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Special issue paper

The role of epigenetics for understanding mental health difficulties and its implications for psychotherapy research

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Many mental health difficulties have developmental origins. Understanding the mechanisms for how psychosocial experiences are biologically embedded and influence lifelong development is a key challenge for the mental health disciplines. In recent years, epigenetic processes have emerged as a potential mechanism mediating the long-lasting vulnerability following the experience of adversity. Animal models provide evidence that early-life adversity can produce enduring epigenetic modifications in the brain, which mediate disorder-like behaviours, and there is emerging evidence to support that environmental factors influence epigenetic processes in humans. The investigation of DNA methylation, a chemical modification of the DNA with a role in gene regulatory processes, is becoming increasingly popular in psychological studies. A particular interest for the psychotherapy field lies in the potential for psychological interventions to influence epigenetic processes. Hence, the focus of this review will be on studies that have investigated intervention-associated changes in DNA methylation. Results of the first few studies will be critically reviewed, and a model of how therapy-associated changes of DNA methylation in peripheral, non-brain tissue might be useful as epigenetic biomarkers of treatment outcome will be presented.

Practitioner points

- Many mental health difficulties have substantial developmental origin. Epigenetic processes have emerged as a potential mechanism mediating the long-term effects of early adversity
- Epigenetic refers to cellular mechanisms that control gene expression states, independent of changes to the underlying DNA sequence. The epigenome can be highly dynamic and potentially influenced by external factors
- A particular interest for the psychotherapy field lies in the potential for psychological interventions to influence epigenetic processes.

Epigenetic mechanisms and the biological embedding of experience

It has long been recognized that many mental health difficulties have substantial developmental origin. A number of prenatal influences such as maternal psychosocial stress, psychopathology, smoking, or malnutrition (Gluckman & Hanson, 2004; Schlotz &

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Phillips, 2009; Thapar *et al.*, 2003) and postnatal adversities such as growing up in institutions, or experiencing abuse, neglect, or other forms of maltreatment have been found to increase risk for a wide range of negative health outcomes (Gilbert *et al.*, 2009; Sonuga-Barke *et al.*, 2017). Understanding the mechanisms for how psychosocial influences are biologically embedded and cause long-term alterations in structure and function of the central nervous system and brain-to-body communication systems is a key challenge for the mental health disciplines. In recent years, epigenetic processes have emerged as a potential mechanism mediating the observed long-lasting vulnerability following early adversity.

Epigenetics

DNA carries biological information. It consists of two chains made up of the four bases cytosine, guanine, thymine, and adenine and a sugar-phosphate backbone, and these chains coil around each other to form a double helix. Specific stretches of DNA contain instructions for the production of functional products, in most cases messenger RNA which act as templates for proteins, the building blocks of cells. This highly regulated process is influenced by epigenetic mechanisms. The most important epigenetic mechanisms are DNA methylation, histone modifications, and the control of gene expression through non-coding RNA.

Essentially, DNA and its associated proteins can be chemically modified without alterations to the underlying sequence, and these chemical modifications influence how genes are expressed, that is turned on or off. What is important is the fact the epigenetic mechanisms are responsive to changes in the environmental context. The implications for psychotherapy are first: how environments can alter and choreograph gene expression to fit different contexts. Second that this patterning of genetic expression can increase vulnerability to mental health problems as well as prosocial and antisocial behaviour. Third and particularly important is that psychotherapeutic and contextual interventions might target the regulation of genes and thereby produce bottom-up change into phenotypic expressions of various traits. Just as we understand now that the brain is more plastic than we thought, and that can be exploited through therapy, so gene expressions may be more plastic than we thought opening new avenues to understand the human mind in terms of how it matures in certain contexts and the potential for new therapeutic interventions.

Epigenetic processes are essential for normal cellular development, differentiation, and regulation of gene activity or function that occurs in the absence of changes to the DNA sequence. In contrast to the DNA sequence, the epigenome can be highly dynamic and potentially influenced by external factors and changes in internal milieu, thus providing a mechanism for the interaction of the genome with environmental influences. Several epigenetic mechanisms involved in the control of gene expression have been described, including DNA methylation, chromatin modification, and control of mRNA expression by non-coding RNAs (Jaenisch & Bird, 2003). Most epigenetic studies in psychology and the behavioural neurosciences focus on DNA methylation, which involves direct chemical modification of the DNA, that is methylation of cytosines in cytosine–guanine (CpG) dinucleotides (although non-CpG methylation rarely occurs). The relationship between DNA methylation and gene regulation is complex, and depends on a number of factors, including genomic localization: broadly speaking, DNA methylation in promoter regions of

genes is associated with reduced gene expression, whereas the opposite is observed for gene body DNA methylation (Schroder *et al.*, 2017; Stricker, Koferle, & Beck, 2017).

