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Higher substance use is associated with low executive control neural activity and higher inflammation

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ABSTRACT

Individuals with substance use problems show lower executive control and alterations in prefrontal brain systems supporting emotion regulation and impulse control. A separate literature suggests that heightened inflammation also increases risk for substance use, in part, through targeting brain systems involved in executive control. Research on neural and inflammatory signaling in substance use, however, has occurred in parallel. Drawing on recent neuroimmune network models, we used fMRI to examine the relationships between executive control-related brain activity (as elicited by an n-back working memory task), peripheral inflammation, as quantified by inflammatory cytokines and C-reactive protein (CRP), and substance use for the past month in 93 participants [mean age = 24.4 (*SD* = 0.6)]. We operationalized low executive control as a neural inefficiency during the n-back task to achieve normative performance, as reflected in higher working memory-related brain activity and lower activity in the default mode network (DMN). Consistent with prediction, individuals with low executive control and high inflammation reported more substance use over the past month, controlling for behavioral performance on the n-back, sex, time between assessments, body-mass-index (BMI), and personal socioeconomic status (SES) (interaction between inflammation and working memory-related brain activity, b = 0.210, p = 0.005; interaction between inflammation and DMN, b = -0.219, $p < 0.001$). Findings suggest that low executive control and high inflammation may be associated with higher substance use. This has implications for understanding psychological, neural, and immunological risk for substance use problems and the development of interventions to target each of these components.

1. Introduction

Among young adults age 20–29, the most commonly used and abused substances are tobacco, alcohol, and marijuana and young adults display elevated rates of these substances relative to other age groups (Delker et al., 2016; Richardson et al., 2014; Wadsworth et al., 2022). Substance use and abuse are major risk factors for disability and premature loss of life (Andrews & Westling, 2016). Recent national data suggests for young adults exposed to low socioeconomic status (SES) environments, the risk for problems related to common forms of substance use are exacerbated (Baptiste-Roberts & Hossain, 2018) and they experience a disproportionate burden of negative social, legal, and health consequences (Collins, 2016; Garrett et al., 2019).

Emerging *neuroimmune network* (NIN) models suggest that stress and adversity generated by low SES environments heightens cross-talk between the brain and immune system in a manner that affects individuals' propensity to use common substances of abuse (Nusslock & Miller, 2016). To date, however, there is minimal empirical research linking neuroimmune signaling to substance use, particularly in rural Black communities that have been subject to decades of economic neglect, residential segregation, and racial discrimination, all of which can stimulate inflammation and undermine neurocognitive development (Blair & Raver, 2016; Milaniak & Jaffee, 2019). Therefore, in this study, we examine the association between neural indicators of executive control, peripheral inflammatory activity, and tobacco, alcohol, and cannabis use in rural Black young adults.

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Growing evidence highlights the role of executive control in the use and misuse of addictive substances (Hester et al., 2010; Mollick & Kober, 2020). Executive control is an umbrella term used to describe several cognitive processes including the ability to inhibit automatic responses, update the contents of working memory, and flexibly shift and regulate behavior (Miller, 2000; Miyake & Friedman, 2012). People with low executive control can find it difficult to regulate their emotions (Johnstone et al., 2007; Young et al., 2016) and they may consume substances to manage their dysphoria (Koob & Volkow, 2016; Volkow et al., 2016). They also can find it hard to inhibit the urge to use addictive or unhealthy substances when in their presence (Hester et al., 2010). Consistent with this view, individuals with, and at risk for, substance use problems show deficits on laboratory tasks designed to probe executive control (Bickel et al., 2014; Nigg et al., 2006; Thush et al., 2008), and in prefrontal brain systems which support emotion regulation, behavioral inhibition, and impulse control (Goldstein & Volkow, 2011; Lowe et al., 2019).

A separate literature suggests that inflammation also increases one's risk for substance use (Hutchinson & Watkins, 2014). Inflammation is one of the first responses of the immune system to infection and injuries, and is coordinated by signaling molecules, known as cytokines, that facilitate tissue repair and the clearance of pathogens (Netea et al., 2017). To date, research on neural and inflammatory models of substance use mostly has occurred in parallel. Recently, however, we and others (Eisenberger et al., 2017; Hutchinson & Watkins, 2014; Nusslock & Miller, 2016; Treadway et al., 2019) have proposed neuroimmune network models that highlight bidirectional signaling between the brain and immune system in both mental and physical health conditions. These models are predicated on the fact that although inflammatory cytokines are predominately released by immune cells (e.g., monocytes, macrophages) in the periphery, they can access the brain via active transport, leaky regions of the blood–brain-barrier, or engaging afferent vagal fibers (Haroon et al., 2012; Irwin & Cole, 2011). Inflammation does not randomly access the brain, but instead targets neural signaling in regions that subserve emotion processing and regulation, as well as executive control (Eisenberger et al., 2010; Harrison et al., 2009; Inagaki et al., 2012; Weber et al., 2017). This is adaptive when regulated and it coordinates a set of defensive and sickness behaviors (e.g., inactivity) that facilitate pathogen removal and wound healing. When dysregulated, however, chronic inflammation can modulate the structure, function, and development of brain regions involved in emotion processing and regulation, including the prefrontal cortex (PFC) (Capuron et al., 2012; Harrison et al., 2009; Meyer, 2013). For example, higher inflammatory biomarkers in the periphery are associated with smaller medial PFC volume, lower cortical white matter integrity, and lower connectivity in resting state networks involved in emotion regulation and executive control (Gianaros et al., 2013; Marsland et al., 2008; Nusslock et al., 2019; Satizabal et al., 2012).

The present study tests the hypothesis that low executive control and high inflammation synergistically compound each other to increase risk for heightened substance use. Recognizing that executive control is a broad construct, we focus specifically on working memory, which refers to one's ability to mentally hold and manipulate a limited amount of information for a brief period (Baddeley, 1998; Miller et al., 2018). Tasks that estimate working memory often require individuals to both repeat back and change a series of stimuli in some way. Working memory facilitates both simple and complex cognitive functions, such as setting goals, making decisions, regulating emotions, and updating or adjusting behavior according to perceived consequences (Diamond, 2013; Finn, 2002; Miller et al., 2018). Deficits in working memory have been associated with impulsivity, poor decision-making, mood and attention disorders, and increased substance use and misuse (Bechara & Martin, 2004; Gärtner et al., 2018; Hinson et al., 2003; Thush et al., 2008).

