Employing Allostasis to Further Transdisciplinary Research

Lorelei Walker

A thesis submitted in partial fulfillment of the requirement for the degree of
Master of Public Health

University of Washington
2012

Committee:
Helene Starks
Stephanie M. Fullerton

Program Authorized to Offer Degree
Public Health - Genetics

University of Washington

Abstract

Employing Allostasis to Further Transdisciplinary Research

Lorelei Walker

Chair of Supervisory Committee:

Helene Starks

Institute for Public Health Genetics (IPHG)

The intersection of biological and social science research is illuminating the causal relationships between societal stressors and chronic disease. The intersection of external pressures and internal responses provides a research opportunity for transdisciplinary investigation into complex research questions aimed at employing the allostatic model of stress exposure and risk for chronic disease. To build the intellectual foundation required for transdisciplinary investigation, one that requires interdisciplinary investigators to ask collective questions) I examined selected articles from the biological sciences that explain the detailed stages of allostasis (load, high load, overload, and dysregulation) and then analyzed how those stages were measured in a selection of social science research articles that use biomarkers as measure of allostatic states. Though the social science literature employed measurement of population allostatic load in a comprehensive manner, there is evidence of misapplications of concepts of the allostatic model as proposed by the biological literature, particularly with respect to the role of the brain in the allostatic system and the distinction between high load and overload. Conversely, the social science literature contributes to a better understanding of the relationship between socio-economic forces and chronic stress by identifying concepts such as double jeopardy (e.g. being a female minority) and riskscapes (e.g. living in poverty and near a pollution source). Both bodies of literature identified characteristics of individuals in a population that may change resilience to psychosocial stress that,

taken together, provide a more comprehensive approach to understanding allostasis as a mechanism for embodied stress responses and how these contribute to chronic disease. Future research investigating population-specific stress pathways in the pursuit of decreasing chronic health conditions will require interdisciplinary researchers from both the social science and biological sciences with clear research aims and a common language.

Acknowledgements

I wish to express appreciation to my cohort for your intense conversations that helped define my interest and strengthen my arguments, especially Kate West, Emmi Bane, and Lizzie Dorfman, who painstakingly reviewed this manuscript.

Thank you to Paula Nurius for providing a productive space for multidisciplinary students to explore transdisciplinary inquiry in social science research.

Thank you to Nancy Press and members of the Interdisciplinary Center for Epigenetics, Science, and Society for including me and allowing me to participate in engaging and informative interdisciplinary discussions. Thank you particularly to Joel Nigg for his insight into the integration of the social science and biological disciplines for epigenetic application and his identification of problematic areas involved in communication and finding common ground for defining allostasis across disciplines.

Thank you to IPHG faculty for creating a place where these concepts are presented, explored, evaluated, and debated.

Thank you to Wylie Burke and members of the Center for Genomics and Healthcare Equality. Your collective knowledge, support, and commitment to training have provided a sandbox for me to work through many facets of this document.

Thank you to my mentors, Helene Starks and Malia Fullerton. You have both been instrumental in my academic development over the last two-and-a-half years. Your pacing, targeted questioning, active listening, and flexibility have allowed me to follow a passion housed as a node in an entire network of disciplines; on what feels like the edge of a wave. You are the reason this was possible.

Thank you to Nancy and David Rehm. You shaped my academic future and opened the world of ethics and philosophy to me. Your knowledge and passion for teaching provided me the tools to navigate the learning process and expand my mind to include an appreciation for ethics and philosophy.

Thank you to my family and friends for being with me through this growth process. Through ups and downs, you were there. Some of you have played dual roles as both intellectual colleagues and emotional support, and for that I am forever changed. Thank you most to my husband, Aaron.

Dedication

I wish to dedicate this work to the facilitation of the larger community of interdisciplinary research on stress-induced mental illness.

Contents

List of Figures

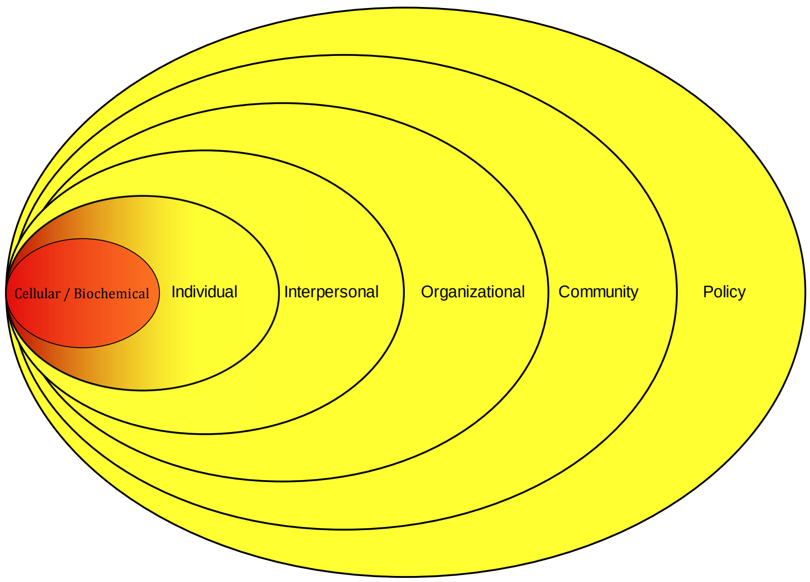
List of Tables

Introduction and Background

Stress, particularly chronic stress related to long-term exposures, is associated with a variety of chronic health conditions (Paradies, 2006). Recent advances in brain-body imaging have provided consistent evidence that negative emotional states, such as those caused by chronic stress, have deleterious effects on physical health (Lane & Wager, 2009). Both the sources and frequency of stressors are not distributed equally in society with heavier burdens borne by those with less advantage, compounding disparities in health (Aneshensel, 2009).

The study of stress and its outcomes requires accurate measurement of stress and related risk prediction at multiple levels and a complex understanding of multiple inputs from external stimuli. The Social Ecological Model (SEM, Figure 1, next page) was conceptualized in the 1970's to describe the layered factors that influence health and well-being, given varying scales at which a person is situated in his or her environment – from the biological/cellular level on a micro scale to policy issues on a macro scale (McLaren & Hawe, 2005). The biological and social sciences have historically pursued the inquiry of stress-induced illness in separate spheres, identifying and validating models using discipline-specific methods. Now, however, research requires more integrated approaches incorporating researchers across all levels of the SEM framework, to leverage the science and to facilitate interventions that promote health and well-being (Life Stress, 2012). More recently, interdisciplinary research teams representing multiple disciplines, have applied the SEM as an organizational framework to contextualize environmental stressors as a cause for poor health outcomes (Gehlert et al., 2008; Gehlert et al., 2010). The SEM allows stress researchers examining specific levels of external exposure, or inter-level interaction, to position their work in the larger social ecological context. In addition to contextualizing exposures, the SEM framework facilitates the identification and categorization of stress-related risk and resilience factors occurring at the societal, communal, interpersonal, individual, and now biological levels.

