Original Investigation

Elevated Plasma Inflammatory Markers in Individuals With Intermittent Explosive Disorder and Correlation With Aggression in Humans

Emil F. Coccaro, MD; Royce Lee, MD; Mary Coussons-Read, PhD

IMPORTANCE Neurochemical studies in human aggression point to a modulatory role for a variety of central neurotransmitters. Some of these neurotransmitters play an inhibitory role, while others play a facilitatory role modulating aggression. Preclinical studies suggest a facilitatory role for inflammatory markers in aggression. Despite this, to our knowledge, no studies of aggression and inflammatory markers have been reported in psychiatric patients or in individuals with recurrent, problematic, impulsive aggressive behavior.

OBJECTIVE To test the hypothesis that plasma inflammatory markers will correlate directly with aggression and will be elevated in individuals with recurrent, problematic, impulsive aggressive behavior.

DESIGN, SETTING, AND PARTICIPANTS Case-control study in a clinical research program in impulsive aggressive behavior at an academic medical center. Participants were physically healthy individuals with intermittent explosive disorder (n = 69), nonaggressive individuals with Axis I and/or II disorders (n = 61), and nonaggressive individuals without history of an Axis I or II disorder (n = 67).

MAIN OUTCOMES AND MEASURES Plasma levels of C-reactive protein and interleukin 6 were examined in the context of measures of aggression and impulsivity and as a function of intermittent explosive disorder.

RESULTS Both plasma C-reactive protein and interleukin 6 levels were significantly higher in participants with intermittent explosive disorder compared with psychiatric or normal controls. In addition, both inflammatory markers were directly correlated with a composite measure of aggression and, more specifically, with measures reflecting history of actual aggressive behavior in all participants.

CONCLUSIONS AND RELEVANCE These data suggest a direct relationship between plasma inflammatory processes and aggression in humans. This finding adds to the complex picture of the central neuromodulatory role of aggression in humans.

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Author Affiliations: Clinical Neuroscience Research Unit, Department of Psychiatry and Behavioral Neuroscience, Pritzker School of Medicine, University of Chicago, Chicago, Illinois (Coccaro, Lee); Department of Psychology, University of Colorado Colorado Springs, Colorado Springs (Coussons-Read).

Corresponding Author: Emil F. Coccaro, MD, Clinical Neuroscience Research Unit, Department of Psychiatry and Behavioral Neuroscience, University of Chicago, 5841 South Maryland Ave, Chicago, IL 60637 (ecoccaro@yoda.bsd.uchicago.edu).

A substantial body of research demonstrates bidirectional relationships between the brain and behavior with immune function[1,2] and vice versa.[3] For example, depressed patients consistently display evidence of elevated inflammatory cytokine levels[4,5] and the therapeutic administration of inflammatory cytokines is associated with increased depressive symptoms.[6,7]

In addition, animal[8-11] and human[12-19] studies suggest that behavioral traits related to hostile, angry, and aggressive disposition are associated with elevations in inflammatory markers. Defensive rage in cats is associated with elevated levels of interleukin 1β (IL-1β) and IL-6 and blocking IL-1β activity reduces these effects[8-10] and mice deficient in inflammatory cytokine receptors fail to exhibit aggressive and defensive behavior even when threatened.[11] Studies in humans, also, suggest a direct relationship between C-reactive protein (CRP) and hostile,[12,13] angry,[14] and aggressive dispositions[15,16]; elevations of IL-6 are associated with the same variables.[16-18,20]

While work in healthy humans suggests a direct relationship between hostility, anger, and aggressive disposition and inflammatory markers, to our knowledge, no study has been performed in psychiatric patients with prominent histories of impulsive aggressive behavior. In this study, we hypothesized that plasma levels of inflammatory markers will be elevated in individuals with a current diagnosis of intermittent explosive disorder (IED), a disorder of impulsive aggressive behavior,[21,22] and that these markers will correlate directly with measures of aggression (and/or impulsivity) in healthy participants and psychiatric patients. We assessed levels of plasma CRP, because it is an acute-phase reactant released in the presence of inflammation,[23] and plasma IL-6, because it is an inflammatory cytokine[24]; both markers have been shown to be elevated as a function of hostility.[16-18,20]

Methods

Participants

One-hundred ninety-seven physically healthy participants were recruited from clinical settings and through newspaper advertisements, seeking out individuals who reported psychosocial difficulty related to 1 or more Axis I or II conditions or who had little evidence of psychopathology. All participants gave written informed consent as approved by the University of Chicago institutional review board. Participants with bipolar disorder, schizophrenia, or mental retardation were excluded. Medical health was documented by comprehensive medical history and examination, which included a screen for drugs of abuse (all participants tested negative).

