Brain, Behavior, & Immunity - Health 18 (2021) 100358

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Full Length Article

The ATTACH™ program and immune cell gene expression profiles in mothers and children: A pilot randomized controlled trial

Kharah M. Ross [a,b,c,*], Steve Cole [d], Harleen Sanghera [e], Lubna Anis [c], Martha Hart [c], Nicole Letourneau [c,f,g,h]

[a] Department of Psychology, University of Athabasca, Canada
[b] Department of Psychology, University of Calgary, Canada
[c] Owerko Centre, Alberta Children's Hospital Research Institute, University of Calgary, Canada
[d] School of Medicine, University of California, Los Angeles, USA
[e] Cumming School of Medicine, University of Calgary, Canada
[f] Faculty of Nursing, University of Calgary, Canada
[g] Department of Pediatrics, University of Calgary, Canada
[h] Department of Psychiatry, Cumming School of Medicine, University of Calgary, Canada

ARTICLE INFO

Keywords:
Parenting intervention
ATTACH™
Immune cell gene expression
CTRA
Domestic violence

ABSTRACT

Background: Children exposed to adversity and toxic stress are at increased risk for poor health across the lifespan, possibly through alterations to immune pathways. Parenting interventions could buffer the effect of adversity on child immune activity. The purpose of this study was to test whether mothers and children who were randomly assigned to a parenting intervention (ATTACH™) had healthier post-intervention immune cell gene expression patterns, as indexed by the Conserved Transcriptional Response to Adversity (CTRA), compared with mothers and children in a wait-list control group.

Methods: A sample of 20 mother-child dyads were recruited from a domestic violence shelter in Calgary, AB, Canada. The ATTACH™ program is a 10-week psycho-educational intervention that fosters maternal reflective function, i.e. how to understand and respond to mental states. Dyads were randomly assigned to an intervention or wait-list group. Dried blood spots were collected from both groups post-intervention, subjected to RNA sequencing, and assessed for CTRA gene expression using mixed effect linear model analysis. Covariates were age, child sex, maternal race/ethnicity, and maternal medication use.

Results: In unadjusted models, differences by treatment group were detected, $F(1,1794) = 4.26$, $p = .039$. Mothers and children who completed the ATTACH™ intervention had lower CTRA scores, indicating healthier immune cell gene expression profiles ($Mn = -0.36$, $SE = 0.17$), compared with mothers and children in the wait-list control group ($Mn = 0.11$, $SE = 0.15$). Results persisted after controlling for covariates.

Discussion: ATTACH™ participation predicted healthier immune cell gene expression profiles post-intervention compared with wait-list controls. Parenting interventions could decrease the impact of toxic stress on maternal-child immune health.

1. Introduction

Early life exposure to adverse childhood experiences (ACEs), such as domestic violence, is associated with a range of poor health outcomes across the lifespan, including increased risk for cardiovascular disease, obesity, and depression (Brent, 2013; Cuijpers et al., 2011). The immune system is one pathway through which adverse early life exposures affect child health outcomes (Miller et al., 2011). ACEs can increase risk for poor health behaviours, such as poor eating habits and less physical activity, and affect activation of stress axes [hypothalamic-pituitary-adrenal (HPA) and sympathetic-adrenal medulla (SAM) axes], which can have downstream effects on the immune system, potentially skewing towards a pro-inflammatory state, with increased risk for suboptimal health outcomes (Irwin and Cole, 2011; Sapolsky et al., 2000). As such, identifying factors that buffer the effect of early life adversity on the immune system could have implications for

* Corresponding author. Department of Psychology, University of Athabasca, Canada.
E-mail address: kharahr@athabascau.ca (K.M. Ross).

https://doi.org/10.1016/j.bbih.2021.100358
Received 23 September 2021; Accepted 25 September 2021
Available online 2 October 2021

reducing risk for inflammatory-related diseases in children affected by adversity.

