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Allostatic load associations to acute, 3-year and 6-year prospective depressive symptoms in healthy older adults

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ABSTRACT

Allostatic load represents the strain that chronic stress exerts on interconnected biological systems. Associated algorithms are related to numerous deleterious physical outcomes in older populations, and yet few studies have assessed associations to mental health outcomes like geriatric depression. Using data from the Douglas Hospital Longitudinal Study of Normal and Pathological Aging, we assessed whether using an allostatic load index derived from seven biomarkers could detect self-rated depressive symptoms in 58 healthy older adults followed longitudinally over a 6-year period. Our results revealed that increased allostatic load was associated with increased depressive symptoms on the same year of assessment. After 3 years, AL was prospectively associated with depressive symptoms, but entering age and sex as covariates attenuated this effect to a trend. Only age emerged as a significant predictor of depressive symptoms over 6 years. These findings suggest that increased AL in older age is only associated with depressive symptomatology acutely. Over longer periods of time, however, the physical and psychological sequelae of advanced age may contribute to increased depressive symptoms via pathways otherwise undetectable using allostatic load indices of sub-clinical physiological dysregulations.

1. Introduction

Depression currently affects 8–20% of older adults [1]. Aging populations worldwide need improved detection strategies that are sensitive to the antecedents of geriatric depression and associated physiological recalibrations that ensue. A promising framework is the allostatic load model [2], which posits a temporal physiological sequence whereby chronic stress renders individuals more susceptible to developing pathologies.

The term *allostasis* [3] refers to the adaptive physiological responses organisms activate when homeostasis is disrupted. For example during acute stress, real or interpreted threats to homeostasis initiate the *sympathetic–adrenal–medullary* (SAM) axis release of catecholamines and the *hypothalamic–pituitary–adrenal* (HPA) axis secretion of glucocorticoids that mobilize energy necessary for fight-or-flight responses [4]. When chronically activated, allostatic mechanisms become physiologically taxing — or an *allostatic load* (AL) — that consequently increase one's susceptibility to disease [5]. AL therefore represents the physiological strain organisms experience when allostasis is repeatedly activated [2].

Multiple allostatic mediators function as part of a non-linear network that contributes to the development of AL [6]. At first, over-activation of *primary mediators* such as stress hormones and pro- and anti-inflammatory cytokines exact *primary effects* on cellular activities [7,8]. Subsidiary systems in turn recalibrate their own activities to compensate for the over and/or under production of primary mediators. This leads to *secondary outcomes*, whereby metabolic, cardiovascular, and immune biomarkers become dysregulated. AL becomes overloading when *tertiary outcomes* emerge with the manifestation of clinical endpoints such as mortality, cardiovascular disease, and depression.

By incorporating AL composite measures [9], a growing body of literature has demonstrated augmented prediction of numerous deleterious outcomes in comparison to traditional biomedical methods that focus almost exclusively on remediating clinically significant biomarker levels (for a review, see [35]). Because the AL index incorporates multiple biomarkers before they fall within clinical ranges, stronger prediction of pathological states is possible [10]. This is particularly the case for detecting physical conditions; although an alternative method is to use physiological recalibrations to assess

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impending psychiatric symptoms. To date, only a paucity of evidence links AL in association to psychiatric ailments, although mental health outcomes are postulated as important areas to explore further. Because exposures to life stressors contributes strongly to the pathogenesis of experiencing major depression [11], it follows that the AL model could theoretically be applied to detect emerging physiological recalibrations in older adults at risk of developing depressive symptoms.

A rich theoretical literature addressing AL and depression [12–18] has begun to be empirically substantiated in aging populations. Using the Taiwanese Social Environmental and Biomarkers of Aging Study (SEBAS), Seplaki and collaborators have found that dysregulation of AL biomarkers relate concurrently to higher self-reported depressive symptoms [19–21]. Using the same cohort, 3-year mortality risk, mobility limitations, cognitive declines, and depressive symptomatology were predicted by higher AL; however, these outcomes were driven differentially by traditional clinical risk-factors, neuroendoimmunological mediators, and attenuated by health controls [22]. These analyses suggest that AL is associated to acute and 3-year prospective symptoms of geriatric depression, yet this association is modulated by preexisting factors. Although encouraging, no studies have assessed whether increased AL levels can predict increased geriatric depressive symptoms beyond a 3-year timeframe, and whether the results obtained with the Taiwanese cohort can be applied to older individuals from Occidental societies.

In the present study, we used data from the Douglas Hospital Longitudinal Study of Normal and Pathological Aging [23–27] in order to assess whether AL indices are correlated with depressive symptoms acutely, 3 years later, and 6 years later in a cohort of 58 healthy older adults. We hypothesized that increased AL indices would be associated with increased symptoms of geriatric depression at all time points independently of sex or age effects.

