




Stimulant use disorder indicative of increased serum soluble intercellular adhesion molecule-1 concentrations with altered brain reward and interoceptive processing

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ARTICLE INFO

Keywords:

Substance use disorder
Stimulant use disorders
Amphetamine/methamphetamine use disorders
fMRI
Monetary incentive delay (MID) task
Visceral interoceptive awareness (VIA)
Stop signal task (SST)
Serum soluble intercellular adhesion molecule-1

ABSTRACT

Stimulant use disorders (STIM): (1) elicit compulsive behaviors that can lead to altered brain structure and function; and (2) trigger inflammatory responses by inducing the release of immune molecules, suggesting potential adverse effects. Our previous findings show that amphetamine use disorder is associated with altered neural processing during reward, interoception, and inhibitory control tasks. To extend these findings, we investigated links between neural processing and inflammation that may contribute to STIM. Participants from the first half of the Tulsa-1000 (T1000) study ($n = 500$) met criteria for either group: (1) stim+ ($n = 49$) reported methamphetamines/amphetamines as their current drug of choice and met criteria for past-year STIM; or (2) stim- ($n = 90$) endorsed no past-year diagnosis other than nicotine use disorder. Immunoassays were used to measure six inflammatory analytes. We examined blood oxygen-level-dependent (BOLD) responses to monetary incentive delay (MID), visceral interoceptive awareness (VIA), and inhibitory control with the stop signal task (SST) performed during functional magnetic resonance imaging. The stim+ group exhibited higher serum soluble intercellular adhesion molecule-1 (sICAM-1) concentrations than the stim- group, no significant differences or associations were found with the other inflammatory factors. Within the stim+ group, greater sICAM-1 levels were associated with: (1) lower right nucleus accumbens (NAc) BOLD signal during MID reward anticipation; and (2) higher right amygdala BOLD signal during interoceptive attention. No significant sICAM-1 associations emerged for the SST in stim+. Inflammation may play a central role in stimulant use as indicated by increased sICAM-1, which may point to central mechanisms. The association between high inflammation and reduced NAc reward activation or higher interoceptive signals in STIM may reflect an STIM-sICAM-1 feedback loop mechanism.

1. Introduction

Substance use disorder (SUD) is a complex mental health disorder that affects brain and behavior, leading to struggles with recurrent use of substances such as alcohol, illicit drugs, prescription medications, or tobacco, despite facing negative consequences (Rosenthal et al., 2022). Chronic drug exposure adversely affects the same brain regions [insula, striatal regions (caudate, putamen, and nucleus accumbens-NAc) and amygdala] and processes that are involved in cognitive functions such as

learning, memory, and reason (Gould, 2010; Kozak et al., 2019). Over time, SUD is thought to be associated with compulsive behaviors, cravings, tolerance, and withdrawal symptoms that relate to altered brain structure and function (i.e., heightened sensitivity, dependency, or changes in neuroplasticity) (Koob and Volkow, 2016).

SUD has been linked to higher concentrations of cytokines, including interleukin (IL)-8, IL-10, and tumor necrosis factor (TNF) (Wei et al., 2020; May et al., 2021). Previous work by our research team showed that females with SUD exhibited lower C-reactive protein (CRP)

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concentrations compared to females without SUD, which was replicated in an independent sample, indicating that SUD-associated inflammation may be dependent on moderating factors including sex and time of exposure (May et al., 2021; Stewart et al., 2024). SUD is also associated with heightened CRP concentrations, suggesting potential pro-inflammatory effects (Wei et al., 2020; Morcuende et al., 2021). Additionally, cell adhesion molecules, such as serum soluble intercellular adhesion molecule-1 (sICAM-1), appear upregulated during the inflammatory processes associated with SUD, including stimulant use disorders (STIM) (Loftis et al., 2011).

STIM includes both amphetamine (AMPH) and methamphetamine (METH) use disorders as categorized by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (in *Diagnostic and statistical manual of mental disorders*, 2013; Hasin et al., 2013). STIM comprises dependence, leading to development of tolerance and withdrawal symptoms (in *Diagnostic and statistical manual of mental disorders*, 2013). Amphetamine-type stimulants (amphetamine and methamphetamine) are highly addictive psychostimulants that can lead to physical, mental, and social health hazards (Tran et al., 2021; Paulus and Stewart, 2020), and are the second most common drug used after cannabis (Unodc, 2023; Drugs, U. N. O. o. Crime. World Drug Report, 2016). The adverse effects from STIM include restlessness, hyperthermia, and insomnia (Chan et al., 2019). Because amphetamines (both amphetamine and methamphetamine) act on the central nervous system (CNS), (i.e., the ability to cross the blood brain barrier), chronic use can lead to mood disturbances, agitation, paranoia, addiction, elevated rates of suicide, and cognitive impairments, with unsustainable treatment options (Glasner-Edwards and Mooney, 2014; McKetin et al., 2016; Siefried et al., 2020). Clinical heterogeneity within STIM is related to limited treatment response. This heterogeneity may be linked to amphetamine-type stimulants' ability to promote inflammation as defined by increase in serum and plasma cytokine levels including TNF, IL-1 beta (β), and IL-6 (Luo et al., 2022; Re et al., 2022; Kuo et al., 2018).

Amphetamine use can trigger inflammatory responses by inducing the release of immune biomarkers in response to oxidative stress, which may occur through the disruption of gut health, activation of downstream inflammatory pathways, and/or general toxicity (Wei et al., 2020; Anderson et al., 2018). Several classes of inflammatory biomarkers, such as acute phase proteins, interleukins, intercellular adhesion molecules, interferons, and chemokines can induce neuroinflammation, and more specifically, be altered in AMPH (Agarwal et al., 2022). In response to persistent use of high-dose amphetamines, chronic inflammation can lead to memory loss, depression, anxiety, and other comorbid psychiatric disorders (Huckans et al., 2015; Loftis and Janowsky, 2014). Therefore, identifying the association of peripheral inflammatory analytes with brain alterations implicated in reward, attention to bodily sensations known as interoception, and decision-making may provide insight into stimulant-moderated inflammatory mechanisms impacting neural circuitry and cognitive dysfunction.

