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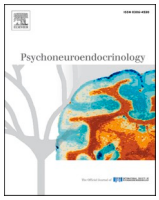

Chronic inflammation is associated with worsening working memory performance: Preliminary evidence from a diverse, longitudinal cohort of adolescents and young adults

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ABSTRACT

Many depressed individuals experience cognitive difficulties that persist when depression is in remission. Inflammation is hypothesized to play a role in cognitive dysfunction in depression; however, many aspects of this relationship are not well characterized. The current study examined whether inflammation is associated with specific cognitive deficits in individuals with a history of depression and with progressively worsening working memory over time. Adolescents who participated in a prospective, longitudinal study of adolescent-onset depression were recruited to complete a follow-up cognitive assessment. The sample was comprised of 82 participants (52.4% female; 37.8% white; 42.7% low socioeconomic status) who were aged 22.61 years ($SD = 1.50$) at the time of the follow-up cognitive assessment. Prior to the follow-up cognitive assessment, they had completed an average of 6.24 ($SD = 1.80$) prior annual assessments over 6.24 years ($SD = 2.08$) as part of the parent longitudinal study in which C-reactive protein (CRP), depressive symptoms, and working memory were assessed repeatedly. First, using linear regression, we tested whether individuals exhibiting inflammation (CRP $\geq$3 mg/L) at multiple timepoints and a history of likely depression (Children's Depression Inventory $\geq$19) exhibited differentially worse executive functioning, episodic memory, or psychomotor speed. Second, using hierarchical linear modeling, we tested whether the combination of inflammation and likely past depression was associated with poorer working memory over time. Chronic inflammation was associated with worsening working memory over time, but no significant associations were observed in cross-sectional analyses. These preliminary data indicate that chronic inflammation may lead to progressive decline in working memory over time.

1. Introduction

Depression affects approximately 300 million individuals worldwide and accounts for 40% of total days lost to poor mental health, making it the leading cause of mental health-related global disease burden (Liu et al., 2020). Cognitive dysfunction is common in depression and contributes substantially to the overall disease burden by increasing functional impairment and the likelihood of relapse (Lam et al., 2014). Despite the clinical significance of cognitive dysfunction in depression, little is known about why it occurs, who it is likely to affect, or how it can be effectively treated. Thus, a better understanding of why cognitive dysfunction occurs in depression is critically needed.

Depressed individuals perform worse across a broad range of cognitive domains (e.g., psychomotor speed, executive function, and episodic memory) when compared to non-depressed controls (Rock et al., 2014; Wagner et al., 2012). These deficits are observed at first onset, (Lee et al., 2012) in both medicated and unmedicated samples, and in both community, out-patient, and in-patient samples (Porter et al., 2007). However, not only are cognitive deficits observable in individuals who are acutely depressed, but they frequently persist when

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depression is in remission and are most pronounced in executive function and episodic memory domains (Semkovska et al., 2019). Despite a wealth of data demonstrating persistent cognitive difficulties in people with depression, relatively little is known about why cognitive deficits, particularly executive function and episodic memory, persist in remission.

Distinct inflammatory physiology may contribute to persistent cognitive difficulties in depression, such as executive dysfunction and poorer episodic memory (Carvalho et al., 2014). Inflammatory physiology likely plays a causal role in depression, at least for a subset (≈30%) of individuals (Osimo et al., 2019). Depressed individuals exhibit elevated circulating levels of peripheral (Kohler et al., 2017) and central (Mechawar and Savitz, 2016) inflammatory biomarkers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), and a meta-analytic review of longitudinal studies found modest prospective associations of these immune biomarkers with later depression (Mac Giollabhui et al., 2021a). Anti-inflammatory agents have been shown to exert antidepressant effects, (Köhler-Forsberg et al., 2019) particularly in individuals exhibiting an inflammatory phenotype (Miller and Raison, 2022) and inflammation has been linked with a specific symptom profile (i.e., fatigue, anhedonia) (Moriarity et al., 2020, 2023). There also is a growing body of literature implicating inflammatory physiology in cognitive dysfunction.

Peripheral inflammation can act directly upon the central nervous system and disrupt neuronal processes (e.g., synaptic plasticity, neurogenesis) as well as affect brain regions and their respective cognate associates (e.g., hippocampus: episodic memory) (Hoogland, 2015; Harrison et al., 2014). Prior observational and clinical studies have linked peripheral inflammation with poorer performance on a range of cognitive tasks, particularly executive function and episodic memory dependent tasks (Mac Giollabhui et al., 2021b, 2021c, 2020a; Grassi-Oliveira et al., 2011; Tampubolon, 2016). Multiple plausible biological pathways exist by which peripheral inflammation could impact cognitive function. For instance, inflammation may impact episodic memory via inhibited neurogenesis, (Chesnokova et al., 2016) psychomotor speed via reduced dopamine signaling in the basal ganglia (see Lucido et al. 2021 for excellent review), and executive function by slowing the myelinating processes during development and/or modulation of neurotransmitters important to executive function (e.g., glutamate, serotonin) (Nusslock and Miller, 2016). Thus, inflammation could plausibly exert long-lasting effects on cognitive abilities and explain why specific cognitive difficulties persist in remitted depression. In particular, this literature provides plausible mechanisms linking peripheral inflammation with the kind of cognitive difficulties (i.e., executive dysfunction, poor episodic memory) that persist in remitted depression.

