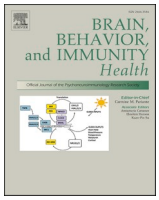
Brain, Behavior, & Immunity - Health 33 (2023) 100682

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx



Elucidating individual differences in chronic pain and whole person health with allostatic load biomarkers

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ARTICLE INFO

Keywords:
Allostatic load
Chronic pain
Socioenvironmental factors
Brain structure
Knee pain
Stress

ABSTRACT

Chronic pain is a stressor that affects whole person functioning. Persistent and prolonged activation of the body's stress systems without adequate recovery can result in measurable physiological and neurobiological dysregulation recognized as allostatic load. We and others have shown chronic pain is associated with measures of allostatic load including clinical biomarker composites, telomere length, and brain structures. Less is known regarding how different measures of allostatic load align. The purpose of the study was to evaluate relationships among two measures of allostatic load: a clinical composite and pain-related brain structures, pain, function, and socioenvironmental measures. Participants were non-Hispanic black and non-Hispanic white community-dwelling adults between 45 and 85 years old with knee pain. Data were from a brain MRI, questionnaires specific to pain, physical and psychosocial function, and a blood draw. Individuals with all measures for the clinical composite were included in the analysis (n = 175). Indicating higher allostatic load, higher levels of the clinical composite were associated with thinner insula cortices with trends for thinner inferior temporal lobes and dorsolateral prefrontal cortices (DLPFC). Higher allostatic load as measured by the clinical composite was associated with greater knee osteoarthritis pathology, pain disability, and lower physical function. Lower allostatic load as indicated by thicker insula cortices was associated with higher income and education, and greater physical functioning. Thicker insula and DLPFC were associated with a lower chronic pain stage. Multiple linear regression models with pain and socioenvironmental measures as the predictors were significant for the clinical composite, insular, and inferior temporal lobes. We replicate our previously reported bilateral temporal lobe group difference pattern and show that individuals with high chronic pain stage and greater socioenvironmental risk have a higher allostatic load as measured by the clinical composite compared to those individuals with high chronic pain stage and greater socioenvironmental buffers. Although brain structure differences are shown in individuals with chronic pain, brain MRIs are not yet clinically applicable. Our findings suggest that a clinical composite measure of allostatic load may help identify individuals with chronic pain who have biological vulnerabilities which increase the risk for poor health outcomes.

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https://doi.org/10.1016/j.bbih.2023.100682
Received 23 June 2023; Received in revised form 12 August 2023; Accepted 26 August 2023
Available online 31 August 2023

1. Introduction

Persistent pain is stressful and high levels of psychosocial stress can contribute to increased pain and disability (Meints and Edwards, 2018). The brain is the central hub for receiving, interpreting, and responding to all stimuli, both threatening and non-threatening (King et al., 2016; McEwen, 1998a, 2000a, 2007; Apkarian et al., 2005). Consistent with the allostasis model, occasional and intermittent demands with adequate recovery and buffers promote an adaptive response and enhances stress system functioning (McEwen, 2004, 2005). However, persistent and prolonged activation of the stress regulatory systems without adequate recovery and/or sufficient buffers can contribute toward higher allostatic load as indicated by stress system dysregulation (McEwen and Stellar, 1993; McEwen, 1998b). Associated with increased risk of morbidity and mortality (Freire et al., 2020; Guidi et al., 2021; McEwen and Seeman, 1999; Seeman et al., 2001), allostatic load can be assessed by brain structure, a clinical composite of stress system measures (metabolic, neuroendocrine, inflammatory, cardiovascular), and telomere length, Fig. 1 (McEwen, 2007, 2015; Sibille et al., 2012a; Zalli et al., 2014; Bobba-Alves et al., 2023).

Abbreviations:

CRP	c-reactive protein
DBP	diastolic blood pressure
DHEA	Dehydroepiandrosterone
DLPFC	dorsolateral prefrontal cortex
EOD	Experience of Discrimination
GCPS	Graded Chronic Pain Scale
HAS	Health Assessment
HR	heart rate
IGF-1	insulin-like growth factor-1
KL	Kellgren-Lawrence
QST	Qualitative Sensory Testing
SBP	systolic blood pressure
SPPB	Short Physical Performance Battery
SVI	Social Vulnerability Index
UAB	University of Alabama at Birmingham
UF	University of Florida
UPLOAD-2	Understanding Pain and Limitations in Osteoarthritic Disease 2 study
WHR	waist to hip ratio

To better evaluate the biological interface of chronic pain, we developed a pain measure based on physiological principles where levels of severity are determined specific to four domains: frequency, intensity, duration, and total number of pain sites (Sibille et al., 2016, 2017a; Tanner et al., 2021a, 2021b). With designations of low = 0 and high = 1 for each domain, a summed total results in a classification of five *stages of chronic pain* (Tanner et al., 2021b; Sibille et al., 2016, 2017a). Chronic pain stage is associated with a composite of inflammatory and metabolic measures in a dose-response fashion in a large population-based study (Sibille et al., 2016). In a study of individuals with knee pain, telomere length differed significantly in those individuals with low chronic pain stage compared to those with high chronic pain stage (Sibille et al., 2017a). Additionally, multiple clinical composite measures of allostatic load were positively associated with individuals' reporting frequent and severe pain in the English Longitudinal Study of Aging (Sibille et al., 2017b). Importantly, chronic pain is only one form of stress, stressful life experiences also contribute in a cumulative fashion to an individual's allostatic load (Seeman et al., 2001; Mauss et al., 2016; Thayer et al., 2017),[2,] (Lunde and Sieberg, 2020; Chapman et al., 2008).

