Interleukin-6 and Memory Functions of Encoding and Recall in Healthy and Depressed Elderly Adults

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Activation of proinflammatory cytokines is associated with depressed mood, feelings of fatigue, and changes in cognitive function. This study examined the relationships between cognitive performance and circulating cellular markers of inflammation, interleukin-6 (IL-6) and C-reactive protein (CRP), in moderately depressed and comparison healthy older adults. We conducted a cross-sectional analysis of 87 volunteers (45 nondepressed and 42 depressed) in which participants completed the Structured Clinical Diagnostic Interview and were evaluated by a geriatric psychiatrist for dementia, depression, stroke risk, and neurologic disorders. Volunteers also completed an electrocardiogram, standard battery of laboratory tests, and neuropsychological examination that assessed memory functions of Encoding and Recall, Executive Function, and Attention/Processing. Mid-morning IL-6 and CRP levels were assessed. The data analysis showed that Encoding and Recall were inversely associated with IL-6 across diagnostic groups after controlling for chronological age, Mini-Mental State Examination, body mass index, literacy level, depression severity, and sex. CRP was not associated with cognition. Depression status was associated with recall independent of IL-6 levels. In conclusion, IL-6 serum levels among elderly individuals is a significant correlate of memory performance. Women, in particular, appear sensitive to IL-6 fluctuations across diagnostic groups. (Am J Geriatr Psychiatry 2012; 20:753–763)

Key Words: Aging, cognition, cytokines, dementia, depression, geriatric, immune system

Advancing age is associated with disruption of homeostasis in the immune system or immunosenescence.[1] Although the effects of aging on immune function are poorly understood, the aging brain has been characterized by a shift from the homeostatic balance of inflammatory mediators observed in mid-adulthood to a proinflammatory profile in late life.[2] The increased neuroinflammation is represented by increased numbers of activated and primed microglia,[3] increased steady state levels of inflammatory cytokines,[4,5] and decreased functionality of humoral and cellular immune responses.[1,6,7] This shift has been associated with increased vulnerability to neurodegenerative and chronic

diseases, which increase exponentially during late life.[6,8–11]

The effect of this immunologic shift on cognitive performance is unclear. Some longitudinal studies have indicated a relationship between high cytokine levels, for example, interleukin-6 (IL-6) and C-reactive protein (CRP), in peripheral plasma and development of multiple forms of dementia through complex mechanisms.[9,11,12] On the contrary, data from the MacArthur Study of Successful Aging indicated that there was no effect of inflammatory status on baseline cognitive function or the rate of longitudinal cognitive change after correcting for potential confounders.[13] However, when the investigators examined subgroups, they found that persons in the top tertile of IL-6 concentrations were at an increased risk of incident declines on a short mental status test. The finding could result from underlying pathology or preclinical cognitive impairment associated with incident dementia, as the MacArthur Study investigators suspected. Another explanation is that the increased inflammatory level could contribute causally to cognitive changes that are independent of an underlying neuropathology, but the change is statistically significant only at the extreme end of a spectrum.

Immune status has also been associated with major depressive disorder (MDD) relative to healthy individuals[14] through the more prolonged adaptive immune response and the transient acute phase response.[14–17] Acute phase response in MDD includes increased serum concentrations of positive acute phase proteins, which includes CRP, and lowered serum concentrations of negative acute phase proteins such as albumin and transferrin.[18] Adaptive changes are based on evidence of in vivo secretion of cytokines, particularly IL-6, interleukin-1 beta (IL-1β), and interleukin-8,[19,20] and the associations are stronger when melancholy is present.[21,22] An early meta-analysis by Herbert and Cohen[16] reported that immune alterations include lower proliferative response of lymphocytes to mitogens, lower natural killer cell activity, and changes in levels of several white blood cell populations.[16] The changes were more pronounced in older populations and appeared to be linearly related to the severity of the depressive episode. Studies of experimental sleep loss, a common problem among depressed individuals, report a marked and transient increase in IL-6, increased nuclear factor-kappa B, and a threefold increase in

transcription of IL-6 messenger RNA after a single night of sleep loss.[23,24] Despite the differences in the strength of the association between cytokines and sleep loss, IL-6 activity remains characteristic of major depression with or without sleep disorders.[19] Elevated levels of IL-6 occur concurrent with depressive symptoms in patients with renal failure,[25] cardiovascular disease,[26] advanced cancer,[27] rheumatoid arthritis,[28] and irritable bowel syndrome.[29] Adaptive immunologic changes are thought to represent a chronic neuroinflammation in which responses of microglial cells contribute to and expand the neurodestructive effects of the initial acute neuroinflammation, worsening the disease process.

