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Salivary cortisol awakening levels are reduced in human subjects with intermittent explosive disorder compared with controls

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ABSTRACT

Background: The role of the hypothalamic-pituitary-adrenal (HPA) axis in human aggressive behavior is poorly characterized, though some studies report that, unlike depression, circulating or salivary levels of cortisol are low compared with controls.

Methods: In this study, we collected three salivary cortisol levels (two in the morning and one in the evening) on three separate days in 78 adult study participants with (n = 28) and without (n = 52) prominent histories of impulsive aggressive behavior. Plasma C-Reactive Protein (CRP) and Interleukin-6 (IL-6) were also collected in most study participants. Aggressive study participants meet DSM-5 criteria for Intermittent Explosive Disorder (IED) while non-aggressive participants either had a history of a psychiatric disorder or no such history (Controls).

Results: Morning, but not evening, salivary cortisol levels were significantly lower in IED ($p < 0.05$), compared with control, study participants. In addition, salivary cortisol levels correlated with measures of trait anger (partial $r = -0.26$, $p < 0.05$) and aggression (partial $r = -0.25$, $p < 0.05$) but not with measures of impulsivity, psychopathy, depression, history of childhood maltreatment, or other tested variables that often differ in individuals with IED. Finally, plasma CRP levels correlated inversely with morning salivary cortisol levels (partial $r = -0.28$, $p < 0.05$); plasma IL-6 levels showed a similar, though not statistically significant ($r_p = -0.20$, $p = 0.12$) relationship with morning salivary cortisol levels.

Conclusion: The cortisol awakening response appears to be lower in individuals with IED compared with controls. In all study participants, morning salivary cortisol levels correlated inversely with trait anger, trait aggression, and plasma CRP, a marker of systemic inflammation. This suggests the present of a complex interaction between chronic-low level inflammation, the HPA axis, and IED that warrants further investigation.

1. Introduction

Intermittent Explosive Disorder (IED) (Coccaro and Lee, 2020) is a behavioral disorder with wide impact on both the afflicted individual and our communities that occurs, over the lifetime, in up to four percent in the U.S. population. IED is characterized by impulsive and aggressive verbal or physical outbursts that are disproportional to a preceding stressor or trigger (American Psychiatric Association, 2013) and that are associated with distress or impairment in social or work-related function. For example, untreated IED carries the risks of higher job loss, divorce, incarceration, and suicide (Coker et al., 2014; DeLisi et al., 2017; McLaughlin et al., 2012; Mundt et al., 2013; Scott et al., 2007; Smith et al., 2021).

IED, and impulsive aggression, is also characterized by a variety of neurobiological features including low serotonin (5-HT) function (Coccaro et al., 2009), reduced grey matter volume in cortico-limbic circuits (Coccaro et al., 2016), increased amygdala reactivity to social threat (Coccaro et al., 2007; McCloskey et al., 2016), compared with non-aggressive controls, all of which are influenced by the hypothalamic-pituitary-adrenal (HPA) axis. Specifically, brain 5-HT turnover (Heinz et al., 2002) and brain grey matter volume (Echoufo-Tcheugui et al., 2018) exhibit inverse relationships with endogenous

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cortisol. In addition, endogenous cortisol responses to emotional stimuli have been associated with an inverse relationship with ventro-medial pre-frontal and a direct relationship with amygdala, activity (Root et al., 2009), similar to what has been reported in fMRI studies in IED (Coccaro et al., 2007; McCloskey et al., 2016). These findings suggest a role for circulating cortisol in aggression but one that is still to be clarified. For example, the inverse relationship between cortisol and 5-HT turnover and grey matter volume suggests that cortisol should be high in those with IED while the positive relationship between cortisol and amygdala reactivity to social threat suggests that cortisol should also be high in those with IED. In individuals with aggressive behavior (Böhnke et al., 2010; Raine, 2002), however, cortisol appears to have an inverse relationship with aggression. Accordingly, it is of interest to explore the relationship between the HPA axis in those with IED compared with non-aggressive controls.

Levels of circulating cortisol typically follow a diurnal cycle (Van Cauter et al., 1996). In addition, cortisol is released in response to acute environmental stressors (Del Giudice et al., 2011). Cortisol levels typically reach maximum levels within the first 30 min of waking (defined as the cortisol awakening response) and proceed to fall over the course of the day before reaching a low point in the evening (Van Cauter et al., 1996). A healthy HPA axis provides protective and adaptive responses including maintenance of energy production, memory retention, and our immune systems (McEwen and Seeman, 1999).

