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REGULAR RESEARCH ARTICLE

Association Between Inflammatory Cytokines, Executive Function, and Substance Use in Patients With Opioid Use Disorder and Amphetamine-Type Stimulants Use Disorder

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Abstract

Background: Long-term opioid and amphetamine-type stimulants (ATS) abuse may affect immunological function and impair executive function. We aimed to determine whether biomarkers of inflammation and executive function were associated with substance use in individuals with opioid use disorder (OUD) and ATS use disorder (ATSUD). The interactions between these biomarkers were also explored.

Methods: We assessed plasma cytokines [tumor necrosis factor (TNF)-α, C-reactive protein (CRP), interleukin (IL)-8, IL-6, transforming growth factor (TGF)-β1, brain-derived neurotrophic factor (BDNF), and executive function in terms of the Wisconsin Card Sorting Test (WCST) and Continuous Performance Test (CPT) in OUD and ATSUD patients and healthy controls (HC). OUD and ATSUD patients were followed for 12 weeks, and their urine morphine and amphetamine tests, cytokine levels, and executive function were repeatedly measured.

Results: We enrolled 483 patients and 145 HC. Plasma TNF-α, CRP, IL-8, IL-6, and BDNF levels and most subscale scores on the WCST and CPT significantly differed between OUD and ATSUD patients and HC. Increased TNF-α levels and more

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Significance Statement

Opioid and amphetamine-type stimulants abuse may affect immunological function and impair executive function. In the current study, we found that patients with opioid use disorder (OUD) and amphetamine-type stimulants (ATS) use disorder (ATSUD) had higher inflammatory markers and worse executive function than those in healthy controls. Higher inflammatory markers and worse executive function were associated with more urinary drug-positive results in OUD and ATSUD patients. Higher inflammatory markers were also associated with worse executive function in OUD and ATSUD patients. Our study is the first study to link the association between inflammatory markers and substance use behavior as well as the association between inflammatory markers and executive function in OUD and ATSUD patients. Further studies on regulating the inflammatory process and enhancing executive function in patients with OUD and ATSUD may be needed.

perseveration error on the WCST were significantly associated with more urine drug-positive results and less abstinence. Plasma IL-6 and CRP levels were significantly negatively correlated with WCST and CPT performance.
Conclusion: OUD and ATSUD patients had more inflammation and worse executive function than HC. Inflammatory markers and WCST performance were associated with their urinary drug results, and higher inflammation was associated with poor executive function. Studies on regulating the inflammatory process and enhancing executive function in OUD and ATSUD are warranted.

Keywords: Opioid use disorder, amphetamine-type stimulants use disorder, brain-derived neurotrophic factor, cytokines, executive function

INTRODUCTION

Opioid and amphetamine-type stimulants (ATS) use is a public health crisis. Although some standardized treatments are available for substance use disorder (SUD), such as methadone maintenance treatment for opioid use disorder (OUD) (Soyka et al., 2011) or the MATRIX model for ATS use disorder (ATSUD) (Rawson et al., 2004), the outcomes vary in different patients. Notably, only limited percentages of patients completed the treatment program and achieved remission from substance use behavior (Rawson et al., 2004; Hser et al., 2016). The complexity of the etiology for addictive disorders may account for the modest effect size in treating SUD. Moreover, the clinical heterogeneity of patients with OUD and ATSUD may also be related to the limited treatment response in the current clinical addiction treatment model (Kwako et al., 2016). Identifying addiction biomarkers will have significant improvement in treatment approaches for OUD and ATSUD (Milivojevic and Sinha, 2018). Biomarkers for addiction could be any indicators of vulnerability, association with etiologic process, or presence of a DSM-defined addictive disorder (Kwako et al., 2018). In the current study, we investigated biomarkers potentially correlated with OUD and ATSUD from the perspectives of the inflammatory process and executive function.

Classical theory of addiction suggests that the molecular mechanisms of reward produced by drugs of abuse produce elevated signaling of the mesolimbic dopamine reward pathway and present as a rewarding and reinforcing drive (Volkow et al., 2016). By contrast, during withdrawal stage, the dopaminergic transmission in the nucleus accumbens decreased (Weiss et al., 1992). While at the preoccupation and anticipation stage, cue-associated craving increased dopamine release in the striatum (Koob and Volkow, 2010). Moreover, the neuroimmune system may havea complex interaction with dopamine function. Recent studies showed that astrocytes, which regulate inflammation in the central nervous system, are active components of dopaminergic signaling in the reward system and mediate dopamine- and amphetamine-evoked synaptic regulation and amphetamine-induced locomotor effects (Sofroniew, 2015; Corkrum et al., 2020). In addition, direct injection of astrocyte-conditioned medium containing cytokines and chemokines into the nucleus accumbens in mice may cause more preference for methamphetamine- or morphine-paired place than in mice injected with control medium (Narita et al., 2006). Attenuators of proinflammatory glial activation could block methamphetamine- and morphine-induced conditioned place preference (Narita et al., 2006), and morphine-induced elevations of dopamine in the nucleus accumbens (Bland et al., 2009). Some researchers also suggested that larger doses and long-term substance use were associated with immune system dysregulation, which damages neurons and triggers additional glial cells to increase the release of proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, C-reactive protein (CRP), and interleukin (IL)-6 (Coller and Hutchinson, 2012), and to decrease the release of anti-inflammatory cytokines, such as transforming growth factor (TGF)-β1 (Nabati et al., 2013; Lu et al., 2017). However, other data suggested administration of opioids may suppress the immune system (Eisenstein, 2019). Therefore, it is important to investigate whether inflammation correlates with substance use behavior.

