Jadhav S, Mcewen BS, Vyas A, Chattarji S. Stress duration modulates the spatiotemporal patterns of spine formation in the basolateral amygdala. Proc Natl Acad Sci USA 2005;**102**:9371–9376.
21. Vyas A, Jadhav S, Chattarji S. Prolonged behavioral stress enhances synaptic connectivity in the basolateral amygdala. Neuroscience 2006;**143**:387–393.
22. Woon FL, Hedges DW. Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: a meta-analysis. Hippocampus 2008;**18**:729–736.
23. Pruessner JC, Baldwin MW, Dedovic K et al. Self-esteem, locus of control, hippocampal volume, and cortisol regulation in young and old adulthood. Neuroimage 2005;**28**:815–826.
24. Wilner AP, De Varennes B, Gregoire PA, Lupien S, Pruessner JC. Glucocorticoids and hippocampal atrophy after heart transplantation. Ann Thorac Surg 2002;**73**: 1965–1967.
25. De Bellis MD, Keshavan MS, Shifflett H et al. Brain structures in pediatric maltreatment-related posttraumatic stress disorder: a sociodemographically matched study. Biol Psychiatry 2002;**52**:1066–1078.
26. Nemeroff CB, Vale WW. The neurobiology of depression: inroads to treatment and new drug discovery. J Clin Psychiatry 2005;**66**(Suppl. 7):5–13.
27. Engelmann M, Landgraf R, Wotjak CT. The hypothalamic-neurohypophysial system regulates the hypothalamic-pituitary-adrenal axis under stress: an old concept revisited. Front Neuroendocrinol 2004;**25**: 132–149.
28. Aguilera G, Rabadan-Diehl C. Vasopressinergic regulation of the hypothalamic-pituitary-adrenal axis: implications for stress adaptation. Regul Pept 2000;**96**:23–29.
29. Sandi C. Stress, cognitive impairment and cell adhesion molecules. Nature reviews. 2004;**5**:917–930.
30. Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. Annu Rev Physiol 2005;**67**:259–284.
31. Rentesi G, Antoniou K, Marselos M, Fotopoulos A, Alboycharali J, Konstandi M. Long-term consequences of early maternal deprivation in serotonergic activity and HPA function in adult rat. Neurosci Lett 2010;**480**:7–11.
32. Heim C, Mletzko T, Purselle D, Musselman DL, Nemeroff CB. The dexamethasone/corticotropin-releasing factor test in men with major depression: role of childhood trauma. Biol Psychiatry 2008;**63**:398–405.
33. Weiss EL, Longhurst JG, Mazure CM. Childhood sexual abuse as a risk factor for depression in women: psychosocial and neurobiological correlates. Am J Psychiatry 1999;**156**:816–828.
34. Shea A, Walsh C, Macmillan H, Steiner M. Child maltreatment and HPA axis dysregulation: relationship to major depressive disorder and post traumatic stress disorder in females. Psychoneuroendocrinology 2005;**30**:162–178.
35. Heim C, Plotsky PM, Nemeroff CB. Importance of studying the contributions of early adverse experience to neurobiological findings in depression. Neuropsychopharmacology 2004;**29**:641–648.
36. Rasmusson AM, Lipschitz DS, Wang S et al. Increased pituitary and adrenal reactivity in premenopausal women with posttraumatic stress disorder. Biol Psychiatry 2001;**50**:965–977.
37. Yehuda R, Bierer LM, Schmeidler J, Aferiat DH, Breslau I, Dolan S. Low cortisol and risk for PTSD in adult offspring of holocaust survivors. Am J Psychiatry 2000;**157**:1252–1259.
38. Holsboer F. The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology 2000;**23**:477–501.
39. Clarke AS, Wittwer DJ, Abbott DH, Schneider ML. Long-term effects of prenatal stress on HPA axis activity in juvenile rhesus monkeys. Dev Psychobiol 1994;**27**:257–269.
40. Liu D, Diorio J, Tannenbaum B et al. Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. Science (New York, NY) 1997;**277**:1659–1662.
41. Sterlemann V, Ganea K, Liebl C et al. Long-term behavioral and neuroendocrine alterations following chronic social stress in mice: implications for stress-related disorders. Horm Behav 2008;**53**:386–394.
42. Pryce CR. Postnatal ontogeny of expression of the corticosteroid receptor genes in mammalian brains: Inter-species and intra-species differences. Brain Res Rev 2008;**57**:596–605.