While high cortisol activity is often associated with depressive mood and depressive disorders (Juruena et al., 2018), low cortisol activity has been linked to aggressive and violent behaviors (Böhnke et al., 2010; McBurnett et al., 2000; Raine, 2002). Lower morning cortisol activity, in the form of a reduction of the cortisol awakening response, has been observed in a number of clinical populations including those with Oppositional Defiant Disorder (Freitag et al., 2009), Conduct Disorder (Pajer et al., 2001), and those with psychopathic traits (Cima et al., 2008; Holi et al., 2006; O'Leary et al., 2006), disorders that include aggressive behavior but not necessarily impulsive aggressive behavior. In addition, a recent meta-analysis reported that nine of eleven studies conducted in adolescents found an inverse relationship between morning cortisol levels and "aggression" (Blankenstein et al., 2022). The measure used in these studies, primarily, was the "Disruptive or Aggressive Behavior" subscale from the Young Mana Rating Scale (Young et al., 1978). While IED is the prototypical disorder of impulsive aggression, to our knowledge, no work on the function of the HPA axis has been published in individuals with IED and few studies have prospectively used measures designed primarily to assess aggression.

In order to fill this gap, we measured morning and evening salivary cortisol levels in study participants with IED and in non-aggressive human control participants. Note that salivary cortisol reflects free cortisol, the active component most relevant to effects on brain (Hellhammer et al., 2009). Based on prior research (Blankenstein et al., 2022; Cima et al., 2008; Freitag et al., 2009; Holi et al., 2006; O'Leary et al., 2006; Pajer et al., 2001), we hypothesized that morning cortisol levels would be lower in study participants with IED compared to non-aggressive controls. In addition, we looked at the effect of basal inflammatory state on the cortisol awakening response given the inverse relationship between cortisol and inflammation (Silverman, 2012), and reports of chronic low-level inflammation in individuals with aggression (Coccaro, 2006; Marsland et al., 2008; Suarez, 2003, 2004) and/or IED (Coccaro et al., 2014a, 2014b). We hypothesized that there would be an inverse relationship between salivary cortisol levels and basal inflammatory state as manifest by circulating levels of C-Reactive Protein (CRP) and/or Interleukin-6 (IL-6).

2. Materials and methods

2.1. Participants

Ninety physically healthy adult individuals of both sexes participated in this study from December 2015 through November 2019. Participants were recruited from a larger study of inflammatory markers and aggression involving a total of 135 adult individuals. Participants were recruited through public service announcements, newspaper, other media, and advertisements seeking out individuals who reported psychosocial difficulty related to impulsive aggression or to one or more psychiatric conditions, as well as healthy controls. All participants gave informed consent and signed the informed consent document approved by The University of Chicago's Institutional Review Board. Study participants in this project were not the same as those in our previous studies (Coccaro, 2006; Coccaro et al., 2014a, 2014b).

2.2. Assessment

Diagnoses were made according to DSM-5 criteria (American Psychiatric Association, 2013). Assessments were completed using information from: (a) the Structured Clinical Interview for DSM Diagnoses (SCID-I; First et al., 1997); (b) the Structured Interview for the Diagnosis of Personality Disorder (SIDP; Pfohl et al., 1997); (c) clinical interview by a research psychiatrist; and, (d) review of all other available clinical data. Research diagnostic interviews were conducted by individuals with a masters or doctorate degree in Clinical Psychology. All diagnostic raters went through a rigorous training program that included: lectures on DSM diagnoses and rating systems; videos of expert raters conducting SCID/SIDP interviews; and practice interviews/ratings until the raters were deemed reliable by the trainer. This process resulted in good to excellent inter-rater reliabilities (kappa of.84 (±).05; range:.79 to.93) across the diagnosis of anxiety, mood, substance use, impulse control, and personality disorders. Final diagnoses were determined by team-based best-estimate consensus procedures involving research psychiatrists and clinical psychologists (Coccaro et al., 2012). While information for assigning syndromal (formally Axis I) diagnoses were collected through the use of the SCID-I, more than sufficient information was available to update these diagnoses from DSM-IV to those of DSM-5. DSM-5 diagnoses for personality disorders, based on the SIDP, are the same for DSM-IV. Participants with a diagnosis mutually exclusive to the diagnosis of IED were excluded from the study. Exclusion criteria included active substance use disorders, a lifetime history of bipolar disorder, schizophrenia (or other psychotic disorder), and those with an intellectual disability. Data for age, sex assigned at birth, and ethnicity were self-reported by the study participant; socio-economic status was estimated by the method of Hollingshead (Hollingshead, 1975).