Quality parenting is one factor that could buffer the effect of early life adversity on child outcomes (Barlow, 2013; Morris et al., 2017). Quality parent-child relationships are a key foundation for healthy child social, behavioural, and mental development (Letourneau et al., 2015). Growing evidence suggests that quality parenting is associated with better immune and health outcomes as well. For example, in a sample of 163 adults, secure attachment with a parent at 12- to 18-months of age was prospectively associated with a lower risk for inflammatory illness, such as cardiovascular disease and asthma, at 32-years of age (Puig et al., 2013). Another study of 242 mothers and children reported that higher maternal sensitivity was associated with reduced risk of the child's development of atopic dermatitis, a common precursor to asthma and allergies, both inflammatory diseases (Letourneau et al., 2017). Problematic parental behaviours, such as lower parental monitoring, lower frequency of positive parenting behaviours, and higher frequency of aggressive parenting behaviours, are associated with higher pro-inflammatory marker C-reactive protein (CRP) at 10 years of age (Byrne et al., 2017), and these differences persist into the teenage years (Byrne et al., 2017). And among infants exposed to adversity (parental depression), those who did not have secure parent attachment demonstrated higher scores on a pro-inflammatory composite [calculated from salivary interleukin (IL)-1β, IL-6, IL-8 and tumor necrosis factor(TNF)-α] at 17-months of age, compared with infants who were securely attached to parents (Measelle and Ablow, 2018). Collectively, this suggests that quality parent-child relationships are associated with more optimal inflammatory profiles, even for children exposed to adversity.

As such, interventions that promote quality parenting in the context of adverse circumstances could, theoretically, buffer the effect of those circumstances on child inflammatory and immune outcomes. The majority of parenting intervention studies that have assessed impact on biomarkers have focused on the HPA axis. Evidence suggests that parenting interventions in the context of adversity (foster care, maternal drug addiction, domestic violence, and poverty) predict improved diurnal cortisol patterns (Bakermans-Kranenburg et al., 2008; Bernard et al., 2012, 2015; Dozier et al., 2006; Field et al., 1998; Fisher et al., 2000, 2006) and stress-induced cortisol responses (Berlin et al., 2019; Dozier et al., 2008). (For null results, see DePasquale et al., 2018; Singla et al., 2015). Outside the HPA axis, one other study examined the effect of a parenting intervention on child body mass index (adipose tissue produces inflammatory markers) and reported that an intervention during infancy predicted lower body mass index at 3-years of age (Paul et al., 2018). Only one study was identified that examined the effect of a parenting intervention on child immune and inflammatory outcomes. The Strong African American Families (SAAF) psychosocial intervention focused on improving parenting, strengthening family relationships, and building youth competencies among low socioeconomic status (SES) African Americans from rural Georgia. The seven-week intervention occurred when the children were 11 years old, with a follow-up at age 19 years. Compared with control participants, 19 year-olds who had completed the intervention had lower pro-inflammatory phenotype (Miller et al., 2014) and lower immune-derived DNA methylation age (Brody et al., 2016). Although this is only one study, findings from the SAAF intervention suggest that interventions that improve parenting could help buffer the effect of childhood adversity (low SES) on child immune activity, with implications for future health risks.

Challenges in parenting programs include high burden due to many months of program delivery, and specificity to narrow populations that makes them difficult to implement broadly in community settings (Anis et al., 2020). The Attachment and Child Health (ATTACH™) program is designed to address these issues: It is relatively short (10 weeks) and designed for a variety of client populations affected by ACEs, including families affected by homelessness, poverty, addiction, domestic violence and mental health issues (Anis et al., 2020; Letourneau et al., 2020). The ATTACH™ intervention aims to promote secure attachment in families exposed to adverse experiences by teaching parental reflective function skills. Parental reflective function is the ability for parents to imagine mental states (e.g., thoughts, feelings, desires, beliefs, and intentions) in themselves and their children (Fonagy et al., 2002; Slade, 2005, 2007). Parental reflective function could be crucial for sensitive and responsive interactions between parents and their children (Fonagy et al., 2002; Midgley and Vrouva, 2012). Indeed, in randomized control trials, participating in the ATTACH™ program predicted improvements in parental reflective function, parent-child interaction quality, and child developmental outcomes, such as personal-social outcomes (Anis et al., 2020), and improvements in child attachment (Letourneau et al., 2020). The impact of the ATTACH™ program on health or biological outcomes has not been tested. But if interventions like ATTACH™, which are designed to be low-burden and implementable in diverse community contexts, do predict improved health and biological outcomes, they have the potential to be broadly rolled out and reduce the disease burden of children affected by adversity.

Additionally, although the primary aim of parenting interventions is to improve *child* outcomes, it is also possible that they could benefit *parental* outcomes. Parenting in the context of adversity could also be a stressful experience, and exposure to current chronic stress or adverse circumstances is also associated with poor health outcomes, including pro-inflammatory immune activity (Cole, 2019; Fredrickson et al., 2013; Ross et al., 2019). Giving parents the tools that help them be more confident in their parenting, even in the context of adversity and chronic stress, could alleviate the effect of that stress on parental health and well-being. The effect of parenting interventions on *parental* health and well-being, however, has not been tested.