43. Ridder S, Chourbaji S, Hellweg R et al. Mice with genetically altered glucocorticoid receptor expression show altered sensitivity for stress-induced depressive reactions. J Neurosci 2005;**25**:6243–6250.
44. Zhang TY, Meaney MJ. Epigenetics and the environmental regulation of the genome and its function. Annu Rev Psychol 2010;**61**(439–466):C431–433.
45. Caiafa P, Zampieri M. DNA methylation and chromatin structure: the puzzling CpG islands. J Cell Biochem 2005;**94**:257–265.
46. Bonasio R, Tu S, Reinberg D. Molecular signals of epigenetic states. Science 2010;**330**:612–616.
47. Hoffmann A. Spengler D. Neuroscience: DNA memories of early social life, 2012.

https://doi.org/10.1111/j.1601-5215.2012.00683.x Published online by Cambridge University Press

48. Szyf M. DNA methylation and demethylation probed by small molecules. Biochim Biophys Acta 2010;**1799**:750–759.
49. Lee JY, Lee TH. Effects of histone acetylation and CpG methylation on the structure of nucleosomes. Biochim Biophys Acta 2012;**1824**:974–982.
50. Bannister AJ, Kouzarides T. Regulation of chromatin by histone modifications. Cell Res 2011;**21**:381–395.
51. Margueron R, Trojer P, Reinberg D. The key to development: interpreting the histone code? Curr Opin Genet Dev 2005;**15**:163–176.
52. Lessard JA, Crabtree GR. Chromatin regulatory mechanisms in pluripotency. Annu Rev Cell Dev Biol 2010;**26**:503–532.
53. Racki LR, Narlikar GJ. ATP-dependent chromatin remodeling enzymes: two heads are not better, just different. Curr Opin Genet Dev 2008;**18**:137–144.
54. Hota SK, Bartholomew B. Diversity of operation in ATP-dependent chromatin remodelers. Biochim Biophys Acta 2011;**1809**:476–487.
55. Erdel F, Krug J, Langst G, Rippe K. Targeting chromatin remodelers: signals and search mechanisms. Biochim Biophys Acta 2011;**1809**:497–508.
56. Magistri M, Faghihi MA, St Laurent G 3rd, Wahlestedt C. Regulation of chromatin structure by long noncoding RNAs: focus on natural antisense transcripts. Trends Genet 2012;**28**:389–396.
57. Qureshi IA, Mehler MF. Epigenetic mechanisms underlying human epileptic disorders and the process of epileptogenesis. Neurobiol Disease 2010;**39**:53–60.
58. Davis-Dusenbery BN, Hata A. Mechanisms of control of microRNA biogenesis. J Biochem 2010;**148**:381–392.
59. Saxena A, Carninci P. Long non-coding RNA modifies chromatin: epigenetic silencing by long non-coding RNAs. BioEssays: news and reviews in molecular, cellular and developmental biology. 2011;**33**:830–839.
60. Aalto AP, Pasquinelli AE. Small non-coding RNAs mount a silent revolution in gene expression. Curr Opin Cell Biol 2012;**24**:333–340.
61. Shukla GC, Singh J, Barik S. MicroRNAs: processing, maturation, target recognition and regulatory functions. Molecular Cell Pharmacol 2011;**3**:83–92.
62. Schratt G. Fine-tuning neural gene expression with microRNAs. Curr Opin Neurobiol 2009;**19**:213–219.
63. Weaver IC. Shaping adult phenotypes through early life environments. Birth Defects Res C Embryo Today 2009;**87**:314–326.
64. Lenroot RK, Giedd JN. Annual research review: developmental considerations of gene by environment interactions. J Child Psychol Psychiatry 2011;**52**:429–441.
65. Anda RF, Felitti VJ, Bremner JD et al. The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. Eur Arch Psychiatry Clin Neurosci 2006;**256**:174–186.
66. Bradley RG, Binder EB, Epstein MP et al. Influence of child abuse on adult depression: moderation by the corticotropin-releasing hormone receptor gene. Arch Gen Psychiatry 2008;**65**:190–200.
67. Chapman DP, Whitfield CL, Felitti VJ, Dube SR, Edwards VJ, Anda RF. Adverse childhood experiences and the risk of depressive disorders in adulthood. J Affect Disord 2004;**82**:217–225.
68. Szyf M. The early life environment and the epigenome. Biochim Biophys Acta 2009;**1790**:878–885.
69. Meaney MJ, Szyf M, Seckl JR. Epigenetic mechanisms of perinatal programming of hypothalamic-pituitary-adrenal function and health. Trends Mol Med 2007;**13**:269–277.
