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Inflammatory cytokine levels implicated in Alzheimer's disease moderate the effects of sex on verbal memory performance

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ABSTRACT

Despite having an initial verbal memory advantage over men, women have greater rates of Alzheimer's disease and more rapid cognitive decline once diagnosed. Moreover, although Alzheimer's disease is influenced by inflammation, which itself has known sex differences, no study has investigated whether sex differences in memory are moderated by peripheral inflammatory activity. To address this issue, we analyzed data from 109 individuals (50 women, $M_{age} = 71.62$, range = 55–87) diagnosed as cognitively normal, or having mild cognitive impairment or Alzheimer's disease dementia. We then followed the sample for 12 months, as part of a longitudinal study of aging and Alzheimer's disease. At baseline, we assessed levels of the inflammatory cytokines interleukin (IL)-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) in plasma. At baseline and 12 months, we assessed verbal memory using the Rey Auditory Verbal Learning Test and nonverbal memory using the Brief Visuospatial Memory Test-Revised. As hypothesized, for the full sample, women exhibited stronger verbal (but not nonverbal) memory than men. In women, but not men, higher IL-1β at baseline related to poorer verbal learning across both time points and delayed recall at 12 months. The effect of sex on memory also differed by IL-1β level, with women exhibiting a memory advantage both at baseline and 12 months, but only for those with low-to-moderate IL-1β levels. Therefore, high peripheral inflammation levels may lead to a sex-specific memory vulnerability relevant for Alzheimer's disease.

1. Introduction

Nearly six million people in the United States are currently diagnosed with Alzheimer's disease (AD; Hebert et al., 2013), with the associated public health costs estimated at $305 billion in 2020 alone (Alzheimer's Association, 2020). Two-thirds of these AD sufferers are women (Hebert et al., 2013), and women decline faster following diagnosis (Buckley et al., 2018; Hua et al., 2010). These sex disparities are due in part to women's greater longevity, but recent research has emphasized the importance of additional contributors, including menopause (Brinton et al., 2015) and greater susceptibility to genetic effects (Altmann et al., 2014; Chen et al., 2017; Neu et al., 2017) and health comorbidities (e.g., Okereke et al., 2005).

Inflammation, which facilitates and generates AD pathology (Kinney et al., 2018; Park et al., 2020), may also play a role. Inflammatory responses differ by sex (Klein and Flanagan, 2016), and sex disparities in disease prevalence are well-established in other disorders that have an inflammatory component, including depression (Slavich and Sacher, 2019) and multiple sclerosis (Bove and Chitnis, 2013). Notwithstanding this knowledge, it remains unknown whether inflammation plays a sex-specific role in AD. This has occurred despite the fact that better understanding the role that inflammation plays in AD may offer new opportunities to reduce AD risk in women using established inflammation-reducing interventions and also contribute to better understanding the pathophysiology of other disorders that have an inflammatory component (Furman et al., 2019).

A growing literature has characterized sex differences in AD. One area of interest is the inconsistency between lifetime verbal memory advantage in women versus men (Brunet et al., 2020; McCarrey et al., 2016), and greater rates of this memory-targeting disease in women. Women maintain a memory advantage despite measureable AD pathology, including brain beta amyloid (Aβ) positivity on positron

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emission tomography (Caldwell et al., 2017, 2019), reduced brain glucose metabolism (Sundermann et al., 2017), and hippocampal atrophy (Sundermann et al., 2016). These studies suggest that women with AD have greater pathological burden than men at similar clinical disease stages. As inflammation both generates and arises in response to AD-associated Aβ accumulation (Park et al., 2020), women may also have greater inflammation at similar disease stages, which adds to their risk of steeper decline. However, no studies to date have examined links between inflammation and sex-specific memory trajectories in AD.

Inflammation is associated with poorer memory (Bettcher et al., 2019, 2012), longitudinal cognitive decline (Beydoun et al., 2018, 2019; Weaver et al., 2002), and risk for dementia and AD (Engelhart et al., 2004; Schmidt et al., 2002; Tan et al., 2007). Studies in rodents have suggested that peripheral inflammation reduces long-term potentiation (Murray and Lynch, 1998) and increases glial activation and cell death in the hippocampus (Semmler et al., 2005). However, findings linking inflammation and memory are not consistent, due in part to the assessment of different inflammatory markers and inclusion of varying demographic and medical covariates. In this context, a recent review highlighted three pro-inflammatory cytokines as potential AD biomarkers: interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α; Park et al., 2020). These three cytokines have been studied extensively in biobehavioral research, as they are acute phase proteins that initial the inflammatory cascade that can become health-damaging if activated too frequently or chronically (Slavich, 2020a, 2020b). Interestingly, these three cytokines also are regulated by the female sex hormone estrogen, which generally promotes inflammation at low levels and dampens inflammation at high levels (Klein and Flanagan, 2016). Consequently, there are several mechanistic reasons to focus on these three peripheral inflammatory markers in order to better understand sex differences in AD.

