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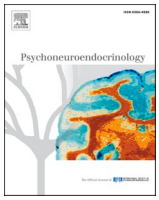

The role of stress in the biological embedding of experience - ISPNE 2023 Dirk Hellhammer Award

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ABSTRACT

Exposure to early adversity is one of the most important and pervasive risk factors for the development of nearly all major mental disorders across the lifespan. In the search for the mediating mechanisms and processes that underlie long-term stability of these effects, changes to stress-associated hormonal and cellular signalling have emerged as prime candidates. This review summarises evidence showing that experience of early adversity in the form of childhood abuse or neglect and exposure to severe institutional deprivation influences multiple interconnected bio-behavioural, physiological and cellular processes. This paper focusses on dysregulations of hormonal stress regulation, altered DNA methylation pattern, changes to transcriptomic profiles in the context of stress-immune interplay, and mitochondrial biology. Consistent findings that have emerged include a relative cortisol hypoactivity and hyporeactivity in response to challenge, increased activity of pro-inflammatory genes, and altered mitochondrial function. The majority of investigations have focussed on single outcomes, but there is a clear rationale of conceiving the implicated physiological processes as interconnected parts of a wider stress-associated regulatory network, which in turn is connected to behaviour and mental disorders. This calls for integrated and longitudinal investigations to come to a more comprehensive understanding of the role of stress in the biological embedding of experience. The review concludes with considerations of how stress research can contribute to translational efforts through characterising subtypes of mental disorders which arise as a function of early adversity, and have distinct features of behavioral and biological stress processing.

1. Introduction

How and why does the social become biological? This question, which featured as one of the top ten social science questions in 2010 (Giles, 2011), has also been framed by asking how "stress gets under the skin" (McEwen, 2012), or how "experience are biologically embedded" (Hertzman, 2012b). These questions are of relevance not only for our fundamental understanding of how living beings adapt to ever changing environments, both in the short and long run, but also have important social and clinical implications. It is now firmly established that exposure to adverse environments particularly early in life compromise well-being and pose long-term risk for many mental and physical disorders. The field of psychobiological stress research, or more specifically Psychoneuroendocrinology (PNE) and its sister Psychoneuroimmunology (PNI) are exquisitely well-positioned to contribute answers to these important questions. First, PNE/PNI are firmly situated in a bio-psycho-social theoretical framework, which provides for a model to explain the multifactorial aetiology of mental and other complex disorders. It emphasizes the role of biological factors by taking into account genetic risk factors and neurophysiological processes, but at the same recognises the importance of the psychosocial environment, both in relation to risk and resilience. Importantly, it has "stress" at its center ("diathesis-stress-model"), as a key precipitating factor for mental disorders. Second, PNE/PNI are concerned with describing cross-talk between the psychosocial and the physiological. Essentially, our field provides theory and methods to describe the mechanisms of signalling from brain to periphery and back to achieve psychophysiological adaptations needed in light of increased demands -

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or stress. These signals not only set in motion ultra-short and short-term changes, they are also capable of inducing long-term adaptations in a sense of "programming" physiology and behaviour to cope with anticipated environmental demands, forecasted through characteristics of early environmental and psychosocial exposures. In the past years knowledge has advanced regarding the way stress signals are transduced and how they influence physiology down to the level of the cell - including gene regulatory mechanisms and mitochondrial biology - and importantly, how theses signals might retain their stability. Different bio-behavioural systems have emerged as targets of the effects of the (early) environment, including stress physiology, social affiliation systems, prefrontal and limbic brain structure and function, the microbiome, gene regulation and mitochondrial biology, to name a few. These have been studied on individual level of analysis, and more recently, using more systems-oriented networks approaches, which take into account within and cross-level interaction; in the best case, investigators adopt longitudinal life-span approaches.

This review takes a non-exhaustive approach with a focus on the author's own contributions to the field, summarising work on long-term consequences of early adversity (including institutional deprivation) on stress regulation and stress-associated cellular adaptions.

2. The effects of early adversity and severe deprivation on HPA axis regulation

The hypothalamic–pituitary–adrenal (HPA) axis represent a particularly well-studied target for the effects of adverse childhood experiences. Both retrospective and longitudinal prospective studies have shown dsyregulations of the HPA axis, investigating diurnal cortisol secretion or cortisol patterns following awakening, and especially following exposure to acute psychosocial stress exposure, using experimental protocols like the Trier Social Stress Test (TSST). Whereas the first study linking adverse childhood experience (ACE) to differences in stress regulation found markedly increased ACTH and cortisol responses to psychosocial laboratory stress (most pronounced in women suffering from current depression (Heim et al., 2000), the majority of studies reports a relative cortisol hyporeactivity (Carpenter et al., 2007; Elzinga et al., 2008; Power et al., 2012; Schwaiger et al., 2016). This is corroborated by a meta-analysis including 30 studies, with results favouring relative cortisol hyporeactivity following acute stress exposure (Bunea et al., 2017). It has been suggested that when chronic stress first begins, there is an initial HPA hyperactivity, which diminishes as time passes. Exaggerated counter-regulation eventually results in below normal levels (Trickett et al., 2010). This is supported by a meta-analysis showing that cortisol outputs decreases as a function of time elapsed since stress exposure (Miller et al., 2007). A relative hypoactivity on the level of cortisol output can reflect changes in adrenal sensitivity in a concomitant state of CRH hyperactivity. This type of dysregulation can have substantial detrimental downstream effects, as negative counter-regulatory activity of cortisol is missing ("when not enough is too much"). This is especially relevant in the context of low-grade or systematic inflammation (Raison and Miller, 2003), one of the most replicated correlates of exposure to ACE in humans (see below).

Notwithstanding robust associations between early-life stress and HPA dysregulations, investigation of the long-term effects of early adversity often have the limitation of relying on retrospective reports of environmental events, which might be confounded by individual differences in personality and possible recall bias. Furthermore, heterogeneity in exposure type, timing and severity and confounding between initial early and continuing adversity, can make interpretation difficult. Naturally, it remains challenging to validate these results experimentally in humans given constraints on exposing participants to adverse experiences.

One way to address these problems is to make use of "natural experiments". We and others have studied the long-term developmental sequelae of children reared in institutions who were then placed in supportive families. One such investigation is the English and Romanian Adoptees (ERA) study, a prospective longitudinal study investigating children adopted from Romanian institutions of the Ceauşescu regime into the UK in the early 1990 s. Adopted children had spent varying periods of their first few years (0–42 months) in institutions that provided conditions of extreme pervasive deprivation. Studies like the ERA study allows the examination of the effects of precisely timed, and radical change from a profoundly depriving environment to a supportive one in the adoptive families (Rutter et al., 2012). Importantly, almost all of the children had been admitted to the institutions in very early infancy (or at birth), so that there was not a confound that would occur if children were admitted to the institution because of their own psychological problems.