Brain imaging has improved our understanding of the neurobiological interface of chronic pain, however, it is not currently a practical

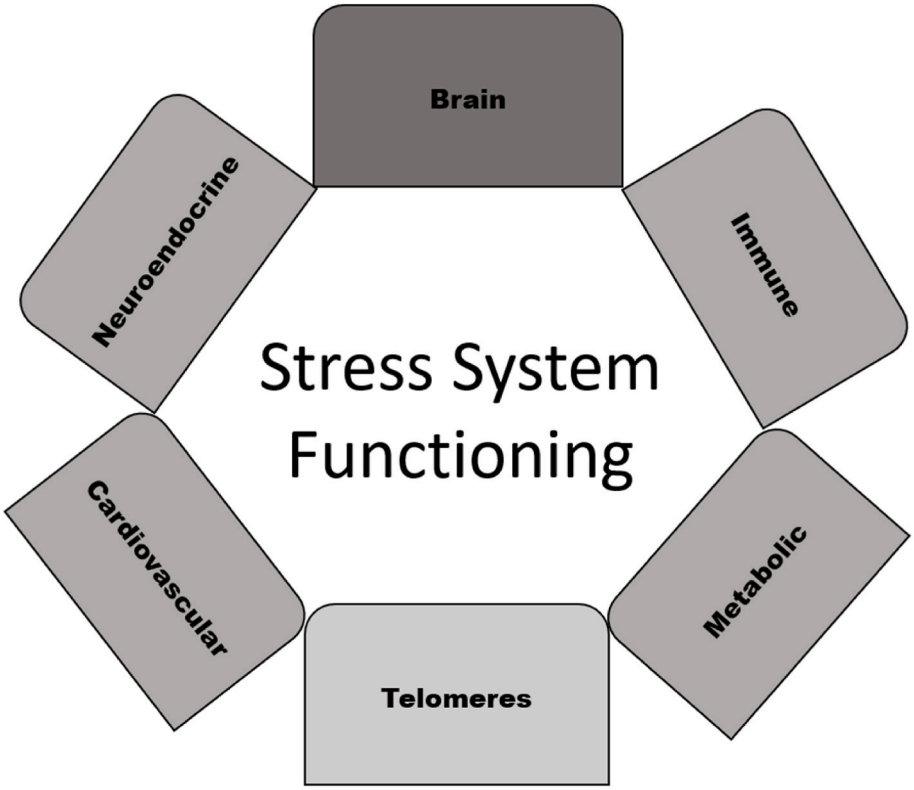

Fig. 1. Measures of allostatic load: Stress system biomarkers.

clinical assessment tool. If a clinical composite measure of allostatic load aligns with brain imaging findings, it may have potential utility in the assessment and treatment of individuals with chronic pain. As the brain initiates and regulates the stress response, the brain is an important measure of allostatic load (McEwen, 2000b, 2007; McEwen and Gianaros, 2010). Designed to be adaptive in response to stress and consistent with the hormesis, inverted U pattern; brain gray matter would initially increase indicating an adaptive response and with repeated and unrelenting stress activation, eventual gray matter decreases would be expected (McEwen et al., 2015).

We and others have shown that mild to moderate chronic pain is associated with greater gray matter structure; persistent, longer duration, and more severe chronic pain is associated with less gray matter (Tanner et al., 2021c; Rodriguez-Raecke et al., 2009). As the relationship between chronic pain and the brain is not anticipated to be linear, we applied a non-linear analysis in a prior study and demonstrated the hypothesized inverted U pattern (Tanner et al., 2021b). Importantly, we also observed that the relationship between chronic pain and the brain is associated with other factors. Specifically, in individuals with high chronic pain stage, non-Hispanic black adults with greater socioenvironmental risk factors had thinner temporal cortical gray matter than non-Hispanic white adults with greater socioenvironmental buffering factors (Tanner et al., 2021b). Social and environmental stressors have been linked to brain physiology (McEwen and Gianaros, 2010; Ganzel and Morris, 2011; Ganzel et al., 2010; Farah, 2017). Additionally, findings highlight the importance of considering socioenvironmental factors when investigating the allostatic load of chronic pain.

The purpose of this study was to determine: (1) relationships between measures of allostatic load:

a clinical composite and pain-related brain structures; (2) associations among measures of allostatic load, clinical pain, function, and socioenvironmental measures; (3) if clinical pain, function, and socioenvironmental measures with consideration for additional explanatory variables are predictive of measures of allostatic load; and (4) if the clinical composite might serve as a brain-imaging surrogate by aligning with previously reported temporal lobe structural findings (Tanner et al., 2021b). We hypothesized: (1) the clinical composite will inversely associate with pain-related gray matter; (2) the clinical composite will positively associate with clinical pain, functional limitations, and socioenvironmental risk, and pain-related brain structure will inversely relate to pain and positively associate with protective socioenvironmental factors;

(3) a consistent pattern showing greater allostatic load with greater socioenvironmental risk and clinical pain. Lastly, (4) we expected that in the group comparisons by low/high socioenvironmental groups and low/high chronic pain stage, the group with the greater socioenvironmental risk and high chronic pain stage, will have thinner temporal lobe gray matter and higher clinical composite compared to the other groups.

2. Materials and methods

2.1. Participants

The current study is a cross-sectional analysis of data collected as part of the Understanding Pain and Limitations in Osteoarthritic Disease 2 study [UPLOAD-2]. Adults 45–85 years of age who identified as non-Hispanic Black (NHB) or non-Hispanic White (NHW) with knee pain were eligible to participate. Subjects were recruited between 2015 and 2017 from the Gainesville, Florida or Birmingham, Alabama community and learned about the study via fliers, radio and newspaper announcements, and word-of-mouth referral (Thompson et al., 2018). The University of Florida (UF) Institution Review Board and the University of Alabama at Birmingham (UAB) Institution Review Board approved the study. All participants provided verbal and written informed consent. The manuscript follows the STROBE reporting guidelines (Cuschieri, 2019).

2.2. Procedures

Participants attended a baseline Health Assessment (HAS) visit where health, demographic, and pain questionnaires were collected. Knee radiographs were also collected. At the second visit, blood draws were collected and participants completed Qualitative Sensory Testing (QST). At the third visit, brain magnetic resonance imaging (MRI) data were obtained. Study visits were conducted within a week whenever possible. All participants who reported knee pain in the past month at the HAS visit and had complete clinical composite measures were included in the analysis (n = 175). The measures described are specific to those included in the current investigation.