Since the first reports of associations between epigenetic alterations and cancer pathology, epigenomic changes have been correlated with the exposure to various nutritional, chemical, and physical risk factors (Feil & Fraga, 2012). The epigenetics field became particularly relevant for psychology with the seminal work published by the Meaney at the beginning of this century. Variations in the levels of maternal care were shown to program the stress response of rats, and these lifelong stable differences were mediated via epigenetic modifications of a gene critically involved in stress regulation. Specifically, low levels of maternal care during the first 10 days of life increased hippocampal DNA methylation in the promoter of exon 1_7 of the glucocorticoid receptor gene (*Gr, Nr3c1)*, which codes for the receptor for the stress hormone cortisol. Increased levels of DNA methylation decreased GR expression, which resulted in impaired negative feedback sensitivity of the hypothalamus–pituitary–adrenal axis (Weaver *et al.*, 2004). These programming effects were not limited to regulation of the stress response, as the effects of maternal care extended to fear-related behaviour and attentional processes under stressful conditions, synaptogenesis and cognitive development, female reproductive behaviour, and maternal care itself (Zhang & Meaney, 2010). Animal models thus provide powerful evidence that early-life adversity can produce enduring epigenetic modifications in the brain, which mediate disorder-like behaviours (Kundakovic & Champagne, 2015). It follows that many researchers have since been interested whether these findings translate to humans, specifically asking (i) whether psychosocial adversities lead to DNA methylation changes; (ii) whether DNA methylation changes are associated with psychopathology; and importantly, (iii) whether DNA methylation changes mediate the effects of psychosocial adversity on psychopathology.

A growing number of studies have provided evidence for an association between exposure to a range of psychosocial adversities early in life and altered DNA methylation levels. These include prenatal factors like maternal anxiety and depression (Hompes *et al.*, 2013; Oberlander *et al.*, 2008), self-reported maternal stress (Rijlaarsdam *et al.*, 2016), as well as objectively recorded maternal stress during natural disasters like the Quebec ice storm (Cao-Lei *et al.*, 2014). Postnatal risk exposures include poverty (Borghol *et al.*, 2012), childhood stress (Essex *et al.*, 2013), institutional rearing (Esposito *et al.*, 2016; Kumsta *et al.*, 2016), childhood maltreatment in the family context (Cecil, Smith, *et al.*, 2016), and bullying (Ouellet-Morin *et al.*, 2013). Because of the small overlap with respect to risk exposure and design of the published studies, it is currently difficult to come to integrative conclusions, and the notion of a specific adversity-related epigenetic signature awaits confirmation. Of note, a negative finding has been reported in a very well-powered study (sample size of > 1.600) embedded in the longitudinal E-RISK study. There was no evidence between exposure to adversity in childhood or adolescence and DNA methylation levels, neither genome-wide nor in selected stress-related genes (Marzi *et al.*, 2018).

The situation is similar with regard to studies that have examined associations between DNA methylation and mental disorders. There is evidence of altered epigenetic processes in a range of psychopathologies, including disorders of childhood and adolescence (reviewed by Barker, Walton, & Cecil, 2018), depression (Story Jovanova *et al.*, 2018), schizophrenia (Pries, Guloksuz, & Kenis, 2017), and Alzheimer's disease (De Jager *et al.*, 2014; Lunnon *et al.*, 2014). Of note, several of these studies have investigated post-mortem brain tissue and have taken further steps to biologically characterize DNA methylation associated processes, strengthening functional interpretation of observed alterations. Similar to the studies cited above, however, there was little overlap in the

identified differentially methylated sites, again most likely due to differences in analytical strategy and study design. Also, studies of mental disorders were cross-sectional, and findings might reflect reverse causation, that is an effect of psychopathology on DNA methylation levels. To establish a mediation model in which altered DNA methylation levels link exposure to psychopathology risk, the exposure should occur before DNA methylation. As recently reviewed by Barker *et al.* (2018), only four studies so far have examined DNA methylation in relation to both risk exposures and outcomes, three of which come from the longitudinal ALSPAC study. To cite an example, Cecil, Walton, *et al.* (2016) investigated epigenome-wide, prospective associations between DNA methylation in cord blood and blood samples taken at age 7 years and substance use in adolescence. DNA methylation variation at 65 CpGs at birth was associated with an earlier age of abuse onset among users and greater levels of substance use during adolescence. Collectively, these CpG sites mediated the influence of maternal smoking during pregnancy on adolescent substance use. Interestingly, across the three ALSPAC studies, only DNA methylation variation at birth but not at later time points was identified as mediator of prenatal influences (Barker *et al.*, 2018).

Overall, compared to animal models, the picture of environmental regulation of the epigenome and its role in psychopathology appears more heterogeneous in humans. Despite some difficulties in the interpretation of findings, few doubt that epigenetic processes are highly relevant developmental mechanisms that will help to explain how characteristics of the early environment are linked to health and disorder later in life. As argued by others, further understanding of the basic biology of gene regulation, as well as improvements in analytical approaches and study design, will increase chances of determining cause and effect in longitudinal studies and will clarify the extent to which DNA methylation pattern may truly mediate psychosocial influences on the development and course of psychopathology (Barker *et al.*, 2018; Lappalainen & Greally, 2017; Mill & Heijmans, 2013).

