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History of child maltreatment and telomere length in immune cell subsets: Associations with stress- and attachment-related hormones

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Abstract

Experiencing maltreatment during childhood can have long-lasting consequences for both mental and physical health. Immune cell telomere length (TL) shortening might be one link between child maltreatment (CM) experiences and adverse health outcomes later in life. While the stress hormone cortisol has been associated with TL attrition, the attachment-related hormone oxytocin may promote resilience. In 15 mothers with and 15 age- and body mass index-matched mothers without CM, we assessed TL in peripheral blood mononuclear cells and selected immune cell subsets (monocytes, naive, and memory cytotoxic T cells) by quantitative fluorescence in situ hybridization, as well as peripheral cortisol and oxytocin levels. Memory cytotoxic T cells showed significantly shorter TL in association with CM, whereas TL in monocytes and naive cytotoxic T cells did not significantly differ between the two groups. Across both groups, cortisol was negatively associated with TL, while oxytocin was positively associated with TL in memory cytotoxic T cells. These results indicate that long-lived memory cytotoxic T cells are most affected by the increased biological stress state associated with CM. Keeping in mind the correlational and preliminary nature of the results, the data suggest that cortisol may have a damaging and oxytocin a protective function on TL.

Child maltreatment (CM) experiences constitute an enormous psychological stressor and are associated with both poor mental health (e.g., depression and anxiety disorders) and physical health (e.g., diabetes and cardiovascular diseases) across the life span (Hamilton, Micol-Foster, & Muzik, 2015). Early life stressors trigger the response of stress-reactive networks that comprise not only the central nervous system but also the endocrine and the immune systems. As immune cells mount the responses to external and internal stressors, they are of particular importance for understanding the impact of chronic stress on health and disease outcomes. Shortened telomere length (TL) in immune cells has been suggested as a risk factor for several age-related diseases (Von Zglinicki & Martin-Ruiz, 2005), which are observed at higher rates in CM-affected individuals. Therefore, TL shortening has been proposed as one link between early life stress and poor physical health (Puterman & Epel, 2012). However, as not all affected individuals develop adverse health outcomes later in life, resilience factors may influence how deep psychological stress gets under the skin (Cicchetti, 2013; Hamilton et al., 2015).

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CM Is Associated With Telomere Attrition

Telomeres, which are noncoding, chromosomal end-standing DNA–protein complexes, maintain chromosomal stability and prevent the loss of functionally coding segments during DNA replication, thereby protecting cellular integrity (Chan & Blackburn, 2004). With each cell division, telomeres (with an average length of 6–15 kilobases in human cells) shorten by 20–300 base pairs (Aubert & Lansdorp, 2008). Once TL is critically short, telomeres can no longer maintain their protective function and trigger cellular senescence (Calado & Young, 2009), which eventually results in a comprised tissue renewal capacity and function. Based on this gradual decline, TL has been described as an estimate for biological age (Harley, Futcher, & Greider, 1990). With increasing age, progressive shortening of mean TL can be observed in peripheral blood mononuclear cells (PBMC; Iwama et al., 1998). Besides several endogenous factors (e.g., inflammation, oxidative stress, and DNA damage), behavioral (e.g., smoking, physical activity, sleeping patterns, and meditation) and psychosocial factors (e.g., chronic and acute stress exposure, emotion regulatory processes, and social connections) have been described to either contribute to or protect against telomere attrition in PBMC (Jacobs et al., 2011; Puterman & Epel, 2012). To this end, TL has been

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suggested as a global sensor of changing cellular environments (Drury, 2015) and as a biomarker that integrates the cumulative effects of both adversity and resiliency factors on complex disease risk (Puterman & Epel, 2012).

Tyrka et al. (2010) provided first evidence for an association between CM and shortened PBMC TL decades later in life. Thus far, several studies replicated this finding in leukocytes and buccal cells in adults (Price, Kao, Burgers, Carpenter, & Tyrka, 2013; Ridout et al., 2017), and a prospective longitudinal study in children exposed to violence provided further support for a direct association between CM and a higher rate of TL erosion in buccal cells (Shalev et al., 2013). However, there are also contrary studies that found no association between the exposure to CM and PBMC TL in adulthood (e.g., Mason, Prescott, Tworoger, DeVivo, & Rich-Edwards, 2015; Verhoeven, van Oppen, Puterman, Elzinga, & Penninx, 2015). PBMC encompass diverse cell subsets of the innate (e.g., monocytes) and the adaptive immune system (e.g., T cells), which differ with respect to TL and rate of telomere attrition with age (Hodes, Hathcock, & Weng, 2002; Lin et al., 2015). Moreover, stress exposure may induce adaptive changes in the subset composition of PBMC (Morath et al., 2014; Sommershof et al., 2009). Shortened TL in PBMC could therefore reflect (a) changes in the PBMC subset composition with an increase of cell subsets presenting shorter TL, (b) equally shortened TL in all cell subsets, or (c) shortened TL in particularly vulnerable cell subsets. The results from a previous study by Karabatsiakis, Kolassa, Kolassa, Rudolph, and Dietrich (2014) already suggested that cytotoxic T cells were more severely affected than T helper cells and B cells by shortened TL in acutely depressed patients compared to healthy controls. The fraction of cytotoxic T cells can be further divided into naive cytotoxic T cells, which decline in number and function with age, and long-living memory cytotoxic T cells, which ensure a lifelong protection upon recurrent pathogen encounters (Herndler-Brandstetter, 2013). Previous studies already showed that telomerase activity was lowest (Lin et al., 2010) and the rate of TL attrition over a time period of 18 months was highest in a subset of terminally differentiated memory cytotoxic T cells (Lin et al., 2016).