Although elevated cytokine levels have tentatively been associated with cognitive decline in healthy older adults, the same cognitive–cytokine relationship has not been examined among elderly depressed individuals, despite their known cognitive deficits relative to healthy controls.[30,31] One reason for the lack of definition of the relationship is the general nature of the cognitive testing: clinical studies use short screening tests with general memory questions, and experimental studies use animal models. General memory questions cannot clarify whether poor memory performance is a result of poor encoding of material or inability to recall it. Encoding imbues a stimulus with meaning and creates the neural imprint, and recall is the executive search and reactivation of the target memory. Elderly, moderately depressed individuals without mild cognitive impairment show slow encoding ability but comparable ability in recall relative to healthy comparison individuals.[32] Behaviorally, individuals with encoding deficits are not helped functionally with cues or reminders, while those same reminders or cues can be of help to individuals who encoded the material accurately but have difficulty retrieving the information. The question is what kind of memory dysfunction is related to an increased cytokine level. In addition to memory deficits, executive dysfunction and attention/processing deficits are common among depressed older adults and may be related to increased cytokine levels.[30,31,33–35]

This study examined the type of memory deficit associated with cytokine levels in both healthy and depressed older adults under the hypothesis that IL-6 and CRP would be associated negatively with cognitive performance across diagnostic groups. We also expected that depressed individuals would show

a stronger association with cognitive performance than that observed in the comparison group. We also posed a research question as to whether executive dysfunction and attention/processing deficits are related to increased cytokine levels.[34–37] As depression is more common among women, we examined a potential cytokine-by-sex interaction on cognitive performance.

METHODS

Study Site, Design Overview, Participant Sampling, and Procedures

Volunteers (major depressed, N = 45; and healthy comparison, N = 42) were recruited as part of an ongoing study of late-life depression at University of California Los Angeles (UCLA). Prospective subjects who were 60 years of age or older with English proficiency were screened with the Structured Clinical Interview for DSM-IV (SCID). Depressed patients were diagnosed by a geriatric psychiatrist according to Diagnostic and Statistical Manual of Mental Disorders–IV criteria for MDD and a score 15 or more on the 17-item Hamilton Depression Rating Scale. Exclusionary criteria were 1) history of substance abuse or other Axis I disorder per the SCID; 2) clinical evidence of dementia or Mini-Mental State Examination (MMSE) $\leq$ 26; 3) history of transient ischemic attack; 4) history of head trauma or lifetime loss of consciousness; 5) current or unstable serious medical illness; 6) chronic neurologic disease that could affect cognitive function; or 7) history or evidence of psychotic symptoms or concurrent Axis I psychiatric disorder. Stable chronic conditions such as diabetes mellitus, hypertension, or history of cancer were not exclusionary. Depressed volunteers were drug-free for antipsychotics, anxiolytics, and antidepressant medications for at least 2 weeks prior to inclusion in the study, and many were drug naive. After describing the study, which was approved by the institutional review board of UCLA, we obtained written informed consent.

After being screened with the SCID, patients were administered MMSE, Hamilton Depression Rating Scale, Beck Depression Inventory (BDI), Cerebrovascular Risk Factor Assessment,[38] and Cumulative Illness Rating Scale.[39] The Cerebrovascular Risk Factor Assessment quantifies the vascular risk for future stroke according to the American Heart Association guidelines, which are available on the American Heart Association website (http://stroke.ahajournals.org/content/39/5/1647). The Cumulative Illness Rating Scale is commonly used to assess medical comorbidity by quantifying medical burden in primary organ systems. Following the neurologic evaluation, patients completed an electrocardiogram, a standard battery of laboratory tests, and neuropsychological assessment.

