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Invited review

The role of DNA methylation in stress-related psychiatric disorders

Torsten Klengel [a], Julius Pape [a], Elisabeth B. Binder [a,b,**], Divya Mehta [a,c,*]

[a] Department of Translational Research, Max Planck Institute of Psychiatry, Munich 80804, Germany
[b] Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA 30322, USA
[c] Queensland Brain Institute, University of Queensland, Brisbane 4072, Australia

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ABSTRACT

Epigenetic modifications in response to traumatic experience and stress are emerging as important factors in the long-term biological trajectories leading to stress-related psychiatric disorders, reflecting both environmental influences as well as individual genetic predisposition. In particular, recent evidence on DNA methylation changes within distinct genes and pathways but also on a genome-wide level provides new insights into the pathophysiology of stress related psychiatric disorders. This review summarizes current findings and concepts on DNA methylation changes in stress-related disorders with a focus on major depressive disorder and posttraumatic stress disorder (PTSD). We highlight studies of DNA methylation in animals and humans pertinent to these disorders, both focusing on candidate loci as well as genome-wide studies. We describe molecular mechanisms of how exposure to stress can induce long lasting changes in DNA methylation and how these may relate to the pathophysiology of depression and PTSD. We discuss data suggesting that DNA methylation, even in peripheral tissues, appears to be an informative reflection of environmental exposures on the genome and may have potential as a biomarker for the early prevention of stress-related disorders.

This article is part of a Special Issue entitled 'Neuroepigenetic disorders'.

1. Introduction

Exposure to stressful or traumatic life events is one of the strongest risk factors for a number of psychiatric disorders, especially major depression and post-traumatic stress disorders (PTSD) (Kendler et al., 1999, 1995; Kessler et al., 1997; Molnar et al., 2001). Epigenetic modifications including DNA methylation, post-translational histone modifications, small RNA signaling and chromatin conformation changes are candidate mechanisms for long-term, stress-exposure-induced effects on gene transcription and in consequence neural functioning (Levenson and Sweatt, 2005; Maddox et al., 2013; Mill and Petronis, 2007; Miller and Sweatt, 2007; Mitchell et al., 2013; Tsankova et al., 2007). The installment of such epigenetic marks by exposure to adverse life events and its moderation by genetic factors is likely a critical factor in risk or resilience to stress-related disorders. In this review we will focus on one of these mechanisms, DNA methylation and demethylation which involve the transfer or removal of a methyl group on the C5 position of the nucleobase cytosine in the context of CG dinucleotides, which to date is the best-characterized mechanism of epigenetic regulation in the mammalian genome (Novik et al., 2002) DNA methylation changes within a gene can occur at any stage during the life cycle of a cell and might completely silence, diminish or even augment gene transcription (Sutherland and Costa, 2003). This chemically stable covalent modification of the DNA has been extensively characterized in the context of cell lineage determination and transcriptional activation or repression and has long been regarded as predominantly irreversible. But DNA methylation not only programs cell identity but also contributes to shaping of the transcriptional response to changing environmental factors. In recent years, the dynamic, environmentally responsive role of DNA methylation in gene regulation has become increasingly clear. The long-term impact of environmental factors on DNA methylation pattern has been supported by studies in rodents and also humans, exploring for example epigenetic differences in monozygotic twins, in response to exposure to toxicants or exposure to early adverse life events (Cortessis et al., 2012; Feil and Fraga, 2011; Klengel et al., 2013; Labonte et al., 2012a,b; McGowan et al., 2009; Mehta et al., 2013; Skinner et al., 2010; Sutherland and Costa, 2003). Animal studies indicate that these stress-induced marks maybe reversible and

* Corresponding author. The Queensland Brain Institute, The University of Queensland, St Lucia, QLD 4072, Australia. Tel.: +61 7 3346 6300.
** Corresponding author. Department of Translational Research, Max Planck Institute of Psychiatry, Munich 80804, Germany. Tel.: +49 30622301.
E-mail addresses: ebinder@emory.edu (E.B. Binder), dmehta1@uq.edu.au (D. Mehta).

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there is a capacity for remodeling of epigenetic marks across the lifespan (Szyf, 2009; Weaver et al., 2004) although this issue still remains unclear in humans. Although highly controversial, DNA methylation marks might be even transmitted to subsequent generations thus influencing disease risk in the offspring by exposure to environmental factors in precedent generations (Champagne, 2008; Jirtle and Skinner, 2007; Skinner, 2008; Skinner et al., 2010; Whitelaw and Whitelaw, 2008; Youngson and Whitelaw, 2008). This review will summarize the evidence that changes in DNA methylation are critical for the long-term molecular but also behavioral effects of exposure to stressful life events and are involved in mediating risk and resilience to psychiatric disorders.

2. An overview of mechanisms involved in DNA methylation

In the following section, we detail some of the molecular mechanisms that could mediate trauma/stress-related changes in DNA methylation. Both increased and decreased methylation has been reported in response to exposure to stressful life events, hence mechanisms for both addition and removal of methyl groups are important.

De-novo methylation is mediated by the DNA methyltransferases DNMT3a and DNMT3b that add a methyl group to an unmethylated cytosine at the C5 position of the cytosine base. Maintaining DNA methylation in the context of replication and cell division is accomplished primarily by DNMT1 that adds a methyl group to the unmethylated strand on hemi-methylated DNA. It has been shown that transcription factors and chromatin proteins direct recruitment of DNA methyltransferases, but how DNMTs target specific regions in the genome is still unclear. One theory is that transcription factors that bind to specific DNA elements recruit DNMTs for methylation (Brenner et al., 2005) or protect unmethylated DNA from being methylated (Lienert et al., 2011).

With regards to stress-induced psychiatric disorders, one study investigated the effect of genetic polymorphisms in genes encoding DNMTs and found that a genetic variant in the 3′ UTR of DNMT3b was associated not only with suicide attempts but also with global levels of DNA methylation (Murphy et al., 2013). Furthermore, it has been suggested that DNMT mRNA expression is altered in neuronal tissues of suicide completers with major depression as compared to controls (Poulter et al., 2008). The relevance of DNMT signaling in stress-induced psychiatric disorders is also supported by a study in rat primary neuronal cells where antidepressant drugs reduced DNMT1 activity via the histone methyltransferase G9a, linking antidepressant action with epigenetic remodeling (Zimmermann et al., 2012).

In contrast to methylation, demethylation by an active process has been discussed controversially in the past. It was known that passive demethylation could occur when maintenance methylation does not take place before cell division. But passive demethylation during cell cycle would not explain the remarkably fast and flexible reconfiguration of DNA methylation in mammalian cells upon stimulation. In addition, breaking the stable carbon–carbon bond would require significant levels of energy making a direct removal of methyl groups unlikely and favoring pathways with intermediate, less energy-consuming steps. Several mechanisms have been proposed for active demethylation.

2.1. Active demethylation through proteins that remove methylcytosines by DNA repair mechanisms

Thymidine DNA glycosylase (TDG) and Methyl-CpG-binding domain protein 4 (MBD4) are proteins that are capable of directly removing 5 mC by deamination. These enzymes remove damaged DNA bases facilitating the complementation of the missing base by DNA polymerase beta via an unmethylated cytosine. However, direct excision and replacement of a DNA base is an energy-consuming process making this pathway less likely to be relevant for fast environmentally induced changes.

Other enzymes involved in direct demethylation are deaminases of the AID/APOBEC (Activation-induced deaminase/apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like) family. These deaminases can directly deaminate methylcytosine leading to a T:G mismatch that is subsequently recognized by TDG and MBD4 followed by base excision. However, the preferred mechanism might work via TET mediated oxidation (see below) to hydroxymethylcytosine followed by AID guided deamination leading to hydroxymethyluracil that is subsequently removed by base excision mechanisms.

