Brain, Behavior, & Immunity - Health 48 (2025) 101078

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Characterization of inflammatory and neurofunctional markers in the context of early life stress among a clinical sample of people maintained on buprenorphine for opioid use disorder

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A B S T R A C T

Early life stress (ELS) is associated with an increase in expression of inflammatory cytokines and opioid addiction-related behaviors. Maintenance on medication for opioid use disorder (OUD) can opposingly affect these endpoints. The study aimed to determine whether a history of ELS is associated with a distinct inflammatory and/or neurofunctional phenotype within a population of individuals maintained on buprenorphine for OUD. In this secondary analysis of 21 adults (16M/5F), High and Low ELS groups were determined by number of items endorsed on the Trauma History Questionnaire occurring before 18 years old. Peripheral blood levels of 10 cytokines, CRP, LBP, and MCP-1 were assessed. Participants also completed assessments of six neurofunctional domains: reward, cognition, negative emotionality, interoception, metacognition, and sleep. Individuals in the Low ELS group (n = 11; 9M/2F) experienced a median of 3 [range: 0–3] traumatic events and individuals in the High ELS group (n = 10; 7M/3F) experienced a median of 8.5 [4–13] traumatic events. ELS groups did not differ with respect to age, sex, buprenorphine dose, BMI, smoking status, psychiatric or substance use disorder comorbidity. Proinflammatory cytokines IFNγ ($p < 0.001$) and IL-6 ($p < 0.0001$) were elevated in the High ELS group compared to the Low ELS group. Anti-inflammatory IL-13 was higher in the Low ELS group ($p = 0.012$). There were no neurofunctional differences between ELS groups. Results extend previous findings of an ELS-associated pro-inflammatory state to this OUD treatment population. Future work with larger samples balanced by sex may inform precision medicine strategies to tailor buprenorphine-based OUD treatment to individuals' biopsychosocial needs.

1. Introduction

Exposure to early life stress (ELS) is one putative risk factor for the development of a wide range of mental health and behavioral disorders, including opioid use disorder (OUD). Here, we use the term ELS broadly to refer to exposure to physical, sexual, and emotional abuse or neglect, maltreatment, trauma, household dysfunction, and other sources of community adversity and disaster prior to the age of 18 (Chapman et al., 2004; Felitti et al., 1998). Studies have reported a high prevalence of ELS in individuals with OUD, with one recent meta-analysis finding that 38–48 % of people with OUD reported ELS (Santo et al., 2021). Beyond OUD prevalence, ELS has also been associated with earlier initiation of opioid use (Guarino et al., 2021) and increased likelihood of return to use during OUD treatment (Derefinko et al., 2019). Studies in populations with other substance use disorders (Elliott et al., 2014; Rothman et al., 2008; Shin et al., 2013) and depression (Nanni et al., 2012; Nelson et al., 2017) also show that ELS is associated with greater disorder severity and poorer treatment outcomes. This body of work suggests that ELS exposure may be contributing to heterogeneity of treatment outcomes observed amongst individuals with the same Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnosis, including OUD. Treatment attrition and substance use recurrence rates remain high amongst individuals with OUD, despite the availability of evidence-based pharmacological and behavioral treatment (Shulman et al., 2021; Smyth et al., 2010). Implementation of a precision medicine-based research framework that accounts for social and

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https://doi.org/10.1016/j.bbih.2025.101078
Received 31 December 2024; Received in revised form 18 July 2025; Accepted 27 July 2025
Available online 29 July 2025

environmental factors such as ELS may aid in tailoring OUD treatment options to an individual's biopsychosocial needs.

To identify and characterize the neurofunctional heterogeneity within OUD towards the goal of expanding precision medicine, prior studies have employed the use of a deep phenotyping battery that encompasses six critical domains: reward, cognition, negative emotionality, interoception, metacognition, and sleep (Keyser-Marcus et al., 2021; Parlier-Ahmad et al., 2023). Recent studies using a three-domain phenotyping framework in individuals with alcohol use disorder have shown that ELS is associated with increases in negative emotionality (Kirsch et al., 2024a). The successful implementation of this neurocognitive phenotyping in an alcohol use disorder population suggests that exploring the association between ELS and neurofunction within an OUD patient population may yield similarly informative results. Although ELS is associated with deficits in other neurocognitive domains such as cognition (Acheson et al., 2019), reward processing (Novick et al., 2018), greater maladaptive metacognitive beliefs (Horvath et al., 2024; Martin and Strodl, 2023), and higher prevalence of sleep problems (Greenfield et al., 2011; Kajeepeta et al., 2015) in non-OUD populations, the extent to which ELS is associated with these effects amongst individuals with OUD is unknown. It is also unknown whether maintenance on medication for OUD (MOUD), such as buprenorphine, mitigates potential ELS-associated neurofunctional differences.