Use of stimulants such as amphetamines result in alterations in both functional and structural abnormalities with functional magnetic resonance imaging (fMRI) (Fowler et al., 2007). fMRI studies with drugs of abuse have shown: (1) reductions in cortical volume, including in the prefrontal cortex (PFC), insula, and anterior cingulate cortex (ACC); (2) increased activation to drug cue-reactivity in addicted individuals in prefrontal and orbitofrontal regions (Wilson et al., 2004) and ACC, amygdala, and NAc (Kühn and Gallinat, 2011); and (3) reduced grey matter volume compared to healthy controls (Daumann et al., 2011). For structural MRI, thinner cortices are seen in dorsal PFC and insula, which are elements of the brain reward circuit (Makris et al., 2008). Moreover, a meta-analysis reported neuroimaging abnormalities in stimulant-dependent individuals, with studies showing consistently diminished gray matter in PFC regions that are associated with self-awareness and self-regulation (Ersche et al., 2013).

Our research team has previously shown that compared to individuals without amphetamine use, individuals with amphetamine use

exhibit: (1) blunted dorsal and ventral striatum signals when anticipating wins and losses during a monetary incentive delay (MID) task (May et al., 2024); (2) blunted insula signals when focusing attention to stomach sensations during a visceral interoceptive awareness (VIA) task (Stewart et al., 2020); but (3) elevated insula and amygdala signals when engaging in inhibitory control during a stop signal task (Stewart et al., 2023). Taken together, these findings suggest reduced neural resources allocated to reward prediction as well as tracking internal bodily responses (interoception), but increased neural effort expended to engage in successful executive functioning.

A crucial gap remaining in the literature is the extent to which peripheral inflammation shares variance with these neural alterations in individuals with STIM. Knowledge of this overlap will inform the potential for anti-inflammatory drugs to target neural mechanisms impaired in STIM, with the hope that these interventions will reduce symptoms of addiction. To address this gap, our secondary data analysis project integrates blood-based biomarker and neuroimaging data from the Tulsa-1000 (T1000) study. We hypothesized that individuals with STIM (stim+) would exhibit greater levels of inflammatory analytes than individuals without STIM (stim-), based on prior research showing increased inflammation in AMPH (Wang et al., 2023; Collier and Hutchinson, 2012). Increased inflammation in stim+ would, in turn, be associated with lower striatal brain responses during reward anticipation, lower insula signals during interoceptive attention, and higher insula/amygdala results during inhibitory control.

2. Materials and Methods

2.1. Participants

The T1000, a naturalistic, longitudinal study, consists of 1000 healthy individuals and individuals seeking treatment with mood, anxiety, SUD, and eating disorders (Victor et al., 2018). Several channels were used for recruitment for T1000 including the Laureate Psychiatric Clinic and Hospital, other local mental health providers, and the community at-large with newspaper, flyer, radio and other media advertisements in Tulsa, Oklahoma and the surrounding areas. The T1000 study received approval from the Western Institutional Review Board, and all participants were compensated for their participation upon providing written, informed consent.

2.2. Demographics and Questionnaires

Study assessment collection included age, sex, exercise, body mass index (BMI), percent body fat (PBF), medication status, race/ethnicity, education, employment, and income. Participants from the 1st half of the T1000 study (n= 500) who completed baseline assessments were allocated into stim- (n= 90) and stim+ (n= 49) groups (see Stewart et al., 2023 for selection flowchart). Briefly, "selection of the participants from the first 500: 1) individuals met criteria for amphetamine dependence or use disorder (n= 95); 2) exclusions for opioids, alcohol, cannabis, and barbiturates based on the Customary Drinking and Drug Record (CDDR) Drug of choice (n= 42); 3) individuals with amphetamines as the CDDR drug of choice (n= 53); and 4) exclusions for poor brain alignment, excessive motion, and no successful stop trials (n= 4) during fMRI. For potential individuals without STIM from the first 500: 1) individuals did not meet criteria for amphetamine dependence or use disorder (n= 405); 2) exclusions based on the MINI for other substance dependence/use disorder, current MDD, anxiety or stress disorders, or antisocial personality disorder (n= 308); 3) inclusion for no disorders or past MDD (n= 97) based on the MINI; and 4) exclusions for missing behavioral data, poor brain alignment, excessive motion, and incomplete SST (n= 2)." Comorbidity with major depressive disorder (MDD) was determined by Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV and the Mini International Neuropsychiatric Inventory (MINI) (Sheehan et al., 1998; Association, 1994). The stim- group has no current MDD

comorbidity ($n = 36$ met criteria for past MDD), while the stim+ group has only 1 current comorbid MDD ($n = 21$ met criteria for past MDD).

The stim+ group met criteria for past-year amphetamine dependence (DSM-IV), or stimulant use disorder with specifier for amphetamine-type substance (DSM-5) (in *Diagnostic and statistical manual of mental disorders*, 2013) and amphetamine ($n = 3$) or methamphetamine ($n = 46$) as their current drug of choice. Supplemental Table 1 lists measures from the CDDR for the stim- and stim+ groups. The stim-group had no past year DSM-IV or DSM-5 diagnosis other than nicotine use disorder. Exclusion criteria included MRI contraindications, moderate to severe traumatic brain injury, current active suicide, positive alcohol/drug screen, and physical health conditions not controlled by medication.

Study assessment also included collection of several measures such as physical activity [the International Physical Activity Questionnaire-IPAQ (Craig et al., 2003) (Category- Hepa active, inactive, or minimally active; and minutes)]; anxiety, depression, alcohol use, and sleep disturbance [the Patient-Reported Outcomes Measurement Information System- PROMIS (Cella et al., 2010)]; and smoking (Fagerstrom Test for Nicotine Dependence- FTND (Heatherton et al., 1991)).