Epigenetics in psychotherapy research

Intervention-associated changes of DNA methylation

As outlined above, exposures to unfavourable environments can lead to long-lasting alterations in DNA methylation. Given that DNA methylation patterns are more dynamic than previously thought (Wong *et al.*, 2010), and given that DNA methylation continues to be responsive to environmental influences across the life-span (Dekkers *et al.*, 2016; Joehanes *et al.*, 2016), there is growing interest in the potential for psychological interventions to influence these biological processes. So far, six studies have been published that assessed DNA methylation before and after therapeutical intervention. These will be briefly reviewed, differences and commonalities will be discussed, and caveats in the interpretation of results will be outlined.

The first study to investigate epigenetic alterations as therapy-associated markers was conducted in combat veterans with PTSD (Yehuda *et al.*, 2013). Given the role of stress in the aetiology of PTSD and findings of altered HPA axis function, the focus was on two genes with important regulatory function for the HPA axis: *NR3C1* and *FKBP5*. Patients received prolonged exposure psychotherapy for 12 weeks, and biomaterial was sampled at pre-treatment, post-treatment, and after 3-month follow-up. Half of the patients showed a therapy response, whereas the other half still met PTSD diagnostic criteria. Higher *NR3C1* pre-treatment DNA methylation levels were associated with lower post-treatment PTSD symptom severity and a reduction of symptoms from pre- to post-treatment. *NR3C1* DNA methylation levels did not change over the course of therapy. *FKBP5* DNA methylation,

however, showed a therapy response-associated change, with a decrease of DNA methylation levels in therapy responders and an increase in non-responders. This pilot study (sample size $n = 16$) thus showed that DNA methylation levels of two genes important for stress regulation may be used as a predictive marker for therapy success (*NR3C1*) and that changes in DNA methylation might associate with treatment outcome (*FKBP5*), respectively.

The same two genes were investigated in a sample of children around the age of 10 years ($n = 98$) with anxiety disorders undergoing cognitive behaviour therapy (Roberts *et al.*, 2015). There was no association between pre-treatment DNA methylation in any of the CpGs in both genes and treatment response, defined as change in primary anxiety disorder severity from pre-treatment to follow-up. Furthermore, there was no change in DNA methylation form pre- to post-treatment when considering the group as a whole. Taking into account therapy response, however, there was a significant association between DNA methylation change in one of four CpGs and treatment outcome for the FKBP5 gene. In contrast to the PTSD study outlined above, a decrease in DNA methylation was associated with a greater reduction in symptom severity. The authors also investigated the interaction between genotype and DNA methylation on treatment outcome and found that therapy-associated *FKBP5* DNA methylation change was only observed in individuals carrying one or more minor alleles (designated as risk alleles) of five FKBP5 SNPs. A previous study has also demonstrated a *gene* by *environment* by *DNA methylation* interaction for the *FKBP5* gene (albeit at a different locus), where childhood trauma was associated with decreased DNA methylation in a genotype-dependent manner, which mediated the effect of early-life adversity on PTSD risk (Klengel *et al.*, 2013). These results suggest a genetic influence on differential responsivity towards both negative and positive environmental influences realized through genotype-dependent DNA methylation dynamics.

The same sample of children ($n = 116$) (Roberts *et al.*, 2014) was also investigated for DNA methylation of the serotonin transporter gene (*SLC6A4*), the most widely studied candidate gene in psychiatry. DNA methylation levels did not differ between pre- and post-treatment in the whole group; however, there were significant differences between responders and non-responders. Patients defined as responders at 6-month follow-up (but not at post-treatment) showed a small increase in *SLC6A4* methylation during the treatment period of one CpG site, whereas non-responders showed a decrease in DNA methylation. The difference in DNA methylation change was thus observed between those who continued to improve during the follow-up period, and those who worsened. For broad anxiety response, defined as the absence of all anxiety diagnoses, a similar pattern of results was observed.

Perroud *et al.* (2013) studied 115 patients with borderline personality disorder (BPD). Given the role of childhood maltreatment in the development of BPD, and given altered BDNF protein levels in BPD patients, the BDNF gene was considered as a target for epigenetic modifications as a consequence of early-life adversity. *BDNF* DNA methylation levels were assessed before and after a 4-week course of intensive dialectical behaviour therapy. Compared to controls, BPD patients had significantly higher DNA methylation levels (expressed as mean percentage across CpG sites in the two investigated regions), and there was a positive association between number of endorsed childhood trauma categories and DNA methylation levels. After therapy, DNA methylation increased in non-responders, whereas responders displayed no change or decreased when depression response was used as criterion. It needs to be noted, however, that DNA methylation levels were very low (below 1%) and that DNA methylation changes were below 0.3%. Furthermore, no association was observed between *BDNF* DNA methylation levels and BDNF protein levels in plasma.