Figure 1: Social Ecological Model



The cellular / biochemical level has been added to this minimalist depiction of the Social Ecological Model.

By overlaying stress research domains onto the SEM, Figure 1 depicts a reductionist representation of research domains of the biological sciences (in red) and the social sciences (in yellow). The biological domain focuses on examination of human and animal physiologic and cellular stress-mechanisms. The biological sciences in this sense broadly represent many specialized disciplines such as Neuroendocrinology, Cell Biology, and Psychiatric Genetics. These disciplines have typically employed animal models to study stress at the cellular and individual levels by manipulating external stimuli, limiting inter-individual variation, and directly measuring biochemical levels or brain function. The social sciences, representing a multitude of disciplines including Epidemiology, Sociology, and Social Work have concentrated their effort on understanding interactions at the inter-individual, family, community and society levels of the SEM. In seeking to identify and understand the stress phenomena, the social science field has detailed highly complex models of human socio-ecologic interactions as causal agents of chronic disease outcomes such as cardiovascular disease, atherosclerosis, diabetes, metabolic syndrome, arthritis, and chronic fatigue syndrome (Juster, McEwen, & Lupien, 2010). .

A complete understanding of the stress response, its underlying mechanisms, and its physical outcomes, is required for planning effective interventions in different populations and across the life course (Editorial, 2012). The social sciences have theorized the relationships between stress, social position and health outcomes, and proposed interventions across all levels of the SEM (Thoits, 2011). However, measuring the relationship between stressors and health outcomes is difficult because stress responses are both immediate and long-term, so it is not always clear which exposure (short- or long-term) is being measured at a given point in time. Thus, there is a need for accessible biochemical measures and biomarkers of long-term stress exposure to validate interventions of well-established stress models (Stewart, 2006).

The allostatic model, developed by researchers form chemistry, cell biology, zoology and neuroscience, articulates the mechanisms by which human physiologic responses are activated under stressful experiences. The allostatic model is conceptually direct but nuanced in its application. Though these nuances are found in different phases of the model, they have direct application to the measurement and interpretation of stress in human populations, and misapplication of this model could lead to poor science and misguided interventions. However, a more expansive application of the allostatic model that integrates concepts from both the biological and social sciences would be a useful tool for understanding and intervening on the causes of chronic disease, and one that could help research teams to ask common questions, use a common language, and devise common interpretation strategies to correctly integrate, measure, and evaluate the diverse and complex pathway from external stress to chronic illness.

The search for biomarkers by social epidemiologists and biostatisticians resulted in a set of tools to measure stress-induced changes within and across populations. Seeman et al. created a list of 10 biomarkers to describe internal levels of physiologic activity across a range of body systems that are associated with disease risk (Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). The biomarkers are grouped to represent parameters of different component systems describing cardiovascular activity, metabolic activity, HPA axis activity, and immune function. Social scientists who use these tools as part of intervention studies use concepts from the allostatic model to help explain causal mechanisms. What is not clear, however, is how accurately the social sciences are translating the nuanced concepts of the allostatic model in their application of biomarkers. This matters because of potential confounding of the results if the measures of stress do not correspond to the biological pathways of the allostatic model. Mismeasurement attenuates the estimation of the effect of interventions and may lead to under- or over-estimating the relationship between stress and particular health outcomes.

An example can highlight this issue: in studying a population of mothers with chronically ill children to assess the biologic damage from chronic stress, interpretation of biochemical marker levels relies on knowledge of an individual's resilience factors. If a mother of a chronically ill child has access to financial and social support it will impact how she approaches new challenges. If her partner earns an income adequate to provide food and shelter, she will have a better mental response to new challenges posed by her child's illness. Instead of worrying about the stability of her living environment, she can tackle managing doctors' appointments and intermittent hospital visits. If she has family support to assist in caretaking duties, she will have more time to recuperate from the chronic demands of caring for her ill child. Alternatively, a mother who is single and working two jobs to support her child's needs, daycare costs, food, and housing acquisition, encounters more stressful experiences. These environmental demands reduce her access to periods of rest and catabolic repair, and, as outlined below, cause a higher biochemical load on the body. However, there are at least two ways to interpret the biochemical mediators circulating in the body: (1) The overly stressed mother in this example could display high levels of these mediators reflecting a high physiologic burden, or load, she is experiencing. Or (2) she could display low levels indicative of system-wide dysregulation, a harbinger of disease. In this case, low levels could be interpreted not as dysregulation but as normal, and any attempt to causally-relate poor health outcomes with external societal pressures would not be reflected.

The objective of my thesis project was to investigate how social scientists are applying concepts from the allostatic model to guide their use of biomarkers as measures of stress. To this end, I focused on understanding the allostatic concept as described by multiple researchers in the biologic domain through their discourse in selected articles published during 2009-2012. Then, I assessed how several research articles drawn from the social science literature employed concepts from the allostatic model to measure the stress-response mechanism across populations experiencing different exposures along the SEM pathway. My goal was to identify areas of discourse that are relevant to the integration of these two domains looking specifically for confusion or absence in the application of the allostatic model and its measurement. To center the reader in this work, I first explain the broad concept of allostasis as background to understanding my analysis.

The Broad Concept of Allostasis

The allostatic concept was coined in 1988 by Sterling and Eyer (Sterling & Eyer, 1988) as a distinct process of individual adaptation to challenging perturbations from the environment. It is generally known in fields undertaking stress research that an individual stress response occurs when an individual perceives an inability to meet the demands of an external threat (i.e. predator attack, food shortages, or bullying). Life requires body conditions to remain within strict homeostatic limits (i.e. pH levels, body temperature, oxygen levels). When confronted with a stressor, the body must alter its internal condition to respond to environmental demands while remaining within homeostatic limits. The individual being challenged interprets the threat and responds through a series of biochemically-mediated physiologic responses involving the brain, sympathetic nervous system (SNS), hypothalamic-pituitary-adrenal (HPA) axis, metabolism, cardiovascular system and immune system. Collectively, adaptation to environmental stressors requires non-linear multisystem regulation for internal conditions to match external demands. This process is known as allostatic accommodation.

Without intervening periods of catabolic repair, the biochemical mediators active in an allostatic response become destructive. The internal wear and tear caused by excess exposure is a load the body must function under – termed allostatic load. For example, increased blood pressure over extended periods of time is a load to which the arterial system must accommodate during daily activities and in response to future stressors. If this load remains through time, the cardiovascular system will begin to make physiologic changes to accommodate the sustained increase in blood pressure, such as thickening the arterial wall. If stress remains chronic, these secondary changes occur in different body systems and dysregulation ensues. At the transition into dysregulation, the body is in a state of allostatic overload. These differences are described further as part of my analysis.

