ORIGINAL ARTICLE

Impact of Allostatic Load on Cognitive Level, Memory and Left Ventricular Mass

Impacto de la carga alostática en el nivel cognitivo, la memoria y la masa del ventrículo izquierdo

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ABSTRACT

Background: 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, no research has been conducted in Argentina related to its impact on the heart and brain.
Objective: The aim of this study was to evaluate the association of AL, functionally defined by a range of measurements from the sympathetic and parasympathetic systems, hypothalamic-pituitary-adrenal axis, and inflammatory, cardiovascular and metabolic systems, with the cognitive level (CL), memory and left ventricular mass in middle-aged adults.
Results: A total of 86 patients were evaluated with mean age of 53.5 years (95% CI: 51.3 - 55.7). Allostatic load had a significant inverse association with the CL (coefficient -1.1; standard error: 0.5; p=0.04) that was independent of age, sex and educational attainment (adjusted square R: 0.40; p <0.001). Of the seven systems evaluated, only the cardiovascular and inflammatory systems had significant inverse associations with AL. An inverse relationship was also observed between AL and memory. In the heart, a positive correlation was found between AL and left ventricular (LV) mass (coefficient: 10.86; p <0.001; adjusted square R: 0.23; p <0.001),
Conclusions: Allostatic load is an objective tool to measure chronic stress. The results obtained indicate that high AL damages the brain (early cognitive and memory deficits) and the heart (increased LV mass).

Key words: Chronic stress – Allostatic load – Cognitive deficit – Memory- Left ventricular mass

RESUMEN

Introducción: La carga alostática (CA) se ha propuesto como un marco general para comprender los efectos acumulativos del estrés a lo largo de la vida de las personas. A pesar de su creciente interés no se han realizado, en la Argentina, investigaciones que relacionen su impacto en el corazón y en el cerebro.
Objetivos: Evaluar la asociación de CA, definida en forma operativa por un rango de mediciones de los sistemas simpático, parasimpático, el eje hipotálamo hipofisario adrenal, y de los sistemas inflamatorio cardiovascular y metabólico), con el nivel cognitivo (NC), la memoria y la masa del ventrículo izquierdo en adultos de mediana edad.
Resultados: Fueron estudiados 86 pacientes con un promedio de edad de 53,5 años IC (intervalo de confianza) 95% de 51,3 a 55,7. La CA se asoció en forma inversa y significativa con el NC: coeficiente -1,1 Error estándar (EE) 0,5 p = 0,04 independientemente de la edad, el sexo y el nivel educacional R cuadrado ajustado 0,40 p < 0,001. De los 7 sistemas estudiados solo el cardiovascular y el inflamatorio mantuvieron una asociación inversa y significativa. También la CA se asoció en forma inversa con la memoria. En cuanto a su impacto en el corazón, la CA se asoció en forma positiva con la masa del ventrículo izquierdo (VI), coeficiente 10,86 p < 0,001. R cuadrado ajustado 0,23 p < 0,001.
Conclusiones: La CA nos permite contar con una herramienta objetiva para medir el estrés crónico. Los resultados obtenidos indican que el incremento de la CA produce un daño en el cerebro (déficit cognitivo y en la memoria tempranos) y en el corazón (incremento de la masa del VI).

Palabras clave: Estrés crónico - Carga alostática - Déficit cognitivo - Memoria - Masa del ventrículo izquierdo

Abbreviations

A	Adrenaline	**LV**	Left ventricular
ACE	Addenbroke's Cognitive Examination	**LVH**	Left ventricular hypertrophy
AL	Allostatic load	**MIDUS**	Midlife in the United States
BMI	Body mass index	**NA**	Noradrenaline
CI	Confidence interval	**NHANES**	National Health and Nutrition Examination Survey
CL	Cognitive level	**PSS**	Psychosocial stress
CRP	C-reactive protein	**PSNS**	Parasympathetic nervous system
CVD	Cardiovascular disease	**PWV**	Pulse wave velocity
DBP	Diastolic blood pressure	**SBP**	Systolic arterial pressure
EA	Educational attainment	**SE**	Standard error
HPA	Hypothalamic-pituitary-adrenal axis	**SNS**	Sympathetic nervous system
HTN	Hypertension	**WHR**	Waist-hip ratio

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INTRODUCTION

The concept of "allostasis" has played a significant role in recent research of stress in animals and humans. People are exposed to numerous stressful factors, both psychosocial and environmental, which induce a stress response. (1) Allostasis is a process of fluctuating activity of the organism's physiological systems as a response to these factors. The primary mediators of allostasis and the stress response include the neuroendocrine axis, the sympathetic nervous system (SNS) and the immune, metabolic, cardiovascular and hypothalamic-pituitary-adrenal (HPA) systems.