70. Murgatroyd C, Wu Y, Bockmuhl Y, Spengler D. Genes learn from stress: how infantile trauma programs us for depression. Epigenetics 2010;**5**:194–199.
71. Champagne FA. Epigenetic mechanisms and the transgenerational effects of maternal care. Front Neuroendocrinol 2008;**29**:386–397.
72. Mcleod J, Sinal CJ, Perrot-Sinal TS. Evidence for non-genomic transmission of ecological information via maternal behavior in female rats. Genes Brain Behav 2007;**6**:19–29.
73. Franklin TB, Russig H, Weiss IC et al. Epigenetic transmission of the impact of early stress across generations. Biol Psychiatry 2010;**68**:408–415.
74. Fernandez-Guasti A, Fiedler JL, Herrera L, Handa RJ. Sex, stress, and mood disorders: at the intersection of adrenal and gonadal hormones. Horm Metab Res 2012;**44**:607–618.
75. Weaver IC, Cervoni N, Champagne FA et al. Epigenetic programming by maternal behavior. Nat Neurosci 2004;**7**:847–854.
76. Murgatroyd C, Spengler D. Epigenetics of early child development. Front Psychiatry/Front Res Found 2011;**2**:16.
77. Uchida S, Hara K, Kobayashi A et al. Early life stress enhances behavioral vulnerability to stress through the activation of REST4-mediated gene transcription in the medial prefrontal cortex of rodents. J Neurosci 2010;**30**:15007–15018.
78. Levine A, Worrell TR, Zimnisky R, Schmauss C. Early life stress triggers sustained changes in histone deacetylase expression and histone H4 modifications that alter responsiveness to adolescent antidepressant treatment. Neurobiol Dis 2012;**45**:488–498.
79. Tognini P, Pizzorusso T. MicroRNA212/132 family: molecular transducer of neuronal function and plasticity. Int J Biochem Cell Biol 2012;**44**:6–10.
80. Weaver IC. Epigenetic effects of glucocorticoids. Semin Fetal Neonatal Med 2009;**14**:143–150.
81. Maestripieri D. Early experience affects the intergenerational transmission of infant abuse in rhesus monkeys. Proc Natl Acad Sci USA 2005;**102**:9726–9729.
82. Zhang TY, Bagot R, Parent C et al. Maternal programming of defensive responses through sustained effects on gene expression. Biol Psychol 2006;**73**:72–89.
83. Bagot RC, Van Hasselt FN, Champagne DL, Meaney MJ, Krugers HJ, Joels M. Maternal care determines rapid effects of stress mediators on synaptic plasticity in adult rat hippocampal dentate gyrus. Neurobiol Learn Mem 2009;**92**:292–300.
84. Szyf M, Weaver IC, Champagne FA, Diorio J, Meaney MJ. Maternal programming of steroid receptor expression and phenotype through DNA methylation in the rat. Front Neuroendocrinol 2005;**26**:139–162.
85. Weaver IC, D'Alessio AC, Brown SE et al. The transcription factor nerve growth factor-inducible protein a mediates epigenetic programming: altering epigenetic marks by immediate-early genes. J Neurosci 2007;**27**:1756–1768.
86. Cervoni N, Szyf M. Demethylase activity is directed by histone acetylation. J Biol Chem 2001;**276**:40778–40787.

https://doi.org/10.1111/j.1601-5215.2012.00683.x Published online by Cambridge University Press

87. Mcgowan PO, Sasaki A, D'Alessio AC et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci 2009;**12**:342–348.
88. Alt SR, Turner JD, Klok MD et al. Differential expression of glucocorticoid receptor transcripts in major depressive disorder is not epigenetically programmed. Psychoneuroendocrinology 2009;**35**:544–556.
89. Binder EB, Salyakina D, Lichtner P et al. Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. Nat Genet 2004;**36**:1319–1325.
90. Willour VL, Chen H, Toolan J et al. Family-based association of FKBP5 in bipolar disorder. Mol Psychiatry 2009;**14**:261–268.
91. Binder EB, Bradley RG, Liu W et al. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. JAMA 2008;**299**:1291–1305.
92. Brent D, Melhem N, Ferrell R et al. Association of FKBP5 polymorphisms with suicidal events in the Treatment of Resistant Depression in Adolescents (TORDIA) study. Am J Psychiatry 2010;**167**:190–197.
93. Supriyanto I, Sasada T, Fukutake M et al. Association of FKBP5 gene haplotypes with completed suicide in the Japanese population. Prog Neuropsychopharmacol Biol Psychiatry 2011;**35**:252–256.