2.2. Active demethylation through proteins that interact with methylcytosine by DNA modifications

Oxidation of methylcytosine leads to the formation of hydroxymethylcytosine, an epigenetic mark that is most common in neuronal tissues and embryonic stem cells. Hydroxymethylcytosine is considered an intermediate step in DNA demethylation. Oxidation of methylcytosine to hydroxymethylcytosine is mediated by the ten-eleven translocation proteins (TET proteins- TET1, TET2, and TET3). These proteins can promote further oxidation of hydroxymethyl- to formyl- and subsequently carboxylcytosine that are suggested to be additional intermediates of the demethylation process. Formation of intermediate cytosine modifications by TET leads to a less stringent recognition of the particular DNA sequence by the methylation maintenance proteins and methyl-binding proteins, possibly favoring a passive demethylation of these sites. Intermediates of the TET pathway can also recruit proteins involved in DNA damage repair and base excision such as thymidine DNA glycosylase (TDG) that have been shown to remove formyl- and carboxylcytosine. Despite this, excision of the alternative modifications such as formyl- and carboxylcytosine might not be necessary since readers and writers of DNA methylation might not be able to recognize these variations thus facilitating the controlling and timing of various biological functions. In neuronal cells, activity-dependent activation of the TET system has been shown to impact global hydroxymethylcytosine distribution as well as specific demethylation at BDNF and Fgf1B promoters (Guo et al., 2011b). Hydroxymethylcytosines are most common in human brain tissue suggesting a prominent role of the TET protein family and the formation of hydroxymethylcytosine in the process of activity dependent demethylation in post-mitotic neurons. Over lifetime, hydroxymethylcytosines accumulate in the human brain primarily in gene bodies and downstream the transcription start site (Szulwach et al., 2011) and most recently the formation of hydroxymethylation has been implicated in fear extinction in mice (Bredy, 2013).

2.3. Active demethylation through proteins that indirectly interact with methylcytosine

Binding of sequence-specific proteins other than direct modulators of DNA methylation has been shown to be involved in the active demethylation of DNA. For example, the nuclear glucocorticoid receptor (GR) has been shown to induce demethylation in and around glucocorticoid receptor binding sites (GREs) in the rat tyrosine aminotransferase gene (Tat) (Thomassin et al., 2001) that was stable over a 3 months period and led to an increased transcriptional sensitivity of the target gene. Our group showed that childhood abuse leads to a lasting DNA demethylation at intronic FKBP5 GREs in peripheral blood cells but also hippocampal

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progenitor cells, presumably via activating the GR receptor (Klengel et al., 2013). These GR-induced effects could explain some of the DNA methylation changes in response to stress exposure. Several recent studies suggest that other DNA-binding proteins such as estrogen-receptor alpha, FOXA1, REST and CTCF can lead to a local demethylation in and around their binding sites (Metivier et al., 2008; Serandour et al., 2011; Stadler et al., 2011). Several mechanisms for this transcription factor guided demethylation have been proposed, involving protein–protein interactions with methyl-DNA binding proteins and DNA repair mechanisms. One of these involve the Gadd45 (growth arrest and DNA damage 45) protein family including Gadd45 alpha, beta and gamma that may function as a hub for protein–protein interactions in demethylation processes by recruiting nucleotide and base excision repair mechanisms in order to facilitate the demethylation of the DNA. The action of Gadd45 beta might be of particular interest in understanding activity-dependent DNA demethylation in post-mitotic neurons in the context of stress-induced psychiatric disorders. Electroconvulsive stimulation in mice leads to an increased expression of Gadd45 beta that is related to a demethylation of the BDNF IX and Fgf1B promoters, both implicated in neurogenesis and synaptic plasticity (Ma et al., 2009). In parallel, stimulation of metabotrophic glutamate receptors increased the binding of Gadd45 beta to the promoters of BDNF, reelin and GAD67 and that correlates with the demethylation of these three genes. Furthermore, the Gadd45 proteins interact with nuclear hormone receptors (Yi et al., 2000) and Gadd45 beta has shown to be activated in fear-related learning and memory, linking environmental experience with epigenetic modifications in memory formation (Zovkic and Sweatt, 2013). The alpha isoform of Gadd45 has been shown to interact with TDG and MBD4 to promote demethylation and surprisingly also interacts with DNMT1 that showed a demethylase activity in this context (Chen et al., 2013).

2.4. Influence of methyl-DNA binding protein MeCP2 on psychiatric disorders

Active DNA methylation and demethylation can also be triggered by neuronal activation (Guo et al., 2011a). The methyl-binding protein MeCP2 plays an important role in activity-driven gene transcription in neuronal cells during the process of learning and memory storage. For a long time it has been thought that MeCP2 binds to methylated CpGs and acts as a transcriptional repressor though it also has been shown that MeCP2 interacting with CREB can promote transcriptional activation (Chahrour et al., 2008). However, recent work suggested that MeCP2 acts more globally as a chromatin-remodeling enzyme. It is modified by post-translational phosphorylation to regulate neuronal development and behavior (Cohen et al., 2011). The function of MeCP2 as transcriptional repressor has been investigated also in the context of psychiatric and behavioral phenotypes. For example, MeCP2 is bound to the methylated promoter of BDNF. Neuronal activation triggers the phosphorylation of MeCP2 and by this the release of the protein and other co-repressors from the promoter site. The promoter region can then be activated by transcription factor binding (Martinowich et al., 2003). Another study revealed that this mechanism may mediate the sustained hypomethylation of the promoter region of the AVP gene in the paraventricular nucleus (PVN) in mice exposed to early life stress (Murgatroyd et al., 2009). The CpG sites undergoing demethylation are located in the binding site of the MeCP2 protein. The authors showed that early life stress triggers the phosphorylation of MeCP2 leading to dissociation from the promoter region and permitting the transcriptional activation in AVP expressing cells from the PVN. Interestingly, marked difference in MeCP2 phosphorylation and protein occupancy at the promoter site without changes in methylation shortly after maternal separation are followed by differences in DNA methylation without differences in MeCP2 phosphorylation later in life. This suggests a sequential establishment of epigenetic marks through activity dependent MeCP2 phosphorylation that leads to a hypomethylation at the AVP promoter that in turn results in a reduced binding of the MeCP2 repressor. Using MeCP2 knockout mice, Nuber et al. (2005) were able to show that Fkbp5, Sgk1 and other glucocorticoid responsive genes are also targets of MeCP2 in the rodent brain. These knockout mice showed elevated mRNA levels of Fkbp5 and Sgk1 without increased plasma glucocorticoid levels. The authors concluded that MeCP2 might function as a modulator of glucocorticoid function in neuronal tissue, a finding that is of particular relevance to stress-induced psychiatric disorders since changed glucocorticoid hormones have been repeatedly implicated in the pathophysiology of stress-related disorders.

2.5. Importance of developmental windows for DNA methylation

Epigenetic regulation is a time-dependent and highly controlled process. DNMT expression is highest in developing and differentiating cells and is reduced in cells that have reached their terminal differentiation but can be detected in post-mitotic cells such as neuronal cells. The type and extent of epigenetic impact of environmental factors not only depends on individual genetic differences but also the developmental stage or age at which they occur. The timing of these events therefore seems to play an important role in the epigenetic consequences of stressors. Early environmental factors such as maternal care in rats, early life stress paradigms in mice and childhood trauma in humans have repeatedly been shown to lead to long-term changes in global and regional DNA methylation profiles. The developing organism thus seems to be most vulnerable to environmental factors that modify epigenetic profiles in neuronal tissue.

Initial reports focused on rodent models of early life adversity and human childhood abuse. A recent study by Witzmann et al. (2012) illustrates the importance of the type and timing of the environmental exposure on GR promoter methylation. In contrast to the initial report by Weaver and colleagues (Weaver et al., 2004) the authors used ten to twelve weeks old rats and subjected them to a chronic stress model. Although the authors could show that chronic stress exposure in adult rats leads to some degree of DNA methylation changes in the GR I_7 promoter, the pivotal CpG site at the NGFI-A recognition site remained unchanged. The importance of the type and timing of the environmental exposure is also supported the fact that promoter methylation in the human GR in brain remained unchanged in individuals suffering from major depression but not exposed to early trauma although differential expression of NGFI-A and promoter I_7 usage was observed (Alt et al., 2010). In contrast, differential methylation of the promoter at the NGFI-A site was observed in suicide victims exposed to child abuse (McGowan et al., 2009). Another example of the importance of the timing of environmental exposure has been observed for FKBP5. The GR agonist-induced de-methylation of the intron 7 enhancer element in FKBP5 in neuronal precursor cells was also only stable when the cells were treated during the proliferation and differentiation phase, but not after cells had differentiated (Klengel et al., 2013). This matches the fact that FKBP5 genotype interacts with child abuse, but not adult trauma to predict psychopathology (Binder et al., 2008). As mentioned above, we could also show that DNA methylation pattern in patients with PTSD who all had experienced trauma in adulthood where distinct in dependence of additional exposure to child abuse (Mehta et al., 2013). This suggests that the timing and history of trauma leads to specific long lasting changes in DNA methylation.