A possible biological mechanism underlying an association between ELS exposure and addiction-related deficits in neurocognition is a heightened inflammatory state. Meta-analyses have shown that people with a history of ELS have elevated peripheral levels of IL-6, TNF-α, and c-reactive protein (CRP) (Baumeister et al., 2016). These inflammatory markers have been associated with reduced reward sensitivity (Phillips, 2024), impairments in learning and memory (Prieto et al., 2019), and negative emotionality (Miller et al., 2009). Opioid exposure similarly upregulates proinflammatory cytokines such as IL-6, TNF-α and IL-1β (Chan et al., 2015; Pacifici et al., 2000). However, the literature regarding the effects of MOUD on peripheral inflammation in patients with OUD is mixed and still evolving. Some studies have found that initiation on MOUD produces a within-subjects decrease in peripheral inflammatory markers such as TNF-α (Salarian et al., 2018), while others have found opposing results (Neri et al., 2005; Sacerdote et al., 2008). Overall, these studies indicate that inflammatory profiles of individuals in treatment for OUD likely differ from the inflammatory profiles of healthy controls or people actively using opioids. Further, in treatment-seeking OUD patients, higher plasma levels of IL-6 were significantly correlated with poor MOUD compliance and early dropout from treatment (Lu et al., 2019), suggesting that inflammatory markers may be important to consider in the development of personalized medicine practices for OUD.

In sum, the current literature suggests that in addition to ELS exposure producing long-lasting changes in the individual's neurocognitive functioning, it may also elevate circulating inflammatory factors in adulthood. Further, the neurocognitive and inflammatory profiles of individuals maintained on MOUD may differ from individuals with OUD who are not in treatment. Accordingly, the primary goal of this study is to identify potential differences in inflammation based on ELS history amongst a sample of individuals maintained on buprenorphine treatment for OUD. Secondarily, we will describe other differences across the neuofunctional domains of reward, cognition, negative emotionality, interoception, metacognition, and sleep by ELS history. This initial step towards identification of an ELS-associated, unique inflammatory profile and neuroclinical presentation in this patient population may ultimately aid in tailoring buprenorphine-based OUD treatment regimens to individuals' biopsychosocial needs.

2. Methods

The current study utilized data collected during randomized, double-blind, placebo-controlled phase 1b/2a drug-drug interaction study for the orexin 1 and 2 receptor antagonist lemborexant with buprenorphine-naloxone in participants with opioid use disorder (Martin et al., 2025). Data were collected at the VCU Collaborative Advanced Research Imaging (CARI) facility and the VCU Clinical Research Unit (CRU).

2.1. Participants

A full description of eligibility criteria for the parent study can be found in a previous publication (Martin et al., 2025). Relevant to the current secondary analysis, participants were between 18 and 65 years-of-age and met current DSM-5 criteria for OUD of at least moderate severity, as determined by the Mini-International Neuropsychiatric Interview for DSM-5 (MINI). Additional eligibility criteria included maintenance on 8–24 mg sublingual buprenorphine-naloxone. Buprenorphine adherence was verified by urine drug test prior to CRU admission. Notable exclusionary criteria include uncontrolled serious psychiatric or major medical disorder, significant current suicidal or homicidal ideation, a history of suicide attempt with the past six months, or a score $\geq$8 on the Suicidal Behaviors Questionnaire-Revised (SBQ-R). Participants were recruited from outpatient treatment centers at VCU and the local Richmond area.

The current secondary analysis included all participants who completed baseline assessments (N = 21; 16 cisgender men, 5 cisgender women). Importantly, only baseline participant data is included in the current study. That is, for the purposes of this study, participants continued taking their regular buprenorphine dose but never consumed the parent study drug of lemborexant.

2.2. Measures

Upon study enrollment, participants completed an initial visit to the research laboratory for collection of demographics, clinical, psychosocial (including ELS), and neurofunctional measures. Approximately 1.5 weeks later, participants completed a baseline outpatient visit on the CRU where they provided blood samples at three timepoints relative to buprenorphine intake. For the current secondary analysis, these blood samples were used to determine peripheral levels of inflammatory markers. Detailed information on data collection procedures is below.

2.2.1. Demographics and clinical measures

Participants reported their age, sex, gender identity, race, ethnicity, buprenorphine dose, date of buprenorphine initiation, and past medical history. Participant weight and body mass index (BMI) was determined by a physical exam and buprenorphine dose and medical history were verified by electronic medical record (EMR) review. Current diagnosis of a co-morbid substance use disorder or psychiatric disorder was determined by the MINI, and nicotine use was determined by the Fagerstrom Test for Nicotine Dependence (Heatherton et al., 1991; Pomerleau et al., 1989).

2.2.2. Early life stress

Early life stress was assessed using the Trauma History Questionnaire (THQ) (Hooper et al., 2011). The THQ is a survey in which participants are asked whether they experienced 24 ELS events such as crime, general disaster, or sexual and physical assault using a yes/no format. Respondents are asked to provide the frequency of the event and their age at the time of the event. The THQ has been found to be psychometrically sound with regard to both reliability and validity (Hooper et al., 2011). The items on the THQ generally map onto the common dimensions of physical and sexual abuse, as well as community adversity and disaster from the childhood adversity and maltreatment literature (Chapman et al., 2004; Duprey et al., 2023; Felitti et al., 1998). Consequently, previous studies have used the THQ to estimate levels of ELS and have independently reported different types of ELS events (Hammersley et al., 2003; Spertus et al., 2003). Following this precedent, we reported

different types of ELS events captured by the THQ to provide greater clinical context: victim of sexual abuse, physical abuse, crime, serious accident/natural disaster/illness/injury, and witness to death/injury/serious illness of another. Additional psychosocial measures were assessed to provide more clinical context regarding participants' OUD recovery.