The purpose of this study is to test whether the ATTACH™ program predicts more optimal indicators of immune activity in both mothers and children, as indexed by immune cell gene expression. Specifically, this study focused on the Conserved Transcriptional Response to Adversity (CTRA) (Cole, 2019), a pattern of gene expression robustly predicted by exposure to a range of adverse contexts, and characterized by higher pro-inflammatory gene transcripts and lower anti-viral gene transcripts. Higher CTRA scores are associated with risk for disease and poor health, including cardiovascular disease and decreased antiviral responses (Cole, 2019). It was hypothesized that mothers and children who completed the ATTACH™ program would demonstrate lower CTRA scores compared to mothers and children in the wait-list control group.

2. Methods

2.1. Participants

A sample of 20 mother-child dyads were recruited from a domestic violence shelter in Calgary, AB, Canada. The domestic violence shelter houses women and families who left a male abuser (mothers were not the abusers). The shelter is specifically designed to protect the families from the abuser: The address is not publicly available, all visitors are screened by staff in a locked entry cubicle before admittance, and only visitors on an expected visitor list are given entry. To be eligible, parents were required to read and write in English, have a child less than six years of age for whom they were the primary custodian (i.e., vs. child apprehended by child welfare or in the care of a partner or kin), and were not planning to relocate in the next three months. Sample characteristics are presented in Table 1. Mothers were on average 31.5 ± 4.93 years old, and children 40.4 ± 32.8 months old. Children were evenly split by sex (55% female). The sample was also diverse, with 70% of mothers identifying as not White (35% Indigenous).

2.2. Procedure

The families were randomized to treatment group ($n = 9$) and control group ($n = 11$) by study personnel based on a random assignment schedule created by an unbiased third-party research staff before

Table 1
Sample characteristics.

	Total (N = 20)	Intervention (N = 9)	Control (N = 11)
	% (N) or Mn ± SD	% (N) or Mn ± SD	% (N) or Mn ± SD
Child Sex (female)	55% (11)	56% (5)	55% (6)
Parent race/ethnicity			
White/Caucasian	30% (6)	22% (2)	36% (4)
Indigenous	35% (7)	56% (5)	18% (2)
African-American/ Black	10% (2)	0% (0)	18% (2)
Asian	15% (3)	22% (2)	1% (1)
Hispanic or Latin	5% (1)	0% (0)	1% (1)
Middle East	5% (1)	0% (0)	1% (1)
Maternal Age (years)	31.5 ± 4.93	31.4 ± 6.78	31.6 ± 3.05
Child Age (months)	40.4 ± 32.8	34.8 ± 20.1	44.9 ± 40.8
Maternal medication use	21% (4)	22% (2)	18% (2)

recruitment (Doig and Simpson, 2005) The treatment group received the ATTACH™ intervention immediately; the waitlist control group also received the ATTACH™ intervention, but after the treatment group had completed the intervention and post-intervention assessment. Social support (e.g., information about community resources, emotional and affirmational support) is also provided, as needed, to both mothers in the ATTACH program and on the wait-list control, by interventionists and/or community agency staff. Dried blood spots (DBS) were collected once from mothers and children after the treatment group completed the ATTACH™ intervention, and before the wait-list control families began the ATTACH™ intervention.

2.3. The ATTACH™ program

The ATTACH™ program is comprised of a brief 10-week psychoeducational parenting intervention with dyadic (mother and child) and triadic (mother, child, and co-parenting support person) components to foster parental reflective function through practice (Supplemental Figure 1; Anis et al., 2020; Letourneau et al., 2020). It is a broadly targeted to families affected by adversity (i.e., not tailored to a specific client population), and is designed to be minimally burdensome, to be provided in addition to or to complement existing agency programming, and to be deliverable by community agency staff (for more details, see Anis et al., 2020; Letourneau et al., 2020). During weekly sessions, the facilitator helps the parents learn new reflective function skills, accomplished through leading by example, asking questions and providing ample opportunities to practice reflective function skills. ATTACH™ intervention sessions include three components. First, parent-child interactions are videotaped during 3–5 minutes of free-play for review and discussion. During the video feedback, the ATTACH™ facilitator explores the parents' perceptions of themselves and their children, and maximizes opportunities to practice reflective function, e.g., a mother may be asked to consider what may be happening in her mind and the mind of her child during a shared smile in the videotaped interaction. Second, a hypothetical, mildly stressful situation is discussed. Hypothetical situations encourage imagining others' thoughts and feelings in a common daily hassle, such as during dinner when the child throws food on the floor. Finally, day-to-day real-life stressful situations are discussed. Real-life stressful situation reviews revolve around parents' and others' thoughts and feelings as the stressful situation is described in detail then re-evaluated using the parents' developing reflective function skills. When co-parents are present, only the free-play videotaped interactions and hypothetical situations are examined, as discussing real-life stressful situation may induce conflict. Once the therapeutic relationship is established (after six one-on-one sessions of therapy), parents invite a friend or family member to be a co-participant in the intervention, and to provide additional parenting support (termed "co-parents,"e.g., grandparents, relatives, friends, or other support person). Co-parents co-attend 2–3 sessions, typically at sessions 7 and 9, spaced 2 weeks apart.

