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Association between Plasma IL-6 Response to Acute Stress and Early Life Adversity in Healthy Adults

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Abstract

Increased production of peripheral cytokines and other pro-inflammatory markers has been linked to psychiatric disorders such as major depressive disorder and posttraumatic stress disorder (PTSD). Recent research has pointed to early life stress, particularly childhood maltreatment, as an independent and preventable risk factor for systemic inflammation in adulthood. Some data suggest that adults with a history of childhood maltreatment exhibit a heightened inflammatory response to acute stress challenge. To further elucidate the relationship between childhood maltreatment and pro-inflammatory cytokine production, we examined plasma IL-6 response to the Trier Social Stress Test (TSST) in 69 healthy adult subjects without depression or PTSD. Serial plasma IL-6 concentrations were measured during a standardized psychosocial stressor in n=19 subjects with moderate-severe childhood maltreatment (MAL) and n=50 controls without maltreatment (CTL), as indicated by self-ratings on the Childhood Trauma Questionnaire (CTQ). CTQ total scores were positively correlated with change in overall change in IL-6 response, as

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Disclosure/Conflict of Interest

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well as the maximum IL-6 concentration during the TSST. Greater acute IL-6 release and higher IL-6 concentrations over time were observed for the MAL group relative to the CTL group. Inflammation may be an important developmental mediator linking adverse experiences in early life to poor adult physical and mental health. The results of this preliminary study warrant further investigation in a larger sample.

Keywords

Trier Social Stress Test; stress; cortisol; cytokines; Childhood; Maltreatment; CTQ; IL-6

Introduction

A growing body of research has established that pro-inflammatory cytokines, such as interleukin-6 (IL-6), have systemic effects far beyond the canonical immune response. These immunomodulators have been implicated in a number of psychiatric disorders, particularly major depressive disorder (Groer and Morgan, 2007; Koo and Duman, 2008; O'Brien *et al*, 2004; Pace *et al*, 2006) and anxiety disorders (Bauer *et al*, 2010; Hoge *et al*, 2009; von Kanel *et al*, 2007). The pro-inflammatory response is not restricted to pathological states; acute psychological stress produces a transient rise in peripheral cytokines in healthy adult humans (Miller *et al*, 2005; Steptoe *et al*, 2007).

However, early life stress, such as childhood maltreatment, appears to be an independent risk for systemic inflammation in otherwise healthy adult humans (Danese *et al*, 2007). Neuroendocrine-immunological abnormalities established during a stressful childhood are thought to mediate the development of the pro-inflammatory phenotype in adulthood (Chida *et al*, 2007; Elenkov, 2008; Powell *et al*, 2009). In a study of stress-induced immune response in men with and without major depressive disorder (MDD), men with MDD and a history of early life stress displayed an exaggerated IL-6 response to an acute psychosocial stressor as compared to non-depressed male subjects (Pace *et al*, 2006). We previously reported a finding of low cortisol response to stress among adults with exposure to childhood maltreatment (Carpenter *et al*, 2009), and others have reported an inverse relationship between cytokine release and cortisol release to mild psychological stress challenge (Kunz-Ebrecht *et al*, 2003). To further elucidate the role that childhood stress exposure plays in the cytokine response to acute stressors encountered in adulthood, we examined the IL-6 response to the Trier Social Stress Test (TSST) in a cohort of healthy adults without psychiatric disorders.