The Impaired Response Inhibition and Salience Attribution model has been proposed to explain the underlying neurocognitive mechanisms for addition (Goldstein and Volkow, 2002). In this model, despite the mesolimbic dopamine circuit, which has been traditionally associated with the acute reinforcing effects of a drug, frontal lobe dysfunction is also involved in various aspects of addiction, including reinforcing responses to drugs during intoxication, activation during craving, and deactivation during withdrawal (Goldstein and Volkow, 2002). Therefore, addiction is associated with poorer top-down cognitive control of behavior (executive functions), which eventually impacts key stages of the addictive cycle and psychosocial and treatment outcomes (Dominguez-Salas et al., 2016). Systematic reviews and meta-analyses have established the link between substance use and impairment of executive function in various classes of SUD, including methamphetamine and opioids (Baldacchino et al., 2012; Dean et al., 2013).

Executive functions, such as sustained attention, response inhibition, cognitive flexibility, and decision-making, are higher-order processes critical to achieve successful goal-directed behavior in addiction treatment (Blume and Marlatt, 2009) and have been associated with treatment adherence and relapse in SUD (Dominguez-Salas et al., 2016). In addition, to better classify patients with SUD, some researchers proposed the model of Addictions Neuroclinical Assessment (Kwako et al., 2016). In the model, executive function is one of the major neuropsychological domains and is used as an indicator to stratify patients (Kwako et al., 2016). Thus, we hypothesized that executive function may be a potential biomarker that predicts outcomes of OUD and ATSUD.

Moreover, neuroimmune factors also play a critical role in perpetuating substance-induced neuronal injury and cognitive function impairment. Neuroinflammation can impair the neurobiological mechanisms regulating cognitive processes through various possible pathways, including the following: (1) changing the expression and activity of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor and therefore impairing plasticity (Stellwagen et al., 2005), (2) inhibiting long-term potentiation and plasticity (Murray and Lynch, 1998; Tancredi et al., 2000), (3) dysregulating the tryptophan-kynurenine pathway (Andre et al., 2008), (4) impairing neurotrophin metabolism (Tong et al., 2012), and (5) dysregulating the HPA axis (Pace and Miller, 2009). Immune system dysregulation is involved in cognitive alterations across psychiatric diseases, ranging from mood disorder and schizophrenia to posttraumatic stress disorder (Fourrier et al., 2019). However, few studies have investigated the association between cognitive dysfunction and neuroinflammation in human studies of SUD. Our previous study found that TNF-α and IL-6 levels were negatively correlated with visual and verbal memory performance in patients with OUD (Wang et al., 2018). Therefore, we hypothesize that the biomarkers of inflammation and executive function may also be intercorrelated with each other in OUD and ATSUD.

In the current study, we aimed to investigate whether inflammatory markers and executive functions are biomarkers related with substance use severity. We first tested the hypothesis that these biomarkers are different between OUD and ATSUD patients and healthy controls (HC) and then explored the association of these biomarkers with substance use. The association between inflammatory markers and executive function was also investigated.

METHODS

Patients

The research protocol was approved by the Institutional Review Board for the Protection of Human Subjects at National Cheng Kung University Hospital (NCKUH). The study was performed in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki. The procedures were completely explained to each participant before they were asked to sign the informed consent form. OUD and ATSUD patients were recruited from the NCKUH addiction treatment clinics. This study is a subgroup analysis of clinical trials (trial registration: NCT01189097, NCT01189214, and NCT03729128 at https://register.clinicaltrials.gov/), which evaluated the effects of add-on dextromethorphan/memantine for 12 weeks on patients with OUD or ATSUD. Patients with opioid dependence were also undergoing methadone maintenance therapy. Each patient was initially interviewed and diagnosed by a board-certified psychiatrist (author T.-Y.W.) and then screened by a research team member well trained in using the DSM-IV (American Psychiatric Association, 2000) criteria and the Chinese Version of the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). The MINI was used because completing 4–6 hours of structured interviews, such as the Chinese Version of the Modified Schedule of Affective Disorder and Schizophrenia-Lifetime (Endicott and Spitzer, 1978), is difficult for OUD and ATSUD patients. The MINI has good reliability and has been widely used in clinical trials and epidemiological studies (Ritchie et al., 2004), and its interrater reliability in the Chinese version was approximately 0.75 in previous studies (Kuo et al., 2003). The inclusion criteria were as follows: adult males or females between 18 and 65 years old who met the DSM-IV criteria for current opioid abuse/dependence or ATS abuse/dependence. The exclusion criteria were as follows: having a cognitive disorder, being pregnant or nursing an infant, having taken any anti-inflammatory medications within 1 week before the study, and having a history of 1 or more uncontrolled major physical conditions, such as diabetes mellitus or hypertension. Patients with other psychiatric comorbidities, such as anxiety, depression, alcohol use disorder, and antisocial personality disorder, were not excluded from the study.

HC were volunteers recruited from the community. The Chinese Version of the Modified Schedule of Affective Disorder and Schizophrenia-Lifetime (Endicott and Spitzer, 1978; Huang et al., 2004) was used to screen their psychiatric conditions. All controls were free of present and past mental illness, including substance abuse/dependence disorder, and none had a family history of psychiatric disorder among their first-degree relatives.

We followed the OUD and ATSUD patients for 12 weeks. Their plasma TNF-α, CRP, IL-8, IL-6, TGF-β1, and brain-derived neurotrophic factor (BDNF) levels were measured at baseline and at weeks 1, 4, 8, and 12. Urinary morphine and amphetamine tests were also examined at the same timepoints. Executive function was assessed using the Wisconsin Card Sorting Test (WCST) and Conners' Continuous Performance Test (CPT) at baseline and week 12. Plasma TNF-α, CRP, IL-8, IL-6, TGF-β1, and BDNF levels and executive function were examined cross-sectionally in HC.