Assessment of Cognitive Function

The cognitive battery utilized well-established clinical measures to assess multiple domains: *Literacy:* Wechsler Test for Adult Reading Scale;[40] *Encoding*: California Verbal Learning Test, Version 2 (CVLT) trials 1–5 and trial 5,[41] and immediate recall score from Visual Reproductions (VR) (i.e., reproduction of the stimulus immediately after it has been removed);[42] *Recall:* CVLT short (5 minutes) and long (20 minutes) delayed free recall, VR 20-minute delayed recall, and Rey Osterrieth Complex Design 20-minute delayed recall and percent retention;[43] *Executive Function*: Matrix Reasoning[44] number correct for deductive analysis, Stroop Part 3 time to completion for response inhibition,[45] Wisconsin Card Sort Test[46] categories correct for abstract conceptualization and generalization, Letter-Number Sequences number correct for working memory manipulation;[44] and *Attention and Processing*: Trail making Parts A and B[47] time to completion, Stroop Part 1,[45] time to completion, and Digit Symbol Substitution[44] number completed. Cognitive test results were normed using published norms. After examining each variable for normative performance, z scores were formed from raw scores for each test variable using the mean and standard deviation of the control group with timed tests reversed so that higher scores represented better performance. Composite variables were computed for Encoding, Recall, Executive Function, and Attention/Processing. Percent retention of the Rey Osterrieth Complex Design was included to avoid penalizing a participant twice for an initial error because no advance warning of a later recall is given in this test.

IL-6 and CRP Assays

Blood samples were drawn mid-morning from participants through routine venipuncture after they

completed a questionnaire and provided height and weight measurements for a computation of body mass index (BMI). (One subject did not complete the height and weight measurements.) CRP was measured using high-sensitivity immunoassay on a BN-II System (Dade-Behring, Newark, DE). Samples were automatically diluted 1:20 with N Diluent. This technique has a limit of detection of 0.175 mg/L and intra- and interassay coefficients of variation of less than 4%.

Plasma levels of IL-6 were quantified by means of high sensitivity enzyme-linked immunosorbent assay methods (R & D Systems, Minneapolis, MN) with all samples from both groups assayed at the same time, in a single run with a single lot number of reagents and consumables employed by a single operator, with intra-assay coefficients of variation for all variables less than 5%.

Statistical Plan

Sex was a variable of interest, so it was decided a priori to be a covariate due to its association with depression. Age and literacy levels were covariates due to their association with both cytokine level and cognitive performance. Literacy level is a better indicator of intellectual function than years of education, race, economic status, or occupation. Variables were examined for distribution. IL-6 and CRP were skewed so natural log transformations were computed, which improved distribution sufficient for analysis. The interrelationships of scores (Cronbach's αs) were computed for each of the composite indices with the following results: Encoding of verbal and nonverbal information ($\alpha = 0.94$), Recall of information ($\alpha = 0.83$), Executive Function ($\alpha = 0.72$), and Attention and Processing ($\alpha = 0.75$). BMI scores were computed from laboratory assessments. Diagnostic groups differed on the Recall and Encoding indices. Analysis of intercorrelations found that MMSE was associated with all cognitive measures so it was added as a covariate. Two-tailed partial correlations were computed to determine the associations between IL6 and the four cognitive indices after controlling for age, sex, and MMSE. Significant associations were further explored using a multiple hierarchical regression approach. This approach allows the inclusion of multiple covariates and testing for potential interaction effects between different predictors.

RESULTS

The diagnostic groups were comparable on all demographic variables except the BDI and the CIS, on which depressed patients were expected to report more symptoms than controls (see Table 1). The depressed group had both early- and late-onset patients. Diagnostic groups differed on Recall and Encoding indices, but they did not differ on serum cytokine levels.

After partialing out the effects of age, sex, literacy level, and MMSE, Recall was associated with IL-6 ($r_{79} = -0.34$, p <0.002). It was in the expected inverse direction with increasing IL-6 levels corresponding to lower performance (see Figure 1). Encoding correlated inversely with IL-6 ($r_{79} = -0.30$, p = 0.007). IL-6 correlation coefficients with executive function and attention/processing were not significant so analyses were stopped on those variables. CRP was not significantly related to any of the cognitive indices and was dropped from further analysis.