When both physical and psychosocial stressors reach an elevated level, or are chronic, repeated over time, the brain as well as the rest of the organism pay a price for the adaptation, known as allostatic load (AL). (2)

Allostatic load implies injury in the regulatory mechanisms of multiple systems, as those acting in the primary response to stress and the traditional risk factors, which also depend on constitutional and genetic factors.

Up to the end of the last century, psychosocial stress (PSS) was subjectively measured by situational or perceived stress. Nowadays, a battery of biomarkers can measure objectively AL. The focus is targeted on how the individual perceives AL and whether he/she has or not the capacity to adapt his/her life experiences to that load.

At the beginning, Seeman et al. described 10 biomarkers of AL, (3, 4) which were well supported by physiological researches and were able to predict cognitive decline in elderly subjects. (5, 6)

The Midlife in the United States (MIDUS) study (8) performed in 2014, identified AL markers by systems: cardiovascular, glucose metabolism, lipid metabolism, inflammation, HPA axis, SNS, and parasympathetic nervous system (PSNS).

Some authors consider the impact of AC either on mortality, (7, 9, 10) or morbidity. (11-13) However, the impact of accumulated stress not only affects the body but also the brain, producing, among others, cognitive, memory, attention and visual-spatial impairment. (14-19)

Concerning the impact of AL on cognition and health, it is important to highlight the study by Seeman et al, who measured AL in 1,189 men and women aged between 70 and 79 years and evaluated four health categories. A high AL score was significantly associated with increased risk of mortality, cardiovascular events, cognitive decline and lower physical function, resulting in a better predictor than the metabolic syndrome. (20)

In 2012, Kobrosly et al. (21) studied 4,511 middle-age adults participating in the NHANES III study, and investigated the relationship between AL and cognitive function. Results suggested that AL is associated with work memory.

In 2014, Booth et al. (22) published a study associating AL with brain volume and cognitive ability measured in a large cohort of elderly adults. They found that AL was inversely correlated with total brain and white matter volume, and positively with hippocampal volume. Moreover, it was negatively associated with general cognitive ability.

Between 2001 and 2010, the NHANES study (23) assessed AL in disabled and non-disabled persons with mean age of 29.4±23.6 years. Disabled persons has significantly higher body mass index (BMI), C-reactive protein, percentage of neutrophils and lower HDL cholesterol, i.e. higher AL than non-disabled persons.

The MIDUS study (8) examined the association between AL and cognitive performance, in a large population of young, middle-age and elderly individuals and found a strong age-independent inverse correlation between AL and episodic memory and executive function. Among the 7 systems considered to assess AL, only the cardiovascular system was associated with both episodic memory and executive function, while inflammation was related with episodic memory and glucose metabolism with executive function.

In the last years, there has been special interest in the study of PSS associated with cardiovascular disease (CVD), both myocardial infarction and stroke. (24, 25) However, few studies assessing intermediate CVD markers are available, such as increased LV mass, presence of plaques, and increased pulse wave velocity (PWV).

Animal studies show that chronic stress exacerbates hypertension (HTN), as well as LV hypertrophy, LV diastolic dysfunction, fibrosis and oxidative stress, and also increases cardiac and visceral adipose tissue inflammation. (26) Similarly, acculturation was associated with LV mass. (27)

Pickering studied the relationship between psychological stress and development of HTN and coronary heart disease and concluded that men in high strain jobs had more probability of being hypertensive and presenting LV hypertrophy (LVH) than men in less stressful jobs. (28)

Siegrist et al. pose the relationship between HTN, LVH and psychosocial risk and conclude that the greatest incidence of CVD among the lowest socioeconomic groups is explained by a co-manifestation of established risk factors, including LVH and psychosocial factors measuring chronic stress at work. (29)

The association between AL and LVH might be attributed to the cardiovascular component of this multi-system index of AL. However, other factors derived from neurohormonal activity could participate, such as SNS activation, PSNS dysfunction and HPA axis or inflammatory component activation. It could be enquired whether increased AL could predict the increase in LV mass.