Methods and Materials

Subjects

Subjects were 69 adults (42 women, 27 men) ages 18–64, selected from the community. The subjects in this study were a subset of a larger study cohort that we examined in previous studies (Carpenter *et al*, 2007; Carpenter *et al*, 2009). Voluntary written informed consent was obtained from healthy adults who were recruited to participate in a study about stress. The study was approved by the Butler Hospital Institutional Review Board. Subjects who

scored in the “moderate” to “severe” range on at least one of the five subscales of the Childhood Trauma Questionnaire (CTQ) comprised the maltreated (MAL) group (n = 19). Subjects scoring “minimal” or “none” on all 5 CTQ subscales, comprised the control group (CTL, n = 50). All subjects were free of pregnancy, significant medical illness, and recreational drug use, as evidenced by complete physical and neurological examination and standard laboratory tests, including electrocardiogram, complete blood count, serum electrolytes, thyroid-stimulating hormone, urine toxicology and urinalysis. Oral contraceptives and estrogen replacement therapies were allowed, and menstrual cycle phase at time of testing was recorded for female subjects. Body mass index (BMI) was calculated as weight (kg) divided by height (meters)^2. Exclusion criteria included major medical illness or use of any psychotropic medication or other drug thought to influence HPA axis function (including psychotropic medications, beta blockers, angiotensin-converting enzyme inhibitors, ketoconazole, metyrapone, and corticosteroids). Structured clinical Interview for DSM-IV for Axis I Disorders (SCID-I) was used for psychiatric diagnostic assessments. Diagnoses leading to exclusion included a current or lifetime diagnosis of a primary psychotic disorder or bipolar disorder, current substance dependence or abuse, and current major mood or anxiety disorder. Subjects with prominent personality pathology, as detected through clinical interviews and interactions with research staff during the first two visits, were also excluded. Subjects were remunerated for their time and travel.

Assessment of Maltreatment History, Current Mood/Anxiety Symptoms and Well-Being

In addition to diagnostic interviews, subjects completed a battery of self-report assessments at baseline, including the Inventory for Depressive Symptoms – Self-Rated (IDS-SR; (Rush AJ, 1996), the State-Trait Anxiety Inventory (STAI; (Spielberger, 1983), the Perceived Stress Scale (PSS;(Cohen S, 1983), the Quality of Life - Enjoyment and Satisfaction Questionnaire (QLESQ;(Endicott *et al*, 1993), and the Childhood Trauma Questionnaire (CTQ; (Bernstein *et al*, 2003). The CTQ Version 3 is a 28-item self-report instrument comprising five subscales (emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect).

The Acute Stress Protocol

The Trier Social Stress Test (TSST) is a standardized laboratory psychosocial stress protocol that involves public speaking, role-play and mental arithmetic tasks in front of a panel of confederate judges (Kirschbaum *et al*, 1993). The protocol consists of an anticipation period followed by a 10-minute test period, during which the subject must deliver a monologue speech about his/her qualifications for a chosen vocation and perform mental calculation and recitation of serial subtraction by 13’s. Blood samples, heart rate, and blood pressure data were obtained before, during and after the role-play/arithmetic stressor to monitor for safety and physiologic arousal (−30, 0, +30 and +45 minutes). An intravenous (IV) catheter was established at 11:00 AM to allow time for subjects to accommodate to the biological testing suite environment. Plasma samples were collected via intravenous access at 0 minutes (1:45 PM), and at +15 (2:00 PM), +30 (2:15 PM), +45 (2:30 PM), +60 (2:45 PM), +75 (3:00 PM) and +90 (3:15 PM). Subjects met briefly with the judges immediately after the 0 time point and were told about the public speech role-play, then prepared their speech during the anticipation period (1:50 to 2:00 pm). Subjects were debriefed after the role-pla.y Self-

ratings of emotional states, as described elsewhere (Carpenter *et al*, 2007; Carpenter *et al*, 2009), were completed at 0, + 30, and +75 minutes. Subjects remained awake in bed for the remainder of the protocol.

Assays

Plasma IL-6 was assayed using high-sensitivity ELISA available from R&D Systems (Minneapolis, MN). Quality assessment samples (concentration, 2.47 pg/ml) have been determined with intra- and inter-assay CVs of 3.3% and 8.9%, respectively.