CM May Affect Glucocorticoid Signaling

In response to a stressor, the hypothalamus–pituitary–adrenal (HPA) axis and its effector molecule cortisol mainly coordinate the physiological adaptation of stress-reactive networks. As the HPA axis matures throughout childhood, this extended period of development constitutes a sensitive time window that shapes the body's stress response. The experience of adverse early life events has therefore been associated with persistent changes in HPA axis functioning, affecting both cortisol secretion (e.g., Carpenter et al., 2007; Cicchetti & Rogosch, 2001; Gonzalez, Jenkins, Steiner, & Fleming, 2009; Heim et al., 2000) and glucocorticoid signaling at the cellular level (e.g., Palma-Gudiel, Córdova-Palomera, Leza, & Fañanás, 2015; Tyrka, Price, Marsit, Walters, & Carpenter, 2012; Van Der Knaap et al., 2014). In vitro studies suggested that cortisol has the potential to inhibit the activity of telomerase, an enzyme that is expressed in continuously replicating cells and attenuates TL attrition (Choi, Fauce, & Effros, 2008). A growing body of animal (Cai et al., 2015; Haussmann, Longenecker, Marchetto, Juliano, & Bowden, 2012) and human research (Epel et al., 2006; Gotlib et al., 2015; Tomiyama et al., 2012) further provided evidence for a negative association between TL and cortisol exposure in both chronically stressed subjects and healthy individuals. However, whether cortisol also contributes to TL shortening in individuals with CM has not been examined so far.

CM and the Oxytocinergic System

The neuropeptide oxytocin plays a key role during parturition and within the postpartum period and is pivotally involved in the regulation of social behavior and affiliation (Feldman, Weller, Zagoory-Sharon, & Levine, 2007; Insel & Young, 2001). Furthermore, oxytocin was described to be stress protective with the potential to suppress the secretion of cortisol (Ditzen et al., 2009; Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Mantella, Vollmer, Rinaman, Li, & Amico, 2004; Neumann, Krömer, Toschi, & Ebner, 2000) via both direct (e.g., suppression of ACTH release; Windle et al., 2004) and indirect (e.g., supporting social buffering pathways) actions on HPA axis activity (Hostinar, Sullivan, & Gunnar, 2014). The experience of CM is often associated with a negative impact on the development of social behavior, affecting emotion regulation (Kim & Cicchetti, 2010) and adult attachment (Stalker & Davies, 1995). On a neurobiological level, this may be mediated by (mal)adaptive alterations within the oxytocinergic system (Veenema, 2012). While previous investigations on oxytocin levels have produced inconsistent results (Heim et al., 2009; Mizuki & Fujiwara, 2015; Olff et al., 2013; Opacka-Juffry & Mohiyeddini, 2011; Pierrehumbert et al., 2010), recent studies provided evidence for a hypermethylation of the oxytocin receptor (*OXTR*) gene in individuals who experienced early life stress or low maternal care (Smearman et al., 2016; Unternaehrer et al., 2015). Besides its regulatory role in social behavior, oxytocin also has potent immune regulatory properties, including anti-inflammatory and antioxidant actions (reviewed in Wang et al., 2015). Like diverse central and peripheral tissues, immune cells (and predominantly cytotoxic T cells) express the *OXTR* gene and are accessible to circulating oxytocin (Martens, Kecha, Charlet-Renard, Defresne, & Geenen, 1998). As differences in the oxytocinergic system (single nucleotide polymorphisms within the *OXTR* gene) were shown to be associated with an individual's capacity for resilience in the face of acute and traumatic stressors (Chen et al., 2011; Cicchetti & Rogosch, 2012), we hypothesized that peripheral oxytocin levels (either via direct effects involving oxytocin receptor signaling or indirectly via dampening HPA axis reactivity and cortisol secretion) may buffer TL shortening associated with CM.

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Materials and Methods

Study participants

This study was part of a larger project investigating stress resilience in the transgenerational transmission of CM in mother–infant dyads (see Boeck et al., 2016; Koenig et al., 2016; Krause et al., 2016; Schury et al., 2017). All procedures were approved by the ethics committee of Ulm University and were in accordance with the Declaration of Helsinki (World Medical Association, 2013). Because of ethical reasons, no invasive biological samples were obtained from the infants; therefore, the focus of this study was on mothers with and without a history of CM. Women giving birth in the maternity ward of the University Hospital Ulm were invited to participate in the study. Exclusion criteria comprised age under 18 years, insufficient knowledge of the German language, severe complications during parturition, severe health problems of mother and/or child (i.e., mothers or children had to be treated at the intensive care unit or the gynecological department; information provided by medical staff of the maternity ward), current drug consumption, and lifetime psychotic disorders as assessed by self-report. Two hundred forty women gave written informed consent and provided basic sociodemographic information within 6 days after parturition (t_0; see online-only supplementary Figure S.1 for detailed description of study flow). Oversampling for higher severity of CM, 112 mothers were invited for a follow-up interview 3 months postpartum (t_1), of which 67 participated. There were no differences in key sociodemographic variables (e.g., maltreatment load, socioeconomic status, and relationship status) between participating mothers and mothers who did not follow the invitation to participate at t_1. Participating mothers were, however, slightly older than nonparticipating mothers (33.5 $\pm$ 5.2 vs. 31.3 $\pm$ 5.7 years, $p = .04$). At t_1, demographic and medical data were assessed by self-report including age, body mass index (BMI), current smoking and alcohol consumption, regular physical activity (at least once per week), ethnicity, highest educational degree as a measure for socioeconomic status, chronic and acute diseases, and any medication taken in the past 3 months. At t_1, women were also asked whether they were breastfeeding their child. Furthermore, depression and anxiety symptoms were evaluated with the Hospital Anxiety and Depression Scale (Herrmann, Buss, & Snaith, 1995); perceived stress during the past 4 weeks was assessed by the four-item version of the Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983), and the perceived level of social support received by the mothers from partners, parents, in-laws, and others during the postpartum period was determined using the Postpartum Social Support Questionnaire (Hopkins & Campbell, 2008). Due to technical reasons, peripheral blood could only be obtained from 60 of the 67 women who participated at t_1.

Assessment of CM experiences

At t_0, maltreatment experiences that occurred below the age of 18 years were assessed with the German version of the Childhood Trauma Questionnaire (CTQ; Bader, Hänny, Schäfer, Neuckel, & Kuhl, 2009). As the postpartum period constitutes a particularly emotional and potentially stressful time for the mothers, the questionnaire was applied in the form of an interview conducted by trained psychologists. The CTQ assesses the severity of CM experiences on the five subscales physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect. Each subscale is covered by five items that are rated on a 5-point Likert scale (from 1 = *never true* to 5 = *very often true*). Based on the cut-off criteria described by Bernstein and Fink (1998), the severity of CM experiences can be classified on four levels (none, low, moderate, and severe) depending on the sum scores of each subscale. Subjects who reported moderate to severe CM experiences in any of the five subscales (i.e., a subscale sum score of emotional abuse $>$ 13, physical abuse $>$ 10, sexual abuse $>$ 8, emotional neglect $>$ 15, or physical neglect $>$ 10) were classified as positive for a history of childhood trauma (CM+). Out of the remaining 45 women, 15 women, who were classified negative for the experience of childhood trauma in all of the five subscales (CM–), were matched for age and BMI to the CM+ group.