Successful working memory involves the activation of task-relevant executive control brain regions, and the deactivation or suppression of the default mode network (DMN) (Bressler & Menon, 2010). Task-relevant regions include the bilateral dorsolateral prefrontal cortex (DLPFC) and the superior frontal gyrus, which mediate executive functions such as working memory and inhibitory control, and the posterior parietal cortex, involved in attention and multimodal sensory perception (Boisgueheneuc et al., 2006; Bressler & Menon, 2010; Dosenbach et al., 2006; Gordon et al., 2018; Philip et al., 2013; Sweet et al., 2008). Increased task difficulty and greater effort are associated with increased activity in these regions, reflecting heightened vigilance and executive control (Dosenbach et al., 2006; Gordon et al., 2018; Sweet et al., 2006). The DMN, by contrast, includes the bilateral medial and dorsal medial prefrontal cortex, the posterior cingulate cortex and precuneus, the angular gyrus, and inferior parietal cortices. The DMN often is involved in task-irrelevant mental processes, including mental simulations of the past and future, self-monitoring and mind wandering (Raichle, 2015). These regions are frequently suppressed in order to optimally perform a cognitively demanding task, and greater deactivation of DMN regions is typically associated with increased task difficulty and increased effort (Buckner et al., 2008; Duda et al., 2019; Owens et al., 2018; Philip et al., 2013; Raichle, 2015; Sweet et al., 2008; Sweet, Jerskey, et al., 2010; Syan et al., 2019).

Researchers have taken different approaches to studying variations in working memory-related brain activity. The first aims to identify the profile of brain activity associated with a worse performance on working memory tasks. These studies report that individuals with low executive control, as well as substance use disorders and other psychiatric conditions, display lower activity in task-relevant brain regions, such as the DLPFC, while failing to suppress activity in the DMN, causing them to be easily distracted and commit errors in performance (Fassbender et al., 2009; Hugdahl et al., 2004; Metin et al., 2015; Squeglia & Gray, 2016; Weissman et al., 2006). A second set of studies equates or statistically controls for performance on a working memory task and examines the profile of brain activity required to achieve normative performance. These studies report that people with conditions characterized by low executive control, including substance use problems, display excessive activity in task-relevant brain regions, and, in some cases, an excessive suppression of the DMN to achieve normative performance (Gärtner et al., 2018; Sweet et al., 2010b; Wang et al., 2015). These findings are interpreted from a neural inefficiency perspective and suggest that people with lower executive control need to overcompensate and put forth more effort to successfully perform cognitively demanding tasks (Duda et al., 2019; Owens et al., 2018; Philip et al., 2013; Sweet et al., 2008; Sweet, Jerskey, et al., 2010).

Here we examined the relationships between working memory-related brain activity, as measured by the n-back task, peripheral inflammatory biomarkers, as quantified by inflammatory cytokines and C-reactive protein (CRP), and substance use during the past month. Though prior studies have examined the separate relationships between executive control neural activity, peripheral inflammation, and substance use, no study has examined if lower executive control and higher peripheral inflammation compound each other to heighten risk for substance use. We statistically controlled for behavioral performance on the n-back task in all analyses to equate for performance and to examine the profile of working memory-related brain activity required to achieve normative performance. We predicted that people with low executive control and high inflammation would display more substance use. Importantly, neuroimmune dysregulation is viewed as a risk factor for engaging in a broad range of unhealthy and potentially addictive behaviors (Nusslock et al., 2024; Nusslock & Miller, 2016). Thus, we predicted that low executive control and high inflammation would be associated higher overall substance use, rather than any one specific substance. We operationalized low executive control as a neural inefficiency on the n-back task to achieve normative performance (i.e., after statistically controlling for behavioral performance), as reflected in greater task-relevant brain activity and greater DMN suppression. Participants were rural African Americans who were 25 years of age. We

focused on rural African Americans because they are disproportionately exposed to inflammation-triggering stressors including childhood adversity, racial discrimination, and economic hardship (Acevedo-Garcia et al., 2008; DeNavas-Walt & Proctor, 2014; Slopen et al., 2010). Furthermore, the vast majority of human brain imaging research has been performed on White persons, with minimal attention given to racial and/or ethnic variation (Nusslock & Farah, 2022). We focus on 25-year-olds because prefrontal brain systems involved in executive control are going through their final stages of development at this age (Gu et al., 2015; Somerville & Casey, 2010), and this is a critical developmental juncture when rates of substance use rapidly escalate among African Americans (Cooper et al., 2005; Substance Abuse and Mental Health Services Administration, 2016).

2. Methods

2.1. Participants

The present study involved 119 young African American men and women (53.78 % women) from rural Georgia who were randomly selected from a larger longitudinal parent study to complete an MRI session. Participants were 24.4 years old (SD = 0.6) when they completed data collection for the present analyses. In the original parent study, 667 families were randomly recruited from rural communities in Georgia when the participants were 11 years old [M = 11.2, SD = 0.34; see Brody et al. (2014) for details]. At the beginning of the longitudinal study, the sample could be characterized as working poor; primary caregivers worked an average of 39.4 h per week, yet 46.3 % of the sample lived below federal poverty standards. The subsample of 119 participants included in the present analyses did not differ from the larger sample at baseline on family poverty status, single-parent status, family income, parent age, parenting and parent–child relationship, parental depression, or children's self-esteem and self-control.

Participants were right-handed and were screened to exclude those who had MRI contradictions or a history of chronic illness, including asthma, cancers, diabetes, heart diseases, persistent infections, autoimmune conditions, and major psychiatric disorders. Participants were free of any psychiatric medications for at least one month before participating. Subsequent analyses excluded 26 participants because of inadequate performance on the n-back task (n = 19), excessive movement (n = 4), or other artifacts (n = 3). Thus, the final analytic sample for this study was 93 participants (49.5 % female). Participants provided written informed consent. (See Table 1 for demographic information).

Table 1
Participant Characteristics.