Studies investigating the association of inflammatory biomarkers and cognitive dysfunction in depression overwhelmingly have focused on acute depression. Inflammation has been linked repeatedly with cognitive dysfunction in depressed individuals; (Chang et al., 2012; Krogh et al., 2014; Goldsmith et al., 2016) however, null results also have been observed (Slaney et al., 2023) and a recent meta-analysis reported a weak overall association ($r = -0.13$) (Morrens et al., 2022). Inconsistent results are likely driven by: (1) limited assessment of neuropsychological function that makes it unclear whether inflammation exerts specific (e.g., psychomotor speed, executive function) or generalized effects on cognition, (Snyder et al., 2015) and (2) limited assessment of immune markers (known to fluctuate over time) that increases the likelihood of misclassifying transiently elevated inflammation due to situational factors (e.g., recent physical activity, illness) as chronic, low-grade inflammation (Walsh et al., 2023). Thus, repeated assessment of cognitive function and immune biomarkers may be required to accurately characterize profiles of cognitive function as well as true cases of chronic, low-grade inflammation.

Prior longitudinal work has linked: elevated inflammatory biomarkers with both increased depression and worsening cognitive performance (Mac Giollabhui et al., 2020a; Zheng and Xie, 2018) and depression with worsening executive function via increases in inflammatory biomarkers (Zainal and Newman, 2022a, 2022b). However, other studies report that a link between inflammation and worse cognition is independent of depression or psychiatric history (Mac Giollabhui et al., 2021b; Cullen et al., 2017). It remains unclear whether inflammation is independently associated with cognition or whether it must be accompanied by features of depression, such as stress that disrupts the integrity of the blood-brain-barrier and permits inflammation in the periphery to impact the central nervous system, leading to cognitive dysfunction? (Medina-Rodriguez and Beurel, 2022) Thus, further work is needed to determine whether inflammation is an independent risk factor for cognitive dysfunction (i.e., is independent of depression history) and to determine how inflammation and depression are related over time (e.g., is inflammation associated with progressive decline in cognitive function for those with a history of depression?).

1.1. The present study

The current study investigated (1) whether depression and inflammatory biomarkers are independent risk factors for cognitive dysfunction or whether these factors compound so that individuals with a history of depression and chronic inflammation experience greater difficulties in specific cognitive abilities than individuals with either depression or chronic inflammation alone and (2) whether inflammation is associated with a progressive decline in working memory in individuals with a history of depression or whether the relationship between inflammation and progressive decline in cognitive abilities is independent of depression history. Specifically, these questions are investigated in a subset of adolescents who participated in a longitudinal study (referred to throughout as the 'parent study') during which depressive symptoms, inflammatory biomarkers, and working memory were repeatedly assessed during adolescence and young adulthood and who later completed a follow-up study that included an extensive neuropsychological evaluation.

Hypothesis 1. Youth with chronic inflammation (consistently elevated CRP at 2+ timepoints) and a history of elevated depressive symptoms (repeatedly assessed over time) would exhibit worse future executive functioning and episodic memory than those with chronic inflammation or depression alone, controlling for relevant covariates. Hypothesis 1 used data from the longitudinal parent study (during which time inflammatory biomarkers and depressive symptoms were repeatedly assessed) and from the follow-up study of cognition (when an extensive neuropsychological evaluation was conducted).

Hypothesis 2. A combination of chronic inflammation and a history of depressive symptoms would be differentially associated with progressively poorer working memory performance over time, controlling for relevant covariates. Hypothesis 2 used data from the parent study of adolescent depression that repeatedly assessed working memory, inflammatory biomarkers, and depression.

2. Methods

2.1. Participants

2.1.1. Parent study

The Adolescent Cognition and Emotion Study (ACE) is a prospective, longitudinal study of adolescent-onset depression that tracked 636 adolescents and their caregivers annually (Alloy et al., 2012). Participants were recruited from Philadelphia's public and private middle schools (68% of the sample) as well as advertisement in Philadelphia-area newspapers (32% of the sample). Recruitment began in May 2009 and was completed in May 2020. English-speaking adolescents who identified as Caucasian/White, African-American/Black, or Biracial, aged 12–13, were eligible to participate if their mother/female caregiver

(92% were the biological mothers) also was willing to participate. Participants were excluded if either the adolescent or mother had insufficient English reading/speaking skills to complete the assessments, or had a severe psychiatric, developmental, medical, or learning disorder. Detailed information on recruitment and sample characteristics has been published elsewhere (Alloy et al., 2012). The sample is 52.6% African-American/Black, 53% female and 50% report being in receipt of free school lunch or possessing a family income of less than $15,000, indicative of low socio-economic status (SES).