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In summary, both animal and human studies suggest that timing and type of the stressor leads to differential DNA methylation patterns even at the same locus. This could account for differences in the subsequent response of the stress hormone system and in turn in psychopathology.

In the next section, we will highlight changes in DNA methylation, likely mediated by the above mechanism in specific genes in animals and humans in relationship to stress and stress-related psychiatric disorders.

3. DNA methylation of HPA axis candidates and other genes

Differences in early life experiences are associated with life-long impact on health and disease trajectories in animals and humans. Dysregulation of the stress hormone system and associated disease-risk is one of the most prominent findings in psychiatric disorders and these observation triggered detailed genetic and epigenetic studies investigating the effect of trauma and early life stress on the hypothalamus–pituitary–adrenal axis (HPA axis) and their relevant genes (Arborelius et al., 1999). A number of studies suggest that the long term effects of early life experience on stress hormone system regulation is embedded via epigenetic changes in key genes of this axis albeit other signaling cascades such as the serotonergic and neurotrophic system have been implicated in this regulation as well. Briefly, the hypothalamic neuropeptides CRH and AVP stimulate the release of ACTH from the pituitary that in turn leads to the release of glucocorticoids (GC) from the adrenal gland. GC bind to the glucocorticoid receptor (GR), a nuclear receptor that functions as a transcription factor and allows the physiological adaptation to stress exposure as well as the negative feedback necessary for the shutdown of the axis once the threat is over. Thus, this axis directly links the environmental trigger through an endocrine response to DNA transcription and allows gene specific and genome wide modifications of this system. In the following paragraph, we will illustrate how early stress and environment lead to long-term changes in endocrine and behavioral response via epigenetic programming of genes within this axis.

3.1. DNA methylation studies in animals and humans

A number of studies in animal models of maternal behavior and stress-induced depressive like behaviors have reported changes in DNA methylation of the GR gene (NR3C1) (Kosten et al., 2013; Kundakovic et al., 2013; Liberman et al., 2012; McGowan et al., 2011; Weaver et al., 2004), but this is not observed by all (Daniels et al., 2009; Kember et al., 2012). So far the positive studies point to a hypermethylation of regulatory areas of the GR gene with exposure to early adverse life events with the initial studies by Weaver showing a decrease in GR transcription and an impaired negative feedback of the stress hormone system. This is followed by a de-repressed stress response with higher levels of glucocorticoids released at every subsequent stress exposure. The following molecular mechanisms eliciting these changes in DNA methylation have been proposed:

Low levels of maternal care in rats are linked to reduced hippocampal serotonin signaling in the rat. This is associated with decreased nerve growth factor-inducible protein A (NGFI-A) expression in the hippocampus (Weaver et al., 2004). This transcription factor binds to a response element within the exon I_7 sequence of the GR-promoter influencing the expression of GR mRNA. Weaver et al. showed that the methylation status of the promoter and especially the NGFI-A binding site is influenced by maternal care. Following low levels of maternal care hypermethylation of the NGFI-A binding site with reduced binding of NGFI-A and decreased GR expression was observed. In-vitro experiments demonstrated that 5-HT stimulation led to significantly decreased methylation of the 5′ CpG dinucleotide of the NGFI-A response element. A partial inhibition of NGFI-A gene resulted in complete inhibition of the 5-HT mediated demethylation at the NGFI-A binding site (Weaver et al., 2007). Further in-vitro studies showed that overexpression of NGFI-A and transfection of HEK 293 cells with a methylated construct of the GR exon I_7 sequence led to significant demethylation of the promoter sequence. This demethylation is likely the result of an interaction of NGFI-A and the CREB binding protein CBP. Co-immunoprecipitation experiments showed that NGFI-A and CBP form a complex that binds to the exon I_7 GR promoter leading to an active demethylation. Here, CBP acts as a histone acetyltransferase and leads to increased levels of histone 3 lysine 9 acetylation (H3K9) at the exon I_7 promoter. This process results in transcriptionally active chromatin (Hellstrom et al., 2012; Weaver et al., 2007). This suggests that NGFI-A has a dual role in this process. In early life, NGFI-A mediates stress-induced methylation change of its binding site via serotonin signaling and interaction with histone modification enzymes. In adulthood, it increases GR transcription through binding to its unmethylated response element within the GR promoter region (Weaver et al., 2007). The change in DNA methylation thus leads to an alteration of the expression of the GR that finally alters the HPA axis function.

Even though these data convincingly describe the cascade of molecular events of how early environment leads to transcriptional changes in a specific gene, it is unlikely that early life stress elicits the broad range of behavioral, endocrine and molecular outcomes through changes on a single gene promoter. Consequently, McGowan et al. investigated a much broader area around the GR gene in the rat hippocampus encompassing about 7 million base pairs on chromosome 18 (McGowan et al., 2011). The results suggest that the epigenetic response to maternal care is coordinated across large stretches of DNA not only including gene promoters but also intragenic and intergenic regions. Offspring of rats with higher maternal care showed higher transcriptional activity across several genes within the locus examined. This non-random and gene-specific transcriptional adaptation is associated with broad changes in DNA methylation including hyper- and hypomethylation of DNA, with about equal distribution to hypermethylated and hypomethylated regions. Comparing the DNA methylation profile of high maternal care and low maternal care, the authors found that hypermethylated regions were enriched for the transcription start site as well as exonic regions including the first and last exon. Hypomethylated regions were significantly depleted in the first exon and enriched in intergenic and in intronic regions of the locus. The genomic region investigated in this study also included the cluster of functionally related protocadherin genes that are involved in synaptic plasticity. In response to higher maternal care this gene cluster exhibits an overrepresentation of differentially methylated regions and in turn showed a coordinately increase in gene expression.

Besides the GR, other key genes of the HPA axis are epigenetically affected by early life stress, most prominently the genes encoding the neuropeptides AVP and CRH. CRH is expressed in a number of brain regions, including the hypothalamus but also limbic brain regions such as the amygdala and the septum. Evidence from preclinical and clinical studies suggest that CRH is a central regulator of the physiological stress response as well as a neurotransmitter important for behaviors related to depression and anxiety. Indeed, a number of studies in human, including human genetic studies have implicated the CRH system in the pathophysiology of anxiety and mood disorders (Binder and Nemeroff, 2010). AVP is also synthesized in the hypothalamus and the limbic system and act synergistically with CRH on the release of ACTH. Similar to CRH, AVP also functions as a central

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Table 1
Summary of studies on DNA methylation in stress related psychiatric disorders sorted by analyzed gene(s).

Reference	Year	Sample size, ethnicity, gender	Trauma	Outcome phenotype	Tissue	Gene(s) analyzed	Method	Findings
Zill et al.	2012	$n = 162$ 81 MDD 81 Controls Caucasian 70 male 92 female		MDD	Peripheral blood	ACE	Direct Sanger bisulfite sequencing	Hypermethylation of a functional important region of the ACE gene promoter in depressed patients and a significant inverse correlation between the ACE serum concentration and ACE promoter methylation frequency
Keller et al.	2010	$N = 77$ 44 Suicide 33 Controls white ethnicity		Suicide	Brain tissue extracted from the Wernicke area	BDNF	Pyrosequencing	Postmortem brain samples from suicide subjects showed a statistically significant increase of DNA methylation at specific CpG sites in *BDNF* promoter/exon IV compared with nonsuicide control subjects
Fuchikami et al.	2011	$n = 38$ 20 Depression 18 Controls Japanese		MDD	Peripheral blood	BDNF	MassArray system (SEQUENOM)	Significant Difference between the methylation profiles within the CpG island at the promoter of exon I of the BDNF gene of patients with MDD and healthy controls
Kang et al.	2013	$N = 108$ 108 MDD		MDD	Peripheral blood	BDNF	Pyrosequencing	Greater BDNF methylation was significantly associated with a previous suicidal attempt history as well as with suicidal ideation during treatment and at the last evaluation in the 12-week antidepressant treatment
Unternaehrer et al.	2012	$n = 76$ 43 female 33 male			Peripheral blood	BDNF, OXTR: DNA methylation status before and after the Trier social stress test	Sequenom's EpiTYPER	DNA methylation of one target sequence of OXTR was increased from pre- to post-stress (10min) and decreased from post-stress to follow-up (90min)
Ursini et al.	2011	$n = 84$ 84 healthy 84 Caucasian 32 male 52 female			Peripheral blood	COMT	Pyrosequencing	Methylation of the COMT Val158 allele of Val/Val humans is associated negatively with lifetime stress and positively with working memory performance and inversely related to mRNA expression and protein levels
Norrholm et al.	2013	$n = 270$ 98 PTSD 172 no PTSD 89% African American 100 male 170 female	Different trauma types (TEI)	PTSD	Peripheral blood	COMT	Illumina Human Methylation27 BeadChip	Higher methylation at CpG sites in the promoter region of COMT is associated with impaired fear inhibition
Poulter et al.	2008	Caucasian from Hungary		Suicide	Samples of different brain regions	DNMT-1, -3A, -3B GABAA receptor alpha 1 subunit	qPCR bisulfite mapping by subcloning and sanger sequencing	Increased DNMT mRNA expression in the frontopolar cortex in suicides. This was