Based on these considerations, the aim of the present study was to determine the impact of AL on the brain and heart of middle-age adults.

METHODS

The target population consisted of middle-age patients with cardiovascular risk factors, no history of known CVD or other invalidating chronic diseases.

The sample comprised patients consecutively attending an ambulatory cardiology clinic, agreeing to participate in the study and fulfilling the inclusion and exclusion criteria of the target population. Ninety-eight patients were included and 86 completed all the studies. Educational attainment (EA) was measured according with the following scale: *(0) no education, (1) incomplete primary school, (2) complete primary school, (3) incomplete secondary school, (4) complete secondary school, (5) incomplete tertiary or university education, and (6) complete tertiary or university education.*

A color Doppler ultrasound of the heart, neck and femoral arteries was performed and the indexed LV mass per square meter of body surface area, presence of plaques, carotid intima-media thickness and PWV were obtained.

A multi-system index, as in the MIDUS study, (8) was used to measure AL, including the following indicators:

Cardiovascular: Systolic blood pressure (SBP) ≥143 mmHg, resting pulse pressure ≥65 mmHg and resting heart rate ≥77 beats per minute, considering an average of three measurements.

Glucose metabolism: Glycosylated hemoglobin ≥6.1%, fasting blood sugar ≥105 mg/dl and homeostasis model assessment (HOMA) of insulin resistance ≥4.04.

Lipid metabolism: BMI ≥32.3 kg/m2, waist-hip ratio (WHR) ≥0.97, LDL cholesterol ≥128 mg/dl, HDL cholesterol ≤41.4 mg/dl and serum triglycerides ≥160 mg/dl.

Inflammation: C-reactive protein (CRP) ≥3.18 mg/l and fibrinogen ≥390 mg/dl.

GPA axis: Urinary cortisol ≥21 µg/g of urine creatinine and dehydroepiandrosterone (DHEA) sulphate ≤31µg/dl.

SNS: Urinary adrenaline (A) ≥2.54 µg/g of urine creatinine and urinary noradrenaline (NA) ≥33.3 µg/g of urine creatinine.

PSNS: (heart rate variability): Electrocardiographic RR interval standard deviation (SD) ≤23.5 ms.

Each system had a score ranging from 0-1, and the sum corresponded to the overall AL. Each system was considered to be disregulated when 50% or more measurements were above normal values, or when patients, despite not exceeding these values, were receiving treatment (e.g. lipid-lowering agents, antihypertensive drugs, etc.).

Addenbroke's Cognitive Examination (ACE) was used to assess the cognitive level (CL). It consists of a brief test battery, lasting 15-30 minutes, recently developed and validated in English by Mathuranath et al., (30) to detect early dementia, corrected by Mioshi et al. (31) and validated in Spanish by García Caballero and by Sarasola et al. (32, 33)

The maximum score for the *modified ACE test was 100, composed by 10 points for orientation, 8 for attention, 26 for memory, 14 for verbal fluency, 26 for language and 16 for visual-spatial activities.*

Statistical analysis

Statistix software package was used to perform the analysis. Continuous variables were described as mean, standard error and 95% confidence interval (CI) and dichotomous variables as percentage and 95% confidence interval.

Student's t test was used to compare continuous variables and the chi-square test for discrete variables. The association between variables adjusted by EA, age and sex was analyzed by multiple linear regression analysis.

Ethical considerations

Patients attending the ambulatory cardiology clinic signed an informed consent form to participate in the study.

RESULTS

Among a total of 98 patients consecutively included in the study, 86, with mean age of 53.5 years (95% CI 51.3 to 55.7), completed all the studies. Thirty-eight patients were men with mean age of 52.7 years (95% CI 50.5 to 56.8) and 48 were women with mean age of 53.3 years (95% CI 50.1 to 56.5).

Table 1 describes the percentage of individuals with different AL system abnormalities according to sex. It also analyzes age, systolic blood pressure (SBP), diastolic blood pressure (DBP), left ventricular (LV) mass and number of individuals discriminated by sex. The Table shows that most patients had one or more risk factors, SNS, PSNS and HPA axis and immune system abnormalities.

Table 2 analyzes global ACE results and attention, memory, visual-spatial activities and verbal fluency scores, in addition to the EA variable associated with CL in all the studies.

Relationship of allostatic load and its constitutive subsystems with cognitive level

A multilinear regression model was used with CL through the ACE score as dependent variable and AL adjusted by age, sex and EA. The results show a strong inverse association between AL and global CL, indicating that the greater the AL the lower the CL.