2.3. Measures

2.3.1. Demographic and health information

Demographic and health information (n = 175) include age, biological sex (1 = male, 2 = female), self-reported ethnic/race identity (1 = NHB, 2 = NHW), smoking history (0 < 100 cigarettes lifetime, 1 ≥ 100 cigarettes lifetime), alcohol history (0 = no alcohol usage, 1 = drinks alcohol), and current comorbidities. Comorbidities were selected from a pre-specified list including high blood pressure, heart disease, cancer, diabetes, asthma/breathing problems, kidney disease, thyroid problem, stroke, seizure, chronic pain, neurological disorder, depression, other mental health condition, and other health problems. The Montreal Cognitive Assessment (MoCA) was completed (Nasreddine et al., 2005).

2.3.2. Socioenvironmental

Individual factors include education level (n = 175) and income (n = 171). Education levels were as follows: 1 = less than high school, 2 = high school, 3 = some college/university, 4 = college/university, 5 = master's, 6 = doctorate or equivalent. Income levels were as follows: 1 = $0 – $9,999, 2 = $10,000 – $19,999, 3 = $20,000 – $29,999, 4 = $30,000 – $39,999, 5 = $40,000 – $49,999, 6 = $50,000 – $59,999, 7 = $60,000 – $79,999, 8 = $80,000 – $99,999, 9 = $100,000 – $149,999, 10 = $150,000 or higher annually.

Experiences of Discrimination (EOD) measures self-reported feelings of discrimination due to race, ethnicity, sex, age, religion, physical appearance, sexual orientation, or other characteristics (Williams et al., 1997). Scoring is in two parts, part one is lifetime discrimination (EOD Lifetime) indicating the number of times individuals have been treated unfairly over the course of their lifetime with a score range of 0–11, (n = 172). Part two is daily discrimination (EOD Daily) indicating how often individuals experience unfair treatment on a day-to-day basis with a score range 10–60, (n = 172). Higher scores indicate greater experiences of discrimination. The EOD has shown to have good internal consistency (α = 0.74 or greater), test-re-test reliability coefficients (α = 0.70) in previous research and good consistency in our sample (α = 0.70) (Krieger et al., 2005).

The Center for Disease Control Social Vulnerability Index (SVI) incorporates community-level environmental factors including: number of individuals below poverty level, unemployment, income, no high school diploma, aged 65 or older, aged 17 or younger, older than age 5 with a disability, single-parent households, minority, speak English "less than well", multi-unit structures, mobile homes, crowding, no vehicle, and group quarters. The SVI can be calculated at the county level and the census level. Due to many participants residing within similar counties and overlap with the study site variable (UF and UAB), the county measure was not included. The census level was calculated and included in the study using the 2018 dataset (Tarling, 2017).

2.3.3. Clinical

Kellgren-Lawrence (KL) Scores. Knee radiographs (n = 170) were

read by a rheumatologist blinded to participant characteristics and scored using the Kellgren-Lawrence (KL) scoring system (0–4) (Kellgren and Lawrence, 1957). Scores of 2 or greater meet clinical criteria for radiographic osteoarthritis.

Number of Pain Sites. Participants were asked if they had pain more days than not over the past 3 months at specific body sites based on a preselected list (n = 175). Bilateral body sites included hands, arms, shoulders, neck, head/face, chest, stomach, upper back, lower back, knees, legs (other than knees), or feet/ankles (0–28 sites).

Graded Chronic Pain Scale (GCPS) assesses the chronicity of knee pain and its impact on daily activities over a 6-month period (Von Korff et al., 2020). Two subscales from the GCPS were included in the study, characteristic pain intensity and pain disability, both with a score range 0–100 (n = 175). Greater scores indicate higher pain intensity and greater functional limitations. The GCPS has demonstrated good internal consistency in previous research (α = 0.74) and the current sample (α = 0.71) (Von Korff et al., 1992).

Chronic Pain Stage is a measure of chronic pain severity designed to capture the non-linear neurobiological and physiological changes consistent with hormesis model. Four domains of pain are included in the measure: frequency, intensity, time, and total pain sites (Sibille et al., 2016, 2017c). Frequency was determined by asking "On average, how many days per week do you experience pain in your knee?". Intensity was determined by the GCPS characteristic pain intensity. Time or duration was reported as length of time in months experiencing knee pain. Total number of pain sites was based on a list as described above. For each of the four domains, a 1 is given for above the median or 0 if below the median and then summed for a total score 1 = low stage of pain to 5 = high/severe stage of pain (n = 175). Chronic pain stage is associated with multiple measures of allostatic load including a clinical composite, telomere length, and brain structures (Sibille et al., 2016, 2017c; Tanner et al., 2021a, 2021b).

Short Physical Performance Battery (SPPB) consists of a standing balance task, repeat 5 times chair stand, and a 4-m walking course at their usual speed (Cesari et al., 2017; Guralnik et al., 1994). Scores range from 0 to 12 with higher scores indicating higher functional capabilities (n = 175).

2.3.4. Clinical composite

During the QST visit, blood was drawn, spun down, and stored at −80 Celsius until analysis. Ten measures reflecting four stress systems (cardiovascular, immune, metabolic, and neuroendocrine) were used to create the clinical composite. *Cardiovascular measures* included systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR). Heart rate and blood pressure were measured four continuous times prior to QST testing. Participants were seated for at least 15 min prior to taking measurements. The first measurement was excluded and the average of all three remaining measurements was used in the analysis. *Immune measures* included fibrinogen and C-reactive protein (CRP). *Metabolic measures* included insulin-like growth factor-1 (IGF-1), albumin, and waist-to-hip ratio (WHR). WHR was calculated from waist and hip measurements that were collected using a tape measure during the HAS visit. *Neuroendocrine measures* included Cortisol and Dehydroepiandrosterone (DHEA) using the TOSOH AIA-900, CRP with Pointe Scientific reagent (Canton, MI) and Albumin determined on a Sirrus Stanbio analyzer (Boerne, TX), and IGF-1 and Fibrinogen measured using ALPCO ELISA kits (Salem, NH). Samples were, processed using high quality standards by the University of Alabama at Birmingham Diabetes Research Center Human Physiology Core Laboratory under the guidance of Dr. Barbara Gower.