2.1.2. Overview of follow-up study

The follow-up study included an extensive cognitive assessment in 82 individuals. Initially, 200 participants from the parent study who were without medical conditions known to influence immune function (e.g., autoimmune disorders, diabetes) and who had completed two or more blood draws separated by at least one year were invited to participate in this study. Recruitment took place between September, 2019 and May, 2021. During the COVID-19 pandemic, recruitment was halted between March, 2020 and August, 2020 and when resumed, it occurred in person and additional screening procedures were implemented such that participants and assessors did not have sickness symptoms and masks/face-shields were worn when in person. The sample was comprised of 82 adolescent participants (52.4% female; 37.8% white; 42.7% low socioeconomic status) who were aged 22.61 years (SD = 1.50) at the time they completed the follow-up cognitive assessment. Prior to the follow-up cognitive assessment, they had completed an average of 6.24 (SD = 1.80) prior assessments over 6.24 years (SD = 2.08) as part of the parent study. Two individuals did not complete the full cognitive assessment and four others did not have two (or more) valid CRP values and were not included in analyses, leaving N=76 included in analyses.

2.2. Measures

2.2.1. Dependent variables

An extensive neuropsychological assessment was completed during the follow-up cognitive assessment and working memory was assessed in both the follow-up cognitive assessment and the parent study. Complete information on measures is provided as supplementary information and a list of the specific tests used to assess each cognitive domain is detailed in Table 1.

Table 1
List of Neuropsychological Measures Assessed.

Cognitive Domain	Test	Assessment Point	
		Parent Study	Follow-up Study of Cognition
Intelligence Quotient (IQ)	Kaufman Brief Intelligence Test-Second Edition		✔
EF: Auditory Working Memory	Wechsler Adult Intelligence Scale – Fourth Edition: Digit Span Forwards/Backwards	✔	✔
EF: Sustained Attention	CANTAB: Rapid Visual Information Processing		✔
EF: Spatial Working Memory	CANTAB: Spatial Working Memory		✔
EF: Planning	CANTAB: One Touch Stockings of Cambridge		✔
EM: Immediate Visual	CANTAB: Paired Associates Learning		✔
EM: Immediate Verbal	Hopkins Verbal Learning Test-Revised		✔
Psychomotor Speed	CANTAB: Reaction Time		✔

EF = Executive Function; CANTAB = Cambridge Neuropsychological Test Automated Battery; EM = Episodic Memory.

2.2.2. Independent variables

2.2.2.1. Depressive symptoms (completed during follow-up cognitive assessment and during the parent study). During the parent study, depressive symptoms were measured approximately every 6 months using the Children's Depression Inventory (CDI), a valid, reliable measure of current depressive symptoms in youth (Kovacs, 1992). This self-report instrument consists of 27 items, scored on a three-point scale ranging from zero to two. Items were summed, with higher scores indicative of higher levels of depressive symptoms; missing items on the CDI were imputed if >80% of items were present. The CDI demonstrated good internal consistency throughout the parent study (Cronbach's α ≥0.83). During the follow-up cognitive assessment (when participants were adults), the Beck Depression Inventory-II – an established self-report measure of depressive symptom severity in individuals aged 13 years and older – was administered as a measure of current depressive symptoms (Dozois et al., 1998). Probable history of depression was defined as a score ≥19 on the Children's Depression Inventory (Kovacs, 1983) and participants completed the CDI an average of 12.14 times (SD = 4.76) throughout the study. Participants reported a score ≥19 on zero occasions (n = 58), on one occasion (n = 5), on two occasions (n = 6), and on three or more occasions (n = 7).

2.2.2.2. Chronic inflammation (completed during the parent study). Blood (10 mL) was obtained primarily in the late afternoon to control for diurnal variation and was collected via antecubital venipuncture by a certified phlebotomist. The blood was centrifuged to separate the plasma fraction (BD Hemogard with K2 EDTA) and stored at −80°C until the day of assay. High-sensitivity CRP was determined via singleplex assay using an electrochemiluminescence platform and a QuickPlex SQ 120 imager for analyte detection. The analytes for CRP and other inflammatory biomarkers were run in duplicate, with intra-assay coefficients varying from 1.94% to 4.38%. Values were referenced to a standard curve generated from seven calibrators with known concentrations. CRP is present in sera at higher concentrations, and thus, plasma was diluted to correspond to the standard curve. Values were converted to mg/L units and were quantified down to 0.1 mg/L. At the time of blood draw, participant temperature was assessed orally; participants were rescheduled when fever-range temperatures were observed following oral assessment. In order to utilize repeated blood draws over time, chronic inflammation was defined as CRP values ≥3 mg/L at ≥65% of assessments across a maximum of four blood draws (all 76 individuals had CRP values on two occasions, 62 on a third occasion, and 42 on a fourth occasion). CRP ≥3 mg/L was selected as it is an established clinical index of systemic inflammation (Mac Giollabhui et al., 2020b). Although it is well-known that multiple factors contribute to variability in circulating CRP, CRP ≥3 mg/L is typically considered to be a measure of chronic, low-grade inflammation and no guidelines exist on defining chronic inflammation using multiple assays of CRP. As such 65% was arbitrarily chosen as a cut-off and further research is needed to more accurately characterize chronic inflammation in longitudinal samples. Sensitivity analyses also were performed in which chronic inflammation was operationalized as the median value of CRP across repeated assessments. As this median value of repeated CRP was non-normally distributed (skewness = 4.35; kurtosis = 24.15), it was subsequently log-transformed (skewness =0.30; kurtosis = 2.47).