In patients with panic disorder (PD; $n = 28$), DNA methylation levels in blood cells and their change over the course of a 6-week exposure-based cognitive behavioural therapy was assessed in a region covering exon 1 and parts of intron 1 of the monoamine oxidase A (MAOA) gene (Ziegler *et al.*, 2016). Given its location on the X chromosome, only females were investigated. The study also included a control group and a replication sample. As previously observed, MAO DNA methylation was lower in PD patients compared to controls, and there was a negative correlation between DNA methylation and PD severity. The experience of a lower number of panic attacks at post- versus pre-treatment was defined as the response criterion. In therapy responders, average *MAOA* DNA methylation (mean of 13 CpGs) increased, whereas it decreased in non-responders. There was no such therapy response-dependent change in DNA methylation in the replication sample when the same therapy response criterion was used. However, amelioration of agoraphobic avoidance correlated with DNA methylation increases in the replication sample.

Guided by findings from an epigenome-wide study on BPD, Knoblich *et al.* (2018) investigated DNA methylation in the APBA2 and in the MCF2 gene. Patients underwent a 12-week dialectical behaviour therapy, with DNA available for 24 patients who completed treatment. No differences in DNA methylation were observed between patients and controls, and no change in DNA methylation was observed between pre- and post-treatment. However, DNA methylation status of both genes predicted therapy outcome, in that higher DNA methylation at pre-pretreatment was observed in those who responded to therapy ($n = 7$).

As shown in Table 1, the studies conducted so far are very heterogeneous in terms of investigated samples, selected candidate genes, type of intervention, sampled tissue, and biochemical analyses of DNA methylation. A striking commonality of all studies is the observation that therapy responders and non-responders show divergent direction in their DNA methylation changes from pre- to post-intervention. DNA methylation change might thus be regarded as a marker or epigenetic correlate of therapy outcome.

However, caution is needed in the interpretation of findings with regard to several aspects. First, except for one study, no control group was investigated, so that possible stochastic fluctuations in DNA methylation over time cannot be ruled out. Second, the observed changes are small, and further, biological characterization is needed to confirm functional significance of the findings. Furthermore, the applied methods mostly have insufficient sensitivity to reliably assess such small DNA methylation differences. Third, it is unclear whether differences in DNA methylation pre-to-post-intervention reflect true DNA methylation changes and not changes in cell composition. Last, it is important to reflect on the meaning of peripheral DNA methylation changes, and to consider carefully whether – as suggested by some – changes observed in peripheral surrogate tissue can indeed inform about neuronal activity-dependent – that is learning-associated – changes in DNA methylation in neuronal tissue. The two latter important considerations will be discussed in more detail below.

Considerations for the study of DNA methylation in psychotherapy

Cell composition

In psychology and psychiatry, the most commonly used DNA sampling methods are cheek swabs, saliva samples, or blood samples. Both saliva samples and cheek swabs include buccal epithelial cells and white blood cells, with cheek swabs representing the more homogenous sample type. Blood includes up to ten major and several minor cell types. In contrast to the DNA sequence, which is largely identical across cell types (although

Table 1. Overview of studies that assessed DNA methylation before and after therapeutical intervention

	Disorder	*N*	Intervention	Gene	#CpGs	Tissue	Method	Control for cell composition	Control group
Yehuda *et al.*, (2013)	PTSD	16	Prolonged exposure psychotherapy	*NR3C1 FKBP5*	39 38	PMBCs	Bisulphite genomic sequencing of bacterial clones	No	No
Roberts *et al.*, (2015)	Anxiety disorders	98	CBT	*NR3C1 FKBP5*	4 4	Buccal cells	Epityper	No	No
Roberts *et al.*, (2014)	Anxiety disorders	116	CBT	*SLC6A4*	6	Buccal cells	Epityper	No	No
Perroud *et al.*, 2013)	Borderline Personality Disorder	115	Dialectical behaviour therapy	*BDNF*	26	PBMCs	High resolution melting analysis (HRM)	No	Not assessed longitudinally
Ziegler *et al.*, (2016)	Panic Disorder	28	Exposure-based CBT	*MAOA*	13	Whole blood	Bisulphite genomic sequencing of PCR products	No	Yes
Knoblich *et al.*, (2018)	Borderline Personality Disorder	24	Dialectical behaviour therapy	*APBA2 MCF2*	2 1	Whole blood	Pyro-sequencing	No	Not assessed longitudinally

mosaicism exists), DNA methylation patterns are highly cell type-specific. In case–control studies, a well-recognized source of variability of DNA methylation is the presence of systematic differences in cell-subtype proportions between the tested groups (Houseman *et al.*, 2012; Jaffe & Irizarry, 2014), with cell type within a tissue representing the second-biggest contributor to DNA methylation variation (Farre *et al.* 2015). This has important implications for the interpretation of DNA methylation differences between groups, and between time points in the same individuals. If two samples, for example pre- and post-intervention, with different cell type compositions are compared, then the differences between the samples will primarily reflect those differences in cell type, which might be unrelated to the effect of intervention (Figure 1). The composition of the circulating leucocyte pool is dynamic and influenced by various external factors, including infections or stress exposure – indeed, leucocyte composition can rapidly change in response to stress (Cole, 2010). It is thus critical to account for cell composition when attempting to elucidate the causal effects of intervention on DNA methylation changes.