Twenty-nine participants had no evidence of any past or present psychiatric diagnosis including personality disorder (Healthy Controls: HC); 29 met criteria for a lifetime diagnosis of a syndromal psychiatric and/or a personality disorder (Psychiatric Controls: PC), and 32 met criteria for Intermittent Explosive Disorder (IED). Of the 61 participants assessed with a psychiatric disorder, most (68.6%) reported history of formal psychiatric evaluation and/or treatment (51.4%) or of behavioral disturbance during which the participant, or others, thought they should have sought mental health services but did not (17.1%). Despite this history, no study participant was engaged in any psychologic, or psychiatric, treatment (i.e., medication-free) at the time of entry into, or during the duration of, the study.

2.3. Medical clearance

After signed informed consent, study participants were medically evaluated by medical history, physical examination, standard laboratory studies (e.g., hematology, chemistry, etc.) and ECG. In addition, this assessment confirmed that study participants had no signs of physical trauma, or skin rash, and had not received any vaccinations in the previous six months.

2.4. Collection, processing, and assays of salivary cortisol

After signed informed consent, study participants were given a home salivary collection kit (Salimetrics, USA) containing nine tubes for collection of saliva for three days. Each tube included an outer tube, inner tube, absorption swab, and cap. Participants were instructed to collect saliva samples in the morning, immediately after waking up, 30 min after waking up, and in the evening before they went to sleep. Participants were also instructed not to take anything by mouth for 30 min before each sample, to write down the time and date for each sample, and to place the sample tube in their home refrigerator immediately after sample collection. Specific instructions included: a) removing the cap from the inner tube (without removing the inner tube from the outer tube, b) guiding the tube and swab to their mouth, c) chew on the absorption swab (without touching the absorption swab with their hands) for one minute at which point the swab is saturated with saliva and, d) spitting the absorption swab into the inner tube, then sealing the tube with the cap and placing it in a zip-locked bag in their home refrigerator. After the three samples for the day were collected, participants were instructed to take the samples from their refrigerator and place the tubes in the package provided to send the samples overnight (via FEDEx at room temperature) to our laboratory. Upon receipt, each tube was centrifuged for 15 min and the saliva supernatant was pipetted into a polypropylene tube and frozen at -80^0 Celsius until assay at the University of Chicago Clinical Research Center (CRC) core laboratory. Samples were assayed for unbound cortisol, in duplicate, using the Salimetrics HS Salivary Cortisol EIA Kit. This assay had a lower limit of sensitivity from 0.007 to 1.2 μg/dL, with a mean inter-assay CV between 3.9% and 7.1%, and mean inter-assay CV between 6.7% and 6.9%, for high and low concentrations, respectively. Twelve study participants (13.3%) did not provide complete samples for each of the three days and were excluded from analysis. The proportion excluded did not differ among the groups [HC: 3 of 29 (10.3%); PC: 4 of 30 (13.3%); IED: 5 of 31 (16.1%); Chi-Square = 0.43, df = 2, p = 0.81]. This left full three-day salivary cortisol data from 26 participants in each group. Excluded participants did not differ from included participants in mean age, distribution sex or ethnicity, or in mean Hollingshead Socio-Economic Status.

2.5. Collection, processing, and assays of plasma inflammatory markers

Finally, as part of this protocol, most (76%: 59 of 78) participants had three samples for plasma C-Reactive Protein (CRP) and Interleukin-6 (IL-6) collected during the overall time of collection of the salivary cortisol samples. These samples were collected by venipuncture, between 9 and 11 am, into EDTA tubes, placed on ice, centrifuged for plasma, and stored at -80^0 C until assayed. Inflammatory marker samples were assayed in the laboratory of one of the co-authors (MRI) and levels reported represent the mean of the duplicates. Plasma CRP was assayed using a high-sensitivity ELISA assay by R&D Systems (Minneapolis, MN) and plasma IL-6 was assayed using a multiplex assay by Meso Scale Discovery (Rockville, Maryland). The sensitivity of the assays for CRP and IL-6 were 0.20 mg/L and 0.21 pg/ml, respectively. Mean intra- and inter- assay CVs for CRP were 1.0% and 6.1%; mean intra- and inter- assay CVs for IL-6 were 1.0% and 4.0%.