2.2.3. Inflammatory markers

Participants arrived at the CRU at approximately 6:30 a.m. The participant took their prescribed dose of buprenorphine at 8:00 a.m., and blood samples were taken by trained medical staff at three different timepoints relative to buprenorphine intake: 1 h before (7:00 a.m.), 2 h after (10:00 a.m.), and 8 h after (4:00 p.m.). These timepoints were selected based on reported clinical pharmacokinetics of buprenorphine (Elkader and Sproule, 2005). Blood samples were immediately frozen, stored at −80 °C, and thawed prior to analysis. Using the MSD VPLEX Proinflammatory Panel 1 Human Kit, serum levels (pg/ml) of TNFα, IFNγ, IL-1β, IL-2, IL-6, IL-8, IL-12p70, IL-4, IL-10, and IL-13 were determined for each individual at each of the three timepoints. All blood samples for this panel were run undiluted, and in total, each subject had 3 repeated measures at each time point for each of the 10 markers. Serum levels of Lipopolysaccharide Binding Protein (LBP), CRP, and the chemokine MCP-1 were only determined from pre-buprenorphine (7:00 a.m.) samples, due to the more stable nature of these inflammatory markers. Two dilutions of each blood sample were run for LBP, CRP, and MCP-1. These common inflammatory markers were selected because they provide a comprehensive assessment of inflammation and these markers align with previously studies reporting ELS-associated inflammation (Baumeister et al., 2016; Coelho et al., 2014).

2.2.4. Neurofunctional measures

Six neurofunctional domains from the NIDA Phenotyping Assessment Battery (PhAB) (Keyser-Marcus et al., 2021) were assessed with the following validated instruments: 1) Reward (Short Impulsive Behavior Scale [SUPPS-P](Cyders et al., 2014), 2) cognition (5-Trial Adjusting Delay Discounting Task [5-DD](Koffarnus and Bickel, 2014)), 3) negative emotionality (Patient-Reported Outcomes Measurement Information System, [PROMIS](Cella et al., 2010; Rothrock et al., 2020), for anxiety [PROMIS-A] and for depression [PROMIS-D]; Distress Tolerance Scale [DTS](Simons and Gaher, 2005); Buss Perry Aggression Questionnaire (Bernstein and Gesn, 1997)), 4) interoception (Multidimensional Assessment of Interoceptive Awareness [MAIA](Mehling et al., 2012)), 5) metacognition (Metacognition Questionnaire 30 [MCQ-30] (Wells and Cartwright-Hatton, 2004)), and 6) sleep (Pittsburgh Sleep Quality Index [PSQI] (Buysse et al., 1989)). A detailed description of these individual measures and associated reporting practices has been previously published (Keyser-Marcus et al., 2021). For the 5-DD task, the Effective-Delay-50 (ED50; time required for a delayed monetary reward to diminish in subjective value by 50 %) is reported, which was generated by taking the reciprocal of the observed discounting rate (Koffarnus and Bickel, 2014).

2.2.5. Other psychosocial measures

PTSD symptomatology was assessed with the Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5) (Blevins et al., 2015). Quality of life was assessed with the World Health Organization Quality of Life assessment (WHO-QOL Bref)(Skevington et al., 2004). Social determinants of health variables assessed included education, healthcare access and quality, economic stability, neighborhood and built environment, social and community context. These were collected from the Addiction Severity Index self-report form (ASI-SR) (Ljungvall et al., 2020) and EMR review. These data are reported in Supplemental Materials Table S1.

2.3. Data preparation and analysis

High and low ELS groups were determined by number of events endorsed on the THQ that occurred before 18 years old (above vs. below sample median). This practice of summing types of exposures to determine a total numerical score is consistent with the widely-used Adverse Childhood Experiences (ACEs) Questionnaire (Felitti et al., 1998) and the cumulative dose model of childhood adversity (Turner and Lloyd, 1995). Additionally, the decision to dichotomize ELS using the median value aligns with methods implemented by prior studies (Cohen et al., 2012; Spertus et al., 1999). Levels of inflammatory markers that were above or below the assay limits of detection were excluded from analysis. For ELS group comparisons, we modeled repeated measures of the 10 inflammatory markers (TNFα, IFNγ, IL-1β, IL-2, IL-6, IL-8, IL-12p70, IL-4, IL-10, IL-13) using a multivariate mixed-effects model, adjusting for age, sex, and BMI. We compared group differences in marginal means by post-hoc comparisons with Tukey's adjustment. For CRP, MCP-1 and LBP, separate linear mixed-effects models with each of the three markers as the outcome variable, adjusting for age, sex and BMI, were fit to assess the ELS group difference. Participant demographic, clinical, psychosocial, and neurofunctional measures are reported and compared between ELS groups using a two-sample *t*-test, Fisher's exact test, or independent samples median test, as appropriate. Analyses were conducted in SPSS (29.0), and R Studio v. 4.4 (RStudio, 2020).