In a single event of allostatic accommodation, the core emotional regions of the brain perceive and interpret an environmental change. These regions include areas of the hippocampus, amygdala, and prefrontal cortex. The brain then dictates the required physiologic response by communicating with the hypothalamic-pituitary-adrenal axis, sympathetic nervous system, metabolism, cardiovascular and immune system, through specific biochemical mediators. Once the threat has resolved, feedback systems recognize that high levels of mediators are no longer required and terminate the stress response. In allostatic accommodation, biochemical mediators are adaptive, properly deployed, and properly terminated.

An intense example of allostatic accommodation is a single episode of physical assault. Upon capture by an aggressor, a victim is jolted by the realization of immediate physical threat. The brain releases necessary biochemical mediators to trigger the HPA axis to respond. The flood of adrenaline and cortisol increases the heart rate and blood pressure, sharpens the senses, triggers sweating, mobilizes glucose, and imprints a strong memory of fear on the brain (Hughes, 2012). In short bursts, this response is critical to empowering the assaulted individual to fight and escape. It also leaves a salient memory informing behavior in future novel environments. In a well-functioning allostatic response, once the threat has passed, the same biochemical mediators are reduced and the individual returns to internal stability. The biochemical mediators have beneficial short term effects allowing for rapid physiologic response, however as we will see in the next example, chronic exposure to activated levels leads to dysregulation of physiologic systems.

In modern environments, the stress response can be triggered to a lesser extent by smaller, daily physical and social threats. In educational settings with too many children and not enough resources, students can become restless and excited through the day, increasing classroom noise levels and interactions. Increased classroom disorder may act on the teacher's blood pressure and heart rate, increasing both. Through time, if the teacher's biochemical mediators remain high, secondary demands are placed on the cardiovascular system (allostatic load). The arterial walls must thicken to withstand the daily pressure spike and continued chronic exposure leads to increased risk for atherosclerosis and cardiovascular disease (allostatic overload). The outcome is cardiovascular dysregulation, increasing the teacher's risk of chronic disease and perhaps requiring antihypertensive drugs to reduce risk of cardiovascular-related death. Without resources providing resilience, low levels of repeated stress elicit ongoing allostatic accommodation increasing background levels of biochemical mediators, and thus, allostatic load.

The allostatic system, as described by the biological sciences, functions differently depending on the strength, length, and type of stressor. Individuals responding successfully to moderate stressors should exhibit healthy ranges of biochemical mediators. Individuals experiencing stress increasing in frequency and duration will exhibit high levels of mediators (a high allostatic load), and individuals in overload will exhibit mediator levels indicative of a dysregulated system.

Though many of the general concepts of allostasis have been incorporated into recent social science research, what has not translated well are the nuanced variables that are required for measuring and interpreting allostatic measurements. First, there is diverse individual variation in resilience to stress, both in coping strategies employed during the interpretation of stress in the brain and in the body's capacity to withstand high load. Second, confusion in distinguishing between biochemical mediator levels indicative of normal states versus dysregulation leads to incorrect conclusions. Because of the potential for misinterpretation of allostatic measurements, the details regarding the application of the allostatic concept become important in planning study designs and during analysis.

The biological sciences are pushing forward in researching the complexities of the internal pathways activated by stress that lead to disease. The field is both refining details of what constitutes load, overload, and dysregulation and the precision with which the physiologic response is measured. Insights from neuroimaging techniques are elucidating the brain-body relationship to further understand the nuanced differences associated with clinical outcomes (Lane & Wager, 2009). It is unclear, however, how the social sciences will integrate this knowledge into their employment of the allostatic system. The goals of this study are to reduce confusion in the application and interpretation of the allostatic model and to assist future interdisciplinary efforts in identifying how insights about and measurements of allostasis align across disciplines. As allostatic measurements provide insights into the mechanisms, treatment, and epidemiology of stress-related disorders, accurate application and interpretation is crucial to understanding the etiology of chronic disease.

Methods

To understand the translation of the allostatic concept from the biological sciences to the social sciences, I conducted a two-phase discourse analysis of published articles from the biological and social sciences. I addressed the following research questions:

1a: How is the concept of allostasis described by the biological sciences?

1b: What are the variables involved in the measurement of allostatic load as described in the identified biological literature?

2a: How has the concept and measurement of allostasis been translated into the social science literature?

2b: In what ways does the different understanding (and measurement) of allostasis in the social science literature suggest limitations in the employment of the allostatic model?

Discourse Analysis

Discourse studies, or discourse analysis, are a group of approaches to analyze written, spoken, or sign language, or other semiotic events. The art of discourse is an attempt to inform, integrate and apply knowledge through language. Tracing back to Aristotle, the word discourse is loosely defined as logic and politics (Rorty, 1996). Ultimately, discourse analysis is about conveying a specific meaning of identity and activity with a purpose (Gee, 2011). It is the goal of identifying how language conveys various meanings that makes discourse analysis the appropriate method to accomplish my goal. In the context of my analysis, it is the study of how a concept from one discipline (biological sciences) is taken up and used by another (social sciences). Discourse analysis also allows me to identify which themes are present and/or absent in both sets of literature. A nuanced understanding of the allostatic framework provided by the biological literature is required to understand the overlap and divergence of the two bodies of literature. Through elucidating each article's description and employment of the allostatic concept I will be able to understand how the allostatic concept is described and employed in the biological literature and how it is employed by the social sciences literature.

Identification of Source Articles

To identify a set of articles to analyze, I began by conversing with mentors from the biological and social sciences to identify the concepts of interest around the allostatic model and to identify key terms, journals, and authors that capture the biological literature on allostasis. I then conducted a search on PubMed and Google Scholar (similar to Web of Science) for 2009-2012 articles from the biological, psychiatric, and psychological literature using these search terms:

- Allostatic load,
- Allostatic load AND
  - Psychiatry,
  - Psychology,
  - Epidemiology,
  - Social Work
- Allostatic load AND
  - Stress,
  - SES,
  - Disparities,
  - Clinical

Once I identified an initial set of articles relevant to both the biologic and social science literature, I sorted the articles by number of citations, departments of authors (as a proxy for their disciplines), and journal of publication (as a proxy for their audience). From this, I was able to create two subgroups of documents and have depicted them by how I used them in each phase of analysis.

<u>Phase I</u>: Central to the allostatic concept is the role of the core emotional regions of the brain in maintaining homeostasis, thus, the articles identified to represent the biological literature focus on the brain through neurobiology, psychiatry, psychology, and human development. This group of articles was heavily influenced by Bruce McEwen's work, confirmed through discussions with key informants, as to his influence in the formulation of the allostatic concept. One of the articles, "What is in a name?