	Number (%) or Mean (SD)
Age at study entry, years	24.4 (0.6)
Female, percent	46 (49.5 %)
Single	66 (70.9 %)
Cohabited	21 (22.6 %)
Married	6 (6.5 %)
Years of education	13.1 (1.9)
Full time employed	53 (57.0 %)
Part time employed	14 (15.0 %)
Disability	1 (1.1 %)
Unemployed	25 (26.9 %)
Household income < 15,000	16 (17.2 %)
Household income 15,000 – 30,000	37 (39.8 %)
Household income 30,000 – 45,000	7 (7.5 %)
Household income 45,000 – 60,000	5 (5.4 %)
Household income 60,000 – 75,000	4 (4.3 %)
Household income > 75,000	4 (4.3 %)
Body Mass Index (BMI)	29.7 (9.8)
Mean correct response on 2-back task	0.82 (0.08)
C-reactive protein (CRP mg/L)	3.5 (5.3)
Interleukin (IL) 6 (pg/ml)	2.1 (2.2)
Interleukin (IL) 10 (pg/ml)	1.5 (2.4)
Tumor necrosis factor alpha (TNFa; pg/ml)	3.8 (1.3)
Substance use	3.2 (3.5)

2.2. Procedures

We assessed neural activity during a working memory paradigm (n-back task), peripheral inflammatory biomarkers, and substance use for the past month using procedures outlined below. Working memory-related brain activity and peripheral inflammation were measured on the same day, and substance use was assessed an average of ninety days before the neuroimmune assessments (SD = 58 days).

2.3. fMRI Working Memory Paradigm

The n-back task was administered during functional imaging to measure working memory performance and associated brain responses. This is a widely employed functional MRI paradigm (Jaeggi et al., 2010; Owen et al., 2005) that has been shown to reliably elicit activation responses from brain regions associated with working memory and executive control, including the dorsolateral prefrontal cortex (DLPFC), superior frontal gyrus, and posterior parietal cortex, among other regions (Owens et al., 2018; Sweet et al., 2008; Yaple et al., 2019). The n-back also deactivates or suppresses activity in brain regions involved in the DMN, including the bilateral medial and dorsal medial prefrontal cortex, the posterior cingulate cortex and precuneus, the angular gyrus, and inferior parietal cortices (Duda et al., 2019; Owens et al., 2018; Philip et al., 2013; Sweet et al., 2008; Sweet, Jerskey, et al., 2010; Syan et al., 2019).

The n-back task requires participants to buffer, update, match, encode, and respond to patterns of consonants. Stimulus presentation parameters were based on previous studies (Braver et al., 1997; Sweet et al., 2008). The present study included two n-back conditions: a 2-back and a 0-back. During the 2-Back, six series of 15 consonants (excluding "L" due to ambiguity in lower-case) were presented visually in 45-second blocks. A consonant was presented every 3 s (500 ms with a 2500 ms inter-stimulus interval). Participants were asked to use a two-button response box to indicate "yes" if a consonant was the same as the consonant presented two earlier in the series, and "no" if it was not. Capitalization was randomized and each consonant block contained 33 % targets (i.e., correct "yes" responses). The 0-back control task required participants to respond "yes" when they saw a predetermined target consonant ("H" or "h") and "no" for any other consonants. This condition included six series of nine consonants presented in 27-second blocks at the same rate and with the same target frequency as the 2-back. In total, there were two six-minute imaging runs of three 0-back/2-back cycles each. Behavioral performance was quantified as the proportion of correct responses to total responses during the 2-Back.

In line with prior research (Oshri et al., 2022; Sweet et al., 2006; Sweet et al., 2010b), we took a number of steps to equate or match working memory performance across participants to examine the profile of working memory-related brain activity required to achieve normative performance. First, we included performance on the 2-back task during fMRI scanning as a covariate in all analyses to control variance associated with performance accuracy in statistical models. Second, participants were trained to perform the n-back task and asked to practice. Practice consisted of a 15 consonant 2-back task, which was administered a minimum of twice: at least once with feedback from the administrator, followed by as many subsequent attempts as necessary to achieve a criterion score of 73 % correct responses. Finally, in line with prior research (Sweet et al., 2008; Sweet, Jerskey, et al., 2010), we excluded participants who did not achieve 60 % accuracy on the 2-back or 80 % accuracy on the 0-back (n = 19), as this is a requirement of using the task. We selected 60 % as an exclusion criterion for the 2-back because 10 % is approximately one standard deviation above 50 % and thus we can be confident that participants are performing above chance.

2.4. fMRI Acquisition and Image Processing

Imaging data were collected using a GE Signa HDx 3 T scanner (GE Healthcare, Chicago, IL) with an 8-channel head coil at the University of Georgia's Bio-Imaging Research Center. Structural images were acquired for anatomical reference using a high-resolution T1-weighted, fast-spoiled gradient-echo scan (TR = 7.8 ms; TE = 3.0 ms; FOV = 256 x 256 mm; matrix = 256 x 256; flip angle = 20°; 160 contiguous 1 mm axial slices; voxel size = 1 mm^3). Functional images were acquired using T2* echo-planar imaging (EPI) with a single-shot, gradient-echo pulse sequence (TR = 2,500 ms, TE = 25 ms, FOV = 224 x 224 mm; flip angle = 90°; matrix = 64 × 64, 38 contiguous 3.5-mm axial slices, voxel size = 3.5 mm^3).

MRI data were processed using Analysis of NeuroImages software (AFNI) (Cox, 1996). Standard preprocessing of the raw data included concatenation of EPI imaging runs, alignment of EPI to T1 anatomical volumes, EPI volume registration to the 3rd volume of the first imaging run, censoring any volumes that exhibited outlying values or excessive movement (>0.3 mm between volumes), and transformation into standard stereotaxic space (Talairach & Tournoux, 1988). Participants exhibiting greater than 25 % censored volumes were excluded from analyses. Spatial blurring over a 6-mm radius was applied using a Gaussian kernel to compensate for typical variations in functional neuroanatomy across participants.

A voxelwise General Linear Model (GLM) was conducted to quantify neural responses to the n-back paradigm. For each voxel of every individual, a GLM of the temporal pattern of the 2-back presentation (including hemodynamic transitions modeled as a gamma function), the 0-back control task, and covariates (movement quantified during the EPI volume registration process, linear drift) was performed using the BOLD signal over time as the dependent variable. The 0-back control task was the baseline to which neural activity during the 2-back was compared (i.e. 2-back vs 0-back contrast).