(*continued on next page*)

Table 1 (*continued*)

Reference	Year	Sample size, ethnicity, gender	Trauma	Outcome phenotype	Tissue	Gene(s) analyzed	Method	Findings
								associated with increased methylation of the GABAA receptor alpha 1 gene whose transcript is underexpressed in suicide/major depressive disorder (MDD) brains
Murphy et al.	2013	79 suicide attempters 80 non-attempters Irish		Suicide	Peripheral blood	DNMT-1, -3B	Genotyping Global methylation analysis (Methylflash Methylated DNA Quantification Kit)	An SNP (rs2424932) residing in the 3′ UTR of the DNMT3B gene was associated with suicide attempts compared with a non-attempter control group. SA had significantly higher levels of global DNA methylation compared with controls
Klengel et al.	2013	$N = 76$ 30 $\geq$ 2 ct 46 no ct 72 African American 2 Caucasian 1 Mixed 1 Other	Sexual and physical child abuse (CTQ)	PTSD	Peripheral blood	FKBP5	Pyrosequencing of bisulfite-treated DNA	Functional polymorphism in the FK506 binding protein 5 (FKBP5) gene increased the risk of developing stress-related psychiatric disorders in adulthood by allele-specific, childhood trauma–dependent DNA demethylation in functional glucocorticoid response elements of FKBP5
Rusiecki et al.	2013	$n = 148$ 74 postdeployment PTSD 74 no PTSD 119 White 29 Black 98 male 50 female	Afghanistan war (Deployment was used as a proxy for the potentially traumatic event)	PTSD	Peripheral blood	IGF2, H19, IL8, IL16, and IL18	Pyrosequencing of bisulfite-treated DNA	Controls showed reduced methylation levels of H19 and IL18 after deployment. Cases showed increased levels of IL18 after deployment
Rusiecki et al.	2012	$n = 150$ 75 postdeployment PTSD 75 no PTSD 120 White 30 Black 100 male 50 female	Afghanistan war (Deployment was used as a proxy for the potentially traumatic event)	PTSD	Peripheral blood	LINE-1 and Alu	Pyrosequencing	LINE-1: hypermethylated in controls post- versus pre-deployment and hypomethylated in cases versus controls postdeployment Alu: hypermethylated for cases versus controls predeployment
McGowan et al.	2009	$n = 36$ 12 abused + suicide 12 nonabused + suicide 12 control French-Canadian origin, 36 male	Childhood abuse (CECA.Q Childhood Experience of Care and Abuse Questionnaire)	Suicide	Hippo-campal samples	NR3C1	Bisulfite mapping by subcloning and sanger sequencing, qPCR	Increased CpG Methylation of NR3C1 Promotor, decreased NGFI-A binding, reduced hippocampal glucocorticoid receptor (NR3C1) expression in suicide victims with childhood abuse
Alt et al.	2009	$n = 12$ 6 MDD 6 controls 7 male 5 female		MDD	Samples of different brain regions	NR3C1	Pyrosequencing	Changes in GR expression in patients with MDD are not caused by epigenetic programming of GR promoters

Perroud et al.	2011	$n = 215$ 101 BPD (male 4) 99 MDD (male 35) 15 MDD + PTSD (male 4)	Childhood sexual abuse (CTQ Childhood Trauma Questionnaire)		Peripheral blood	NR3C1	Pyrosequencing of bisulfite-treated DNA	Childhood sexual abuse, its severity and the number of type of maltreatments positively correlated with NR3C1 methylation
Radtke et al.	2011	$n = 24$ 8 prenatal exposure to maternal stress 16 no prenatal exposure to maternal stress 8 male 16 female different ethnicity	Intimate partner violence during pregnancy (composite abuse scale) (CAS)		Peripheral blood	NR3C1	Bisulfite mapping by subcloning and sanger sequencing	The methylation status of the GR gene of adolescent children is influenced by their mothers exposure to intimate partner violence during pregnancy
Edelman et al.	2012	$n = 92$ 92 healthy 46 female 46 male			Saliva	NR3C1	Pyrosequencing	A single CpG site located in the GR exon 1F noncanonical nerve growth factor-inducible protein A (NGFI-A) transcription factor was a highly significant predictor of total salivary cortisol output in female subjects who participated in the Trier Social Stress Test (TSST)
Tyrka et al.	2012	$n = 99$ 99 healthy 58 female 41 male	Childhood trauma		Peripheral blood	NR3C1	Pyrosequencing	Disruption or lack of adequate nurturing, as measured by parental loss, childhood maltreatment, and parental care, was associated with increased NR3C1 promoter methylation
Suderman et al.	2012	$n = 24$ 12 abused + suicide 12 controls French-Canadian origin, 24 male	Childhood abuse (CECA.Q Childhood Experience of Care and Abuse Questionnaire)	Suicide	Hippo-campal samples	NR3C1	Methylated DNA immuno-precipitation followed by microarray hybridization	Human methylation profiles of NR3C1 compared to methylation profiles of rats
Labonte et al.	2012	$N = 56$ 21 abused + suicide 21 nonabused + suicide 14 control French Canadian descent 56 male	Childhood abuse (CECA.Q Childhood Experience of Care and Abuse Questionnaire)	Suicide	Hippo-campal samples	NR3C1	Pyrosequencing	Differential hippocampal glucocorticoid receptor exon 1B, 1C and 1H expression and methylation in suicide completers with a history of childhood abuse
Melas et al.	2013	$n = 1668$ 392Depression 1276 Controls Swedish nationals 675 male 993 female		Depression	Saliva	NR3C1 and MAOA	Sequenom EpiTYPER platform	MAOA methylation levels were decreased in depressed females compared to controls
Steiger et al.	2013	$N = 96$ 32 BN + CT 32 BN no CT	Childhood trauma (Childhood Trauma Interview)		Peripheral blood	NR3C1	Sequenom's EpiTYPER	Association of BN (when accompanied by BPD or suicidality) with

(*continued on next page*)

Table 1 (*continued*)