2.3. Blood data collection and immunoassays

BD Vacutainer serum collection tubes were used for venous blood collection, which was then centrifuged at 1,300 xg for 10 minutes (min) at room temperature (RT). Samples were stored at -80°C until analysis. Interleukin 1 receptor antagonist (IL-1ra) was measured with the Human Quantikine ELISA kit (R & D Systems, Minneapolis, USA). For the ELISA, the optical density was determined at 450 nanometers (nm) with a microplate reader. IL-6, IL-8, and TNF-alpha (α) were measured with the Proinflammatory Panel 1 human kit [Meso Scale Diagnostics (MSD, a high-sensitivity multi-array technology that detects electrochemiluminescence), Maryland, USA]. CRP and sICAM-1 were measured with the Vascular Injury Panel 2 human kit (MSD). Two subjects were missing blood samples, resulting in final analytic samples of 89 stim- and 48 stim+ subjects for immunoassays. Serum samples for each assay were run in duplicate. All analytes were above detection limit. A protein standard curve for each assay was used to determine protein concentrations either through electrochemiluminescence (MSD) or optical density (ELISA). Supplemental Table 2 lists the immunoassays, dynamic ranges, inter- and intra-assay coefficients of variation, and number of outliers for each analyte.

2.4. fMRI tasks and data preprocessing

The MID task, a paradigm designed to measure the neural response to the anticipation of a potential win or loss, was administered to each participant across two runs (Victor et al., 2018), with each run consisting of 45 trials, and a duration of 562 s. At the start of a trial, the participant would see a cue (a circle, indicating to the participant a possible win, or a square, signifying a possible loss) and a cue magnitude (0, 1, or 5 US dollars). A short delay would then serve as an anticipation period, before the participant was presented with a target (a white triangle). On seeing this target, the participant was instructed to press a button on their handheld button device as quickly as possible, with the speed at which they press the button determining whether they win or avoid losing the dollar amount, or the magnitude, indicated by the cue. To calibrate the difficulty of the task, participant success was restricted to approximately two-thirds of the trials, done by recording each participant's reaction time during a practice run, and incorporating this value into the trials to be completed in the scanner. The programming for this task was completed in PsychoPy (Cox, 1996), and responses made by participants were collected with a handheld four-button device. (Current Designs, Philadelphia, PA).

The VIA task examines interoceptive attention. Participants completed two runs of the VIA task (Stewart et al., 2020; Simmons et al.,

2013; Avery et al., 2014) during fMRI. During this task (Stewart et al., 2020), participants were presented with three attention modulation conditions cued by a word: (1) heart: internal attention towards heart-beat sensations; (2) stomach: internal attention towards stomach sensations; and (3) target: external attention for word color changes. Each run consisted of 6 trials per condition (total of 36 trials; 10 s/trial).

In the SST (Matthews et al., 2005), participants were asked to respond to "Go" signals as quickly as possible, while inhibiting their response if abruptly presented with a "Stop" signal. The SST was performed as outlined in Stewart et al. (Stewart et al., 2023). Before data acquisition for the SST, participants completed 4 practice SST trials and the final mean response time was used to calibrate the data acquisition session, where trial ($n = 288$) were divided into 6 blocks of 48 trials, which lasted 1,300 ms/trial. Stop signal trials ($n = 72$, $n = 12$ per block) consisted of a tone and target color change to let participants know to inhibit their response. To calibrate hard stop signals, stop signals were presented at 0, 100, and 200 ms, prior to participant's mean response time, while easy stop signals were presented at 300, 400, and 500 ms before participant's mean response time.

For neuroimaging, two identical GE MR750 3T scanners were used, with the following parameters: TR/TE = 2000/27mc, FOV/slice = 240/2.9 mm, 128×128 matrix, and 39 axial slices. To acquire Structural T1-weighted high-resolution images, the following parameters were used: TR/TE = 5/2.012 ms, FOV/slice = $240 \times 192/0.9$ mm, and 186 axial slices. The AFNI software package (Cox, 1996) was used to preprocess neuroimaging data across all tasks as follows: the first three TRs were discarded, followed by despiking, slice timing correction, co-registration to anatomical volumes, motion correction, normalization to Montreal Neurological Institute space (with a final voxel size of $2 \times 2 \times 2$ mm), and application of a 4 mm Gaussian full-width at half-max smoothing kernel.

To model the BOLD response relative to each anticipatory task condition (-5 , -1 , -0 , $+0$, $+1$, $+5$), four-second block regressors were convolved with a canonical hemodynamic response function. Nuisance regressors were integrated for the first four polynomial terms and six motion parameters. At the regression step, censoring removed volumes with either a Euclidean norm of the derivatives of the six motion parameters greater than 0.3 or greater than 10 % outlier voxels, which was determined by 3dToutcount. The estimated beta coefficient from single-subject analysis was used for percent signal change, which was relative to the implicit baseline during unmodeled fixation. Model regressors included the first 4 polynomial baseline terms, 6 motion parameters (roll/pitch/yaw/x/y/z translation), and cue magnitude of large loss (-5), small loss (-1), no loss (-0), no win ($+0$), small win ($+1$), and large win ($+5$). Motor responses were not explicitly modeled.

SST-related brain activation was simulated employing the general linear model, utilizing five regressors: successful easy stops, successful hard stops, unsuccessful easy stops, unsuccessful hard stops, and successful go trials. Six motion parameters and four baseline polynomials were implemented as nuisance regressors. Any TR with a considerable amount of the derivatives of the six motion parameters exceeding 0.3 or an outlier fraction greater than 0.1 (established by 3dToutcount) was filtered at the regression step.

For the VIA task, block regressors were merged with a standard hemodynamic response function and set to model BOLD response for heart, stomach, and target conditions. For each region, the average beta values for heart, stomach, and target were extracted, restricting to voxels with a temporal signal-to-noise ratio above 50. To obtain percent BOLD signal change from baseline, beta values were multiplied by 100, serving as a dependent variable in further analysis. The referenced baseline condition was composed of fMRI data collected during the intertrial interval.