When using blood samples, simple blood cell count can be used to strip away variations in DNA methylation that can be attributed to differences in leucocyte subset

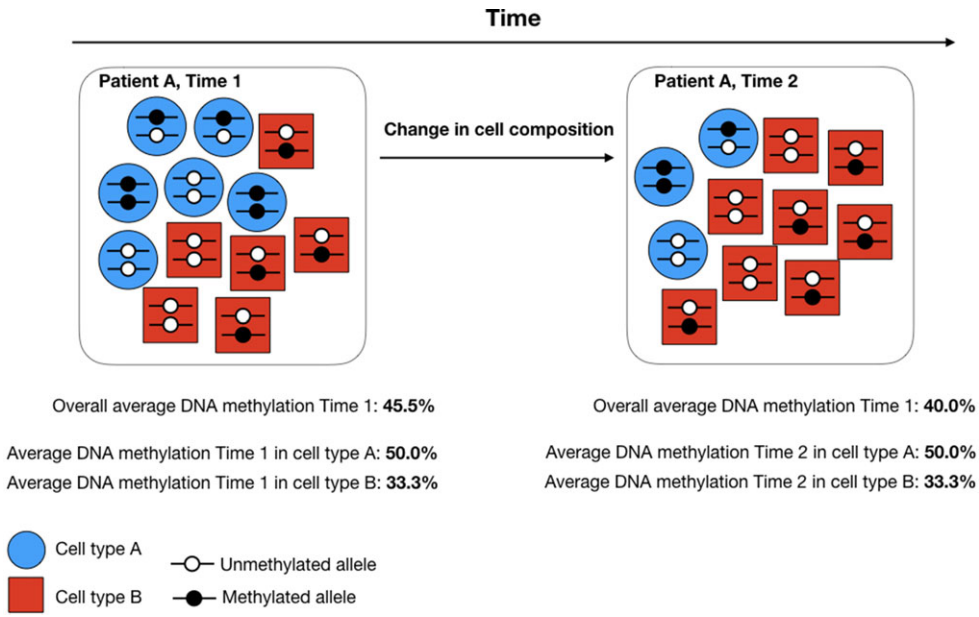

Figure 1. shows hypothetical tissue sample with two cell subtypes A and B at two sampling points, for example pre- and post-intervention. In a single cell, the cytosine on a pair of chromosomes can be methylated on both (representing 100% DNA methylation), neither (representing 0% DNA methylation), or one of the alleles (representing 50% DNA methylation). In patients' DNA samples, up to a few millions of cells are measured at the same time, so that DNA methylation is expressed as a continuous measure with ranges from 0 to 100%. Change in the overall DNA methylation of a sample can be the result of either cellular reprogramming, that is change of DNA methylation at specific CpG sites (not shown), or the result of changes in cellular composition. In that case, DNA methylation in respective subtypes of cells does not change, but the overall DNA methylation of the tissue will differ because of a higher abundance of cell types with a different DNA methylation patterns. This highlights the importance of taking into account cell composition when interpreting change over time. [Colour figure can be viewed at wileyonlinelibrary.com]

composition. More labour-intensive methods include physical isolation of cells via cell sorting or immunomagnetic isolation (Schwaiger *et al.*, 2016). In epigenome-wide association studies, the relative proportions of cell types can be inferred and controlled for through comparison with DNA methylation profiles created from isolated cell types (available for brain and commonly used surrogate tissues such as blood, cheek swab, and saliva (Houseman *et al.*, 2012; Smith *et al.*, 2015)). For less well characterized cell types, reference-free methods exist (Lutsik *et al.*, 2017; Rahmani *et al.*, 2016).

The meaning of DNA methylation changes in peripheral cells

An extensively discussed question concerns the utility of quantifying DNA methylation variation in cells derived from peripheral tissues when the brain is the primary organ of interest (Heijmans & Mill, 2012; Mill & Heijmans, 2013). Surrogate tissue can be informative even if the investigated tissue are not directly involved in the phenotype of interest, as they might reflect the exposure to environmental influences (as has been shown, e.g., for the effects of prenatal subnutrition (Tobi *et al.*, 2018), chemicals (Leung *et al.*, 2018), psychosocial adversity (Kumsta *et al.*, 2016), or combat (Rutten *et al.*, 2018). Thus, although variation in peripheral tissue may not directly reflect epigenetic variation in the brain, they may still represent useable biomarkers as they report of an exposure that causes the phenotype in a different tissue (Hannon, Lunnon, Schalkwyk, & Mill, 2015).