2. Methods and materials

2.1. Protocol

We analyzed data from the Douglas Hospital Longitudinal Study of Normal and Pathological Aging in affiliation with the World Health Organization previously reported in greater detail elsewhere [23–27]. Briefly, the medical status of each participant was continually assessed by complete physical examination, including ECG, EEG, CAT scan, and a battery of laboratory tests for kidney, liver, and thyroid functions, hemogram, vitamin B12, folate levels, as well as neuropsychological assessment. Previous studies using this cohort have found no significant changes in the circadian rhythm nor CBG levels in these participants nor were sex differences in cortisol history detected. Data from 1994 to 2002 waves were incorporated in the present analyses. The complete cohort consisted of 93 which was reduced to 58 older adults (26 females and 32 males) between the ages of 52 and 80 in 1994 ($M = 67.55$, *S.E.M.* = 1.03) in the current analyses.

2.2. Biomarkers and allostatic load indices

On years of assessment, fasting morning blood samples were collected to assess plasma cortisol, total cholesterol, high-density lipoprotein- (HDL) cholesterol, triglycerides, and glucose levels. Aggregated systolic and diastolic blood pressure values based on three auscultatory recordings taken during annual physical examinations were also incorporated. Each biomarker's levels were tabulated and compared to cut-off points determined by quartile ranges with respect to the sample's distributions. AL indices were then constructed using the original one-tailed formulation [28,29] calculated by summing the number of values falling at or past the upper 75th percentile for every biomarker, except HDL-cholesterol, whereby the lowest 25th percentile denoted high risk. AL indices thus ranged from 0 to 7. AL indices in 1995, 1998, and 2001 were calculated with adjacent years (1994 or 1996 for 1995, 1997 and 1999 for 1998, and 2000 or 2002 for 2001) used for missing values. These three time points were then configured into baseline, 3-year, and 6-year intervals based on correspondence with repeated measures of geriatric depressive symptoms. For situations whereby a configuration needed to be chosen among 1995 and 1998, we opted to always take 1995 data first and only take 1998 data if the former was not available. While this methodology deviates slightly from classical longitudinal analyses that uses one baseline, our solution allowed for the inclusion of as many participants as possible as well as the incorporation of allostatic load data collected before psychometric administrations.

2.3. Questionnaires

The 30-item Geriatric Depression Scale [30] was used over six consecutive years (1997 to 2002). Responses in 1998 and 2001 were used in the present analyses and missing values were replaced by adjacent years (1997 or 1999 for 1998 and 2000 or 2002 for 2001). Because we did not administer this questionnaire in 1995, we were not able to assess acute associations with AL using that time-point.

2.4. Covariates

Prevalence rates of depression are higher in elderly women [31] and AL indices increase with age [32], so we accordingly entered sex and age as covariates. Preliminary analysis revealed that medication use (e.g., synthetic glucocorticoids, antihypertensive, statins) and body mass index ($M = 27.15$, *S.E.M.* = .54) did not confound AL indices nor depressive symptoms, so we did not include them in our analyses. Participants included in the current analysis were moreover free of anti-depressant medication use throughout.

2.5. Statistical analysis

Paired-sample *t*-tests were used to determine changes over time in AL indices and depressive symptoms. To assess whether differences existed among participants in our 6-year analysis for those lost to attrition and those remaining ($n = 32$), we executed two repeated-measures ANOVAs with attrition (0 = lost and 1 = remained) as the independent variable, acute and 3-year configurations of depression or AL indices entered as the dependent variables separately, and sex and age entered as covariates.

Our main analyses incorporated three hierarchical regressions computed in two steps: (1) AL indices and (2) covariates (sex and age). As illustrated in Fig. 1, we used different waves of data to investigate whether AL indices could predict acute, 3-year, and 6-year prospective depressive symptoms. We report the coefficient weights, R^2 effect sizes and associated change statistics, as well as ANOVA outputs at an $\alpha = .05$ level. All analyses were computed using the Statistical Package for the Social Sciences 18.0 Macintosh Edition. After each of these analyses, we followed with respective post-hoc power analyses using G*Power 3.1 Macintosh Edition [33,34]. Power $(1-\beta)$ was calculated based on the obtained effect sizes, sample size, number of predictors, and at $\alpha = .05$.

3. Results

3.1. Descriptive statistics

The AL indices at baseline ($M = 2.21$, *S.E.M.* = .22), 3 years ($M = 2.19$, *S.E.M.* = .2), and 6 years ($M = 2.06$, *S.E.M.* = .269, $n = 32$) did not differ according to paired-sample *t*-tests ($ps > .20$). Likewise, geriatric depressive symptoms measured acutely ($M = 5.12$, *S.E.M.* = .62) and 3 years later ($M = 5.52$, *S.E.M.* = .62) were similar ($ps > .65$). Repeated-measures ANOVAs assessing differences due to attrition revealed no group nor covariate effects on AL indices ($ps > .30$) nor depression scores ($ps > .60$), revealing no differences among those that were lost or remained part of the final 6-year analysis.