Diagnostic Assessment

Axis I and Axis II diagnoses were made by *DSM-IV* criteria[25]; IED diagnoses were made by research criteria.[22] Research assessments were performed by individuals with master's/doctoral degrees in clinical psychology with interrater (κ) reliability ranging from 0.79 to 93 (mean [SD], 84 [0.05]) across mood, anxiety, substance use, impulse control, and personality disorders. Final diagnoses were assigned by previously described best-estimate consensus procedures,[26-28] using information from (1) Structured Clinical Interview for *DSM-IV* Axis I Disorders[29]; (2) Structured Interview for *DSM-IV* Personality: SIDP-IV[30]; (3) clinical interview by a research psychiatrist; and (4) review of all available clinical data.

Sixty-nine participants met criteria for current IED, 61 for other current/lifetime Axis I and/or Axis II disorder (psychiatric controls [PC]), and 67 without evidence of any *DSM-IV* disorder (healthy controls [HC]). Among participants with IED and PC, 112 had current history of an Axis I disorder, 125 had lifetime history of an Axis I disorder, and 105 had an Axis II personality disorder. About one-third (35%) of participants with IED and PC had history of psychiatric treatment. Specific diagnoses for participants with IED and PC are listed in the eAppendix in the Supplement.

Psychometric Measures: Relevant Aggression, Impulsivity, and Related Behavioral Dimensions

Aggression was assessed with the Aggression Scale from Life History of Aggression[31] (LHA) and the Buss-Perry Aggression Questionnaire[32] (BPAQ). Impulsivity was assessed with the Life History of Impulsive Behavior[33] (LHIB) and Barratt Impulsiveness Scale[34] (BIS-11). The LHA and LHIB assess the number of times a person has engaged in aggressive, or impulsive, behavior in his or her life and the BPAQ and BIS-11 assess a person's disposition to act aggressively, or impulsively, as a personality trait. Life history of suicidal behavior was assessed during the Structured Clinical Interview. Other assessments included the Beck Depression Inventory[35] for state depression, Life Experiences Survey[36] for stressful life events over the past 6 months, and Eysenck Personality Questionnaire[37] for control dimensions of general personality. The Global Assessment of Function[25] Scale served as the variable for psychosocial functioning. Racial data, collected by diagnostic assessors, reflected self-identified racial characteristics of participants.

Assessment of Plasma CRP and IL-6 Levels

Participants were free of all medications for at least 4 weeks. Whole blood, anticoagulated with EDTA, was obtained between 9 and 11 AM through venipuncture of a forearm vein. Plasma was processed after centrifugation and stored at −80°C until assay. The CRP and IL-6 levels were detected by commercially available (R&D Systems) enzyme-linked immunosorbent assay kits and assayed according to the manufacturer's instructions. Sensitivity and coefficient of variation were 0.035 mg/L and less than 6% for CRP and 0.70 pg/mL and less than 6% for IL-6, respectively. Samples were run together in the same assay and levels reported represent the mean of the duplicates.

Statistical Analysis and Data Reduction

Comparisons between groups were performed by *t* test, analyses of variance and covariance, and χ^2 tests. Correlational analyses were conducted by parametric and nonparametric methods as necessary. An α of .05 denoted statistical significance. Plasma CRP levels were normally distributed; IL-6 levels were not and were log-transformed for analysis. Given the known

relationship between body mass index, age, state depression (Beck Depression Inventory), psychological stress (Life Experiences Survey), and inflammation,[3-5] data were first analyzed without these variables and then with these variables as covariates. Selected demographic and lifestyle variables were also used as covariates. Finally, composite variables for "aggression" and "impulsivity" were created in a data-reduction step by taking the average of each participant's *z* scores for the primary behavioral measures (LHA and BPAQ; LHIB and BIS-11).