Blood sampling

Three months postpartum (average 92 days, see Table 1), peripheral blood (30 ml) was drawn from antecubital veins into EDTA-buffered collection tubes (Sarstedt, Nümbrecht, Germany) for the isolation of buffy coat. The blood drawings took place between 12:30 p.m. and 2 p.m. to limit circadian variations in peripheral hormone levels. On average, peripheral blood was collected at 1 p.m., with no significant differences in blood collection times between the CM+ and CM– groups (Table 1). Immediately after blood drawings, PBMC were isolated by Ficoll–Hypaque gradient centrifugation according to the manufacturer's protocol (GE Healthcare, Chalfon St Giles, UK) and isolated cells were stored at –80 °C in cryopreservation medium (dimethyl sulphoxide; Sigma-Aldrich, St. Louis, MO; fetal calf serum: Sigma-Aldrich; dilution 1:10). In addition, peripheral blood samples were collected for plasma and serum preparation. For plasma sampling, 7.5 ml of peripheral blood was drawn into prechilled (4 °C) EDTA-coated monovettes (Sarstedt) and centrifuged immediately at 1300 g for 15 min at 4 °C. For serum sampling, 7.5 ml of peripheral blood was drawn into prechilled (4 °C) Z-Gel monovettes (Sarstedt) and centrifuged at 1500 g for 10 min at 4 °C. Plasma and serum samples were aliquoted and stored at –80 °C until analysis.

Separation of leukocyte subpopulations

For the separation of PBMC into selected immune cell subsets, cell stocks were thawed, counted, and resuspended in cell separation buffer (phosphate-buffered saline [PBS], 0.5% bovine serum albumin, 2 m*M* EDTA; Miltenyi Biotec, Bergisch-Gladbach, Germany). Subsequently, cells were

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Table 1. *Demographic characteristics, health behaviors, and psychosocial variables*

	CM– ($N = 15$)	CM+ ($N = 15$)	$t/W/\chi^{2\ a}$	*df*	*p*
Age, $M \pm SD$ (years)	31.5 ± 5.56	30.9 ± 6.4	0.27	28	.79
Ethnicity: Caucasian, *n* (%)	15 (100)	14 (93.3)	1.03	1	.31
University degree: yes, *n* (%)	9 (60.0)	5 (33.3)	0.21	1	.14
BMI, $M \pm SD$ (kg/m^2)	25.4 ± 6.4	25.2 ± 6.6	117		.87
Smoking status: yes, *n* (%)[b]	1 (6.7)	7 (53.9)	7.6	1	.006
Alcohol consumption: yes, *n* (%)[c]	6 (40)	4 (30.8)	2.4	2	.30
Physical activity: yes, *n* (%)	5 (33.3)	3 (20)	0.68	1	.41
Chronic diseases, *n* (%)	5 (33.3)	5 (33.3)			
Thyroid disease, *n* (%)	2 (13.3)	3 (20.0)			
Hypertension, *n* (%)	1 (6.7)	1 (6.7)			
Chronic bronchitis, *n* (%)	0	1 (6.7)			
Colitis ulcerosa, *n* (%)	1 (6.7)	0			
Allergy, *n* (%)	0	1 (6.7)			
First pregnancy: yes, *n* (%)	10 (66.6)	5 (33.3)	2.13	1	.14
Vaginal delivery: yes, *n* (%)	15 (100)	15 (100)			
Time interval between parturition and t_1, $M \pm SD$ (days)	91.9 ± 9.4	93.1 ± 7.8	0.36	28	.72
Breastfeeding status: yes, *n* (%)	15 (100)	10 (66.7)	6	1	.01
Blood collection time, $M \pm SD$[d]	13.0 ± 0.4	13.1 ± 0.5	94.5		.47
Time interval between last food intake and blood drawing (min)[e]	141.9 ± 128.2	112.1 ± 127.7	105.5		.50
CTQ sum score	32.1 ± 5.2	53.5 ± 12.1	6.29	19	<.001
Emotional abuse sum score	6.7 ± 2.0	12.9 ± 5.8	156.5		.001
Physical abuse sum score	5.3 ± 0.6	8.9 ± 4.7	182		.04
Sexual abuse sum score	5.1 ± 0.3	8.3 ± 5.4	184.5		.05
Emotional neglect sum score	9.4 ± 2.8	15.2 ± 4.6	4.16	28	<.001
Physical neglect sum score	5.6 ± 1.0	8.2 ± 3.7	186.5		.06
HADS depression sum score	3.8 ± 2.0	4.7 ± 4.0	86		.29
HADS anxiety sum score[f]	4.6 ± 2.5	7.9 ± 3.6	−2.85	27	.008
PSS sum score	3.5 ± 2.4	4.7 ± 3.1	−1.25	28	.22
PSSQ sum score[b]	123.1 ± 25.5	137.2 ± 27.4	1.40	26	.17

Note: CM, child maltreatment; BMI, body mass index; CTQ, Childhood Trauma Questionnaire; HADS, Hospital Anxiety and Depression Scale; PSS, Perceived Stress Scale; PSSQ, Postpartum Social Support Questionnaire.
[a]Two-tailed Student *t* tests/Wilcoxon–Mann–Whitney tests/χ^2 tests.
[b]Two missing values in CM+ group.
[c]Reported alcohol intake was maximally two glasses of wine or beer per week.
[d]Blood collection time was calculated as hours from midnight to blood drawings.
[e]Three missing values, *N*(CM–) = 13, *N*(CM+) = 14.
[f]One missing value in CM– group.

stained accordingly to the manufacturer's protocol by addition of appropriate volumes of the following antibodies: 10 μl/10^7 cells CD14-APC, 5 μl/10^7 cells CD3-PE-Vio770, 10 μl/10^7 cells CD8-FITC, 5 μl/10^7 cells CD45RA-PE (Miltenyi Biotec). Stained cells were subjected to fluorescent-activated cell sorting (FACS) using a BD FACSAria III cell sorter (BD Biosciences, Heidelberg, Germany) for isolation of monocytes ($CD14^+CD3^-$), naive cytotoxic T cells ($CD3^+CD8^+CD45RA^+$), and memory cytotoxic T cells ($CD3^+CD8^+CD45RA^-$). Propidium iodide staining was used to distinguish dead from living cells. Separated cell fractions were fixated in a 3:1 (v/v) solution of methanol (Sigma-Aldrich) and glacial acetic acid (VWR, Radnor, PA).