2.5. Statistical analysis

2.5.1. Demographics and clinical ratings

Independent t-tests were used to compare continuous variables (age, BMI, PBF, income, IPAQ Minutes, PROMIS anxiety, depression, alcohol

use, and sleep disturbance) between the stim+ and stim- groups. Chi-square tests were used to compare stim+ and stim- groups on categorical variables, including sex, race/ethnicity, employment, smoking, IPAQ Category, exercise, and comorbid MDD.

2.5.2. Immunoassay group analyses

Outliers were defined as values with an absolute z-score greater than 3 (i.e., more than three standard deviations above or below the mean) and were coded as missing. Shapiro-Wilks tests were used to ensure distributions were normalized; log-transformations were completed for any distributions with non-Gaussian findings. To evaluate group differences (stim+ versus stim-) accounting for age, sex, and BMI, a linear regression model was applied. All analytes used were corrected by False Discovery Rate (FDR) correction for multiple comparisons.

2.5.3. Neuroimaging group analyses

AFNI's group analysis program 3dttest++ using the model $\beta \sim \text{Group} * \log(\text{sICAM-1})$ was used to evaluate the slope difference in the relationship between the one inflammatory analyte showing differences between groups (sICAM-1) and percent fMRI BOLD signal change on (1) gain versus non-gain and loss versus non-loss contrasts during the MID task; (2) the contrast of heart and stomach interoception versus the target exteroceptive condition during the VIA task; and (3) error versus correct and stop versus go contrasts during the SST. The ClustSim option was used to estimate probability of false positives. Clusters with a significant interaction were selected based on a voxel wise $p < 0.01$, and $\alpha < 0.05$. Small volume correction was performed by applying this cluster-wise correction for different regions of interest (left and right insula, caudate, putamen, nucleus accumbens, and amygdala) that were selected a priori. Follow up regression analyses were conducted in R for significant clusters.

3. Results

3.1. Demographics

Table 1 indicates that groups did not differ on age, sex, BMI, PBF, race/ethnicity, IPAQ, exercise, medication status, nor the PROMIS anxiety, depression, and sleep disturbance scores. However, stim+ reported lower educational attainment, employment, and income than stim- along with greater alcohol use and greater frequency of nicotine smoker status.

3.2. Immunoassays

Table 2 illustrates that stim+ showed significantly higher sICAM-1 concentrations than stim- ($p_{corrected} = 0.048, d = 0.537$) after controlling for age, sex, and BMI and correcting for multiple comparisons. No significant differences were observed with the other factors (CRP, IL-1ra, IL-6, IL-8, and TNF- α) after controlling for age, sex, and BMI and multiple comparison correction.

3.3. Neuroimaging results

Fig. 1 shows that there was a significant slope difference between serum sICAM-1 concentration and % fMRI signal change for the MID gain vs. no gain contrast between stim+ and stim- groups within right NAc (center-of-mass = -29.2, 9.9, -10.2; peak = -29, 11, -9; peak $t = -3.22$). Correlations within stim+ indicated that higher sICAM-1 concentrations were associated with lower right NAc signal ($r = -0.51, p < 0.001$), but no correlations emerged within stim-. Fisher's r -to- z transformations indicated that the relationship between serum sICAM-1 and NAc signal was significantly more negative in stim+ than stim- ($z = -3.99, p < 0.001$).

Fig. 2 illustrates a significant group slope difference between serum sICAM-1 concentration and % fMRI signal change for the VIA

Table 1
Demographic variables for stim- and stim+ groups.

	stim- (n = 90) Mean (SD)	stim+ (n = 49) Mean (SD)	p-value
Age	33.53 (11.60)	34.72 (8.33)	0.527
Sex = Male (%)	33 (36.7)	20 (40.8)	0.765
BMI	28.43 (5.47)	28.43 (4.23)	0.999
Percent Body Fat	33.58 (11.07)	30.92 (10.00)	0.176
Race Ethnicity (%)			0.165
Asian	3 (3.4)	0 (0.0)	
Black	3 (3.4)	2 (4.1)	
Hispanic	5 (5.6)	3 (6.1)	
Native American	11 (12.4)	13 (26.5)	
Other	2 (2.2)	3 (6.1)	
White	65 (73.0)	28 (57.1)	
Consolidated Education	6.67 (1.48)	4.45 (1.83)	<0.001
Employed = Yes (%)	65 (77.4)	4 (8.2)	<0.001
Fagerstrom Smoker = Yes (%)	6 (14.3)	20 (57.1)	<0.001
Income	34739.24 (48089.91)	7500.71 (27247.51)	<0.001
IPAQ Category (%)			0.065
HEPA Active	51 (57.3)	27 (56.2)	
Inactive	17 (19.1)	16 (33.3)	
Minimally Active	21 (23.6)	5 (10.4)	
IPAQ Minutes	4777.03 (4272.91)	4758.21 (4565.31)	0.981
Exercise = Yes (%)	55 (61.1)	27 (55.1)	0.612
Medicated = Un-medicated (%)	37 (41.1)	24 (49.0)	0.475
PROMIS Alcohol Use	44.90 (7.04)	49.72 (2.42)	<0.001
PROMIS Anxiety	51.55 (9.81)	52.67 (7.85)	0.491
PROMIS Depression	50.88 (10.32)	50.22 (6.69)	0.691
PROMIS Sleep Disturbance	48.68 (8.93)	45.80 (11.56)	0.106

Demographic variables for stim- and stim+ groups. Continuous and categorical variables were analyzed using t -test and chi-square tests, respectively. IPAQ: The International Physical Activity Questionnaire; PROMIS: Patient-Reported Outcomes Measurement Information System total score. Consolidated Education, coded as 1 – no school through kindergarten; 2 – grade 1–11; 3 – grade 12 (no diploma); 4- regular high school diploma; 5- general educational development (GED) or alternative credential; 6- some college, no degree; 7- associate's degree; 8- bachelor's degree; 9- master's degree; 10- professional degree beyond a bachelor's; 11- doctoral degree.

Table 2
Inflammatory analyte concentrations in stim- and stim+ groups.