Following removal from institutional care, children showed remarkable recovery in both physical and psychological development. Nevertheless, impairments persisted in a substantial minority of children, especially in those who experienced extended deprivation lasting 6 months or longer. Deprivation-specific problems appeared early and affected social and cognitive functioning, with symptoms of autism spectrum disorder (ASD), disinhibited social engagement (DSE), inattention/overactivity (I/O; essentially ADHD), and cognitive impairment (Kennedy et al., 2017; Kennedy et al., 2016; Kumsta et al., 2015; Kumsta et al., 2010b).

Whereas risk of emotional problems was low in childhood and early adolescence, Romanian adoptees who experienced extended deprivation displayed a striking rise in emotional problems between adolescence and young adulthood, with elevated risk for both depression and general anxiety-related symptomatology in young adulthood (Sonuga-Barke et al., 2017). Testing a developmental cascade model, we found that a latent neurodevelopmental factor (including age 6 deprivation-specific problems) predicted adult depression and anxiety through the effects of early neurodevelopmental problems on later social and vocational functioning, such as difficulties in late adolescent/ early adult relationship functioning, and problems in the world of work. In contrast, we did not find evidence that perceived stress reactivity, i.e. a self-reported stress reactivity in young adulthood, mediated the effects of institutional deprivation on late-appearing emotional problems (Golm et al., 2020). However, due to the unavailability of multiple measures of psychological and physiological stress processing across development, we cannot rule out that early deprivation induced a latent vulnerability to later stress, contributing to depression and/or anxiety problems only in face of increasing social or other demands in late adolescence (McCrory et al., 2017). Despite these limitations, we do provide evidence of long-term alterations to HPA-axis functioning. In the ERA study, cortisol measures were assessed for the first time during young adulthood, about 20 years after adoption, at the age of 22–24 years of age. Both the cortisol awakening response (CAR), an important HPA axis marker, which combines features of a reactivity index with aspects tied to circadian regulation (Stalder et al., 2016), and the diurnal cortisol slope were assessed. In contrast to the UK comparison group of non-deprived adoptees, who displayed a typical pattern of cortisol increase after awakening, the CAR was strikingly absent in the group of Romanian adoptees with extended deprivation experience, with no apparent increase in cortisol over the first 45 min after awakening. The group of Romanian adoptees with less than 6 months of deprivation experience showed an attenuated CAR. In contrast to morning cortisol levels, we did not observe differences in the diurnal cortisol trajectories measured at multiple time points throughout the day. However, group differences in cortisol secretion extended beyond the CAR, with the late adopted group showing a less pronounced decline in cortisol levels between 45 and 1 h and 15 min after awakening (Kumsta et al., 2017).

Results of behavioral and clinical pattern observed in the ERA study are consistent with those of other investigations of formerly deprived children and adolescents. Significant delays in motor, cognitive, socio-emotional and language development were observed, including those in the neurodevelopment domain (van IJzendoorn et al., 2011), which

we termed deprivation-specific (Kumsta et al., 2010a). A high degree of consistency can also be observed with regard to findings on HPA axis regulations, as there is a fairly uniform observation of a pattern of relative hypocortisolism in institutionalized and postinstitutionalized children at much younger ages. For instance, it was observed that children adopted after about 1.5 years of age showed a blunted cortisol awakening response, while those adopted earlier showed a response similar to children growing up in homes (Leneman et al., 2018). Furthermore, it was shown that late removal from institutions (between 18 and 24 months) is associated with hyporeactivity in response to stress (Koss et al., 2016). This was also shown in the Bucharest Intervention Project, which compares care-as-usual in post-communist Romanian institutions (with much better provision of care and not comparable to Ceausescu era circumstances) to randomly assigned placement into foster families. Here, children placed by age 2 years had similar stress reactivity to non-insitutionalized children, whereas children who were placed later and those in the care-as-usual group showed a markedly blunted cortisol stress response (McLaughlin et al., 2015).

We also addressed the question whether exposure to severe deprivation might be associated with alterations in brain volume and structure in young adulthood. Both animal and human studies suggest that brain regions with close links to HPA regulations, such as amygdala, hippocampus, and prefrontal cortex are particularly vulnerable to the effects of early life stress. Romanian adoptees had substantially smaller total brain volumes than non-deprived adoptees, with a dose-response relationship between deprivation duration and volume loss, but suprisingly, no deprivation-related effects were observed in limbic regions, including hypothalamus and amygdala (Mackes et al., 2020).

In summary, we and others provide evidence that not only abuse or neglect experienced in family context (often reported retrospectively) is associated with long-term HPA axis dysregulation, but also that psychosocial deprivation in early childhood leads to persistent changes in cortisol activity and reactivity. Studies of post-institutionalised samples are important, as they provide the opportunity to study specific timing of adversity (usually followed by supportive environments), and the effects of its duration, allowing to address the question of possible sensitive time periods and to establish the impact of dose of deprivation. Overall, results show that the HPA axis is a target for the effects of early adversity, and it is likely HPA axis dysregulations contribute to increased vulnerability to mental health problems. The question of plasticity or reversibility is most likely not only a matter of timing, but also of severity of deprivation. In the ERA study, the children experienced particularly harsh and global deprivation, and for almost all investigated phenotypes, including HPA axis regulation, we observed a 6-month cut-off after which the risk of long-term and stable deficits increased dramatically, and intervention (here, adoption) did not reverse outcomes for the majority of children. In case of less severe deprivation, or institutional care more generally, the period of plasticity seems to extend to around the middle or end of the 2nd year of life.

An important question relates to the mechanistic meaning of aberrant cortisol pattern in the sequelae from deprivation to behavioural and clinical outcomes. In the ERA study, we did not observe a mediating effect of atypical CAR in the association between institutional deprivation and change in emotional problems from adolescence to young adulthood (Kumsta et al., 2017), similarly to perceived stress reactivity (Golm et al., 2020). However, it appears that the association between blunted cortisol patterns and mental health outcomes is more common to problems in the externalizing domain, with increased cortisol production being associated with internalizing problems. For instance, hypocortisolism mediated the association between deprivation and attention and externalizing problems in formerly institutionalised children (Koss et al., 2016), and Pitula et al. (2019) reported that hypocortisolism and ADHD symptoms mediated the association between adversity and peer difficulties in kindergarten children. It remains to be seen whether and to what degree atypical patterns of cortisol regulation will contribute to mental and physical health problems across the adoptees' life-span as psychosocial risk exposures accumulate.

3. Epigenetics

Since the publication of the seminal work by Meaney and colleagues showing that fundamental gene regulatory processes are sensitive to variation in the early psychosocial environment (Weaver et al., 2004), epigenetic mechanism have emerged as prime candidates for explaining how psychosocial or, more broadly, socio-environmental and physical influences might be biologically embedded.

Variations in the levels of maternal care were shown to program the stress response of rats, through epigenetic modifications of the glucocorticoid receptor gene. Although the observed programming effects were not limited to regulation of the stress response, and extended to fear-related behaviour and attentional processes under stressful conditions, synaptogenesis and cognitive development, female reproductive behavior and maternal care itself (Zhang and Meaney, 2010), involving a number of other genes, replication and translational efforts focussed on the GR gene (*NR3C1*) and other HPA axis related genes. Research using rodent models has shown that the extent of maternal care determined DNA methylation patterns in the regulatory regions of HPA axis genes, including *Crf* (Chen et al., 2012), *Avp* (Murgatroyd et al., 2009), and *Nr3c1* (Weaver et al., 2004). Low maternal care and the respective epigenetic changes were associated with HPA axis hypersensitivity and impaired negative HPA axis feedback sensitivity.