94. Luijk MP, Velders FP, Tharner A et al. FKBP5 and resistant attachment predict cortisol reactivity in infants: gene-environment interaction. Psychoneuroendocrinology 2010;**35**:1454–1461.
95. Shibuya N, Suzuki A, Sadahiro R et al. Association study between a functional polymorphism of FK506-binding protein 51 (FKBP5) gene and personality traits in healthy subjects. Neurosci Lett 2010;**485**:194–197.
96. Hartmann J, Wagner KV, Liebl C et al. The involvement of FK506-binding protein 51 (FKBP5) in the behavioral and neuroendocrine effects of chronic social defeat stress. Neuropharmacology 2012;**62**:332–339.
97. Lee RS, Tamashiro KL, Yang X et al. Chronic corticosterone exposure increases expression and decreases deoxyribonucleic acid methylation of Fkbp5 in mice. Endocrinology 2010;**151**:4332–4343.
98. Murgatroyd C, Patchev AV, Wu Y et al. Dynamic DNA methylation programs persistent adverse effects of early-life stress. Nat Neurosci 2009;**12**:1559–1566.
99. Lopez-Leon S, Janssens AC, Gonzalez-Zuloeta Ladd AM et al. Meta-analyses of genetic studies on major depressive disorder. Mol Psychiatry 2007;**13**:772–785.
100. Sarapas C, Cai G, Bierer LM et al. Genetic markers for PTSD risk and resilience among survivors of the World Trade Center attacks. Dis Markers 2011;**30**:101–110.
101. Mcewen BS, Alves SE. Estrogen actions in the central nervous system. Endocr Rev 1999;**20**:279–307.
102. Weiser MJ, Foradori CD, Handa RJ. Estrogen receptor beta in the brain: from form to function. Brain Res Rev 2008;**57**:309–320.
103. Bodo C, Rissman EF. New roles for estrogen receptor beta in behavior and neuroendocrinology. Front Neuroendocrinol 2006;**27**:217–232.
104. Kirschbaum C, Kudielka BM, Gaab J, Schommer NC, Hellhammer DH. Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamus-pituitary-adrenal axis. Psychosom Med 1999;**61**:154–162.
105. Kumsta R, Entringer S, Koper JW, Van Rossum EF, Hellhammer DH, Wust S. Sex specific associations between common glucocorticoid receptor gene variants and hypothalamus-pituitary-adrenal axis responses to psychosocial stress. Biol Psychiatry 2007;**62**:863–869.
106. Cameron NM, Shahrokh D, Del Corpo A et al. Epigenetic programming of phenotypic variations in reproductive strategies in the rat through maternal care. J Neuroendocrinol 2008;**20**:795–801.
107. Caspi A, Sugden K, Moffitt TE et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 2003;**301**:386–389.
108. Lesch KP, Bengel D, Heils A et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 1996;**274**:1527–1531.
109. Kendler KS, Kuhn JW, Vittum J, Prescott CA, Riley B. The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: a replication. Arch Gen Psychiatry 2005;**62**:529–535.
110. Murphy DL, Moya PR. Human serotonin transporter gene (SLC6A4) variants: their contributions to understanding pharmacogenomic and other functional GxG and GxE differences in health and disease. Curr Opin Pharmacol 2011;**11**:3–10.
111. Alessandro S, Kato M. The serotonin transporter gene and effectiveness of SSRIs. Expert Rev Neurother 2008;**8**:111–120.
112. Karg K, Burmeister M, Shedden K, Sen S. The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. Arch Gen Psychiatry 2011;**68**:444–454.
113. Philibert R, Madan A, Andersen A, Cadoret R, Packer H, Sandhu H. Serotonin transporter mRNA levels are associated with the methylation of an upstream CpG island. Am J Med Genet B Neuropsychiatr Genet 2007;**144B**:101–105.
114. Van Ijzendoorn MH, Caspers K, Bakermans-Kranenburg MJ, Beach SR, Philibert R. Methylation matters: interaction between methylation density and serotonin transporter genotype predicts unresolved loss or trauma. Biol Psychiatry 2010;**68**:405–407.
115. Kochanska G, Philibert RA, Barry RA. Interplay of genes and early mother-child relationship in the development of self-regulation from toddler to preschool age. J Child Psychol Psychiatry 2009;**50**:1331–1338.
