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Association of allostatic load with brain structure and cognitive ability in later life

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ABSTRACT

Allostatic load (AL) has been proposed as a general framework for understanding the cumulative effects of life stress on individuals. Despite growing interest in AL, limited research has been conducted on aging samples. We consider the association of AL (operationalized by a range of inflammatory, cardiovascular, and metabolic measures) with a range of brain volume measurements and cognitive ability in a large cohort sample of older adults ($n = 658$, mean age = 72.5 years, standard deviation = 0.7) using structural equation modeling. AL was significantly inversely associated with total brain volume (range of standardized $\beta = -0.16$ to -0.20) and white-matter volume (-0.35 to -0.36) and positively with hippocampal volume (0.10–0.15) but not gray-matter volume (0.04). AL was also significantly inversely associated with general cognitive ability (range $\beta = -0.13$ to -0.20), processing speed (-0.20 to -0.22), and knowledge (-0.18 to -0.20) but not memory or nonverbal reasoning. The associations of AL with cognitive abilities were not mediated by these brain volume measures. AL did not predict cognitive change from age 11 to approximately age 73. The findings suggest a link between AL and later life brain health and cognitive functioning.

1. Introduction

The concept of "allostasis" has played a prominent role in recent stress research in both human and nonhuman animals. In brief, individuals are exposed to multiple stressors, both social and environmental, which induce a stress response. Allostasis refers to the process of fluctuating activity of the body's physiological systems in response to such stressors (Sterling and Eyer, 1988). The primary systems of allostasis and the stress response include the neuroendocrine, sympathetic nervous, immune, metabolic, cardiovascular, and hypothalamic-pituitary-adrenal axis (Seplaki et al., 2006). Common markers of allostatic load (AL) in the applied research include blood pressure, pulse pressure, heart rate variability, blood glucose, body mass index (BMI), high- and low-density lipoproteins (LDLs), fibrinogen, C-reactive protein (CRP), interleukin-6 (IL-6), epinephrine, and norepinephrine, to name but a few (see Karlamangla et al., 2013; Juster et al., 2010). Regular or acute exposure to stressors may result in chronic imbalance across 1 or multiple of these systems, referred to as the "allostatic state." Over time, the biological aftermath of allostatic states accumulates, resulting in AL. AL, therefore, can be thought of as the biological "wear and tear" on the body as a result of its inability to cope with the stressful stimuli and events (McEwen and Stellar, 1993). Two principal concepts in AL theory are important with respect to the present study; namely, cumulative load and the central role played by the brain in allostasis.

As has been noted earlier, AL theoretically represents the accumulated damage of the allostatic process on the body over time. Therefore, time, in the case of the human life course, development and aging are important aspects of research into AL. Indeed, many models of life stress and AL focus on phasic periods of increased sensitivity to the detrimental effects of stressors in development (e.g., Del Giudice et al., 2011, Adaptive Calibration Model), whereas

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Table 1
Descriptive statistics of all study variables (for participants with MMSE scores >25)