As compared to men and male rodents, women and female rodents have been shown to have greater acute immune responses to virus exposure or following stimulation of receptors involved in viral recognition (e.g., Furman et al., 2014; Torcia et al., 2012). Women also exhibit increases in inflammation during menopause (Abu-Taha et al., 2009) and greater inflammation with aging than men (Furman et al., 2014). Moreover, female sex has been linked to greater inflammation-related gene expression in the hippocampus with aging (Mangold et al., 2017). A separate line of research has proposed that levels of inflammation in women mediate the association between estrogen levels and cognitive decline (Au et al., 2017). This hypothesized role for inflammation in structuring sex differences in health outcomes is not unique to AD. In multiple sclerosis, for example, current neuroinflammation has been linked to reductions in processing speed (Bellmann-Strobl et al., 2009), and in adolescents at risk for psychopathology, interpersonal life stress exposure has been related to increases in depressive symptoms over time specifically in girls exhibiting greater social stress-induced inflammatory reactivity (Slavich et al., 2020; see also Giletta et al., 2018).

Despite this background work, it is unknown whether peripheral inflammation relates to memory in women across the spectrum from normal cognition to AD dementia. Specifically, research has yet to elucidate whether pro-inflammatory cytokines that are implicated in AD and regulated by estrogen moderate women's established memory advantage over men, contributing to poorer memory in women with AD despite women's known early memory advantages. Gaining this knowledge is critical, as inflammation is a process that can be assessed and targeted for early intervention to reduce AD risk, and also targeted earlier in life to reduce risk for other disorders that have an inflammatory component (Furman et al., 2019; Slavich, 2020b).

To address these issues, we examined how inflammation relates to verbal learning and memory at baseline and 12 months later in men and women who were cognitively normal or had mild cognitive impairment (MCI) or AD. To accomplish this, we focused on three key pro-inflammatory cytokines that are part of the acute phase response and that prior research has suggested play a role in AD and estrogen regulation, namely IL-1β, IL-6, and TNF-α. Based on the research described above, we hypothesized that pro-inflammatory cytokine levels would moderate sex effects on verbal learning and memory at both baseline and 12 months later, and, more specifically, that women with high levels of inflammation would not show a verbal learning and memory advantage over men. To examine the specificity of these effects, we also examined nonverbal memory, which was not expected to differ by sex.

2. Method

2.1. Participants and procedure

Participants were 109 adults [50 women; 43 normal cognition (NC), 50 MCI, 16 AD] recruited from the longitudinal Center of Biomedical Research Excellence (COBRE) study at the Cleveland Clinic Lou Ruvo Center for Brain Health. Diagnosis was based on expert consensus of the lead neuropsychologist and neurologist directing the clinical core, based on neuropsychological assessment and Clinical Dementia Rating score (CDR; informant interview; Morris, 1993). In brief, NC was defined as CDR = 0 and ≤ 1 neuropsychological test scores below 1.5 *SD* on age-normed means. MCI was defined as CDR = 0.5 and ≥ 2 neuropsychological test scores 1.5 *SD* below the mean on published age-normed means. AD was defined as CDR ≥ 1 and ≥ 2 neuropsychological test scores 1.5 *SD* below the mean on published age-normed means.

To be included in the present analysis, individuals had to have baseline neuropsychological testing and a baseline blood draw that was used to assess immunologic markers. Additionally, neuropsychological testing data were available 12 months later for 77 individuals (35 women; 35 NC; 36 MCI; 6 AD). Written, informed consent was obtained from all participants, and the research was carried out in accordance with the Declaration of Helsinki and approved by the local Institutional Review Board.

Demographic characteristics of the sample by diagnosis and sex are presented in Table 1. For the full sample, participants had a mean age of 71.62 years old, mean education level of 15.98, and mean body mass index (BMI) of 27.20. The sample was 91.7% white and 93.5% non-Hispanic. Men were significantly more educated, $t(107) = 2.14$, $p = 0.04$, and had higher BMI, $t(107) = 3.75$, $p < 0.001$, than women. Additionally, men were marginally older than women, $t(105) = 1.85$; $p = 0.07$.

2.2. Blood sample collection and inflammatory cytokine assays

Plasma samples were collected at the baseline study visit. Participants were screened for acute infection during the visit, with the overall screening including measurement of vital signs, comprehensive medical and neurological examination, and extensive laboratory workup including comprehensive metabolic panel, complete blood count, and urinalysis. Individuals with active infections were instructed to return for follow up after clearance of their infection, at which point their recovery was verified by study staff. Standard protocol for collecting plasma samples was followed by a certified phlebotomist to ensure uniformity in sample quality. Participants were instructed to hydrate properly at least an hour prior to blood collection. Whole blood was drawn in an EDTA-coated tube and centrifuged at 2000 rpm for 10mins at 18 °C within an hour after collection. Plasma was then carefully collected and aliquoted into sterile 1.5 ml cryotubes. Cryotubes were immediately stored in −80 °C freezer until use.