Blood Samples and Cytokine Analysis

The fasting blood samples were collected between 8:00 and 10:00 AM in each participant. After 20 mL of blood was drawn from each participant, the plasma was isolated from the whole blood by centrifugation at 3000 *g* for 15 minutes at 4°C. Then blood was immediately stored at –80°C. TNF-α, CRP, IL-8, IL-6, TGF-β1, and BDNF levels were quantified using an antibody pair assay system (Flexia; BioSource Intl., Camarillo, CA, USA). All laboratory procedures were double-blind, and all assays were performed in duplicate.

Executive Function Assessment

The WCST measures the domains of executive function in categorization, abstraction, reasoning, maintaining sets, set switching, strategic planning, and modulating impulsive responding (Heaton et al., 1993). The interrater liability is 0.88–0.93, within-rater reliability is 0.91–0.96, and test-retest reliability is 0.57. Performance on the WCST was scored in terms of the total number of errors (TNE), perseverative errors (PE), number of categories completed (NCC), trials to complete the first category (TCC), and conceptual level responses (CL).

The CPT (Conners and Sitarenios, 2000) was used to assess the maintenance of focused attention and inhibitory control, which is also a part of executive function (Dominguez-Salas et al., 2016). An adequate level of arousal combined with executive control to resist distraction and inhibit responses to stimuli resembling targets is required to perform correctly. Participants were asked to press the space bar on a computer keyboard when any letter other than "'X'" appeared. The interstimulus intervals were 1, 2, and 4 seconds, and the display time was 250 milliseconds. The CPT produces a standard set of performance measures that include the number of errors of omission and errors of commission: (1) errors of omission occurred when the patient did not respond to the target stimulus; (2) errors of commission occurred when the patient responded to a nontarget (X) stimulus; (3) hit reaction time (HRT) represents the mean response time (milliseconds) for all target responses over the full 6 trial blocks; and (4) HRT standard error (SE) represents the consistency of response times and expresses the SE response to targets (Chang et al., 2015). The split-half reliability is 0.66–0.95, and the test-retest reliability after 3 months is 0.55–0.84. The CPT has good reliability and validity for Han Chinese living in Taiwan (Hsieh et al., 2005).

Statistical Analysis

Pearson χ^2 analysis was used to examine the categorical variables. Fisher's exact test was substituted for the χ^2 test when values were smaller than expected (<5). We used a *t* test to examine the continuous variables. Because cytokine and BDNF levels were erratically distributed and showed a significant level of positive skew, arithmetic transformations were used to produce normal distributions for further analysis: log (x + 1) was used for cytokine levels. Multivariate analysis of covariance (MANCOVA) was used to compare biomarkers in the SUD and HC groups. For data with repeated measurements, the generalized estimating equation (GEE) method (Zeger et al., 1988) was used for multiple linear regression in repeated-measures analyses that accommodate randomly missing data (Shen and Chen, 2012). We used GEE analysis to investigate the correlations of changes in plasma cytokine and BDNF levels and substance use severity. Potential prognostic factors, such as age, sex, education, treatment with add-on dextromethorphan or memantine, disease duration, psychiatric comorbidities, and treatment duration (from baseline to week 12), were controlled. The substance use severity was defined by the urinary morphine and amphetamine test results. The abstinence group was defined as those who had zero samples of urinary morphine- and amphetamine-positive results and completed the 12 weeks of follow-up. Significance was set at $P < .05$. SPSS 18.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

RESULTS

We recruited 483 patients with OUD and ATSUD and 145 HC, and 337 OUD and ATSUD patients and 142 HC completed executive function assessments (Table 1). We excluded 6 patients in the analysis of the CPT because they did not pay attention to the task, with extreme values of omission T-score (O-TS). The positive rate of urine opioid or amphetamine tests was 70.3% (282 urine samples were positive results in a total 401 urine samples) in OUD and ATSUD patients (Table 1). Most of them mainly used opioids (82.6%); however, 37.9% of patients (n = 183) reported combined opioid and ATS use. Compared with HC, OUD and ATSUD patients were older, were more likely to be male, and had fewer years of education (Table 1). Most of the biomarkers (unadjusted raw data) of cytokines and BDNF levels and executive function significantly differed between the patients and HC groups (Table 1).

We used MANCOVA to control for possible confounding factors, and the results are shown in Figures 1 to 3. An overall multivariate effect of the diagnostic group for baseline cytokines and BDNF levels was noted (Pillai's V = 0.29, $F_{[6,619]} = 43.00$, $P < .001$). In general, the OUD and ATSUD patients had higher levels of proinflammatory markers and lower levels of BDNF than HC (Figure 1). The log TNF-α ($P < .001$), log CRP ($P < .001$), log IL-8 ($P < .001$), and log IL-6 levels ($P < .001$) were significantly higher, and log BDNF levels ($P < .001$) were significantly lower in OUD and ATSUD patients than those in HC (Figure 1). An overall multivariate effect of the diagnostic group for baseline WCST (Pillai's V = 0.07, $F_{[5,378]} = 5.58$, $P < .001$) and CPT (Pillai's V = 0.08, $F_{[4,392]} = 8.00$, $P < .001$) was also found. Overall, the OUD and ATSUD patients performed worse than HC on the WCST and CPT. Figure 2 shows that the OUD and ATSUD patients had significantly higher scores in TNE ($P = .03$) and PE ($P = .03$) and lower scores in NCC ($P < .001$) and CL ($P = .009$) than HC did on the WCST. The OUD and ATSUD patients had significantly higher scores of omission T-score (O-TS) ($P < .001$), commission T-score (C-TS) ($P = .002$), and HRT standard error T-score (HRT SE-TS) ($P < .001$) than HC did on the CPT (Figure 3).