Regions of interest (ROI) previously identified as nodes of working memory and default mode networks were selected using Neurosynth (neurosynth.org), a large-scale online database that uses a *meta*-analytic approach to aggregate the results of published neuroimaging studies associated with terms of interest (Yarkoni et al., 2011). This approach to ROI extraction is consistent with published work in the field (Gutierrez-Colina et al., 2021; Tso et al., 2018). Aggregated data related to the search terms "Working Memory" and "Default Mode" were used to form association statistical inference maps, which indicates whether activation in a given voxel occurs more consistently among studies that mention the search term than for studies that do not using a false discovery rate (FDR) corrected voxel threshold of $p < 0.01$. These inference maps were resampled to match our dataset geometry (i.e., 3.5 mm^3 isometric voxel resolution in standard Talairach space) and further thresholded to resolve the eight most robust nodes greater than 10 voxels for each network (see Table 2 and Fig. 1). DMN nodes that crossed the midline (i.e., orbitofrontal cortex and posterior cingulate/precuneus) were divided into right and left ROIs. The final FDR corrected voxel thresholds for ROI generation were $z > 8.41$ for the working memory Network and $z > 6.93$ for the DMN. Region names were based on center of mass using the Human Connectome Project (HCP) anatomical atlas in AFNI (Glasser et al., 2016). Mean beta coefficients for the 2-back vs 0-back contrast within each of these ROIs were extracted for subsequent analyses. To manage multiple comparisons, and consistent with our prior work (Hallowell et al., 2019), we averaged the 8 working memory ROIs to form a working memory composite score, and the 8 Default Mode ROIs to form a Default Mode composite score. We weighted each ROI by its number of voxels when forming composite scores. To complement analyses with composite scores, we also present follow-up analyses with individual working memory and DMN ROIs in the Results section and Supplementary Materials.

As expected, the mean value of the working memory composite score was a positive number ($M = 0.22$; $SD = 0.22$) and the mean value of the DMN composite score was a negative number (M = -0.16; $SD = 0.15$), indicating that the working memory network was activated at the group level and the DMN was deactivated at the group level during the n-back task. Furthermore, each of the 8 individual working memory ROIs were activated during the n-back task (i.e., had a positive mean value) and each of the DMN ROIs were deactivated (i.e., had a negative mean value).

Table 2
Working Memory and Default Mode Network (DMN) Regions-of-Interest (ROI).

Working Memory ROIs Area	Cluster Size	Center-of-Mass Coordinates (x,y, z)
Left Rostral Middle Frontal Gyrus	106	−44.4, 17.7, 29.3
Left Inferior Parietal Lobule	86	−36.4, −52.3, 44
Right Rostral Middle Frontal Gyrus	82	41.3, 35.6, 26.2
Right Inferior Parietal Lobule	70	39.8, −48.8, 44.2
Right Caudal Middle Frontal Gyrus	62	30.5, 5.4, 53.8
Left Caudal Middle Frontal Gyrus	47	−27.3, −1.7, 54.3
Left Superior Frontal Gyrus	17	−3.4, 15.4, 47.3
Right Superior Parietal Lobule	10	10.5, −68.6, 53.8
Default Mode Network ROIs		
Left Precuneus	97	−4.2, −52.3, 28.5
Right Precuneus	91	4.6, −53.7, 27.2
Left Medial Orbitofrontal Gyrus	69	−3.2, 51.3, 6.8
Left Angular Gyrus	69	−47, −65.8, 33
Right Angular Gyrus	69	49.7, −63.1, 31.3
Right Medial Orbitofrontal Gyrus	59	3.9, 49.2, 2.7
Left Middle Temporal Gyrus	10	−60.9, −15.3, −17.3
Right Superior Frontal Gyrus	10	24.5, 29.8, 46.4

Note: Talairach Coordinates are reported in LPI orientation

As noted above, and in line with theory and prior research (Gärtner et al., 2018; Sweet., et al., 2010b; Wang et al., 2015), we operationalized low executive control as a neural inefficiency on the n-back task to achieve normative performance (i.e., after equating or statistically controlling for performance on the n-back task). This neural inefficiency is reflected in greater task-relevant activity in working memory and executive control brain regions, and greater suppression of DMN-related brain activity to achieve this normative performance. Support for this approach are studies showing that greater task-relevant brain activity and greater DMN suppression during the n-back task (after equating for behavioral performance) are associated with greater effort to achieve normative performance, mental and physical health problems, and exposure to early life adversity (Duda et al., 2019; Owens et al., 2018; Philip et al., 2013; Sweet et al., 2008; Sweet, Jerskey, et al., 2010; Syan et al., 2019). To further validate this metric of neural inefficiency in the present data set, we examined the relationships between reaction time on the n-back task with the working memory and DMN composite score, after statistically controlling for behavioral performance on the n-back task. As expected, individuals with greater working memory neural activity had a slower (i.e., less efficient) reaction time on the n-back task after statistically controlling for behavioral performance ($r_{partial} = 0.22$, $p = 0.04$). There was no relationship, however, between DMN neural activity and reaction time after statistically controlling for behavioral performance ($r_{partial}$ = -0.04, $p = 0.074$; although this relationship was present and in the expected direction when behavioral performance was excluded from the model, r = -0.20, $p = 0.055$).

2.5. Inflammation Biomarkers

From antecubital blood, we quantified serum levels of CRP, interleukin (IL)-6, IL10, and tumor necrosis factor alpha (TNFα). Although IL-10 functionally is an anti-inflammatory cytokine, it is expressed only under conditions of inflammation. Thus, statistically, it behaves like the inflammatory cytokines such that higher levels reflect more inflammatory activity. The inflammatory markers were assayed in a single batch

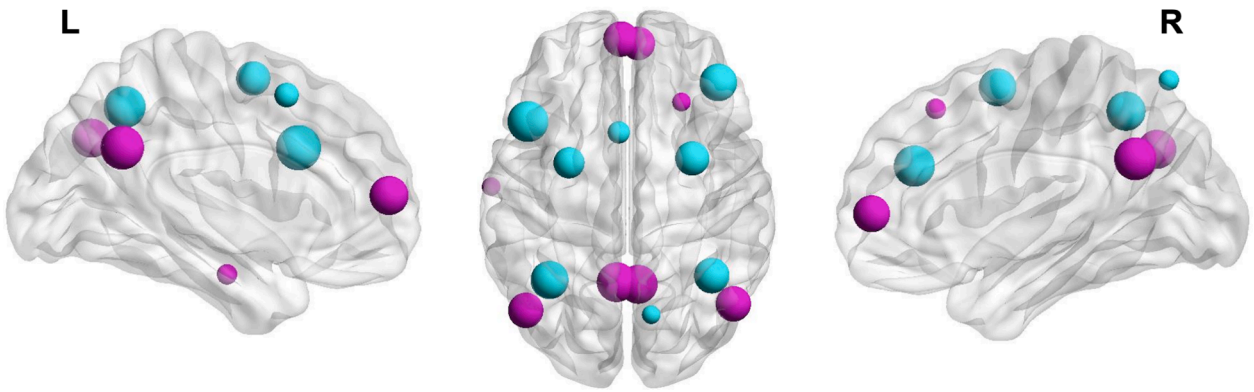

Fig. 1. Working Memory and Default Mode Network (DMN) Regions-of-Interest (ROI). Axial and both left (L)- and right (R)-hemisphere sagittal views of the working memory and DMN ROIs. Working memory ROIs are depicted in turquoise and DMN in purple. The size of the sphere is scaled to the cluster size of the ROI (see Table 2). The spheres are merely visual depictions of the ROIs that were generated using Neurosynth (see Methods). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