To simultaneously quantify levels of IL-1β, IL-6, and TNF-α in plasma, we used a suspension multiplex array system (Bio-Plex 200 Systems, 2020). Frozen plasma samples were thawed on ice and spun for 10mins at 10,000×*g* in 4 °C centrifuge to completely remove platelets and precipitates. The 1:4 diluted plasma samples were prepared with the standard diluent (provided in the Bio-Plex Pro Human Cytokine Screening Panel, 48-Plex #12007283). Diluted plasma samples were

Table 1
Demographic characteristics by sex and diagnosis.

	Men			Women		
	NC	MCI	AD	NC	MCI	AD
N	21	29	9	22	21	7
Age	71.33 (6.93)	73.45 (7.33)	73.78 (9.27)	68.82 (6.50)	71.24 (5.43)	72.14 (6.67)
Education	16.68 (2.06)	16.21 (2.80)	16.56 (2.60)*	16.27 (2.55)	15.33 (2.99)	12.71 (2.50)*
White	90.50%	96.60%	88.90%	90.90%	90.50%	85.70%
Non-Hispanic	95.20%	93.10%	100%	86.40%	95.00%	100%
BMI	29.36 (3.21)*	28.61 (4.35)*	27.70 (2.07)	25.41 (5.30)*	25.20 (6.44)*	25.89 (2.92)

Note: Data shown are means and standard deviations. AD: Alzheimer's disease; BMI: body mass index; MCI: mild cognitive impairment; NC: normal cognition.
*Significant sex differences within each diagnostic category $p < 0.05$.

assayed following the manufacturer's protocol with modification.[1] Samples were run in duplicate.

Results were analyzed using the Bio-Plex Manager version 6.1.1 Build 794. Data were normalized using the protein levels from the NC group. Inter-assay %CVs were calculated as follows: means and standard deviations were calculated using the replicate measured values of the same NC sample (provided in the Bio-Plex Pro Human Cytokine Screening Panel, 48-Plex #12007283) per plate per target analyte and subsequently used to estimate the %CVs [=(*SD*/Mean) × 100]. The NC %CVs for each analyte per plate were then averaged to determine the inter-assay %CVs per analyte. For intra-assay %CVs, means and standard deviations were calculated using the replicate measured values of all the samples per plate per target analyte, and subsequently used to estimate the %CVs [=(*SD*/Mean) × 100]. All %CVs for each analyte per plate were then averaged to determine the intra-assay %CVs per analyte. Intra-assay coefficients of variability (CV%) were as follows: IL-1β = 7.0%, IL-6 = 6.0%, and TNF-α = 8.2%. Inter-assay CV% were: IL-1β = 4.9%, IL-6 = 1.2%, and TNF-α = 13.4%.

2.3. Neuropsychological measures

Memory measures were administered at baseline ($n = 109$) and 12-month visits ($n = 77$), and included the well-validated Rey Auditory Verbal Learning Test (RAVLT), an assessment of verbal learning over 5 trials, and 30-minute delayed free recall (Rey, 1964), and Brief Visuospatial Memory Test-Revised (BVMT-R; Benedict and Groninger, 1995), a well-validated measure of nonverbal learning for designs over 3 trials, and 30-minute delayed free recall. For both measures, raw total learning and delayed recall scores were included in the analysis, with higher scores representing better performance.

2.4. Covariates

We included age, education, and BMI as *a priori* covariates. Age (in years) and education were based on self-report at the baseline visit. For education, participants reporting a General Education Development certificate were coded as 11 years of education and high school graduates as 12 years. Beyond high school, years of education was coded as follows: Associate's Degree = 14, Bachelor's Degree = 16, Master's Degree = 18, Juris Doctorate = 19, Doctor of Philosophy or Medical Doctorate = 20. Finally, we assessed BMI at baseline for all participants.

2.5. Data analysis

Analyses were performed using Statistical Package for the Social Sciences (SPSS; IBM SPSS Statistics for Windows, 2015) version 23 and the Process Macro (Hayes, 2013). All variables were analyzed for violations of normality. Of the inflammatory cytokines assessed, IL-1β and IL-6 exhibited significant skew and were thus log transformed for analyses.