The impact of the different AL subsystems on CL was also analyzed. Among the 7 subsystems, only the cardiovascular and inflammatory subsystems showed a strong inverse relationship with global CL evaluated by ACE and adjusted by age, sex and EA (Table 3).

Relationship of allostatic load and the cardiovascular and inflammatory subsystems with memory adjusted by age, sex and EA

A multilinear regression model with memory as dependent variable and AL adjusted by age, sex and EA as independent variable showed an inverse association between AL and memory, i.e. the greater the AL the lower the memory.

The cardiovascular and inflammatory components of AL were also inversely related with memory adjusted by age, sex and EA (Table 4).

Impact of global allostatic load and its cardiovascular, lipid metabolism and inflammatory subsystems on left ventricular mass

Mean LV mass was 127.9± 7 g/m2 of body surface area (95% CI 118.5 to 137.2). In men, it was 131.1±7.7 g/m2 (95% CI 115.3 to 146.8) and in women 125.4±5.8 (95% CI 113.6 to 137.2). (Table 2)

Global AL adjusted by age and sex had a positive impact on LV mass. Cardiovascular, lipid metabolism and inflammation abnormalities adjusted by age and sex were also positively associated with LV mass (Table 5)

Table 1. Description of the systems constituting allostatic load, age and left ventricular mass

	Totals	Women	Males	p
Age	53.5 ± 1.12	53.3 ± 1.60	53.7 ± 1.55	0.17
Cardiovascular disorderss	48 (56)	26 (54)	22 (58)	0.72
SBP	138.2 ± 2	139.5 ± 2.8 mmHg	136.5 ± 2.7 mmHg	0.13
DBP	81.5 ± 1.4	79.2 ± 1.8 mmHg	84.2 ± 2.0 mmHg	0.07
Carbohydrate metabolism disorders	17 (20)	12 (25)	5 (13)	0.17
Lipid metabolism disorders	26 (30)	13 (27)	13 (34)	0.47
Inflammatory disorders	31 (36)	20 (42)	11 (29)	0.25
Abnormal HPA	46 (54)	26 (54)	20 (54)	0.99
Abnormal SNS	60 (69)	39 (81)	21 (55)	0.01
Abnormal PSNS	17 (20)	5 (10)	12 (32)	0.03
Allostatic load	2.83±0.13	2.9±0.18	2.7±0.2	0.46
LV mass, g/m2	127±4.7 IC 95% 118.5 to 137.2	125.4±5.8	131.1±7.7	0.37
N	86	48 (56)	38 (44)	

SBP: Systolic blood pressure. DBP: Diastolic blood pressure. HPA: Hypothalamic-pituitary-adrenal axis. SNS: Sympathetic nervous system. PSNS: Parasympathetic nervous system. N: Number of individuals. 95% CI: Results expressed in proportions and mean and standard error; p: statistical significance by Student's t test for continuous variables and chi-square test for discrete variables.

Table 2. Global Addenbroke's cognitive examination scores and adjusted by systems and educational attainment

	Totals	Women	Males	p
ACE: maximum 100 points	85.6±0.8	85.02±1.1	86.4±1.3	0.41
Orientation: maximum 10 points	9.9±0.03	9.9±0.05	9.9±0.04	0.92
Attention: maximum 8 points	7.8±0.1	7.7±0.1	7.9±0.06	0.22
Memory: maximum 26 points	19.5±0.4	19.4±0.5	19.6±0.6	0.86
Fluency: maximum 14 points	10.9±0.3	10.7±0.3	11.2±0.6	0.44
Visual.spatial activivities: maximum16 points	15±0.2	14.7±0.2	15.4±0.3	0.08
Educational attainment	3.3±0.16	3.1±0.20	3.5±0.25	0.23
N	86	48 (56%)	38 (44)	

ACE: Modified Addembrooke´s Cognitive Examination. Mean and standard error; p: statistical significance by Student's t test.

Trends not attaining statistical significance

Allostatic load and cardiovascular abnormalities were inversely associated with visual-spatial activities, but without attaining statistical significance (p=0.09). The SNS was positively associated with LV mass (p=0.08).

Although there was a positive trend between AL, presence of plaques and PWV, this did reach statistical significance.