at the end of the study. CRP was measured by high-sensitivity immunoturbidimetric assay on a Roche/Hitachi cobas c 502 analyzer (Roche Diagnostics, Basel, Switzerland) (lower limit of detection, 0.2 mg/L). The average intra- and inter-assay coefficients of variation obtained for this particular assay were 2.5 % and 5.6 %. The cytokines were measured in duplicate by electrochemiluminescence on a SECTOR Imager 2400A (Meso Scale Discovery, Rockville, MD) with a Human ProInflammatory Ultra-Sensitive assay kit (Meso Scale Discovery), following the manufacturer's instructions. The kit's lower limits of detection range from 0.19 pg/mL (IL-6) to 0.57 pg/mL (IL10). Across runs, the intra-assay coefficients of variation obtained for this batch of assays for duplicate pairs were 4.01 % (IL-6), 4.59 % (IL-10), and 3.80 % (TNFa). Following previous work (G. E. Miller et al., 2014; Nusslock et al., 2019), we Z-scored the values of each biomarker and then summed them to form a composite inflammatory biomarker score. A higher score on this composite reflects higher systemic inflammation. The composite inflammatory biomarker score was significantly associated with each of the individual inflammatory biomarkers at $p < 0.001$ (IL-6, $r = 0.72$; IL-10, $r = 0.60$; TNFα, $r = 0.72$; CRP, $r = 0.68$). There are several advantages to using a composite inflammatory score. First, a composite score lowers the chance of a Type I Error by reducing the number of tests performed (in this case, by 75 %). Second, by virtue of including multiple proteins, the composite represents a conservative approach to defining inflammation, because obtaining a high score requires having an elevated score on more than one biomarker. Third, it considers the dynamic activity among the inflammatory markers of interest acting on target cells and the cascading manner in which these markers are released. To supplement analyses of the composite, we present separate models for each inflammatory biomarker in the Supplemental Materials.

2.6. Substance Use

Participants reported their past-month frequencies of cigarette smoking, alcohol use, heavy drinking, and marijuana use with items from the Monitoring the Future Study (Johnston et al., 2007). A response set ranging from 0 (not at all) to 6 (more than two packs a day) was used for cigarette smoking; a scale ranging from 0 (none) to 5 (20 or more times) was used to measure alcohol use, heavy drinking, and marijuana use. We predicted that low executive control and high inflammation would be associated with higher overall substance use, rather than any one specific substance. Accordingly, we summed the responses for each of the individual substances to form a substance use composite ($\alpha = 0.66$), a procedure that is consistent with our own and others' prior research (Brener et al., 2022; Chen et al., 2018; Weigard et al., 2021). This substance use measure has demonstrated predictive validity among samples of Caucasian and Black adolescents (Johnston et al., 2007) and among Black adolescents and young adults (Brody et al., 2019). Modest internal consistency is common with composite measures indexing different forms of substance use (Spoth et al., 2009). Because the distributions of substance use were skewed, we used a Poisson model for analyses involving substance use data. To compliment analyses with the substance use composite score, we present primary analyses for each separate substance in the Supplemental Materials.

2.7. Personal Socioeconomic Status (SES)

Participants reported their average monthly gross personal incomes and the highest level of education they have completed as 1 = Grade 9 or below, 2 = Grade 10, 3 = Grade 11, 4 = High school graduate or GED, 5 = Some college or trade school, 6 = Trade school diploma or certificate or associate of arts degree, 7 = Bachelor's degree, 8 = Some graduate training, 9 = Master's degree, and 10 = Doctorate or Professional degree. We standardized participants' income and education achievement and summed them to form a personal SES score.

2.8. Data Analysis

To test our primary hypothesis that low executive control and high inflammation are associated with increased substance use, we conducted two linear regression models where we regressed the substance use composite score- onto (a) the composite inflammatory biomarker score, (b) the working memory composite score (Analysis I) or the DMN composite score [Analysis II], and (c) the interaction between the inflammation composite score and the respective neural composite score (working memory for Analysis I; DMN for Analysis II). We statistically controlled for variance associated with sex, behavioral performance on the 2-back task, the number of days between the substance use and neuroimmune assessments, body mass index (BMI), and personal socioeconomic status (SES) in all analyses. Significance was two-tailed, $\alpha < 0.05$, and we employed Fisher's protected t tests to minimize familywise error rate which requires a significant omnibus analysis to proceed to follow-up analyses (Cohen et al., 2003). We also used composite scores for each of the three primary variables (inflammation, neural activity, substance use) to minimize familywise error rate. Significant interaction terms were interpreted by plotting the estimated frequency of substance use for the different levels of working memory activation and DMN suppression by different levels of inflammation (low = 1 *SD* below the mean, high = 1 *SD* above the mean). To further probe significant interactions, we ran separate regression models for each individual ROI that comprised a significant working memory and/or DMN composite score to examine the influence of each specific brain region in

a network.

3. Results

We present the scatter plots of the single order relationships between composite working memory and DMN neural activity with the inflammatory composite score in the Supplemental Materials.

3.1. Composite Working Memory and Default Mode Network Activity by Inflammation on Substance Use

Table 3 presents the results of analyses regressing the substance use composite score onto the composite inflammatory score and composite working memory (Analysis I) and DMN (Analysis II) neural activity. A significant interaction between inflammation and working memory neural activity on substance use emerged (B = 0.210, 95 % CI [.062, 0.358], $p = 0.005$), independent of main effects and covariates. The top panel of Fig. 2 presents this interaction with slopes. Consistent with prediction, simple-slopes analyses indicated that inflammation was positively associated with substance use among participants with high levels of working memory neural activity during the n-back task (i.e., those with low executive control, who had to recruit more working memory neural resources to achieve the same performance; b = 0.493 [se = 0.130], $p < 0.001$; rate ratio = 1.64, 95 % CI [1.27, 2.12). For participants with low levels of working memory neural activity, inflammation and substance use were unrelated (b = 0.073 [se = 0.084], $p = 0.385$; rate ratio = 1.08, 95 % CI [0.910, 1.271]). Similarly, a significant interaction between inflammation and DMN neural activity on substance use also emerged (B = -0.219, 95 % CI [-0.335, −0.104], $p = 0.001$), independent of main effects and covariates. The bottom panel of Fig. 2 presents this interaction with slopes. Consistent with prediction, simple-slopes analyses indicated that inflammation was positively associated with substance use among participants with low levels of DMN reactivity (i.e., those who needed to suppress the DMN more to achieve the same behavioral performance; b = 0.367 [se = 0.087], $p < 0.001$; rate ratio = 1.44 % CI [1.214, 1.716]). For participants with high levels of DMN neural activity, inflammation and substance use were unrelated (b = -0.071 [se = 0.102], $p = 0.490$; rate ratio = 0.93, 95 % CI [0.760, 1.141]). (See Supplemental Materials for analyses involving each inflammatory biomarker and each separate substance with the composite working memory and DMN neural activity).[1]