T-tests compared men and women in the full sample and each diagnostic category (i.e., NC, MCI, and AD) on verbal and nonverbal learning and recall scores, as well as on pro-inflammatory cytokine levels. A one-way ANOVA using the full sample compared cytokine levels by diagnosis. Partial correlations for the full sample, separated by sex, examined how cytokines related to verbal learning and recall, controlling for baseline age, education, and BMI as *a priori* covariates. Correlations that were significant in women were directly compared to the analogous correlations in men using Fisher's r-to-z transformation.

Finally, for the full sample of participants, across diagnoses, eight moderation regressions were used to examine whether cytokine levels moderated demonstrated effects of sex on verbal learning and recall at baseline and 12-month follow-up, for the full sample of participants. For each time point (i.e., baseline and 12-month follow-up), four moderation regressions were run. Two of these included sex as the independent variable, verbal learning scores as dependent variables, and either IL-1β or IL-6 as moderators. Similarly, two moderation regressions at each time point included sex as the independent variable, verbal recall scores as dependent variables, and either IL-1β or IL-6 as moderators. For all moderation regressions, age, education, and BMI were included as *a priori* covariates.

For correlational analyses, two outliers that were > 2 *SD*s above the mean for cytokine levels were identified by visual inspection of scatterplots and removed. For moderation analyses, outlying and influential data points were defined by failure of two of three thresholds: Cook's D ($D > 4/(n - k - 1)$), where n = participants, and k = predictors; leverage ($(2k + 2)/n$); and Mahalanobis value greater than Chi-square cutoff ($p < 0.0001$; $df = 5$). Results are presented for data after outlier removal.

3. Results

3.1. Sex differences in memory

As hypothesized, baseline verbal learning, $t(105) = -3.15$, $p = 0.002$, and delayed recall scores, $t(105) = -3.15$, $p = 0.002$, were significantly greater for women than men; in contrast, baseline nonverbal learning and delayed recall scores did not differ by sex [Learning: $t(105) = -1.41$, $p = 0.161$; Delay: $t(105) = -1.49$, $p = 0.141$]. At 12 months, women continued to show significantly better verbal learning, $t(75) = -2.03$, $p = 0.05$, and marginally better delayed recall as compared to men, $t(75) = -1.90$, $p = 0.06$. In contrast, no sex differences were observed for nonverbal learning at 12 months, $t(76) = -1.56$, $p = 0.124$, though a trend toward better performance was observed for women for nonverbal delayed recall, $t(76) = -1.87$, $p = 0.07$. These sex differences were driven by NC participants and were absent in AD individuals (See Table 2 for the full results broken down by diagnosis, test, and assessment time point).

[1] An extended time of 1hr was used during the incubation of the samples, blanks, and standards with the coupled magnetic beads, and a total of 45mins during the incubation with detection antibody.

Table 2
Sex differences in RAVLT and BVMT performance by time point and diagnosis.

	Men		Women			
	M	*SD*	*M*	*SD*	*t*	*p*
Time 1						
Full Sample						
RAVLT Learning	31.53	10.8	38.29	11.33	−3.15	**<0.01**
RAVLT Delayed Recall	3.69	4.05	6.37	4.74	−3.15	**<0.01**
BVMT Learning	14.00	7.91	16.31	8.99	−1.41	0.16
BVMT Delayed Recall	4.98	4.16	6.18	4.18	−1.49	0.14
NC[a]						
RAVLT Learning	40.38	8.96	46.43	6.25	−2.53	**<0.01**
RAVLT Delayed Recall	6.48	3.86	9.76	2.28	−3.36	**<0.01**
BVMT Learning	20.1	6.91	23.48	5.83	−1.71	0.09
BVMT Delayed Recall	7.67	3.67	9.33	2.60	−1.73	0.09
MCI[b]						
RAVLT Learning	28.24	7.81	35.1	10.37	−2.67	**0.01**
RAVLT Delayed Recall	2.55	3.49	4.86	4.78	−1.97	**0.05**
BVMT Learning	12.24	5.82	12.62	7.00	−0.21	0.84
BVMT Delayed Recall	4.38	3.68	4.71	3.55	−0.32	0.75
AD[c]						
RAVLT Learning	20.25	7.04	23.43	3.6	_[d]	_[d]
RAVLT Delayed Recall	0.5	1.4	0.71	0.76	_[d]	_[d]
BVMT Learning	4.38	2.77	5.86	3.85	_[d]	_[d]
BVMT Delayed Recall	0.13	0.35	1.14	1.86	_[d]	_[d]
Time 2						
Full Sample						
RAVLT Learning	32.90	10.62	38.11	11.89	−2.03	**0.05**
RAVLT Delayed Recall	4.05	3.75	5.86	4.62	−1.90	0.06
BVMT Learning	15.02	7.93	17.94	8.61	−1.56	0.12
BVMT Delayed Recall	5.05	3.93	6.74	4.04	−1.87	0.07
NC[e]						
RAVLT Learning	39.32	9.06	46.13	8.21	−2.31	**0.03**
RAVLT Delayed Recall	5.53	3.88	8.25	3.62	−2.13	**0.04**
BVMT Learning	18.63	6.36	24.19	4.76	−2.88	**<0.01**
BVMT Delayed Recall	6.74	3.45	9.5	2.07	−2.81	**<0.01**
MCI[f]						
RAVLT Learning	28.10	9.37	32.81	10.62	−1.41	0.17
RAVLT Delayed Recall	3.25	3.28	4.56	4.52	−1.01	0.32
BVMT Learning	13.48	7.65	14.63	6.57	−0.48	0.63
BVMT Delayed Recall	4.19	3.86	5.19	3.71	−0.79	0.43
AD[g]						
RAVLT Learning	24.33	2.89	23.67	1.53	_[d]	_[d]
RAVLT Delayed Recall	0	0	0	0	_[d]	_[d]
BVMT Learning	3.00	2.00	2.33	1.16	_[d]	_[d]
BVMT Delayed Recall	0.33	0.58	0.33	0.58	_[d]	_[d]