A hierarchical multiple linear regression that examined Recall's association with IL-6 used Recall as the dependent variable with covariates of chronological age, literacy level, sex, diagnosis, MMSE, and BMI as the independent variables in the first step. The second step added IL-6, and the third step added the interaction terms for diagnosis-by-MMSE, sex-by-IL-6, and IL-6-by-diagnosis. Cumulatively, the interactions explored if cognitive scores varied across diagnostic groups as a function of MMSE scores or IL-6 levels, or across men and women based on IL-6 levels.

As shown in Table 2, the original model explained the Recall scores well, but the model was significantly improved with the addition of IL-6. Adding interaction terms did not add to the explanatory power of the model ($\Delta R^2 = 0.04$, $F_{[3,73]} = 1.80$, p = 0.15) (not shown in the Table) although the MMSE-by-diagnosis interaction was individually significant and was retained ($t_{73} = -2.26$, p = 0.03). In the final model, IL-6 continued to be significant after accounting for age, sex, literacy level, MMSE, diagnosis, and the MMSE-by-diagnosis interaction. The interaction, shown in Figure 2, improved the model again ($\Delta R^2 = 0.04$, $F_{[3,73]} = 5.82$, p = 0.02). Analysis of the interaction indicated that comparison subjects increased more in Recall per unit increase in MMSE than did depressed

TABLE 1.   Clinical and Demographic Characteristics of Diagnostic Groups

	Total Sample by Diagnostic Group (N = 87)		Model Values		
	Comparison(n = 45)	Depressed (n = 42)	df	t	p
Age	69.2 (±7.1)	69.7 (±7.9)	85	−0.28	0.78
Education	16.2(±2.0)	15.8 (±2.8)	85	0.68	0.50
Sex (female/male)	34/11	28/14	1	$\chi^2 = 0.84$	0.36
MMSE	29.2 (±0.9)	29.0 (±1.2)	85	0.57	0.57
CVRF, age adjusted	4.9 (±3.4)	4.9 (±2.3)	84	−0.01	0.99
CIRS categories	2.8 (± 2.1)	4.0 (±2.1)	84	−2.42	0.02
Systolic blood pressure	129.7 (±18.2)	132.0 (±15.8)	85	−0.63	0.53
VIQ estimate per WTAR	114.6 (±7.3)	113.1 (±9.8)	85	0.84	0.40
Body mass index (BMI)	24.9 (±3.7)	25.6 (±4.4)	79	−0.69	0.49
Age of onset	na	46.4 (±23.6)			
Hamilton Depression Rating	na	18.7(±2.9)			
Current duration, months	na	77.7 (±75.41)			
Beck Depression Scale	1.7 (±1.9)	25.3(±7.6)	85	−20.03	<0.01
Ethnicity			3	$\chi^2 = 3.46$	0.32
Asian	3	0			
Caucasian	35	37			
African American	5	3			
Hispanic	2	2			
Handedness (L/R)	3/39	3/37	2	$\chi^2 = 0.15$	0.93
Interleukin 6	0.5 (±0.5)	0.7 (±0.6)	85	−1.10	0.27
C-reactive protein	0.3 (±0.6)	0.4 (±0.4)	85	−0.75	0.45
Memory Index	0.28 (±0.84)	−0.05 (±0.67)	85	2.05	0.04
Attention/Processing Index	0.04 (±1.22)	−0.42(±1.05)	84	1.86	0.07
Executive Index	0.34 (±0.80)	0.12 (±0.56)	83	1.45	0.15
Encoding Index	0.00 (±0.97)	−0.51 (±0.91)	85	2.55	0.01

Notes: CIRS: Cumulative Illness Rating Scale; CVRF: Cerebrovascular Risk Factor; MMSE: Mini-Mental State Examination; VIQ: estimated verbal intelligence quotient interpreted from Wechsler Test for Adult Reading results. Standard deviations are in parentheses.

patients. The final model explained 40% of the variance in recall performance.