Reference	Year	Sample size, ethnicity, gender	Trauma	Outcome phenotype	Tissue	Gene(s) analyzed	Method	Findings
		32 controls 96 female						hypermethylation of certain GR exon 1C promoter sites.
Hompes et al.	2013	$n = 83$ 83 pregnant women 77 Belgian 5 European 1 Non European			Saliva (Mother) for Cortisol levels, Cord blood for DNA methylation	NR3C1	Sequenom's EpiTYPER	Psychological data and diurnal cortisol data were assessed to evaluate maternal stress once each trimester. The child's methylation state of CpG9 was significantly associated with maternal emotional wellbeing
Gross et al.	2012	$N = 64$ French Canadian descent 64 male		Suicide	Tissue from Brodmann area 44	OAZ1 OAZ2 AMD1 ARG2	Sequenom's EpiTYPER	Significant site-specific differences in methylation in the promoter of ARG2 and AMD1 that were also significantly negatively correlated with gene expression
Ressler et al.	2011	$N = 107$ (both sexes)	Different trauma types (TEI)	PTSD	Peripheral blood	PAC1 (ADCYAP1R1)	Illumina Human Methylation27 BeadChip	Methylation of ADCYAP1R1 was significantly associated with total PTSD symptoms
Fiori et al.	2011	$n = 20$ 10 Suicide 10 Controls French Canadian descent 39 male		Suicide	Samples from the dorsolateral prefrontal cortex	SAT1	Bisulfite mapping by subcloning and sanger sequencing	CpG methylation across a 1880-bp region of the SAT1 promoter was significantly negatively correlated with SAT1 expression.
Chang et al.	2012	$n = 320$ 62 PTSD 258 controls Subset with methylation data $n = 83$ 16 PTSD 67 controls	Different trauma types (assessed by a modified version of the PTSD checklist)	PTSD	Peripheral blood	SLC6A3	Illumina HumanMethylation27 BeadChip	In the full analytic sample, 9R allele carriers had almost double the risk of lifetime PTSD compared to 10R/10R genotype carriers. In the subset 9R allele carriers showed an increased risk of lifetime PTSD only in conjunction with high methylation in the SLC6A3 promoter locus
IJzendoorn et al.	2010	$n = 143$ 91% Caucasian	Different trauma types (assessed by the Adult Attachment Interview AAI)	psycho-logical problems due to unresolved loss or trauma	EBV transformed lymphoblast cell lines	SLC6A4	Quantitative mass spectroscopy	Associations between 5HTTLPR polymorphisms and psychological problems (due to unresolved loss or trauma) are significantly altered by environmentally induced methylation patterns
Beach et al.	2010	$n = 192$	Childhood abuse (assessed by two specific questions)		EBV transformed lymphoblast cell lines	SLC6A4	Quantitative mass spectroscopy	Methylation levels of the CpG island upstream from SLC6A4 are associated with report of abuse during childhood in both males and females
Beach et al.	2011	$n = 155$	Childhood abuse (assessed by two specific questions)	Antisocial Personality Disorder (ASPD)	EBV transformed lymphoblast cell lines	SLC6A4	Quantitative mass spectroscopy	Significant effect of childhood sex abuse on methylation of the 5HTT promoter region and a significant effect of methylation at 5HTT on symptoms of ASPD
Koenen et al.	2011	$n = 100$ 23 PTSD-affected	Different trauma types (Participants	PTSD	Peripheral blood	SLC6A4	Illumina Human Methylation27 BeadChip	*SLC6A4* methylation status was not associated with PTSD but

		77 PTSD-unaffected 14% white, 79% African American, 7% other race 60 female 40 male	chose PTE's from a list of 19 events)					persons with more traumatic events and lower methylation levels were at increased risk for PTSD levels. Persons with more traumatic events and higher methylation levels were protected from this disorder.
Alasaari et al.	2012	$n = 49$ 24 high stress 25 low stress Finnish		Burnout/ Depression	Peripheral blood	SLC6A4	Direct Sanger bisulfite sequencing Verification with Methylation 450k BeadChip	Nurses with stress had significantly lower promoter methylation levels at all five CpG residues compared to nurses with low stress. Burnout/Depression was not significantly associated to methylation levels
Vijayendran et al.	2012	$n = 158$ 26 Childhood abuse 132 no abuse 149 White 2 African American 3 White of Hispanic origin 4 Other 158 female	Childhood abuse (assessed by two specific questions)		EBV transformed lymphoblast cell lines	SLC6A4	Illumina Human Methylation 450k array	Methylation of four CpG residues in the SLC6A4 gene were associated with SLC6A4 expression. Methylation of two CpG was influenced by genotype and childhood abuse. The other two only by childhood abuse
Kang et al.	2013	$n = 108$ 108 MDD		MDD	Peripheral blood	SLC6A4	Pyrosequencing	Higher SLC6A4 promoter methylation status was significantly associated with childhood adversities, family history of depression, higher perceived stress, and more severe psychopathology
Zhao et al.	2013	$n = 168$ 84 twin pairs with depressive symptoms 84 White		Depressive symptoms	Peripheral blood	SLC6A4	Quantitative bisulfite pyrosequencing	Variation in DNA methylation level of the serotonin transporter gene promoter region is associated with variation in depressive symptoms
Kim et al.	2013	$N = 286$ 286 2 weeks after stroke, 222 were followed 1 year later		Poststroke Depression (PSD)	Peripheral blood	SLC6A4	Pyrosequencing	Higher SLC6A4 promoter methylation status was independently associated with PSD at 2 weeks after stroke, and was significantly associated with the worsening of depressive symptoms over one year in patients with the SLC6A4 linked promoter region (5-HTTLPR) polymorphism
Ouellet-Morin et al.	2013	$n = 56$ 28 monozygotic twin pairs 92.9% Caucasian	One twin was bullied at least occasionally		Buccal cells	SLC6A4	Sequenom EpiTYPER platform	Bullied twins had higher SERT DNA methylation at the age of 10 years compared with their non-bullied MZ co-twins
Ernst et al.	2009	$N = 39$ 28 Suicide 11 Controls French Canadian descent 39 male		Suicide	Samples of nine frontal cortical regions and the cerebellum	TrkB	Bisulfite mapping by subcloning and sanger sequencing	Association between the methylation state of the TrkB promoter region and decreased expression of TrkB.T1
McGowan et al.	2008	$n = 30$ 18 suicide		Suicide	Hippo-campal samples	rRna promoter methylation		rRNA was significantly hypermethylated throughout

(*continued on next page*)

Table 1 (*continued*)

Reference	Year	Sample size, ethnicity, gender	Trauma	Outcome phenotype	Tissue	Gene(s) analyzed	Method	Findings
		12 controls French-Canadian origin 30 male					Bisulfite mapping by subcloning and sanger sequencing qPCR	the promoter and 59 regulatory region in the brain of suicide subjects, consistent with reduced rRNA expression in the hippocampus
Uddin et al.	2011	$n = 100$ 23 PTSD-affected 77 PTSD-unaffected 14% white, 79% African American, 7% other race 60 female 40 male	Different trauma types (Participants chose PTE's from a list of 19 events)	PTSD	Peripheral blood	33 candidate genes associated with PTSD based on gene expression	Illumina Human Methylation27 BeadChip	Patients with both higher *MAN2C1* methylation and greater exposure to PTEs showed a marked increase in risk of lifetime PTSD
Uddin et al.	2010	$n = 100$ 23 PTSD-affected 77 PTSD-unaffected 14% white, 79% African American, 7% other race 60 female 40 male	Different trauma types (Participants chose PTE's from a list of 19 events)	PTSD	Peripheral blood	Genomewide methylation profiles for over 14 000 genes	Illumina HumanMethylation27 BeadChip	The number of uniquely methylated genes was significantly higher in PTSD affected patients
Uddin et al.	2011	$n = 100$ 33 MDD 67 controls 14 White 79 Black 7 Other		Depression	Peripheral blood	Genome-wide methylation profiles for over 14 000 genes	Illumina HumanMethylation27 BeadChip	Genome-wide methylation profiles distinguish individuals with versus without lifetime depression in a community-based setting, and show coordinated signals with pathophysiological mechanisms previously implicated in the etiology of this disorder
Smith et al.	2011	$n = 110$ 25 PTSD + childhood trauma (ct) 25 PTSD no ct 26 controls + ct 34 controls no ct African American	Childhood abuse (CTQ)	PTSD	Peripheral blood	Global and site-specific methylation	Illumina Human Methylation27 BeadChip	Increased global methylation in subjects CpG sites in five genes (TPR, CLEC9A, APC5, ANXA2, and TLR8) were differentially methylated in subjects with PTSD with PTSD compared to controls.
Labonte et al.	2012	$N = 61$ 25 abused + suicide 20 nonabused + suicide 16 control French Canadian descent 61 male	Childhood abuse (CECA.Q Childhood Experience of Care and Abuse Questionnaire)	Suicide	Hippo-campal samples	Genome-wide DNA methylation	Methylated DNA immuno-precipitation followed by microarray hybridization	362 differentially methylated promoters in individuals with a history of abuse compared with controls. Genes involved in cellular/neuronal plasticity were among the most significantly differentially methylated
Sabunciyan et al.	2012	$n = 65$ 39 MDD 26 Controls		MDD	Postmortem frontal cortex samples	Genome-wide DNA methylation scan	Comprehensive High-throughput Arrays for Relative Methylation	224 candidate regions with DNAm differences >10%. These regions are highly enriched for neuronal growth and development genes
Uddin et al.	2013	$n = 100$ 23 PTSD-affected 77 PTSD-unaffected 14% white,	Different trauma types (Participants chose PTE's from a list of 19 events)	PTSD	Peripheral blood	Genomewide methylation profiles for over 14 000 genes	Illumina HumanMethylation27 BeadChip	Low socioeconomic position modifies the relationship between methylation and risk of PTSD in genes predominantly