Results

Demographic/Lifestyle/Behavioral Characteristics of Participants

Participants did not differ in distribution of sex or race (**Table 1**). The groups did differ in age and Hollingshead socioeconomic status score. Differences in age were due to a younger age among HC vs participants with IED and PC; differences in socioeconomic status were due to a greater proportion of participants with higher socioeconomic status (eg, categories I and II) among HC (76%) and PC (77%) vs participants with IED (51%). Neither mean body mass index nor rate of obesity (ie, body mass index >30 [calculated as weight in kilograms divided by height in meters squared]) differed across groups. The rate, or degree, of current cigarette smoking also did not vary across groups. While the groups did not differ in rate of current social drinking, participants with IED reported a higher mean number of drinks per day and a higher rate of consuming more than 2 drinks per day (HC = PC<participants with IED). As expected, the groups differed in LHA/BPAQ aggression, LHIB/BIS-11 impulsivity, Beck Depression Inventory, and Life Experiences Survey scores (participants with IED>PC>HC) and in Global Assessment of Function scores (participants with IED<PC<HC).

Inflammatory Markers in Participants With IED, HC, and PC

Multivariate analysis of variance revealed a significant difference among the groups with both inflammatory markers (Wilks $\lambda = 0.43$; $F_{6,374} = 32.66$; $P < .001$; CRP: $F_{2,189} = 21.67$; $P < .001$; log IL-6: $F_{2,189} = 70.85$; $P < .001$). In both cases, participants with IED displayed higher inflammatory marker levels than either HC or PC (**Figure 1**). Addition of the a priori covariates of body mass index, age, state depression, and recent psychological stress did not change this result (**Table 2**).

Inflammatory Markers as a Function of Axis I or Axis II Disorders

Analysis of variance of plasma CRP and log IL-6 levels revealed significant IED vs PC differences for participants with IED in the context of other current Axis I disorders (CRP: $F_{1,124} = 8.54$; $P = .004$; log IL-6: $F_{1,122} = 190.09$; $P < .001$), participants with IED in the context of lifetime Axis I disorders (CRP: $F_{1,122} = 6.25$; $P = .01$; log IL-6: $F_{1,120} = 147.07$; $P < .001$), and participants with IED in the context of Axis II personality disorder cluster (CRP: $F_{1,126} = 6.90$; $P = .01$; log IL-6: $F_{1,124} = 157.69$; $P < .001$). Analysis of variance of participants with IED and PC with current Axis I disorders (ie, removing participants with only life history of Axis I disorder) did not change the group results (mean [SD], CRP: participants with IED = 2.36 [0.70] vs PC = 1.48 [1.35] mg/L; $F_{1,109} = 20.36$; $P < .001$; log IL-6: participants with IED = 0.23 [0.29] vs PC = −0.90 [0.55] mg/L; $F_{1,109} = 225.97$; $P < .001$). Adding history of psychiatric treatment to the analysis did not change these group results.

Inflammatory Markers as a Function of Demographic and Lifestyle Variables

Neither levels of CRP nor log IL-6 differed as a function of sex (mean [SD], CRP: male = 1.65 [1.07] vs female = 1.83 [1.18] mg/L; $t_{195} = 1.11$; $P = .27$; log IL-6: male = −0.21 [0.66] vs female = −0.31 [0.076] pg/mL; $t_{193} = 0.95$; $P = .34$). Among all demographic variables, overall, only age covaried at a trend level of significance with CRP (multiple regression: $F_{4,192} = 2.73$; $P = .06$; partial $r = 0.18$; $P < .02$), and only race covaried significantly with log IL-6 levels (multiple regression: $F_{4,190} = 5.79$; $P < .001$; partial $r = 0.30$; $P < .001$). The influence of age on the inflammatory markers was already accounted for as an a priori covariate in the earlier analyses (Table 2); adding race as a covariate did not affect the group results for log IL-6 levels ($F_{2,186} = 12.93$; $P < .001$). While the groups did not differ in the proportion of obese participants, the presence of obesity was associated with elevated levels of CRP (mean [SD], 2.33 [1.15] vs 1.59 [1.08] mg/L; $t_{195} = 3.85$; $P < .001$) and log IL-6 (mean [SD], 0.01 [0.64] vs −0.34 [0.72] pg/mL; $t_{193} = 2.87$; $P = .005$). Removal of obese participants did not change the group results (CRP: $F_{2,153} = 24.46$; $P < .001$; log IL-6: $F_{2,151} = 57.81$; $P < .001$). While the groups also differed in mean drinks per day (and in the rate of participants consuming >2 drinks per day), this variable had no effect on levels of CRP ($F_{1,193} = 0.83$; $P = .37$) or log IL-6 ($F_{1,191} = 0.69$; $P = .41$) when added to the statistical model; removal of participants reporting more than 2 drinks per day did not change the group results (CRP: $F_{2,181} = 21.14$; $P < .001$; log IL-6: $F_{2,179} = 61.74$; $P < .001$). The smoking variable, current packs per day, also had no effect on levels of CRP ($F_{1,192} = 0.80$; $P = .37$) or log IL-6 ($F_{1,190} = 0.40$; $P = .85$) when added to the statistical model; removal of current smokers did not change the group results (CRP: $F_{2,151} = 18.95$; $P < .001$; log IL-6: $F_{2,150} = 55.29$; $P < .001$).