Integrating homeostasis, allostasis and stress" (B2) explicitly described the divergent areas of allostasis from homeostasis and was cited over 40 times at the inception of this study. The journals of publication spoke to the audience that sourced this work: the Annual Review Medicine, Hormones & Behavior, Psychological Review from the American Psychological Association, and Trends in Cognitive Science. The four documents chosen for analysis represented different facets of the allostatic concept:

- B1 described allostasis in terms of stress-induced brain plasticity,
- B2 described allostasis in terms of how it differs from homeostasis,
- B3 described allostasis in terms of the stress process and utility to the social sciences,
- B4 described allostasis in terms of resistance, resilience, and vulnerability

Phase II: The second group of articles was chosen to understand how the social science literature employed the allostatic model and its measurement. The disciplines represented in this group of articles included Community Health Prevention, Health Sciences, Demographic Research, Epidemiology, Social Epidemiology, Allied Health Sciences, Anthropology, Sociology, Psychology, Public Health Clinical Medicine, and Stress Research. Journals of publication included Health & Place, Journal of Epidemiology Community Health, Social Science & Medicine, Psychophysiology, Advances in Psychosomatic Medicine, and Annals of Behavior Medicine.

In total, 6 articles were chosen that represent multiple sources of allostatic activation in specific populations:

- SS5 explored the relationship between environmental riskscapes, gender, and double jeopardy using the allostatic model to assess risk for chronic disease outcomes,
- SS6 was a literature review exploring the relationship between socio-economic status, cortisol measures, and the allostatic load model,
- SS7 explored the relationship between social disparities and periodontal disease outcomes using the allostatic model,
- SS8 explored the relationship between minority status and chronic health conditions using the allostatic model,
- SS9 explored the relationship between socio-economic status, age, social relationships, and health through the allostatic model,

- SS10 explored the relationship between social and material adversity and health outcomes using the allostatic model

Table 1 summarizes the results from the literature searches. Table 2 (next page) provides details about the ten articles (B1-SS10) used in the discourse analysis.

Table 1 Keyword Search

	Biological Literature				**Social Sciences Literature**					
	B1	B2	B3	B4	SS5	SS6	SS7	SS8	SS9	SS10
Publication year	2010	2009	2010	2011	2011	2009	2011	2010	2011	2011
Google Citations	48	44	51	1	1	58	7	14	3	2
Allostasis	X	X	X	X						
+ Psychiatry	X		X							
+ Psychology	X		X		X					
+ Epidemiology					X	X	X	X		
+ Reviews	X	X	X							
+ Social Work		X	X							X
Allostatic Load	X	X	X				X	X		
+ Stressors			X				X		X	
+ Dev. Psychology			X							
+ Community	X		X							
+ Disparities					X		X	X		

Table 2 Article Descriptions

	Article Title	Year	Journal	Authors	Aim/Focus
B1	Stress – and Allostasis – Induced Brain Plasticity	2010	Annual Review Medicine	Bruce McEwen, Peter Gianaros	Provide evidence supporting the argument that the brain is the central organ of stress resilience & vulnerability
B2	What is in a name? Integrating homeostasis, allostasis and stress	2009	Hormones & Behavior	Bruce McEwen, John Wingfield	Define the concept of allostasis and how it differs from homeostasis
B3	Allostasis and the Human Brain: Integrating Models of Stress From the Social and Life Sciences	2010	Psychological Review; American Psychiologic Assoc	Barbara Ganzel, Pamela Morris, Elaine Wethington	Examine the relationship between the stress process and the allostatic concept
B4	Psychobiological allostasis: resistance, resilience and vulnerability	2011	Trends in Cognitive Science; Cell Press	Ilia Karatsoreos, Bruce McEwen	Explore relationships between resilience and plasticity to stress at the cellular and individual level
SS5	Allostatic load in an environmental riskscape: The role of stressors and gender	2011	Health & Place	Christine Mair, Malcolm Cutchin, M. Kristen Peek	Test associations between stress and higher allostatic load (AL: composite and component score); test the predictive power of AL by gender and AL outcomes; test the different AL outcomes by gender of 1072 residents in Texas City, TX
SS6	Socio-economic status, cortisol and allostatic load: A review of the literature	2009	International Journal of Epidemiology	Jennifer Dowd, Amanda Simanek, Allison Aiello	Review of SES literature for SES association with blunted cortisol secretion and SES association with increased allostatic load indexes. Allostatic load association employs both composite and component allostatic load scores. Only animal studies in community populations were reviewed across 7 articles
SS7	Social disparities in periodontitis among U.S. adults: The effects of Allostatic Load	2011	Journal of Epidemiology and Community Health	Luisa Borrell, Natalie Crawford	Tests the association between allostatic load and periodontitis in an NHANES study population of 3092 individuals and if the association differs by age, race/ethnicity, education, and income
SS8	Allostatic load is associated with chronic conditions in the Boston Puerto Rican Health Study	2010	Social Science & Medicine	Josiemer Mattei, Serkalem Demissie, Luis Falcon, Jose Ordovas, Katherine Tucker	To add the Puerto Rican perspective to the ethic health disparity research by testing the association of being Puerto Rican in 1116 individuals aged between 45-75 years with a higher allostatic load and the association between allostatic load and increased chronic disease
SS9	Mediators of the relationship between socioeconomic status and allostatic load in the Chicago health, Aging, and Social Relations Study (CHASRS)	2011	Psychophysiology	Louise Hawkley, Leah Lavelle, Gary Berntson, John Cacioppo	Tests the pathways for SES to affect allostatic load in 200 participants aged 51-69 year old adults of Black, White, and Hispanic ethnic status through mediators of stress, personality & psychosocial variables, coping styles, social networks, and health behaviors associated with SES and allostatic load
SS10	Social and Material Adversity from Adolescence to adulthood and Allostatic Load in middle-aged women and men: results from the Northern Swedish Cohort	2011	Annals of Behavioral Medicine	Per Gustafsson, Tores Theorell, Anne Hammarstrom	To test the life course origins of AL and accumulated risk for increased allostatic load over the life course from exposure to social and material adversities measured at age 16, 18, 21, 30, and 43 in a prospective study of 822 individuals

Coding of Allostasis Discourse

Phase I

My goal was to define and understand the concept of allostasis and the specifics of this model and its measurement as discussed in the biological literature. I first read all four articles I identified as part of the biological literature (B1 – B4). I was looking for terms and concepts that surfaced both from prior discussions I conducted with mentors and during interdisciplinary seminars focused on the embodiment of stress. This process is known as initial coding (Birks & Mills, 2011). I conducted this initial coding in Atlas.ti version 6, using the codebook described in Table 3. Italicized words were found directly in the literature and prompted assignment of the corresponding code. Otherwise, a general description of concepts that prompted assignment of the code is provided.