2.4. Inflammatory gene expression

A non-fasting blood sample was collected from the parent and child onto a DBS card and assayed for genome-wide transcriptional profiles using RNAseq, as described below. Samples were collected at the community agency by trained research staff. Briefly, a finger was lanced, and capillary blood collected on filter paper. DBS cards were allowed to dry overnight, and then stored at −80 °C at the Owerko Centre, University of Calgary.

DBS were shipped to the UCLA Social Genomics Core Laboratory for RNA extraction, as previously described (McDade et al., 2016). RNA samples were converted to cDNA libraries using the QuantSeq 3′ mRNA-Seq Library Prep Kit FWD for Illumina (Lexogen Inc. Greenland, NH) and sequenced using an Illumina HiSeq 4000 instrument (Illumina Inc., San Diego CA), following the manufacturer's standard protocol. The QuantSeq assay is highly sensitive and produces reliable results even for moderately degraded samples (valid down to RNA Integrity Number value of 3) and is thus well suited for assay of DBS-derived RNA samples. Sequencing targeted > 10 million reads per sample (average = 16.8 million), each of which was mapped to the hg38 reference human transcriptome sequence using the STAR aligner (Dobin et al., 2013) (average 91.9% mapping) for quantification of gene-specific read counts per million total mapped reads. Transcript abundance values were subsequently normalized to equate expression of 11 human reference genes (Eisenberg and Levanon, 2013), floored at 1 transcript per million to suppress spurious variance, log2-transformed to stabilize variance, screened to exclude transcripts that varied by < 0.5 log2 units across participants (to remove genes that were generally undetectable or showed no appreciable variation in expression levels across samples), and z-score standardized within gene to facilitate analysis by linear statistical models as outlined below.

2.5. Data analysis

Gene expression data were analyzed using standard methods for targeted hypothesis testing for the CTRA profile in genome-wide transcriptional data (Cole et al., 2003, 2005; Fredrickson et al., 2013). Primary analyses examined the effect of intervention group (ATTACH™ vs control) on average expression of an a priori-specified set of 19 pro-inflammatory gene transcripts (e.g., *IL1B, IL6, IL8/CXCL8, COX2/PTGS2, TNF*) and 34 Type I interferon- and antibody-related gene transcripts (e.g., *IFNB, IRF7, IFI27, MX1, OAS1*; all sign-inverted to reflect their inverse contribution to the CTRA profile) (Cole, 2019). Six of the pre-specified indicator genes were unavailable for analysis (excluded due to minimal variation; SD < 0.5 log2 units), leaving a total of 47 CTRA indicator genes for analysis. Data were analyzed using mixed effect linear models that treated the 47 available CTRA indicator genes as a repeated measure, specified a random subject-specific intercept nested within a random family-specific intercept to account for association among residuals across the repeated measures, and quantified the association between average indicator gene expression and experimental condition while controlling for parent vs child status. Secondary analyses also controlled for variables that could be related to immune cell gene expression patterns: Age, child sex, ethnicity, and maternal medication use. None of the mothers reported presence of any acute infection at blood sampling; no medication use was reported for any of the children.

3. Results

Unadjusted models were first run to test differences in CTRA gene expression in mothers and children in the ATTACH™ program treatment and wait-list control groups. Results of primary analyses showed

significant differences in CTRA indicator gene expression based on treatment, $F(1,1794) = 4.26$, $p = .039$. Specifically, mothers and children who had completed the ATTACH™ program had lower CTRA index scores ($Mn = -0.36$, $SE = 0.17$), compared with mothers and children in the wait-list control group ($Mn = 0.11$, $SE = 0.15$). To test whether the effect of the intervention differed for mothers and children, a treatment-by-mother/child interaction was also tested. The interaction term was not significant, $F(1,1794) = 0.19$, $p = .662$, suggesting that the effect of the intervention on CTRA profiles was similar for both mothers and children (Fig. 1).

Models were also run adjusting for participant age, ethnicity, and medication use. Independent of covariates, a significant effect of the ATTACH™ program on mother and child CTRA scores continued to emerge, $F(1,1702) = 4.07$, $p = .044$.