Note: AD: Alzheimer's disease; BVMT: Brief Visuospatial Memory Test; NC: normal cognition; MCI: mild cognitive impairment; RAVLT: Rey Auditory Verbal Learning Test. [a]Men = 21, Women = 22; [b]Men = 29, Women = 21; [c]Men = 9, Women = 7; [d]*t*-test not conducted due to small *n;* [e]Men = 19, Women = 16; [f]Men = 20 (BVMT = 21), Women = 16; [g]Men = 3, Women = 3.

3.2. Sex differences in inflammatory markers

No sex differences were observed for the pro-inflammatory cytokines assessed, either across the full sample or separately by diagnosis (See Table 3).

Table 3
Sex differences in inflammatory markers.

	Men ($n = 59$)		Women ($n = 50$)			
	M	*SD*	*M*	*SD*	*t*	*p*
IL-1β	1.99	0.87	1.90	0.97	0.73	0.47
IL-6	3.82	1.76	4.45	4.03	−0.85	0.40
TNF-α	78.02	19.59	81.04	18.40	−0.82	0.41

Note: Raw cytokine values are shown for means and standard deviations. *T*-tests use log transformed values for IL-1β and IL-6. IL-1β: interleukin-1β; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α.

3.3. Diagnostic differences in inflammatory markers

No diagnostic differences in pro-inflammatory cytokines were observed [IL-1β: $F(103) = 0.09$, $p = 0.93$; IL-6: $F(103) = 1.00$, $p = 0.37$; TNF-α: $F(103) = 0.10$, $p = 0.91$].

3.4. Relationship of verbal memory and inflammatory markers in women

Given women's better performance on verbal learning and recall, but not nonverbal measures, we further examined associations of verbal learning and recall and inflammatory levels in women. Greater IL-1β was associated with poorer baseline verbal learning, $r = -0.33$, $p < 0.05$, and recall, $r = -0.33$, $p < 0.05$, and marginally associated with 12-month verbal delayed recall, $r = -0.35$, $p = 0.10$. In contrast, neither IL-6 nor TNF-α were related to verbal learning or recall in women. See Table 4 for additional details.

Table 4
Partial correlations between memory and inflammatory markers.

	Full Sample			
		IL-1β	IL-6	TNF-α
Time 1				
	RAVLT Learning	−0.15	0.30	0.01
	RAVLT Delayed Recall	−0.13	0.01	0.12
Time 2				
	RAVLT Learning	−0.11	0.18	0.20
	RAVLT Delayed Recall	−0.08	0.08	0.12
	Women			
		IL-1β	IL-6	TNF-α
Time 1				
	RAVLT Learning	−0.33*	0.06	0.13
	RAVLT Delayed Recall	−0.33*	−0.05	0.20
Time 2				
	RAVLT Learning	−0.19	0.23	0.20
	RAVLT Delayed Recall	−0.35**	−0.06	0.21
	Men			
		IL-1β	IL-6	TNF-α
Time 1				
	RAVLT Learning	0.03	−0.07	0.07
	RAVLT Delayed Recall	0.09	0.08	0.04
Time 2				
	RAVLT Learning	−0.02	0.20	0.10
	RAVLT Delayed Recall	0.19	0.32**	−0.09

Note: Partial correlations use log transformed values for IL-1β and IL-6. RAVLT: Rey Auditory Verbal Learning Test; IL-1β: interleukin-1β; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α. All correlations include age, education, and body mass index as control variables. * $p < 0.05$. ** $p < 0.01$.