Within the analytic sample of 76 individuals, all individuals had CRP values on two occasions, 62 a third, and 42 a fourth [a small number of participants completed a fifth (n = 28), sixth (n = 11) and seventh (n = 1) blood draw]. Across individuals, 38 (50%) had a CRP value ≥3 mg/L 0% of the time, 12 (15.8%) had a CRP value ≥3 mg/L 25% of the time, 5 (6.6%) had a CRP value ≥3 mg/L 33% of the time, 12 (15.8%) had a CRP value ≥3 mg/L 50% of the time, 2 (2.6%) had a CRP value ≥3 mg/L 67% of the time, 1 (1.3%) had a CRP value ≥3 mg/L 75% of the time, and 6 (7.9%) had a CRP value ≥3 mg/L 100% of the time. For the group with

CRP ≥3 mg/L at ≥65% of occasions ($n = 9$), 6 individuals had elevated inflammation on every occasion, 1 at 75% of occasions and 2 on 66.6% of occasions with two individuals possessing two blood draws, three individuals possessing three blood draws and four individuals possessing four blood draws. For the group without CRP ≥3 mg/L at ≥ 65% of occasions ($n = 67$), 38 individuals exhibited elevated inflammation on 0 occasions, 12 at 25% of occasions, 5 at 33% of occasions, and 12 at 50% of occasions with 12 individuals possessing two blood draws, 17 individuals possessing three blood draws and 38 individuals possessing four blood draws. No significant difference on the mean number of vists attended was observed comparing the group with CRP ≥3 mg/L at ≥65% of occasions (mean = 3.22) and the group without CRP ≥3 mg/L at ≥65% of occasions (mean = 3.39), $t(74) = 0.60$, $p = .55$.

2.2.2.3. Demographic variables. Age, sex assigned at birth (herein, referred to as "sex"), race and socioeconomic status were assessed using self-report. Within sex, 'female' is coded as one and 'male' as zero. Participants identifying as Black/Biracial were coded as zero and White as one. For SES, receipt of National School Lunch Program or a familial income less than $15,000, indicative of low SES, was coded as 'one' and all other participants were coded as 'zero'.

2.3. Procedure

Adolescents completed two types of assessments during the parent study. Comprehensive assessments occurred at baseline and at subsequent annual appointments (with briefer assessments occurring at 6 month intervals). In terms of the data being analyzed in the current manuscript, comprehensive assessments included behavioral assessment of auditory working memory (Digit Span) and a self-report questionnaire of depressive symptoms (CDI). Comprehensive assessments were supplemented with shorter assessments every six-month that assessed depressive symptoms (CDI). Data on depressive symptomatology and auditory working memory were gathered from baseline assessment or from five subsequent comprehensive assessments. Participants completed the Digit Span (WISC-IV) from Time 1 until they turned 16, after which they began to take the adult version of the WISC-IV: WAIS-IV. During the follow-up cognitive assessment, participants completed an extensive battery of neuropsychological measures in addition to self-report questionnaires.

2.4. Data analysis

An analytic plan was pre-registered (Mac Giollabhui, 2022) with the Open Science Framework after data collection was complete and before data analysis was conducted. Current analyses deviate from the registered protocol in two ways. First, the criteria used to define chronic inflammation was made more conservative as a substantial number of cases ($n = 12$) exhibited CRP ≥3 mg/L for exactly 50% of observations. In order to reduce ambiguity as to whether these cases better reflect the presence or absence of chronic inflammation, the criteria for chronic inflammation was changed from 50% of observations to ≥65% of cases. Prior research has found that multiple assessments are required to reliably measure immune parameters and that each assessment confers incremental improvement in reliability, although the precise number of assays required to measure specific immune parameters in humans is unknown (Segerstrom and Laudenslager, 2009). Second, data from the Test of Everyday Attention was not analyzed as there was a very substantial increase in mean performance in the sample across timepoints (> 1 SD). In order to facilitate transparency of reporting, we note for readers that, had the initial cut-off of 50% been implemented the following change in results would have been observed: (1) for observational analyses, a significant interaction of CRP status by depression history status would have been observed, such that individuals with a history of depression and elevated CRP exhibit worse executive function, controlling for IQ and current depressive symptoms and (2) the significant interaction of time by CRP status predicting worse working memory (digit span backwards) would no longer have been observed.

All analyses were conducted using R 4.1.0. and multilevel models with random intercepts and fixed slopes were estimated using lmer4. Bivariate correlations were examined initially for the neuropsychological measures (in the context of established theory) to determine whether the creation of composite measures was appropriate; variables to be included in composite measures of executive function and episodic memory were z-standardized to create comparable metrics. Composite measures were calculated by summing z-standardized variables. Subsequently, descriptive statistics and bivariate correlations were produced for main study variables. Analyses should be considered exploratory in nature.