DISCUSSION

The study indicates that the multi-system score used to assess AL has a strong inverse association with global CL, particularly memory, in a sample of ambulatory patients.

Also, the cardiovascular and inflammatory components of AL were inversely related with global CL and memory.

It is worth mentioning that the relationship of inflammation and HTN with changes in the hippocampus (34) provide a biological framework to the results of the study.

The MIDUS II study, (8) involving 1,076 individuals (much larger than the 86 patients included in our study) and with an average age of 57 years, higher than that in our study of 53.5 years, found an inverse association to both, episodic memory and executive function. In the same study, the cardiovascular system was inversely related both with episodic memory and executive function and inflammation only with episodic memory.

The way of administering the cognitive test was another important difference; in our case it was performed through personal interviews, while in the MIDUS study this was done by telephone interviews. We consider that the personal interviews provide preci-

Table 3. Multiple linear regression analysis between allostatic load and cardiovascular and inflammatory systems. Cognitive level as dependent variable

Predictive variables	Coefficient	SE	p
AL	-1.09	0.52	0.04
Age	0.04	0.06	0.49
EA	3.17	0.47	<0.001
Sex	-0.04	1.32	0.97

Adjusted square R 0.40 p <0.001. AL: Allostatic load. EA: Educational attainment.

Predictive variables	Coefficient	SE	p
Cardiovascular	-3.00	1.32	0.02
Age	0.07	0.06	0.26
EA	3.33	0.46	<0.001
Sex	0.21	1.31	0.87

Adjusted square R 0.42 p <0.001

Predictive variables	Coefficient	SE	p
Inflammation	-2.87	1.38	0.04
Age	0.02	0.06	0.71
EA	3.37	0.46	<0.001
Sex	-0.52	1.32	0.69

Adjusted square R 0.41 p < 0.001

Table 4. Multiple linear regression analysis between allostatic load and cardiovascular and inflammatory systems. Memory as dependent variable

Predictive variables	Coefficient	SE	p
AL	-0.63	0.28	0.02
Age	0.02	0.03	0.41
EA	1.20	0.26	<0.001
Sex	-0.45	0.72	0.52

Adjusted square R 0.26 p <0.001

Predictive variables	Coefficient	SE	p
Cardiovascular	-1.69	0.72	0.02
Age	0.04	0.03	0.20
EA	1.29	0.25	<0.001
Sex	-0.30	0.72	0.67

Adjusted square R 0.26 p <0.001

Predictive variables	Coefficient	SE	p
Inflammation	-2.20	0.73	0.003
Age	0.01	0.03	0.72
EA	1.28	0.24	<0.001
Sex	-0.78	0.70	0.26

Adjusted square R 0.31 p <0.001

sion and validity to the test administration.

Age did not influence the association between AL and CL and memory in both studies, suggesting that the association was not restricted to elderly adults.

Another limitation of the MIDUS and our study was that they were both cross-sectional studies and, although the multiple linear regression analysis used in the present study was adjusted by age, sex and EA, it could not be controlled by all the environmental and genetic factors. It is important to point out that a causal relationship cannot be established through a cross-sectional study, since the CL could also increase the AL.

An additional limitation is that lab tests were not performed in a single central laboratory, although all measurements were expressed in the same units for all the patients.

Regarding the association between PSS and LV mass, animal studies conclude that chronic stress exacerbates HTN as well as LVH, LV diastolic dysfunction, fibrosis and oxidative stress. In addition, it enhances cardiac and visceral adipose tissue inflammation. (26) These observations provide biological support to our observations about a positive association between AL and LV mass.

Although some studies relate PSS with LVH (28, 29) and that several authors (35, 36) consider the increase in LV mass as a secondary marker of AL, no studies were found in the literature associating AL with LV mass.

CONCLUSIONS

Both global AL as its inflammatory and cardiovascu-

Table 5. Multiple linear regression analysis between allostatic load and cardiovascular and inflammatory systems and lipid metabolism. Left ventricular mass as dependent variable

Predictive variables	Coefficient	SE	p
CA	10.86	3.10	<0.001
Age	1.36	0.39	<0.001
Sex	11.18	8.32	0.18

Adjusted square R 0.23 p <0.001

Predictive variables	Coefficient	SE	p
Cardiovascular	20.42	8.34	<0.01
Age	1.48	0.40	<0.001
Sex	11.87	8.33	0.15
Inflammation	22.25	8.93	<0.001

