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# Childhood trauma and parental style: Relationship with markers of inflammation, oxidative stress, and aggression in healthy and personality disordered subjects

Jennifer R. Fanning [a], Royce Lee [a], David Gozal [b], Mary Coussons-Read [c], Emil F. Coccaro [a,*]

[a] Clinical Neuroscience Research Unit, Department of Psychiatry and Behavioral Neuroscience, Pritzker School of Medicine, University of Chicago, Chicago, IL, United States
[b] Department of Pediatrics, Pritzker School of Medicine, University of Chicago, Chicago, IL, United States
[c] Department of Psychology, The University of Colorado, Colorado Springs, CO, United States

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ABSTRACT

Recent studies suggest that early life trauma is associated with elevations in circulating markers of inflammation in human subjects. History of aggression as a behavior, or aggression as a personality trait, is also associated with elevations of these inflammatory markers. Since early life trauma is associated with the development and maintenance of aggression in later life we examined the relationship of early life adversity, plasma inflammation markers (IL-6 and CRP) and oxidative stress markers (8-OH-DG and 8-ISO), and aggression in adult subjects with ($n = 79$) and without ($n = 55$) personality disorder. We used a series of mediated and moderated path models to test whether the effects of early adversity on later aggression may be mediated through markers of inflammation. Childhood abuse and parental control were associated with basal IL-6 and CRP concentrations. Path modeling suggested that childhood abuse was associated with aggression indirectly through CRP while parental control influenced aggression indirectly through IL-6 and CRP. Furthermore, these effects were independent of the effect of current depression. The results suggest that disruption of inflammatory processes represent one pathway by which early adversity influences aggression.

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## 1. Introduction

The role of inflammatory responses in psychiatric disorder, depression in particular, has been the subject of increased interest recently. Specifically, a growing body of literature points to depression as a disorder characterized by hyperactivity of the immune response. Depressed individuals have been shown to have elevated concentrations of interleukin-6 (IL-6) and C-reactive protein (CRP) in blood serum and plasma (Dowlati et al., 2010; Howren, Lamkin, & Suls, 2009; Raison, Capuron, & Miller, 2006) and some studies have observed a correlation between inflammatory markers and depressive symptom severity (Miller, Stetler, Carney, Freedland, & Banks, 2002; Thomas et al., 2005).

Stress is a common precipitant of depression and a growing literature suggests that stress activates proinflammatory processes in the body and central nervous system (Deinzer et al., 2004; Goebel, Mills, Irwin, & Ziegler, 2000; O'Connor et al., 2003). Recent studies have linked early life trauma with increased inflammatory activity in response to stress and to elevations in circulating markers of inflammation in human subjects. Specifically, adult subjects with a history of childhood abuse have greater C-reactive protein (CRP) and interleukin-6 (IL-6) responses to laboratory stressors compared with those without such a history (Carpenter et al., 2010; Danese, Pariante, Caspi, Taylor, & Poulton, 2007a; Pace et al., 2006; Taylor, Lehman, Kiefe, & Seeman, 2006a). Other studies have found that history of childhood trauma is associated with greater concentrations of inflammatory markers including IL-6, CRP, and TNF-α in adults, including adults with chronic stress (Danese et al., 2009; Danese, Pariante, Caspi, Taylor, & Poulton, 2007b; Kiecolt-Glaser et al., 2011). The results of prospective studies of adversity and inflammation and a recent review of this literature suggest that early adversity may lead to longer-range (as opposed to short-range) baseline hyperinflammation (Danese et al., 2007; Slopen, Koenen, & Kubzansky, 2012; Slopen, Kubzansky, McLaughlin, & Koenen, 2013).

* Corresponding author at: Clinical Neuroscience Research Unit, Department of Psychiatry and Behavioral Neuroscience, The University of Chicago, 5841 South Maryland Avenue, Chicago, IL 606373333, United States. Fax: +1 773 834 7427.
*E-mail address:* ecoccaro@bsd.uchicago.edu (E.F. Coccaro).

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Stressful and adverse experiences in childhood, such as exposure to abuse, neglect, and harsh parenting style are associated with a greater propensity to aggression (Dodge, Bates, & Pettit, 1990; Fanning, Meyerhoff, Lee, & Coccaro, 2014; Lee, Meyerhoff, & Coccaro, 2014). In previous analyses using this sample we have found that elevations in circulating CRP (Coccaro, Lee, & Coussons-Read, 2014b; Coccaro, 2005), IL-6 (Coccaro, Lee, & Coussons-Read, 2014b), and oxidative stress markers (Coccaro, Lee, & Coussons-Read, 2014a) distinguished aggressive research volunteers from non-aggressive participants. Other groups have also reported a relationship between inflammatory markers and aggression (Marsland, Prather, Petersen, Cohen, & Manuck, 2008; Suarez, 2003, 2004). These associations remain significant even after controlling for a variety of potentially confounding factors associated with the elevation of inflammatory and/or oxidative stress markers. It is unclear, however, whether proinflammatory processes may explain part of the association between trauma and aggression.