Statistical Analyses

Analyses were conducted using SPSS 16.0.1. The IL-6 values and age (years) were log10 transformed to fulfill requirements for normal distribution in statistical analyses. All tests were two-tailed with significance defined as p-value <.05. Chi-square and t-test statistics were calculated to compare the two groups on baseline clinical and demographic variables. Baseline variables that differed significantly between groups were entered in post-hoc models as covariates. A final set of post-hoc analyses were performed with estrogen use (n=42) and menstrual cycle phase (n=37) as covariates for women in the sample with available data.

To isolate absolute magnitude of IL-6 rise in response to stress challenge, the summary variable “delta(IL-6)” was calculated as change from time 0 (baseline) to peak IL-6 value after introduction of the stressor. Pair-wise bivariate Pearson correlation matrices were run to evaluate relationships between IL-6 values (time 0, max, and delta) and baseline clinical and demographic variables, including the total CTQ score (continuous data). These were followed by partial correlation analyses, controlling for age and BMI, to examine the relationships between total CTQ score and IL-6.

Two types of general linear models (GLM) were used to examine possible effects of maltreatment group on IL-6 response to the stress test. In the primary analysis, GLM univariate analysis was performed with delta(IL-6) as the dependent variable; group was defined as a fixed factor, and covariates in the model included those found to be statistically related to IL-6 (age and BMI). Post-hoc tests included the same model with the addition of several other covariates, including baseline characteristics that differed between groups and others which theoretically could impact response to acute stress (sub-threshold depression symptoms, state and trait anxiety, level of perceived stress, menstrual cycle phase, and estrogen use). A similarly constructed GLM, with age and BMI as covariates, was also used to examine post-hoc group differences in IL-6 concentration at a single time point (time 0) before exposure to stress in the TSST protocol.

The second analysis strategy used repeated measures GLMs to test effects of maltreatment group on the IL-6 response to the TSST over time. The SPSS GLM repeated measures procedure models dependent variables measured at multiple times using analysis of variance (ANOVA), and the predictor variables may be categorical factors (maltreatment group in our case) or continuous covariates (we included age, BMI, and others). For our models, the dependent variable (IL-6 concentration) was represented by 7 measurement times.

Subgroups in the population and covariates are conceived as “control” variables in this analysis. In contrast to the summary variable delta(IL-6), which captures the maximal change in IL-6 concentration during the period of observation (time 0 to 90 minutes), the repeated measures GLM analysis strategy permits comparisons within and between groups during of multiple phases of the response curve over time. The Huynh-Feldt correction was applied when sphericity assumptions were not met.

Results

Bivariate Pearson correlation coefficients revealed significant positive relationships between indices of IL-6 and age, BMI, and CTQ total. No significant correlations emerged for any of the IL-6 measures and sex, depression symptoms, quality of life score, state anxiety, trait anxiety, or perceived stress level. After controlling for age and BMI, we found that CTQ total scores were positively correlated with delta(IL-6) (r=0.33, p=.006) and with max IL-6 (0.37, p=0.002), but not with baseline (time 0) IL-6 (r=0.15, p=0.23).

Clinical and demographic characteristics for the CTL and MAL groups are shown in Table 1. Results of t-tests showed that compared with controls, the group reporting childhood maltreatment was significantly older (t=2.4, p=.03), had a higher mean BMI (t=2.4, p=.03), and higher trait anxiety scores (t=2.1, p=.04). There was a nonsignificant trend (p=.09) toward higher subthreshold depressive symptoms in the maltreated group. State anxiety, perceived stress, and quality of life scores did not differ significantly between groups. The proportion of women did not statistically differ across groups (56% versus 74%; χ^2 = .27, p=.14).