In the case of intervention-associated DNA methylation changes, the situation appears more complex. The role of epigenetic mechanisms in learning and memory processes is well established; however, any learning-associated changes in chromatin or DNA methylation will be specific for neuronal cells. As buccal epithelium or leucocytes do not have a biologically realistic link to cellular processes occurring in neurons, intervention-associated epigenetic changes triggered by neuronal activity will most likely not be reflected in peripheral surrogate tissue (Figure 2). But again, although leucocytes or buccal cells might not be a 'window to the brain', it might still be of value to investigate therapy-associated DNA methylation changes in peripheral cells as biomarkers of therapy outcome. In the case where the effects of intervention on stress–immune interplay are of interest, blood cells may even be the primary tissue of interest (see below). Following a brief introduction to epigenetic mechanisms of learning, a model that incorporates potential pathways that might convey intervention effects to peripheral cells will be introduced below.

Epigenetics of learning

Psychological interventions such as cognitive behaviour therapy and especially exposure therapy rely on learning and other memory-related processes, and it is increasingly recognized that learning-associated changes in neuronal plasticity represent the neurobiological basis for psychological treatments (Margraf & Zlomuzica, 2015). As noted by Kandel (1998), substantive changes in behaviour following psychotherapy will have been brought about by intervention-associated alternations in gene expression. As epigenetic mechanisms control gene expression states, they represent prime candidates to understand cellular mechanism of learning processes, and to understand how psychological interventions that rely on fundamental learning principles can lead to stable extinction of old as well as formation of new memories.

A definition of epigenetics readily embraced by researchers of memory processes is of 'structural adaptation of chromosomal regions so as to register, signal, or perpetuate

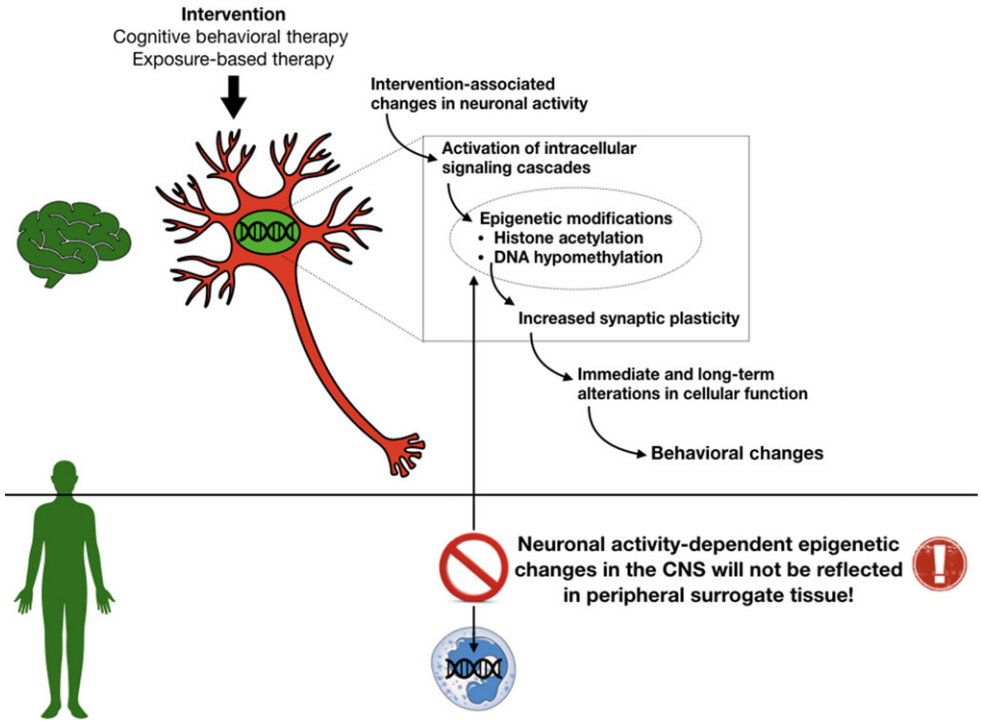

Figure 2. Many psychological interventions rely on learning mechanisms, and learning-associated rewiring of neuronal circuits is thought to contribute to therapy-associated behavioural changes. Epigenetic processes triggered by changes in neuronal activity are involved in synaptic plasticity and are likely involved in stabilization of new and extinction of old memories, respectively. These activity-dependent epigenetic changes will not be reflected in peripheral cells. [Colour figure can be viewed at wileyonlinelibrary.com]

altered activity states' (Bird, 2007). This definition implies that epigenetic modifications react to neuronal activity triggered, for example by learning of new information, and that they can convey such information into specific gene expression programs, a prerequisite for the formation of long-lasting memories (Kandel, 2001). Neuronal activity results in a variety of coordinated modification to chromatin and DNA methylation (Graff & Tsai, 2013; Nagy, Vaillancourt, & Turecki, 2018). Although the exact mechanisms are still being elucidated, there is convincing evidence that learning-associated changes of neuronal activity transiently induce epigenetic modifications, which lead to altered gene expression patterns driving synaptic plasticity and ultimately result in memory formation and modification. This brief excursion was meant to highlight that epigenetic mechanisms are critical for learning and memory, and thus of great relevance for psychotherapy research. However, there is no plausible way to explain why these transient and activity-dependent alterations of chromatin and the possibly more stable alterations in DNA methylation in neuronal cells should be reflected in peripheral surrogate tissue.