Human studies have investigated post-mortem brain tissue, providing evidence for somewhat comparable epigenetic alterations of the *NR3C1* promoter region in individuals exposed to adversity early in life (Labonte et al., 2012; McGowan et al., 2009), and further research has shown associations between early adversity and altered DNA methylation in non-neuronal cells of *NR3C1* and other genes involved in HPA axis regulation (Klengel et al., 2013; Non et al., 2016).

With regard to *NR3C1*, in studies of children and adults reporting childhood adversity (Argentieri et al., 2017; Parade et al., 2021), the majority noted positive associations of *NR3C1* DNA methylation with early adversity. However, magnitude of reported differences is rather small, also for other genes, and the biological significance of minor differences in DNA methylation levels has been questioned (Vinkers et al., 2015).

Given that the effects of the early environment on epigenetic modifications are unlikely to be limited to genes involved in direct HPA axis control, unbiased approaches using epigenome-wide screens have been performed. A well-powered study, embedded in the longitudinal E-RISK study ($N > 1.600$ for subsample with DNA methylation levels), reported no evidence for an association between exposure to childhood or adolescence victimisation and altered DNA methylation levels. In addition to the epigenome-wide association study (EWAS) across about 450.000 CpG sites, the authors further tested differential DNA methylation in specific candidate genes involved in HPA axis regulation (*NR3C1, FKBP5, BDNF, AVP, CRHR1, SLC6A4*), and also found no evidence for differential DNA methylation (Marzi et al., 2018). In the ERA study, with much more limited sample size, we identified a deprivation-associated differentially methylation region consisting of 9 CpGs in the promoter regulatory region of the cytochrome P450 2E1 gene (*CYP2E1*), but not in genes directly associated with HPA axis function (Kumsta et al., 2016).

In one notable example, investigators not only investigated the direct link between early adversity and DNA methylation differences, but tested for the mediating role of differential DNA methylation in the association between early adversity and cortisol stress reactivity. Houtepen et al. (2016) found an association between whole blood DNA methylation of one CpG at the Kit ligand gene (*KITLG*) locus which was associated with the cortisol stress response to the TSST, and could replicate the finding in two independent samples (one using whole blood, one buccal cells). *KITLG* DNA methylation mediated to a considerable extent the link between early adversity and the cortisol

reactivity, although this was only observed in the discovery sample. KITLG codes for a ligand of tyrosine-kinase receptor, and is involved in fundamental processes of cellular development such as hematopoiesis, neurogenesis and neuroprotection, with limited direct evidence for a possible role in HPA axis regulation. We failed to replicate the association between *KITLG* DNA methylation in monocytes in the link between early adversity and cortisol stress regulation (Frach et al., 2020).

To conclude, although it is likely that epigenetic mechanisms play their part in the biological embedding of environmental risk, the notion of a specific adversity-related epigenetic signature, or "epigenetic fingerprint of early adversity" still awaits confirmation. Several reasons have been discussed, and among others, include i) the still limited coverage of the epigenome by commercially available arrays (true epigenome-wide studies are still cost-prohibitive in epidemiological settings); ii) the limited overlap with respect to risk exposure and design of the published studies; iii) the open question to what extent peripheral DNA methylation marks reflect central nervous tissue pattern, and might thus be functionally informative or might "only" be useful as biomarkers; iv) the question to what degree environmentally induced DNA modifications persist throughout the life course; v) and the role of genetic background in shaping differential DNA methylation following early adversity (Kumsta, 2019). Lastly, we have to consider the possibility that peripheral cells, at least in healthy tissue, do not accommodate environmental perturbations at all (Loyfer et al., 2023). Longitudinal studies that assess DNA methylation pattern proximal to risk exposure (Mattonet et al., 2022), incorporating comprehensive measures of the exposome and repeated assessment of behavrioal and clinical outcomes across the life-span will help to clarify the mediating role of DNA methylation signatures involved in stress regulation (Barker et al., 2018).

4. Stress-immune genomics

Another intersection point between psychosocial stress exposure and physiology can be found on the level of gene regulatory processes, in particular with regard to influence of stress on immune function. Both acute and chronic stress influence the immune system in complex ways, and it has been shown that immune response genes are highly sensitive to social-environmental conditions (Bower and Kuhlman, 2023). Chronic stress seems to shift the immune response from antiviral to a more proinflammatory orientations, thought to serve adaptive purposes by protecting against bacterial infection and tissue damage typically associated with fight-or-flight situations (Cole, 2019). In fact, these stress-related alterations in immune response gene expression programs have been hypothesized to be one of the pathways through which environmental adversity influences disease processes (Irwin and Cole, 2011). This specific transcriptional profile, termed Conserved Transcriptional Response to Adversity (CTRA), is characterized by enhanced expression of pro-inflammatory immune response genes and a reciprocal downregulation of antiviral immune response genes. It has been observed in different species and was associated with different types of stress in humans. For instance, it has been observed in people diagnosed with breast cancer, individuals experiencing loneliness and chronic isolation, low socioeconomic status, bereavement and post-traumatic stress disorder (reviewed by Cole, 2019). Mechanistic and bioinformatic analyses revealed that i) upstream signalling driving CTRA expression profile involved up-regulated activity of SNS-responsive signaling pathways and pro-inflammatory factors, and down-regulated activity of interferon response factors (IRFs) and, more variably, the glucocorticoid receptor (GR); ii) among the heterogeneous leukocyte population, monocytes and dendritic cells seem to be the most responsive to changes in socioenvironmental conditions and mediate many of the transcriptional effects of social adversity (Cole et al., 2011).

As the majority of investigations assessed basal gene expression profiles, mostly in adults experiencing current chronic stress or in patients afflicted with mental disorders, we set out to investigate transcriptional profiles in the context of acute stress in adults who were free of current mental or physical health problems. Individuals were exposed to the Trier Social Stress Test and compared to a matched control group. In addition to psychological and endocrine stress measures, we investigated genome-wide mRNA profiles in monocytes before and at two time points after stress exposure (Schwaiger et al., 2016).

In line with previous reports, adults reporting childhood adversity showed blunted ACTH and cortisol responses to stress exposure, with similar increases in psychological distress compared to the control group. On the level of gene expression, a considerable number of genes were differentially expressed, especially pronounced 3 h post-stressor. Differences between groups in stress-induced gene expression were observed for genes involved in hormone activity, steroid binding, and G-protein coupled receptor binding. Furthermore, there were differences in cortisol-associated changes in gene expression between the groups, which further support adversity-related alterations in stress-induced transcriptional regulation of genes involved in immunoregulation and signal transducer activity. Higher order bioinformatic analyses identified increased activity of pro-inflammatory upstream signaling in the early adversity group as a potential driver of both baseline and stress-associated differences in gene expression (Schwaiger et al., 2016). Similar results were observed in adolescents exposed to childhood adversity, who demonstrated larger increases in inflammatory gene expression following acute stress exposure (Kuhlman et al., 2022).