For Hypothesis 1, cognitive data from the follow-up cognitive assessment was used combined with longitudinal data from the parent study of adolescent depression where chronic inflammation (CRP ≥3 mg/L) and elevated depressive symptoms (CDI ≥19) were repeatedly assessed. Multivariate regression analysis of these cross-sectional cognitive data examined whether individuals with chronic inflammation *and* a history of elevated depressive symptoms (interaction of chronic inflammation*elevated depressive symptoms), as repeatedly assessed during the parent study, exhibited worse i) executive functioning, ii) episodic memory, and/or iii) psychomotor speed (as assessed during the follow-up cognitive assessment) than those with chronic inflammation or depression alone. Covariates that have been linked with outcome variables based on established theory and that were significantly associated with outcome variables using appropriate statistical measures of association were included in regression analysis.

For Hypothesis 2, cognitive data gathered both during the follow-up cognitive assessment and the parent study of adolescent depression were used (i.e., working memory); data on chronic inflammation (CRP ≥3 mg/L) and elevated depressive symptoms (CDI ≥19) were drawn from the parent study of adolescent depression only. Longitudinal analyses of working memory used repeated measurements of these constructs in both the parent study and the follow-up cognitive assessment within a hierarchical linear model (random intercept, fixed slope) to test whether a combination of chronic inflammation and a history of depressive symptoms was differentially associated with poorer working memory development over time (variations of interaction of chronic inflammation* elevated depressive symptoms*time), after controlling for relevant covariates (e.g. socioeconomic status). Analyses did not disaggregate between and within person variability. Univariate associations tested for significant associations between socioeconomic status/gender/race/age and cognitive outcomes.

Sensitivity analyses were performed to i) determine the conditionality of effects observed based on covariates and ii) replicate analyses for Hypotheses 1 and 2 replacing the dichotomous variable for chronic inflammation (CRP ≥3 mg at ≥65% of occasions) with the log-transformed median value of CRP at all occasions (as described in Section 2.2.2.2.).

3. Results

Descriptive statistics and bivariate correlations for the main study variables are presented in Table 2 for the 76 individuals who completed the follow-up cognitive assessment. Correlations among key predictors and cognitive variables are presented as supplementary information – see Supplementary Table 1 – and two measures of executive functioning assessed (inhibition and set-shifting) were not included in the composite measure given their inconsistent associations with other dimensions of executive function.

Table 2
Descriptive statistics and bivariate correlations for participants who completed the study (N = 76).

Measure	1	2	3	4	5	6	7	8	9	10	11	12
1: Age	-											
2: Female	-0.06	-										
3: White	-0.05	-0.09	-									
4: Low SES	-0.19	0.14	-0.26*	-								
5: Depression Hx.	-0.01	0.16	-0.23*	0.20	-							
6: Depressive Sxs.	0.08	0.11	-0.08	0.02	0.45***	-						
7: Elevated CRP	.10	0.10	-0.28*	0.01	0.18	0.13	-					
8: Median CRP	.17	0.13	0.07	-0.19	-0.04	0.01	0.62***	-				
9: EF Composite	0.04	-0.05	0.06	-0.20	0.03	0	-0.11	0.01	-			
10: EM Composite	-0.11	0.26*	0.16	-0.12	0.12	0.07	0.01	0.07	0.43***	-		
11: Psychomotor Speed	-0.19	-0.01	0.06	0.06	-0.01	-0.20	-0.07	-0.12	0.27*	0.26*	-	
12: IQ (Standardized Score)	-0.12	0.00	0.18	-0.15	0.17	0.19	-0.06	-0.03	0.48***	0.50***	0.22	-
Mean	22.55	0.53	0.37	0.43	0.24	9.10	0.11	-0.20	0.00	0.00	251	95.32
SD	1.51	0.50	0.49	0.50	0.43	8.79	0.33	1.78	0.68	0.80	49.50	11.97

SES = Socio-economic status; Hx. = History; Sxs. = Symptoms; CRP = C-reactive protein; Median CRP = log-transformed median value of CRP across assessments; EF = Executive Function; EM = Episodic Memory; IQ = Intelligence Quotient estimate; Composite variables are the sum of standardized (z-transformed) variables; SD = Standard Deviation;* = p<0.05; ** = p<0.01; *** = p<0.001.

3.1. Cross-sectional analyses of cognitive data: predicting specific deficits in executive function, episodic memory, and psychomotor speed

Cross-sectional analyses (i.e., examining cognitive data at a single timepoint, namely the follow-up study of cognition when an extensive neuropsychological assessment occurred) evaluated whether individuals with chronic inflammation and a history of elevated depressive symptoms (as repeatedly assessed during the parent study) exhibited worse executive functioning, episodic memory and/or psychomotor speed (as assessed during the follow-up cognitive assessment) than those with chronic inflammation or depression alone. Covariates significantly associated with outcome variables were included in regression analysis. General intelligence was associated with better performance on both composite measures of executive functioning and episodic memory and psychomotor speed (see Table 3). More severe current depressive symptoms were associated with slower psychomotor speed and females performed better on the composite measure of episodic memory. The combination of a history of depressive symptoms and chronic inflammation was not associated with worse executive function, episodic memory or psychomotor speed.