Telomere staining procedure

TL was assessed in fixated cells using quantitative fluorescent in situ hybridization (qFISH). In short, 10^5 cells per sample were spread out onto *superfrost* slides (Menzel-Glaeser, Braunschweig, Germany), washed twice in PBS (5 min/wash), and were permeabilized using a pepsin solution for 10 min at 37 °C. Following two additional washing steps with PBS (5 min/wash), slides were stained with Cy3-labeled peptide nucleic acid telomere oligonucleotides (Panagene, Daejeon, Korea) for 2 hr at room temperature in a humid chamber, washed twice with a washing buffer consisting of formamide, 1 *M* Tris, and 10% bovine serum albumin (20 min/wash), twice with TBS-Tween (1%) (5 min/wash), and twice with PBS (5 min/wash). Cell nuclei were counterstained with DAPI using Vectashield Mounting Medium (Vector Laboratories, Burlingame, CA) for the exclusion of false-positive perinuclear signals. Analysis of TL in stained cells was performed using a Leica DM5000 B fluorescent microscope (Leica Microsystems, Wetzlar, Germany), and images were captured at a 1000-fold magnification.

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Analysis of telomere fluorescence intensity (TFI)

For the evaluation of TFI, the image acquisition software TFL-TeloV2 (Poon & Lansdorp, 2001) was used, and mean TFI was measured in 100 cells per sample. In three cases it was not possible to analyze 100 cells per sample due to insufficient cell numbers sorted for high purity by FACS resulting from a restricted starting amount of total PBMC. In these cases, a minimum of 69 cells was analyzed. As the standard deviation was comparable to other samples, all samples were included in the statistical analyses. Mean TFI was calculated as an average of all TFI values for each sample.

Southern blot based standard curve for conversion of TFI to kilobases

We established a standard curve covering the expected TL range based on three human cell lines (Hela, HCT116, 293THek) and PBMC from a healthy donor as described by Linkus et al. (2016). In short, TL of the selected standards was measured in kilobases by southern blot, and standard cells were co-stained with each individual qFISH run. Based on the TL assessed by southern blot analysis, a standard curve was modeled by linear regression for each individual experimental run (on average $R^2 = .85$), and TFI values of the assayed samples were converted into corresponding kilobase values applying the respective linear equations.

Peripheral hormone levels

Serum cortisol levels were analyzed using a chemiluminescence immunoassay (IBL International, Hamburg) according to the manufacturer's protocol (intraassay coefficient of variation [CV] of 2.7%–4.0% and interassay CV of 6.3%–7.2%) by the biopsychology work group of Professor Kirschbaum at the University of Dresden, Germany. As the total level of serum cortisol is a measure for both the unbound, biologically active fraction (up to 10% of total cortisol) and the fraction of cortisol that is bound to proteins (up to 90%), we additionally assessed the serum level of cortisol-binding globulin (CBG). CBG is the major transport protein of cortisol in peripheral blood and binds 80%–90% of cortisol, while albumin, as a second carrier protein, binds up to 10% of cortisol. Serum CBG levels were determined using a sandwich enzyme immunoassay (IBL International) according to the manufacturer's protocol. Intraassay CV was described to be 1.2%–2.2% and interassay CV 6.8%–7.3% by the manufacturer. One outlier (>3.5 *SD* from the mean) with extraordinarily high CBG serum levels was excluded from the statistical analyses. Oxytocin levels were quantified in plasma samples after extraction using a highly sensitive and specific radioimmunoassay (RIAgnosis, Sinzing, Germany) as described in Kagerbauer et al. (2013). This procedure was standardized and validated in numerous animal and human studies to reliably detect bioavailable oxytocin (Landgraf & Neumann, 2004) with an assay sensitivity in the 0.1 pg/sample range and an intra- and interassay variability of less than 10%.

The study cohort comprised women in the postpartum period of which 83.3% reported breastfeeding their children at t_1 (Table 1). Oxytocin is known to play a pivotal role in lactation; however, it has only a very short half-life of less than 5 min in peripheral blood and is robust to fluctuations if not sampled during lactation (Feldman et al., 2007). One study participant reported breastfeeding her child within 15 min prior to blood sampling and was therefore excluded from analyses regarding oxytocin. Another study participant was excluded due to the intake of oral contraceptives, which is a known confound for peripheral oxytocin, cortisol, and CBG levels. As from one study participant no plasma sample could be obtained, oxytocin was analyzed in 15 subjects with and 12 subjects without CM experiences. In accordance with previous reports (Feldman et al., 2007; Van der Post et al., 1997), the breastfeeding status did not show a significant influence on peripheral oxytocin levels ($W = 64.5$, $p = .57$).

Data analysis

All biological measurements were performed blinded with respect to group assignment. Statistical data analysis was conducted using R 3.2.4 (R Core Team, 2013). The significance level was set at $p < .05$. Group comparisons with respect to sociodemographic and clinical variables were calculated using two-tailed *t* test (parametric) or Wilcoxon–Mann–Whitney *U* test (nonparametric) depending on normal distribution of the data. Chi-square tests were employed for categorical variables. Pearson correlation coefficients (parametric) and Kendall rank correlation coefficients (nonparametric) were calculated where appropriate to test for an association between cortisol and oxytocin, as well as for correlation analyses between immune cell TL and sociodemographic variables (age and BMI). Group differences in TL were calculated using analyses of covariance, adjusting for potential confounding factors in follow-up analyses by separately including age, smoking status, breastfeeding status, anxiety symptoms, and parity as covariates in the statistical models. To test for an association between immune cell TL and peripheral hormone levels, linear regression models were calculated entering serum cortisol level as predictor in one model, plasma oxytocin level as predictor in a separate model, and group as a covariate in each of the regression models. In order to examine whether the association between cortisol and TL as well as between oxytocin and TL differed depending on a history of CM experiences, an interaction of group and peripheral hormone level was introduced into the linear regression models in a second step. All linear regression models met the requirements for parametric testing.