Log Concentration	stim- (n = 89) Mean (SD)	stim+ (n = 48) Mean (SD)	p-value	FDR corrected p-value	Cohen's d
CRP	13.96 (1.48)	13.69 (1.33)	0.296	0.338	0.188
IL-1ra	6.07 (0.52)	5.92 (0.47)	0.100	0.177	0.299
IL-6	-0.68 (0.73)	-0.87 (0.61)	0.139	0.177	0.272
IL-8	2.02 (0.39)	2.16 (0.39)	0.049	0.153	0.358
sICAM-1	12.86 (0.22)	13.00 (0.31)	0.003	0.048	0.537
TNF- α	0.85 (0.26)	0.87 (0.29)	0.640	0.650	0.085

Inflammatory analyte concentrations in stim- and stim+ groups. Linear regression model was used to evaluate the group difference controlling for age, sex, and BMI. False Discovery Rate (FDR) correction for multiple comparisons was used across all analytes. CRP: C-reactive protein; IL-1ra: interleukin-1 receptor antagonist; IL-6: Interleukin-6; IL-8: Interleukin-8; sICAM-1, soluble intercellular adhesion molecule-1; TNF- α , Tumor necrosis factor alpha. Raw concentration was in pg/mL.

interoception versus exteroception contrast within right amygdala (center-of-mass = -26.8, 2.9, -20.3; peak = -27, 3, -21; peak $t = 3.63$).

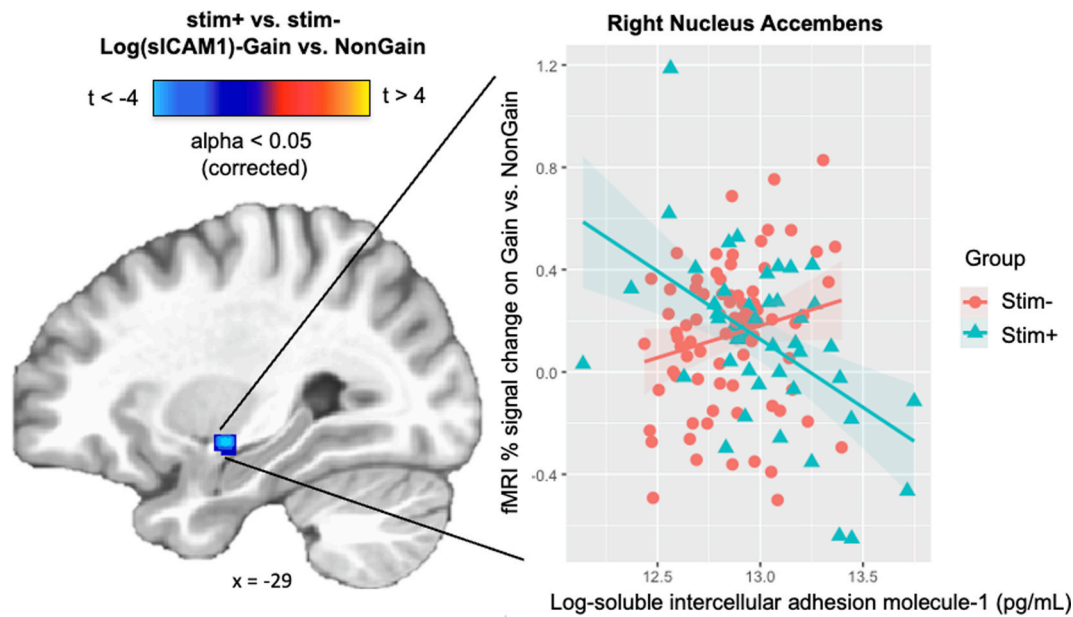


Fig. 1. Correlations between serum sICAM-1 and % fMRI signal change for the MID gain vs. no gain contrast between stim+ and stim- groups. Within stim+, higher sICAM-1 concentrations were associated with lower fMRI BOLD signal change for the MID gain vs. no gain contrast in right NAC. Within stim- group, no significant relationship between sICAM-1 concentrations and fMRI BOLD signal change for the MID gain vs. no gain contrast were observed.

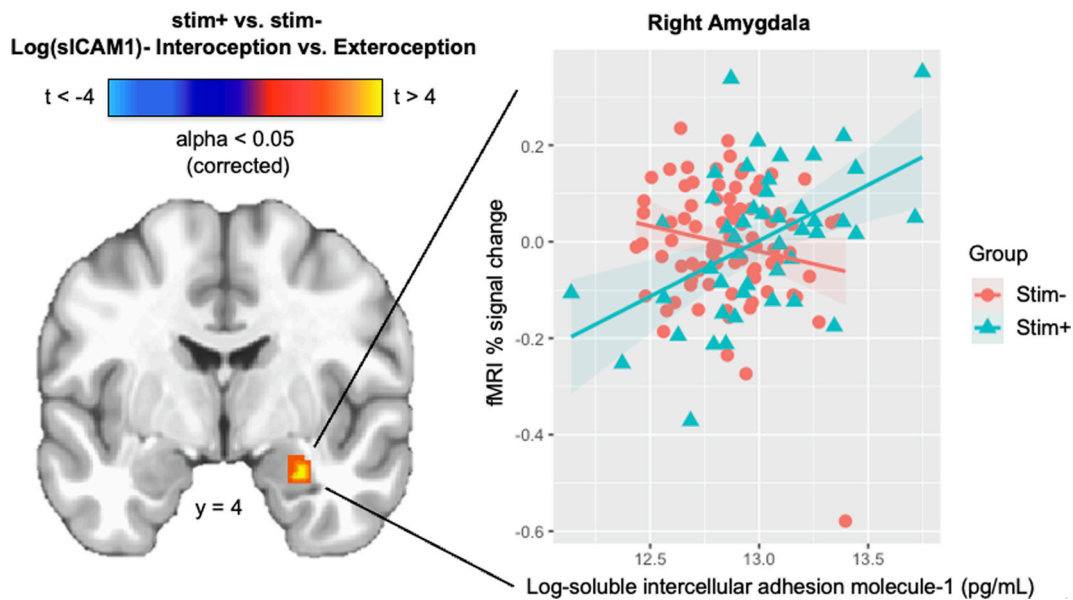


Fig. 2. Correlations between serum sICAM-1 and % fMRI signal change for interoception versus exteroception contrast during the VIA task between stim+ and stim- groups. Within stim+, higher sICAM-1 concentrations were associated with higher fMRI BOLD signal change for the VIA interoception versus exteroception contrast in right amygdala. Within stim- group, no significant relationship between sICAM-1 concentrations and fMRI BOLD signal change for the VIA interoception versus exteroception contrast were observed.