The upper quartiles were identified for SBP, DBP, HR, fibrinogen, CRP, WHR and cortisol. An individual was assigned 1 point per marker if the individual's marker was at or above the upper quartile. The lower quartiles were identified for IGF-1, albumin, and DHEA. An individual was assigned 1 point per marker if the individual's marker was at or below the lower quartile. Points were then summed across markers to create a composite with a range from 0 to 10, (n = 175) (Slade et al., 2012).

2.3.5. Brain imaging

MRI data were acquired using a 3 T Philips Achieva (32-channel head coil at UF and an 8-channel at UAB) using the following acquisitions at both the University of Alabama at Birmingham and the University of Florida. Three-dimensional (3D) magnetization-prepared rapid acquisition gradient-echo (MP RAGE) T1-weighted imaging TE: 3.2 ms, TR: 7.0 ms, flip angle: 8°, 1 mm iso voxels, FOV: 240 × 240 × 176, sagittal acquisition.

MP-RAGE images were acquired and used for analyses after processing by trained personnel using FreeSurfer 6.0 software (Fischl and Dale, 2000; Fischl et al., 2002, 2004). Analyses were conducted as previously reported (Tanner et al., 2021b, 2021c). Based on our previous work and the work of others (McEwen and Gianaros, 2010; McEwen, 2001), brain regions in the study included bilateral thickness for the insula, postcentral gyrus, inferior temporal lobe (entorhinal, fusiform, inferior, and middle temporal gyri) (Jack et al., 2015, 2017s; Magon et al., 2018; Schwedt et al., 2015; Petersen et al., 2019), and superior/middle dorsolateral prefrontal cortex (DLPFC, n = 139); and bilateral volume for the amygdala and hippocampus (n = 137) (Tanner et al., 2021b, 2021c). A total of 36 participants were missing MRI due to contraindications or issues with the scanner acquisition. Mean thickness or volume for each brain region was exported bilaterally and averaged or summed by region across hemispheres. Amygdala and hippocampus volumes were adjusted for estimated total intracranial volume (Buckner et al., 2004).

2.4. Statistical analyses

Data were checked for normality, outliers, missing data and multicollinearity. A total of four participants were missing information on income ($n = 4$) missing data were imputed based on the sample's median income, adjusted for education using the equation: 3.25 + 1.14*(hh_education-0.37). No other imputation was completed. Predictor variables included pain and socioenvironmental variables. Outcome variables were the measures of allostatic load measures: the clinical composite and brain structures. Additional explanatory variables included: age, sex, sociodemographic group, and study site (to account for possible scanner differences between UF and UAB). All available data were used for each analysis. Sample sizes are identified in Methods and Tables.

To test question 1, *identify relationships between measures of allostatic load: clinical composite and pain-related brain structures,* Spearman correlations were calculated and tested against a null hypothesis that the true correlation is zero. Spearman correlations were chosen due to the ordinal nature of our clinical composite variable. Pain-related brain structures showing a significant association ($p < 0.05$) or a *rho* = 0.1 or greater with the clinical composite were included in additional analyses.

Similar to question 1, to test question 2, *determine associations among allostatic load measures and socioenvironmental and pain measures*, Spearman correlations were calculated and hypotheses tests were conducted. Variable selection for question 3 was based on significant correlations ($p < 0.05$) or variables showing an association of *rho* = 0.1 or greater, and no indication of multicollinearity (*rho*≥0.6).

To test question 3, *evaluate the clinical composite and pain-related brain structures with consideration for pain measures, socioenvironmental factors, and additional explanatory variables*. A multiple linear regression model was fit to the data with outcomes being the clinical composite and brain structures, predictor variables including income, education, SVI census, KL index, GCPS disability, chronic pain stage, and SPPB total and additional explanatory variables being age, sex, sociodemographic group, and study site. The GCPS CPI was excluded due to high multicollinearity with GCPS disability (rho>0.6) and because is a component in chronic pain stage.

To test question 4, *determine if the clinical composite aligns with the*

previous temporal lobe brain structural findings (Tanner et al., 2021b). Consistent with the prior published analysis, we conducted a test of interaction between sociodemographic groups and low chronic pain stage (1 and 2; n = 58) and high chronic pain stage (4 and 5; n = 61). The middle chronic pain stage group (n = 57) was excluded to compare the phenotypic extreme groups. An ANCOVA was completed with the clinical composite as dependent variable and chronic pain stage (low/high) and sociodemographic group, and the interaction between chronic pain stage and sociodemographic group. Covariates included income, education, study site, age, and MoCA total score. Due to the small sample size, an additional two group ANCOVA with covariates limited to those associated with the clinical composite (age and BMI) was run. Statistical analyses were completed using SAS, V.9.4 (SAS Institute, Cary, North Carolina, USA) and SPSS (v.28). All tests were considered statistically significant at a $p < 0.05$. Given the novelty and potential clinical relevance, observed p-values are reported without multiple analysis adjustment.

3. Results

3.1. Descriptives

Participant characteristics are presented in Table 1. The participant sample included 50.9% NHB, 61.7% women, and a median age of 57 years old. There were significant differences between the ethnic/race groups on variables including: age, education, income, discrimination, social vulnerability index, and MoCA scores. Thus, only a subsample was represented for each group. As such, interpretation of ethnic/race group differences would not be accurate. Additionally, the term *sociodemographic groups* rather than ethnic/race groups is used as it is a more accurate description of the groups since they differ on a number of demographic and socioenvironmental variables.