Then we corrected for multiple possible confounding factors (age, sex, years of education, psychiatric comorbidity, duration of substance use and treatment, and treatment groups). GEE analysis showed the association between urinary morphine and amphetamine test results and changes in biomarkers in patients with OUD and ATSUD during 12 weeks of follow-up. Because approximately 40% of patients combined opioid and ATS use and 14.8% of urine samples had both positive results in morphine and amphetamine, we counted the urine positive test for either morphine- or amphetamine-positive results. Baseline PE in WCST and baseline plasma log TNF-α levels were significantly positively correlated with urinary morphine- and amphetamine-positive results ($P = .03$ and .01, respectively; Table 2). Repeated measurements of the plasma log TNF-α levels during the 12 weeks of follow-up were also associated with urinary morphine- and amphetamine-positive results ($P = .03$; Table 2). The abstinence group had significantly lower baseline log TNF-α levels than the relapse group ($P = .04$; Table 3). However, baseline executive functions were not associated with the state of abstinence.

Table 4 shows the correlation between baseline cytokine and BDNF levels and executive function in all participants. In general, increased inflammatory cytokine levels, such as TNF-α, CRP, IL-8, and IL-6, and decreased BDNF levels were correlated with poor executive function on a variety of subscales of the WCST and CPT. We further used GEE to analyze the association between changes in cytokines and executive functions from baseline to week 12 in OUD and ATSUD participants, controlling for possible confounding factors. We found that changes in log IL-6 levels were positively correlated with PE in WCST ($P = .02$; Figure 4) and TCC in WCST ($P = .01$; Figure 5), and log CRP levels were positively correlated with O-TS in CPT ($P = .05$; Figure 6).

DISCUSSION

We hypothesized that inflammatory markers and executive functions were important biomarkers in OUD and ATSUD. We first demonstrated that these biomarkers, including peripheral TNF-α, CRP, IL-8, IL-6, and BDNF levels and WCST and CPT scores,

Table 1. Demographic Data, Baseline Cytokine Levels, and Executive Function in the OUD and ATSUD Group and HC

Variables	OUD and ATSUD	HC	Statistics	*P*
Case numbers (n)	483	145		
Age (y)	38.2 ± 8.3	32.5 ± 8.4	t = 7.23	<.001**
Sex (male/female)	410/73	79/66	χ^2 = 59.8	<.001**
Education (y)	10.6 ± 2.7 (n = 375)	15.6 ± 1.8	t = 21.0	<.001**
Main substance use class (opioid/amphetamine-type stimulants, n)	399/84	NA		
Duration of substance use (y)	8.1 ± 7.3 (n = 448)	NA		
Urine opioid or amphetamine results (+)/(–)	282/119 (n = 401)	NA		
Psychiatric comorbidity (+/–)	150/321 (n = 471)	NA		
WCST (n)	337	142		
TNE	46.79 ± 21.85	30.28 ± 17.06	8.03	<.001**
PE	26.41 ± 18.55	15.45 ± 10.21	6.63	<.001**
NCC	4.85 ± 2.94	7.54 ± 2.46	–9.55	<.001**
TCC	19.31 ± 16.96	17.67 ± 12.65	1.03	.31
CL	53.01 ± 22.67	71.18 ± 17.55	–8.53	<.001**
CPT(n)	331	142		
O-TS	59.76 ± 29.66	47.70 ± 13.65	4.64	.001*
C-TS	49.87 ± 11.23	48.65 ± 9.59	1.13	.26
HRT-TS	50.24 ± 13.32	45.48 ± 9.48	3.86	<.001**
HRTSE-TS	54.15 ± 15.75	43.22 ± 11.22	7.49	<.001**
Cytokines(n)	483	145		
TNF-α (pg/mL)	3.16 ± 3.09	1.36 ± 1.46	6.79	<.001**
CRP (μg/mL)	2.87 ± 2.77	1.70 ± 1.40	4.89	<.001**
IL-8 (pg/mL)	7.38 ± 15.83	1.99 ± 3.24	4.07	<.001**
IL-6 (pg/mL)	2.52 ± 2.35	1.64 ± 1.68	4.19	<.001**
TGF-β1 (ng/mL)	31.17 ± 18.99	30.73 ± 17.87	0.25	.81
BDNF (ng/mL)	13.99 ± 10.23	18.00 ± 9.57	–4.20	<.001**

Abbreviations: BDNF, brain-derived neurotrophic factor; CL, conceptual level; CPT, Continuous Performance Test; CRP, C-reactive protein; C-TS, commission T-score; HRTSE-TS, HRT standard error T-score; HRT-TS, hit reaction time T-score; IL, interleukin; NCC, number of completed categories; O-TS, omission T-score; PE, perseveration error; TCC, trials to complete the first category; TGF-β1, transforming growth factor-β1; TNE, total number error; TNF-α, tumor necrosis factor α; WCST, Wisconsin Card Sorting Test.
*P < .05; **P < .001.

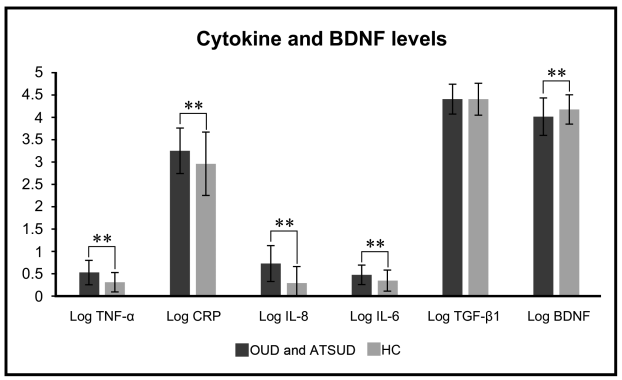

Figure 1. Significant differences in cytokine and BDNF levels between OUD and ATSUD patients and HC by MANCOVA. Covarying for age and sex. *P < .05; **P < .001. Abbreviations: ATSUD, amphetamine-type stimulants use disorder; BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; HC, healthy controls; IL-6, interleukin-6; IL-8, interleukin-8; MANCOVA, multivariate analysis of covariance; OUD, opioid use disorder; TGF-β1, transforming growth factor-β1; TNF-α, tumor necrosis factor α.