Table 3 Codebook groupings for theme development

Code	Definition
Adaptation	*adapt, adaptation, adjust, accommodation*
Allostasis	allostasis, allostatic model
Allostasis: Mediators/ Organs/Systems	Reference to the biochemical mediators or the component organ systems involved in allostatic response
Allostatic Load/Overload	*load, overload, wear and tear, dysregulation, accumulation of damage*
Anticipation	*anticipation, anticipatory changes/events, perception*
Disease/Health/Outcome	Reference to a disease or health outcome was linked to an allostatic response
Future Research	Reference to next steps or future research directions were discussed
Homeostasis	*homeostasis, homeostatic concept*
Individual/Genetic Differences	Reference to a variable associated with individual difference was discussed
Intervention/Treatment	Reference to an intervention, point of intervention, or treatment were discussed
Life Course	Reference to life course or a specific developmental stage was mentioned (post-menopausal, early life)
Lifestyle Behaviors	Reference to any behaviors individuals have a direct ability to modify (smoking, exercise, drinking, etc)
Multidisciplinary	Reference to different disciplines were discussed or a call for integrated research was made
Resilience/Response Feedback/Regulations	Reference to resilience in responding to stress or wear and tear was mentioned or the regulation of the allostatic system through feedback mechanisms was discussed
SES	*socioeconomic status, social standing, income, education*
Sleep	Reference to circadian cycles, sleep hygiene/health, or sleep disruption
Social Environment	*social*
Stress/Environment/Challenge	Reference to stress, stressors, environmental stress, social or physical challenges
Stress: Coping	Reference to coping mechanisms used to combat stress
Transgenerational	Reference to effects on offspring from stressor exposure to parent

As discourse analysis is an iterative process, the next step was to compare codes using both inductive and deductive reasoning to relate the codes in Table 3 across all four documents from the biological sciences. From analysis, conceived as a network, four core themes surfaced in the discourse of the allostatic process that were common to all four articles. Within these themes, subthemes were clarified to varying degrees based on whichever facet of the allostatic model was the focus of the article. These themes and subthemes are listed below.

Themes and subthemes from the biological literature (articles B1-B4)

1. Allostatic Response
    a. Allostatic Accommodation: Central and Peripheral Response
    b. Allostatic Load: Load Accrual, High Load, and Dysregulation
2. External Threats
    a. Social Threats
    b. Physical Stimuli
3. Individual Capacity
    a. Lifestyle & Behaviors
    b. Genetic Predisposition
    c. Brain Condition & Social Behaviors
    d. Body Condition
4. Allostatic Load Biochemical Mediators and Component Physiologic Systems

As the themes and subthemes were derived from the language of each code removed from its source document, I then re-read B1 – B4 asking the questions below to confirm that the themes and subthemes that had surfaced were informative in answering the questions I originally set out to answer.

1. How is the allostatic concept defined and employed in the biological literature?
2. How are the stress descriptors organized and employed in the biological literature?
3. How are the physiological mediators of allostatic load categorized and employed in the biological literature?
4. What are the findings relevant to allostatic load?

Phase II

After the biological literature themes and subthemes had been identified and verified using the methodology above, I conducted initial coding of all six social science documents (SS5 – SS10) for only those themes and subthemes; i.e., I did not attempt to identify additional novel themes in this analysis. I conducted this analysis, again using Atlas.ti, to pull the separate themes and subthemes for analysis for comparison across the six articles, and then asked the same questions listed above of each article. Once areas of consistency, divergence, and enhancement were identified, I focused on those subthemes to further explore in what ways the translation of the allostatic concept was confused or problematic, signifying potential barriers to use of the allostatic framework as conceptualized by the biological literature, i.e., what was lost in translation.

Two themes in the social science literature built upon the biological discourse by delineating specifics relevant to human populations; the themes of External Threat and Individual Capacity. These themes are discussed in the Phase II section of the Results below.

Results

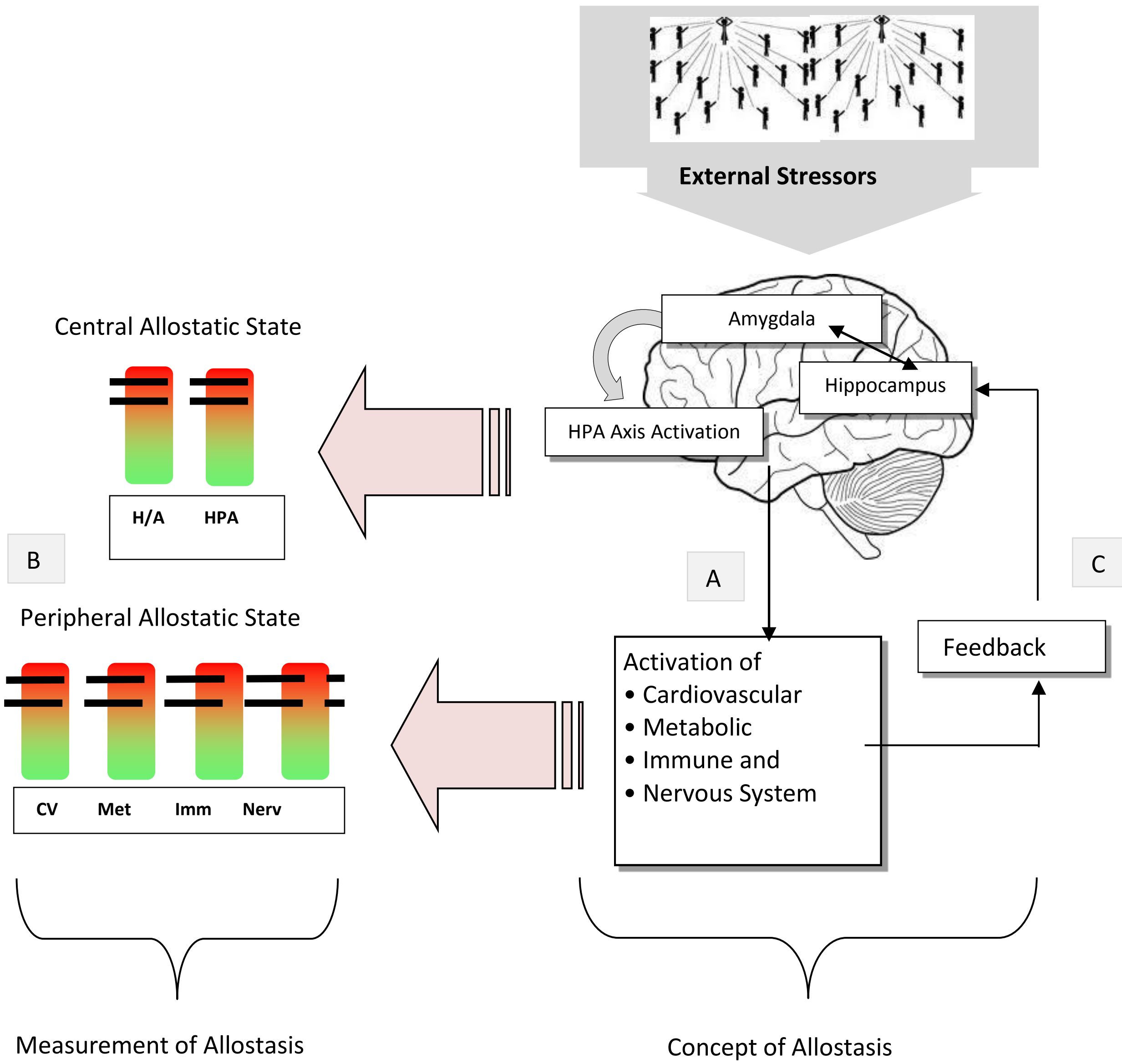
Phase I: Themes in the Biological Discourse

A nuanced understanding of the allostatic concept as described in the biological sciences is required to assess the allostatic discourse in the social sciences. Articles B1-B4 provided different perspectives of the allostatic concept. The results of the Phase I analyses discussed in this section are a synthesis of these perspectives. I focused on delineating the important distinctions of the allostatic response. The distinctions I found important in each theme are listed below and discussed in the same order in this section.