3. Results

3.1. Sample demographics and clinical variables

The current study sample (N = 21) was over 76 % male and over 95 % non-Hispanic or Latino (Table 1). The median duration of buprenorphine receipt was 1.4 years, with a range of 0.1–5.9 years. Most participants were currently using tobacco (81.0 %), not utilizing nicotine replacement therapy (85.7 %), and had a comorbid substance use disorder (52.4 %) or psychiatric disorder (66.7 %). A variety of concomitant medications were reported, including three individuals taking anti-inflammatory medication. One individual also reported a medical history of an autoimmune disorder.

3.2. Determination of ELS groups

The number of items endorsed on the THQ that happened before age 18 ranged from 0 to 13, with a median of three ELS events reported by the study sample. Given the descriptive nature of the study's objective, individuals who endorsed three or fewer events prior to age 18 (n = 11, 52.4 % of sample) were categorized as "Low ELS" (median traumatic events = 3) and individuals who endorsed more than three events on the THQ prior to age 18 (n = 10, 47.6 % of sample) were categorized as "High ELS" (median traumatic events = 8.5). While High vs. Low ELS groups did differ by race ($p = 0.0468$), there were no significant differences between ELS groups for any of the other demographic or clinical variables examined (Table 1).

3.3. Inflammatory markers by ELS group

There were significant ELS group differences in three inflammatory markers (Fig. 1). Averaged across timepoints in post-hoc comparisons, the proinflammatory cytokines IFNγ and IL-6 were elevated in the High ELS group (the estimated IFNγ was 2.039 pg/mL [SE 0.385] higher in the High ELS group than in the Low ELS group, $p < 0.0001$; and the estimated IL-6 was 2.387 pg/mL [SE 0.385] higher in the High ELS group than the Low ELS group, $p < 0.0001$). Anti-inflammatory IL-13 was lower in the High ELS group (estimated group difference 0.975 pg/mL, SE 0.385, $p = 0.012$). No significant differences were detected between High and Low ELS groups with respect to CRP, LBP, MCP-1, or other cytokines.

Table 1
Participant demographic and clinical variables, concomitant medications, and medical history. ELS: early life stress; SUD: substance use disorder; PTSD: posttraumatic stress disorder.