significantly differed between individuals with OUD and ATSUD and HC. Then we found that the TNF-α levels and PE in WCST were associated with urinary drug test results and abstinent state, suggesting that inflammatory markers and executive function may be related with their substance use. Finally, we found a significant association between these biomarkers. Increased levels of inflammatory markers and decreased levels of BDNF were associated with a decline in multiple domains of executive function in all participants. More specifically, increased IL-6 and CRP levels were significantly associated with poor performance in WCST and CPT in OUD and ATSUD patients. To the best of our knowledge, the current study was the first to examine the complex association between peripheral inflammation and executive dysfunction and their association with substance use behavior.

Although aberrant inflammatory processes have been linked with many psychiatric disorders (Goldsmith et al., 2016a), studies exploring the relationship between inflammation and addiction are in the beginning stages. Most studies have suggested that inflammation contributes to addiction in animal studies with evidence showing activation of microglia or astrocytes and elevated inflammatory markers in the CNS when using substances

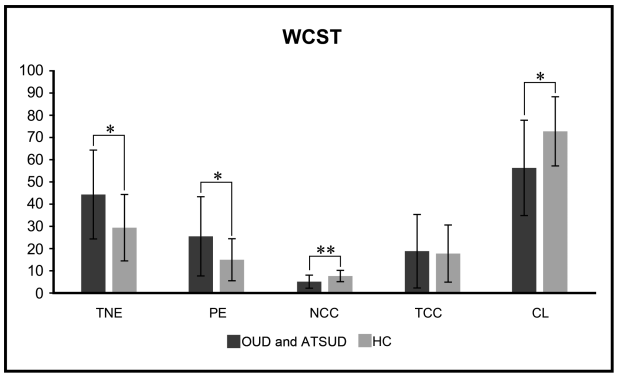

Figure 2. Significant differences in WCST performance between OUD and ATSUD patients and HC by MANCOVA. Covarying for age, sex, and years of education. *P < .05; **P < .001. Abbreviations: ATSUD, amphetamine-type stimulants use disorder; CL, conceptual level; HC, healthy controls; MANCOVA, multivariate analysis of covariance; NCC, number of completed categories; OUD, opioid use disorder; PE, perseveration error; TCC, trials to complete the first category; TNE, total number error; WCST, Wisconsin card sorting test.

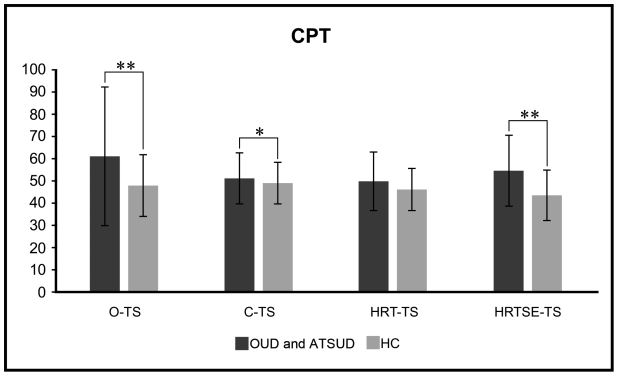

Figure 3. Significant differences in CPT performance between OUD and ATSUD patients and HC by MANCOVA. Covarying for age, sex, and years of education. *P < .05; **P < .001. Abbreviations: ATSUD, amphetamine-type stimulants use disorder; CPT, Continuous Performance Test; C-TS, commission T-score; HC, healthy controls; HRTSE-TS, HRT standard error T-score; HRT-TS, hit reaction time T-score; MANCOVA, multivariate analysis of covariance; O-TS, omission T-score; OUD, opioid use disorder.

(Coller and Hutchinson, 2012). Compared with the CNS, peripheral inflammatory markers are easier to assess, but whether peripheral inflammation could contribute to the etiology and progression of SUD is controversial. However, a recent large meta-analysis containing 5649 patients with SUD and 4643 HC showed that people with SUD have higher peripheral concentrations of IL-6, IL-8, TNF-α, and CRP (Wei et al., 2020). Although many studies have investigated the association between inflammatory markers and SUD, most studies were cross-sectional and rarely linked the severity of inflammation and severity of substance use behavior (Wei et al., 2020). Our results were consistent with the results of the meta-analysis. Furthermore, we observed that inflammatory markers in OUD and ATSUD individuals may be associated with their substance use. Our previous study showed that peripheral inflammatory markers were associated with treatment outcomes in patients with OUD (Lu et al., 2019). In the current study, we found the association between peripheral inflammatory markers and substance use behavior not only in patients with OUD but also in those with ATS use or combined use. Therefore, aberrant inflammation might have a pleiotropic effect on the development and progression of different classes of SUD.