The original model was recomputed with Encoding as the dependent variable (Table 3). The first step explained the variation in Encoding satisfactorily, but the inclusion of IL-6 again improved the model significantly. In the third step (not shown), adding the interaction terms improved the model ($\Delta R^2 = 0.10$, $F_{[3,73]} = 4.50$, p = 0.006) but only the sex-by-IL-6 interaction was individually significant ($\beta = -0.95$, $t_{73} = -2.53$, p = 0.01) and was retained. The final model showed age, literacy level, MMSE, diagnosis, and the sex-by-IL-6 interaction as significant predictors. IL-6 and sex were marginal independent predictors. Examination of the sex-by-IL-6 interaction (Figure 3) showed that women declined more in Encoding of memories per unit increase in IL-6 than did men.

To determine whether depression severity rather than the categorical depression diagnosis added to the model's explanatory power for Recall, the linear regression was recomputed with BDI scores entered

at the first step instead of depression diagnosis. The results were essentially the same for the full model at
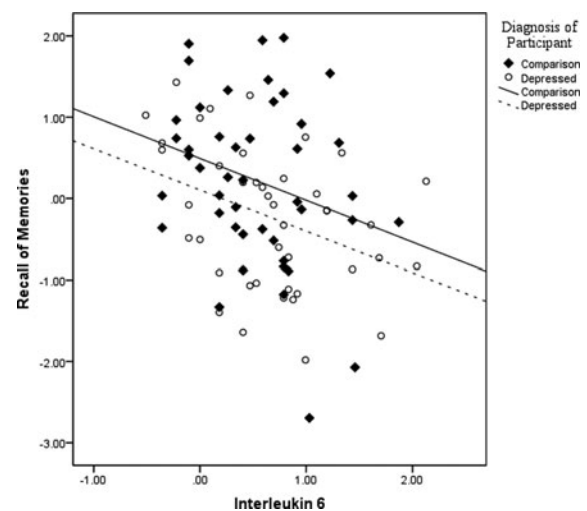
FIGURE 1.

TABLE 2. Hierarchical Regression Coefficients of IL-6 and Other Variables Predicting Recall Performance

	Variable Values				Model Values				Change Parameters	
	B	β	t	p	R^2	F	p	df	ΔR^2	Significance of F Change
1st step										
Age	−0.03	−0.29	−2.93	0.004						
WTAR	0.01	0.11	1.10	0.28						
Sex	−0.33	−0.20	−2.02	<0.05						
Diagnosis	−0.33	−0.21	−2.17	0.03						
MMSE	0.18	0.25	2.43	0.02						
BMI	−0.03	−0.02	−0.16	0.88						
					0.28	5.08	<0.001	6,77		
2nd step										
Age	−0.03	−0.25	−2.59	0.01						
WTAR	0.01	0.12	1.20	0.23						
Sex	−0.25	−0.15	−1.54	0.13						
Diagnosis	−0.26	−0.18	−1.81	0.08						
MMSE	0.22	0.30	3.07	<0.01						
BMI	<0.01	0.02	0.20	0.84						
IL-6	−0.39	−0.30	−3.08	<0.01						
					0.36	6.19	<0.001	7,76	0.08	0.003
Final model										
Age	−0.02	−0.24	−2.62	0.01						
WTAR	0.01	0.11	1.23	0.22						
Sex	−0.33	−0.20	−2.17	0.03						
Diagnosis	9.20	6.14	2.35	0.02						
MMSE	0.41	0.58	3.92	<0.01						
IL-6	−0.30	−0.23	−2.43	0.02						
MMSE × Dx	−0.33	−6.31	−2.41	0.02						
					0.40	7.58	<0.001	7,79	0.04	0.02

Notes: df for the *t* tests corresponds to the model's denominator df given in the table. *B*: unstandardized betas; *β*: standardized betas; BMI: Body Mass Index; IL-6, interleukin 6; Dx: diagnosis; MMSE: Mini-Mental State Examination; WTAR: Wechsler Test of Adult Reading.

all steps, most likely attributable to the strong differences between the groups in BDI mean scores. Adding the BDI instead of depression diagnosis to the model predicting Encoding also produced very similar results to the original model including the marginally significant interaction between BDI and IL-6 ($\beta = 0.33$, $t_{79} = 1.86$, p = 0.07).