Results

Sociodemographic, clinical, and endocrine characteristics of study participants, demographic characteristics, health behaviors, and psychosocial variables of all study participants are summarized in Table 1. The severity of CM experiences in each of the five subscales of the CTQ was signifi-

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cantly higher in the CM+ group, while the CM– group presented lower subscale sum scores than those reported in a representative sample of the German population (Iffland, Brähler, Neuner, Häuser, & Glaesmer, 2013). There were no significant differences between the two age- and BMI-matched groups with regard to alcohol consumption, physical activity, ethnicity, and socioeconomic status as estimated by the number of study participants holding a university degree. At t_1, all study participants reported to be in a committed relationship and the CM+ and CM– groups did not differ with respect to the current level of perceived social support. Furthermore, group comparisons revealed no significant differences in depressive symptom severity and the level of perceived stress between CM+ and CM– women. The number of smokers and the level of anxiety symptoms were significantly higher in the CM+ compared to the CM– group. Moreover, fewer women of the CM+ group were breastfeeding their child 3 months postpartum. With regard to endocrine levels, CM+ and CM– women presented no significant group differences in serum cortisol levels and plasma oxytocin levels assessed at t_1 (Table 2). After exclusion of one outlier with extremely high CBG serum levels (>3.5 *SD* from the mean), the CM+ women showed, however, a marginally significant decrease in serum CBG levels compared to the CM– group (Table 2). Correlation analyses revealed no significant associations between peripheral cortisol and oxytocin levels ($\tau = -0.19$, $p = .162$).

PBMC subset composition

We first tested if the PBMC subset composition was altered in women with a history of CM compared to CM– women. As shown in Table 2, there were no significant differences between the CM+ and CM– groups with respect to the percentage amounts of monocytes, B cells and natural killer (NK) cells, total T cells, and T cell subsets.

TL in immune cells

PBMC TL and TL in immune cell subsets were not significantly associated with age, BMI, socioeconomic status, or alcohol consumption. While smokers presented significantly shorter TL in PBMC, $t\ (26) = 2.24$, $p = .03$, no significant group differences were evident in monocytes, or naive or memory cytotoxic T cells. Furthermore, physical activity was associated with shorter PBMC TL, $t\ (26) = 2.91$, $p = .007$, while there were no group differences in TL for any of the immune cell subsets. The CM+ group presented

Table 2. *Biological variables in women with a history of CM (CM+) and without (CM–)*

	CM– (*N* = 15)	CM+ (*N* = 15)	*t/W/F*[a]	*df*	*p*
		PBMC Subset Composition (%)[b]			
Monocytes	10.2 ± 3.1	11.4 ± 6.3	224.5		.74
T cells	56.7 ± 9.4	59.8 ± 10.2	205		.27
Cytotoxic T cells	15.2 ± 6.9	15.4 ± 5.0	0.12	28	.90
Naive cytotoxic T cells	10.0 ± 5.0	9.7 ± 3.9	232		1.00
Memory cytotoxic T cells	3.5 ± 2.1	3.7 ± 1.7	0.27	28	.79
Noncytotoxic T cells	41.5 ± 6.8	44.4 ± 8.8	0.99	28	.33
B cells and NK cells	33.0 ± 8.2	28.9 ± 7.0	201.5		.20
		Telomere Length (kb)			
PBMC	7.8 ± 1.6	7.1 ± 1.2	1.68	1,28	.21
Monocytes	7.8 ± 1.2	7.9 ± 1.3	0.04	1,28	.85
Naive cytotoxic T cells	9.1 ± 1.8	9.1 ± 1.9	0.01	1,28	.95
Memory cytotoxic T cells	8.5 ± 1.5	7.4 ± 1.2	5.41	1,28	.03
		Peripheral Hormone Levels			
Cortisol level (ng/ml)	233.9 ± 94.6	218.2 ± 47.7	127.0		.57
CBG level (μg/ml)[c]	33.7 ± 4.1	31.0 ± 3.9	1.76	27	.09
Oxytocin level (pg/ml)[d]	0.8 ± 0.4	0.9 ± 0.4	66.0		.25

Note: Values are mean ± standard deviation. CM, child maltreatment; PBMC, peripheral blood mononuclear cells; CBG, cortisol-binding globulin.
[a]Two-tailed Student *t* tests/Wilcoxon–Mann–Whitney tests/analyses of variance were calculated where appropriate.
[b]Percentage fractions of 100% living cells. Cell subsets were defined by the following cell surface markers: monocytes: $CD3^-CD14^+$; T cells: $CD3^+$; cytotoxic T cells: $CD3^+CD8^+$; naive cytotoxic T cells: $CD3^+CD8^+CD45RA^+$; memory cytotoxic T cells $CD3^+CD8^+CD45RA^-$; noncytotoxic T cells: $CD3^+CD8^-$; B cells and NK cells: $CD3^-CD14^-$.
[c]One outlier (>3.5 *SD* of mean) was excluded in the CM+ group.
[d]*N* (CM–) = 12, *N* (CM+) = 15.

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shorter mean TL in PBMC compared to the CM– group (Table 2); however, this group difference did not reach statistical significance. We next analyzed CM-associated differences in TL of immune cell subsets and found no significant group difference with respect to TL in monocytes and naive cytotoxic T cells. The CM+ group showed, however, a significant reduction of TL in memory cytotoxic T cells compared to the CM– group. Follow-up analyses did not reveal any significant main effects of age, BMI, smoking status, anxiety levels, or parity on TL in memory cytotoxic T cells, while the main effect of group remained significant after the inclusion of these covariates.