4. Discussion

The purpose of this study was to determine if completing a parenting intervention (ATTACH™), designed for a broad range of populations and clients, to be integrated into existing community agency programming, and to be administered by community agency staff, predicts more optimal inflammatory outcomes, as indexed by the CTRA. Results indicated that both mother and child CTRA indices were lower in the intervention group, as compared with the wait-list control, suggesting that completing the ATTACH™ program predicts healthier immune cell gene expression for both mothers and children. This work contributes to the growing body of evidence suggesting that parenting interventions for families affected by adversity could also benefit physical health through reduced pro-inflammatory phenotypes.

Exposure to early adversity and chronic stress can adversely affect health indirectly, by impacting health behaviours like exercise and eating habits, and directly, through activation of stress neuroendocrine pathways, such as the HPA and SAM, with downstream repercussions for immune activity (Irwin and Cole, 2011; Sapolsky et al., 2000). Higher quality parent-child relationships, however, could act as a buffer that ameliorates the impact of adversity on child health. As such, interventions that bolster parenting quality in the context of adversity should be associated with improvements in child biomarkers and health outcomes. Most of the evidence to date has focused on stress-related axes, especially cortisol and the HPA axis. This study contributes to growing evidence that parenting interventions could also benefit child immune

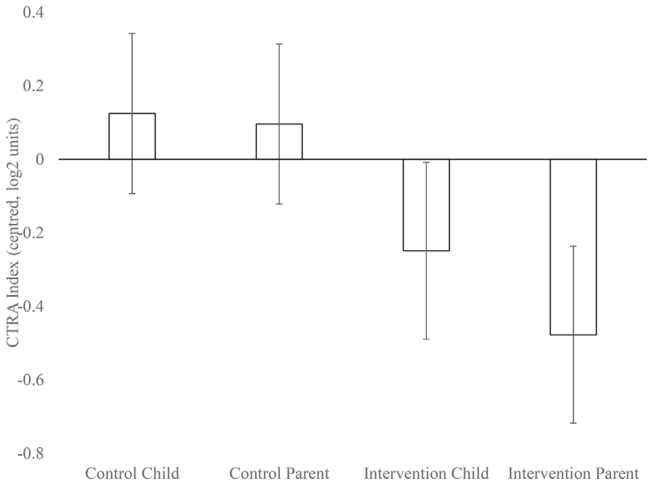

Fig. 1. CTRA index scores for mothers and children in the ATTACH™ program treatment and wait-list control groups. Mothers and children who completed the ATTACH™ program had lower CTRA scores compared with those in the wait-list control group. No significant difference in CTRA scores emerged for mothers and children by treatment, suggesting that the intervention equally benefited both mother and child CTRA profiles.

function. Evidence from the SAAF intervention suggests that improvements in parenting mediated the differences in inflammatory outcomes observed between children in treatment and control groups (Miller et al., 2014). Although previous work suggests that the ATTACH™ program successfully improves parental reflective function, with implications for parent-child relationship quality and attachment and child development (Anis et al., 2020; Letourneau et al., 2020), reflective function could not be tested here as a mediator due to small sample size (N = 20 mother-child dyads or 40 total participants). Future research will examine whether changes in reflective function account for treatment differences in CTRA scores.

This study is additionally novel in that *parental* immune cell gene expression was also considered. Most parenting interventions focus on child outcomes only. Although the focus on the child is crucial, parenting in adverse circumstances (including the context of domestic violence) is a stressful experience. Although it is probable that giving parents the tools to be more effective parents would alleviate a parent's experience of stress in the context of adversity, with implications for parental health and well-being, this is not often tested. Maternal immune cell gene expression was also considered in this study, and findings suggest that completing the ATTACH™ program was just as beneficial for maternal CTRA profiles. This suggests that parenting interventions could additionally benefit the health and well-being of parents affected by adversity. Future studies need to examine effects of parenting interventions on parental as well as child outcomes.

These findings need to be interpreted in the context of a few limitations. First, this is a pilot study with a small sample size (N = 20 mother-child dyads). Although these are promising first results, these findings need to be followed-up in a larger sample. Also due to the small sample size, analyses testing whether intervention-driven changes in parental quality mediated differences in CTRA indices by treatment group were not possible. In addition, although diversity was a strength of this study (with 70% of the sample being not White), it would be valuable to determine whether intervention effectiveness varies by sociodemographic characteristics. Additional studies of the ATTACH™ program (e.g. to evaluate the effectiveness of a community agency-delivered program, rather than a researcher-delivered program) continues, and subsequent studies will be larger and sufficiently powered to test mediation and moderation. Another limitation is that, although ATTACH™ is designed to be a broadly deliverable intervention, this study focused on mother-child dyads affected by domestic violence. Whether these findings extend to other adversity contexts, or is equally beneficial across adverse contexts, is not known. Future research will include parent-child dyads recruited from several community agencies that serve different client populations. Finally, although a treatment difference in CTRA scores was detected in this study, it is also not clear whether these differences persist long-term. The effects of SAAF were detected almost 10 years after the intervention (Brody et al., 2016; Miller et al., 2014), suggesting that these effects could persist. Nonetheless, research is needed to determine whether changes in parental quality and CTRA indices persists long-term, and whether these differences have implications for disease risk or other health outcomes.