	Total Sample N (%) N = 21 (100 %)	Low ELS N (%) N = 11 (52.4 %)	High ELS N (%) N = 10 (47.6 %)	p-value
ELS events median [range] [1] Scale range: 0-24	3 [0–13]	3 [0–3]	8.5 [4–13]	**<0.001**
Crime-related events[2]	8 (38.1)	1 (9.1)	7 (70.0)	**0.008**
Sexual abuse[2]	10 (47.6)	3 (27.3)	7 (70.0)	0.086
Physical abuse[2]	16 (76.2)	8 (72.7)	8 (80.0)	1
Serious accident/ natural disaster/ illness/injury to self[2]	9 (42.9)	2 (18.2)	7 (70.0)	**0.030**
Witness to death/ injury/serious illness of another[2]	12 (57.1)	3 (27.3)	9 (90.0)	**0.008**
Demographic				
Age (years) mean (SD)[c]	39.5 (10.3)	40.9 (13.0)	37.9 (6.6)	0.516
Sex[b]				0.635
Male	16 (76.2)	9 (81.8)	7 (70.0)	
Female	5 (23.8)	2 (18.2)	3 (30.0)	
Race[b,d]				**0.0468**
Black	9 (42.9)	7 (63.6)	2 (20.0)	
White	11 (52.4)	3 (27.3)	8 (80.0)	
Other	1 (4.8)	1 (9.1)	0 (0)	
Ethnicity[b]				0.476
Non Hispanic or Latino	20 (95.2)	11 (100)	9 (90.0)	
Declined to answer	1 (4.8)	0 (0)	1 (10.0)	
Clinical				
BMI mean (SD)[c]	28.1 (5.9)	26.9 (5.2)	29.4 (6.5)	0.335
Buprenorphine daily dosage (mg) median [range] [a,c]	16 [8–24]	16 [8–24]	18 [8–24]	0.183
Buprenorphine duration (years) median [range] [a,3,e]	1.7 [0.1–5.9]	0.46 [0.1–5.8]	1.8 [0.1–5.9]	0.853
Current tobacco smoking status[b]				1
Yes	17 (81.0)	9 (81.8)	8 (80.0)	
No	4 (19.0)	2 (18.2)	2 (20.0)	
Nicotine replacement therapy[b]				0.0902
Yes	3 (14.3)	0 (0)	3 (30.0)	
No	18 (85.7)	11 (100)	7 (70.0)	
Comorbid SUD (any)[b]				0.395
Yes	11 (52.4)	7 (63.6)	4 (40.0)	
No	10 47.6)	4 (36.4)	6 (60.0)	
Type of comorbid SUD (sub-sample n = 11)[f]				
Alcohol use disorder	3 (27.3)	2 (28.6)	1 (25.0)	
Cannabis use disorder	5 (45.5)	3 (42.9)	2 (50.0)	
Stimulant use disorder	7 (63.6)	4 (57.1)	3 (75.0)	
Psychiatric comorbidity (any)[b]				0.361
Yes	14 (66.7)	6 (54.5)	8 (80.0)	
No	7 (33.3)	5 (45.5)	2 (20.0)	
Type of psychiatric comorbidity (sub-sample n = 14)[f]				
Mood disorder	10 (71.4)	5 (83.3)	5 (62.5)	
Anxiety disorder	2 (14.3)	1 (16.7)	1 (12.5)	
Personality disorder	2 (14.3)	2 (33.3)	4 (50.0)	
Psychotic disorder	1 (7.1)	0 (0)	1 (12.5)	
Concomitant Medications and Medical History				
Psychiatric medication (any)[b]				0.387
Yes	8 (38.1)	3 (27.3)	5 (50.0)	
No	13 (61.9)	8 (72.7)	5 (50.0)	
Type of psychiatric medication (sub-sample n = 8)[f]				
SSRI	4 (50.0)	1 (33.3)	3 (60.0)	
DA agonist	1 (12.5)	0 (0)	1 (20.0)	
Antipsychotic	3 (37.5)	1 (33.3)	2 (40.0)	
NDRI	1 (12.5)	1 (33.3)	0 (0)	
Stimulant	1 (12.5)	0 (0)	1 (20.0)	
Other concomitant medications (any)[b]				0.395
Yes	10 (47.6)	4 (36.4)	6 (60.0)	
No	11 (52.4)	7 (63.6)	4 (40.0)	
Type of concomitant medication (sub-sample n = 10)[f]				
Cholesterol	2 (20.0)	2 (50.0)	0 (0)	
Antihypertensive	3 (30.0)	2 (50.0)	1 (16.7)	
Diabetes	1 (10.0)	1 (25.0)	0 (0)	
Anticoagulant	1 (10.0)	0 (0)	1 (16.7)	
Anti-inflammatory	3 (30.0)	0 (0)	3 (50.0)	
Acetaminophen	1 (10.0)	0 (0)	1 (16.7)	
Gabapentin	2 (20.0)	1 (25.0)	1 (16.7)	
Antihistamine	3 (30.0)	1 (25.0)	2 (33.3)	
Gastrointestinal	2 (20.0)	1 (25.0)	1 (16.7)	
Genitourinary	1 (10.0)	1 (25.0)	0 (0)	
Hormonal contraceptive	1 (10.0)	1 (25.0)	0 (0)	
Dietary supplement	1 (10.0)	0 (0.0)	1 (16.7)	
Past medical history (any)[b]				0.149
Yes	15 (71.4)	6 (54.5)	9 (90.0)	
No	6 (28.6)	5 (45.5)	1 (10.0)	
Type of medical history (sub-sample n = 15)[f]				
HCV	6 (40.0)	2 (33.3)	4 (44.4)	
Pulmonary	3 (20.0)	1 (16.7)	2 (22.2)	
Cardiovascular	6 (40.0)	3 (50.0)	3 (33.3)	
Endocrine	2 (13.3)	1 (16.7)	1 (11.1)	
Musculoskeletal	3 (20.0)	1 (16.7)	2 (22.2)	
Chronic pain	3 (20.0)	1 (16.7)	2 (22.2)	
Autoimmune	1 (6.7)	0 (0)	1 (11.1)	
Neurological	1 (6.7)	0 (0)	1 (11.1)	
Hematologic	1 (6.7)	0 (0)	1 (11.1)	
Gastrointestinal	2 (13.3)	0 (0)	2 (22.2)	
Genitourinary	2 (13.3)	1 (16.7)	1 (11.1)	

[a] Independent samples median test used to assess difference between high and low ELS.
[b] Fisher's exact test used to assess difference between participants of high and low ELS.
[c] Unpaired *t*-test used to assess difference between participants of high and low ELS.
[d] Participants could self-identify as White, Black, American Indian, Alaskan Native, Asian/Pacific Islander, Hispanic-Mexican, Hispanic-Puerto Rican, Hispanic-Cuban, or Other.
[e] Based on participant-reported estimated buprenorphine start date.
[f] individuals could have >1 type, so totals can be >100 %.

3.4. Inflammatory markers by timepoint

Averaged across ELS groups, IL-6 was significantly elevated at the end of the day (4:00 p.m., $p < 0.001$) compared to the morning (7:00 a.m. or 10:00 a.m.). This is consistent with clinical evidence of diurnal IL-6 patterns in the context of ELS (Hori et al., 2022). Additionally, IL-8 was significantly elevated during mid-morning (10:00 a.m., $p = 0.01$) compared to the early morning (7:00 a.m., Fig. S1). This result aligns with a previous study finding that IL-8 peaks a few hours after wake (Rahman et al., 2015). No other cytokines tested exhibited significant differences across timepoints.