To clarify which memory scores were most closely associated with IL-6, the individual test scores within the Recall and Encoding indices were correlated with IL-6 values after controlling for age, sex, and MMSE. No differences emerged between diagnostic groups in the partial correlation coefficients based on Fisher's Z testing, so scores were combined. Six of the eight tests of both delayed recall and encoding of information were correlated with IL-6 levels, and the two remaining tests (CVLT short-delayed recall and VR immediate recall) trended toward significance.
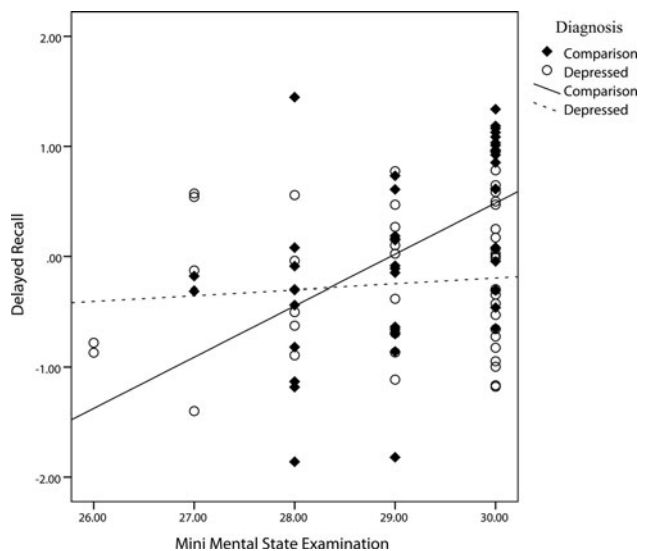
FIGURE 2.

**TABLE 3. Hierarchical Regression Coefficients of IL-6 and Other Variables Predicting Encoding Performance**

	Variable Values				Model Values				Change Parameters	
	B	*β*	*t*	*p*	R^2	*F*	*p*	df	ΔR^2	**Significance of F Change**
1st step										
Age	− 0.04	− 0.33	− 3.36	<0.01						
WTAR	0.03	0.26	2.57	0.01						
Sex	− 0.08	− 0.05	− 0.51	0.61						
Diagnosis	− 0.22	− 0.14	− 1.43	0.16						
MMSE	0.15	0.20	2.00	<0.05						
BMI	− 0.03	− 0.15	− 1.54	0.13						
					0.3	5.60	<0.001	6,77		
2nd step										
Age	− 0.03	− 0.30	− 3.06	<0.01						
WTAR	0.03	0.26	2.70	<0.01						
Sex	− 0.01	− 0.01	− 0.05	0.96						
Diagnosis	− 0.16	− 0.10	− 1.09	0.28						
MMSE	0.19	0.25	2.50	0.02						
BMI	− 0.02	− 0.12	− 1.28	0.21						
IL-6	− 0.33	− 0.25	− 2.55	0.01						
					0.36	6.07	<0.001	7,76	0.06	0.01
Final model										
Age	− 0.03	− 0.32	− 3.53	<0.01						
WTAR	0.03	0.24	2.60	0.01						
Sex	0.34	− 0.20	1.71	0.09						
Diagnosis	− 0.29	− 0.18	2.02	<0.05						
MMSE	0.19	0.26	2.76	<0.01						
IL-6	0.78	− 0.58	1.74	0.09						
Sex × IL-6	− 0.67	− 0.92	− 2.62	0.01						
					0.41	7.77	<0.001	7,79	0.05	0.01

Notes: df for the *t* tests correspond to the model's denominator df given in the table. *B*: unstandardized betas; *β*: standardized betas; BMI: Body Mass Index; IL-6: interleukin 6; MMSE: Mini-Mental State Examination; WTR: Wechsler Test for Adult Reading.