BDNF is a member of the neurotrophin family and exerts its effects by binding tropomyosin receptor kinase B receptor (Barbacid, 1995). BDNF has been shown to promote survival after cytotoxic insults in several neuronal cell types, including striatal (Ventimiglia et al., 1995), motor (Wang et al., 1997), and hippocampal neurons (Kume et al., 1997). Chronic administration

Table 2. Correlation Between Levels of Cytokines and BDNF, Executive Function, and Urine Morphine- or Amphetamine-Positive Results

	Urine morphine- and amphetamine-positive results		
Variables	*B*	Wald χ^2 (95% Wald CI)	*P*
Executive function[a]			
Baseline			
WCST			
TNE	−0.04	1.10 (−0.10 to 0.03)	.30
PE	0.03	4.77 (0.003 to 0.05)	.03*
NCC	−0.03	0.05 (−0.26 to 0.20)	.82
TCC	0.005	0.24 (−0.02 to 0.03)	.62
CL	−0.02	0.17(−0.09 to 0.06)	.68
CPT			
O-TS	0.004	0.83 (−0.005 to 0.01)	.36
C-TS	−0.01	0.58 (−0.05 to 0.02)	.45
HRT-TS	−0.001	0.003 (−0.03 to 0.03)	.96
HRTSE-TS	0.005	0.15 (−0.02 to 0.03)	.70
Cytokines[b]			
Baseline			
Log TNF-α	0.92	6.72 (0.23 to 1.62)	.01*
Log CRP	0.02	0.009 (−0.33 to 0.36)	.92
Log IL-8	0.38	2.46 (−0.09 to 0.85)	.12
Log IL-6	0.34	0.66 (−0.49 to 1.17)	.42
Log TGF-β1	0.24	0.39 (−0.51 to 0.98)	.53
Log BDNF	−0.40	1.54 (−1.04 to 0.23)	.21
Longitudinal			
Log TNF-α	0.65	4.72(0.06 to 1.23)	.03*
Log CRP	−0.09	0.32 (−0.40 to 0.22)	.57
Log IL-8	0.05	0.06 (−0.34 to 0.44)	.80
Log IL-6	0.07	0.04 (−0.59 to 0.73)	.84
Log TGF-β1	−0.24	0.75 (−0.79 to 0.31)	.39
Log BDNF	−0.26	1.27 (−0.72 to 0.19)	.26

Abbreviations: BDNF, brain-derived neurotrophic factor; CL, conceptual level; CPT, Continuous Performance Test; CRP, C-reactive protein; C-TS, commission T-score; HRTSE-TS, HRT standard error T-score; HRT-TS, hit reaction time T-score; IL-6, interleukin-6; IL-8, interleukin-8; NCC, number of completed categories; O-TS, omission T-score; PE, perseveration error; TCC, trials to complete the first category; TGF-β1, transforming growth factor-β1; TNE, total number error; TNF-α, tumor necrosis factor α; WCST, Wisconsin card sorting test.

[a]Covarying for age, sex, years of education, psychiatric comorbidity, duration of substance use and treatment, and treatment groups.

[b]Covarying for age, sex, psychiatric comorbidity, duration of substance use and treatment, and treatment groups.

Reference group: urine morphine- and amphetamine-negative group.

*P < .05.

Table 3. Correlation Between Baseline Levels of Cytokines and BDNF, Executive Function, and Abstinence

	Abstinence		
Variables	*B*	ORs (95% CI)	*P*
Executive function[a]			
Baseline			
WCST			
TNE	0.07	1.07 (0.93 to 1.22)	.34
PE	−0.07	0.93 (0.85 to 1.01)	.10
NCC	0.11	1.12 (0.74 to 1.68)	.60
TCC	0.001	1.001 (0.97 to 1.04)	.94
CL	0.03	1.03 (0.91 to 1.17)	.66
CPT			
O-TS	−0.007	0.99 (0.97 to 1.01)	.48
C-TS	0.01	1.01 (0.94 to 1.08)	.79
HRT-TS	−0.03	0.97 (0.91 to 1.04)	.41
HRTSE-TS	0.02	1.02 (0.97 to 1.07)	.50
Cytokines[b]			
Baseline			
Log TNF-α	−1.53	0.22 (0.05 to 0.91)	.04*
Log CRP	−0.12	0.89 (0.44 to 1.81)	.74
Log IL-8	−0.72	0.49 (0.18 to 1.34)	.16
Log IL-6	−0.86	0.43 (0.07 to 2.71)	.37
Log TGF-β1	−0.14	0.87 (0.18 to 4.28)	.87
Log BDNF	1.03	2.79 (0.60 to 13.03)	.19

Abbreviations: BDNF, brain-derived neurotrophic factor; CL, conceptual level; CPT, Continuous Performance Test; CRP, C-reactive protein; C-TS, commission T-score; HRTSE-TS, HRT standard error T-score; HRT-TS, hit reaction time T-score; IL, interleukin; NCC, number of completed categories; O-TS, omission T-score; PE, perseveration error; TCC, trials to complete the first category; TGF-β1, transforming growth factor-β1; TNE, total number error; TNF-α, tumor necrosis factor α; WCST, Wisconsin card sorting test.

[a]Covarying for age, sex, years of education, psychiatric comorbidity, duration of substance use and treatment groups.

[b]Covarying for age, sex, psychiatric comorbidity, duration of substance use, and treatment groups.

Reference group: not achieving abstinent group.

*P < .05.

of opioids significantly reduced BDNF levels in the addiction-related area of the rat brain (Chen et al., 2012). BDNF is also protective against the toxic effects of ATS in neurons (Matsuzaki et al., 2004). Human studies also showed that serum BDNF levels were significantly lower in ATS abusers during early withdrawal (Chen et al., 2014) and in chronic heroin users (Angelucci et al., 2007). Our study results support previous findings (Angelucci et al., 2007; Chen et al., 2014) but did not find the BDNF levels were correlated with urine drug test results or abstinent state. In summary, we suggest that peripheral TNF-α levels may be useful and easily assessable biomarkers that correlate with substance use in OUD and ATSUD patients.