3.2. Relationships between the clinical composite and pain-related brain structures

A significant association between the insula (−0.21, p = 0.013) was found indicating higher clinical composite score with thinner insula cortices. Additionally, a non-significant inverse trend was noted for the inferior temporal lobe (−0.16, p = 0.067) and the DLPFC (−0.15, p = 0.074). There were no significant associations between the clinical composite and the other pain-related brain areas. Pain-related brain structures showing a significant association ($p < 0.05$) or a *rho* = 0.1 or greater with the clinical composite which included the insula, inferior temporal lobe, and DLPFC were included in further analyses.

3.3. Relationships between measures of allostatic load and socioenvironmental and pain measures

Clinical composite. No associations were observed between the clinical composite and socioenvironmental measures. Regarding pain measures, the clinical composite was positively associated with KL scores (0.25, p = 0.001) and disability measured by the GCPS (0.17, p = 0.027) and inversely associated with physical function measured by the SPPB (−0.26, p = 0.001). Thus, higher allostatic load as measured by the clinical composite was associated with higher OA pathology, greater functional limitations, and lower functional performance (Table 2).

Pain-related brain structures. Income (0.17, p = 0.044) and education (0.19, p = 0.030) were significantly associated with the insula such that higher income and education were associated with thicker insula cortices. There were no associations between the inferior temporal lobe or DLPFC and socioenvironmental measures. Regarding pain measures, the insula was inversely associated with the chronic pain stage (−0.18, p = 0.031) and positively associated with physical function as measured by the SPPB (0.24, p = 0.004). The DLPFC was inversely associated with the chronic pain stage (−0.21, p = 0.015). The inferior temporal lobe was not associated with pain measures. Hence, thicker insula and DLPFC were associated with lower chronic pain stage and a thicker insula cortices was also associated with better physical performance (Table 2).

Table 1
Baseline demographic, health, socioenvironmental, and clinical measures.

Variable	Total Sample (n = 175)	Sociodemographic Groups		*P*-Value
		NHB (n = 89)	NHW (n = 86)	
Demographics				
Age, median [IQR]	57.0 [12.0]	56.0 [9.0]	59.0 [14]	0.0084
Study Site, N (%)				0.1635
UF	111 (63.4)	52 (58.4)	59 (68.6)	
UAB	64 (36.6)	37 (41.6)	27 (31.4)	
Sex, N (%)				0.3641
Male	67 (38.3)	37 (41.6)	30 (34.9)	
Female	108 (61.7)	52 (58.4)	56 (65.1)	
Health Measures				
No. Comorbidities (0–14), N (%)				0.1320
0	51 (29.1)	22 (24.7)	29 (33.7)	
1-2	95 (54.3)	52 (58.4)	43 (50)	
3+	29 (16.6)	15 (16.9)	14 (16.3)	
Waist to Hip Ratio, median [IQR]	0.91 [0.12]	0.90 [0.1]	0.92 [0.13]	0.3958
>100 Cigarettes Lifetime, N (%)	87 (49.7)	47 (52.8)	40 (46.5)	0.3246
Current alcohol use, N (%)	81 (46.3)	34 (38.2)	47 (54.7)	0.0296
MoCA, median [IQR]	24.0 [5.0]	23.0 [4.0]	26.0 [5.0]	<0.0001
Socioenvironmental Factors				
Education, N (%)				0.0009
High school or less	116 (66.3)	51 (57.3)	32 (37.2)	
Higher education	59 (33.7)	38 (42.7)	54 (62.8)	
Income, N (%)				0.0002
$0–29,999	98 (56.0)	62 (69.7)	36 (41.9)	
$30,000–79,999	51 (29.1)	20 (22.5)	31 (36)	
$80,000+	26 (14.9)	7 (7.9)	19 (22.1)	
EOD-Daily, median [IQR]	14.8 [21.0]	18.5 [22.5]	8.0 [21.0]	<0.0001
EOD-Lifetime, median [IQR]	5.0 [15.0]	12.5 [13.5]	0.0 [4.5]	<0.0001
SVI Census, median [IQR]	7.0 [2.5]	7.8 [2.7]	6.5]1.8]	0.0002
Clinical Measures				
KL Score, N (%)				0.4780
0-2	124 (70.8)	61 (68.5)	63 (73.26)	
3-4	46 (26.3)	24 (27.0)	22 (25.6)	
Not Reported	5 (2.9)	4 (4.5)	1 (1.2)	
No. pain sites, median [IQR]	5.0 [4.0]	5.0 [4.0]	5.0 [4.0]	0.6911
GCPS Pain, median [IQR]	56.6 [36.7]	70.0 [26.7]	43.3 [30.0]	<0.0001
GCPS Disability, median [IQR]	46.7 [53.3]	56.7 [40.0]	30.0 [50.0]	<0.0001
Chronic Pain Stage median [IQR]	2.0 [2.0]	2.0 [1.0]	2.0 [2.0]	0.0129
SPPB Total, median [IQR]	9.0 [3.0]	9.0 [2.0]	10.0 [2.0]	0.0175

UF=University of Florida; UAB=University of Alabama at Birmingham; NHB=Non-Hispanic Black; NHW=Non-Hispanic White; EOD = Experience of Discrimination; SVI=Social Vulnerability Index; GCPS = Graded Chronic Pain Scale; SPPB=Short Physical Performance Battery.

3.4. Relationships between measures of allostatic load with combined socioenvironmental and pain measures

Significant relationships were observed for the clinical composite, insular and inferior temporal lobes (Table 3). Age was associated with the allostatic load measures such that higher age was associated with greater clinical composite and thinner insular and inferior temporal lobe

Table 2
Spearman correlation between measures of allostatic load, socioenvironmental factors, and pain measures.