2.6. Assessment of aggression and anger

Aggression was assessed with the aggression scale of the Life History of Aggression (LHA; Coccaro et al., 1997). The LHA assesses history of overt aggressive behavior and is conducted as a semi-structured interview and has good psychometric properties (α = 0.86). Anger was assessed using the Anger Expression Index (AEI) score from the Spielberger State-Trait Anger and Expression of Anger Inventory (STAXI-2; (Spielberger, 1999). The AEI is a 32 item self-report assessment that considers anger expression (α = 0.89) and anger control (α = 0.94) in one variable with higher numbers signifying greater anger.

2.7. Assessment of aggression related variables: impulsivity and psychopathy

Impulsivity was assessed with the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995). The BIS-11 assesses the tendency to be impulsive and has good psychometric properties (α = 0.86). Psychopathy as assessed with the Psychopathic Checklist-Screening Version (Hart et al., 2003) as previously described (Coccaro et al., 2014a, 2014b: α = 0.79).

2.8. Assessment of state depression, perceived stress, and history of childhood maltreatment

State depression was assessed by the Beck Depression Inventory-II (BDI-II; Beck and Brown, 1996: α = 0.96). Perceived stress over the past month was assessed by the Perceived Stress Scale (PSS; Cohen et al., 1983), a 10-item, Likert-scale questionnaire: α = 0.92). History of childhood maltreatment was assessed by the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003), a 28-item, Likert-scaled, questionnaire inquiring about physical, emotional, and sexual abuse as well as physical and emotional neglect: α = 0.87). These variables were included because of their relevance to, and potential impact on, the HPA Axis (Counts et al., 2022; Nandam et al., 2019; Zorn et al., 2017).

2.9. Statistical analysis and data reduction

The primary outcome variables for categorical and dimensional analyses were the DSM-5 diagnosis of Intermittent Explosive Disorder, LHA Aggression, and STAXI-2 AEI Anger scores. Secondary outcome variables were BIS-11 Impulsivity and the PCL-SV Psychopathy scores. Other outcome variables included the BDI-II, PSS, and the CTQ. Statistical procedures included Chi-Square, t-test, Analyses of Covariance (ANCOVA), Repeated Analysis of Covariance (RM-ANCOVA), Pearson Correlation, Partial Correlation, and Multiple Regression. Analyses included age, sex assigned at birth, ethnicity, and socio-economic status; body mass index was added as a covariate in analyses involving pro-inflammatory markers. Salivary cortisol levels (μ/dL), and CRP (mg/dL) / IL-6 (pg/ml) levels, were log-transformed because these variables were not normally distributed. A two-tailed alpha value of 0.05 was used to denote statistical significance. Statistical procedures were performed using SPSS 28.

3. Results

3.1. Demographic characteristics of sample and sub-samples

The 90 participants recruited for this study did not differ in demographic variables (age, sex assigned at birth, ethnicity, and socio-economic status) from those remaining in the sample that participated in our larger study of inflammatory markers and aggression (n = 135; Supplemental Table 1a); there were also no differences in demographic variables between the study participants in the final sample (n = 78) with complete salivary cortisol data and participants those excluded due to incomplete salivary cortisol data (n = 12; Supplementary Table 1b). Study participants with complete both salivary cortisol and inflammatory marker data (n = 59) also did not differ on demographic variables compared with those without inflammatory marker data (n = 31; Supplemental Table Ic).

3.2. Demographic, psychometric, and diagnostic characteristics of the final sample

Table 1 displays demographic, body mass index (BMI), and relevant psychometric variables for the final sample with full three-day salivary cortisol data. The groups did not differ in age, distribution of sex or

Table 1
Demographic and Psychometric Characteristics of Study Participants.

	HC (N = 26)	PC (N = 26)	IED (N = 26)	p	Group Differences
Demographic Variables					
Age	31.2 + 9.1	29.9 + 8.9	33.7 + 9.4	= 0.310	HC = PC = IED
Sex (% Male)	26.9%	53.8%	46.2%	= 0.129	HC = PC = IED
Ethnicity (% White / African-American / Other)	31% / 46% / 23%	39% / 38% / 23%	31% / 50% / 19%	= 0.935	HC = PC = IED
SES Score	44.0 + 7.7	41.4 + 10.8	37.8 + 11.2	= 0.088	HC = PC > IED
Psychometric Variables					
Aggression (LHA)	3.7 + 3.3	5.4 + 3.0	18.5 + 3.7	< 0.001	HC = PC < IED
Anger Expression (STAXI-2)	-10.5 + 7.2	-6.0 + 9.2	13.7 + 7.8	< 0.001	HC = PC < IED
Impulsivity (BIS-11)	52.2 + 7.1	56.9 + 4.3	66.8 + 10.1	< 0.001	HC = PC < IED
Psychopathy (PCL-SV)	0.2 + 0.5	2.1 + 2.5	8.5 + 3.9	< 0.001	HC < PC < IED
Beck Depression Inventory	2.0 + 2.9	5.6 + 8.4	12.5 + 8.9	< 0.001	HC = PC < IED
Perceived Stress (PSS)	21.4 + 2.4	20.6 + 3.5	24.6 + 3.1	< 0.001	HC = PC < IED
Childhood Maltreatment (CTQ)	30.5 + 7.9	36.6 + 12.8	49.2 + 21.6	< 0.001	HC = PC < IED
Other Variables					
Body Mass Index (BMI)	26.4 + 4.0	25.2 + 2.9	26.1 + 3.8	= 0.464	HC = PC = IED