3.5. Neurofunctional measures by ELS group

Participant scores on neurofunctional measures of reward, cognition, negative emotionality, interoception, metacognition, and sleep are shown in Table 2. When applicable, instrument sub-scale scores are also reported. Scores on the PSQI were high, due to the inclusion criteria of the parent study. There were no significant differences between ELS groups on any of the neurofunctional endpoints.

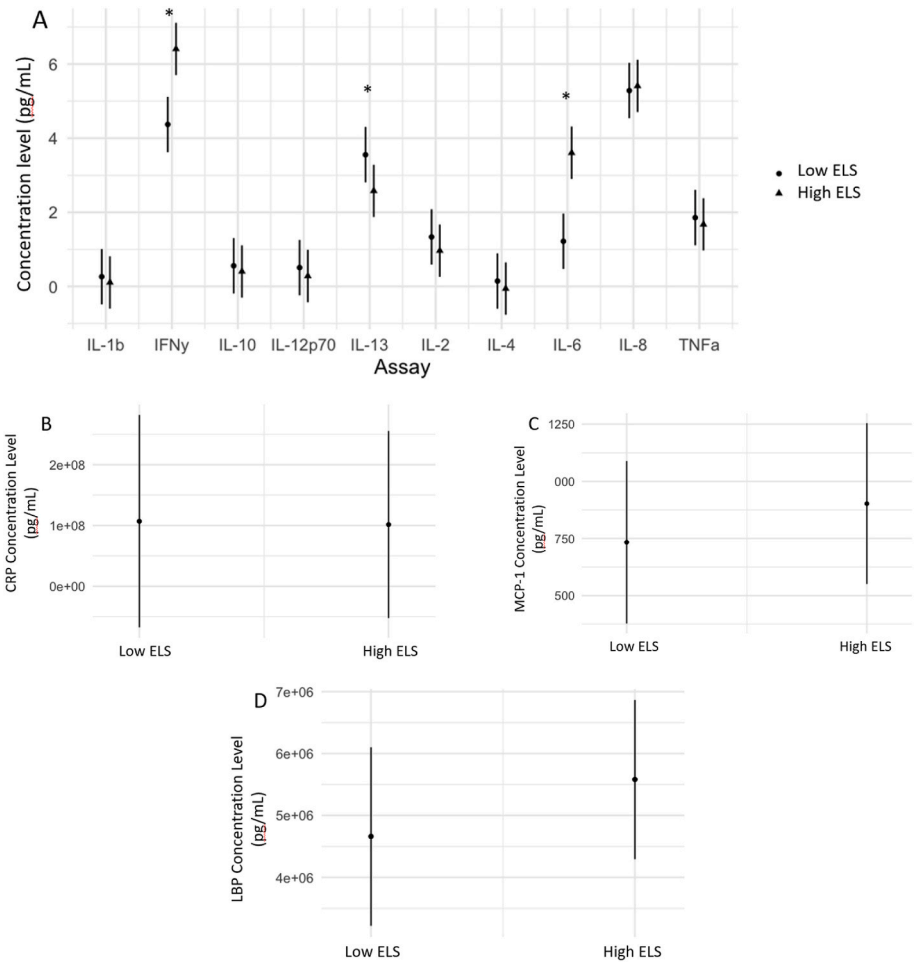

Fig. 1. Inflammatory markers by ELS groups. A) cytokine panel, B) CRP, C) MCP-1, D) LBP. Points represent group mean, adjusted for age, sex, and BMI. Bars represent 95 % confidence intervals. *Significant difference between ELS groups ($p < 0.05$). High ELS n = 10, 7M/3F; Low ELS n = 11, 9M, 2F.

4. Discussion

This study sought to identify ELS-associated differences in inflammation and neurocognition amongst individuals maintained on buprenorphine treatment for OUD. There were two main findings.

First, we found that amongst a clinical sample of buprenorphine-stabilized OUD patients, there are inflammatory differences between individuals of high and low ELS exposure that are evident in adulthood and after stabilization in MOUD treatment. Specifically, we found that individuals with high ELS exposure (i.e., experience of >3 traumatic events on the THQ) had higher peripheral levels of pro-inflammatory IFNγ and IL-6, and lower anti-inflammatory IL-13 levels compared to individuals with low ELS exposure (i.e., experience of ≤3 traumatic events on the THQ). These results provide preliminary evidence towards extending previous findings of an ELS-associated pro-inflammatory state among people with OUD (Wei et al., 2020), the general population (Baumeister et al., 2016; Coelho et al., 2014; Levine et al., 2015; Nemeroff, 2016) and an alcohol use disorder population (Kirsch et al., 2024a) to our clinically-relevant OUD treatment population engaged in medication treatment with buprenorphine. These results indicate that ELS is associated with biological endpoints that are not easily and immediately observable to researchers or medical professionals. A practical research implication of this result is that comprehensive social and environmental histories should be included as part of routine assessment when patients enter clinical trials for OUD. Inclusion of these additional variables, such as ELS, would allow for further analysis of sub-populations in pursuit of a personalized medicine approach.