1. Allostatic response
    a. Central allostatic accommodation versus peripheral allostatic accommodation
    b. Allostatic load: load accrual, high load, and dysregulation
2. External stressors
    a. Social threats
    b. Physical stimuli
3. Individual capacity to handle increasing allostatic load
    a. Lifestyle & behaviors
    b. Genetic predisposition
    c. Brain condition & social behaviors
    d. Body condition
4. The biochemical mediators of allostatic response and their component physiologic systems

To illustrate my synthesis of the allostatic concept, I present Figures 2 and 3 to represent an integrated model resulting from the Phase I discourse analysis. Figure 2 (next page) describes the network of variables and measurements involved in the allostatic response. When physical and social threats require appraisal, the brain must assess the individual's abilities and resources in context of the abilities and resources required to overcome the stressor. This interpretation occurs in the core emotional regions (amygdala, hippocampus, prefrontal cortex (PFC)), identifying qualities of the stressor, such as intensity and context, shaping the extent of the allostatic response. In the amygdala, the "rapid assignment of emotional salience to environmental events" occurs supporting the "coordination of stress-evoked changes in behavior and peripheral physiological reactivity" (B1, pg. 435).

Figure 2: Allostatic concept overview surfaced from Phase I analysis.



The stress response starts in the brain with an appraisal of individual abilities and resources. In healthy individuals, the core emotional regions of the brain direct level of biochemically mediate response required by the body (a). The response in the brain and body can be measured using biomarkers for the central accommodation in the brain and peripheral accommodation occurring in the body (b). The biochemical mediators altered in this response are part of a feedback loop to inform the brain for future stressors (c). The right side of this figure represents the concept of allostasis; the left side represent how this process is measured.

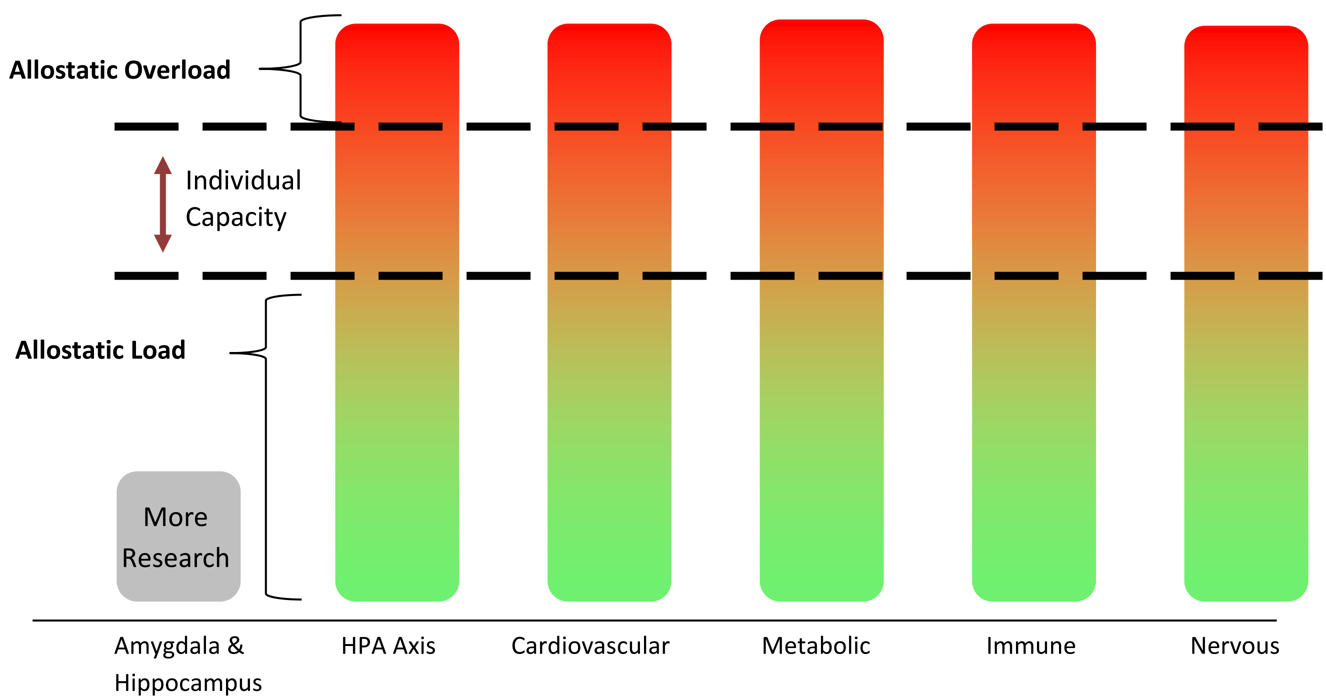
The appraisal system in the brain signals the body to accommodate the stressor. Because stressors are first appraised and responded to by the brain, the brain is the site of central accommodation. This central accommodation triggers a secondary response known as a peripheral response. Communication between central accommodation in the brain and peripheral accommodation in the body includes activation of the hypothalamic-pituitary-adrenal (HPA) axis to signal sympathetic nervous system (SNS) activation of the metabolism, cardiovascular system, and immune system. This is depicted by box A in Figure 2.

The array of biochemical mediators activated in central and peripheral responses are a biomarker of the stress response. In Figure 2 box B, this biomarker array is depicted to reflect the systems it is intended to measure. The levels of biochemical mediators circulating in the bloodstream inform feedback systems located in the peripheral system and the central system as depicted by box C. This feedback loop alters structures involved in central accommodation, such as hippocampal and amygdala function, to inform appraisal of future stressors and the stress response.

Figure 3 focuses on the biochemical mediators active in an allostatic response and depicts how allostatic activation can be adaptive or destructive. During a stressful event, biochemical mediators are up-regulated in each component system to mobilize energy stores, increase heart rate, and prepare for a fight-or-flight response. In short bursts, or with ample recovery time, the physiologic biochemical exposure is healthy. This is represented by the green coloration in Figure 3 and is the same response one experiences when engaged in team physical activity, such as playing soccer.

When levels of stress-related biochemical mediators are chronically high due to repeated activation, they damage component systems, such as when chronic high blood pressure leads to cardiovascular disease. The maladaptive properties of these mediators, when levels are high, are depicted by the color gradient changing from green to red. When these mediator levels do not subside, causing wear and tear, the allostatic system becomes overloaded and the individual is at an increased risk for dysregulation. As discussed below, the threshold of when stress-activated biochemical up-regulation causes long-term damage is variable and dependent on an individual's capacity to buffer or accommodate those biochemical mediator levels. This capacity involves behavioral, developmental, and genetic features by conveying resilience or susceptibility to physiologic dysregulation. Though much research has focused on the mediators involved in the peripheral system, it is unclear how the mediators activated in the brain relate to the response and how these mediators should be used as biomarkers of this process. This is represented by the grey bar in Figure 3.