	Allostatic Load			
	Clinical Composite	Insula Cortices	Inferior Temporal Lobe	DLPFC
	(n = 175)	(n = 137)	(n = 139)	(n = 139)
Socioenvironmental Measures				
Income	−0.097	**0.172***	0.087	0.105
Education	−0.042	**0.185***	0.017	0.044
EOD lifetime	0.068	0.067	−0.072	0.058
EOD daily	0.089	0.063	−0.015	0.018
SVI census	−0.050	−0.136	−0.038	−0.032
Pain and Function Measures				
KL Index	**0.250***	−0.096	−0.162	−0.099
No. pain sites	0.014	0.057	0.049	−0.048
GCPS pain intensity	0.148	−0.108	−0.112	−0.076
GCPS disability	**0.167***	−0.052	−0.12	−0.085
Chronic pain stage	0.130	**−0.185***	−0.166	**−0.206***
SPPB total	**−0.261****	**0.244***	0.147	0.134

*p < 0.05, **p < 0.001, p < 0.0001.
KL=Kellgren Lawrence; GCPS = Graded Chronic Pain Scale; SPPB=Short Physical Performance Battery; DLPFC = Dorsolateral Prefrontal Cortex.

cortices thickness. Lower SPPB scores were associated with higher clinical composite scores (p = 0.032). Individuals in the greater socioenvironmental risk factor group had decreased insula thickness (p = 0.046). Finally, there was a significant site difference for the inferior temporal lobes thickness (p = 0.011).

3.5. Measures of allostatic load, low and high chronic pain stage, and sociodemographic groups

We evaluated if the sociodemographic and chronic pain stage group findings in bilateral temporal lobe brain structures observed in a previous study were replicated in the allostatic load clinical composite (Tanner et al., 2021b). There was no significant sociodemographic group (p = 0.058, partial η^2 = 0.048), chronic pain stage group (p = 0.172), or sociodemographic*chronic pain stage interaction (p = 0.267; partial η^2 = 0.014). However, sample sizes are small for the analysis completed. A second analysis was completed limited to the high chronic pain stage low socioenvironmental risk (n = 15) and high chronic pain stage and high socioenvironmental risk (n = 32) with age and BMI as covariates due to association with the outcome variable. A significant difference between groups was observed (p = 0.041). The pattern of findings reported in our prior publication specific to the temporal lobes by the four groups was similar to the group patterns observed in the clinical composite (Tanner et al., 2021b) (Fig. 2).

4. Discussion

The purpose of this study was to evaluate the relationship between measures of allostatic load, a clinical composite and pain-related brain structures, specific to clinical pain, function, and socioenvironmental measures. Regarding our first hypothesis, there was a significant association between a higher clinical composite and thinner insular lobes with a non-significant trend toward thinner inferior temporal lobes and DLPFC. In line with our second hypothesis, higher allostatic load as measured by the clinical composite was related to knee OA pathology and greater functional limitations, it was not associated with pain intensity or socioenvironmental measures. Thicker bilateral insula was related to higher education, income, and physical function. As anticipated, thinner insula and DLPFC were associated with higher chronic pain stage. In multilinear regression models with pain and socioenvironmental measures as predictors, the anticipated allostatic load patterns were indicated for the clinical composite and two pain-related brain structures, the insular and inferior temporal lobes. Lastly, the chronic pain stage and sociodemographic group patterns previous reported in the bilateral temporal lobes of the brain were replicated in the clinical composite measure with the individuals with high chronic pain and greater socioenvironmental risk having a higher clinical composite score. *Importantly, (1) findings indicate that it is the combination of chronic pain and socioenvironmental stress that contributes to greater health-related*

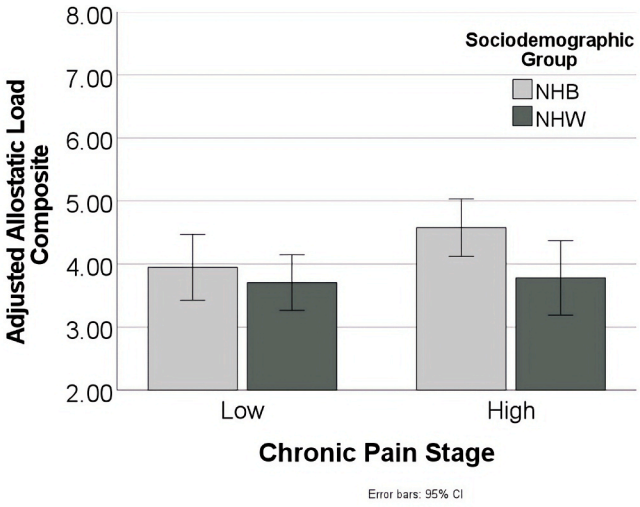

Fig. 2. Clinical composite and chronic pain stage by sociodemographic group.

Table 3
Adjusted analyses of the association between measures of allostatic load and socioenvironmental and pain measures.

	Allostatic Load					
	Clinical Composite n = 162		Insula Cortices n = 127		Inferior Temporal Lobe n = 129	
	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value
Age	**3.96 (1.26)**	**0.0465**	**−0.00 (0.00)**	**0.0092**	**−0.00 (0.00)**	**0.0396**
Sex	0.03 (0.01)	0.8984	−0.03 (0.02)	0.2155	0.02 (0.02)	0.5007
Sociodemographic Groups	0.03 (0.2)	0.3956	**−0.05 (0.03)**	**0.0464**	−0.05 (0.03)	0.0737
Study Site	0.18 (0.22)	0.6175	−0.04 (0.02)	0.0764	**−0.06 (0.02)**	**0.0107**
Income	−0.1 (0.2)	0.4166	0.00 (0.01)	0.6626	0.01 (0.00)	0.2700
Education	−0.04 (0.05)	0.7764	0.02 (0.01)	0.0948	−0.00 (0.01)	0.7764
SVI Census	0.03 (0.09)	0.2220	−0.00 (0.01)	0.5242	−0.00 (0.01)	0.7741
KL Index	−0.07 (0.06)	0.0625	−0.01 (0.01)	0.5104	−0.01 (0.01)	0.1288
GCPS Disability	0.12 (0.07)	0.1964	0.00 (0.00)	0.6859	−0.00 (0.00)	0.3078
Chronic Pain Stage	0.01 (0)	0.7637	−0.01 (0.01)	0.4924	−0.01 (0.01)	0.5892
SPPB Total	**0.03 (0.09)**	**0.0320**	0.01 (0.01)	0.2523	−0.00 (0.01)	0.7981

SVI Census = Social Vulnerability Index Census Level; KL=Kellgren Lawrence; GCPS = Graded Chronic Pain Scale; SPPB=Short Physical Performance Battery.

vulnerabilities and (2) the clinical composite measure of allostatic load may help identify individuals with chronic pain who have biological vulnerabilities which increase the risk for poor health outcomes.