The problem of etiological and functional heterogeneity among individuals with addiction is not new. Identifying the etiological factors and functional outcomes that unify people addicted to different agents or differentiate people addicted to the same agent is important in the translation of neuroscience findings to clinical practice (Kwako et al., 2016). Executive function has been suggested as an important indicator to classify people with addiction (Kwako et al., 2016). Although our data support that individuals with OUD and ATSUD had worse executive function than HC in multiple domains, only PE subscales in WCST correlated with their treatment outcomes. The proposed measures of the Addictions Neuroclinical Assessment in executive function, including CPT and WCST (Kwako et al., 2016), were assessed in this study. However, other domains of executive function, such as decision-making and attentional bias, were not measured in our current study. Although some studies supported the association between the performance of WCST and treatment outcomes in cocaine dependence (Turner et al., 2009), further studies to combine the data of the decision-making process and attentional bias toward addicted substance in different classes of SUD individuals may provide more information related with their prognosis.

Across-diagnosis associations of inflammation and cognitive dysfunctions have been suggested (Fourrier et al., 2019). In patients with bipolar disorder, IL-6 was positively correlated with the cognitive deterioration index (Hamdani et al., 2015), and higher CRP levels were associated with lower global cognitive performance (Dickerson et al., 2013). Higher IL-6 and CRP were also associated with worse cognitive performance on various domains of cognition, such as visual attention, visuomotor processing speed, semantic and working memory, task-switching ability, and executive control function in schizophrenia patients (Frydecka et al., 2015). IL-6 was positively correlated with the number of perseverative errors and negatively correlated with the number of categories completed in the WCST in patients with obsessive and compulsive disorders (Karaguzel et al., 2019). In those with major depressive disorder, elevated plasma levels of IL-6 and CRP were associated with impaired cognitive performance in the domains of attention, executive function, and psychomotor speed (Chang et al., 2012; Goldsmith et al., 2016b). However, most of the studies did not focus on patients with SUD. Past studies showed that IL-6 levels predicted worse cognitive flexibility within cocaine-dependent women in a limited sample size (n = 42) (Levandowski et al., 2016). Our current study had the strength of using longitudinal follow-up data to investigate the relationship between cytokines and BDNF levels and executive function with a feasible sample size. Therefore, evidence to support that higher IL-6 and CRP levels were significantly associated with poor performance in WCST and CPT in OUD and ATSUD patients would be more robust. Our past study reported that TNF-α and IL-6 levels were negatively correlated with the visual memory index and verbal memory index in patients with OUD (Wang et al., 2018). Combining the findings from both studies, we supported the notion that neuroinflammation reflected by peripheral inflammatory markers may play an important role in modulating cognitive dysfunction in OUD and ATSUD.

In our current study, 37.9% of patients (n = 183) reported combined opioid and ATS use. Also, 14.8 % of urine samples had both positive morphine and amphetamine results. Because patients with SUD often combined use of multiple substances, it was difficult to recruit patients who used only 1 class of substance in clinical practice. In addition, our current sample size in patients with ATSUD was limited. To separate analysis in OUD and ATSUD was difficult to have enough power to obtain conclusive results. A meta-analysis study found a persistent pattern of elevated inflammatory cytokines across different classes of SUD (Wei et al., 2020). Another meta-analysis study to investigate general cognition and executive function deficits on addiction treatment outcomes also found a consistent association between general cognition and treatment adherence and between

Table 4. Pearson Correlations (*r*) of Baseline Plasma Cytokine and BDNF Levels and Executive Function in all Participants

Variable	Log TNF-α	Log CRP	Log IL-8	Log IL-6	Log TGF-β1	Log BDNF
WCST						
TNE	0.15#	0.09*	0.15#	0.12#	0.02	−0.09
PE	0.12#	0.05	0.13#	0.09*	<0.001	−0.08
NCC	−0.18#	−0.10*	−0.16#	−0.13#	−0.03	0.10*
TCC	0.04	−0.04	−0.005	0.08	−0.003	−0.06
CL	−0.16#	−0.09	−0.14#	−0.11*	−0.009	0.10*
CPT						
O-TS	0.04	0.12*	0.16#	0.08	0.06	0.006
C-TS	−0.01	−0.02	0.03	0.02	0.07	0.05
HRT-TS	0.13#	0.06	0.14#	0.11*	−0.08	−0.08
HRTSE-TS	0.10*	0.12#	0.20#	0.14#	0.005	-0.05

Abbreviations: BDNF, brain-derived neurotrophic factor; CL, conceptual level; CPT, Continuous Performance Test; CRP, C-reactive protein; C-TS, commission T-score; HRTSE-TS, HRT standard error T-score; HRT-TS, hit reaction time T-score; IL-6, interleukin-6; IL-8, interleukin-8; NCC, number of completed categories; O-TS, omission T-score; PE, perseveration error; TCC, trials to complete the first category; TGF-β1, transforming growth factor-β1; TNE, total number error; TNF-α, tumor necrosis factor α; WCST, Wisconsin card sorting test.
*$P < .05$; #$P < .01$.

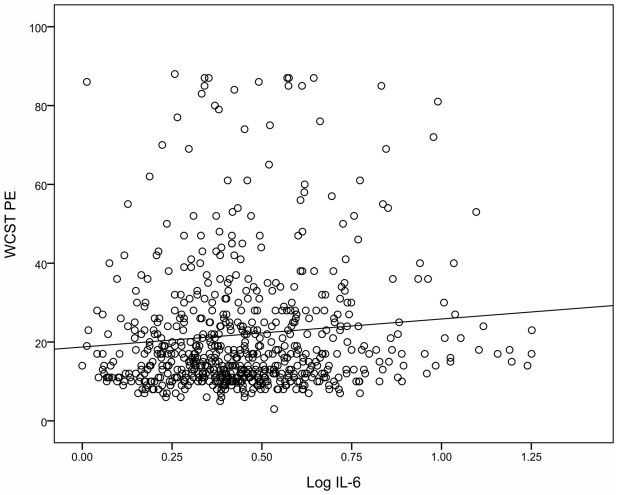

Figure 4. A significant positive correlation between changes in log IL-6 levels and WCST PE performance. Covarying for age, sex, years of education and substance use, visits, psychiatric comorbidities, and treatment group. Abbreviations: IL-6, interleukin-6; PE, perseveration error; WCST, Wisconsin card sorting test.