Results of the GLM analysis of delta(IL-6), controlling for age and BMI, showed a significant effect of group (F=8.5, p=.005), such that greater stress-induced increase in IL-6 concentration was associated with a history of maltreatment. The independent effect of maltreatment group remained significant when all other covariates (depression, state and trait anxiety, quality of life, and perceived stress scale scores) were also included the model (F=6.9, p=.01). None of the other variables in the model had a significant effect on delta(IL-6). When menstrual cycle was examined in a subsample of female subjects, maltreatment group retained its significant effect on delta(IL-6), and menstrual phase did not emerge as a significant independent effect. Similarly, the main finding was unchanged when estrogen use was examined as a covariate; estrogen use was not a significant predictor of delta(IL-6). Comparison of IL-6 concentrations immediately before exposure to the stressor (time 0) revealed no significant baseline difference between MAL and CTL groups, after controlling for BMI and age (p=.14).

With the repeated measures GLM model, we observed a significant between-groups effect on IL-6 response to TSST (F=4.6, p=.03), after controlling for effects of age and BMI. There was not a significant interaction effect of time X group, indicating that response curve generated by the MAL group was significantly elevated, but essentially parallel to that of the CTL group (Figure 1). When a post-hoc repeated measures model was constructed to include the additional covariates listed above, the independent effect of maltreatment group was reduced to trend level (F=3.3, p=.07), and a trend-level interaction effect of time X

group emerged (F=1.9, p=.09). None of the covariates produced a significant effect on lL-6 except BMI (between-subjects effect, F=26.8, p<.01) and depression score (multivariate effect, F=54, p=.02). Estrogen use and menstrual cycle phase did not emerge as significant effects in the repeated measures model.

Discussion

Previous studies found that subjects with MDD exhibit an exaggerated IL-6 response to acute psychosocial stress (Miller *et al*, 2005; Weinstein *et al*, 2010). However, the role of early life environment in the stress-related inflammatory response has not been established. Pace *et al* (2006) demonstrated that men with MDD reporting childhood maltreatment were found to have a greatly increased IL-6 response to the TSST. The present study sought to clarify the role of early life stress in mediating the IL-6 response, and to disentangle the effects of MDD and early-life maltreatment by assessing the acute inflammatory response in adults without depression. The results of this small pilot study indicate that adverse early environment, measured here by self-reported childhood abuse or neglect, is significantly linked to pro-inflammatory response to acute psychosocial stress in otherwise healthy adults. Subjects in our sample with childhood maltreatment showed greater overall peripheral release of IL-6 during a standard stress challenge, and significantly elevated IL-6 concentrations throughout the TSST observation period, as compared to the control group.

Significant group differences in age and BMI were a limitation of this study. Recent studies have demonstrated that exposure to early life stress increases adult obesity (Boynton-Jarrett *et al*, 2010; D'Argenio *et al*, 2009), while others have reported a relationship between BMI and cytokine response to stress (Benson *et al*, 2009; Brydon *et al*, 2008). The correlation between BMI and early life stress was also robust in our sample (r=.41, p<.01). Our finding of heightened IL-6 response in the maltreatment group emerged after statistically controlling for effects of BMI (and age). However, insufficient power and collinearity between the variables precluded our ability to elucidate a possible interaction or mediating effect of BMI and childhood maltreatment in the generation of plasma IL-6 responses. Future investigation into this question, with larger groups of subjects matched by age and BMI, will be an important next step for unraveling the relationships among adverse early life environment, obesity, and inflammatory response to acute stress. A larger sample size will also permit examination of different subtypes of childhood maltreatment as independent predictors of cytokine response to stress.

The clinical consequences of having an exaggerated cytokine response to stress are not clear, particularly in healthy adults without major medical disorders. IL-6 is produced by numerous tissues in the body, and identifying the original source of IL-6 measured in plasma is not a straightforward process. In the periphery, IL-6 is produced by leukocytes, skeletal myocytes (Keller *et al*, 2005), adipocytes (Fried *et al*, 1998), and splenocytes (Merlot *et al*, 2004). Animal models have demonstrated that exposure to acute stress increases the expression of pro-inflammatory cytokines both in the periphery (LeMay *et al*, 1990; Zhou *et al*, 1993) and within the central nervous system (Butterweck *et al*, 2003; Suzuki *et al*, 1997). While there is evidence that peripheral cytokines can be transported across the blood-brain barrier (Threlkeld *et al*, 2010), the majority of relevant human studies have assessed basal or

stimulated IL-6 production in the periphery, likely painting an incomplete picture of the dynamic interaction between the immune system and other physiological systems.