Association between cortisol levels and TL

Linear regression analysis accounting for a history of CM (main effect of group: β = –0.45, p = .005) revealed that the total serum cortisol level was significantly associated with TL in memory cytotoxic T cells (main effect of cortisol level: β = –0.49, p = .003). The linear regression model explained 35% of the variance in TL for memory cytotoxic T cells, adjusted R^2 (R^2_{adj}) = 0.35, F (2, 27) = 8.91, p = .001. As illustrated in Figure 1a, while the CM+ group presented shorter telomeres than the CM– group, higher cortisol levels were across both groups associated with reduced TL in memory cytotoxic T cells. The results remained significant after the inclusion of potentially confounding covariates into the linear regression model. Follow-up analyses entering an interaction of group and peripheral cortisol level into the linear regression model did not reveal a significant interaction effect on TL in memory cytotoxic T cells (p = .870). Cortisol did not show any significant main effect on TL in PBMC, monocytes, or naive cytotoxic T cells (see online-only supplementary Table S.1).

Association between oxytocin levels and TL

While a history of CM was negatively associated with TL (main effect of group: β = –0.47, p = .010), plasma oxytocin showed across both groups a positive association with TL (main effect of oxytocin: β = 0.43, p = .017), explaining in total 29% of the TL variance in memory cytotoxic T cells, R^2_{adj} = 0.29, F (2, 24) = 6.21, p = .007 (Figure 1b). Inclusion of potentially confounding covariates into the linear regression model did not significantly alter the results. Modeling an interaction in the linear regression analysis did not reveal a significant interaction effect of group and the peripheral oxytocin level on TL in memory cytotoxic T cells (p = .857). No significant main effect was found for oxytocin on TL in PBMC, monocytes, or naive cytotoxic T cells (see online-only supplementary Table S.2).

In order to verify the independent results of the previous analyses, a linear regression model was tested including main effects of group, serum cortisol, and plasma oxytocin levels on TL in memory cytotoxic T cells. In this model, which explained in total 44% of the TL variance in memory cytotoxic T cells, R^2_{adj} = 0.44, F (3, 23) = 7.69, p = .001, the main effects of group (β = –0.50, p = .003) and serum cortisol (β = –0.43, p = .012) remained significant, while the main effect of oxytocin was reduced to marginal significance (β = 0.30, p = .071).

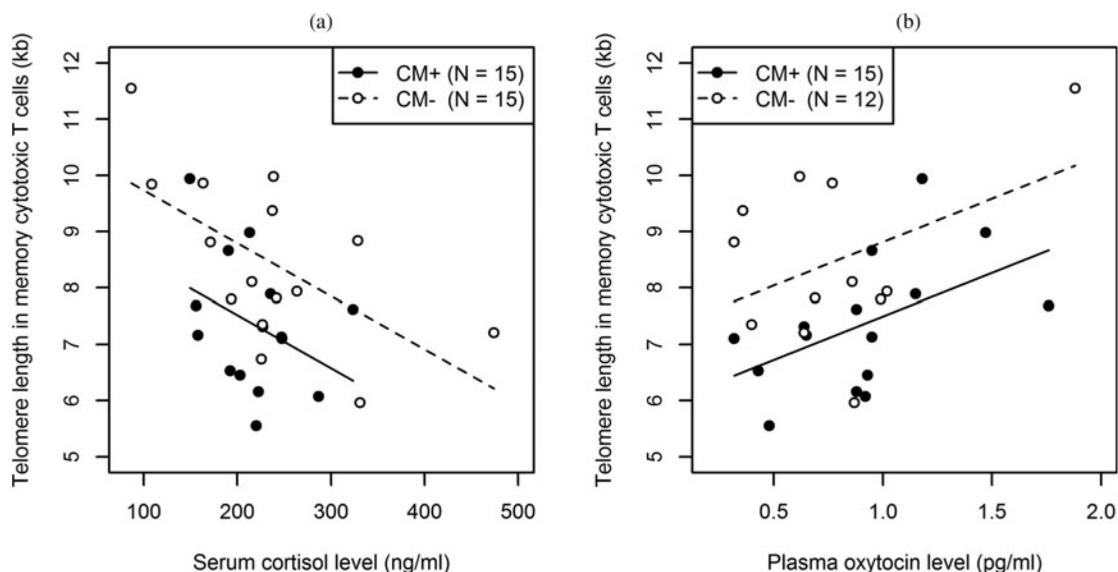

Figure 1. Influence of cortisol and oxytocin on telomere length in women with and without child maltreatment (CM). (a) Serum cortisol levels and a history were both negatively associated with telomere length in memory cytotoxic T cells. (b) Although women with CM displayed shorter telomeres, plasma oxytocin levels were across both groups positively associated with telomore length in memory cytotoxic T cells. CM+, women with maltreatment experiences during childhood; CM−, women without a history of child maltreatment; kb, kilobases.

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Discussion

The findings of this study suggest that memory cytotoxic T cells are particularly vulnerable to shortened TL in the context of traumatic early life experiences. Furthermore, we provide here the first evidence that cortisol levels are negatively associated with TL, while oxytocin levels are positively associated with TL in memory cytotoxic T cells in mothers both with and without a history of CM experiences.

Shortened TL in immune cell subsets with CM

Findings from previous studies already suggested that the overall cell population of cytotoxic T cells was more vulnerable to shortened TL than T helper cells and B cells (Karabatsiakis et al., 2014) and also most sensitive for telomerase inhibition by cortisol exposure in vitro (Choi et al., 2008). The long-living subset of memory cytotoxic T cells was further shown to react more sensitively than naive cells to norepinephrine stimulation with the induction of inflammatory cytokine expression in vitro (Slota, Shi, Chen, Bevans, & Weng, 2015). This finding implies that these cells also show a particular vulnerability to the activation of the sympathetic nervous system during acute and chronic stress responses. Memory cytotoxic T cells are a hallmark of the adaptive immune system and play a pivotal role in fighting recurrent infections by rapidly developing to cytolytic effector cells and producing greater amounts of cytokines after antigenic stimulation compared to naive T cells (Zimmerman, Brduscha-Riem, Blaser, Zinkernagel, & Pircher, 1996). They are further characterized as long-lived circulating cells, which are most exposed to and therefore potentially most affected by stress hormones in the peripheral blood. Cell-type specific differences in the expression or sensitivity of the glucocorticoid and oxytocin receptor might render memory cytotoxic T cells specifically vulnerable to the influence of peripheral hormones. To the best of our knowledge, no study has investigated the functional characteristics of these hormone signaling cascades differentiating between specific immune cell subsets so far. Whether shortened TL in memory cytotoxic T cells is also most relevant for health remains to be elucidated. Replicative senescence of memory cytotoxic T cells, which is characterized by TL shortening, is associated with impairments in cellular cytokine release, cytolytic, and antiviral function (Klebanoff, Gattinoni, & Restifo, 2006). Clinically, this might result in a compromised protection of the host from pathogen challenges, recrudescent diseases due to reactivation of latent viruses, and reduced immune surveillance, potentially increasing the risk for carcinogenesis. Shortened TL in memory cytotoxic TL might thus offer one potential link for the association of early life stress and adverse health outcomes observed decades later in life.