3.2. Longitudinal analyses predicting scaled scores of working memory

Longitudinal analyses of working memory used repeated measurements from both the parent study and the follow-up cognitive assessment. Length of time in study was associated with improved simple auditory attention (Digit Span Forward) and individuals with chronic inflammation experienced decline in auditory working memory (Digit Span Backwards; Fig. 1). The combination of depression history and chronic inflammation was neither associated with worse performance on tests of simple auditory attention or auditory working memory nor progressive decline over time – complete details are presented in Table 4. Examination of group-based differences visualized in Fig. 1 using pairwise comparisons indicated that working memory for individuals with chronic inflammation did not differ at different assessment points [1 standard deviation below mean (0.29 Years): estimate = −0.09, p =.90; mean value (2.94 Years): estimate = −0.74, p =.32; 1 standard deviation above mean (5.58 Years): estimate = −1.39, p =.09]. Estimation of Johnson–Neyman intervals indicates that the threshold at which individuals with chronic inflammation differ from those without chronic inflammation in terms of working memory is after 7.02 years of observation in the study.

3.3. Sensitivity analyses

Sensitivity analyses were performed to i) determine the conditionality of effects observed based on covariates (see Supplementary Table 2) and ii) replicate analyses for Hypotheses 1 and 2 replacing the dichotomous variable for chronic inflammation (CRP ≥3 mg at ≥65% of occasions) with the log-transformed median value of CRP at all occasions (see Supplementary Tables 3 and 4). When comparing the

Table 3
Linear regression analyses predicting to three domains of cognitive functioning at follow-up cognitive assessment: executive function, episodic memory and psychomotor speed (n = 76).

	Predictors	Domains of Cognitive Functioning		
		Executive Functioning Composite	Episodic Memory Composite	Psychomotor Speed
Model A: Key Predictors	Chronic CRP	-.12	-0.01	-0.07
	History of Depressive Symptoms	0.05	0.12	0.01
Model B: Key Predictors and Interaction Term				
	Chronic CRP	.02	0.06	-0.06
	History of Depressive Symptoms	0.12	0.15	0.01
	Chronic CRP* History of Depressive Symptoms	-0.23	-0.11	-0.03
Model C: Addition of Interaction Term				
	Chronic CRP	.10	0.12	-0.02
	History of Depressive Symptoms	0.07	0.06	0.09
	Chronic CRP* History of Depressive Symptoms	-0.28	-0.16	-0.03
	Intelligence Quotient	0.51***	0.51***	0.26*
	Current Depressive Symptoms	-0.07	-0.05	-0.28*
	Female	-	0.26*	-

p<0.05; ** = p<0.01; *** = p<0.001.

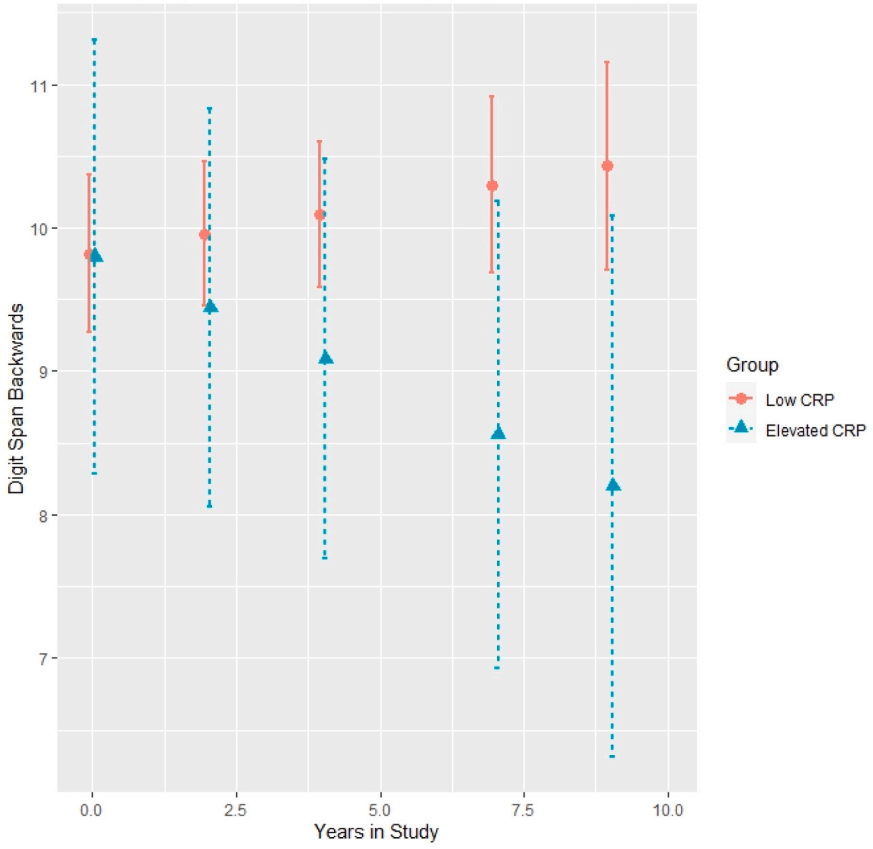

Fig. 1. Digit Span Backwards by Chronic Inflammation Over Time.