ethnicity, or BMI, though IED participants had non-significantly lower SES scores compared with HC and PC controls (Table 1). As expected, the groups differed in the psychometric variables related to aggression, anger, impulsivity, and psychopathy, in which IED study participants displayed higher scores on each variable compared with HC and PC study participants. Variables related to depression, perceived stress, and history of childhood maltreatment were also elevated in IED study participants compared with both sets of controls. Despite this, PC and IED study participants did not meaningfully differ in current or lifetime DSM-5 disorders (Table 2).

3.3. Log salivary cortisol levels in IED and control participants

Repeated measures ANCOVA revealed that the two morning log salivary cortisol levels did not differ significantly by time ($F[1,71] = 0.85$, $p = 0.32$; Marginal Means + SEM: Time 1 = 1.36 + 0.02; Time 2 = 1.41 + 0.03) but did differ by HC/PC/IED diagnostic group ($F[1,71] = 3.11$, $p < 0.05$) with lower log morning salivary cortisol levels among participants with IED compared with participants in both control groups ($\eta^2p = 0.081$), who did not differ in this respect. There was no effect of Age, Sex, Ethnicity, and SES, with morning log salivary cortisol levels, and no significant interactions among variables (all $p > 0.51$). For subsequent analyses, the two log morning cortisol levels were combined into one mean log morning cortisol level (Fig. 1, left). Log mean morning salivary cortisol levels did not differ as a function of Non-IED Disorders (e.g., Depressive Disorder, Anxiety Disorder, etc.). Finally, and in contrast, mean log evening (Time 3, at bedtime) salivary cortisol levels did not differ by group or as a function of any of the covariates (Fig. 1, right).

3.4. Log salivary morning cortisol levels and aggression and anger

Partial correlation analyses revealed statistically significant inverse relationships between mean log salivary morning cortisol levels and

Table 2
DSM-5 Diagnoses Among Study Participants with a Psychiatric Disorder.

	Psychiatric Controls (N = 26)	Intermittent Explosive Disorder (N = 26)	P	Group Differences*
Current Syndromal Disorders				
Any Depressive Disorder	1 (3.8%)	2 (7.7%)	0.557	PC = IED
Any Anxiety Disorder	6 (23.1%)	7 (26.9%)	0.749	PC = IED
Post-Traumatic Stress Disorder	2 (7.7%)	8 (30.8%)	0.075	PC = IED
Any Substance Use Disorder	0 (0.0%)	0 (0.0%)	0.999	PC = IED
Lifetime Syndromal Disorders				
Any Depressive Disorder	14 (53.8%)	11 (24.3%)	0.579	PC = IED
Any Anxiety Disorder	9 (34.6%)	10 (38.5%)	0.999	PC = IED
Post-Traumatic Stress Disorder	4 (15.4%)	13 (50.0%)	0.017	PC = IED
Any Substance Use Disorder	13 (50.0%)	11 (42.3%)	0.781	PC = IED
Personality Disorders				
Odd Cluster	0 (0.0%)	3 (11.3%)	0.235	PC = IED
Dramatic Cluster	2 (7.7%)	6 (19.2%)	0.419	PC = IED
Anxious Cluster	4 (15.4%)	10 (38.5%)	0.116	PC = IED
PD-Not Otherwise Specified	6 (23.1%)	11 (42.3%)	0.237	PC = IED

* $p < 0.05$ after correction for multiple comparisons (uncorrected $p < 0.0032$).

