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Original Article

A Mixed-Effects Model of Associations Between Interleukin-6 and Hippocampal Volume

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Abstract

Previous studies report hippocampal volume loss can help predict conversion from normative aging to mild cognitive impairment to dementia. Additionally, a growing literature indicates that stress-related allostatic load may increase disease vulnerability. The current study examined the relationship between stress-related cytokines (ie, interleukin-6 [IL-6]), cognition as measured by Mini-Mental State Examination (MMSE) scores, and hippocampal volume. Mixed models were employed to examine both within- (across time) and between-subject effects of IL-6 and hippocampal volume on MMSE score among 566 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI). The within-subject analysis found left hippocampal volume significantly (p = .009) predicted MMSE score. Between-subject analysis found the effect of IL-6 on MMSE was moderated by right hippocampal volume (p = .001). These results replicate previous findings and also extend prior work demonstrating stress-related cytokines may play a role in Alzheimer's disease progression.

Keywords: Cognitive decline, Inflammation, Memory, Stress-related cytokines

Advancing age (in the brain) can be characterized by a disruption in homeostasis creating an imbalance of inflammatory mediators present in mid-adulthood to an increase in neuroinflammation (1). Increased presence of inflammatory mediators in individuals with Alzheimer's disease (AD) combined with epidemiological studies linking anti-inflammatory drugs with decreased risk of dementia further supports that neuroinflammation plays a role in AD (2). Longitudinal studies have highlighted a relationship between high cytokine levels, such as C-reactive protein and interleukin-6 (IL-6), in the development of multiple forms of dementia (3,4). Similarly, data from the MacArthur Study of Successful Aging found that people in the top tertile of IL-6 concentrations were at an increased risk of declines on a mental state examination, which the study investigators suggest could be indicative of underlying pathology or preclinical cognitive impairment (5).

Stress-related cognitive decline is thought to result from the effects of prolonged elevations of cortisol, a hypothalamic–pituitary–adrenocortical (HPA) axis response to chronic stress. Repeated exposure to stressors can alter the HPA axis releasing various patterns of biomarkers (6). Individuals with larger cortisol response to an acute stressor also have shorter telomeres (DNA–protein complexes that form protective caps on the ends of chromosomes) suggesting accelerated aging (7). This activation of the HPA axis is linked to increases in inflammatory cytokines (eg, IL-6) that may lead to neuroinflammation as well as a decrease in the immune response (8). IL-6, which is a highly versatile cytokine with both beneficial (9) and destructive potential as it relates to inflammation, has been linked to AD pathological lesions. IL-6 has also been found in elevated amounts around amyloid plaques in AD brains and is known

to induce tau protein which contributes to tangle formation (10). In accordance with the biological-embedding model, it has been posited that stressful experiences early in life are programmed into cells that regulate inflammation, in turn promoting greater psychological and biological stress throughout one's life (11). This model has been supported by research findings on daily stressors where IL-6 levels were 2.35 times greater in individuals with a history of childhood abuse compared with participants who had no abuse history (12). Together, these findings suggest that individuals exposed to chronic psychosocial stress, particularly adverse childhood events (ACEs), may be more prone to the development of dementia via chronic increases in IL-6.

The chronic activation of the HPA axis has also been found to target specific brain regions including the hippocampus, amygdala, and prefrontal cortex (13). Research using both animal and human studies have provided evidence that psychosocial stress can lead to an array of changes in the hippocampus at the cellular level (14) due to the high number of glucocorticoid/cortisol receptors in this area (15–17). In addition, chronic stress has been associated with reduced hippocampal volume, an area of the brain critical for episodic memory and one of the first brain areas to show neurocognitive changes (18,19). Encoding and recall of memories have both been reported to be negatively affected by IL-6 levels; as IL-6 levels increased, recall decreased for information learned 5–20 minutes earlier along with the ability to encode (20). This supports that the hippocampus not only plays a critical role in memory formation but that it is also vulnerable to the adverse effects of peripheral inflammatory cytokines such as IL-6. These prior findings combined with research that IL-6 levels are predictive of subsequent cognitive decline among both middle-aged (21) and elderly persons (22) led to the present study which examines the associations between IL-6, hippocampal volume, and global cognitive impairment as measured by the Mini-Mental State Examination (MMSE) total score, which comprises subscores representing each cognitive domain: memory, orientation, attention, language, and construction.