pattern of results observed for our two measures of CRP (CRP ≥3 mg at ≥65% of occasions vs. median CRP), some notable differences were observed: i) for the Digit Span Forward, the interaction of Chronic CRP and History of Depressive Symptoms changed from $\beta = -0.17$, $p = .14$ to $\beta = -0.22$, $p = .04$ and ii) for the Digit Span Backwards, the interaction of Chronic CRP and History of Depressive Symptoms changed from $\beta = -0.12$, $p = .04$ to $\beta = -0.09$, $p = .09$.

4. Discussion

Depression and cognitive dysfunction both reduce quality of life in those afflicted with either or both conditions (Lam et al., 2014; Withall et al., 2009). Consequently, research investigating putative mechanisms of these characteristics is necessary to reduce their considerable public health burden. Results from this study suggest that chronically elevated inflammation might be one such mechanism. Prior research did not thoroughly examine whether the combination of depression and elevated CRP is differentially associated with worse performance in specific cognitive abilities and whether this combination is associated with progressive decline in cognitive performance over time. In a diverse sample of youth, our results found that elevated CRP was associated with progressively worse performance on working memory tasks over time relative to their peers independent of depressive symptomatology, although cross-sectional analyses did not find any association of elevated CRP with worse psychomotor speed, episodic memory, or executive function.

These results align with a growing body of work linking inflammatory biomarkers with poorer executive functioning (including working memory) in population-representative samples across the lifespan (Mac Giollabhui et al., 2021b; Zainal and Newman, 2022b). Specifically, results from the current study found inflammation-related cognitive difficulties in working memory, at least during adolescence and young adulthood. Although an association between inflammatory biomarkers and executive function has been repeatedly observed in youth, (Mac Giollabhui et al., 2021c, 2020a; Cullen et al., 2017; Mac Giollabhui and Hartman, 2022) the decline in working memory observed in longitudinal data is novel and of particular concern, given the importance of executive function to academic, occupational and social functioning (Best and Miller, 2010). It is important to note that elevated CRP was not significantly associated with worse executive functioning in the cross-sectional data; however, the effect size ($r = -0.11$) is similar to that published in a previous meta-analysis (Morrens et al., 2022). This longitudinal association of higher levels of inflammatory biomarkers and worse executive function over time has previously been observed in adolescent samples (Mac Giollabhui et al., 2020a; Mac Giollabhui, 2021) and highlights the potential clinical significance that a relatively small effect size might exert over the course of the lifespan. Nonetheless, we caution against over-interpreting the results of this study given the small sample size and biases inherent in attrition in longitudinal studies.

It is unclear whether data presented here represent a decline in working memory or attenuated growth in working memory abilities; however, the sensitivity of a core executive function – working memory – to immune dysfunction may not be surprising given that the neural substrates underpinning executive function exhibit an extended maturation process throughout this period and that inflammation has been shown to impact cognition (Best and Miller, 2010; Mac Giollabhui, 2021). It should be kept in mind that scores on tests of executive functioning are reliant on multiple cognitive processes, such as attention, psychomotor speed, processing speed, and motivation, and although the deficits observed in this study are indeed specific to working memory, we cannot rule out the possibility that these specific deficits are driven by the effect of inflammation on non-specific processes, such as motivation and fatigue, via alterations in frontrostriatal circuity (Harrison et al., 2014). Indeed, prior work has linked poorer executive function

Table 4
Hierarchical linear model analyses of longitudinal data predicting scaled scores of working memory (n = 76).

	Predictors	Standardized coefficients	
		Digit Span Forward	Digit Span Backward
Model A: Key Predictors	Chronic CRP	-.01	-0.08
	History of Depressive Symptoms	0.06	-0.06
	Time	0.07*	0.03
Model B: Key Predictors and Interaction Term			
	Chronic CRP	.09	-0.04
	History of Depressive Symptoms	0.11	-0.04
	Time	0.07*	0.03
	Chronic CRP* History of Depressive Symptoms	-0.17	-0.07
Model C: Addition of Interaction Term			
	Chronic CRP	.00	0.00
	History of Depressive Symptoms	0.06	-0.06
	Time	0.08*	0.06
	Chronic CRP* Time	-0.02	-0.12*
Model D: Addition of Interaction Term			
	Chronic CRP	.09	0.06
	History of Depressive Symptoms	0.06	0.01
	Time	0.05	0.09
	Chronic CRP* Time* History of Depressive Symptoms	-0.07	0.05
Observations		464	463

p<0.05; ** = p<0.01; *** = p<0.001.

with fatigue, energy loss, and motivational deficits (Kraft et al., 2023). Further research is needed demonstrating the specific neural pathways by which inflammation impacts executive function in depression.