Table 3
Substance use regressed on inflammation and composite working memory (Model 1) and default mode network (Model 2) neural activation.

	B	95 % CI	*p*
Model 1. Working memory composite neural activity			
Intercept	1.119	0[.998, 1.241]	0.000
Sex	0.526	0[.271, 0.782]	0.000
Performance on n-back	0.101	[-0.024, 0.225]	0.113
Time[1]	0.004	0[.001, 0.006]	0.001
Body mass index (BMI)	−0.025	[-0.169, 0.119]	0.735
Personal SES	−0.079	[-0.155, −0.002]	0.043
Inflammation	0.283	0[.128, 0.438]	0.000
WM composite	0.079	[-0.037, 0.195]	0.182
WM X Inflammation	0.210	0[.062, 0.358]	0.005
Model 2. Default mode network composite neural activity			
Intercept	1.078	0[.955, 1.202]	0.000
Sex	0.499	0[.241, 0.757]	0.000
Performance on n-back	0.130	0[.006, 0.255]	0.040
Time[1]	0.003	0[.000, 0.005]	0.023
Body mass index (BMI)	0.033	[-0.115, 0.181]	0.664
Personal SES	−0.074	[-0.150, 0.002]	0.056
Inflammation	0.148	0[.002, 0.294]	0.047
DMN composite	−0.064	[-0.184, 0.057]	0.303
DMN x Inflammation	−0.219	[-0.335, −0.104]	0.000

[1] number of Days between substance use and neuroimmune assessments; WM, working memory; DMN, default mode network; SES, socioeconomic status.

3.2. Follow-up Analyses with Individual Working Memory and Default Mode Network Regions-of-Interests

Table 4 presents the results of follow-up analyses regressing the substance use composite score onto the composite inflammatory score and each individual working memory and DMN ROI separately. Within the working memory network, there was a significant ROI by inflammation interaction in the left rostral middle frontal gyrus (B = 0.224, 95 % CI [.076, 0.373], $p = 0.003$), the right inferior parietal lobule (B = 0.225, 95 % CI [.0790, 0.360], $p = 0.001$), the left caudal middle frontal gyrus (B = 0.184, 95 % CI [.048, 0.319], $p = 0.008$), the left superior frontal gyrus (B = 0.128, 95 % CI [.006, 0.249], $p = 0.039$) and the right superior parietal lobule (B = 0.234, 95 % CI [.060, 0.408], $p = 0.008$). Consistent with prediction, simple slope analyses indicated that inflammation was positively associated with substance use among participants with high levels of working memory neural activity in each of the significant working memory ROIs (See Supplemental Fig. 1 Materials). Among the DMN regions, there was a significant ROI by inflammation interaction in the left precuneus (B = -0.147, 95 % CI [-0.260, −0.035], $p = 0.010$), right precuneus (B = -0.344, 95 % CI [-0.344, −0.090], $p < 0.001$), left medial orbitofrontal gyrus (B = -0.253, 95 % CI [-0.398, −0.108], $p =< 0.001$), left angular gyrus (B = -0.226, 95 % CI [-0.355, −0.097], $p =< 0.001$), right angular gyrus (B = -0.209, 95 % CI [-0.365, −0.052], $p = 0.009$), and the right medial orbitofrontal gyrus (B = -0.3132, 95 % CI [-0.494, −0.171], $p < 0.001$). Consistent with prediction, simple slope analyses indicated that inflammation was positively associated with substance use among participants with low levels of DMN activity in each of the significant DMN ROIs (See Supplemental Fig. 2 Materials).

4. Discussion

Consistent with prediction, we found that individuals who displayed both low executive control and high inflammation reported higher substance use behaviors over the past month. We statistically controlled for behavioral performance on the 2-back task, and excluded participants who performed poorly on this task, in order to equate for performance and to examine the profile of executive control-related brain activity required to achieve normative performance. We defined low executive control as a neural inefficiency during the n-back task to achieve this normative performance; meaning that participants with low executive control had to work harder to exhibit valid or normative task performance. This profile of neural inefficiency is characterized by higher working memory-related neural activity on the n-back, and lower activity in the DMN after statistically equating for behavioral performance. In line with prediction, both high levels of working memory neural activation and low levels of DMN activation after statistically equating for performance interacted with inflammation to predict higher substance use. We also controlled for sex, the number of days between the substance use and neuroimmune assessments, BMI, and SES. We excluded participants with a chronic physical illness or a major psychiatric diagnosis, and participants were free of any psychiatric medications for at least one month before participating, suggesting that our findings are not confounded by a comorbid health condition.

Low executive control and heightened inflammation have both been associated with substance use in separate literatures (Hutchinson & Watkins, 2014; Koob & Volkow, 2016). The present study tested the

[1] The results remain unchanged if outliers of inflammatory biomarkers are removed either by winsorizing or excluding inflammatory data that are more than two standard deviations away from the mean. This is true regardless of whether outliers are removed before or after generating the composite inflammatory biomarker score.