Previous research has consistently found that hippocampal atrophy is related to early stages of AD (23,24) with decreases in hippocampal volume over a 1-year period predicting AD from normal aging (25,26). Yet, it is unclear whether there are laterality differences in that contribution. Given that the left and right hippocampi have been linked to different aspects of memory functioning, it may be that they also contribute differentially to dementia. There is some evidence to support this hypothesis. For example, the right hippocampus is larger than the left in individuals experiencing normative aging (27,28), and this asymmetry is apparently decreased in AD (29). Scheef et al. (30) found that the right hippocampal volume decreases, not left, underlying subjective memory complaints and a decline in object memory over a 3-year period. The results observed by Scheef et al. (30) were replicated and extended by Van Etten et al. (31) in that right hippocampal volume predicted subjective memory complaints and that relationship was mediated by hypertension status. Based on these findings, the left and right hippocampus may have different relationships with cognitive status. Knowing that hippocampal volume has been shown to predict conversion from cognitive complaint and mild cognitive impairment (MCI) to dementia (32–34), it is important to further characterize the potential differential roles of left and right hippocampi.

The goal of the current study was to examine the relationship between IL-6, hippocampal volume, and cognitive status as measured by the MMSE. Based on previous studies, IL-6 was expected to predict MMSE score. Additionally, hippocampal volume, specifically right hippocampal volume, was predicted to interact with the relationship between IL-6 and MMSE. Lastly, hippocampal volume was predicted to be associated with change in MMSE score over time. Data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database were used to test these hypotheses.

Method

ADNI Data

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. The MRI protocol used for this study has been summarized in prior publications, most notably Jack et al. (35) and Leow et al. (36). In brief, data collection focused on consistent structural imaging on 1.5T scanners using T1- and dual-echo T2-weighted sequences. Scans used a volumetric three-dimensional magnetization-prepared rapid gradient echo (3D MP-RAGE) sequence with a fixed number of parameters. Scans were then processed using FreeSurfer version 4.3. Each series in each exam also underwent 2 levels of quality control at Mayo Clinic (Rochester, MN) to allow for the selection of the scan with the highest quality. Scan quality was graded by trained analysts who determined whether data had failed adherence to the protocol parameters and were thus deemed unusable. An example of hippocampal volume neuroimaging using this protocol with an AD participant can be seen in Figure 1.

Sample Description

The sample (n = 566) was comprised overwhelmingly of participants who were Caucasian (94.5%), and having no AD (80.2%). In terms of gender, males constituted 62% of the sample. (Race was categorized as Caucasians and others which included African Americans, American Indians or Alaskan Natives, Asians, Native Hawaiians or other Pacific Islanders, and more than one race. Alzheimer was binary Yes/No.) The youngest participants were born in 1952, the oldest in 1916. As of 2020, participants averaged 88.7 years old (±7.4). The sample was diverse in terms of education, ranging from grade 4 (0.4%) to PhD/MD (11.8%). About 13.1% of the sample were high school graduates. Another 24.7% had a bachelor's degree, and 18.2% a master's degree.

At baseline, participants' MMSE ranged from 20 to 30, with average MMSE of 26.6 (±2.3), left hippocampal volume 1 814 mm^3 (±378), right

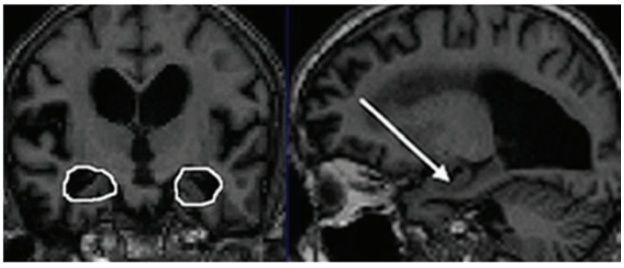

Figure 1. Illustration of hippocampal delineation of an Alzheimer's disease (AD) participant. *Note*: The images above are from an 80-year-old male AD participant. The image on the left is a coronal view of the hippocampus. The image on the right is a sagittal view.