3.5. Inflammation moderates the effects of sex on memory

As hypothesized, IL-1β levels moderated the above-described effects of sex on verbal learning, $t(97) = -2.34$, $p = 0.02$. Specifically, women with low or moderate IL-1β levels exhibited better verbal learning than men at baseline [low: $t(97) = 4.41$, $p < 0.0001$; moderate: $t(97) = 4.28$, $p < 0.0001$], but women with high IL-1β did not, $t(97) = 1.28$, $p = 0.20$. Similarly, women with low-to-moderate IL-1β had stronger verbal delayed recall than men at baseline [low: $t(96) = 4.15$, $p = 0.0001$; moderate: $t(96) = 3.90$, $p = 0.0002$], but women with high levels of IL-1β did not, $t(96) = 0.88$, $p = 0.38$. At 12 months, a similar, marginally significant pattern was observed for verbal delayed recall only (See Table 5).

In contrast, and counter to hypotheses, IL-6 levels did not moderate the above-described sex effect on memory at baseline. At 12 months, however, women with low-to-moderate IL-6 levels outperformed men on verbal delayed recall [low: $t(64) = 2.96$, $p = 0.004$; moderate: $t(64) = 2.08$, $p = 0.04$], but women with high IL-6 did not, $t(64) = 0.18$, $p = 0.86$. Finally, no moderation effects were observed for TNF-α (See Table 5).

4. Discussion

The present study is the first to demonstrate that, as hypothesized, low-to-moderate levels of IL-1β were associated with a verbal learning and recall advantage for women over men at baseline and marginally associated with recall advantage 12 months later, whereas this was not true for women with high IL-1β levels. This finding was specific to verbal learning and recall, and is consistent with prior research linking systemic inflammation with cognitive decline and AD risk (Beydoun et al., 2018, 2019; Schmidt et al., 2002; Tan et al., 2007). This finding is also consistent with research on other disorders (e.g., multiple sclerosis, depression) suggesting sex-specific effects of inflammation on disease (Bellmann-Strobl et al., 2009; Miyata et al., 2020; Slavich and Sacher, 2019). The present study bridges these literatures and raises the possibility that sex differences in AD may be driven at least in part by women exhibiting high systemic inflammation.

Women's well-established verbal memory advantage over men may relate to lifetime estrogen exposure and the supportive effects of estrogen on hippocampal integrity, metabolism, and plasticity (Maki and Resnick, 2000; Rentz et al., 2017; Weber et al., 2014). In contrast, low levels of estrogen, such as those seen in women after menopause, relate to greater levels of pro-inflammatory cytokines, including IL-1β (Klein and Flanagan, 2016). Consistent with support for the involvement of IL-1β in AD (Park et al., 2020), higher IL-1β levels are associated with damage to the hippocampus, and estradiol administration can counter this process (Kajta et al., 2006). Although inflammation may impact the hippocampus in several ways, for women in particular, inflammatory facilitation of amyloid accumulation may be key to sex differences in AD onset and course, as women with increased genetic risk for AD have stronger associations than men between baseline amyloid and subsequent changes in tau, which is known to accumulate first in entorhinal cortex and hippocampus (Buckley et al., 2019; Hohman et al., 2018).

The present findings may also help resolve somewhat contradictory findings and perspectives in the research literature on sex differences in AD. For example, despite research showing that women are at greater risk for developing AD (Buckley et al., 2018), some studies have found greater pathological burden in males (Ossenkoppele et al., 2020) and greater pro-inflammatory cytokines in men after age 65 (Márquez and Chung, 2020). Studies have also suggested that X-linked genes may protect women from early mortality and early symptom presentation (Davis et al., 2020). Our findings showing that sex effects on cognition vary by inflammatory levels emphasize the need to consider sex-related variables including genetics, sex hormones, and inflammation as potential factors that may influence sex-related AD risk and trajectory patterns.

Our findings demonstrating sex-specific associations linking higher levels of specific inflammatory related cytokines and memory may offer a target for future mechanistic work and AD risk-reduction interventions for women. Lifestyle interventions for reducing AD risk have recently gained recognition, given that as many as 40% of current AD cases may be attributed to modifiable risk factors (Livingston et al., 2020). Among these factors, diet and exercise modification interventions have shown promise in large intervention studies designed to reduce risk of cognitive decline in elderly individuals, though not all studies are supportive (for a recent review, see Kivipelto et al., 2018). Diet and exercise have been shown to influence inflammation (e.g., Barbaresko et al., 2013; Cerqueira et al., 2020), including in interactive ways, such as a less inflammatory diet ameliorating inflammatory effects of low physical activity (e.g., Arouca et al., 2019). However, whether sex differences in inflammation effects on cognition play a role in lifestyle intervention outcomes is unknown. Pharmacologically reducing inflammation to reduce AD risk in humans has not yet been shown to be effective (e.g., Breitner et al., 2015), but the role of sex in drug interventions that target inflammation may also warrant additional investigation.