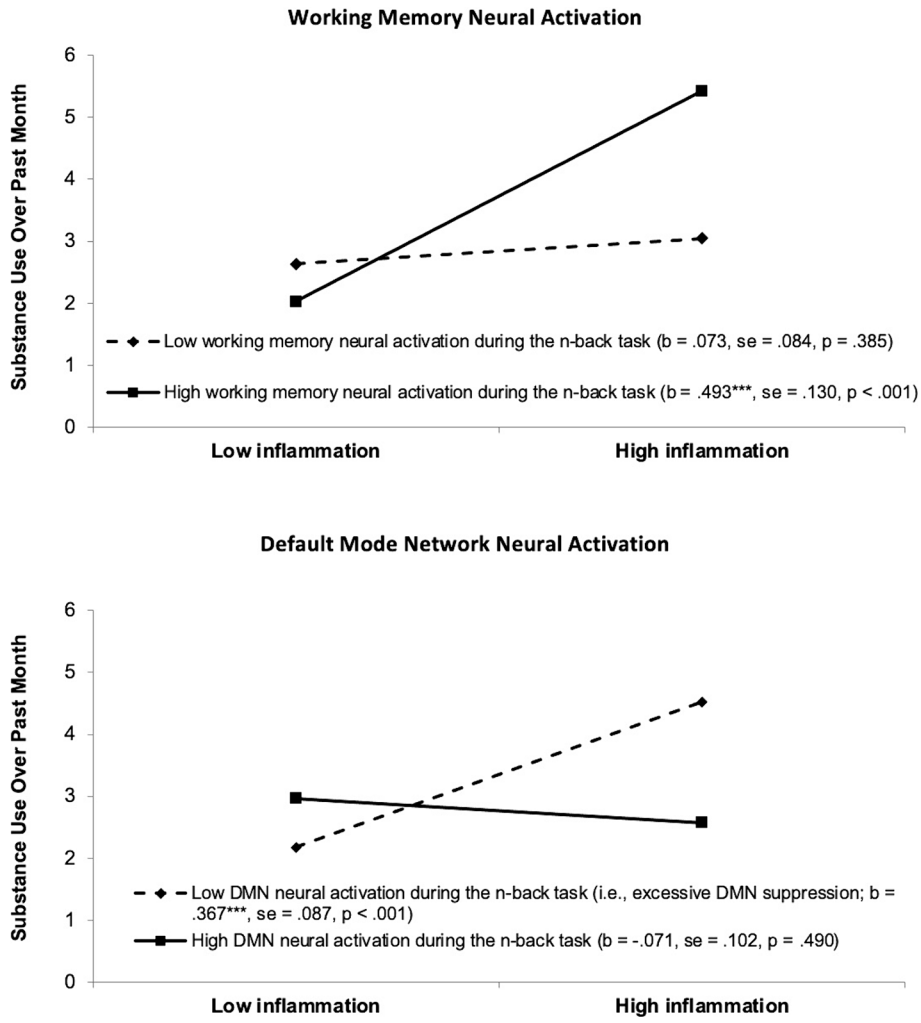

Fig. 2. Relationship between inflammation and composite working memory (top panel) and default mode network (bottom panel) neural activation on substance use over the past month. High = 1 standard deviation above the mean; low = 1 standard deviation below the mean; DMN = default mode network.

Table 4
Substance use regressed on inflammation and individual working memory and default mode network (DMN) regions-of-interests.

	B	95 % CI	*p*
Interaction of inflammation and working memory ROIs on substance use			
Left Rostral Middle Frontal Gyrus	0.224	0[.076, 0.373]	0.003
Left Inferior Parietal Lobule	0.127	[-0.018, 0.273]	0.087
Right Rostral Middle Frontal Gyrus	0.099	[-0.042, 0.240]	0.168
Right Inferior Parietal Lobule	0.225	0[.090, 0.360]	0.001
Right Caudal Middle Frontal Gyrus	0.039	[-0.117, 0.196]	0.621
Left Caudal Middle Frontal Gyrus	0.184	0[.048, 0.319]	0.008
Left Superior Frontal Gyrus	0.128	0[.006, 0.249]	0.039
Right Superior Parietal Lobule	0.234	0[.060, 0.408]	0.008
Interaction of inflammation and DMN ROIs on substance use			
Left Precuneus	−0.147	[-0.260,- 0.035]	0.010
Right Precuneus	−0.217	[-0.344,- 0.090]	0.000
Left Medial Orbitofrontal Gyrus	−0.253	[-0.398, −0.108]	0.000
Left Angular Gyrus	−0.226	[-0.355, −0.097]	0.000
Right Angular Gyrus	−0.209	[-0.365, −0.052]	0.009
Right Medial Orbitofrontal Gyrus	−0.332	[-0.494, −0.171]	0.000
Left Middle Temporal Gyrus	−0.043	[-0.168, 0.081]	0.497
Right Superior Frontal Gyrus	−0.045	[-0.169, 0.078]	0.472

Note. All models controlled for sex, behavioral performance on the 2-back, number of days between substance use and neuroimmune assessments, body mass index (BMI), and socioeconomic status (SES). ROIs, regions-of-interest.

hypothesis that the interaction between low executive control and high inflammation is associated with heightened substance use. Based on emerging neuroimmune network perspectives (Hutchinson & Watkins, 2014; Nusslock & Miller, 2016; Treadway et al., 2019), we propose that by altering executive control, inflammation weakens the ability of the prefrontal cortex to regulate stress and limbic reactivity, thus heightening negative emotions and dysphoria. In line with this view is evidence that lower activity and connectivity in brain regions involved in executive control are associated with negative emotions, depression, and anxiety (Johnstone et al., 2007; Sylvester et al., 2012; Warren et al., 2021). Next, lower executive control should predispose people to use substances like alcohol, cigarettes, and cannabis, in part to self-medicate their dysphoria (Volkow et al., 2016). Increased substance use further deteriorates brain regions implicated in executive control and generates deficits in working memory, cognitive flexibility, and response inhibition (Goldstein & Volkow, 2011). Substance use may be especially harmful to individuals transitioning to adulthood, as in the present study, given that regions of the prefrontal cortex involved in executive control continue to develop into the late twenties (Gu et al., 2015; Somerville & Casey, 2010). If the inflammation triggered by these behaviors spreads to the brain, it could establish an unhealthy cycle, whereby reduced executive control facilitates proinflammatory behaviors, which, in turn, further reduces executive control, and so on. When combined with evidence that inflammation also lowers signaling in the brains reward's circuit (Felger & Treadway, 2017; Miller et al., 2013),

another marker of risk for substance use (Bart et al., 2021; Büchel et al., 2017), this unhealthy neuroimmune cycle could generate risk for problematic substance use and addiction.

Stress and adversity heighten cross-talk between the brain and immune system and set the foundation for neuroimmune dysregulation that has been associated with mental and physical health problems (Nusslock & Miller, 2016). The African-American participants in the present study live in low-resource communities in the southeastern US and are disproportionately exposed to structural inequities, social adversities, and racial discrimination (Acevedo-Garcia et al., 2008; DeNavas-Walt & Proctor, 2014; Slopen et al., 2010). Integrative neuroimmune network models that specify the mechanisms through which social adversity generate health disparities can facilitate the development of preventative interventions that target both behavior and biology, and, ideally, bring attention to structural inequities that can be targeted through policies (Nusslock & Farah, 2022; Nusslock & Miller, 2016; Treadway et al., 2019). Related, it will be important for future research to examine the extent to which stress and adversity moderate the relationship between neuroimmune signaling and substance use behaviors.