hippocampal volume 1 873 mm^3 (±386), IL-6 receptor (IL-6r) 1.5 μg/mL (±0.1), and geriatric depression (GD) total score 1.5 (±1.4). Box plots for these time-varying variables are presented in Supplementary Figures 1–5. After 12 months, scores on MMSE ranged from 5 to 30 with average MMSE reduced to 25.8 (±3.9), left hippocampal volume to 1 757 mm^3 (±387), and right hippocampal volume to 1 805 mm^3 (±395). GD total score increased to 1.8 (±1.9). IL-6r on average remained unchanged.

Statistical Approach

Mixed-effects models were used to examine associations between IL-6r and cognitive functioning as measured by MMSE score. The following specification was adopted for the analyses:

$$\text{Level1}: Y_{it} = \beta_{0i} + \beta_1 X_{1it} + \beta_2 X_{2it} + \beta_3 X_{1it} X_{2it} + \varepsilon_{it}$$

$$\text{Level2}: \beta_{0i} = \beta_{01} + \beta_{02} Z_i + \beta_{03} \bar{X}_{1i} + \beta_{04} \bar{X}_{2i} + \beta_{05} \bar{X}_{1i} \bar{X}_{2i} + u_{0i}$$

$$\beta_1 = \beta_{10}$$

$$\beta_2 = \beta_{20}$$

$$\beta_3 = \beta_{30}$$

where Y_{it} is the response of participant i at occasion t, X_{1it} and X_{2it} are time-varying predictors, Z_i time-invariant covariate, and $\bar{X}_i$ individual-specific means of X_{it}. X_{it} was centered at individual-specific means, and the individual-specific means were included in the second level. In this manner, effects of X_{it} are within-person, while effects of $\bar{X}_i$ are between-person. Random intercept (u_{0i}) was used to account for correlation among repeated measures. In this study, we examined the interaction between IL-6r and right hippocampal volume (represented by X_{1it} X_{2it} at level 1 and $\bar{X}_{1i}\bar{X}_{2i}$ at level 2). Other included time-varying variables were left hippocampal volume, GD total score, and time (coded 0 for baseline and 1 for month 12). Time-invariant covariates consisted of race, gender, education, age, and presence of AD. Individual-specific means were grand mean-centered before the interaction was formed. Variance inflation factor (VIF) suggested multicollinearity was not concerning (ie, VIF ranged between 1.04 and 4.59). Boxplots and frequencies were used to confirm the absence of irregular observations.

Results

Between-Person Effects

The effect of IL-6 was moderated by right hippocampal volume (p = .001, Cohen f^2 = 0.01) (Table 1). Probing the interaction revealed that the effects of IL-6 on MMSE were negative for right hippocampal volume in the lower range of approximately 1 250 or below (Supplementary Figure 6). As such, higher IL-6 was associated with lower MMSE. For right hippocampal volume in the higher range of approximately 1 900 mm^3 or above, the effects of IL-6 on MMSE were positive such that higher IL-6 was associated with higher MMSE. (The minimum of individual-specific right hippocampal volume was 734.12 mm^3 and the maximum was 2942.15 mm^3.) For right hippocampal volume between 1 250 mm^3 and 1 900 mm^3, the effects of IL-6 on MMSE were not significant. An illustration of the moderated associations between IL-6 and MMSE is demonstrated (see Supplementary Figure 7). For right hippocampal volume = 1 250 mm^3, the fitted line was downward sloping, while for right hippocampal volume = 1 950 mm^3, the fitted line was upward sloping. For right hippocampal volume = 1 550 mm^3, the slope of the fitted line was relatively flat, and indeed not significant. While left hippocampal volume could explain within-person change, it was not able to explain between-person differences in MMSE. There was also no evidence supporting the effects of GD total.

Effects of Demographic Covariates

People who reported having AD were expected to have lower MMSE (p < .0001, Cohen f^2 = 0.22). Higher education was associated with higher MMSE (p = .007, Cohen f^2 = 0.01). All other demographic covariates were statistically insignificant (Table 2).