In the present sample, IL-6 and TNF-α were largely unrelated to verbal learning and recall in women. Given existing evidence for the potential involvement of these two pro-inflammatory cytokines in AD (Park et al., 2020) and their known regulation by estrogen (Klein and Flanagan, 2016), this result was somewhat surprising. The lack of findings in the present sample may be due to the inclusion of the full spectrum of AD, from clinically normal to AD dementia, and/or to our inclusion of clinically normal participants who may not go on to develop AD. Another possibility is that the shorter half-life expression of TNF-α (Chen et al., 2017; Oliver et al., 1993; Simó et al., 2012), renders it more difficult to assess. In addition, as IL-6 can be produced in response to levels of TNF-α (Hussein Zineldeen et al., 2010; Libermann and Baltimore, 1990; Neurath and Finotto, 2011; Tanabe et al., 2010), it may be expected that findings are similar for these cytokines. Our result could also relate to IL-6 having both pro- and anti-inflammatory effects depending on receptor solubility (Rose-John, 2012, 2017). The lack of significant findings for TNF-α, in turn, may have to do with the high inter-assay variability for this cytokine versus the others, or with

Table 5
Summary of regression analyses showing inflammatory moderation of sex effects on verbal memory.

	IL-1β									
	RAVLT Total					RAVLT Delay				
Time 1	$p < 0.01$		$F = 5.12$			$p < 0.01$		$F = 3.63$		
	β	*p*	*t*	95% CI		β	*p*	*t*	95% CI	
Sex	15.59	**<.01**	4.14	−31.08	33.82	5.72	**<.01**	3.75	2.69	8.75
Log IL-1β	30.06	0.11	1.63	8.11	23.07	14.95	**0.05**	2.03	0.31	29.6
Sex x IL-1β	−27.77	**0.02**	−2.34	−6.44	66.56	−11.91	**0.01**	−2.49	−21.38	−2.43
Age	−0.15	0.3	−1.05	−51.31	−4.22	−0.07	0.27	−1.05	−0.18	0.05
Education	0.82	**0.03**	2.21	0.09	1.56	0.19	0.21	1.26	−0.11	0.49
BMI	0.38	0.1	1.66	−0.08	0.84	0.06	0.57	0.56	−0.14	0.26
	RAVLT Total					RAVLT Delay				
Time 2	$p < 0.01$		$F = 3.62$			$p = 0.10$		$F = 1.86$		
	β	*p*	*t*	95% CI		β	*p*	*t*	95% CI	
Sex	11.62	**0.02**	2.32	1.64	21.59	6.23	**<.01**	3	2.07	10.37
Log IL-1β	5.78	0.8	0.25	−39.69	51.24	19.06	**0.04**	2.1	0.93	37.19
Sex x IL-1β	−7.28	0.64	−0.47	−37.98	23.41	−14.18	**0.03**	−2.19	−27.09	−1.27
Age	−0.43	**0.03**	−2.23	−0.81	−0.06	−0.03	0.7	−0.38	−0.17	0.12
Education	0.69	0.18	1.35	−0.33	1.71	0.13	0.53	0.64	−0.28	0.53
BMI	0.84	**0.02**	2.44	0.15	1.52	0.13	0.28	0.28	−0.11	0.36
	IL−6									
	RAVLT Total					RAVLT Delay				
Time 1	$p < 0.01$		$F = 3.63$			$p < 0.01$		$F = 3.12$		
	β	*p*	*t*	95% CI		β	*p*	*t*	95% CI	
Sex	12.49	0.09	1.74	−1.8	23.78	5.82	0.07	1.81	−0.55	12.2
Log IL-6	7.72	0.68	0.42	−28.82	44.25	9.52	0.22	1.22	−5.94	24.97
Sex x IL-6	−5.83	0.64	−0.47	−30.62	18.95	−5.09	0.37	−0.9	−16.26	6.09
Age	−0.21	0.18	−1.36	−0.52	0.1	−0.11	0.09	−1.73	−0.23	0.02
Education	0.71	0.08	1.79	−0.08	1.5	0.13	0.83	0.83	−0.19	0.45
BMI	0.41	0.11	1.61	−0.1	0.92	0.05	0.69	0.4	−0.18	0.27
	RAVLT Total					RAVLT Delay				
Time 2	$p < 0.01$		$F = 3.58$			$p = 0.01$		$F = 4.27$		
	β	*p*	*t*	95% CI		β	*p*	*t*	95% CI	
Sex	9.9	0.29	1.07	−8.58	28.37	10.62	**<0.01**	2.91	3.32	17.92
Log IL-6	25.08	0.25	1.16	−18.22	68.38	22.77	**<0.01**	2.73	6.13	39.41
Sex x IL-6	−5.63	0.71	−0.37	−36.01	24.75	−15.32	**0.02**	−2.46	−27.77	−2.88
Age	−0.59	**0.004**	−3.03	−0.97	−0.2	−0.07	0.31	−1.02	−0.022	0.07
Education	1.01	0.06	1.95	−0.03	2.05	0.13	0.49	0.7	−0.25	0.51
BMI	0.53	0.11	1.61	−0.13	1.18	0.09	0.47	0.73	−0.15	0.33
	TNF−α									
	RAVLT Total					RAVLT Delay				
Time 1	$p < 0.01$		$F = 3.81$			$p < 0.01$		$F = 3.63$		
	β	*p*	*t*	95% CI		β	*p*	*t*	95% CI	
Sex	15.06	0.13	1.53	−4.46	34.57	1.6	0.68	0.42	−6.01	9.2
TNFα	0.15	0.42	0.82	−0.21	0.51	0.03	0.7	0.38	−0.11	0.17
Sex x TNFα	−0.07	0.54	−0.61	−0.31	0.16	0.02	0.73	0.35	−0.08	0.11
Age	−0.3	0.06	−1.89	−0.61	0.06	−0.15	**0.02**	−2.36	−0.27	−0.02
Education	0.83	**0.04**	2.12	0.05	1.6	0.25	0.12	1.56	−0.07	−0.02
BMI	0.52	0.07	1.83	−0.04	1.08	0.1	0.4	0.84	−0.13	0.32
	RAVLT Total					RAVLT Delay				
Time 2	$p < 0.01$		$F = 4.00$			$p = 0.06$		$F = 2.15$		
	β	*p*	*t*	95% CI		β	*p*	*t*	95% CI	
Sex	12.2	0.31	1.03	−11.52	35.91	0.77	0.87	0.65	−8.56	10.1
TNFα	0.2	0.33	0.98	−0.21	0.62	−0.001	0.99	−0.02	−0.16	0.16
Sex x TNFα	−0.04	0.8	−0.25	−0.32	0.25	0.02	0.69	0.4	−0.09	0.13
Age	−0.55	**<0.01**	−2.79	−0.94	−0.16	−0.15	**0.05**	−2.05	−0.3	−0.003
Education	1.21	**0.02**	2.33	0.17	2.26	0.28	0.17	1.4	−0.12	0.67
BMI	0.88	**0.01**	2.66	0.22	1.54	0.11	0.38	0.89	−0.14	0.36