Using a systems-based approach, we reanalysed our data using weighted gene co-expression network analysis, a promising approach to complement single gene analyses with additional insights. Focussing on the 3 h post-stress time point, we identified 13 co-expression modules with 4 enriched for genes related to immune system function. Noteworthy, a monocyte activation module in particular was upregulated in the early adversity group and included pro-inflammatory genes, with *IL6* as a hub gene; further hub genes with inflammatory function were *TM4SF1, ADAMTS4, CYR61, CCDC3*. A further noteworthy module was enriched for genes associated with chemokine and platelet activation, important for homeostasis of the immune system and wound healing processes (Dieckmann et al., 2020), which resembles a module that was previously linked to combat-related PTSD.

Taken together, immune gene expression patterns are not influenced by current chronic stress but seem to be programmed by early life adversity. Here, biological embedding is reflected in stable alterations of transcriptional control of stress responsive pathways characterised by increased pro-inflammatory bias, which—when chronically or repeatedly activated—can increase risk for stress-related psychopathology. These findings tie in well with the consistently reported association between early adversity and systemic or low-grade inflammation (Reid and Danese, 2020). Given the high sensitivity of immune function to changes in social-environmental conditions, it is not suprising that various types of psychological interventions can beneficially influence immune function. Both cognitive behavioral therapy and mindfulness-based interventions have been shown to decrease inflammatory activity, particularly at the level of gene expression, and these effects might possibly be mediated through increasing aspects of well-being, including positive affect and eudaimonic well-being (Bower and Kuhlman, 2023).

We recently compared the RNA co-expression profiles of PTSD patients in purified monocytes before and after 6 weeks of in-patient therapy. At baseline, patients who showed a clinically significant reduction of PTSD symptoms after inpatient treatment showed significantly stronger expression of two groups of co-expressed genes. The first set of genes was functionally involved in inflammatory processes and response to cytokine stimulus and contained *IL1R2,* and *FKBP5*, a major negative regulator of the glucocorticoid mediated stress response, as notable members. The second module was enriched for transcripts functionally involved in regulation of fibrinolysis and positive regulation of blood coagulation, previously associated with PTSD (see also above).

Analysis of gene co-expression from pre-to-post therapy showed that activity of two modules changed in responders, but not in therapy non-responders. Expression of the "wound healing module" decreased after PTSD treatment, whereas the expression of a module implicated in the regulation of apoptotic pathways and inflammatory processes increased after therapy. These results add to the findings that gene expression profiles are sensitive to intervention and might possibly be used as predictive biomarkers of response to therapeutic intervention. Our findings further support the association between PTSD and dysregulation of immune system functioning and processes involved in blood coagulation and wound healing, and mark both as potentially therapy sensitive (Kumsta et al., 2023).

5. Mitochondrial biology

Another target for the effects of (early-life) stress that has been proposed recently is mitochondrial biology. Similar to the HPA axis, mitochondria are viewed as both, targets of stress and source of signals, thus contributing to the transduction and biological embedding of psychosocial experiences. Pioneered by Picard and colleagues, the mitochondrial allostatic load (MAL) model suggests that mitochondria are sensitive to stress mediators and can accumulate mitochondrial allostatic load (Picard et al., 2019). Mitochondrial allostasis is defined as an active process of responding to challenges including the demand for energy to maintain cell function and survival, and MAL describes the dysregulation of mitochondrial functions resulting from the structural and functional changes that mitochondria undergo in response to stressors. Several studies suggest that mitochondrial biology is a target for early-life adversity, and that altered mitochondrial function might be mechanistically involved in the long-term effects of early traumatic experience on physical and mental health (Picard and McEwen, 2018a).

For instance, higher mtDNA copy number in participants with childhood adversity were reported (Tyrka et al., 2016). Boeck et al. (2016) reported positive correlations between CTQ total scores and ATP-production-related respiration in PBMCs from women with a history of childhood adversity, supported by findings showing that exposure to childhood maltreatment was linked to a higher mitochondrial respiration and density in females (Gumpp et al., 2020). Gyllenhammer et al. (2022), reported higher levels of mitochondrial respiratory chain enzymatic activities and higher mitochondrial content in offspring of mothers experiencing higher biological stress.

We contributed a proteomics perspective to this body of research. In the same individuals that were investigated for stress-associated transcriptomic changes, we analysed the monocyte proteom using mass spectrometry before and 3 h post stress exposure (Zang et al., 2023). Exposure to the TSST did not lead to major changes in protein levels, however, we showed significant differences between participants with a history of childhood adversity and control participants in protein levels at both time points. Protein interaction networks generated from differentially expressed proteins indicate a conserved network structure of highly connected proteins that play a role mitochondrial biology (about one third of all differentially expressed proteins) and protein synthesis. Proteins related to mitochondrial biology include for example subunits of the cytochrome C oxidase (COX6) the terminal enzyme complex of the respiratory chain (complex IV) as well as subunits of the mitochondrial ATP synthase (ATP5H), the enzyme catalyzing the synthesis of ATP as universal intracellular energy carrier through phosphorylation.

In a complementary approach, we utilised protein co-expression analysis, and identified several modules representing specific aspects of monocytes cellular biology. These modules harbored e.g. proteins relevant for immune response mechanisms or implicated in mitochondrial biology. Expression differences between groups became evident within four modules. One such module was significantly enriched with mitochondrial proteins, showed stronger expression in the early adversity group and was positively correlated with the Childhood Trauma Questionnaire (CTQ) total score, supporting results generated from single protein analyses.

A second co-expression module that was significantly stronger expressed in participants with a history of childhood adversity was enriched for proteins implicated in regulation of immune system responses and harbored proteins involved within IL-12 signaling. This pathway promotes inflammation and facilitates innate as well as adaptive immune responses, modulating differentiation of T helper cells and NK cell toxicity. One notable member of this module is S100A11, a member S100 protein family, which has been reported to stimulate the production of the pro-inflammatory cytokine IL-6 by peripheral blood mononuclear cells (PBMC).

Together this underlines the idea of mitochondria as cellular components particularly involved in developmental mechanisms programming biological systems towards the demands of stressful environments. Our findings provide evidence on the protein level supporting the mitochondrial allostatic load model (Picard et al., 2019) with results derived from $CD14^{+}$ monocytes specifically, and provide further evidence for a key role of mitochondria in integrating stress- and immune-related signalling. A greater amount of mitochondrial respiratory chain proteins in $CD14^{+}$ monocytes could as such reflect rather stable adaptions towards the increase in physiological energy costs resulting from higher pro-inflammatory activities. Alternatively, experiencing early adversity might first cause alterations in cellular or mitochondrial energetics, which in turn induce inflammation (Picard and McEwen, 2018b). Longitudinal studies are needed to establish the directionality of effects.