		79% African American, 7% other race 60 female 40 male						related to nervous system function
Mehta et al.	2013	$n = 169$ 32 PTSD + ct 29 PTSD no ct 108 controls + history of trauma 150 African American 19 Other 48 male 121 female	Childhood trauma (CTQ)	PTSD	Peripheral blood	Genome- wide gene expression and DNA methylation	Illumina Human Methylation 450k array	Gene- expression profiles of the two PTSD Groups were almost nonoverlapping (98%). These gene-expression changes were accompanied and likely mediated by changes in DNA methylation in the same loci to a much larger proportion in the childhood abuse (69%) vs. the non-child abuse-only group (34%)
Labonte et al.	2013	$n = 62$ 46 Suicide 16 Controls 62 French Canadian descent 62 male		Suicide	Postmortem dentate gyrus samples	Genome-wide DNA methylation	Microarray hybridization	366 promoters were differentially methylated in suicide completers relative to compari- son subjects (273 hypermethylated and 93 hypomethylated)
Yang et al.	2013	$n = 192$ 96 abused children 96 controls 17%European-American 38% Hispanic 30%African-American 15%biracial 42% male	Childhood trauma (mean of three substantiated reports of abuse or neglect)		Saliva	Genome-wide DNA methylation	Illumina Human Methylation 450k array	Maltreated and control children had significantly different methylation values at 2868 CpG sites in numerous genes related to health problems associated with early childhood adversity

List of abbreviation: 5HTT, Serotonin transporter protein; 5HTTLPR, Serotonin-transporter-linked polymorphic region; AAI, Adult Attachment Interview; ACE, Angiotensin-converting enzyme; ADCYAP1R1, PAC1 gene; AMD1, Adenosylmethionine Decarboxylase 1; ANXA2, Annexin A2; APC5, Anaphase Promoting Complex Subunit 5; ARG2, Arginase 2; ASPD, Antisocial Personality Disorder; BDNF; Brain Derived Neurotrophic Factor; BPD, Borderline personality disorder; CAS, Composite abuse scale; CLEC9A, C-Type Lectin Domain Family 9 Member A; COMT, Catechol-O-methyl transferase; CTQ, Childhood Trauma Questionnaire; DNMT, DNA methyltransferase; EBV, Epstein–Barr virus; GABA, Gamma-Aminobutyric acid; GR, Glucocorticoid receptor; IGF2, Insulin-like growth factor 2; IL, Interleukin; LINE-1, Long interspersed nucleotide element 1; MAN2C1, Mannosidase, Alpha, Class 2C, Member 1; MAOA, Monoamine oxidase A; MDD, Major Depressive Disorder; NGFI-A, Nerve growth factor-induced protein A; NR3C1, Glucocorticoid receptor; OAZ, Ornithine Decarboxylase Antizyme; OXTR, Oxytocin Receptor; PAC1, Pituitary adenylate cyclase-activating polypeptide type I receptor; PTE, Potentially traumatic event; PTSD, Post Traumatic Stress Disorder; SAT1, Spermidine/spermine N1-acetyl-transferase; SERT, Serotonin transporter; SLC6A4, Solute carrier family 6 member 4; SLC6A3, Solute carrier family 6 member 3; SNP, Single nucleotide polymorphism; TEI, Trauma Experience Integration; TLR8, Toll-like receptor 8; TPR, Translocated promoter region, nuclear basket protein; TrkB, Tropomyosin receptor kinase B; TSST, Trier Social Stress Test; UTR, Untranslated region.

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neurotransmitter neuropeptide and is involved in the regulation of anxiety, depressive-like behavior and social behavior such as maternal care and partner bonding (Neumann and Landgraf, 2012). Murgatroyd et al. (2009) reported that early life stress, modeled by early maternal separation in mice, caused an increased secretion of corticosterone accompanied by changes in gene expression and DNA methylation within the promoter region of the *Avp* gene. Interestingly, the long lasting endocrine phenotype induced by the early life stress could be partly reversed by administration of AVP receptor antagonist, highlighting that understanding epigenetic mechanisms can identify targets for treatment. The authors have identified the molecular mechanisms behind these changes in DNA methylation and we will delineate them in more detail below, when describing the role of the methyl-DNA binding protein MeCP2 in stress-related epigenetic changes. For the *crh* gene, Elliott et al. were the first to show that this gene is epigenetically regulated by exposure of adult mice to a social defeat paradigm (Elliott et al., 2010). Here, mice susceptible to stress exposure exhibited lower DNA methylation in regulatory elements of the *crh* gene with subsequent alterations of mRNA transcription and behavior compared to resilient mice. In addition to these three genes *Fkbp5*, a co-chaperone and regulator of the GR has been implicated in the stress response in mice (O'Leary et al., 2011; Touma et al., 2011). Although no direct evidence for DNA methylation modification of *fkbp5* in response to early life stress in rodents emerged so far, Lee et al. showed that the methylation status of rodent *fkbp5* is a sensitive indicator of the amount of corticosterone released over several weeks and therefore stress exposure (Lee et al., 2010, 2011).

These studies suggest that early life stress is likely to influence the regulation of the stress hormone system at several different levels and a concerted genomic effect of stress on a number of genomic regions is supported by studies investigating the DNA methylation in larger genomic regions or the whole genome.

The majority of studies investigating DNA methylation patterns in humans have been performed in either postmortem brain samples or in peripheral blood cells. These studies can broadly be categorized into those assessing DNA methylation among patients with psychiatric diseases and those assessing DNA methylation in individuals with a history of trauma exposure but no psychiatric diagnosis. Furthermore, both candidate-based as well as unbiased genome-wide studies of DNA methylation have been reported in humans. For instance, disruption or lack of adequate nurturing as evidenced by parental loss, childhood maltreatment and parental care was significantly associated with GR promoter methylation (Tyrka et al., 2012) In other studies, SLC6A4 DNA methylation differences were observed among individuals with a history of childhood physical aggression in one study in T cells and monocytes (Wang et al., 2012) and with early adversity and major depressive disorder in another study in leukocytes (Kang et al., 2013a,b). We summarize these results in Table 1 and highlight findings related to the HPA axis along the lines of the animal studies described above as well as genome-wide studies in the following paragraph. In the next section we will emphasize similarities and differences in DNA methylation findings between animal and human studies and discuss the influence of tissue availability in human studies. Furthermore, in contrast to animal studies in predominantly inbred rodent strains, human studies need to consider genetic variability and thus need to include the individual genetic predisposition in gene by environment interaction approaches.

3.2. Parallel findings between stress-related changes in animals and humans in specific genomic regions

In analogy to the studies by Weaver et al. (Weaver et al., 2004), McGowan et al. (2009), investigated the extent of DNA methylation in the promoter region of the glucocorticoid receptor (*NR3C1*) gene in hippocampal tissues obtained from suicide victims with or without a history of early adversity and controls. The authors investigated the human *NR3C1* promoter homolog of the exon I_7 promoter region previously examined in the rat and found differences in the level of methylation depending on exposure to early adversity. Total glucocorticoid receptor expression was significantly lower in suicide victims with childhood abuse compared to suicide without childhood abuse history. Comparable to the results of the rodent studies the NR3C1 promoter showed altered methylation status with increased DNA methylation at NGFI-A binding sites in abused suicide victims. Using in-vitro patch methylation the authors further demonstrated reduced NGFI-A transcription factor binding to the hypermethylated human promoter and also decreased NGFI-A induced GR gene expression.