4.1. Relationships between measures of allostatic load

Previous studies have investigated allostatic load as a measure independent of brain structure (Booth et al., 2015; Chiappelli et al., 2017; Ottino-González et al., 2017; Savransky et al., 2017). As the brain is the central relay station of stimuli interpretation and the stress response, it is essentially the primary indicator of an individual's allostatic load (McEwen, 2000b, 2007; McEwen and Gianaros, 2010). Unfortunately, evaluating allostatic load from measures of brain structure is complicated for several reasons. First, determining which structures to focus on is challenging due to the numerous potential measures available. Second, areas specific to stimuli activation and/or secondary to heightened stress-related neurochemicals in the brain could possibly serve as indicators of allostatic load. Third, the relationship between physiological measures and stress is well established and is not linear (McEwen, 1998a; McEwen and Gianaros, 2011; Karatsoreos and McEwen, 2011). Fourth, brain structure is highly individualized based on life experiences and exposures. Despite these numerous limitations, we show a significant association between a higher clinical composite and thinner insula cortices with a similar trend indicated in the same direction for the inferior temporal lobes and DLPFC. Interestingly, the insula has a role in immune system regulations (Daëron, 2022; Kerezoudis et al., 2022). Although only a few pain-related brain structures aligned with the clinical composite, the findings are consistent with the allostatic load conceptualization. *Specifically, an individual's life experience in combination with chronic pain is measurable, providing a view of their "whole person functioning status" which could be highly informative for patient care planning.*

4.2. Relationships between allostatic load, socioenvironmental factors, and clinical pain

Numerous publications have identified allostatic load as a conceptual model for understanding the physiological burden of living with chronic pain (King et al., 2016; Sibille et al., 2012a, 2012b; Lunde and Sieberg, 2020; Borsook et al., 2012). Although relationships between the clinical composite and socioenvironmental measures were not apparent, limitations include the constraints of the analyses run and the discrete range and categorical nature of the variables. Clinical composite measures of allostatic load have been associated with socioenvironmental measures in other studies such as income, education attainment, neighborhood quality, environmental conditions (e.g., air quality or toxic exposures), social support, and discrimination (Guidi et al., 2021; Dowd et al., 2009; Ribeiro et al., 2018). McEwen and Davidson described how life experiences influence neuroplasticity (Davidson and McEwen, 2012). In the current study, thicker insula cortices were associated with higher education and income. More studies are reporting on the neurobiological interface between socioenvironmental experiences and brain structure, helping to disentangle the complex array of factors contributing to individual differences and health disparities (Luby et al., 2013; McEwen, 2010; Mackes et al., 2020).

A limited number of studies have investigated the relationship between allostatic load and chronic pain. In our study, allostatic load as measured by the clinical composite score was positively associated with knee OA pathology, a self-report measure of disability, and an objective functional measure. We and others have previously reported findings on clinical composite measures of allostatic load and clinical pain (Sibille et al., 2016, 2017b; Slade et al., 2012). We have also reported relationships between clinical pain and telomere length, another measure of allostatic load (Sibille et al., 2012a, 2017a; Bobba-Alves et al., 2023; McEwen, 2015). When investigating allostatic load based on pain-related brain structure, we identified that higher chronic pain stage was associated with a thinner bilateral insula and DLPFC. The pattern of findings aligns with the hormesis, inverted u physiological response to stress (Li and He, 2009; Calabrese et al., 2017; Mattson, 2008; Li et al., 2019). Although not investigated from an allostatic load conceptualization, multiple studies have indicated the pattern of thicker pain-related brain structure in individuals with early stages of chronic pain and thinner brain structures in more severe persisting stages of pain (Tanner et al., 2021b; Maleki et al., 2013; Moayedi et al., 2012; Schweinhardt et al., 2008; Vachon-Presseau et al., 2016). A non-linear relationship between brain structure and chronic pain severity may explain inconsistent findings in pain-related brain imaging research (Coppieters et al., 2016). Additionally, as an extensive array of life experiences overlap with different pain-related brain structures, "loads" on a structure will differ. Further, in some structures such as the amygdala, activation can result from excitatory and inhibitory responses to pain and stress (Simons et al., 2014; Coppieters et al., 2021).

4.3. Relationships between allostatic load and combined socioenvironmental and clinical pain measures

In 2012, Slade and colleagues reported on a study of socioeconomic status, ethnicity/race, a clinical composite of allostatic load, and pain prevalence in the National Health and Nutrition Examination Survey. There was a positive relationship between pain measures and the clinical composite index. Additionally, a clinical composite of 5 or greater was associated with higher pain prevalence. In the multivariate analyses with types of pain as the outcome, allostatic load was included in the model as a predictor variable along with ethnicity/race group, poverty/income, and smoking. They reported that allostatic load did little to attenuate relationships between pain and the sociodemographic factors. Our approach and findings differ.

Allostatic load represents the physiological and neurobiological functional balance of the "whole person." Thus, socioenvironmental factors, pain symptoms, behavioral factors, and emotional states among other life experiences all contribute to an individual's allostatic load. Even with the limitations in looking at specific brain regions to measure allostatic load, we show that in combined models accounting for demographic, socioenvironmental, and pain factors, a consistent pattern of findings are represented in the clinical composite and cortical brain structures, specifically the insular and inferior temporal lobes.

Further findings specific to the additional explanatory variables are noteworthy. Age was a significant predictor across all models. Sex was not a significant predictor, as typically observed in larger, population based studies (Sibille et al., 2017b). Sociodemographic group was a significant predictor in the insula model but not in the other measures of allostatic load. Although socioenvironmental measures are included in the analyses, numerous factors were not considered (Patel et al., 2022). Additional socioenvironmental variables warrant consideration to further appreciate factors contributing to health disparities. Study site differed in one of the three models. In addition to the possible role of MRI scanner differences, the communities between Gainesville, Florida and Birmingham, Alabama may be a contributing factor that may also be better understood with the inclusion of additional socioenvironmental variables.