Adjusted square R 0.25 p <0.001

Predictive variables	Coefficient	SE	p
Lipids	27.92	8.79	<0.01
Age	1.32	0.38	<0.01
Sex	6.69	8.72	0.37

Adjusted square R 0.21 p <0.001

lar components reduced CL and memory, corrected by EA, age and sex. The greater the AL or its cardiovascular or inflammatory components, the lower the global CL and memory. Global AL and inflammatory, lipid metabolism and cardiovascular components, adjusted by age and sex, increased LV mass. The greater the AL, the greater the LV mass. Dysregulation of systems that respond to chronic stress produces brain injury (early cognitive deficit and memory) and heart damage (increased LV mass). Chronic PSS is not subjectively defined, but objectively identified by means of clinical assessments and measurement of the different biomarkers constituting AL.

Conflicts of interest

(See authors conflicts of interest forms on the website/ Supplementary material)..

REFERENCES

1. Sterling P, Eyer J. Allostasis: a new paradigm to explain arousal pathology. In Fisher S., Reason J. editors, Handbook of life stress, cognition and health, New York: John Willey & Sons 1988: 629-49.
2. McEwen BS, Stellar E. Stress and the individual: mechanism leading to disease. Arch Intern Med 1993;153:2093-101. http://doi.org/ft39sh
3. Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. Proc Natl Acad Sci USA 2001:98:4770-5. http://doi.org/ckzrbx
4. Seeman TE, Singer BH, Ryff CD, Dienberg Love G, Levy-Storms L. Social relationships, gender, and allostatic load across two age cohorts. Psychosom Med 2002;64:395-406. http://doi.org/ctwp
5. Karlamangla AS, Singer BH, McEwen BS, Rowe JW, Seeman TE. Allostatic load as a predictor of functional decline. MacArthur Studies of successful aging. J Clin Epidemiol 2002;55:696-710. http://doi.org/cv5g58
6. Seplaki CL, Goldman N, Weinstein M, Lin YH. How are biomarkers related to physical and mental well-being? J Gerontol A Biol Sci Med Sci 2004;59:201-17. http://doi.org/d7frs7
7. Goldman N, Turra CM, Glei DA, Seplaki CL, Lin YH, Weinstein M. Predicting mortality from clinical and nonclinical biomarkers. J Gerontol A Biol Sci Med Sci. 2006;61:1070-4. http://doi.org/fbp4jr
8. Karlamanga AS, Miler-Martinez D, Lachman ME, Tun PA, Koretz BK, Seeman TE. Biological correlates of adult cognition: Midlife in the United States (MIDUS). Neurobiol Aging 2014;35:387-94. http://doi.org/ctwq
9. Karlamangla AS, Singer BH, McEwen BS, Rowe JW, Seeman TE. Allostatic load as a predictor of functional decline. MacArthur studies of successful aging. J Clin Epidemiol. 2002;55:696-710.
10. Seeman TE, Crimmins E, Huang MH, Singer B, Bucur A, Gruenewald T, et al. Cumulative biological risk and socioeconomic differences in mortality: MacArthur studies of successful aging. Soc Sci Med 2004;58:1985-97. http://doi.org/dngxbm
11. McEwen BS, Stellar E. Stress and the individual: mechanism leading to disease. Arch Intern Med 1993;153:2093-101. http://doi.org/ft39sh
12. Juster RP, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on heath and cognition. Neurosci Biobehav 2001;35:2e16.
13. Seaman E, Singer BH, Rowe J, Horwitz RI, McEwen B. Price of adaptation allostatic load and its health consequences. Arch Intern Med 1997;157:2259. http://doi.org/db4c85
14. Joels M. Corticosteroid effects in the brain: U-shape it. Trends Pharmacol Sci 2006;27:244–50. http://doi.org/b9jqp4
15. Margineanu DG, Gower AJ, Gobert J, Wulfert E. Long-term adrenalectomy reduces hippocampal granule cell excitability in vivo. Brain Res Bull 1994;33: 93-8. http://doi.org/ddgqsz
16. Gould E, McEwen BS, Tanapat P, Galea LA, Fuchs E. Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. J Neurosci 1997;17:2492-8. http://doi.org/ctwr
17. Mirescu C, Gould E. Stress and adult neurogenesis. Hippocampus 2006;16:233-8. http://doi.org/d7txkp
18. Kim DH, Lipsitz LA, Ferrucci L, Varadhan R, Guralnik JM, Carlson MC, et al. Association between reduced heart rate variability and cognitive impairment in older disabled women in the community: women´s health and Aging Study I. J Am Geriatr Soc 2006;54:1751-7. http://doi.org/b2srpn
19. McEwen BS. Physiology and Neurobiology of Stress and Adaptation: Central Role of the Brain. Physiol Rev 2007;87:873–904. http://doi.org/fjpjxn
20. Seeman TE, McEwen B, Rowe J, Singer B. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. Proc Nati Acad Sci USA 2001;98:4770-5. http://doi.org/ckzrbx
21. Kobrosly RW, Seplaki CL, Jones CM, van Wijngaarden E. Physiologic dysfunction scores and cognitive function test performance in