Note: BMI: body mass index; IL-1β: interleukin-1β; IL-6: interleukin-6; RAVLT: Rey Auditory Verbal Learning Test; TNF-α: tumor necrosis factor-α.

potential sex differences in TNF-α receptors (e.g., Aomatsu et al., 2013).

We also did not find sex differences in any pro-inflammatory cytokine for the full sample or by diagnosis. This was unexpected and may also relate to our sample composition, including participants with preclinical and clinical AD, as well as individuals who were clinically normal without evidence of preclinical AD. At the same time, this finding, when paired with our finding of IL-1β as a moderator of sex effects, is consistent with research showing that sex effects in AD are complex and often interactive (Buckley et al., 2018, 2019).

Strengths of the present study include our well-characterized sample, longitudinal assessment, examination of pro-inflammatory cytokines as potential moderators of sex effects on memory, and inclusion of both verbal and nonverbal memory outcomes. There are also several limitations. First, the sample was predominately white, meaning that additional research is needed to examine the generalizability of these results. Second, we did not measure estrogen levels, which could have helped to explain the inflammation effects observed. Third, we cannot infer causation based on these data, although our findings across two longitudinal time points provide some support for inflammation as a predictor, rather than as simply a correlate, of poor memory. Fourth, our sample size limited our ability to conduct all analyses within specific diagnostic groups, and our smaller 12-month sample in particular may have been underpowered to detect significant effects. Given this limitation, these findings should interrogated in larger samples. Finally, we did not assess neuroinflammation, and although it is possible that cytokines differ in specific brain regions, peripheral plasma measures cannot accurately detect these differences. As such, the present data provide an important first step toward understanding sex differences in memory and AD, but they do not speak to inflammatory mechanisms that may be most proximally relevant for memory.

Notwithstanding these limitations, the present data are the first to show that pro-inflammatory cytokine levels moderate the established finding that women have better verbal memory than men. More specifically, we found that women with high levels of IL-1β do not show better verbal learning or recall than men, at baseline or 12 months later. In contrast, women with low-to-moderate levels of IL-1β show an expected verbal memory advantage. This was true across the spectrum from normal cognition to AD dementia. Looking forward, additional research is needed to investigate the contribution of estrogen to inflammation in this context, to assess the role of neuroinflammation in influencing cognition in AD and other disorders, to study other AD-related cognitive processes in addition to verbal and non-verbal memory, and to examine the longitudinal relevance of these processes for risk for developing AD and other chronic diseases with an inflammatory component.

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