Inflammatory Markers and Aggression and Impulsivity

Across all participants, the core features of IED, aggression and impulsivity, displayed a direct relationship with levels of both CRP and log IL-6: composite aggression: CRP: $r = 0.39$; n = 176; $P < .001$; log IL-6: $r = 0.37$; n = 176; $P < .001$; composite impulsivity: CRP: $r = 0.31$; n = 177; $P < .001$; log IL-6: $r = 0.26$; n = 175; $P = .001$. Plasma CRP and log IL-6 were also significantly correlated in these participants ($r = 0.47$; n = 175; $P < .001$). While composite aggression and composite impulsivity scores were highly correlated in these participants ($r = 0.66$; n = 166; $P < .001$), multiple regression analysis ($F_{2,163} = 16.25$; $P < .001$; $R = 0.41$; $R^2 = 0.16$) revealed a unique contribution for composite aggression (partial $r = 0.27$; $t_{163} = 3.57$; $P < .001$), but not for composite impulsivity (partial $r = 0.08$; $t_{163} = 0.97$; $P = .33$) for CRP levels. The same was true for log IL-6 levels ($F_{2,161} = 13.45$; $P < .001$; $R = 0.38$; $R^2 = 0.13$; composite aggres-

Table 1. Demographic, Covariate, Lifestyle, and Behavioral Data Among the Groups

	No. of Participants			
	HC (n = 67)	PC (n = 61)	IED (n = 69)	Group Differences
Demographic variables				
Age, y, mean (SD)	32.0 (9.1)	35.8 (7.4)	35.1 (7.9)	HC<PC = IED[a]
Sex				HC = PC = IED[b]
M	32	28	37	
F	35	36	32	
Race				HC = PC = IED[b]
White	43	49	43	
Nonwhite	24	13	26	
SES category				HC = PC[c] HC ≠ IED[b]
I	9	18	7	
II	41	29	28	
III	6	9	19	
IV	4	2	12	
V	7	3	3	
A priori covariates, mean (SD)				
BMI	27.2 (3.9)	26.2 (5.6)	27.8 (5.2)	HC = PC = IED[a]
State depression score (BDI-II)	2.2 (8.5)	7.1 (7.9)	16.2 (11.8)	HC<PC<IED[a]
Stressful life experiences score (LES: past 6 mo)	5.3 (5.1)	6.5 (5.8)	13.7 (10.6)	HC = PC<IED[d]
Lifestyle variables				
Obesity (BMI >30.0)				HC = PC = IED[c]
Yes	15	12	14	
No	52	49	55	
Current alcohol consumption				HC = PC = IED[c]
Yes	42	41	42	
No	24	21	27	
Participants with >2 alcoholic drinks/d				HC = PC<IED[b]
Yes	2	1	10	
No	65	60	59	
Alcoholic drinks/d (among those drinking currently), mean (SD)	0.8 (0.6)	0.5 (0.6)	1.3 (3.1)	HC = PC<IED[a]
Current smoking				HC = PC = IED[c]
Yes	9	15	19	
No	57	47	50	
Packs/d (among those smoking currently), mean (SD)	0.2 (0.2)	0.5 (0.4)	0.4 (0.3)	HC = PC = IED[e]
Behavioral variable scores, mean (SD)				
LHA aggression	4.4 (3.0)	8.9 (5.6)	20.1 (3.2)	HC<PC<IED[a]
BPAQ aggression	41.5 (14.9)	47.7 (14.9)	74.3 (17.9)	HC = PC<IED[a]
LHIB impulsivity	21.9 (15.7)	45.5 (16.0)	56.0 (17.7)	HC<PC<IED[a]
BIS-11 impulsivity	54.0 (8.5)	63.2 (10.0)	69.4 (11.6)	HC<PC<IED[a]
Psychosocial function (GAF)	83.6 (4.5)	65.7 (10.2)	53.7 (8.0)	HC>PC>ED[a]