In general, there is a growing interest in mitochondrial biomarkers reflecting stress exposure or psychopathological states. Circulating cell-free mtDNA levels have been found elevated in chronically stressed or mentally ill individuals (Picard and Sandi, 2021), and we have shown that acute stress exposure leads to rapid increases in circulating cell-free mtDNA (cf-mtDNA; see also: Trumpff et al., 2019) and cell-free DNA levels (Hummel et al., 2018). In addition to mtDNA copy number, mtDNA mutations, which accumulate under mitochondrial stress, are thought to respresent indicators of MAL. In a recent study, we showed that mtDNA copy number and total number of mtDNA deletions decreased significantly after 6-weeks of in-patient PTSD treatment. Whereas this shows that indicators of MAL were reduced over the course of therapy, the level of change in mitochondrial markers did not correlate with symptom change over time (Hummel et al., 2023).

6. Conclusion and outlook

As living organism, we are highly sensitive to our psychosocial and socio-environmental surroundings, and we have developed multiple ways of sensing and adapting to constantly changing environmental demands. Stress is a balanced and multi-faceted reaction activated in response to increased demands, and serves adaptive purposes. However, perturbation of this intricate balance, characterised by either exaggerated or insufficient activity of one or more of its components can have consequences on proximal and distal components of stress physiology and functioning of the organism as a whole (Agorastos and Chrousos, 2022). This review summarised part of the evidence showing that experience of early adversity can tilt this balance, with long-term alterations observed on multiple and interconnected levels of regulation.

Different bio-behavioural, physiological and cellular processes have been emerged as targets for adverse psychosocial exposures in early development. Dysregulations of hormonal stress regulation, altered DNA methylation pattern, which can potentially alter gene expression pattern across development, and changes to transcriptomic profiles - as more immediate and direct read-outs of gene expression especially in the context of stress-immune interplay - have been observed in individuals of different ages who experienced abuse, neglect, severe deprivation or other types of trauma. Furthermore, on the subcelluar level, different aspects of mitochondrial biology seem sensitive to stress signals, which

can lead to altered mitochondrial function implicated in disease processes.

Overall, this body of research has led to considerable advances of mechanistic knowledge of how exposure to early adversity is linked to increased disease risk across the life-span. Nevertheless, open questions remain, and I will conclude with considerations for future research.

One relates to a deeper understanding of the molecular changes. In keeping with Hertzman`s archeology metaphor (Hertzman, 2012a), the "dig" in uncovering biological embedding of experience has continuously progressed from the surficial stratum of experience and behaviour, to the shallow stratum of physiology, to deeper strata of cellular function and gene regulation. Technological advances have made it possible not only to dig deep, but also enable access to the entirety of the biochemical landscape of different molecular layers within cells using *-omics* approaches. The majority of studies, with few exceptions, have focussed on single or few of these levels, and one future challenge will be to achieve cross-system integration. Systems biology oriented approaches, which focus on the functional interrelation of analytes or cell entities, have been proposed to gain a more comprehensive understanding of the complex multiple interactions between and within layers of analysis (Yan et al., 2018). A growing number of statistical approaches is now available to analyse multi-omics data sets that integrate three or more -omics profiles, which can broadly be classified into supervised and unsupervised approaches (Krassowski et al., 2020; Subramanian et al., 2020).

It can be expected that multi- or cross-omics approaches will have their utility in uncovering molecular changes associated with the experience of stress and early adversity. Currently, the expectations might not yet be met, and certain challenges need to be overcome, such as the imperfect match in number and coverage between the analytes, and the limitations associated with cross-sectional assessments when studying dynamic processes. For instance, our recent work showed that the integrated analysis of cortisol response pattern, DNA methylation, mRNA and protein expression did not lead to better results - both in terms of discriminating groups and uncovering molecular pathways targeted by early adversity - compared to in-depth single layer analysis (Zang et al., 2023)

In the mental health field in general, approaches that integrate multi-omics data with clinical data for biomarker discovery, diagnosis, outcome and treatment response are increasing in number (Sathyanarayanan et al., 2023). These investigations also still face multiple challenges, not only limited to clinical translation, but also related to the question of knowing where to start. Stress research offers the opportunity to combine the advantages of unbiased and hypothesis-free approaches with theory-driven approaches. Models of biopsychosocial interplay, which consider the flow of information from the psychosocial to the biological through stress mediators make it possible to define a search space in the regulatory landscape of cells and to focus on stress-associated changes as starting points for in-depth molecular characterisation. The theoretical framework to define the search-spaces should be centered around dynamic biobehavioral processes, which can be studied through experimental stimulation or interventions, as biomarkers of dysregulated processes are generally best revealed in response to challenge.

In the long run, adopting multi-omics methods in a stress-informed systems biology framework can lead to the identification of patient clusters with a specific early adversity-induced risk profile, and/ or to the development of multi-marker diagnostic panel for - in the best case - early detection of pre-disease risk as well as predictive markers for targeted intervention and personalised treatment approaches.

In general, translation of such basic research findings into practice continues to be one of the major challenges and pressing needs in developmental psychobiology, recognized by researchers, clinicians and policymakers alike (Meyer-Lindenberg et al., 2023). It has been highlighted that exposure to early adversity is one of the most important and pervasive risk factor for the development of nearly all major mental disorders across the lifespan. It influence onset, course, and comorbidity of mental disorders, as well as treatment responses (Teicher et al., 2022), and is among most potent and consistent predictors of physical disease and reduced longevity (Snyder-Mackler et al., 2020). To improve diagnosis, classification, treatment selection, and prediction, it is necessary to characterise in detail the subtypes of mental disorders which arise as a function of early adversity, and have distinct biological and/or behavioral features.

Clearly, the effects of early adversity are not limited to stress regulation and changes to systems outlined in this review, and extend to more broader domains of social, cognitive and emotional development and other brain-body interfaces such as the microbiome. Nevertheless, stress research, concerned in particular with long-term consequences of early adversity through *biological embedding of experience*, will play a pivotal role in advancing translational efforts for improved diagnosis, prevention, and intervention that mitigate early adversity-related health outcomes.

Declaration of Competing Interest

none.

References

Agorastos, A., Chrousos, G.P., 2022. The neuroendocrinology of stress: the stress-related continuum of chronic disease development. Mol. Psychiatry 27, 502–513.

Argentieri, M.A., Nagarajan, S., Seddighzadeh, B., Baccarelli, A.A., Shields, A.E., 2017. Epigenetic pathways in human disease: the impact of DNA methylation on stress-related pathogenesis and current challenges in biomarker development. EBioMedicine 18, 327–350.

Barker, E.D., Walton, E., Cecil, C.A.M., 2018. Annual Research Review: DNA methylation as a mediator in the association between risk exposure and child and adolescent psychopathology. J. Child Psychol. Psychiatry 59, 303–322.