Specifically, within stim+, higher sICAM-1 concentrations were associated with higher right amygdala signal ($r = 0.48, p < 0.001$). Within stim-, no significant correlation was observed. Fisher's r -to- z transformations indicated that the relationship between serum sICAM-1 and amygdala signal was positive in stim+ than AM- ($z = 3.75, p < 0.001$).

No slope differences between sICAM-1 and SST % fMRI signal change were observed. However, at a voxel wise threshold of $p < 0.05$, and $\alpha < 0.05$, a group slope difference emerged between serum sICAM-1 concentration and % fMRI signal change for the SST NOGO versus GO contrast within right amygdala (center-of-mass = -19.1, 4.0, -13.7;

peak = -17, 3, -13; peak $t = 3.57$), with serum sICAM-1 concentrations showing a stronger positive correlation with right amygdala signal in the stim+ than stim-.

4. Discussion

4.1. sICAM-1 concentrations elevated in amphetamine use disorder

Peripheral inflammation is known to play a pathophysiological role in many psychiatric disorders including SUD (Macur and Ciborowski,

2021; Slavich and Irwin, 2014). It is well studied that elevated levels of pro-inflammatory and low levels of anti-inflammatory molecules have been described in the serum of psychostimulant users (Fox et al., 2012). We identified one out of six inflammatory analytes that were elevated in the serum of the stim+ compared to the stim- group, as seen in other studies (Huckans et al., 2015; Wang et al., 2023; Collier and Hutchinson, 2012). Intriguingly, only sICAM-1 was found to be significantly different in the stim+ group. There are plausible speculations as to why the other analytes were not different. Primarily, the stim- group are not healthy comparisons (Stewart et al., 2019). The stim- group included individuals on medications, a history of past illicit substance use, and past MDD. This fact makes it difficult to compare to other studies that have shown differences in these inflammatory markers while comparing STIM to individuals that are healthy (Huckans et al., 2015; Permponputtana et al., 2025; Gürbüzler et al., 2024). Additionally, individuals with STIM were not current users but were abstinent and treatment-seeking. This fact is important as amphetamines may not be in their system to trigger an acute inflammatory response through the innate immune system (Wang et al., 2023).

Second, while sICAM-1 is considered an inflammatory marker, it is also characterized as an adhesion molecule/vascular injury marker (Witkowska and Borawska, 2004). An alternative mechanism for significant sICAM-1 in the stim+ group may be the relationship of drug use and vascular injury. Vascular injuries related to substance use, including vasospasms, inflammation, and endothelial dysfunction can lead to venous, cardiac, and arterial complications and aneurysms (Jaffe, 1983; Middlekauff et al., 2022). Research has suggested the use of sICAM-1 as a biomarker for vascular injury, due to its role in inflammation and cell adhesion processes (Puig et al., 2022). Studies have identified several patterns of vascular injury due to substance use (Benitez and Newell, 1986). For instance, methamphetamine use 1) may promote cardiovascular disease through catecholamine toxicity or directly targeting cardiac and vascular tissue; and 2) is associated with pulmonary hypertension in patients with specific polymorphisms in the methamphetamine catabolizing enzyme carboxylesterase (Kevill et al., 2019). While further research is warranted to elucidate this mechanistic notion, we can present other plausible mechanisms for our current findings.

The inflammatory-mediated increase in individuals with STIM suggests that uptake by dopamine, serotonin, or norepinephrine transporters may lead to production of several inflammatory analytes (Yamamoto et al., 2010). While this is the most plausible case (Grace et al., 2015; Merighi et al., 2013); it is well established in pre-clinical animal and cellular models that methamphetamine activates toll-like receptor 4 (TLR4), leading to the expression of inflammatory analytes (Wang et al., 2014; Vargas et al., 2020), including IL-6, IL-8, and ICAM-1, which have also been implicated in other psychiatric disorders such as depression (Wang et al., 2019; Figueroa-Hall et al., 2020). Xenobiotics or XAMPs are drugs of abuse that exert their effects through TLR4 in the CNS with microglial activation and upregulation of neuroinflammation (Wang et al., 2014). Mechanistically, methamphetamine binds to the lipopolysaccharide binding pocket of the myeloid differentiation 2 (MD2; TLR4 co-receptor) to stabilize the TLR4/MD2 conformation leading to upregulation of IL-6 signaling within the ventral tegmental area and dopamine elevation in the NAc (Wang et al., 2019; Schall et al., 2021). These findings highlight an alternate neurobiological mechanism of reward and may pinpoint to a new target for STIM.

Literature on STIM-induced clinical mechanisms on peripheral inflammation-based analytes is ongoing. Studies have shown that peripheral inflammation leads to blood brain barrier (BBB) disruption and upregulation of adhesion molecules, such as CRP and vascular endothelial growth factor (Turkheimer et al., 2021; Vore et al., 2022). Conversely, there are several mechanistic pre-clinical studies showing how amphetamines modulate neuroinflammation. One study found that methamphetamine exposure led to microgliosis and TNF production, which required microglia-astrocyte crosstalk (Canedo et al., 2021). Moreover, Gonçalves J. et al., revealed that methamphetamine directly

targets the BBB as evidenced by structural alteration of blood vessels, induction of oxidative stress, decreased junction proteins, and upregulated vascular and intercellular adhesion molecules (Gonçalves et al., 2017; Turan et al., 2023). Additionally, Coelho-Santos V. et al., found that methamphetamine triggered TNF release and increased ICAM-1 expression through a nuclear factor-kappa-B (NF-κB) mechanism (Coelho-Santos et al., 2015), further supporting our results.