Within-Person Effects

The estimated effect of left hippocampal volume was significant (p = .009, Cohen f^2 = 0.01) and positive. It implied that an increase in left hippocampal volume from baseline to month 12 was associated with an increase in MMSE. The effect of time was significant (<.0001) and negative. As such, MMSE scores were expected to be reduced between baseline and 12 months after. The effects of right hippocampal volume, IL-6, and GD total were not statistically significant (Table 3).

Discussion

The goal of the current study was to examine the relationship between biomarkers of stress (IL-6), hippocampal volume, and AD. The results confirmed our hypothesis that IL-6 is associated with MMSE score and that right hippocampal volume moderates the relationship. Change in the left hippocampus was associated with change in MMSE score over a 12-month period. Finally, an effect of education was observed such that individuals with higher education had higher MMSE scores. It should be noted that the hippocampus

Table 1. Between-Person Associations Between MMSE and Time-Varying Predictors

	Estimate	SE	*p* Value
Left hippocampal volume	0.001	0.001	.253
Right hippocampal volume	−0.011	0.004	.006
IL-r6	−13.937	4.861	.004
Right hippocampal × IL-r6	−0.008	0.003	.002
GD total	−0.135	0.082	.103

Note: GD = geriatric depression; IL-6r = interleukin-6 receptor; MMSE = Mini-Mental State Examination.

Table 2. Between-Person Associations Between MMSE and Demographic Covariates

	Estimate	*SE*	*p* Value
Alzheimer's disease (yes vs no)	−3.831	0.298	<.0001
Education	0.102	0.038	.007
Gender (female vs male)	0.178	0.244	.466
Race (others vs White)	−0.141	0.527	.789
Age	0.022	0.016	.181

Note: MMSE = Mini-Mental State Examination.

Table 3. Within-Person Associations Between MMSE and Time-Varying Predictors

	Estimate	*SE*	*p* Value
Left hippocampal volume	0.005	0.002	.009
Right hippocampal volume	−0.002	0.002	.239
IL-r6	4.623	2.997	.124
Right hippocampal × IL-r6	−0.018	0.058	.760
GD total	−0.029	0.093	.752
Time	−0.753	0.178	<.0001

Note: GD = geriatric depression; IL-6r = interleukin-6 receptor; MMSE = Mini-Mental State Examination.

is a heterogenous structure and that chronic stress, cognitive aging, and psychiatric disease like GD can have varying effects (37,38).

One of the major findings in the current study is that the relationship between IL-6 and MMSE score is moderated by right hippocampal volume. This effect shows that the combination of larger right hippocampus volume and higher levels of IL-6 results in higher MMSE scores while the reverse is true for individuals with smaller right hippocampal volumes. There is some suggestion that the neuroinflammatory response that results in increased IL-6 can be both beneficial and harmful. It can be beneficial in that the astrocyte and microglia inflammatory driven response may assist in clearing the plaques and tangles linked to AD (39). Barroeta-Espar et al. have proposed that AD resiliency, lack of cognitive decline despite the existence of the stereotypical plaques and tangles, is due to a differential immune response, that is, a differential effect of inflammatory cytokines like IL-6 (39). The current findings may lend support to this hypothesis in that for individuals with larger hippocampi, higher levels of IL-6 was associated with higher MMSE scores, suggesting that IL-6 in this group may have a neuroprotective property. The reverse was found for those with smaller hippocampi; higher levels of IL-6 seemed to have a detrimental effect. Our current results demonstrate the need for further study focused on the role of ACEs and chronic psychosocial stress. Both are linked to elevated IL-6 and smaller hippocampal volume (17,19). Evidence from work by Rajagopalan et al. (40) support this speculation as they found that stress-induced elevated plasma cortisol was associated with larger ventricles and smaller hippocampal volume, predominantly in the right cerebral hemisphere, regardless of age, sex, or cognitive status.