In sum, a short, 10-week parenting intervention focused on teaching parents reflective function skills predicted improvements in mother and child CTRA indices. The ATTACH™ program could benefit maternal-child health, in addition to previously observed benefits to parental reflective function, parent-child relationship quality and child developmental outcomes. Interventions like the ATTACH™ program, designed for a range of adverse circumstances and populations, and to be added onto existing community agency programming, could work to interrupt the link between early childhood adversity and risk for future inflammatory diseases.

Declaration of competing interest

The authors declare the following financial interests/personal

relationships which may be considered as potential competing interests: Drs. J. Martha Hart and Nicole L. Letourneau are co-owners of the not-for-profit company called ATTACH and Child Health Foundation, established to support community delivery of ATTACH™. They did not take part in the analysis for this paper that was overseen by Dr. Kharah Ross. All other authors have no competing financial interests.

Acknowledgements

Funding for this project was provided by the Alberta Children's Hospital Research Institute (ACHRI) Trainee Seed Grant (PI: Ross), ACHRI Behaviour and the Developing Brain Seed Grant (PI: Letourneau, Ross), Calgary Foundation (PI: Letourneau, Hart, Anis), and Harvard Frontiers of Innovation (PI: Letourneau, Hart, Anis).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2021.100358.

References

Anis, L., Letourneau, N., Benzies, K., Ewashen, C., Hart, M.J., 2020. Effect of the attachment and child health parent training program on parent-child interaction quality and child development. Can. J. Nurs. Res. 52 (2), 157–168. https://doi.org/10.1177/0844562119899004.

Bakermans-Kranenburg, M.J., Van Ijzendoorn, M.H., Mesman, J., Alink, L.R., Juffer, F., 2008. Effects of an attachment-based intervention on daily cortisol moderated by dopamine receptor D4: a randomized control trial on 1- to 3-year-olds screened for externalizing behavior. Dev. Psychopathol. 20 (3), 805–820. https://doi.org/10.1017/S0954579408000382.

Barlow, J., 2013. Parenting during the first 2 years and public mental health. In: Knifton, N.Q.L. (Ed.), Public Mental Health: Global Perspectives. McGraw-Hill, pp. 119–126.

Berlin, L.J., Martoccio, T.L., Bryce, C.I., Jones Harden, B., 2019. Improving infants' stress-induced cortisol regulation through attachment-based intervention: a randomized controlled trial. Psychoneuroendocrinology 103, 225–232. https://doi.org/10.1016/j.psyneuen.2019.01.005.

Bernard, K., Dozier, M., Bick, J., Lewis-Morrarty, E., Lindhiem, O., Carlson, E., 2012. Enhancing attachment organization among maltreated children: results of a randomized clinical trial. Child Dev. 83 (2), 623–636. https://doi.org/10.1111/j.1467-8624.2011.01712.x.

Bernard, K., Hostinar, C.E., Dozier, M., 2015. Intervention effects on diurnal cortisol rhythms of Child Protective Services-referred infants in early childhood: preschool follow-up results of a randomized clinical trial. JAMA Pediatr. 169 (2), 112–119. https://doi.org/10.1001/jamapediatrics.2014.2369.

Brent, D.A., 2013. Shedding light on the long shadow of childhood adversity. J. Am. Med. Assoc. 309, 1777–1778.

Brody, G.H., Yu, T., Chen, E., Beach, S.R., Miller, G.E., 2016. Family-centered prevention ameliorates the longitudinal association between risky family processes and epigenetic aging. JCPP (J. Child Psychol. Psychiatry) 57 (5), 566–574. https://doi.org/10.1111/jcpp.12495.

Byrne, M.L., Badcock, P.B., Simmons, J.G., Whittle, S., Pettitt, A., Olsson, C.A., Mundy, L.K., Patton, G.C., Allen, N.B., 2017a. Self-reported parenting style is associated with children's inflammation and immune activation. J. Fam. Psychol. 31 (3), 374–380. https://doi.org/10.1037/fam0000254.