Methamphetamine has also been shown to activate microglia and increase gene expression in striatum, such as caudate and putamen, and other brain regions including the cerebellum and hippocampus (Escubedo et al., 1998; Li et al., 2024). This is evidenced by increased expression of ionized calcium-binding adapter molecule 1 (Iba-1) and the fractalkine receptor (CX3CR1) (Gonçalves et al., 2017); proteins that indicate microglial activation. More importantly, clinical studies found that chronic methamphetamine self-administration led to reactive microgliosis in the midbrain, striatum, thalamus, and orbitofrontal and insular cortices and dopamine and serotonin transporter reduction in striatum and global regions of human brains of individuals with methamphetamine misuse (Volkow et al., 2001; Sekine et al., 2008). In astrocytes, the effects of methamphetamines are numerous, including changes in the excitatory amino acid transporters; cytokine receptors; transcription factor pathways; and glucose uptake mechanisms (Abdul Muneer et al., 2011). Methamphetamine can also induce astrogliosis in the striatum and can stay activated for 30 days after exposure (unlike microglia) (Friend and Keefe, 2013). This is further observed in elevated glial fibrillary acidic protein (GFAP; astroglia marker) immunofluorescence and protein in the hippocampus and striatum (Gonçalves et al., 2017). Thus, glial cell activation not only induces proinflammatory cytokines in response to methamphetamine but may also lead to neuronal injury and neuropsychiatric impairments as can be studied with neuroimaging (Agarwal et al., 2022; Paulus et al., 2002).

4.2. STIM is associated with increased sICAM-1 and reduced reward processing and increased interoceptive signals

Here, we used fMRI (Stewart et al., 2019) to give insight into the inflammation, as observed with sICAM-1, and STIM-related changes in brain reward processing, interoceptive signals, and impulsivity. There were significant relationships between sICAM-1 concentrations and fMRI BOLD signal change for the MID gain vs. no gain contrast. Decreased BOLD signal with inflammation as measured with sICAM-1 was observed in the right NAc, which has been previously reported by our group and others (Felger et al., 2016; Molla et al., 2023; Burrows et al., 2021). Likewise, Crane et al., showed that methamphetamine decreased NAc activation during receipt of monetary reward in contrast to loss (Crane et al., 2023). Another group showed reduced blunted amygdala BOLD response following repeated amphetamine exposure (O'Daly et al., 2014). Elaborating on our previous findings, stim+ exhibited lower bilateral caudate/putamen and left NAc during loss anticipation compared to stim- (May et al., 2024). Not surprisingly, these regions are known to be implicated in neural circuit reward processing (Schultz, 2000), such as the NAc, which are known targets of methamphetamine and central to reward-related behavioral abnormalities (Paulus et al., 2002; Ikemoto and Panksepp, 1999; Knutson et al., 2001).

While we cannot delineate the exact contributions of inflammation (sICAM-1) and STIM to the decreased BOLD signal change during the MID task due to the scarcity of studies in this area of research, we can explore a mechanistic assessment and look to the monoaminergic literature. Research has shown that amphetamines activate reward circuitry and directly target monoaminergic transmission, especially dopamine, and to a lesser extent norepinephrine and serotonin (Sulzer et al., 2005; Cruickshank and Dyer, 2009). Inflammation is known to modify brain activity and induce anhedonic behavior, altering presynaptic striatal dopamine function consistent with decreased dopamine synthesis (Capuron et al., 2012). In the same manner, dopaminergic drugs that

down-regulate the release of dopamine may be related to inflammation and blunted or reduced brain responses (Capuron et al., 2012). In the presence of amphetamines, disruption to dopaminergic transmission and other monoaminergic neurotransmitters may lead to neuronal cell inflammation and necrosis in mesolimbic brain regions such as the PFC and NAc (Shukla and Vincent, 2021), potentially explaining the relationship between elevated sICAM-1 and decreased BOLD signal change. These collective findings may pinpoint to how amphetamines modulate reward processing regions by altering neural responses in the presence of inflammation.

Interoception, or the act of sensing, interpreting, and integrating information about the state of inner body systems has been shown to be dysregulated in SUD (Avery et al., 2014; Khalsa et al., 2018; Verdejo-Garcia et al., 2012). The likelihood of detecting significant altered interoceptive signals in response to amphetamines may depend on drug dose, frequency and route of exposure, and cognitive control, to name a few. It is well established that amphetamines are associated with an increased risk of cognitive dysfunction (Huckans et al., 2015; Wright et al., 2021), including deficits in learning and memory (Weingartner et al., 1982; Hurst et al., 1969; O'Daly et al., 2014), and altered interoceptive signals (Verdejo-Garcia et al., 2012). Here, we show an association of sICAM-1 with higher fMRI BOLD signal during interoceptive vs exteroceptive signals in the right amygdala, which has been previously shown by our group in major depressive and STIM (Stewart et al., 2020; Norris et al., 2004; Burrows et al., 2022). Our novel findings with sICAM-1 may suggest that drugs of abuse, such as stimulants, may heighten one's ability to feel bodily sensations in response to emotional/affective processing during inflammation.

Interoception merges bodily signals and affective processes that are critical for addiction, and upon interoceptive disturbances, shapes cognitive-affective processing (Verdejo-Garcia et al., 2012). In the somatic marker hypothesis (Verdejo-Garcia and Bechara, 2009), markers created by an impulsive system, code a primary inducer related to encountering the drug, which is often associated with the amygdala (Verdejo-Garcia et al., 2012). The secondary inducer represents recall or imagining drug use, primarily localized to the ventromedial PFC (Verdejo-Garcia et al., 2012). Whether the primary or secondary inducer prevails, both systems generate somatic markers (i.e., heart rate, sweating) and brain simulations (i.e., expected to happen in the body), which may be impacted by elevated sICAM-1 as shown here (Paulus et al., 2009). These marker signals shape future responses at implicit and explicit levels, thereby activating striatal and motor cortex circuitry, respectively, and lead to drug-seeking behavior.