Variables	*n*	Mean	SD	Skew	Kurtosis
Age (y)	633	72.49	0.72	0.01	−0.86
Brain imaging					
ICV (cm^3)	633	1450.87	140.35	0.19	−0.33
Total brain volume (cm^3)	630	1124.91	106.62	0.24	−0.03
White-matter volume (cm^3)	628	496.79	83.07	0.45	0.48
Gray-matter volume (cm^3)	629	500.15	71.10	0.18	0.76
Left hippocampal volume (cm^3)	619	3.10	0.46	0.55	0.76
Right hippocampal volume (cm^3)	619	3.33	0.45	0.35	0.54
Cognitive ability					
Logical Memory (immediate recall) WMS-III	633	46.26	10.08	−0.42	0.32
Logical Memory (delayed recall) WMS-III	633	29.25	7.86	−0.51	0.25
Verbal Paired Associates (first recall) WMS-III	625	2.84	2.31	0.61	−0.71
Verbal Paired Associates (second recall) WMS-III	622	6.43	2.08	−1.33	0.83
Spatial Span (forward) WMS-III	632	7.66	1.61	−0.07	−0.45
Spatial Span (backward) WMS-III	631	7.13	1.58	−0.01	−0.32
Verbal Fluency Total Score	632	43.60	12.42	0.29	0.12
National Adult Reading Test	632	34.91	7.75	−0.54	0.00
WTAR	632	41.54	6.45	−0.92	0.68
Simple Reaction Time Mean Score	633	0.27	0.05	1.72	4.59
Choice Reaction Time Mean Score	633	0.64	0.08	0.73	1.17
Inspection Time Total Correct Responses	621	111.66	11.31	−1.02	2.92
Digit Symbol WAIS-III^{UK}	632	56.85	11.97	0.18	−0.25
Digit Span (backward) WAIS-III^{UK}	633	7.96	2.26	0.31	−0.17
Block Design WAIS-III^{UK}	631	34.57	9.96	0.45	0.08
Letter-Number Sequencing WAIS-III^{UK}	633	11.14	2.91	0.43	0.35
Matrix Reasoning WAIS-III^{UK}	632	13.57	4.86	−0.12	−0.94
Symbol Search WAIS-III^{UK}	632	25.01	5.88	−0.26	0.83
AL biomarkers					
Fibrinogen	621	3.31	0.58	0.47	0.61
CRP	617	2.90	5.62	9.91	128.85
After log transformation	617	0.16	0.50	0.05	0.24
IL-6	617	2.05	1.80	3.05	12.49
After log transformation	617	0.20	0.29	0.36	1.26
BMI	633	27.80	4.38	0.89	2.24
Triglyceride	630	1.62	0.78	1.11	1.13
HDL	630	1.47	0.43	0.93	1.17
LDL	629	2.94	1.02	0.36	0.29
HbAlc	627	5.73	0.64	2.21	6.51
Mean DBP	631	77.44	9.68	0.20	0.00
Mean SBP	631	147.40	18.56	0.14	0.29
Medications		Yes	No		
Antihypertensive	633	332	301		
Anti-inflammatory	633	64	569		
Lipid lowering	633	214	419		
Insulin	633	8	625		
Other diabetes	633	40	593		
Any medications	633	559	74		
Demographics					
Years of education	633	10.84	1.14	0.71	2.31
Childhood SES	577	2.91	0.90	0.19	3.61
Adulthood SES	622	2.35	0.95	0.09	1.99
Sex		M	F		
	633	331	302		

Key: AL, allostatic load; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; F, female; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; ICV, intracranial volume; IL-6, interleukin-6; LDL, low-density lipoprotein; M, male; MMSE, Mini-Mental State Examination; SBP, systolic blood pressure; SD, standard deviation; SES, socioeconomic status; WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale; WTAR, Wechsler Test of Adult Reading.

the importance of studying the impact of AL in aging has also been noted (Ganzel et al., 2010; Karlamangla et al., 2002). It is also of interest to note the overlap between suggested lists of biomarkers of aging (e.g., Dowd and Goldman, 2006) and markers of AL (e.g., Juster et al., 2010).

AL is conceptualized as a cumulative process. As such, it is plausible to suggest that even if individuals have low AL during early adulthood, the passage of time may lead to increased AL in later life. Crimmins et al. (2003) found, using the National Health and Nutrition Examination Survey study data, that, whereas AL increased from the 20's to the 60's, levels of AL stabilized during the 70's and 80's. However, caution is required in interpretation of these trends as they are based on cross-sectional data and, therefore, are likely to partially reflect a survival effect, whereby those lowest in AL reach older ages.

A number of studies have considered the impact of AL on mortality (e.g., Goldman et al., 2006; Gruenewald et al., 2006; Karlamangla et al., 2006; Seeman et al., 2004) and cognitive and health declines in aging (for a summary, see Juster et al., 2010, Table 1). With respect to cognitive ability, a recent cross-sectional study by Karlamangla et al. (2013) using data from a subset of the Midlife in the United States Study ($n = 1076$, mean age = 57 [range, 49–66] years) found that AL significantly negatively predicted episodic memory score ($p < 0.001$) and executive function ($p < 0.001$) accounting for 4.9% and 7.3% of the variance, respectively. These results remained significant after adjusting for covariates. In that study, AL was measured based on 24 biomarkers taking percentage risk cut points to produce a single sum score. In a series of analyses using the