Suderman et al. (2012) expanded these studies and investigated DNA methylation profiles of a 6.5 million base pair locus centered at the NR3C1 gene in the hippocampus humans who experienced childhood abuse and non-abused controls and compared these to corresponding loci in rats that received differential levels of maternal care. Specific gene promoter methylation patterns were seen in both species, providing genome-level evidence for analogous cross-species epigenetic regulatory response in response to early life trauma. As suggested by previous results for rat (McGowan et al., 2011), the human locus also showed widespread orchestrated methylation changes, with regions of hyper- and hypomethylation. The human locus revealed a total of 281 differentially methylated regions (DMRs). 126 DMRs showed higher methylation in the controls and 155 showed higher methylation in individuals with childhood abuse history. In rats, the amount of DMRs was twice as much with 373 DMRs in rats more methylated with higher maternal care compared to 350 DMRs with increased methylation with low maternal care. The authors speculate that this difference is possibly due to the larger genetic variability in human and the much more defined environmental exposure to maternal care in rats. Interestingly, only about 8% of all DMRs in rat and human intersect promoter regions. In humans with childhood abuse, differentially methylated regions are enriched in promoter and first as well as last exon regions containing methylation sensitive transcription factor binding sites. In contrast, DMRs in control subjects are depleted for these regions. Interestingly, the most pronounced methylation differences were seen outside of the NR3C1 locus. In rat, the enrichment of DMRs between low and high maternal care was also specific to genomic regions outside of the promoter region but did not exactly match the human findings. This may reflect that the effects of low maternal care are certainly not directly analogous to human childhood abuse. Despite these differences in the environmental challenge, the authors found a strong overlap between DMRs in the protocadherin gene locus in rat and human. In both species, this locus was enriched for DMRs with higher methylation in abused (human) and low maternal care (rat) samples respectively.

4. Gene by environment interaction

DNA methylation and demethylation is one layer of the dynamic response of an organism to environmental factors. The epigenetic adaption in response to environmental cues, however, is influenced by the DNA sequence, i.e. the genetic predisposition of the organism, and its three dimensional organization. The DNA sequence itself encodes information about its methylation status and this has been demonstrated for genetic variants, including single nucleotide polymorphisms (SNPs) that influence the DNA methylation status in *cis* (Gertz et al., 2011; Kerkel et al., 2008). In addition, local DNA sequences can direct and target DNA binding

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factors and enzymes of the DNA methylation machinery (Velasco et al., 2010; Wienholz et al., 2010). Genetic variations not only influence the DNA methylation patterns but also account for differences in the three dimensional organization of the chromatin. In recent years, chromatin conformation capture and related techniques have revealed that DNA organization and regulation is complex and is far from being linear (Lieberman-Aiden et al., 2009; Splinter and de Laat, 2011). In fact, DNA is a three-dimensional construct that forms physical contacts between distal genomic locations or even discrete chromosomes by protein mediated looping (Lomvardas et al., 2006). This non-random organization of the DNA allows regulatory elements distal or proximal to the gene to come in contact with the promoter site and to modify the expression pattern. We are only at the beginning of understanding this three dimensional organization and its implications for psychiatric disorders (Mitchell et al., 2013). First evidence indicates that genetic variations also influence the formation of this complex chromatin structure. For example, we were able to show that an SNP in the intron 2 of the FKBP5 gene influences the loop formation between this intronic enhancer element containing glucocorticoid response elements (GREs) and the transcription start site thus influencing the transcriptional activation of FKBP5 in response to stress (Klengel et al., 2013). This loop formation also effects early trauma exposure dependent DNA methylation status at another enhancer element in intron 7 further influencing FKBP5 gene expression. Thus, a genetic variation shapes the three-dimensional chromatin conformation of the FKBP5 locus leading to a differential transcriptional activation of the gene in response to stress that in turn influences long-term GR-guided changes in DNA methylation in another intron GRE of this gene leading to a deregulation of the negative feedback of the GR and in consequences a dysregulated stress hormone axis response (Klengel and Binder, 2013; Klengel et al., 2013).

In addition to the examples mentioned here numerous studies with a range of different designs investigated the influence of trauma and early life stress on DNA methylation. In Table 1 we summarize human studies focusing on trauma and early life stress but also studies that explore DNA methylation differences in individuals suffering from major depression or PTSD and with suicide attempts. A handful of studies have made use of the powerful discordant twin study design that is able to attribute the methylation changes to individual-specific exposure rather than the genetic makeup or shared familial environment (Byrne et al., 2013; Ouellet-Morin et al., 2013).

5. Genome-wide studies in animals and humans

As described above, McGowan et al. (2011) investigated DNA methylation changes in response to maternal care at a larger genomic region around the rat GR gene and found hyper- as well as hypomethylation that cluster in gene families and pathways. In line with these findings Provencal et al. investigated genome-wide promoter DNA methylation differences in the prefrontal cortex of rhesus monkeys exposed to differential rearing in early life. The authors also found hyper- and hypomethylation in response to the type of rearing condition. They observed that DNA methylation changes tend to cluster in gene families over larger genomic regions and in spite of the relatively low absolute methylation change for each single locus these differences effect transcriptional regulation by co-regulation of gene pathways and families. We discuss this study more detail below with respect to tissue specificity of stress-related effects on DNA methylation (Provencal et al., 2012).

Investigating hippocampal tissue from 25 suicide completers with a history of child abuse and 19 control subjects without child abuse, Labonte and colleagues performed a comprehensive genome-wide promoter screen investigating the extent of DNA methylation changes (Labonte et al., 2012a,b). The authors observed 362 differentially methylated probes distributed evenly across the genome with 248 probes showing higher levels of DNA methylation and 114 showing lower levels of DNA methylation in abused suicide completers compared to controls. Changes in promoter methylation were accompanied by changes in gene expression in a network of genes enriched for neuronal plasticity including cell adhesion and cell plasticity.

The observations that DNA methylation changes are not limited to the brain but are also observed in peripheral systems highlight their system-wide influence. In a recent study, we demonstrated that among individuals with PTSD, distinct patterns of gene expression and higher contribution of DNA methylation underlying gene expression differences are observed among those patients with a history of childhood abuse (Mehta et al., 2013). This study provides evidence for different underlying biological mechanisms of stress-related psychiatric disorders depending on the timing and type of environmental risk factors, in this case the presence or absence of childhood abuse in PTSD patients all exposed to high levels of adult trauma. In fact, the transcripts and in part gene pathways differentially expressed in patients with PTSD exposed to child abuse or with PTSD but no exposure to child abuse as compared to the same trauma exposed controls were non overlapping. We observed that the differences in gene expression were accompanied more often (up to 12 fold more often) by changes in DNA methylation in the same locus in the PTSD cases with child abuse than the cases without exposure to child abuse. This indicates that the biological mechanism underlying the gene expression changes were different among PTSD patients with and without child abuse, with a higher rate of changes in DNA methylation associated with transcripts differentially regulated in PTSD with child abuse. We next questioned whether these DNA methylation changes only accompanied gene expression changes or whether there was a possible mechanistic relationship between the two processes. In fact, for vast majority (73%) of differentially methylated CpGs, methylation levels showed a significant correlation with gene expression of the closest transcript in the whole sample. While for the CpG sites located around the transcription start site, all correlations were negative, positive as well as negative correlations were observed for CpGs located in other gene regions, with almost equal amounts of positive and negative correlations for CpGs located in the gene body or upstream promoter regions. This indicates that early trauma-related effects on DNA methylation were observed in enhancer as well as repressor regions. We then tested whether the case/control differences in gene expression matched the expected case/control differences in DNA methylation. For 94% of the loci, the observed direction of the DNA methylation changes were consistent with what was expected, suggesting that the gene expression differences appear to be mediated by differences in DNA methylation differences. This was the case, even though the case/control differences in DNA methylation levels were modest (98% were less than 5%), highlighting the fact that even small differences in DNA methylation could be of functional relevance. Interestingly, CpGs with significant child abuse-dependent differences in methylation were less likely located in CpGs islands and more common in areas termed open sea, i.e. not close to a CpG island. This was also reflected in a moderate enrichment in the gene bodies, vs. promoter areas. This suggests that early trauma-related changes maybe preferentially impacting more long-range regulatory regions hence widening the search locus instead of a genocentric approach is essential for detection of DNA methylation changes in stress-related disorders.