DISCUSSION

The aging process is defined by a slow disruption of immunologic homeostasis with a shift toward a proinflammatory state. This neuroinflammation is thought to compromise the brain's functioning by increasing its vulnerability to neurotoxicity and impairing neurogenerativity. Our results support this theory in that both encoding and recall of memories were negatively associated with serum IL-6 levels in depressed and healthy elderly adults. As IL-6 levels increased, recall ability decreased for information learned from 5 to 20 minutes earlier as did the ability to encode new information. In addition, the encoding association with IL-6 was modulated by sex, with women showing a greater sensitivity to higher levels of IL-6 than men. Contrary to our hypothesis, patients and controls did not differ in the strength of the relationship between IL-6 and encoding or recall

FIGURE 3.
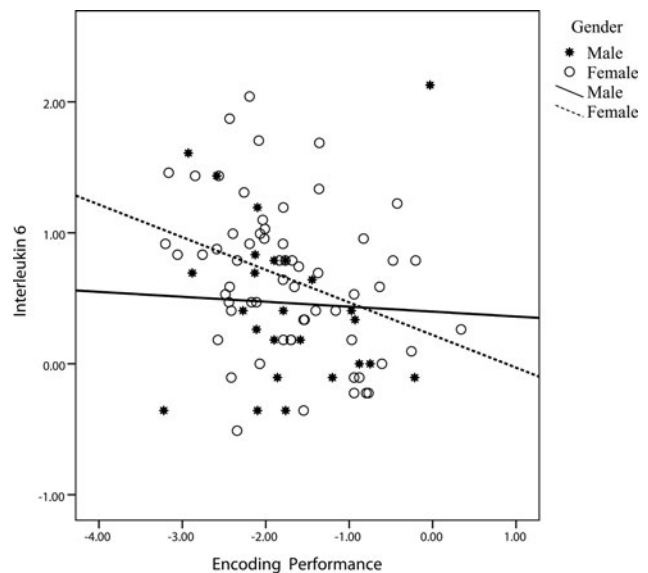
performance. Also, contrary to our hypothesis, IL-6 levels did not correlate negatively with executive function or attention/processing, and CRP was not associated with any cognitive function assessed. The relationship between IL-6 and both memory functions currently assessed is in addition to significant contributions from age, MMSE scores, literacy level, and depression diagnosis.

The effect sizes (standardized betas) from the multiple regression equation for Recall indicate that MMSE and diagnosis are the strongest predictors of recall performance, yet IL-6 makes approximately the same contribution as age or sex. Thus, it is an important and potentially modifiable condition for patients who complain of changes in recall ability. Elderly patients recovering from illness may also experience transient problems with memory with elevated IL-6 levels.

On the other hand, the multiple regression equation for Encoding indicates that IL-6 and the IL-6-by-sex interaction are the strongest predictors of performance and are stronger than age, literacy level, diagnosis, or MMSE score. Unfortunately, poor encoding performance can be mistaken for mild cognitive impairment or prodromal dementia because recall does not improve with the use of cues. When being tested for memory function, cues facilitate recall performance if encoding occurred successfully. When encoding does not occur, cues are not helpful and suggest possible damage in the hippocampal and entorhinal complexes and indicate the need of further investigation. Thus, immunologic imbalance could lead to a misrepresentation of an elderly person's, particularly a woman's, memory problems.

Moderately depressed patients and controls did not differ in their levels of IL-6, yet depressed individuals showed a deficit in memory performance relative to controls. This difference may result from an enhanced sensitivity to the presence of IL-6 among depressed patients if they have experienced earlier episodes or have subtle increases in IL-6 that do not reach statistical significance but that are physiologically important. Trzonkowski and colleagues[48] reported that older depressed individuals showed elevated levels of tumor necrosis factor α (TNF-α) and IL-6 after receiving an anti-influenza vaccination together with insufficient production of the anti-inflammatory IL-10 and natural killer cell cytotoxicity compared with age- and sex-matched controls.[48] Although the differences disappeared when they corrected for anti-CMV anti-bodies, Trzonkowski and colleagues concluded that the depressed patients demonstrated a proinflammatory profile suspected of resulting from prior exposure to elevated levels of IL-6 and deficiency of suppressive IL-10+ cells.