Boeck, C., Koenig, A.M., Schury, K., Geiger, M.L., Karabatsiakis, A., Wilker, S., Waller, C., Gundel, H., Fegert, J.M., Calzia, E., Kolassa, I.T., 2016. Inflammation in adult women with a history of child maltreatment: The involvement of mitochondrial alterations and oxidative stress. Mitochondrion 30, 197–207.

Bower, J.E., Kuhlman, K.R., 2023. Psychoneuroimmunology: an introduction to immune-to-brain communication and its implications for clinical psychology. Annu Rev. Clin. Psychol. 19.

Bunea, I.M., Szentágotai-Tătar, A., Miu, A.C., 2017. Early-life adversity and cortisol response to social stress: a meta-analysis. Transl. Psychiatry 7, 1274.

Carpenter, L., Carvalho, J., Tyrka, A., Wier, L., Mello, A., Mello, M., Anderson, G., Wilkinson, C., Price, L., 2007. Decreased adrenocorticotropic hormone and cortisol responses to stress in healthy adults reporting significant childhood maltreatment. Biol. Psychiatry 62, 1080–1087.

Chen, J., Evans, A.N., Liu, Y., Honda, M., Saavedra, J.M., Aguilera, G., 2012. Maternal deprivation in rats is associated with corticotrophin-releasing hormone (CRH) promoter hypomethylation and enhances CRH transcriptional responses to stress in adulthood. J. Neuroendocr. 24, 1055–1064.

Cole, S.W., 2019. The conserved transcriptional response to adversity. Curr. Opin. Behav. Sci. 28, 31–37.

Cole, S.W., Hawkley, L.C., Arevalo, J.M., Cacioppo, J.T., 2011. Transcript origin analysis identifies antigen-presenting cells as primary targets of socially regulated gene expression in leukocytes. Proc. Natl. Acad. Sci. USA 108, 3080–3085.

Dieckmann, L., Cole, S., Kumsta, R., 2020. Stress genomics revisited: gene co-expression analysis identifies molecular signatures associated with childhood adversity. Transl. Psychiatry 10, 34.

Elzinga, B.M., Roelofs, K., Tollenaar, M.S., Bakvis, P., van Pelt, J., Spinhoven, P., 2008. Diminished cortisol responses to psychosocial stress associated with lifetime adverse events a study among healthy young subjects. Psychoneuroendocrinology 33, 227–237.

Frach, L., Tierling, S., Schwaiger, M., Moser, D., Heinrichs, M., Hengstler, J.G., Walter, J., Kumsta, R., 2020. The mediating role of KITLG DNA methylation in the association between childhood adversity and cortisol stress reactivity does not replicate in monocytes. Psychoneuroendocrinology 116, 104653.

Giles, J., 2011. Social science lines up its biggest challenges. Nature 470, 18–19.

Golm, D., Maughan, B., Barker, E.D., Hill, J., Kennedy, M., Knights, N., Kreppner, J., Kumsta, R., Schlotz, W., Rutter, M., Sonuga-Barke, E.J.S., 2020. Why does early childhood deprivation increase the risk for depression and anxiety in adulthood? A developmental cascade model. J. Child Psychol. Psychiatry 61, 1043–1053.

Gumpp, A.M., Boeck, C., Behnke, A., Bach, A.M., Ramo-Fernández, L., Welz, T., Gündel, H., Kolassa, I.T., Karabatsiakis, A., 2020. Childhood maltreatment is associated with changes in mitochondrial bioenergetics in maternal, but not in neonatal immune cells. Proc. Natl. Acad. Sci. USA 117, 24778–24784.

Gyllenhammer, L.E., Picard, M., McGill, M.A., Boyle, K.E., Vawter, M.P., Rasmussen, J. M., Buss, C., Entringer, S., Wadhwa, P.D., 2022. Prospective association between maternal allostatic load during pregnancy and child mitochondrial content and bioenergetic capacity. Psychoneuroendocrinology 144, 105868.