4.4. Allostatic load, low and high chronic pain stage, and sociodemographic groups

Across the allostatic load measures, a similar pattern is indicated. Among participants with high chronic pain stage, those with greater socioenvironmental risk have thinner temporal cortices and a higher clinical composite compared to those with lower socioenvironmental risk. *If researchers and clinicians are only evaluating pain symptoms, significant differences in individual vulnerabilities will be missed.* Statistically and clinically significant differences were observed in bilateral temporal lobe cortical thickness. Temporal lobe cortical thickness is associated

with risk for Alzheimer's disease and related dementias (Jack et al., 2015; Petersen et al., 2019). We also show that the individuals with the combination of high chronic pain stage and high socioenvironmental risk have higher allostatic load clinical composite. Higher allostatic load is associated with increased risk of morbidity and mortality.

4.5. Strengths, limitations, and future directions

This study has notable strengths including a sample of community dwelling, middle aged and older adults with a balanced representation of NHB and NHW participants from two different study sites in Gainesville, Florida and Birmingham, Alabama. Imaging protocols were identical at both study sites. Data processing was completed on one system, at one site, with well-validated methods to ensure reproducibility. The blood samples were collected following a standardized protocol and all samples were processed and quantified in the Gower Lab, Human Physiology Core, at the University of Alabama at Birmingham following standardized procedures. Finally, the allostatic load clinical composite measures were pre-selected based on work from our lab and others, and a commonly used scoring approach was used (Sibille et al., 2016, 2017b; Slade et al., 2012; Juster et al., 2010).

There are also limitations warranting consideration. First, the allostatic load clinical composite was comprised of values based on quartile splits that were obtained from a research lab, the lower and higher interpretations are relative to the sample. Prior studies indicate that a clinical composite or battery based on clinical ranges is more informative (Sibille et al., 2017b; Ahrens et al., 2016). Incorporating clinically derived values would improve clinical applicability. Second, some participants moved multiple times or were living in different shelters over the duration of the study. Therefore, the social index, SVI, may not be a sensitive marker in those individuals compared to those who have lived in the same area for many years. Third, the chronic pain stage measure is specific to knee pain, limiting the interpretation of an individual's overall chronic pain severity. Fourth, the NHB and NHW participants in the study differed on numerous socioenvironmental factors thus ethnic/race differences should not be interpreted.

Regarding future directions, exploring allostatic load across specific brain structures might not be optimal. Machine learning methods are generating whole brain measures identified as brain age which reflect an individual's neurobiological status (Kaufmann et al., 2019; Bashyam et al., 2020). Brain age may be a more informative brain measure of allostatic load. Second, the indication that a clinical composite measure aligns with patterns of pain-related brain structure findings warrants further investigation in the development of a tool that can be used in clinical practice for assessment and monitoring of treatment progress. Third, the benefit of an allostatic load measure, based on an array of studies, is that it reflects the health status of the whole person experience (Sibille et al., 2016, 2017b). In addition to illuminating differences in chronic pain stage and sociodemographic factors, measures of allostatic load also differ by resilience factors (Tanner et al., 2021b, 2021c; Johnson et al., 2019; Mickle et al., 2022; Holmes et al., 2023). *It is difficult to capture and quantify through questionnaires and interviews the summation of information that is provided in measures of allostatic load.* Our findings demonstrate the importance of considering the health status of an individual's "whole person" experiences helping to explain the high variability observed in pain, function, and treatment response in individuals with chronic pain. A composite of clinical biomarker measures that are frequently captured within medical settings, could help identify those individuals with chronic pain at greater risk for worse health outcomes.

5. Conclusions

Measures of allostatic load reflect the physiological and neurobiological functional balance of the "whole person" experience. Persistent and prolonged activation of the body's stress systems without adequate recovery and buffers contributes toward higher allostatic load resulting in deleterious functional changes in the body and structural changes in the brain. We show measures of allostatic load, a clinical composite and pain-related brain structures, were associated with pain, function, and socioenvironmental measures with consistent patterns across measures. Importantly, findings indicate that differences in pain-related outcomes include a combination of pain experiences and socioenvironmental factors. Additionally, although brain structural differences are shown in individuals with chronic pain, functional brain MRIs are not yet applicable in clinical care. Our findings suggest that a clinical composite measure of allostatic load may (1) help identify individuals with chronic pain who have biological vulnerabilities increasing the risk for poor health outcomes and (2) serve as a clinical tool to assess whole person health and monitor response to clinical interventions.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the NIH/NIA Grants R01AG054370 (KTS) & R01AG054370-05S1 (JJT, KTS); R37AG033906 (RBF), UF CTSA Grant UL1TR001427, UL1TR000064, UAB CTSA Grant UL1TR001417 and UAB's Human Physiology Core which is supported by the UAB Diabetes Research Center (P30DK079626) and the UAB Center for Clinical and Translational Science (U54TR002731). A portion of this work was also performed in the McKnight Brain Institute at the National High Magnetic Field Laboratory's Advanced Magnetic Resonance Imaging and Spectroscopy (AMRIS) Facility, which is supported by National Science Foundation Cooperative Agreement No. DMR-1644779 and the State of Florida. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Declaration of competing interest

The authors declare the following receipt of the following financial support for the research, authorship, and/or publication of this article which may be considered as potential competing interests:

Data availability

Data will be made available on request.

Acknowledgements

The authors would like to thank the UPLOAD-2 participants, research teams, and the Clinical and Translational Science Institute nursing staff and processing labs at the University of Florida and the University of Alabama at Birmingham. We are grateful for the support, guidance, and mentorship provided by Dr. Bruce McEwen which greatly informed the work presented. We also thank Brittany Addison for her keen eye assisting with the final review of the manuscript.

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