116. Devlin AM, Brain U, Austin J, Oberlander TF. Prenatal exposure to maternal depressed mood and the MTHFR C677T variant affect SLC6A4 methylation in infants at birth. PLoS One 2010;**5**:e12201.
117. Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. Epigenetics 2008;**3**:97–106.
118. Russo-Neustadt A. Brain-derived neurotrophic factor, behavior, and new directions for the treatment of mental disorders. Semin Clin Neuropsychiatry 2003;**8**:109–118.
119. Angelucci F, Brene S, Mathe AA. BDNF in schizophrenia, depression and corresponding animal models. Mol Psychiatry 2005;**10**:345–352.

120. Colzato LS, Van Der Does AJ, Kouwenhoven C, Elzinga BM, Hommel B. BDNF Val(66)Met polymorphism is associated with higher anticipatory cortisol stress response, anxiety, and alcohol consumption in healthy adults. Psychoneuroendocrinology 2011;**36**:1562–1569.
121. Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G, Aubry JM. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. Psychiatry Res 2002;**109**:143–148.
122. Aydemir O, Deveci A, Taneli F. The effect of chronic antidepressant treatment on serum brain-derived neurotrophic factor levels in depressed patients: a preliminary study. Prog Neuropsychopharmacol Biol Psychiatry 2005;**29**:261–265.
123. Magarinos AM, Mcewen BS, Flugge G, Fuchs E. Chronic psychosocial stress causes apical dendritic atrophy of hippocampal CA3 pyramidal neurons in subordinate tree shrews. J Neurosci 1996;**16**:3534–3540.
124. Murakami S, Imbe H, Morikawa Y, Kubo C, Senba E. Chronic stress, as well as acute stress, reduces BDNF mRNA expression in the rat hippocampus but less robustly. Neurosci Res 2005;**53**:129–139.
125. Smith MA, Makino S, Kvetnansky R, Post RM. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. J Neurosci 1995;**15**:1768–1777.
126. Taliaz D, Stall N, Dar DE, Zangen A. Knockdown of brain-derived neurotrophic factor in specific brain sites precipitates behaviors associated with depression and reduces neurogenesis. Mol Psychiatry 2010;**15**:80–92.
127. Taliaz D, Loya A, Gersner R, Haramati S, Chen A, Zangen A. Resilience to chronic stress is mediated by hippocampal brain-derived neurotrophic factor. J Neurosci 2011;**31**:4475–4483.
128. Tapia-Arancibia L, Rage F, Givalois L, Arancibia S. Physiology of BDNF: focus on hypothalamic function. Front Neuroendocrinol 2004;**25**:77–107.
129. Patapoutian A, Reichardt LF. Trk receptors: mediators of neurotrophin action. Curr Opin Neurobiol 2001;**11**:272–280.
130. Carlezon WA Jr, Duman RS, Nestler EJ. The many faces of CREB. Trends Neurosci 2005;**28**:436–445.
131. Roth TL, Lubin FD, Funk AJ, Sweatt JD. Lasting epigenetic influence of early-life adversity on the BDNF gene. Biol Psychiatry 2009;**65**:760–769.
132. Roth TL, Sweatt JD. Epigenetic marking of the BDNF gene by early-life adverse experiences. Horm Behav 2011;**59**:315–320.
133. Lubin FD, Roth TL, Sweatt JD. Epigenetic regulation of BDNF gene transcription in the consolidation of fear memory. J Neurosci 2008;**28**:10576–10586.
134. Branchi I, Francia N, Alleva E. Epigenetic control of neurobehavioural plasticity: the role of neurotrophins. Behav Pharmacol 2004;**15**:353–362.
135. Fumagalli F, Molteni R, Racagni G, Riva MA. Stress during development: Impact on neuroplasticity and relevance to psychopathology. Prog Neurobiol 2007;**81**:197–217.
136. Lippmann M, Bress A, Nemeroff CB, Plotsky PM, Monteggia LM. Long-term behavioural and molecular alterations associated with maternal separation in rats. Eur J Neurosci 2007;**25**:3091–3098.
137. Zhang TY, Parent C, Weaver I, Meaney MJ. Maternal programming of individual differences in defensive responses in the rat. Ann N Y Acad Sci 2004;**1032**: 85–103.
138. Balbernie R. Reactive attachment disorder as an evolutionary adaptation. Attach Hum Dev 2010;**12**:265–281.
139. Crews D. Epigenetics and its implications for behavioral neuroendocrinology. Front Neuroendocrinol 2008;**29**: 344–357.

https://doi.org/10.1111/j.1601-5215.2012.00683.x Published online by Cambridge University Press