Heim, C., Newport, D.J., Heit, S., Graham, Y.P., Wilcox, M., Bonsall, R., Miller, A.H., Nemeroff, C.B., 2000. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. Jama 284, 592–597.
Hertzman, C., 2012a. Putting the concept of biological embedding in historical perspective. Proc. Natl. Acad. Sci. USA 109 (Suppl 2), 17160–17167.
Hertzman, C., 2012b. Putting the concept of biological embedding in historical perspective. Proc. Natl. Acad. Sci. USA 109 (Suppl 2), 17160–17167.
Hummel, E.M., Hessas, E., Muller, S., Beiter, T., Fisch, M., Eibl, A., Wolf, O.T., Giebel, B., Platen, P., Kumsta, R., Moser, D.A., 2018. Cell-free DNA release under psychosocial and physical stress conditions. Transl. Psychiatry 8, 236.
Hummel, E.M., Piovesan, K., Berg, F., Herpertz, S., Kessler, H., Kumsta, R., Moser, D.A., 2023. Mitochondrial DNA as a marker for treatment-response in post-traumatic stress disorder. Psychoneuroendocrinology 148, 105993.
van IJzendoorn, M.H., Palacios, J., Sonuga-Barke, E.J., Gunnar, M.R., Vorria, P., McCall, R.B., LeMare, L., Bakermans-Kranenburg, M.J., Dobrova-Krol, N.A., Juffer, F., 2011. Children in Institutional Care: Delayed Development and Resilience. Monogr. Soc. Res Child Dev. 76, 8–30.
Irwin, M.R., Cole, S.W., 2011. Reciprocal regulation of the neural and innate immune systems. Nat. Rev. Immunol. 11, 625–632.
Kennedy, M., Kreppner, J., Knights, N., Kumsta, R., Maughan, B., Golm, D., Rutter, M., Schlotz, W., Sonuga-Barke, E.J., 2016. Early severe institutional deprivation is associated with a persistent variant of adult attention-deficit/hyperactivity disorder: clinical presentation, developmental continuities and life circumstances in the English and Romanian Adoptees study. J. Child Psychol. Psychiatry 57, 1113–1125.
Kennedy, M., Kreppner, J., Knights, N., Kumsta, R., Maughan, B., Golm, D., Hill, J., Rutter, M., Schlotz, W., Sonuga-Barke, E., 2017. Adult disinhibited social engagement in adoptees exposed to extreme institutional deprivation: examination of its clinical status and functional impact. Br. J. Psychiatry 211, 289–295.
Klengel, T., Mehta, D., Anacker, C., Rex-Haffner, M., Pruessner, J.C., Pariante, C.M., Pace, T.W., Mercer, K.B., Mayberg, H.S., Bradley, B., Nemeroff, C.B., Holsboer, F., Heim, C.M., Ressler, K.J., Rein, T., Binder, E.B., 2013. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. Nat. Neurosci. 16, 33–41.
Koss, K.J., Mliner, S.B., Donzella, B., Gunnar, M.R., 2016. Early adversity, hypocortisolism, and behavior problems at school entry: A study of internationally adopted children. Psychoneuroendocrinology 66, 31–38.
Krassowski, M., Das, V., Sahu, S.K., Misra, B.B., 2020. State of the field in multi-omics research: from computational needs to data mining and sharing. Front Genet 11, 610798.
Kuhlman, K.R., Cole, S.W., Craske, M.G., Fuligni, A.J., Irwin, M.R., Bower, J.E., 2022. Enhanced immune activation following acute social stress among adolescents with early-life adversity. Biol. Psychiatry Glob. Open Sci.
Kumsta, R., 2019. The role of epigenetics for understanding mental health difficulties and its implications for psychotherapy research. Psychol. Psychother. 92, 190–207.
Kumsta, R., Kreppner, J., Rutter, M., Beckett, C., Castle, J., Stevens, S., Sonuga-Barke, E. J., 2010a. Deprivation-specific psychological patterns. Monogr. Soc. Res Child Dev. 75, 48–78.
Kumsta, R., Kreppner, J., Rutter, M., Beckett, C., Castle, J., Stevens, S., Sonuga-Barke, E. J., 2010b. III. Deprivation-specific psychological patterns. Monogr. Soc. Res Child Dev. 75, 48–78.
Kumsta, R., Kreppner, J., Kennedy, M., Knights, N., Rutter, M., Sonuga-Barke, E., 2015. Psychological consequences of early global deprivation. Eur. Psychol. 20, 138–151.
Kumsta, R., Marzi, S.J., Viana, J., Dempster, E.L., Crawford, B., Rutter, M., Mill, J., Sonuga-Barke, E.J., 2016. Severe psychosocial deprivation in early childhood is associated with increased DNA methylation across a region spanning the transcription start site of CYP2E1. Transl. Psychiatry 6, e830.
Kumsta, R., Schlotz, W., Golm, D., Moser, D., Kennedy, M., Knights, N., Kreppner, J., Maughan, B., Rutter, M., Sonuga-Barke, E., 2017. HPA axis dysregulation in adult adoptees twenty years after severe institutional deprivation in childhood. Psychoneuroendocrinology 86, 196–202.
Kumsta, R., Zang, J.C., Hummel, E., Müller, S., Moser, D., Herpertz, S., Kessler, H., 2023. Treatment-associated mRNA co-expression changes in monocytes of patients with posttraumatic stress disorder. Front. Psychiatry 23 (14), 1181321.
Labonte, B., Yerko, V., Gross, J., Mechawar, N., Meaney, M.J., Szyf, M., Turecki, G., 2012. Differential glucocorticoid receptor exon 1(B), 1(C), and 1(H) expression and methylation in suicide completers with a history of childhood abuse. Biol. Psychiatry 72, 41–48.
Leneman, K.B., Donzella, B., Desjardins, C.D., Miller, B.S., Gunnar, M.R., 2018. The slope of cortisol from awakening to 30 min post-wake in post-institutionalized children and early adolescents. Psychoneuroendocrinology 96, 93–99.
Loyfer, N., Magenheim, J., Peretz, A., Cann, G., Bredno, J., Klochendler, A., Fox-Fisher, I., Shabi-Porat, S., Hecht, M., Pelet, T., Moss, J., Drawshy, Z., Amini, H., Moradi, P., Nagaraju, S., Bauman, D., Shveiky, D., Porat, S., Dior, U., Rivkin, G., Or, O., Hirshoren, N., Carmon, E., Pikarsky, A., Khalaileh, A., Zamir, G., Grinbaum, R., Abu Gazala, M., Mizrahi, I., Shussman, N., Korach, A., Wald, O., Izhar, U., Erez, E., Yutkin, V., Samet, Y., Rotnemer Golinkin, D., Spalding, K.L., Druid, H., Arner, P., Shapiro, A.M.J., Grompe, M., Aravanis, A., Venn, O., Jamshidi, A., Shemer, R., Dor, Y., Glaser, B., Kaplan, T., 2023. A DNA methylation atlas of normal human cell types. Nature 613, 355–364.
Mackes, N.K., Golm, D., Sarkar, S., Kumsta, R., Rutter, M., Fairchild, G., Mehta, M.A., Sonuga-Barke, E.J.S., team, E.R.A.Y.A.F.-u, 2020. Early childhood deprivation is associated with alterations in adult brain structure despite subsequent environmental enrichment. Proc. Natl. Acad. Sci. USA 117, 641–649.
Marzi, S.J., Sugden, K., Arseneault, L., Belsky, D.W., Burrage, J., Corcoran, D.L., Danese, A., Fisher, H.L., Hannon, E., Moffitt, T.E., Odgers, C.L., Pariante, C., Poulton, R., Williams, B.S., Wong, C.C.Y., Mill, J., Caspi, A., 2018. Analysis of DNA methylation in young people: limited evidence for an association between victimization stress and epigenetic variation in blood. Am. J. Psychiatry appiajp201717060693.
Mattonet, K., Nowack-Weyers, N., Vogel, V., Moser, D., Tierling, S., Kasper-Sonnenberg, M., Wilhelm, M., Scherer, M., Walter, J., Hengstler, J.G., Scholmerich, A., Kumsta, R., 2022. Prenatal exposure to endocrine disrupting chemicals is associated with altered DNA methylation in cord blood. Epigenetics 17, 935–952.
McCrory, E.J., Gerin, M.I., Viding, E., 2017. Annual Research Review: Childhood maltreatment, latent vulnerability and the shift to preventative psychiatry - the contribution of functional brain imaging. J. Child Psychol. Psychiatry 58, 338–357.
McEwen, B.S., 2012. Brain on stress: how the social environment gets under the skin. Proc. Natl. Acad. Sci. USA 109 (Suppl 2), 17180–17185.
McGowan, P.O., Sasaki, A., D'Alessio, A.C., Dymov, S., Labonte, B., Szyf, M., Turecki, G., Meaney, M.J., 2009. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat. Neurosci. 12, 342–348.
McLaughlin, K.A., Sheridan, M.A., Tibu, F., Fox, N.A., Zeanah, C.H., Nelson 3rd, C.A., 2015. Causal effects of the early caregiving environment on development of stress response systems in children. Proc. Natl. Acad. Sci. USA 112, 5637–5642.
Meyer-Lindenberg, A., Falkai, P., Fallgatter, A.J., Hannig, R., Lipinski, S., Schneider, S., Walter, M., Heinz, A., 2023. The future German Center for Mental Health (Deutsches Zentrum für Psychische Gesundheit): a model for the co-creation of a national translational research structure. Nat. Ment. Health 1, 153–156.
Miller, G.E., Chen, E., Zhou, E.S., 2007. If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. Psychol. Bull. 133, 25–45.
Murgatroyd, C., Patchev, A.V., Wu, Y., Micale, V., Bockmuhl, Y., Fischer, D., Holsboer, F., Wotjak, C.T., Almeida, O.F., Spengler, D., 2009. Dynamic DNA methylation programs persistent adverse effects of early-life stress. Nat. Neurosci. 12, 1559–1566.
Non, A.L., Hollister, B.M., Humphreys, K.L., Childebayeva, A., Esteves, K., Zeanah, C.H., Fox, N.A., Nelson, C.A., Drury, S.S., 2016. DNA methylation at stress-related genes is associated with exposure to early life institutionalization. Am. J. Phys. Anthr. 161, 84–93.
Parade, S.H., Huffhines, L., Daniels, T.E., Stroud, L.R., Nugent, N.R., Tyrka, A.R., 2021. A systematic review of childhood maltreatment and DNA methylation: candidate gene and epigenome-wide approaches. Transl. Psychiatry 11, 134.
Picard, M., McEwen, B.S., 2018a. Psychological stress and mitochondria. Psychosom. Med. 80, 141–153.
Picard, M., McEwen, B.S., 2018b. Psychological stress and mitochondria. Psychosom. Med. 80, 126–140.
Picard, M., Sandi, C., 2021. The social nature of mitochondria: Implications for human health. Neurosci. Biobehav. Rev. 120, 595–610.
Picard, M., Trumpff, C., Burelle, Y., 2019. Mitochondrial psychobiology: foundations and applications. Curr. Opin. Behav. Sci. 28, 142–151.
Pitula, C.E., DePasquale, C.E., Mliner, S.B., Gunnar, M.R., 2019. Peer problems among postinstitutionalized, internationally adopted children: relations to hypocortisolism, parenting quality, and ADHD symptoms. Child Dev. 90, e339–e355.
Power, C., Thomas, C., Li, L., Hertzman, C., 2012. Childhood psychosocial adversity and adult cortisol patterns. Br. J. Psychiatry 201, 199–206.
Raison, C.L., Miller, A.H., 2003. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. Am. J. Psychiatry 160, 1554–1565.
Reid, B., Danese, A., 2020. Challenges in researching the immune pathways between early life adversity and psychopathology. Dev. Psychopathol. 32, 1597–1624.
Rutter, M., Kumsta, R., Schlotz, W., Sonuga-Barke, E., 2012. Longitudinal studies using a "natural experiment" design: the case of adoptees from Romanian institutions. J. Am. Acad. Child Adolesc. Psychiatry 51, 762–770.
Sathyanarayanan, A., Mueller, T.T., Ali Moni, M., Schueler, K., members, E.T.N., Baune, B.T., Lio, P., Mehta, D., Baune, B.T., Dierssen, M., Ebert, B., Fabbri, C., Fusar-Poli, P., Gennarelli, M., Harmer, C., Howes, O.D., Janzing, J.G.E., Lio, P., Maron, E., Mehta, D., Minelli, A., Nonell, L., Pisanu, C., Potier, M.C., Rybakowski, F., Serretti, A., Squassina, A., Stacey, D., van Westrhenen, R., Xicota, L., 2023. Multi-omics data integration methods and their applications in psychiatric disorders. Eur. Neuropsychopharmacol. 69, 26–46.
Schwaiger, M., Grinberg, M., Moser, D., Zang, J.C., Heinrichs, M., Hengstler, J.G., Rahnenfuhrer, J., Cole, S., Kumsta, R., 2016. Altered stress-induced regulation of genes in monocytes in adults with a history of childhood adversity. Neuropsychopharmacology 41, 2530–2540.
Snyder-Mackler, N., Burger, J.R., Gaydosh, L., Belsky, D.W., Noppert, G.A., Campos, F.A., Bartolomucci, A., Yang, Y.C., Aiello, A.E., O'Rand, A., Harris, K.M., Shively, C.A., Alberts, S.C., Tung, J., 2020. Social determinants of health and survival in humans and other animals. Science 368.
Sonuga-Barke, E.J.S., Kennedy, M., Kumsta, R., Knights, N., Golm, D., Rutter, M., Maughan, B., Schlotz, W., Kreppner, J., 2017. Child-to-adult neurodevelopmental and mental health trajectories after early life deprivation: the young adult follow-up of the longitudinal English and Romanian Adoptees study. Lancet 389, 1539–1548.
Stalder, T., Kirschbaum, C., Kudielka, B.M., Adam, E.K., Pruessner, J.C., Wust, S., Dockray, S., Smyth, N., Evans, P., Hellhammer, D.H., Miller, R., Wetherell, M.A., Lupien, S.J., Clow, A., 2016. Assessment of the cortisol awakening response: Expert consensus guidelines. Psychoneuroendocrinology 63, 414–432.
Subramanian, I., Verma, S., Kumar, S., Jere, A., Anamika, K., 2020. Multi-omics data integration, interpretation, and its application. Bioinform Biol. Insights 14, 1177932219899051.