Byrne, M.L., Horne, S., O'Brien-Simpson, N.M., Walsh, K.A., Reynolds, E.C., Schwartz, O.S., Whittle, S., Simmons, J.G., Sheeber, L., Allen, N.B., 2017b. Associations between observed parenting behavior and adolescent inflammation two and a half years later in a community sample. Health Psychol. 36 (7), 641–651. https://doi.org/10.1037/hea0000502.

Cole, S.W., 2019. The conserved transcriptional response to adversity. Curr. Opin. Behav. Sci. 28, 31–37. https://doi.org/10.1016/j.cobeha.2019.01.008.

Cole, S.W., Galic, Z., Zack, J.A., 2003. Controlling false-negative errors in microarray differential expression analysis: a PRIM approach. Bioinformatics 19 (14), 1808–1816. https://www.ncbi.nlm.nih.gov/pubmed/14512352.

Cole, S.W., Yan, W., Galic, Z., Arevalo, J., Zack, J.A., 2005. Expression-based monitoring of transcription factor activity: the TELiS database. Bioinformatics 21 (6), 803–810. https://doi.org/10.1093/bioinformatics/bti038.

Cuijpers, P., Smit, F., Unger, F., Stikkelbroek, Y., Ten Have, M., de Graaf, R., 2011. The disease burden of childhood adversities in adults: a population-based study. Child Abuse Negl. 35 (11), 937–945. https://doi.org/10.1016/j.chiabu.2011.06.005.

DePasquale, C.E., Raby, K.L., Hoye, J., Dozier, M., 2018. Parenting predicts Strange Situation cortisol reactivity among children adopted internationally. Psychoneuroendocrinology 89, 86–91. https://doi.org/10.1016/j.psyneuen.2018.01.003.

Dobin, A., Davis, C.A., Schlesinger, F., Drenkow, J., Zaleski, C., Jha, S., Batut, P., Chaisson, M., Gingeras, T.R., 2013. STAR: ultrafast universal RNA-seq aligner. Bioinformatics 29 (1), 15–21. https://doi.org/10.1093/bioinformatics/bts635.

Doig, G.S., Simpson, F., 2005. Randomization and allocation concealment: a practical guide for researchers. J. Crit. Care 20 (2), 187–191. https://doi.org/10.1016/j.jcrc.2005.04.005. ; discussion 191-183.

Dozier, M., Peloso, E., Lewis, E., Laurenceau, J.P., Levine, S., 2008. Effects of an attachment-based intervention on the cortisol production of infants and toddlers in foster care. Dev. Psychopathol. 20 (3), 845–859. https://doi.org/10.1017/S0954579408000400.

Dozier, M., Peloso, E., Lindhiem, O., Gordon, M.K., Manni, M., Sepulveda, S., Ackerman, J., Bernier, A., Levine, S., 2006. Developing evidence-based interventions for foster children: an example of a randomized clinical trial with infants and toddlers. J. Soc. Issues 62, 767–785.

Eisenberg, E., Levanon, E.Y., 2013. Human housekeeping genes, revisited. Trends Genet. 29 (10), 569–574. https://doi.org/10.1016/j.tig.2013.05.010.

Field, T.M., Scafidi, F., Pickens, J., Prodromidis, M., Pelaez-Nogueras, M., Torquiti, J., Wilcox, H., Malphurs, J., Schanberg, S., Kuhn, C., 1998. Polydrug-using adolescent mothers and their infants receiving early intervention. Adolescence 33, 114–143.

Fisher, P.A., Gunnar, M.R., Chamberlain, P., Reid, J.B., 2000. Preventive intervention for maltreated preschool children: impact on children's behavior, neuroendocrine activity, and foster parent functioning. J. Am. Acad. Child Adolesc. Psychiatry 39 (11), 1356–1364. https://doi.org/10.1097/00004583-200011000-00009.

Fisher, P.A., Gunnar, M.R., Dozier, M., Bruce, J., Pears, K.C., 2006. Effects of therapeutic interventions for foster children on behavioral problems, caregiver attachment, and stress regulatory neural systems. Ann. N. Y. Acad. Sci. 1094, 215–225. https://doi.org/10.1196/annals.1376.023.

Fonagy, P., Gergey, G., Jurist, E., Target, M., 2002. Affect Regulation, Mentalization and the Development of the Self. Other Press, LLC.

Fredrickson, B.L., Grewen, K.M., Coffey, K.A., Algoe, S.B., Firestine, A.M., Arevalo, J.M., Ma, J., Cole, S.W., 2013. A functional genomic perspective on human well-being. Proc. Natl. Acad. Sci. U. S. A. 110 (33), 13684–13689. https://doi.org/10.1073/pnas.1305419110.