Abbreviations: ANOVA, analysis of variance; BDI-II, Beck Depression Inventory[35]; BIS-11, Barratt Impulsiveness Scale[34]; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BPAQ, Buss-Perry Aggression Questionnaire[32]; GAF, Global Assessment of Function[25]; HC, healthy controls; IED, intermittent explosive disorder; LES, Life Experiences Survey[36]; LHA, Life History of Aggression[31]; LHIB, Life History of Impulsive Behavior[33]; PC, psychiatric controls; SES, socioeconomic status.

[a] Significant ($P < .05$) after ANOVA (post hoc $P < .05$).

[b] Significant ($P < .05$) after χ^2 test (post hoc by serial χ^2).

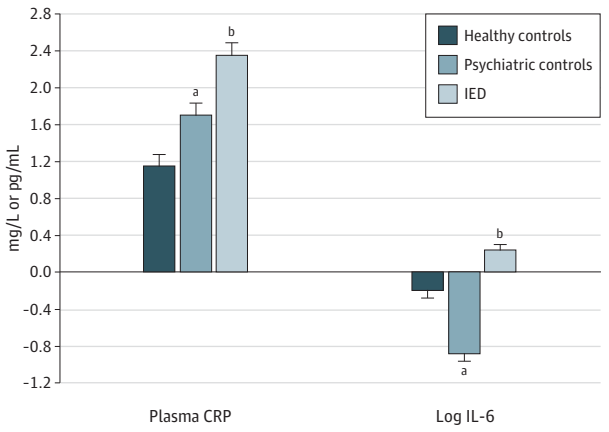
[c] Not significant after χ^2 test.

[d] Significant ($P < .05$) after ANOVA of log-transformed values (post hoc $P < .05$).

[e] Not significant after ANOVA.

sion: partial $r = 0.31$; $t_{161} = 4.14$; $P < .001$; composite impulsivity: partial $r = -0.03$; $t_{161} = 0.41$; $P = .69$). Addition of the a priori covariates (body mass index, age, Beck Depression Inventory score, and Life Experiences Survey score), individually and together, continued to reveal significance for correlations between composite aggression and CRP and log IL-6 (**Table 3**). Examination of the demographic and lifestyle variables did not change the results.

Figure 1. Plasma C-Reactive Protein (CRP) and Log Interleukin 6 (IL-6) Levels as a Function of Participant Status



Plasma CRP levels are measured in milligrams per liter and log IL-6 levels, in picograms per milliliter. IED indicates intermittent explosive disorder.
[a] $P<.05$ different from healthy controls.
[b] $P<.05$ different from healthy and psychiatric controls.

Table 2. Inflammatory Markers in Participants With IED vs HC vs PC

	CRP	Log IL-6
Raw data	$F_{2,194} = 23.92$; $P<.001$; HC<PC<IED[a]	$F_{2,192} = 67.56$; $P<.001$; PC<HC<IED[a]
With a priori covariates		
BMI	$F_{2,193} = 22.50$; $P<.001$; HC<PC<IED[b]	$F_{2,191} = 66.05$; $P<.001$; PC<HC<IED[b]
Age	$F_{2,193} = 22.01$; $P<.001$; HC<PC<IED[b]	$F_{2,191} = 69.18$; $P<.001$; PC<HC<IED[b]
State depression (BDI-II)	$F_{2,184} = 9.90$; $P<.001$; HC<PC<IED[b]	$F_{2,182} = 55.13$; $P<.001$; PC<HC<IED[b]
Life stress (LES)	$F_{2,193} = 25.30$; $P<.001$; HC<PC<IED[b]	$F_{2,191} = 66.99$; $P<.001$; PC<HC<IED[b]
All a priori correlates (BMI, age, BDI-II, LES)	$F_{2,181} = 11.47$; $P<.001$; HC<IED[b]; PC<IED[c]	$F_{2,179} = 52.68$; $P<.001$; PC<HC<IED[b]