The mechanism by which cytokine response to acute stress might lead to development of mental and physical health disorders is unknown, but the findings of this study and the work of other research groups (Benson *et al*, 2009; Chen *et al*, 2006) provide some support for the notion that individuals with this phenotype may be predisposed to illness following repeated exposure to common psychosocial stressors. Elevated IL-6 has been implicated in the pathogenesis of coronary heart disease through a combination of autocrine, paracrine and endocrine mechanisms (Yudkin *et al*, 2000). A recent meta-analysis of studies measuring cytokine concentration in patients with major depression found IL-6 concentrations were significantly higher in depressed subjects compared with control subjects (Dowlati *et al*). The ability of proinflammatory cytokines to inhibit hippocampal neurogenesis was identified as one candidate mechanism for their detrimental effects on mood. Another mechanistic hypothesis, advanced to explain why children reared in unfavorable socioeconomic circumstances show increased susceptibility to chronic diseases of aging in adulthood, is that stress exposure in early life programs biological systems in a persistent and deleterious manner. Miller and colleagues performed genome-wide transcriptional profiling in healthy adults and found a history of socioeconomic stress during childhood was associated with up-regulation of genes bearing response elements for the CREB/ATF family of transcription factors that convey adrenergic signals to leukocytes (Miller *et al*, 2009). Additionally, they found subjects with high stress backgrounds had relative down-regulation of genes with response elements for the glucocorticoid receptor, increased output of cortisol in daily life, heightened expression of transcripts bearing response elements for NF-κB, and greater stimulated production of IL-6. Their results support the notion that exposure to socioeconomic adversity stress in early life leads to exaggerated adrenocortical and inflammatory responses via resistance to glucocorticoid signaling. While such a phenotype could be adaptive during acute threats to well-being, over time increasing allostatic load on the body might contribute to chronic disease processes. Cross-sectional measurements of HPA and immune function in adulthood may thus vary greatly as a function of relative age of an organism when stressed and/or the chronicity of exposure to a remote stressful environment. The relevance of timing and chronicity effects was illustrated by recent preclinical data demonstrating stress exposure in young rats resulted in the opposite direction changes in both central IL1-β and peripheral corticosterone concentrations than were observed when stress exposure was introduced in adulthood (Lu *et al*, 2010).

Consistent with this proposed mechanism, results from our past neuroendocrine investigations (Carpenter *et al*, 2007; Carpenter *et al*, 2009; Tyrka *et al*, 2008a; Tyrka *et al*, 2008b) as well as those reported by many other research groups (reviewed by Bauer *et al*, 2010; Gunnar *et al*, 2009; Heim *et al*, 2008) have associated early life stress with abnormal functioning of the hypothalamic-pituitary-adrenal (HPA) axis. We observed a pattern of relatively diminished cortisol response to the TSST among adults with histories childhood maltreatment (Carpenter *et al*, 2007), a subset of which comprise the sample for this current study of IL-6. However, we had not previously analyzed our cortisol data in relation to inflammatory cytokines or other peripheral markers of immune function. Investigation into

complex relationships between IL-6 and cortisol in this small pilot study was limited by statistical considerations. However, we performed a cursory exploration with Pearson correlation coefficients generated for the individual time point data (plasma cortisol and IL-6 concentrations from the same stress test) in these 69 subjects. Consistent with patterns reported by others (Kunz-Ebrecht *et al*, 2003), we found cortisol concentrations to be inversely related to plasma IL-6 concentrations. The strongest and most statistically significant (negative) correlations emerged at the beginning and at the end of the 90-minute protocol, and were generally persistent after the application of CTQ total score as a control variable i.e., in a partial correlation analyses controlling for early life stress. It is possible that dampened cortisol response to acute stress in subjects with early life stress is partially responsible for the enhanced IL-6 stress response observed in this group (Heim *et al*, 2000) but more definitive studies will be needed to properly elucidate a causal relationship or how they interact to mediate the link between early adverse environment and adult health outcomes.