Figure 3: Measuring allostatic load across component systems.



This image depicts the levels of mediators in each system involved in the allostatic response to an environmental challenge. Upon chronic activation, systems are prone to overload causing dysregulation and damage to the body. A person's individual capacity can alter the threshold from load to overload.

Next, I will continue my synthesis of the major themes of Phase I of this analysis bringing attention to the terminology and concepts relevant for Phase II analysis: the allostatic response to a stressor, what constitutes an external stressor, an individual's capacity to engage in the stress process, and the component systems that biomarkers are measuring.

1. **Allostatic Response**

This theme includes an explanation of how allostatic activation can lead to allostatic dysregulation under chronic stress exposure. Within the theme of allostatic response, the subthemes of allostatic accommodation (central and peripheral) and allostatic load (load accrual, high load from repeat exposure, and dysregulation) distinguish the details of the allostatic response location and different allostatic states, as depicted in the biological literature. These differences are critical for interpreting the relevance of specific biochemical mediators.

1a. *Allostatic Accommodation: Central and Peripheral Response*

The term *allostatic accommodation* has been coined to describe the physical adjustments of parameters within a range to respond to external stimuli. Accommodation is the state of being in homeostatic imbalance followed by the process of either bringing the body back into the previous balance, or finding a new balancing point, a process known as *adaptive plasticity*. If the environmental demands are healthy challenges, the accommodation may support resilience and health; however, if the demands are taxing and chronic, the body responds to high biochemical mediators by adjusting component needs. These secondary adjustments become maladaptive, accumulating over time to lead to mental and physical illness.

There are two distinct responses involved in allostatic accommodation outlined in the biological literature: central and peripheral. Threatening stimuli are appraised for their level of challenge before a response is activated. The appraisal and immediate response occurs in the brain and is referred to as the *central allostatic response*. In allostatic accommodation to a stressor, the central response triggers the peripheral component systems to modify their activity. This secondary modification is the *peripheral allostatic response*. The distinction of the mechanisms occurring in the central response and how they activate peripheral responses in component systems was discussed thoroughly in all four articles.

The biological articles (B1-B4) rely on human and animal studies to demonstrate how the brain is at the center of the stress response coordinating, calibrating, and monitoring physiologic systems to cope with external demands. As the body's master controller, the brain is the "primary point of interface between a given stressor in its physical and social context and an individual's physiological and behavioral accommodation to that stressor" (B3, pg. 139). The core emotional regions, the hippocampus and amygdala, are the primary neural regulators executing functions in cognition, emotions, and impulse control. These regions interpret stressors perceived as threatening based on past experiences (McEwen & Gianaros, 2011).

These two areas of the brain communicate directly with other regions of the brain, such as the HPA axis and the prefrontal cortex. The hippocampus has been shown in animal studies to contain feedback receptors for adrenal steroids and major metabolic hormones, making it capable of monitoring the mediator levels to information further regulation. Healthy hippocampal function enables an individual to make decisions on how to deal with new environments, new information, and new challenges: "The processing of emotional stimuli is regulated by neurotransmitters and neurohormones within this [central allostatic] system, which in turn underlies emotional-related behavioral states and physiological response in the systems external to the CNS [central nervous system]" (B3, pg. 139).

Central response occurs in the brain and peripheral response occurs in other body systems that are peripheral, or secondary, in the chain of allostatic activation. The activation of these component systems is termed *peripheral response* and involves the different component systems mentioned above. The communication across component systems is non-linear where biochemical mediators exert different and complex effects on each other. This explains why high load can lead to different disease outcomes as it is dependent on the communication that occurs within and between systems (Karatsoreos & McEwen, 2011a) .

> *[In humans] individual differences in amygdala reactivity to emotional salience co-vary with physiologic parameters of cardiovascular disease (via basal levels autonomic cardiac controls), changes in blood pressure, and levels of diurnal cortisol. Increasing reactivity to social threatening cues had higher preclinical atherosclerosis while lower preclinical individuals had higher PFC regulation of amygdala.* (B1, pg. 437)

As I describe below, chronic allostatic activation of the central response can lead to dysregulation in the brain expressed as behavioral changes in anxiety and mood disorders. Concurrently, chronic activation of biochemical mediators active in the peripheral response lead to hypertension and inflammation. How much wear and tear a brain and body can accommodate in the central and peripheral system is dependent on individual characteristics such as genetic predisposition, social behaviors, and lifestyle choices.

1b. *Allostatic Load: Load Accrual, High Load, and Dysregulation*

Load Accrual. The allostatic system may be challenged daily through multiple physical and social experiences. Each activation of the allostatic system exposes the body to increased levels of biochemical mediators active in the allostatic accommodation. The quantity and chronicity of mediator levels exposes the body to internal damage known as a *load*. An increase in load increases the pressure for component physiologic systems to make changes to tolerate the increased biochemical burden. In healthy situations, load accrual is low and there is sufficient time between challenges to the system to allow for recovery periods.

The concept of low versus high load is depicted in Figure 3 by the level of each bar. Levels are considered low or high in relationship to the dotted line representing the point at which biochemical mediator exposure leads to physiologic damage. The biologic literature collectively describes this process; B2 (p. 110) articulates this concept as follows: “Attacks by predators or dominant individuals trigger a massive catecholamine response followed by glucocorticoids and other mediators of allostasis. Single ephemeral events such as these probably do not contribute significantly to extended allostatic load in the long term.”

High Load. Repeated hits from multiple stressors on the amygdala activate the HPA axis and autonomic nervous system again and again. “A failure to habituate to a repetition of the same stressor results in a persistent elevation of mediators such as cortisol” (B1, pg. 434). Repeated activation can damage component systems over time through chronic internal exposure to high mediator levels, such as repeated sympathetic nervous system activation from epinephrine and norepinephrine exposure, and cause large surges in blood pressure and cardiovascular activity. As the allostatic response continues, the levels of biochemical mediators remain high. The component systems involved in peripheral accommodation must change in structure to accommodate high levels, i.e., in responding to sustained increase blood pressure the atrial walls begin thicken.

Dysregulation. After multiple insults, and over long periods of time, the feedback system responds to high load levels in a dysregulated fashion where the hippocampus loses control of amygdala and HPA axis regulation, removing the brakes from allostatic response. In animals, the hyperactivity of the amygdala from chronic stress further increases the high load leading to increased aggression between animals living in the same cage. Animal studies provide evidence of structural changes in the prefrontal cortex resulting from stress induced plasticity in amygdala relating to aggression and anxiety (McEwen & Gianaros, 2011).