Abbreviations: ANCOVA, analysis of covariance; BDI-II, Beck Depression Inventory[35]; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CRP, C-reactive protein; HC, healthy controls; IED, intermittent explosive disorder; IL-6, interleukin 6; LES, Life Experiences Survey[36]; PC, psychiatric controls.
[a] After significant analysis of variance (post hoc $P < .05$).
[b] After significant ANCOVA (post hoc $P < .05$).
[c] After significant ANCOVA (post hoc $P < .10$).

History of Aggressive Behavior vs Personality Trait of Aggression

Within the composite aggression variable, multiple regression ($F_{2,175} = 19.54$; $P < .001$; $R = 0.43$; $R^2 = 0.17$) revealed a unique contribution of LHA aggression (partial $r = 0.32$; $t_{175} = 4.52$; $P < .001$), but not of BPAQ aggression (partial $r = 0.00$; $t_{175} = 0.06$; $P = .95$), for plasma CRP. The same was true for log IL-6 ($F_{2,173} = 14.49$; $P < .001$; $R = 0.38$; $R^2 = 0.13$; LHA: partial $r = 0.22$; $t_{173} = 3.02$; $P = .003$; BPAQ: partial $r = 0.09$; $t_{173} = 1.18$; $P = .24$). Moreover, addition of LHA aggression scores to the analysis of covariance model ($F_{6,354} = 19.78$; $P < .001$) reduced differences between participants with IED vs PC vs HC to a nonstatistically significant trend for CRP ($F_{2,179} = 2.40$; $P = .09$) and reduced the IED vs HC difference by 49%. While group differences remained significant for log IL-6 ($F_{2,179} = 45.25$; $P < .001$), the IED vs HC difference for log IL-6 was reduced by 47%. The scatterplots for the correlation between LHA aggression and CRP and log IL-6 levels are displayed in **Figure 2**.

LHA Aggression and Other Personality Variables

Aggression by LHA correlated significantly with both inflammatory makers alone and when examined together with Eysenck personality variables in multiple regression analyses (CRP: partial $r = 0.34$; $t_{173} = 4.79$; $P < .001$; log IL-6: partial $r = 0.30$; $t_{171} = 4.06$; $P < .001$). Coefficients for partial correlations between Eysenck personality variables, with each plasma inflammatory marker, were all nonsignificant.

History of Suicidal Behavior

Among participants with IED and PC, life history of suicide attempt was associated with a trend for higher CRP levels ($F_{1,128} = 2.99$; $P = .09$) and a significant difference for higher log IL-6 levels ($F_{1,126} = 8.26$; $P = .005$). Participants with life history of suicide attempt also had higher LHA aggression scores, (mean [SD], suicide attempt: 18.6 [7.3] vs no suicide attempt: 13.9 [7.1]; $t_{120} = 2.51$; $P = .01$) and adding LHA aggression scores to the analysis of covariance model eliminated these differences for both CRP ($F_{1,118} = 0.02$; $P = .89$) and log IL-6 ($F_{1,116} = 0.06$; $P = .80$).

Discussion

To our knowledge, this is the first study to examine plasma inflammatory markers in a psychiatric sample that includes well-characterized participants with current history of recurrent, problematic, impulsive aggression, diagnosed with IED, and to examine behavioral, nonpersonality-based measures of aggression and impulsivity. In this sample, plasma markers of the inflammatory process displayed a direct relationship with aggression and were elevated, specifically, in participants with IED. Accordingly, this suggests that objective signs of systemic inflammation[23,24] are directly associated with aggression and are present in individuals with IED compared with both HC and PC. While one action of IL-6 is to stimulate production of CRP from the liver,[23] and the 2 markers were correlated in this study, the observation that both independently correlated with aggression suggests that both have unique relationships with aggression. Collateral support for this possibility comes from a population-based study[38] reporting significant elevations for participants with IED in the risk of conditions with inflammatory components (eg, coronary artery disease, cerebrovascular disease, arthritis, and peptic ulcer). Finally, the relationship with history of suicidal behavior, in this particular sample, may be fully mediated by the relationship between aggression and inflammatory markers.