Social genomics

Where does that leave the study of intervention-associated DNA methylation changes in non-neuronal cells? The premise for a meaningful interpretation of such changes is that

therapy-associated changes in thoughts, feelings, behaviour as well as the perception of the social environment are signalled to the periphery, down to the level of cellular function. Two major brain-to-body communication systems enable such cross talk between the CNS and peripheral organs, the autonomic nervous system and the HPA axis. The activation of these bio-behavioural systems under situations of acute threat or stress leads to increased secretion of the stress effectors noradrenalin and adrenalin, controlled through the sympathetic nervous system, and of cortisol, controlled by HPA axis activity. Their concerted effects on a multitude of physiological processes, including immune function and energy metabolism, enable the organism to cope with the stressor and ultimately also lead to the termination of the stress response through negative feedback mechanisms. In various mental disorders, dysregulations of the stress response have been observed and are thought to be causally involved in disorder processes (McEwen, 1998). In the context of this paper, the effects of catecholamines and cortisol on circulating immune cells are of particular interest. Stress system mediators engage cellular receptor system, which ultimately regulate the transcription of genes, with specific biochemical signals inducing specific gene expression responses. Several studies with individuals exposed to social adversity, chronic or traumatic stress, or facing imminent bereavement have revealed a specific transcriptional profile – termed conserved transcriptional response to adversity (CTRA) – characterized by enhanced expression of pro-inflammatory immune response genes and a reciprocal downregulation of antiviral immune response genes (Cole, 2014). Interestingly, randomized controlled studies have shown that CTRA gene expression profiles can be suppressed or reversed by interventions such as cognitive behavioural stress management (Antoni *et al.*, 2012), prosocial behaviour (Nelson-Coffey, Fritz, Lyubomirsky, & Cole, 2017), meditation (Black *et al.*, 2013; Creswell *et al.*, 2012), yoga (Bower *et al.*, 2014), and Tai Chi (Irwin *et al.*, 2014). Apart from intervention effects, an association between a psychological trait and gene expression profiles was reported. Individuals who showed eudaimonic well-being, a form of well-being that stems from devoting one's efforts to purpose outside the self or a noble cause showed lower levels of CTRA-related gene expression compared to people who showed high level of hedonic well-being, a more self-focused form of well-being generated by the pursuit of positive emotional experiences and consummatory self-gratification (Fredrickson *et al.*, 2013, 2015).

Taken together, the emerging field of social genomics provides a framework of the relationship between the social context and genome function. Importantly, this model can also be used to derive testable hypothesis of the relationship between stress mediators, immune cell gene expression profiles, and variation in DNA methylation. It is likely that the observed alteration of gene expression profiles following diverse intervention come about through changes in upstream signalling of stress mediators, which might also lead to changes in DNA methylation, as has been shown for glucocorticoid receptor action (Zannas & Chrousos, 2017). Altered DNA methylation levels might either merely reflect these overall changes in physiological and cellular milieu associated with treatment effects, and thus be regarded as biomarkers of treatment outcome, or they might be causally involved in altered cellular functions and possibly stabilize beneficial effects of intervention through effects on stress receptor function, normalizing cellular responsivity to stress mediators (Figure 3).