Follow-up analyses indicated that activation in several brain regions involved in working memory interacted with inflammation to predict substance use. These brain regions included portions of the DLPFC, which is involved in working memory and executive control, and the parietal cortex, which is involved in focused attention and visual-spatial processing (Bressler & Menon, 2010; Dosenbach et al., 2006; Gordon et al., 2018; Sweet et al., 2008). These findings align with existing research on working memory-related brain activity that statistically controls for or equates for behavioral performance, and suggests that individuals with low executive control have to work harder and expend more neuronal resources to achieve normative performance (Gärtner et al., 2018; Wang et al., 2015). Research on executive control deficits in the DMN is a bit more inconsistent. In line with some work (Sweet, Jerskey, et al., 2010), we observed that low activity after equating for behavioral performance in the precuneus, medial prefrontal cortex, and angular gyrus, all regions implicated in the DMN, interacted with inflammation to predict substance use. These findings align with a neural inefficiency perspective which argues that individuals with low executive control excessively suppress brain activity associated with task-irrelevant mental processes to perform the task at hand and to achieve normative performance (Sweet, Jerskey, et al., 2010). Other studies, however, report that individuals with conditions like ADHD and depression are unable to suppress the DMN activity and task-irrelevant brain activity (Fassbender et al., 2009; Gärtner et al., 2018; Metin et al., 2015). Future research is needed to resolve this and determine whether certain mental and physical health conditions are characterized by distinct profiles of executive control deficits in the DMN. Furthermore, while the present study focused on executive control-related neural activity, there are other brain systems implicated in neuroimmune signaling and risk for substance use (Nusslock et al., 2024; Nusslock & Miller, 2016). Future research should examine the specificity of our findings to working memory and DMN neural activity.

There were limitations to the present study that should be addressed in subsequent research. First, although executive control-related brain activity and peripheral inflammation were measured on the same day, substance use was assessed a few months before the neuroimmune assessments. We controlled for the number of days between the substance use and neuroimmune assessments in all our analyses to try to address this limitation. However, this assumes that rates of substance use stayed relatively constant between the substance use and neuroimmune assessments and does not adjust for the possibility of variation in substance use during this period. It will be important for future research to conduct neuroimmune and substance use assessments on the same day. Second, and related, the cross-sectional and observational nature of our design prevents us from establishing causality. Further, the fact that substance use was measured before neuroimmune assessments prevents us from examining whether the interaction between executive control-related brain activity and inflammation prospectively predicts substance use. A longitudinal study measuring executive control-related brain activity, inflammation, and substance use across development is needed to examine the temporal sequence of events and answer mechanistic questions about how neuroimmune signaling might generate risk for increased substance use. Third, although we observed considerable variation in substance use, the absolute amounts of substance use among the study population was modest. This finding is consistent with other epidemiological findings which show low levels of substance use among Black youth and young adults (Brody et al., 2019). Given the restricted range of substance use in the study sample, it is possible the results reported here could be construed as conservative tests of the study hypotheses. This conjecture will be sorted out in future research that include larger samples that include neuroimmune assessments. Fourth, we focused on African American participants given they are exposed to higher levels of inflammation-triggering stressors, display elevated substance use in middle to late adulthood, and experience disproportionate consequences from substance use (Acevedo-Garcia et al., 2008; Noll et al., 2003; Slopen et al., 2010). Future research should examine whether our results extend to other racial and ethnic groups. Fifth, and related, we excluded participants with a chronic physical illness or a major psychiatric diagnosis, and participants were free of any psychiatric medication for at least one month prior to their neuroimmune assessments. The benefit of this is that it positions us to identify mechanisms and neuroimmune pathways to substance use that are not confounded by comorbid health conditions or medications. A limitation of this exclusion criteria, however, is that might make results less generalizable to clinically vulnerable populations, which should be addressed in subsequent research. Sixth, we operationalized low executive control as a neural inefficiency on the n-back task after equating or statistically controlling for behavioral performance (i.e., greater working memory and executive control neural activity and greater suppression of DMN activity). This approach is consistent with prior research and validated by the fact that this profile of brain activity is associated with greater effort to achieve normative performance on the n-back task and both mental and physical health problems (Duda et al., 2019; Gärtner et al., 2018; Owens et al., 2018; Sweet, Jerskey, et al., 2010; Syan et al., 2019). However, laboratory tests validating this marker of neural inefficiency are lacking and future research is needed to address this issue. Finally, neuroimmune network models postulate that neuroinflammatory dysregulation heightens risk for a broad range of unhealthy and addictive behaviors, rather than any particular class of substances (Nusslock et al., 2024; Nusslock & Miller, 2016). However, the present study is not sufficiently powered to test whether neuroimmune associations with one substance is significantly stronger than associations with the substance use composite score. Future research that is appropriately powered is needed to address this issue. Related, we used a composite inflammatory score because it a) lowers the chance of a Type I Error, b) is a conservative approach to defining inflammation, and c) considers the dynamic activity among inflammatory markers of interest. There are multiple approaches, however, to modeling peripheral inflammatory biomarkers in humans, including data driven (i.e., Principal Component Analysis) methods for generating composite scores (e.g., Moriarity, et al., 2021). Future research that is sufficiently powered should replicate the reported results testing multiple different approaches to modeling peripheral inflammation.

Meanwhile, the present study advances knowledge on neuroimmune signaling in risk for addiction and suggests that low-executive control neural activity and heightened inflammation are associated with elevated substance use. These findings have implications for understanding psychological, neural, and immunological risk factors for problematic substance use and the development of interventions to target each of these components to treat, and ideally prevent, substance misuse.

CRediT authorship contribution statement

Robin Nusslock: Writing – review & editing, Writing – original draft, Conceptualization. **Steven M. Kogan:** Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Tianyi Yu:** Formal analysis, Data curation. **Casey C. Armstrong:** Visualization. **Edith Chen:** Writing – review & editing, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Gregory E. Miller:** Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Gene H. Brody:** . **Lawrence H. Sweet:** Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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.

Data availability

Data will be made available on request.

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None of the authors has a financial holding or conflict of interest to declare related to this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2024.06.018.

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