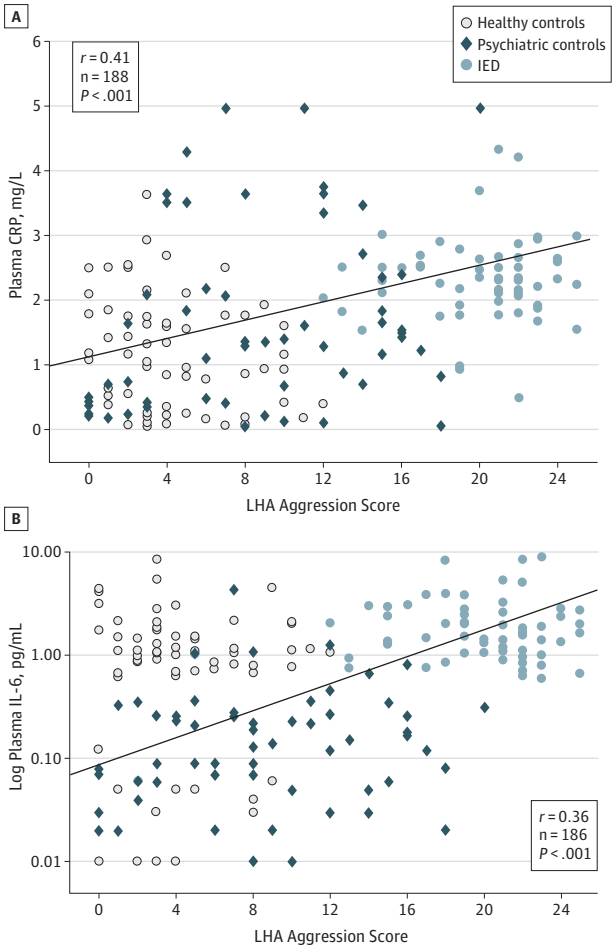
These results are not likely due to other relevant factors. Participants were physically healthy, free of systemic illness or physical injury, free of any medication for at least 4 weeks, and not abusing drugs of any kind. In addition, these results

Table 3. Zero Order and Partial Correlations, With Covariates, for Composite Aggression and Plasma CRP and Log IL-6

	CRP	Log IL-6
Zero-order correlations, composite aggression (raw data)	r_{176} = .39; P<.001	r_{174} = .37; P<.001
With BMI as a covariate	$r_{(partial)175}$ = .37; P<.001	$r_{(partial)173}$ = .35; P<.001
With age as a covariate	$r_{(partial)175}$ = .39; P<.001	$r_{(partial)173}$ = .36; P<.001
With state depression as a covariate (BDI-II)	$r_{(partial)173}$ = .27; P<.001	$r_{(partial)171}$ = .27; P<.001
With life stress as a covariate (LES)	$r_{(partial)175}$ = .40; P<.001	$r_{(partial)173}$ = .37; P<.001
With all covariates (BMI, age, BDI-II, LES)	$r_{(partial)170}$ = .26; P<.001	$r_{(partial)168}$ = .24; P<.001

Abbreviations: BDI-II, Beck Depression Inventory[35]; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CRP, C-reactive protein; IL-6, interleukin 6; LES, Life Experiences Survey.[36]

Figure 2. Life History of Aggression (LHA) Aggression Score With Plasma C-Reactive Protein (CRP) and Log Interleukin 6 (IL-6) Levels in All Participants



A, Plasma CPR levels. B, Plasma log IL-6 levels. IED indicates intermittent explosive disorder.

cannot be accounted for by sex because neither marker differed by sex or by differences in rates of current Axis I conditions. Removal of participants with IED and PC with only a lifetime Axis I condition did not alter these results. More importantly, these findings were not meaningfully changed when adjusted for differences in body mass index, state depression, age, or history of stressful life events This is noteworthy because each of these factors has been associated with elevation of a number of inflammatory markers.[3-5,39] These results were also not due to any influence of demographic or lifestyle factors on plasma CRP or log IL-6 levels. Results were unchanged when demographic variables were added to the statistical models; lifestyle variables were similar across groups and had no relationship with either plasma CRP or log IL-6 levels. These results were also not due to the presence of other Axis I or II conditions, other than IED, which is the categorical expression of the construct of impulsive aggression. Finally, measures of general personality dimensions did not correlate with these inflammatory markers, indicating that the relationship is with impulsive aggression, more specifically, than with general personality dysfunction.