Teicher, M.H., Gordon, J.B., Nemeroff, C.B., 2022. Recognizing the importance of childhood maltreatment as a critical factor in psychiatric diagnoses, treatment, research, prevention, and education. Mol. Psychiatry 27, 1331–1338.
Trickett, P.K., Noll, J.G., Susman, E.J., Shenk, C.E., Putnam, F.W., 2010. Attenuation of cortisol across development for victims of sexual abuse. Dev. Psychopathol. 22, 165–175.
Trumpff, C., Marsland, A.L., Basualto-Alarcon, C., Martin, J.L., Carroll, J.E., Sturm, G., Vincent, A.E., Mosharov, E.V., Gu, Z., Kaufman, B.A., Picard, M., 2019. Acute psychological stress increases serum circulating cell-free mitochondrial DNA. Psychoneuroendocrinology 106, 268–276.
Tyrka, A.R., Parade, S.H., Price, L.H., Kao, H.T., Porton, B., Philip, N.S., Welch, E.S., Carpenter, L.L., 2016. Alterations of mitochondrial DNA copy number and telomere length with early adversity and psychopathology. Biol. Psychiatry 79, 78–86.
Vinkers, C.H., Kalafateli, A.L., Rutten, B.P., Kas, M.J., Kaminsky, Z., Turner, J.D., Boks, M.P., 2015. Traumatic stress and human DNA methylation: a critical review. Epigenomics 7, 593–608.
Weaver, I.C., Cervoni, N., Champagne, F.A., D'Alessio, A.C., Sharma, S., Seckl, J.R., Dymov, S., Szyf, M., Meaney, M.J., 2004. Epigenetic programming by maternal behavior. Nat. Neurosci. 7, 847–854.
Yan, J., Risacher, S.L., Shen, L., Saykin, A.J., 2018. Network approaches to systems biology analysis of complex disease: integrative methods for multi-omics data. Brief. Bioinform 19, 1370–1381.
Zang, J.C.S., May, C., Hellwig, B., Moser, D., Hengstler, J.G., Cole, S., Heinrichs, M., Rahnenfuhrer, J., Marcus, K., Kumsta, R., 2023. Proteome analysis of monocytes implicates altered mitochondrial biology in adults reporting adverse childhood experiences. Transl. Psychiatry 13, 31.
Zang, J.C.S., May, C., Marcus, K., Kumsta, R., 2023. Biological embedding of childhood adversity - a multi-omics perspective on stress regulation. bioRxiv. https://doi.org/10.1101/2023.06.10.544462.
Zhang, T.Y., Meaney, M.J., 2010. Epigenetics and the environmental regulation of the genome and its function. Annu Rev. Psychol. 61, 439–466. C431-433.