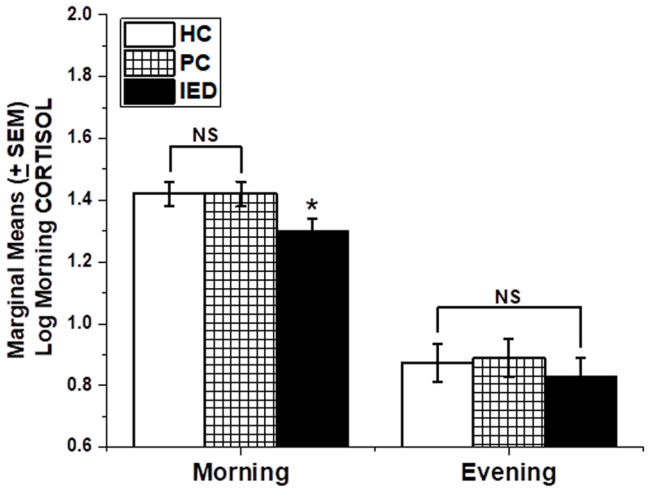

Fig. 1. Marginal means (+ SEM) of Log Morning (upon awakening and thirty minutes later), and Evening (prior to bedtime), Salivary Cortisol Levels in IED, Psychiatric (PC) and Healthy Control (HC) study participants. Asterisk indicates $p < 0.05$ from other groups.

LHA Aggression ($r = -0.25$, $p < 0.05$), and STAXI-2 Anger Expression Index ($r = -0.26$, $p < 0.05$), scores. The partial correlation using a Composite Anger/Aggression score was similar ($r = -0.24$, $p < 0.05$).

3.5. Log salivary morning cortisol levels and impulsivity, psychopathy, and other relevant variables (Table 3)

Though correlated with LHA Aggression and/or STAXI Anger Expression Index scores, no statistically significant relationships were noted between mean log salivary morning cortisol levels and the other secondary behavioral outcome variables in this study. Adding these behavioral variables to the statistical model had no impact on the relationship between mean log salivary morning cortisol levels and Composite Anger/Aggression scores ($r_p = -0.29$, $p < 0.05$; i.e., with demographic variables and with BIS-11, PCL-SV, BDI-II, PSS, and CTQ scores as covariates); Fig. 2. Supplemental Table II lists all partial correlations between log salivary morning cortisol levels and all behavioral variables.

3.6. Mean log morning salivary cortisol levels and plasma pro-inflammatory markers

Partial correlation with demographic variables and body mass index also revealed a significant inverse relationship between mean log plasma CRP levels and mean log salivary morning cortisol levels ($r_p = -0.28$, $p < 0.05$). A similar inverse, but not statistically significant, correlation was also noted with mean log plasma IL-6 level and mean log salivary morning cortisol ($r_p = -0.20$, $p = 0.12$) levels. Multiple regression analysis with log plasma CRP levels and Composite Anger/Aggression scores as predictors of mean log salivary cortisol levels revealed a significant correlation with log plasma CRP level ($\beta = -0.31$, $p < 0.05$; Fig. 3) but a smaller, statistically non-significant, correlation with Composite Anger/Aggression scores ($\beta = -0.14$, $p = 0.31$).

4. Discussion

We investigated the relationship between impulsive aggression and morning/evening salivary cortisol levels in males and females with Intermittent Explosive Disorder (IED) compared with both healthy and psychiatric controls. We also explored the presence of a relationship between salivary cortisol and markers of inflammation (CRP and IL-6) given the presence of an inverse relationship between cortisol and inflammation (Silverman, 2012).

We found a reduction in morning, but not evening, cortisol levels in individuals with IED compared with all control subjects (who were no different from each other in salivary cortisol levels). Consistent with this finding we found statistically significant correlations between mean morning salivary cortisol level and trait anger expression and history of lifetime aggressive behavior. This relationship appeared to be specific to

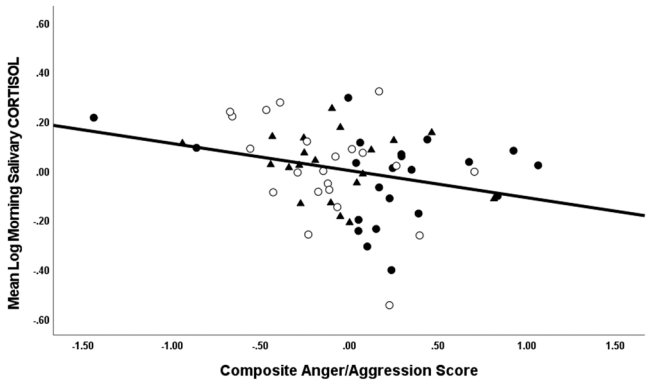

Fig. 2. Partial Correlation between Log Morning Salivary Cortisol levels and Composite Anger/Aggression scores in all subjects (covariates: age, sex, race, ses, and BIS-11, PCL-SV, BDI-II, PSS, CTQ scores). Closed circles designate study participants with IED, closed triangles designate psychiatric control, and open circles designate healthy control, study participants.