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6. Crosstalk between DNA methylation and other epigenetic mechanisms

Epigenetic changes in response to stress and trauma are not exclusively limited to DNA methylation but also include other epigenetic modifications and mechanisms such histone modifications including but not limited to phosphorylation, acetylation, methylation and ubiquitination as well as effects of stress on non-coding RNAs/miRNAs. Over the recent years, it has become clear that these epigenetic mechanisms are not independent but work together in various combinations and cross-regulate each other (Feil and Fraga, 2011; Iorio et al., 2010; Levenson and Sweatt, 2005; Maddox et al., 2013; O'Connor et al., 2012; Sun et al., 2013; Sweatt, 2009; Szulwach et al., 2010; Tsankova et al., 2006). For instance, methylation of histone H3 at lysine 4 (H3K4me2 or H3K4me3) can suppress nearby DNA methylation and hence decrease repression of gene transcription (Ooi et al., 2007). miRNA can down regulate both DNA methylation or histone modifications and conversely DNA methylation or histone modifications can influence miRNA transcription, hence all epigenetic modifications communicate to control cellular function via a common regulatory network (Iorio et al., 2010).

A better understanding of DNA methylation and its link to other epigenetic modifications will be important. Higher resolution detection methods that allow accurate estimation of different epigenetic modifications at the level of a single cell will provide a holistic outlook of the crosstalk interactions between epigenetic regulatory complexes and their downstream effects.

7. DNA methylation – methodological aspects, including tissue specificity

There are other methodological and technical considerations when interrogating DNA methylation patterns. Compared to epigenetic findings from other medical fields such as cancer research, the magnitude of methylation changes observed in these studies is small in size. Methylation differences beyond 10% are not common and many studies even report changes that are sometimes very close to the detection limits of the respective assays. The reason for these small changes might on one hand side be due to the fact that stress, trauma and psychiatric disorders do not lead to an alteration of a broad transcriptional signature such as in cancer but rather induce more discrete adjustments of signal transduction pathways. Also, it is likely that epigenetic changes are present only in specific cell types and assessing mixed tissues such as peripheral blood might dilute these epigenetic differences as compared to tumors where almost all cells will have similar epigenetic changes. On the other side, many studies in the past have focused on areas such as promoter sites and CpG islands that have little or no methylation at all. This raises the crucial question about where one expects DNA methylation changes to be observed in response to stress. Most studies assessing methylation changes are limited to assaying DNA methylation within promoter regions only for reasons of feasibility. Provencal et al. (Provencal et al., 2012) showed that the majority of DNA methylation changes occur throughout long stretches of the genome with a higher prevalence in regulatory elements outside classical promoter areas. Had the authors not examined the entire genomic loci of these genes using a combination of methylated DNA immunoprecipitation (MeDIP) and comprehensive high-density oligonucleotide arrays, they would have missed almost all of the identified differentially methylated regions. This study highlights the importance of locus-wide search for DNA methylation changes in psychiatry.

The location and also extent of DNA methylation changes in response to stress might also depend on the type, timing, intensity and duration of the stressor. Different environmental factors might affect specific CG's in the genome that are vulnerable for modification in a specific developmental window only. This is exemplified by findings in the FKBP5 gene. Exposure to traumatic events in adulthood does not mimic the FKBP5 methylation observed following child abuse even when the genetic predisposition is taken into account. Most of the studies cited in this review link DNA methylation to the risk for a psychiatric disease. But DNA methylation might not only represent an environmentally induced risk factor but also the attempt of the body to adapt to different environmental conditions. DNA methylation in combination with genetic disposition can thus also be a factor influencing the resilience of an organism to environmental threats. This fact needs to be explored in more detail.

An additional issue is that of cause and effect. Most studies performed on DNA methylation in stress related psychiatric disorders were cross-sectional surveys that limit causal inferences. Unless a rigorous longitudinal study is performed where biological and phenotype measures are collected at every time-point, it is difficult to establish if the observed DNA methylation changes are a cause of an effect of the observed phenotype, hence directionality cannot be deduced from most studies assaying DNA methylation.

In addition to the above methodological and technical issues, studies of epigenetic mechanisms such as DNA methylation in humans are constrained by access to tissue. DNA methylation changes are tissue and even cell-specific hence the results need to be considered in the context of the tissue or cells assessed. A critical question is whether it is possible to obtain meaningful information from assaying DNA methylation in peripheral tissues such as blood cells for psychiatric disorders The immune system is responsive to early life stress and there is strong evidence of crosstalk between the brain and the immune system (Miller et al., 2005). Most of the studies listed in Table 1 assessed DNA methylation in peripheral blood cells. For some studies, the investigators included information on the blood cell composition by fluorescence-activated cell sorting (FACS) sorting analysis highlighting the fact that the blood cell composition is not confounded by cell types (Mehta et al., 2013). There are also computational methods by which an existing methylation dataset can be adjusted for different blood cell composition (Houseman et al., 2012). This method relies on methylation datasets that have been generated from different cell subpopulations before.

In addition to the challenge of cell heterogeneity within tissues, the question remains whether it is meaningful to interrogate peripheral tissue in order to investigate psychiatric diseases. While a large number of signaling cascades are specific to the brain and do not have equivalent counterparts in peripheral tissues, some pathways are common among tissues. For the investigation of blood maybe an appropriate tissue to interrogate effects of GR activation, as this receptor is also strongly expression in blood cells. Early life stress results in increased release of glucocorticoids and this could simultaneously target the same genes across diverse tissues since glucocorticoid receptors are present in most tissues (Thomassin et al., 2001). Subsequently, hormones like glucocorticoids, mineralocorticoids and other factors could mediate DNA methylation changes in response to early life stress in several tissues (Szyf, 2009, 2013). For example, we have recently demonstrated that the combination of genetic variation and exposure to early life stress was associated with methylation changes in the stress response regulator FKBP5 gene in white blood cells and that similar DNA methylation changes were observed after glucocorticoid exposure in human progenitor hippocampal neuronal cells (Klengel et al., 2013).

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Perroud and colleagues demonstrated that sexual abuse in childhood was associated with increased NR3C1 promoter methylation in peripheral blood and moreover, severity of childhood abuse and neglect was significantly and positively correlated with NR3C1 promoter methylation (Perroud et al., 2011). The promoter regions tested by the authors were identical to those assessed by McGowan et al. (2009) who assessed methylation in the brains of suicide controls. These findings suggest that methylation patterns in peripheral blood appear to be a good proxy for at least some specific methylation changes in the brain.

Furthermore, Provencal and colleagues assessed DNA methylation changes in early adulthood that were associated with differential rearing in rhesus macaques (Provencal et al., 2012). The authors tested the effects of maternal rearing on DNA methylation in both the frontal cortex and peripheral blood T-cells to investigate tissue-specific DNA methylation patterns and demonstrated that the impact of the early environment on DNA methylation was observed in both brain as well as peripheral T cells. There were indeed a small number of sites, in which similar rearing-dependent changes were observed in both tissues. These findings indicate that while global DNA methylation pattern are tissue specific, the biological consequences of early life stress appear to be detectable in more tissues, including in peripheral blood cells. Interestingly, in our recent study we have demonstrated that brain relevant pathways are enriched among genes with early trauma-related differences in DNA methylation in peripheral blood cells (Mehta et al., 2013). These results have important practical implications for utilization of peripheral blood tissues for identification of biomarkers for psychiatry.

In summary, these studies implicate epigenetic mechanisms as a critical link between early life environmental exposure and sensitivity to stressful events in later life, allowing an integration of preexisting genetic risk factors with and exaggerated response to stress and adult trauma, similar to that observed in patients.

8. Conclusions

The developmental origin hypothesis posits that certain early environmental exposures alter developmental trajectories, subsequently causing permanent changes in physiology and risk of disease (Gluckman et al., 2005). Epigenetic changes such as changes in DNA methylation following exposure to stressful life events provide a potential mechanism for the biological embedding of such environmental factors to regulate health and disease in humans. In this review we have outlined the literature on DNA methylation changes in psychiatric diseases psychiatric diseases including PTSD and MDD among others and provided an overview into possible mechanisms for stress-induced changes in DNA methylation, both on the candidate gene and genome-wide level. Even though DNA methylation pattern are cell-type- and in the context of neuronal wiring likely cell-specific, peripheral tissues can nevertheless reflect biological alterations caused by exposure to stress, highlighting its system-wide influence. Most of the studies that have assessed DNA methylation changes in humans have observed very modest effect sizes. These DNA methylation changes, albeit small, appear to be consistent across studies and seem to mediate gene expression changes in the expected direction, hence are possibly biologically meaningful. Since epigenetic changes such as DNA methylation mirror environmental influences as well as genetic variance, they maybe a more accurate predictor/correlate of disease risk than genetic markers by themselves and consequently have the potential as informative biomarkers for prevention and diagnosis of stress-related psychiatric disorders.

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