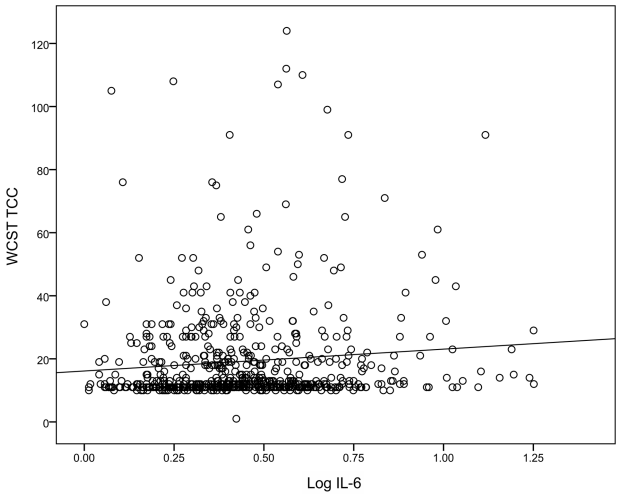

Figure 5. A significant positive correlation between changes in log IL-6 levels and WCST TCC performance. Covarying for age, sex, years of education and substance use, visits, psychiatric comorbidities, and treatment group. Abbreviations: IL-6, interleukin-6; TCC, trials to complete the first category; WCST, Wisconsin card sorting test.

reward-based decision-making and relapse in different classes of SUD (Dominguez-Salas et al., 2016). These findings partly supported that opioid and ATS use may have similar effects on cytokine presentations and executive function. Therefore, in current study, we combined outcome analysis in OUD and ATSUD patients. Our results may provide some insight into the similarity of disease processes across different classes of SUD and be generalized to more SUD patients with multiple substance use.

Our study has some limitations. Although we tested 6 potential peripheral markers in this study, there are many other proinflammatory and anti-inflammatory cytokines and neurotrophic factors that may be correlated with the outcomes of OUD and ATSUD. In addition, the assessment of executive function did not include other domains, such as attentional bias or decision-making. The measurements of substance use severity included only urine tests results and abstinence state without measuring on symptoms loads and craving severity. Nevertheless, our findings indicate the important association between inflammation markers, executive function, and the interplay between these factors and outcomes in OUD and ATSUD patients, which may stimulate future research in this area. There are numerous proposed biomarkers associated with addiction (Milivojevic and Sinha, 2018); therefore, future large-scale studies to combine multidimensional data from epidemiologic, genetic, functional brain imaging, clinical, and treatment variables and analyze big data would represent a more robust prediction model. Additionally, we tried to control for factors that might affect changes in plasma cytokine and BDNF levels, but other factors, for example, metabolic profiles and smoking, might also have affected our findings. Most of our OUD and ATSUD patients smoked, which may potentially interfere with cytokine expression levels. These other factors should be controlled for in future research. Additionally, all our patients

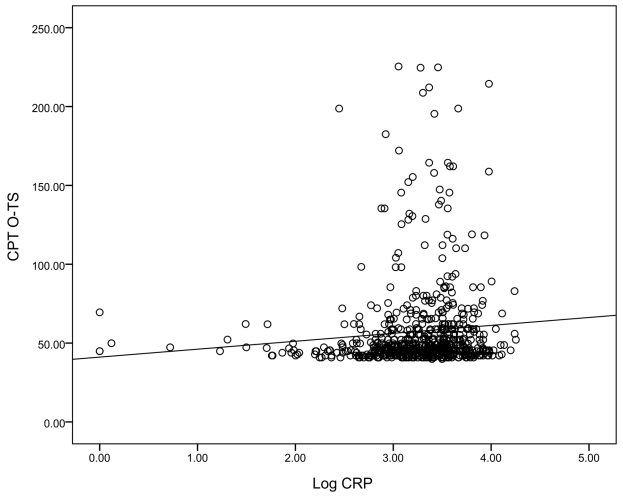

Figure 6. A significant positive correlation between changes in log CRP levels and CPT O-TS performance. Covarying for age, sex, years of education and substance use, visits, psychiatric comorbidities, and treatment group. Abbreviations: CRP, C-reactive protein; CPT, Continuous Performance Test; O-TS, omission T-score.

with OUD were undergoing methadone maintenance therapy, which may affect their executive function. Generalizing our results to abstinent former opioid abusers who did not undergo methadone maintenance therapy might require additional research. Finally, given the limited sample size of participants with pure OUD and ATSUD, future studies to increase sample size with separated groups and examine their potential differences in these biomarkers are required. Given these limitations, our findings should be interpreted with caution.

CONCLUSION

OUD and ATSUD patients had higher levels of inflammatory markers and worse executive function than HC. TNF-α levels and PE on the WCST were associated with their substance use. In addition, higher IL-6 and CRP levels were significantly associated with poor performance on the WCST and CPT in OUD and ATSUD patients. We therefore concluded that peripheral inflammatory markers and executive function may be associated with their substance use in OUD and ATSUD. Additional studies on regulating inflammation and executive function to treat OUD and ATSUD patients may be warranted.

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Author Contribution

R.B.L. and T.Y.W. designed the study and wrote the protocol. S.L.C. supervised the laboratory work. T.Y.W., T.Y.T., S.Y.L., H.H.T., K.C.C., and R.B.L. recruited participants. T.Y.W. wrote the first draft of the manuscript. S.Y.L., Y.H.C., P.S.C., R.B.L., Y.K.Y., and J.S.H. reviewed the literature and contributed to the discussion. All authors contributed to and reviewed the final version of the manuscript.

Interest Statement

All authors declare no conflicts of interest.

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