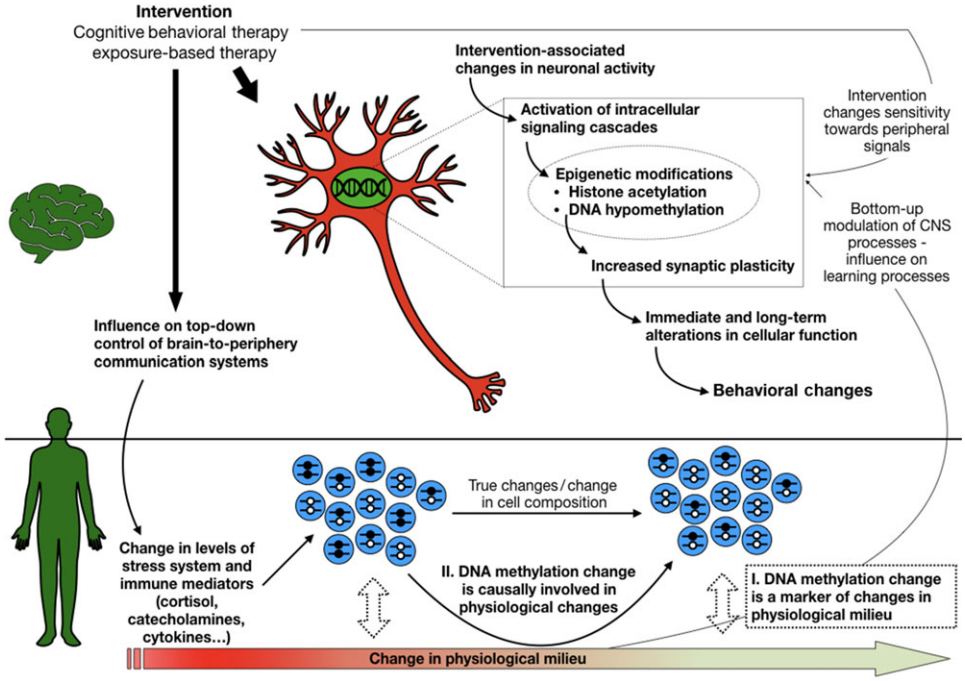

Figure 3. In addition to targeting associative memory processes, many interventions have been shown to influence top-down control of brain-to-body communication systems that relay perceived signals of the social environment (e.g., threat vs. safety). Indeed, many interventions normalize the activity of stress response systems, and changes in the levels or function of circulating stress hormones can influence gene regulatory processes and possibly alter DNA methylation levels. Changes of DNA methylation at known binding sites for transcription factors can help to identify upstream signalling involved in the cellular reprogramming process. Therapy-associated changes of DNA methylation levels might either merely reflect changes in physiological milieu (biomarkers of treatment outcome), or they might be causally involved in altered physiological processes. Extensive bi-directional communication between periphery and central nervous system has been demonstrated, and there is abundant evidence showing the influence of stress and immune effectors on various cognitive and emotional processes. Thus, this bottom-up signalling provides for an additional pathway of intervention effects through changes in peripheral stress–immune interplay. [Colour figure can be viewed at wileyonlinelibrary.com]

Conclusions and outlook

Different interventions work better for some individuals than for others. A long-term goal, not only in the mental health field but in all of medicine, is to realize personalized treatment approaches. To achieve this, relevant mediators and moderators of treatment efficacy need to be identified. Several features are associated with response to psychological therapy, and these can be found in the characteristics of the social environment and the psychological characteristics of patients. However, part of the observed outcome heterogeneity is likely rooted in biological processes.

Epigenetic features might be used in the same fashion to predict outcome as in therapy genetics approaches, where DNA sequence variation is the biological predictor variable

(Bakermans-Kranenburg & van IJzendoorn, 2015; Eley, 2014; Wannemuller, Moser, Kumsta, Johren, & Margraf, 2018). The studies outlined above mark the start of attempts to identify such epigenetic therapy biomarkers. Interestingly, it was not so much the pre-treatment DNA methylation status, but rather the change in DNA methylation levels over the course of treatment that was associated with treatment outcome, with responders and non-responders diverging the direction of change.

An important consideration in the interpretation of these findings is tissue specificity of DNA methylations patterns. Peripheral surrogate tissue will not necessarily reflect DNA methylation status of brain tissue and will most likely not reflect changes in neurons that occur in response to learning and concomitant increases in synaptic activity. Still, DNA methylation changes in leucocytes or buccal epithelium can serve as a valuable peripheral epigenetic marker for treatment outcome, but caution must be exercised in leaping from markers to mechanisms. On the other hand, as the effects of therapy are not restricted to changes in neuronal connectivity, but extend to brain-to-body communication system, and thus influence peripheral stress and immune effectors, the investigation of epigenetic changes in immune cells might indeed be mechanistically informative when studying social regulation of stress–immune interplay (Kim *et al.*, 2016).

To date, there have not been any psychotherapies that have been developed specifically to generate epigenetic effects. Therapies like compassion focused therapy are beginning to explore this arguing that such interventions will likely need to be rooted in evolutionary salient stimuli. The most likely candidates here are basic evolve motivational system rather than specific cognition. For example, possibilities include the switching people from competitive motivational systems into caring motivational systems, which will recruit a different suite of autonomic and central nervous system processes.

It is still early days for therapy *epi*genetics, and so far, only a limited number of candidate genes with limited coverage of CpGs have been investigated. As array-based and next-generation sequence technologies become more affordable, a future goal will be to realize epigenome-wide studies of therapy response in the context of randomized controlled trials. Future studies should also incorporate genetic information, as DNA sequence variation is a major source of DNA methylation variation (Chen *et al.*, 2016). Lastly, studies should be designed in ways that maximize inference of biological significance of epigenetic modifications by including gene expression profiles and assessment of peripheral mediators with putative effects on DNA methylation changes, such as stress hormones and immune system effectors.

In the long run, different types of biomarkers, ranging from genetic variation, DNA methylation patterns and gene expression profiles together with a range of clinical information might help to guide treatment choices and help us move towards more personalized approaches in treatment of mental health difficulties.

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