Second, we did not identify distinct neurocognitive differences by ELS status in this patient population. This may be attributable to the fact that these patients were stabilized on buprenorphine treatment (median 1.4 years on buprenorphine) and maintenance on MOUD may mitigate ELS-associated neurofunctional differences such as delay discounting (Landes et al., 2012) and executive function (Mindt et al., 2022). A future study in a population of patients with OUD who are not in treatment might uncover ELS-associated neurocognitive differences. This may be especially likely in the domain of negative emotionality, given that a recent study of individuals with un-treated alcohol use disorder found that greater ELS was associated with greater negative emotionality (Kirsch et al., 2024a). Several other studies in the general population have also found that a greater number of ELS events is associated with greater depressive symptoms in adulthood (Anda et al., 2005; Chapman et al., 2004; Lee and Chen, 2017; Merrick et al., 2017).

These results and implications should be considered in light of several study limitations. Primarily, this study did not have a matched control group to allow for comparisons isolating the potential effect of buprenorphine and/or OUD history on these inflammatory and neurofunctional markers. Inclusion of these control groups in future studies would allow for conclusions that begin to isolate associations of buprenorphine, OUD history, and ELS history with these endpoints. Additionally, this is an exploratory study in a small sample of participants who were predominantly male. Given the known sex differences in biological responses to stress (Stadtler and Neigh, 2023), sex differences in addiction-related behaviors following ELS (Rincon-Cortes, 2023), and that sex may moderate the effects of ELS on peripheral inflammation in

Table 2
Participant neurofunctional measures.

	Total Sample Mean (SD) N = 21 (100 %)	Low ELS Mean (SD) N = 11 (52.4 %)	High ELS Mean (SD) N = 10 (47.6 %)	p-value[a]
Reward				
SUPPS-P [subscale range: 4–16]				
Negative Urgency	9.62 (2.64)	9 (2.68)	10.3 (2.54)	0.270
Lack of Premeditation	6.33 (1.98)	5.64 (1.75)	7.10 (2.03)	0.091
Lack of Perseverance	5.95 (2.01)	5.82 (1.8)	6.10 (2.28)	0.757
Sensation Seeking	10.48 (2.32)	10.64 (2.06)	10.30 (2.67)	0.749
Positive Urgency	7.48 (2.6)	7.09 (2.55)	7.90 (2.73)	0.491
Cognition				
Delay Discounting (ED50)[b]	117.8 (116.6)	137.8 (150)	102.3 (88.41)	0.563
Negative Emotionality				
PROMIS-D[c]	58.54 (5.85)	58.15 (6.46)	58.97 (5.42)	0.756
PROMIS-A[c]	57.65 (6.38)	56.62 (6.66)	58.78 (6.20)	0.452
Buss Perry Aggression Questionnaire				
Total score [range: 29–145]	75.48 (15.27)	73.45 (16.98)	77.70 (13.69)	0.538
Physical aggression [range: 9–45]	22.24 (6.02)	23.00 (5.85)	21.40 (6.42)	0.557
Verbal aggression [range: 5–25]	14.81 (4.25)	13.91 (4.85)	15.80 (3.46)	0.321
Anger [range: 7–35]	15.90 (4.69)	14.82 (4.54)	17.10 (4.80)	0.276
Hostility [range: 8–40]	22.52 (4.34)	21.73 (4.34)	23.40 (4.60)	0.402
Distress Tolerance Scale[d] [subscale range: 1–5]				
Global	3.37 (0.73)	3.43 (0.69)	3.31 (0.80)	0.732
Tolerance	3.51 (0.86)	3.57 (0.72)	3.44 (1.03)	0.766
Absorption	3.40 (0.97)	3.63 (0.82)	3.15 (1.09)	0.287
Appraisal	3.49 (0.72)	3.53 (0.64)	3.44 (0.83)	0.796
Regulation	3.07 (1.03)	2.97 (1.21)	3.19 (0.85)	0.659
Interoception				
MAIA [subscale range: 0–5]				
Noticing	3.69 (1.11)	3.91 (1.20)	3.45 (1.00)	0.355
Not Distracting	1.92 (0.88)	1.91 (1.03)	1.93 (0.73)	0.952
Not Worrying	3.06 (0.93)	3.15 (1.02)	2.97 (0.88)	0.662
Attention Regulation	3.25 (1.20)	3.27 (1.44)	3.23 (0.94)	0.935
Emotional Awareness	3.63 (1.17)	3.64 (1.48)	3.62 (0.77)	0.975
Self-Regulation	3.15 (1.32)	2.93 (1.72)	3.4 (0.70)	0.432
Body Listening	2.40 (1.33)	2.27 (1.71)	2.53 (0.79)	0.665
Trusting	3.84 (1.22)	4.27 (1.10)	3.37 (1.21)	0.089
Metacognition				
MCQ-30 [subscale range: 6–24]				
Total [range: 30–120]	63.52 (14.78)	63.00 (14.90)	64.10 (15.43)	0.870
Lack of Cognitive Confidence	9.90 (3.46)	8.64 (2.42)	11.30 (4.00)	0.077
Positive Beliefs about Worry	9.43 (4.26)	9.64 (4.27)	9.20 (4.47)	0.822
Cognitive Self-Consciousness	17.62 (4.85)	18.18 (4.75)	17.00 (5.14)	0.590
Negative Beliefs about Uncontrollability	12.86 (4.77)	12.73 (4.13)	13.00 (5.62)	0.900
Danger				
Need to Control Thoughts	13.71 (4.19)	13.82 (4.60)	13.60 (3.92)	0.909
Sleep				
PSQI [subscale range: 0–3]				
Global [range: 0–21]	9.52 (2.44)	9.36 (2.06)	9.70 (2.91)	0.761
Subjective sleep quality	1.71 (0.85)	1.82 (0.75)	1.60 (0.97)	0.568
Sleep latency	1.57 (0.87)	1.82 (0.75)	1.30 (0.95)	0.179
Sleep duration	1.95 (1.20)	2.09 (1.14)	1.80 (1.32)	0.593
Sleep efficiency	2.10 (1.38)	1.64 (1.57)	2.60 (0.97)	0.110
Sleep disturbance	1.01 (0.22)	1.00 (0.00)	1.10 (0.32)	0.306
Use of sleep medication	0.14 (0.48)	0.18 (0.60)	0.10 (0.32)	0.706
Daytime dysfunction	1.00 (0.78)	0.82 (0.87)	1.2 (0.63)	0.270