With increasing age, the thymic output of functional naive T lymphocytes decreases substantially and memory cells gain more and more importance for maintaining an effective immune response. Individuals with a diagnosis of posttraumatic stress disorder showed a decreased percentage of naive cytotoxic T cells and a concomitant increase in the percentage of memory cytotoxic T cells (Morath et al., 2014; Sommershof et al., 2009). In this study, we did not find an overall effect of CM exposure on PBMC subset composition, with similar percentage fractions of naive and memory cytotoxic T cells for mothers with and without CM experiences. One explanation for this inconsistency might be the difference in the chronicity, frequency, and/or magnitude of stress exposure between our current study cohort of relatively young women with a history of CM and individuals who developed posttraumatic stress disorder following the exposure to war and torture.

Cortisol and TL in memory cytotoxic T cells

The present study provides the first evidence for a negative association between cortisol levels and TL in memory cytotoxic T cells. Although the CM+ and CM– groups did not differ in the total level of serum cortisol, the tendency for a reduction in serum CBG levels indicates that the bioactive fraction of unbound cortisol was higher in the CM+ group. These results are in line with previous studies that found no differences in basal cortisol levels when analyzing total serum cortisol (Carpenter et al., 2007; Heim et al., 2000), while studies on salivary cortisol levels, which represent only the bioactive fraction of cortisol, found increased levels in maltreated children (Cicchetti & Rogosch, 2001) and postpartum mothers with a history of CM (Gonzalez et al., 2009). One animal study investigating the biological consequences of early life stress showed that maternal separation was associated with a reduction of peripheral CBG levels in the offspring (Viau, Sharma, & Meaney, 1996). To the best of our knowledge, no human study assessed alterations in CBG levels in association with early life stress so far. CM was further shown to be associated with epigenetic modifications within the glucocorticoid receptor gene *NR3C1* (Palma-Gudiel et al., 2015; Tyrka et al., 2012; Van Der Knaap et al., 2014) and its regulatory co-chaperone FK506 binding protein 5 (*FKBP5*; Klengel et al., 2013; Tyrka et al., 2015), which together may further influence cortisol-mediated effects on a cellular level.

Even though the mean level of free cortisol seemed to be increased in the CM+ group, several CM-exposed women presented serum cortisol levels that were comparable to the nonexposed group. The variance in peripheral cortisol levels could be attributable to heterogeneity within the CM+ group with respect to type and timing of CM experiences, which might confer unique effects on HPA axis outcomes (Kuhlmann, Chiang, Horn, & Bower, 2017). In addition, it was theorized within the framework of the attenuation hypothesis that exaggerated cortisol responses are present during the acute phase following a traumatic event, but are downregulated over time in an adaptive response to protect the organism from the deleterious effects of prolonged cortisol expo-

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sure (Susman, 2006; Trickett, Noll, Susman, Shenk, & Putnam, 2010). It is tempting to speculate that CM-exposed individuals who do not show such an adaptive attenuation (i.e., have high cortisol levels throughout adulthood) might be less resilient, which overlaps with our observation that CM+ women with higher cortisol levels presented the shortest TL in memory cytotoxic T cells.

The negative association between cortisol and TL in memory cytotoxic T cells was not restricted to the CM+ group but was also evident in the CM– group. This finding is in accordance with previous work that shows a universal negative relation between nocturnal urinary cortisol levels as well as the amount of cortisol secretion to an acute stressor with TL in both stressed individuals and healthy control groups (Epel et al., 2006; Gotlib et al., 2015; Tomiyama et al., 2012). On a molecular level, cortisol may be associated with shortened TL through the inhibition of telomerase activity (Choi et al., 2008). In addition, the observation of shortened TL could also be attributable to increased levels of inflammation, triggering a compensatory increase in peripheral cortisol secretion. Inflammation is associated not only with an increased cell turnover promoting TL erosion but also with increased levels of oxidative stress. Telomeres are particularly sensitive to oxidative damage, while treatment with antioxidants is effective in decelerating TL shortening (Von Zglinicki, 2002). Dysregulations in the neuroendocrine stress response system may thereby contribute to such a redox imbalance. In vitro and in vivo studies suggest that cortisol treatment promotes oxidative stress, while it is associated with a concomitant decrease in antioxidative enzyme levels (Costantini, Marasco, & Møller, 2011; McIntosh & Sapolsky, 1996; Patel et al., 2002). On a cellular level, mitochondria, which are the powerhouses and main production sites of reactive oxygen species in our cells, may play a central role in these associations. Mitochondrial respiratory activity was shown to be enhanced in cortical neurons following cortisol exposure (Du et al., 2009). In the current sample, we could recently show that mitochondrial activity of peripheral immune cells was increased in individuals with CM experiences (Boeck et al., 2016). This increase in mitochondrial respiration was accompanied by a higher rate of reactive oxygen species production, increased levels of oxidative stress, and higher levels of proinflammatory cytokine secretion. Longitudinal research is needed to fully elucidate the causal and temporal relations between HPA axis (re)activity, inflammation, mitochondrial alterations, and TL dynamics in individuals with a history of CM.