The second primary finding is the laterality differences in the hippocampus. Investigating the role of hippocampal laterality differences and rate of volume loss over time, Eckerström et al. (41) found that there is a significant overall difference of about 10% in normalized volume between the left and right hippocampus. Additionally, Eckerström et al. found that it was changes in left hippocampal volume that predicted conversion from MCI to dementia in a 2-year period, not right hippocampus. This result was replicated in the current study in that it was changes in left hippocampal volume that predicted changes in MMSE score. We failed to see a relationship between changes in right hippocampal volume and changes in MMSE. The laterality differences observed in this study as well as previous studies warrant further investigation.

There are limitations to be noted including the racial homogeneity of the sample. With nearly 95% of the participant sample being Caucasian, it would be important to test our hypotheses in a more diverse sample. Another limitation is the time interval examined was 12 months. In future studies, it would be beneficial to have another follow-up assessment at 24 or 36 months to better examine conversion from subjective cognitive complaint to MCI to dementia. In addition, no information about childhood socioeconomic status or life stress including childhood trauma was included in the data. Future work will be necessary to disentangle these relationships. It will also be necessary to examine stress and improve recruitment of underrepresented populations. Lastly, while we know there is a relationship between depression and chronic stress and elevated IL-6 levels, we only had measures of GD and not measures of chronic stress.

Overall, the results confirm our hypotheses that stress-related cytokines, IL-6, as well as hippocampal volume are associated with MMSE score. While the effect of IL-6 is moderated by right hippocampal volume, it is change in the left hippocampus that is associated with change in MMSE score over a 12-month period. Even so, we recognize the effect size of the interaction between IL-6 and right hippocampal volume was small, and that it is not possible to quantify the effect size of IL-6 on MMSE. In spite of this, these findings support the need for further study of the developmental trajectory of cognitive decline and the potential effect that chronic stress has on that decline across the life span.

Given rates of dementia and AD are higher in African Americans than in white Americans, it is particularly important that more studies examine racial/ethnic differences in older adults cognitive function in order to achieve health equity. Studies that included African Americans have found that those with higher levels of perceived stress had more rapid declines in global cognition, most notably episodic memory (42). Decades of research has shown that African Americans experience a disproportionate burden of stressful life experiences linked to poverty, racism, and racial segregation due to their relatively low status in society (43–46). Based on the present findings and our knowledge that stressful experiences are associated with conversion from MCI to dementia (18), we contend that resources need to be devoted to studying whether the relationships seen with IL-6 and hippocampal volume persist in older African Americans. It is also recommended that future studies explore whether adversity across the life span including racism-related stress may be contributing to an elevated presence of stress-related cytokines. Significant associations have been documented between early-life adverse stress and reduced hippocampal volume (47,48).

When examining aging, it is also important to consider the cumulative strain that chronic psychosocial stress exerts on immune and cardiovascular systems that ultimately renders individuals more susceptible to developing stress-related diseases including hypertension, diabetes, and cardiovascular disease, all of which has been suggested to contribute to cognitive decline. Individuals who already are experiencing stress-related illnesses mentioned previously may have increased vulnerability amplifying HPA dysregulation and subsequent development of dementia. We examined the medical history data in our sample to see if the data indicated whether the participant had a medical condition related to a system (eg, cardiovascular, endocrinology, renal). A 2-tailed *t* test was performed on MMSE, hippocampal volume, and IL-6 to determine whether these measures were different between participants with the medical condition affecting these systems. However, when examining cardiovascular (hypertension), endocrinology (diabetes), and renal systems, none of the measures showed a significant difference between groups (see Supplementary Table 1 for *p* values from the *t* test). Thus, it is recommended that future studies seek to capture factors that are known to contribute to psychosocial stress and stress-related diseases to help better understand the associations between cognitive decline and functional limitations in daily life. Not only is it important to

determine the types of chronic stressors older adults are experiencing but also the age of onset, recurrence, and severity of other diseases known to impact cognition, including depression and personality dysfunction.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

Acknowledgments

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Author Contributions

E.R.H. assisted with the conception and design of the study; the acquisition of the data; and drafting and revising of the manuscript. C.B. assisted with the analysis and interpretation of data and drafting of manuscript. S.D.N. assisted with the acquisition and interpretation of data and drafting and revising of the manuscript.

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