Our results are consistent with Trzonkowski and colleagues'[48] findings. Although depressed and healthy individuals were comparable in IL-6 levels, the difference in cognitive performance may indicate that moderately depressed patients develop a sensitivity on the basis of prior periods of increases in IL-6 that is independent of absolute IL-6 levels. In our model, depression status could potentially represent this enhanced sensitivity to IL-6 as it was an independent predictor of recall and encoding ability after accounting for IL-6 levels. A recent review by Miller et al.[49] outlines how depressed individuals exhibit features of inflammation including elevations in relevant inflammatory cytokines and their soluble receptors in peripheral blood and cerebrospinal fluid.[49] Peripheral blood concentrations of acute phase proteins, chemokines, adhesion molecules, and inflammatory mediators such as prostaglandins show concurrent elevations during depressed episodes.[14] Thus, depression status may be associated with a broad immunologic disruption of which IL-6 is one factor. Subgroups of depressed patients may experience one or multiple changes, while healthy older adults have a more limited response.

The link between memory ability and cytokines may occur at the molecular level via cytokines' role in neurogenesis, memory consolidation, and synaptic plasticity.[50] Transgenic mice that overexpress IL-6 have a 63% reduction in neurogenesis in the dentate gyrus of the hippocampus, a medial temporal structure critical for memory consolidation.[51] Inflammation resulting from cranial radiation therapy among humans causes cognitive loss that appears associated with impaired neurogenesis in the dentate gyrus via stem cell dysfunction.[52] In addition, the hippocampus and the hypothalamus have the highest expression of inflammatory cytokine receptors for IL-6 and IL-1β in the brain.[53] Synaptic plasticity may be modulated when peripheral cytokine IL-1 elevation induces nuclear factor κB in the brain.[54] This induction in the brain is thought to contribute to changes in neuronal growth and survival, especially through the further induction of nitric oxide and, ultimately, oxidative stress, which has been shown to alter

promoter function for several genes central to synaptic plasticity.[55,56]

Among elderly depressed patients, hippocampal surface contractions have been observed by our research team among elderly depressed patients, particularly among late-onset patients, and the contractions correlate with decreased performance in nonverbal memory (encoding and recall were not tested separately).[57] A postmortem study of brains from depressed individuals reported condensation of neuronal architecture in the hippocampus, which is consistent with neuronal dearborization rather than apoptosis in hippocampal tissue suggestive of a pathodegenerative process[58] such as developing Alzheimer disease. Furthermore, increased levels of IL-1β disrupt long-term potentiation,[59,60] a cellular mechanism believed to be important for recall, one type of memory assessed in this study. In mice, treatment with lipopolysaccharide, which causes an inflammatory response, produces increased IL = 1β, IL-6, and TNF in brain areas including the hippocampus.[61] Pugh et al.[62] demonstrated that injections of lipopolysaccharide or IL-1β directly into the hippocampus disrupted hippocampal-dependent memory consolidation. In mice, the Morris water maze, a hippocampal-dependent test of spatial learning, has been shown to be sensitive to disruption by infection or peripheral immune activation and subsequent upregulation of proinflammatory cytokines.[63] Data from the Longitudinal Aging Study Amsterdam indicates that in persons with a high level of IL-6, there is a negative association between higher homocysteine at baseline and immediate recall.[64] Consequently, people with higher steady state levels of IL-6 appear more vulnerable to current and future cognitive deficits. Future research is needed that explores the links between hippocampal neuronal dearborization, proinflammatory response patterns, decreased cognitive performance, and the onset and severity of mood disorders.

Future research also needs to examine the relationship between IL-6 and IL-1β in depressed and healthy older adults because the relationship of IL-1β to memory functions is variable. At basal levels, IL-1β appears to support memory mechanisms, but changes in the basal level, whether increase or decrease, appear to disrupt memory consolidation and may result in cognitive impairment.[63] Baune et al.[65] reported an association between IL-1β, IL-6, and TNF and cognitive performance among healthy elderly humans in the general population, but the TNF was thought to be protective of processing speed.[66] Finally, longitudinal research is needed to address the question of whether elevated IL-6 predisposes one to developing depressive syndrome or does the onset of the depressive episode from another, as-yet-unknown cause, precipitate either an increased immune response or the failure of the suppression response that causes a cascade of brain changes that have functional implications.

In conclusion, results suggest that influences on memory performance for elderly individuals and depressed patients are multifactorial, but one factor is the serum level of IL-6. Elevated levels of IL-6 are associated with some of the variations in recall performance for all elderly individuals, but encoding ability may be singularly sensitive to fluctuations in IL-6 levels for older women.

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