In this report, we tested the hypothesis that adverse childhood experiences would increase the propensity toward aggression through effects on inflammatory and oxidative stress markers. Oxidative stress, which is associated with reduced neuronal plasticity and survival, is one of several mechanisms implicated in the pathophysiology of the inflammation-depression association (Hayley, Poulter, Merali, & Anisman, 2005), has been linked to chronic stress (Epel et al., 2004), and has been implicated in a diverse range of psychopathologies (Ng, Berk, Dean, & Bush, 2008). We studied these relationships in healthy individuals and in individuals with personality disorder, a group characterized by a high rate of mood disturbance (depression), aggression, and childhood trauma. We used a series of regression-based path mediation models to test the direct and indirect effects of childhood experiences on aggression. Based on the previous literature, we hypothesized that inflammatory markers (IL-6 and CRP) and oxidative stress markers would significantly mediate the relationship between adversity in childhood and aggression.

## 2. Methods

### 2.1. Subjects

One hundred thirty four physically healthy subjects participated in this study. All subjects were medically healthy and were systematically evaluated in regard to aggressive behavior, mood disturbance, and other behaviors as part of a larger program designed to study correlates of impulsive aggression in human subjects. Subjects were recruited through public service announcements, newspaper, and other media advertisements seeking out individuals who: (a) reported psychosocial difficulty related to personality disorder traits or, (b) had little evidence of psychopathology. All subjects gave informed consent in accordance with procedures approved by the local Institutional Review Board. Subjects who showed evidence of recent drug use (based on urine toxicology) or current alcohol intoxication (based on expired breath analysis) were excluded from participation. In addition, subjects currently taking psychotropic medication were excluded from the current analysis.

### 2.2. Diagnostic assessment

Personality disorder and syndromal disorder diagnoses were made according to DSM-5 criteria (American Psychiatric Association, 2013). Diagnoses were established using information from: (a) the structured clinical interview for DSM diagnoses [SCID-I; First, Spitzer, Gibbon, & Williams, 1997] for syndromal disorders and (b) the structured interview for the diagnosis of DSM personality disorder [SIDP; Pfohl, Blum, & Zimmerman, 1997] for personality disorders; (c) clinical interview by a research psychiatrist; and (d) review of all other available clinical data. The research diagnostic interviews were conducted by individuals with a masters or doctoral degree in clinical psychology. All diagnostic raters completed a rigorous training program that included attending lectures on DSM diagnoses and rating systems, reviewing videos of expert raters conducting SCID/SIDP interviews, and completing practice interviews and ratings until the rater was deemed reliable with the trainer. This process resulted in good to excellent inter-rater reliabilities (mean kappa of 0.84 + 0.05; range: 0.79–0.93) across anxiety, mood, substance use, impulse control, and personality disorders. Final diagnoses were assigned by team best-estimate consensus procedures (Kosten & Rounsaville, 1992; Leckman, Sholomskas, Thompson, Belanger, & Weissman, 1982) involving research psychiatrists and clinical psychologists as previously described (Coccaro, Nayyer, & McCloskey, 2012). This methodology has previously been shown to enhance the accuracy of diagnosis over direct interview alone (Klein, Ouimette, Kelly, Ferro, & Riso, 1994). Subjects with a current history of a substance use disorder or with a life history of bipolar disorder, schizophrenia (or other psychotic disorder), or mental retardation were excluded from study.

After diagnostic assignment, 55 subjects had no evidence of any psychiatric diagnosis (healthy controls: HC) and 79 subjects met criteria for a personality disorder (PD). Most PD subjects also met diagnostic criteria for a current or a lifetime syndromal disorder (see Table 1). Of the PD subjects, more than half (56%) reported a history of formal psychiatric evaluation and/or treatment or a history of behavioral disturbance during which the subject or others thought they should have sought mental health services but did not.

### 2.3. Measures of childhood trauma and neglect

History of childhood trauma and neglect was assessed using the 28-item childhood trauma questionnaire [CTQ, Bernstein & Fink, 1998]. The CTQ retrospectively assesses the subject's perception of abuse (physical, emotional, and sexual) and neglect (physical and emotional) in childhood. Items begin with the phrase, "When I was growing up," and go on to describe a specific form of

**Table 1**
Syndromal and personality disorder diagnoses in the sample.

| | Personality disordered subjects ($N = 79$) |
|---|---|
| Current syndromal disorders: | |
| Any depressive disorder | 19 (24.1%) |
| Any anxiety disorder | 18 (22.8%) |
| Any substance use disorder | 0 (0.0%) |
| Intermittent explosive disorder (IED) | 51 (64.4%) |
| Stress and trauma disorders | 16 (20.3%) |
| Obsessive compulsive disorders | 2 (2.5%) |
| Eating disorders | 7 (8.9%) |
| Non-IED impulse control disorders | 1 (1.3%) |
| Lifetime syndromal disorders: | |
| Any depressive disorder | 50 (63.3%) |
| Any anxiety disorder | 22 (27.8%) |
| Any substance use disorder | 26 (32.9%) |
| Intermittent explosive disorder (IED) | 51 (64.4%) |
| Stress and trauma disorders | 22 (27.8%) |
| Obsessive compulsive disorders | 4 (5.1%) |
| Eating disorders | 11 (13.9%) |
| Non-IED impulse control disorders | 5 (6.3%) |
| Any personality disorder: | |
| Cluster A | 14 (17.7%) |
| Cluster B | 41 (51.9%) |
| Cluster C | 29 (36.7%) |
| Personality disorder-NOS | 23 (29.1%) |

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