[a] Unpaired *t*-test used to assess difference between participants of high and low ELS.
[b] N = 16 (low ELS: n = 7; high ELS n = 9). Participants with R squared <0 excluded from analysis.
[c] t-score.
[d] N = 19 (low ELS: n = 10; high ELS n = 9).

adults with alcohol use disorder (Kirsch et al., 2024b), future studies in OUD treatment populations should be adequately powered to detect for sex differences in these inflammatory and neurofunctional endpoints. Also due to the small sample size, sub-analyses were not performed according to the type of ELS experienced. Such sub-analyses may be important to include in future studies given the literature suggesting that different types of ELS (e.g., abuse vs. neglect or physical vs. psychological trauma) may be associated with different inflammatory (Brown et al., 2021; Pereira et al., 2019) and neurocognitive (Lee and Chen, 2017) outcomes. Measures such as the ACEs (Felitti et al., 1998) or Childhood Trauma Questionnaire (Bernstein et al., 1994) would be better suited than the THQ to capture these common domains of ELS and enhance the generality of findings. Finally, the current study did not robustly evaluate whether different inflammatory profiles and/or experiences of ELS were associated with OUD treatment outcomes. Although we do report that the duration of time on buprenorphine was similar between High and Low ELS groups, evaluation of additional OUD treatment and health outcomes such as return to use, opioid overdoses, recovery capital, mortality, years of life lost, or engagement with additional support services is not reported. Subsequent related investigations incorporating these measures may help identify disparities in treatment outcomes and ultimately support equity and patient-centeredness in OUD medication development efforts.

Overall, results of this study suggest that evaluation of a patient's

stress history and inflammatory profile may lead to advancements in precision medicine in OUD treatment. This is a promising area of future research, as a 12-week prospective study found that lower IL-6 levels were associated with better methadone maintenance outcomes (Lu et al., 2019). Thus, evidence of elevated pro-inflammatory cytokines such as IL-6 may be linked to increased craving, propensity for return to use, or inconsistencies in treatment receipt. This knowledge could help researchers devise study protocols investigating personalized treatment plans for OUD patients informed by ELS histories, such as via evaluating how adjunctive treatments to buprenorphine (e.g., medications, behavioral therapies) improve OUD treatment and recovery outcomes.

CRediT authorship contribution statement

Madison M. Marcus: Writing – review & editing, Writing – original draft, Formal analysis. **Tiffany Pignatello:** Investigation, Data curation. **Paul Howell:** Writing – review & editing, Investigation, Data curation. **Shanshan Chen:** Writing – review & editing, Formal analysis. **F. Gerard Moeller:** Resources, Funding acquisition. **Gretchen N. Neigh:** Writing – review & editing, Resources, Funding acquisition, Conceptualization. **Caitlin E. Martin:** Writing – review & editing, Funding acquisition, Conceptualization.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Virginia Commonwealth University (NCT04818086, HM20021136).

Funding

Funding for this study was provided by the VCU Breakthrough Grant, National Institute on Drug Abuse (UG1DA050207 to FGM) and the National Center for Advancing Translational Sciences (UM1TR004360 to FGM). Dr. Martin is supported by K23DA053507 and R01DA059483. Drs. Marcus and Martin are supported by R34DA058494.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to thank the study participants for contributing to this research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2025.101078.

Data availability

De-identified data are potentially available upon request to the principal investigator.

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