Measuring concentrations of other potential mediators, such as norepinephrine, in future studies of early life stress and inflammatory response to acute psychosocial stress will also be fruitful for parsing the complex interactions among the neuroendocrine, immune, and psychological systems (Bierhaus *et al*, 2003). An extensive literature documents a prominent role for sympathetic nervous system activation in both inflammatory and immunodepressive processes (Catania *et al*, 2009; Di Comite *et al*, 2007; Szelenyi and Vizi, 2007), and norepinephrine may offer some measure of neuroprotective effect by reducing brain infiltration of peripheral immune cells driven by increases in chemokine and cell adhesion molecule expression (O'Sullivan *et al*, 2010).

In conclusion, the results of this pilot study contribute to a rapidly growing literature which illuminates the complex relationships between stress and neuroimmune regulation in the pathoetiology of disease. Cytokines such as IL-6 are an integral part of the innate inflammatory response to a physical stressor (*e.g.* infection, inflammation). The mechanisms by which psychosocial stress initiates cytokine response, as well as the clinical consequences of an exaggerated cytokine response to stress, remain to be determined.

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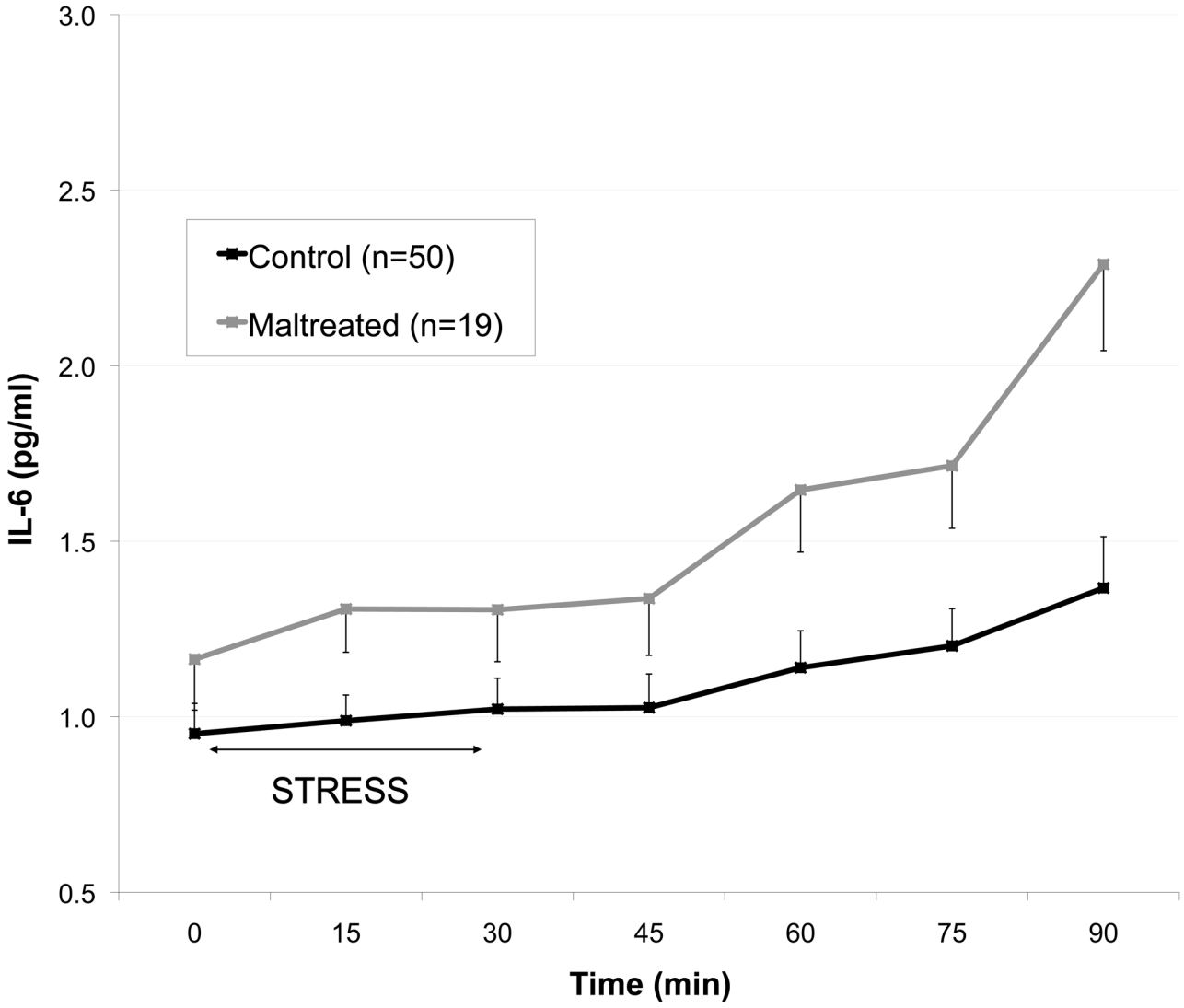