Irwin, M.R., Cole, S.W., 2011. Reciprocal regulation of the neural and innate immune systems. Nat. Rev. Immunol. 11 (9), 625–632. https://doi.org/10.1038/nri3042.

Letourneau, N., Anis, L., Ntanda, H., Novick, J., Steele, M., Steele, H., Hart, M., 2020. Attachment & Child Health (ATTACH) pilot trials: effect of parental reflective function intervention for families affected by toxic stress. Infant Ment. Health J. 41 (4), 445–462. https://doi.org/10.1002/imhj.21833.

Letourneau, N., Tryphonopoulos, P., Giesbrecht, G., Dennis, C.L., Bhogal, S., Watson, B., 2015. Narrative and meta-analytic review of interventions aiming to improve maternal-child attachment security. Infant Ment. Health J. 36 (4), 366–387. https://doi.org/10.1002/imhj.21525.

Letourneau, N.L., Kozyrskyj, A.L., Cosic, N., Ntanda, H.N., Anis, L., Hart, M.J., Campbell, T.S., Giesbrecht, G.F., Team, A.P., 2017. Maternal sensitivity and social support protect against childhood atopic dermatitis. Allergy Asthma Clin. Immunol. 13, 26. https://doi.org/10.1186/s13223-017-0199-4.

McDade, T.W., Ross, K.M., R, L.F., Arevalo, J.M., Ma, J., Miller, G.E., Cole, S.W., 2016. Genome-wide profiling of RNA from dried blood spots: convergence with bioinformatic results derived from whole venous blood and peripheral blood mononuclear cells. Biodemogr. Soc. Biol. 62 (2), 182–197. https://doi.org/10.1080/19485565.2016.1185600.

Measelle, J.R., Ablow, J.C., 2018. Contributions of early adversity to pro-inflammatory phenotype in infancy: the buffer provided by attachment security. Attach. Human Dev. 20 (1), 1–23. https://doi.org/10.1080/14616734.2017.1362657.

Midgley, N., Vrouva, I. (Eds.), 2012. Minding the child: Mentalization-based interventions with children, young people and their families. Routledge, New York, NY.

Miller, G.E., Brody, G.H., Yu, T., Chen, E., 2014. A family-oriented psychosocial intervention reduces inflammation in low-SES African American youth. Proc. Natl. Acad. Sci. U. S. A. 111 (31), 11287–11292. https://doi.org/10.1073/pnas.1406578111.

Miller, G.E., Chen, E., Parker, K.J., 2011. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychol. Bull. 137 (6), 959–997. https://doi.org/10.1037/a0024768.

Morris, A.S., Robinson, L.R., Hays-Grudo, J., Claussen, A.H., Hartwig, S.A., Treat, A.E., 2017. Targeting parenting in early childhood: a public health approach to improve outcomes for children living in poverty. Child Dev. 88 (2), 388–397. https://doi.org/10.1111/cdev.12743.

Paul, I.M., Savage, J.S., Anzman-Frasca, S., Marini, M.E., Beiler, J.S., Hess, L.B., Loken, E., Birch, L.L., 2018. Effect of a responsive parenting educational intervention on childhood weight outcomes at 3 Years of age: the INSIGHT randomized clinical trial. J. Am. Med. Assoc. 320 (5), 461–468. https://doi.org/10.1001/jama.2018.9432.

Puig, J., Englund, M.M., Simpson, J.A., Collins, W.A., 2013. Predicting adult physical illness from infant attachment: a prospective longitudinal study. Health Psychol. 32 (4), 409–417. https://doi.org/10.1037/a0028889.

Ross, K.M., Cole, S., Carroll, J.E., Dunkel Schetter, C., 2019. Elevated pro-inflammatory gene expression in the third trimester of pregnancy in mothers who experienced stressful life events. Brain Behav. Immun. 76, 97–103.

Sapolsky, R.M., Romero, L.M., Munck, A.U., 2000. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr. Rev. 21 (1), 55–89. https://doi.org/10.1210/er.21.1.55.

Singla, D.R., Kumbakumba, E., Aboud, F.E., 2015. Effects of a parenting intervention to address maternal psychological wellbeing and child development and growth in rural Uganda: a community-based, cluster-randomised trial. Lancet Global Health 3 (8), e458–e469. https://doi.org/10.1016/s2214-109x(15)00099-6.

Slade, A., 2005. Parental reflective functioning: an introduction. Attach. Human Dev. 7 (3), 269–281. https://doi.org/10.1080/14616730500245906.

Slade, A., 2007. Reflective parenting programs: theory and development. Psychoanal. Inq. 26 (4), 640–657. https://doi.org/10.1080/07351690701310698.