U.S. adults. Psychosom Med 2012;74:81-8. http://doi.org/cmqs4b
22. Booth T, Royle NA, Corley J, Gow A, Valdés Hernández M del C, Muñoz Maniega S, et al. Association of allostatic load with brain structure and cognitive ability in later life. Neurobiol Aging 2015:1390-9. http://doi.org/ctws
23. Hollar D. Cross-sectional changes in patterns of allostatic load among persons with varying disabilities. NHANES: 2001-2010. Disabil Health J 2013;6:177-87. http://doi.org/f42f4s
24. Rosengren A, Hawken S, Ôunpuu S, Sliwa K, Zubaid M, Almahmeed WA, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study%. Lancet 2004;364:953-62. http://doi.org/dmx3q2
25. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al, INTERSTROKE investigators. Risk factors for ischemic and intracerebral hemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 2010;376:112-23. http://doi.org/d42p38
26. Matsuura N, Nagasaki K, Minagawa Y, Ito S, Sano Y, Yamada Y, et al. Restraint stress exacerbates cardiac and adipose tissue pathology via β-adrenergic signaling in rats with metabolic syndrome. Am J Physiol Heart Circ Physiol 2015;308:H1275-86. http://doi.org/f7b9wx
27. Effoe VS, Chen H, Moran A, Bertoni AG, Bluemke DA, Seeman T, et al. Acculturation is associated with left ventricular mass in a multiethnic sample: the Multi-Ethnic Study of Atherosclerosis. BMC Cardiovasc Disord 2015;3:15:161
28. Pickering TG. Does psychological stress contribute to the development of hypertension and coronary heart disease? Eur J Clin Pharmacol 1990;39:S1–S7. http://doi.org/drcnmw
29. Siegrist J, Peter R, Motz W, Strauer BE. The role of hypertension, left ventricular hypertrophy and psychosocial risks in cardiovascular disease: prospective evidence from blue-collar men. Eur Heart J. 1992 Sep;13 Suppl D:89-95.
30. Mathuranath PS, Nestor PJ, Berrios GE, Rakowicz W, Hodges JR. A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. Neurology 2000;55:1613-20. http://doi.org/ctwt
31. Mioshi1E, Dawson K, Mitchell J, Arnold R, Hodges J. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. Int J Geriatr Psychiatry 2006;21:1078–85. http://doi.org/fh426t
32. García-Caballero A, García-Lado I, González-Hermida J, Recimil M, Area R, Manes F, et al. El Addenbrooke's Cognitive Examination en español para el diagnóstico de demencia y para la diferenciación entre enfermedad de Alzheimer y demencia frontotemporal. Rev Neurol 2005;41:717-21.
33. Sarasola D, Luján-Calcagno M, Sabe L, Crivelli L, Torralva T, Roca M, García-Caballero A, Manes F. "El Addenbrooke's Cognitive Examination en español para el diagnóstico de demencia y para la diferenciación entre enfermedad de Alzheimer y demencia frontotemporal." REV NEUROL 2005; 41 (12): 717-721.
34. Sabbatini M, Catalani A, Consoli C, Martetta N, Tomassoni D, Avola R. The Hippocampus in spontaneously hypertensive rats: an animal model of vascular dementia. Mech Ageing Dev 2002;123:547-59. http://doi.org/fmc7t6
35. McEwen B. Allostasis, Homeostasis, and the Costs of Physiological Adaptation. Edited by Jay Schulkin. Cambridge University Press Oct. 25, 2004:80.
36. George Fink editor, Stress Science: Neuroendocrinology. Bruce McEwen. Stress: Homeostasis, Rheostasis, Allostasis and Allostasis Load. Copyright 2010 Elsevier Inc.:13.