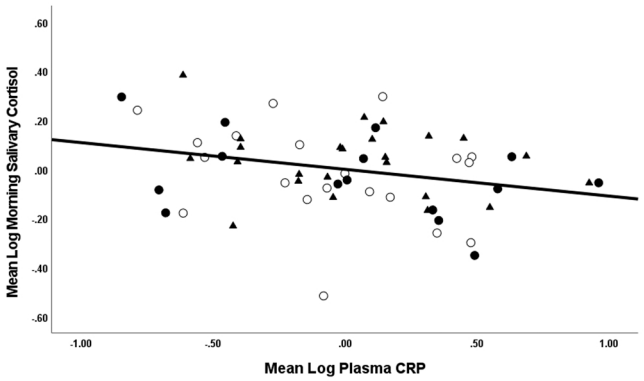

Fig. 3. Partial regression plot for Log Salivary Morning Cortisol levels and Log CRP Plasma Levels in all subjects with these data (covariates: Age, Sex, Ethnicity, SES, BMI, and Composite Anger/Aggression score). Closed circles designate study participants with IED, closed triangles designate psychiatric control, and open circles designate healthy control, study participants.

IED because similar analyses did not find significant differences in mean log morning cortisol level between those who had, or did not have, other Non-IED disorders.

The observation that other behavioral variables, such as impulsivity, depression, psychopathy, perceived stress, and history of childhood maltreatment did not correlate with mean morning salivary cortisol level suggests either a level of specificity for trait anger and aggression in this relationship or the presence of a Type I error. Supporting specificity for a relationship with trait anger and aggression are reports that show that anger induction reduces salivary cortisol levels in both healthy men (Herrero et al., 2010) and women (Herrero et al., 2010; Kazén et al., 2012). To our knowledge, however, there are no reports regarding this dynamic in aggressive individuals.

The observation of lower morning cortisol levels in those with IED, and of an inverse relationship between morning cortisol levels and dimensional measures of trait anger and aggression, is consistent with several reports in the literature. Individuals with aggressive and violent behaviors (Böhnke, 2010; Raine, 2002) have been reported to exhibit lower cortisol activity as do individuals with other psychiatric disorders [e.g., Oppositional Defiant Disorder; (Freitag, 2009) and Conduct Disorder (Pajer, 2001)]. While studies of individuals with psychopathic traits (Cima et al., 2008; Holi et al., 2006; O'Leary et al., 2006) report the same, callous/unemotional psychopathic traits correlate highly with social deviant psychopathic traits, which are largely aggressive in nature (Coccaro et al., 2014a, 2014b). Thus, these findings do not necessarily contradict our observation of an inverse correlation between morning cortisol levels without a similar one for psychopathic traits. Finally, several studies of adolescents have reported inverse correlations between basal morning cortisol levels with secondary measures of "disruptive or aggressive behavior" (Blankenstein et al., 2022).

Lower morning cortisol activity is postulated to be a manifestation of blunted hypothalamic-pituitary axis (HPA) activity. Poor adaptation to chronic stress is thought to lead to flattening of diurnal rhythms of cortisol and subsequently attenuated typical morning rise of cortisol (Sephton et al., 2000). Adults who experienced early life difficulties have been posited to experience stress sensitivity that may reset the HPA axis to a blunted level of activity and responsivity (Miller et al., 2007). In addition, while the HPA axis of those with such stress sensitivity may be more responsive during childhood (e.g., in threatening family environments), such individuals may manifest attenuated HPA activity later during adulthood (Repetti et al., 2011). While we observed no dimensional relationship between morning cortisol levels and history of childhood maltreatment, or with perceived levels of current stress, study participants with IED were significantly higher than both sets of controls on these two variables.

The observation of an inverse relationship between plasma CRP and morning cortisol levels, pointing to a relationship between the HPA axis and basal inflammatory state is of note. In the homeostatic state, the HPA axis activates innate immunity and fosters the inhibition of proinflammatory mediators (Silverman, 2012). Accordingly, this finding is consistent with the possibility that lower HPA activity is associated with higher levels of systemic inflammation. Further, we found that mean plasma CRP levels were a stronger correlate of morning salivary cortisol levels than the composite anger/aggression score. While this suggests that chronically elevated levels of inflammation may drive these relationships, this hypothesis requires further study. Despite this finding, it is important to note that only about half of study participants with IED had plasma CRP data and, while mean CRP levels in this group was higher compared with controls, this difference was not statistically significant. Accordingly, caution should be taken in the interpretation of these data.