These data did not find that the combination of depression and chronic inflammation was associated with any aspect of cognitive functioning. This is aligned with prior findings in some studies, (Mac Giollabhui et al., 2021b; Cullen et al., 2017) but not others (Mac Giollabhui et al., 2021c). Indeed, elevated inflammatory biomarkers often are associated with poorer cognitive performance in clinical samples of depressed individuals; (Chang et al., 2012; Krogh et al., 2014; Goldsmith et al., 2016) however, it is notable that, when studies included non-depressed control groups, elevated inflammatory biomarkers were associated with cognitive dysfunction in both the depressed groups and healthy controls (Krogh et al., 2014). Instead, these data suggest that inflammation is independently associated with worse working memory and may represent a trans-diagnostic process.

This study also underscores the importance of properly phenotyping variables of interest in psychoneuroimmunology. Unlike much of the psychoneuroimmunology literature, this study used repeated measurements to estimate an immune parameter (elevated CRP) and may indicate the importance of longitudinal and repeated assessment of immune parameters to correctly characterize individuals with immune dysfunction. Seminal work in this area by Dr. Segerstrom highlights the importance of repeated measurements to reliably assess immune function in primates; (Segerstrom and Laudenslager, 2009; Segerstrom et al., 2006) it should be noted that this work advised that a minimum of 5 assessments might be necessary for reliable assessment. Indeed, research suggests that inconsistent associations of depression and inflammatory biomarkers that are frequently observed (Mac Giollabhui et al., 2021a) become more consistent when repeated measures of immune function are used (Bell et al., 2017). Moreover, recent work has highlighted substantial intra-individual change in inflammatory biomarkers over time (Walsh et al., 2023) and a need for repeated measures of immune function for longitudinal studies to identify persistent inflammation, particularly in studies lasting more than 3 years (Walsh et al., 2023). However, guidelines defining persistently elevated inflammatory biomarkers are absent; as a result, although CRP ≥3 mg/L is a well-established clinical cut-off for low-grade inflammation, (Mac Giollabhui et al., 2020b) the threshold that CRP ≥3 mg/L be present on ≥65% of assessment timepoints is entirely arbitrary and further research is needed to characterize immune dysfunction using longitudinal data. Thus, it is important for researchers conducting phenotyping research to consider the possibility that heterogeneous clinical features still might be over simplified in terms of how they are operationalized.

This study has several strengths relative to the existing research on this topic. First, it utilizes a sample specifically recruited to increase aspects of racial diversity. Second, it combines both cross-sectional and longitudinal analyses. Third, the sample was composed of adolescents—a developmental period with (i) increased risk for depression, and (ii) less lifetime disease burden than adult samples, and (iii) is an under-represented developmental stage in psychoneuroimmunology. Fourth, this study adds to a relative dearth of psychoneuroimmunological studies that incorporate well-validated, behavioral tasks of cognitive functioning. Fifth, it addresses limitations in prior research by using repeated measures of CRP to identify individuals with chronic inflammation. It is also important to consider this study in light of several weaknesses. First, although black and white Americans were well-represented in this study—due to the parent study's inclusion criteria—adolescents from other racial groups were not included in this study. Second, there are a wide variety of potentially relevant inflammatory proteins that were not included in this study, not to mention functional measures of immunity or direct assessment of immune cell populations. Third, although the clinical cut-offs used in this study were empirically supported, the assessment of clinical depression would have been improved with a structured clinical interview. Fourth, although a cut-off of CRP ≥3 mg/L has been shown to increase risk for a range of physical and psychological disorders, (Osimo et al., 2019; Mac Giollabhui et al., 2021a; Segerstrom et al., 2006) research identifying this cut-off has primarily been conducted in older adults and the current approach runs a risk that youth with more modest levels of inflammation (e.g., CRP at 2–3 mg/L) are being mistakenly assigned to the low CRP group. Finally, these results should be considered in the context of the small sample size and require replication. It is notable that across sensitivity analyses, although the broad pattern of results remains relatively consistent, parameter estimates vary depending on how specific constructs are operationalized and the attendant statistical significance of results is less consistent. This highlights the preliminary nature of these findings and cautions against over-interpretation of results in the absence of replication in adequately powered studies.

5. Conclusions

This study suggests that chronic inflammation is associated with progressive decline in working memory during adolescence and young adulthood. It indicates that chronic inflammation is associated with worse working memory independently of depression status and, given the increased prevalence of chronic inflammation in depression, may explain why some depressed individuals experience persistent difficulties in cognitive function. It adds to accumulating evidence that inflammation in remitted depression may be associated with a specific cluster of symptoms. The results reported here should be considered preliminary in nature and future work is needed to replicate these results and build upon them by directly assessing the neural correlates by which inflammation impacts working memory.

CRediT authorship contribution statement

Murray Susan: Conceptualization, Writing – original draft, Writing – review & editing. **Ellman Lauren:** Supervision, Writing – original draft, Writing – review & editing. **Moriarity Daniel:** Writing – original draft, Writing – review & editing. **Chat Iris Ka-Yi:** Conceptualization, Writing – original draft, Writing – review & editing. **Alloy Lauren B.:** Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing. **Mac Giollabhui Naoise:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Kautz Marin:** Conceptualization, Project administration, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

None.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2024.106992.

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