It is possible that the elevation of inflammatory markers in participants with IED is the result of the "stress" of frequent aggressive interactions. In the present study, participants were studied at rest and no participant reported any meaningful stressor on the day of the sample collection or reported any recent physical injury. In addition, while our measure of stressful life events may not have captured potential stresses close in time to collection of the blood sample, this measure did show clear elevation of stressful life events in the participants with IED vs PC or HC, and controlling for this variable did not change the statistical significance of the findings.

These data are consistent with previous human studies. Self-assessed anger and aggressive disposition are increased in patients treated with cytokine immunotherapy.[6,7] Further, plasma CRP and IL-6 levels correlate directly with related measures of hostility,[12-14,17,18,20] anger,[14] and aggressive dispositon[15,16] in healthy adults. Greater levels of anger and/or hostility are also associated with greater production of inflammatory cytokines from blood monocytes after stimulation by bacterial lipopolysaccharide.[40] Finally, angry marital interactions have also been associated with increases in inflammatory cytokines.[19]

The inflammatory markers in this study appear to be associated specifically with history of actual aggressive behavior (LHA) than with the presence of aggressive tendency (BPAQ) or impulsivity as a behavior (LHIB) or as a personality trait (BIS-11). Despite the univariate correlation between BPAQ and LHIB/BIS measures and inflammatory markers, the observed relationship with both is through its shared variance with history of actual aggressive behavior (LHA). This observation does not contradict reports of similar relationships between inflammatory markers and self-assessed measures of anger and/or hostility.[12-14,17,18,20] However, when history of actual aggressive behavior is included, other related variables may add little beyond what is associated with history of actual aggressive behavior. This observation is consistent with the findings of a recent study in which aggressive disposition (ie, BPAQ), but not cognitive (ie, "hostility") or affective (ie, "anger") compo-

nents of antagonistic characteristics, were associated with elevations of plasma CRP and IL-6.[16]

While inflammatory cytokines exist in the brain, and act as neuromodulators, the markers in this study are largely produced in the periphery. However, circulating cytokines can access the brain through a number of pathways including passage through leaky regions in the blood-brain barrier, active transport through saturable transporters, activation of cells lining the cerebral vasculature that produce cytokines, and binding to receptors on peripheral afferent nerve fibers that can relay cytokine signals to relevant brain regions such as the hypothalamus and other brain structures.[41,42] Further, preclinical study has documented that inflammatory cytokines (eg, IL-1β and IL-2) administered into the medial hypothalamus or periaqueductal gray[10,43-46] increase defensive-rage aggression in cats. Accordingly, it is possible that elevations of peripheral inflammatory proteins can affect aggressive behavior through direct effects on brain regions important in the modulation of these behaviors.

The strengths of this study include a well-characterized sample, multiple validated measures of aggression and impulsivity, and a standardized approach to minimize the effect of extraneous factors on inflammatory marker levels. Limitations include the cross-sectional nature of the study and that correlational analysis cannot establish causality. While many participants had no prior psychiatric treatment, history of psychiatric treatment played no role in these findings. Finally, while our participants were physically healthy by history and examination, other relevant biomedical variables (eg, hematologic, lipid, coagulation, and complement measures) that might aid in fully ruling out existing medical conditions were not collected. Despite this, no participant had a plasma CRP level more than 4.96 mg/L. Given that the upper normal limit of plasma CRP is 10 mg/L, it is unlikely these findings could be accounted for by a known medical cause.

Conclusions

In summary, we report a direct relationship between 2 plasma inflammatory markers and aggression in human participants, particularly in those with IED. This relationship was not accounted for by possible demographic/lifestyle confounds including the presence of other psychiatric disorder or general personality factors other than aggression. Given that IED, a disorder of impulsive aggression, displays a 2% to 3% one-year prevalence rate in the United States,[47] and that currently available treatments bring less than 50% of those cases into remission,[48] additional strategies for the examination and intervention of human impulsive aggression are needed.

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