Fig. 1.

Interleukin-6 (IL-6) response to the Trier Social Stress Test in healthy adults without psychopathology, grouped according to presence or absence of childhood maltreatment. Graph depicts untransformed data, with means adjusted for age and BMI.

Table 1

Comparison of Clinical and Demographic Characteristics of Groups

	Controls CTL (n = 50)	Maltreated MAL (n = 19)	*p*
Age, Mean (SD) years	24.50 (8.83)	32.84 (13.89)	0.03
Range (years)	18–64	18–59	
Gender, n (%)			
Male	22 (44.0%)	5 (26.3%)	n.s.
Female	28 (56.0%)	14 (73.7%)	
Body Mass Index, Mean (SD)	24.61 (3.77)	28.11 (5.92)	0.03
Oral Contraceptive or Estrogen Use, N (%of women/group)	12 (42.8%)	5 (35.7%)	n.s.
Highest Level of Education, N (%)			
Partial High School	1 (2.0%)	1 (5.3%)	
High School Graduate	4 (8.0%)	2 (10.5%)	
Technical Degree	0 (0.0%)	1 (5.3%)	n.s.
Partial College	27 (54.0%)	9 (47.4%)	
College Graduate	13 (26.0%)	4 (21.1%)	
Professional Degree	5 (10.0%)	2 (10.5%)	
Perceived Stress Scale, Mean (SD)	17.76 (6.70)	20.37 (6.31)	n.s.
IDS-SR Total, Mean (SD)	8.86 (6.19)	11.84 (7.24)	0.09
STAI State Anxiety, Mean (SD)	30.00 (7.41)	31.11 (6.54)	n.s.
STAI Trait Anxiety, Mean (SD)	32.41 (8.51)	37.58 (8.93)	0.04
CTQ Total score, mean (SD)	5.98 (0.86)	10.47 (1.81)	<.01
CTQ Subscales (Categorical), N (%) Moderate-Severe			
Emotional Abuse	0 (0%)	11 (57.9%)	
Physical Abuse	0 (0%)	8 (42.1 %)	
Sexual Abuse	0 (0%)	4 (21.1%)	
Emotional Neglect	0 (0%)	9 (47.4%)	
Physical Neglect	0 (0%)	8 (42.1%)	

IDS-SR, Inventory of Depressive Symptomatology-Self Report; STAI, State-Trait Anxiety Questionnaire; CTQ, Childhood Trauma Questionnaire. In right column, “n.s.” denotes t-test or chi-square test comparing CTL and MAL groups was not significant at p<.05.