Finally, no association was found between inflammation (sICAM-1) and the stop signal task (SST). The SST measures impulsivity, which can be defined as the tendency to show sudden reactions to both internal and external stimuli without forethought (Kaboodvand et al., 2024; Fineberg et al., 2014). SUD has been linked to high impulsivity, which consists of several dimensions including lack of premeditation and perseverance, sensation/emotion seeking, and inhibitory control deficits (Czermainski et al., 2017; Ghahremani et al., 2012; Fillmore et al., 2005; Moallem et al., 2018). Our previous research examined sex differences in the relationship between impulsivity and AMPH, which showed larger signals during successful difficult stop trials in the amygdala, NAc, and right anterior/middle insula in the stim+ versus stim- group (May et al., 2024). Several other studies have shown that longer stop signal reaction times are linked to higher drug craving in individuals with amphetamine/methamphetamine misuse (Tabibnia et al., 2011; Monterosso et al., 2005). While Kohno M. et al. found that inflammation (i.e., IL-6) is associated with resting state functional connectivity in individuals with methamphetamine use (Kohno et al., 2018), we found no studies investigating STIM alterations in impulsivity as measured by SST during fMRI signaling. Our lack of significant association between sICAM-1 and impulsivity as measured by SST may reflect the need for future studies with increased sample size.

Future randomized controlled trials could prioritize therapies aimed

at dampening inflammation, particularly targeting adhesion molecules or their upstream mediators. For example, TLR4 antagonists (which inhibit the receptor implicated in drug-induced microglial activation) could reduce the cascade responsible for sICAM-1 upregulation. Additionally, glial modulators or anti-inflammatory medications such as minocycline or ibudilast could be tested to see if they lower sICAM-1 concentrations and, in turn, restore more normative reward and interoceptive signaling. Interventions combining these agents with behavioral therapies (e.g., contingency management, mindfulness-based relapse prevention) would help isolate the contribution of an anti-inflammatory strategy to clinical outcomes. In parallel, targeted lifestyle interventions (e.g., aerobic exercise, specialized nutritional programs) might attenuate peripheral inflammation and could be tested to determine whether they lower sICAM-1 levels and improve fMRI-based markers of reward processing in individuals with STIM.

4.3. Limitations

We recognize there are limitations. First, the data is cross-sectional, and therefore, no direct inferences to causation can be suggested. We also acknowledge that the unbalanced sample size of the stim+ and stim- groups may have affected the study's findings. While our unbalanced groups may reduce statistical power and limit generalizability, unbalanced sample sizes also represent real-world constraints such as participant drop out, where it is especially higher in substance use groups. Nonetheless, our central finding that inflammation may play a central role in stimulant use as indicated by increased sICAM-1 supports our hypothesis that individuals with stimulant use (stim+) would exhibit greater levels of inflammatory analytes than individuals without stimulant use (stim-). Second, although groups did not differ on age, sex, BMI, or PBF, other confounders were not addressed, such as income, employment, education, smoking, and alcohol use. Third, our focus on peripheral-based inflammation does not necessarily inform brain neuroinflammatory status. And fourth, including several tasks within the same scanning session means fatigue may have impacted performance and results. Notwithstanding these limitations, our findings in STIM are an important addition to the continued investigation of inflammatory and fMRI brain-related mechanisms in SUD.

5. Conclusions

sICAM-1 was upregulated in individuals with STIM. sICAM-1 was associated with decreased reward processing, suggesting that a specific STIM—sICAM-1 interaction that may represent a unique brain-mediated mechanism, possibly indicating BBB disruption in STIM. Additionally, sICAM-1 was associated with higher interoceptive signals, which could indicate greater sensation to bodily signals in response to affective processing during inflammation. There was no association with sICAM-1 and SST, reflecting the need for future studies with increased sample size. Next steps are to investigate: (1) TLR4 signaling and if TLR4-related proteins play a role in the increased sICAM-1 observed in the stim+ group; and (2) genetic underpinnings with examination of regulatory mechanisms in astrocyte and microglial-enriched extracellular vesicles from individuals with STIM, as these glial cells may play a role in reward processing and interoception.

CRedit authorship contribution statement

Kaiping Burrows: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Breanna A. McNaughton-Long:** Writing – review & editing, Writing – original draft, Methodology. **Angela K. Yakshin:** Writing – review & editing, Methodology. **Valerio Coussa:** Writing – original draft, Conceptualization. **Rayus Kuplicki:** Writing – review & editing, Validation, Software, Data curation. **Robin L. Aupperle:** Writing – review & editing. **Jonathan B. Savitz:** Writing – review & editing. **Martin P. Paulus:**

Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization. **Jennifer L. Stewart:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Data curation, Conceptualization. **Leandra K. Figueroa-Hall:** Writing – review & editing, Writing – original draft, Conceptualization.

Funding

This work was supported in part by the Laureate Institute for Brain Research, the National Institute of General Medical Sciences Center Grant Award (P20GM121312: PI Paulus), the National Institute of Mental Health (R00MH126950: PI Figueroa-Hall; R01MH123652: PI Savitz), and the National Institute on Drug Abuse (R01DA050677: PI Stewart).

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.

Acknowledgements

We acknowledge the Molecular Core at the Laureate Institute for Brain Research for their support with biobanking and immunoassay analysis, and we thank the Molecular Core staff Konner Hartsell and KeAnna Cruddas for their contributions to data collection. The blood processing and immunoassays were conducted in the Integrative Immunology Center (IIC), which is supported by the School of Community Medicine, The University of Oklahoma, Tulsa, OK and National Institute of General Medical Sciences Center Grant Award (5P20GM109097-08). We thank the IIC staff Ashlee Rempel, Brenda Davis and Chibing Tan for their work and support involved in the data collection and IIC Director Kent Teague for critical review of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bbi.2026.106261>.

Data availability

Data will be made available on request.

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