Oxytocin and TL in memory cytotoxic T cells

This is the first study to also model the impact of biological resilience factors in the form of endogenous oxytocin levels on TL dynamics. We found that across women with and without a history of CM experiences, higher plasma oxytocin levels were associated with less telomere attrition in memory cytotoxic T cells. Plasma oxytocin levels were not significantly associated with serum cortisol levels, suggesting that this effect might be driven by other factors than the HPA axis dampening actions of oxytocin. Due to the correlational nature of our results, we cannot draw any causal conclusions. No previous study has examined the potential association between peripheral oxytocin levels and TL dynamics so far. However, oxytocin was reported to exert anti-inflammatory and antioxidant actions: cell culture (Szeto et al., 2008) and animal studies (İşeri et al., 2005; Nation et al., 2010; Oliveira-Pelegrin, Saia, Carnio, & Rocha, 2013) showed that treatment with physiological concentrations of oxytocin has the potential to attenuate the release of proinflammatory cytokines and to inhibit cellular superoxide and nitrite production. As the telomeric nucleotide sequence is particularly sensitive to oxidative damage and the inflammation-associated increase in cell turnover promotes TL attrition, the antioxidant and anti-inflammatory properties might offer one explanation for how peripheral oxytocin levels influence immune cell TL. Future studies are warranted to further investigate whether these effects are mediated by oxytocin receptor signaling in peripheral immune cells and whether oxytocin also has direct effects on telomerase activity, thereby promoting the preservation and lengthening of telomeres. Although the biomolecular nature of the observed associations needs further investigation, it becomes apparent that endogenous oxytocin levels should be taken into account when analyzing biological disturbances associated with adverse early life experiences.

Strengths and limitations

Strengths of the present study include that we adopted with the qFISH a highly sensitive technique for TL assessment at the single cell level and assessed TL in defined and highly purified cell subpopulations. This methodological approach substantially increases the sensitivity for the assessment of TL changes with CM. Still, the major limitation of the current study is the relatively small sample size and the cross-sectional study design. Because of the exploratory nature of these preliminary results, they should be interpreted with caution and need to be confirmed in larger study cohorts. The CM+ and CM– groups were matched for age and BMI and presented no significant differences with respect to further potential confounds for TL analyses (e.g., gender, physical activity, social support, perceived stress levels, or depressive symptom severity). Because the oxytocinergic system and TL dynamics are both sensitive to gender differences, it will be important to investigate the presented associations in men in future studies in order to show the generalizability of the results.

Biological sampling was conducted 3 months postpartum, which is important to emphasize because pregnancy and the postpartum period are associated with profound changes in both the endocrine and the immune systems. Regarding the immune system, pregnancy and the early postpartum period have been described to be accompanied by a gradual increase in inflammation levels (Christian & Porter, 2014; Groer, Jevitt, & Ji, 2015; Palm, Axelsson, Wernroth, Larson, &

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Basu, 2013) and characteristic changes regarding the numbers of specific T, B, and NK cell subsets (Kieffer, Faas, Scherjon, & Prins, 2017; Watanabe et al., 1997). Pregnancy and parturition constitute an immune challenge to the maternal immune system, and normalization of cellular immune functions takes up to 3 months postpartum (Groer et al., 2015). A recent study by Kieffer et al. (2017) further showed that pregnancy might have persistent effects on the number and activation status of memory cells, which mainly affected CD4+ T-helper cells. While maternal cortisol and CBG levels show a steady increase from the first to the third trimester of pregnancy, they rapidly decrease following parturition (Bloch, Daly, & Rubinow, 2003; Jung et al., 2011). Plasma oxytocin levels were reported to show a high individual stability, with constant levels across the first trimester of pregnancy to the postpartum period (Feldman et al., 2007; Levine, Zagoory-Sharon, Feldman, & Weller, 2007), as well as in men and nonpregnant women over a time period of 6 months (Weisman, Zagoory-Sharon, Schneiderman, Gordon, & Feldman, 2013). According to these literature findings, it can be assumed that pregnancy-related changes in the endocrine system have mostly normalized at the time point of biological assessments in our study. Additional measures, such as physical activity levels, may also be confounded during the postpartum period. Further, postpartum mothers may be particularly sensitive with respect to their history of adverse early life experiences. In order to account for this unique time period, the CTQ was not applied as a questionnaire but as an interview that was conducted by trained psychologists. Future studies are warranted to replicate the presented associations in nonpregnant/nonpostpartum women in order to demonstrate the generalizability of the results.

The current findings are further limited by the type and timing of hormone assessment. Endocrine signaling shows circadian rhythm dynamics with fluctuations in absolute values over the day. In order to account for this major confound, blood collection times were standardized for all participants of this study, and there were no group differences in mean time of blood collection. As cortisol levels peak in the morning and gradually decline in both maltreated and nonmaltreated individuals across the day with no shift in the general diurnal pattern of cortisol secretion (Gonzalez et al., 2009), it can be expected that single afternoon samples lead to an underestimation of cortisol levels resulting in smaller effect sizes in group comparisons. Future studies are warranted that investigate the influence of diurnal cortisol and oxytocin secretion on TL dynamics in individuals with and without a history of CM, optimally in a longitudinal study design, to gain a better understanding of the causal nature and the molecular mechanisms underlying the presented associations.

Conclusion

In conclusion, this study offers the first evidence for a differential vulnerability of immune cell subsets to the biological consequences of early life trauma in the form of CM experiences. We provide data suggesting memory cytotoxic T cells as a particularly sensitive biological target when investigating TL in the context of CM. Addressing this cell type might help to overcome the inconsistencies in study results investigating TL in total PBMC and might further help to identify new strategies to counteract biological consequences associated with CM by psychotherapeutic interventions or pharmacological treatments. Further, we found support for the perspective of a negative association between high levels of the stress hormone cortisol and shortened TL in this particularly stress-sensitive immune cell subset. In addition, this study shows for the first time a positive association between oxytocin and TL in memory cytotoxic T cells, suggesting a potentially protective role of the attachment-related hormone. These associations were independent of a history of CM. Future studies are needed to elucidate the clinical implications of shortened TL in memory cytotoxic T cells, focusing on the modulatory effects of cortisol and oxytocin on disease risk. Finally, it becomes more and more evident that besides an individual's biological makeup, environmental, behavioral, and psychosocial factors can influence how deep psychological stress gets under the skin and may enhance or reduce biological risks of affected individuals (Cicchetti, 2013; Hamilton et al., 2015).

Supplementary Material

To view the supplementary material for this article, please visit https://doi.org/10.1017/S0954579417001055.

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