Other explanations for these findings can be considered. For one, the acute induction of anger in healthy individuals is associated with a reduction in salivary cortisol levels that begins within 25 min of anger induction, persisting for at least a total of 45 min (Kazén et al., 2012). Thus, it is possible that the frequent anger outbursts of those with IED is responsible for lower salivary cortisol levels in these individuals. Aggressive behavior is also related to serotonin (5-HT) and individuals with IED display evidence of reduced central serotonergic function (Coccaro et al., 2010; New et al., 2004; Siever et al., 1999). While 5-HT agents can acutely increase circulating cortisol levels (Coccaro and Kavoussi, 1994), the reduction of 5-HT through acute tryptophan depletion can reduce salivary cortisol levels (Sobczak et al., 2002). If so, low morning cortisol levels would be consistent with low 5-HT function, especially in those with IED (Coccaro et al., 2010).

Another mechanism underlying our findings may be through the relationship between anger and testosterone. This is because anger inducing events have been shown to be associated with increases in salivary testosterone (Peterson and Harmon-Jones, 2012) and testosterone and cortisol may be inversely related (Herrero et al., 2010). However, while there may be an inverse relationship between testosterone and 5-HT (Kindlundh et al., 2003), central levels of testosterone do not correlate with central levels of 5-HT metabolites in human (Virkkunen et al., 1994) and non-human primates (Higley et al., 1996), and high levels of aggression may be observed only in individuals with low central levels of 5-HT coupled with high central levels of testosterone (Higley, 1996; Virkkunen et al., 1994). That said, we did not measure testosterone in this study and, thus, these ideas regarding testosterone represent only speculation.

4.1. Strengths and limitations

This study has a number of strengths and limitations. A major strength was the use of male and female adults who were either healthy or struggled with impulsive aggressive behavior leading to distress and/or interpersonal difficulties. Our investigation of the LHA Aggression, STAXI-2 Anger Expression Index, BIS Impulsivity, BDI-II Depression, PCL-SV Psychopathy, PSS Perceived Stress, and CTQ Childhood Maltreatment scales for participants represents another major strength.

This study also has limitations including the exclusion of individuals with bipolar, and other psychotic, disorders that may also exhibit aggressiveness (Coccaro, 2019) which limits the generalizability of these findings to a broader group of aggressive individuals. In addition, this study did not strictly follow recent recommendations for a standardized assessment of cortisol awakening responses (Stalder et al., 2016). This was because the present study was planned, funded, and implemented prior to the publication of those standards. As a result, this study: a) had only two samples for morning cortisol, and only one for evening cortisol, limiting the reliability of cortisol values and preventing the examination of an integrated Area Under the Curve variable, b) did not use an objective method to verify sampling accuracy (even though clear instructions to participants were given by study staff), and c) pre-study power analyses was not conducted. Unfortunately, a review of relevant publications since 2016, indicates that these standards have yet to be adopted by most investigators in the field (Stalder et al., 2022).

4.2. Conclusion

In this case-control study, male and female adults with IED, compared to similar, but non-aggressive, individuals demonstrated a reduction in mean morning cortisol levels. The cortisol awakening response appears to be lower in individuals with IED compared with controls. In all study participants, morning salivary cortisol levels correlated inversely with trait anger, trait aggression, and plasma CRP, a marker of systemic inflammation. This suggests the present of a complex interaction between chronic-low level inflammation, the HPA axis, and IED that warrants further investigation.

CRediT authorship contribution statement

Alejandro D. Meruelo: Writing – review & editing. **Writing Timmins:** Writing – review & editing. **Michael R. Irwin:** Plasma CRP/IL-6 assays, Writing – review & editing. **Emil F. Coccaro:** Conceptualization, Funding acquisition, Project management, Data collection, Statistical analysis, Writing – review & editing.

Conflict of interest

This work was supported by grants from the National Institutes of Health: RO1 MH 104673 (Dr. Coccaro) and K23 AA026869 (Dr. Meruelo). Dr. Coccaro reports being a member and consultant to the Scientific Advisory Boards of Azevan Pharmaceuticals, Inc., Avanir Pharmaceuticals, Inc., and Boerhinger Ingelheim Pharmaceuticals, Inc. Drs. Meruelo, Timmins, and Irwin have nothing to declare.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2023.106070.

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