After prolonged exposure to high levels of biochemical mediators such as cortisol, component systems become dysregulated. Future responses to additional stressors are extreme, displaying either excited or blunted biochemical mediator levels, reflecting the non-linear regulation of mediators onto themselves. In the central allostatic response, dysregulation can present as hyper reactivity in behavioral responses such as vigilance and anxiety or as depressive symptoms, while peripheral dysregulation is reflected in flattening of diurnal cortisol levels (McEwen & Wingfield, 2010).

Within component systems, prolonged response and/or delayed shutdown can lead to premature hypertension and atherosclerotic heart disease from required internal adaptation to destructive biochemical mediators . Once dysregulation occurs in one system, the hippocampal feedback loop may attempt to adjust biochemical mediators in component systems to compensate for deficiencies created by dysregulation. When the hippocampus detects low cortisol levels indicative of dysregulated HPA axis activity in spite of repeated activation, there is an associated increase in autoimmune and inflammation mediators. One article (B1) speculates that this non-linear component dysregulated may be implicated in fibromyalgia and chronic fatigue syndrome (McEwen & Gianaros, 2011).

When measuring biochemical mediators, it is important to distinguish between high load and dysregulation as the former indicates increased risk for disease and potential intervention points while the latter indicates pre-clinical disease states and requires treatments.

The allostatic response is complex, involving appraisal and instruction from the emotional regions of the brain activating a central response to an external stressor. Central response up-regulates the production of biochemical mediators to stimulate peripheral responses in component systems. Biochemical changes in the brain and body occur to change physiologic functioning to accommodate the stressor. What is interpreted as a stressor is of great importance in that chronic exposure leads to chronic allostatic responses. The internal biologic environment is exposed to high levels of biochemical mediators that can lead to dysregulation. Next, I explore the theme of external stressors in the biologic literature to understand the features of an external stimulus that can activate the allostatic response.

2. **External Threats**

The biological literature clusters around two themes of external stimuli that can activate or ameliorate an allostatic response: Social Threats and Physical Stimuli. Embedded in the subtheme of Social Threat are the topics of social resources and social relationships. The biological discourse addressed these phenomena as able to elicit an allostatic response, but was thin in discussing the qualities of a stressor eliciting the response. Discussions of the subthemes were broad and shallow. The meagerness of the external threat discourse in this collection of articles reflects both my choice to focus on literature describing the allostatic process and the fact that the allostatic model has been heavily researched in animals under experimental conditions.

2a. *Social Threats*

The example of wartime stressors was used to describe serious disruptions in social resources. Social conflicts presented by wartime changes occur in changes to human capital, income, employment, and neighborhood situations that disrupt most facets of social resources. Descriptors of social relationships and social threats clustered around concepts of support, conflict, and the frequency and quality of contact between individuals.

> *Notable, trauma exposure is not uncommon; at least half of all Americans experience one or more traumas in their lifetime with much higher levels of trauma exposure occurring in high risk groups such as those who live in violent neighborhoods or those who are exposed to war. The above results inform our understanding of the well-established association between psychological trauma*

exposure and long-term mental and physical health problems, even in those who initially appear resilient. (B3, p.152)

2b. *Physical Stimuli*

Across the biological literature the theme of physical threat was common. Violence, trauma and abuse, neighborhood characteristics, and housing all were discussed consistently as stimulators of the stress response system and as stimuli that require adaptation. The sleep cycle appeared across the discourse as activating anticipatory physiologic and behavior changes usually associated with day/night and seasonal variation. Half of the articles extended this discussion to include the cognitive stimulation caused by current electric lighting and pattern changes around third shift (all night) employment.

Though the biological literature conceptualized human experiences of social and physical threat, the translation of these concepts into measures or mechanisms was absent in the discourse. As will be reported in the Phase II analysis, the social science literature provides extensive insight into these themes as population-level stressors.

3. **Individual Capacity**

Homogenous exposure groups may have heterogeneous differences in resilience or susceptibility to allostatic overload. These differences influence an individual's threshold for the effects of wear and tear from biochemical mediators (the dotted line depicted in Figure 3). The theme of individual capacity is crucial to understanding individual variation that must be properly accounted for when identifying otherwise homogenous populations. Without properly controlling for variation in an individual's ability to respond to environmental stressors, or individual differences in the ability to recuperate from the effects of biochemical mediators involved in the response, confounding in measurements of allostatic load can lead to attenuated results.

Four subthemes materialized from within the theme of individual capacity that, when combined, shape an individual's ability to both accommodate a single allostatic response and withstand high load from chronic activation. Though allostatic accommodation is a dose-dependent system, it is an individual's capacity that defines the threshold for overload and dysregulation.

In the biological literature, an individual's ability to respond to external stressors and motivations for behavior adjustments are dependent on several aspects of the brain and the body. Since the central response in influenced by prior adaptive responses (feedback from previous stress response and their outcomes), having a clear understanding of the individual differences in population studies is of great importance for proper measurement of the biochemical mediators active in central and peripheral allostatic load, and interpreting what differences in these levels mean. Individual capacity is further explained by the subthemes that surfaced from the biological literature: lifestyles & behaviors, genetic predispositions, brain condition & social behaviors, and body condition.

3a. *Lifestyle & behaviors*

Individuals cope with allostatic high load and overload (dysregulation) in multiple ways, including the use of medications to alleviate the burden experienced by allostatic component systems: "Sleeping pills, anxiolytics, beta blockers, and antidepressants are all used to counteract problems associated with allostatic overload" (B1 pg. 439). Some behaviors may be immediately effective in alleviating the increase in allostatic state caused by an immediate stressor (e.g. taking sleeping aids at night or taking a smoke break during work; both associated with attention, memory, and psychomotor speed), but, depending on the behavior, may lead to component system susceptibility to overload (e.g., smoking-induced deterioration of the lung tissue and cardiovascular system). Other behaviors, such as exercise and diet, can be protective in both short-term stress reduction and long-term physiologic resilience to allostatic wear and tear. The biological discourse collectively describes lifestyle choices that influence resilience or susceptibility to overload with aerobic exercise given as an example of a resiliency factor and susceptibility factors including alcohol consumption, smoking, and substance use.

3b. *Genetic predisposition*

Across all four articles, several genes active in regulating plasticity in the brain are implicated as genetic differences between individual capacity in resilience or susceptibility to increased biochemical mediator levels or to the stressor directly. One article described the evidence for gene–environment interactions that influenced allostatic accommodation and thus physical and mental health.

> *In gene–environment interactions, variations in the DNA sequence interact with environmental stimuli to produce differing outcomes for individuals with differing genetic profiles. …This research suggests that individual differences in DNA sequence may affect the character and magnitude of the load acquired over time as the individual adapts to environmental challenge. (B3, pg. 154; pg. 156)*

One article, B3, was particularly interested in specific examples of gene-environment interactions that alter the effects of allostatic load accrual and behavior changes resulting from high load in the central response system, the brain. B3 focused on the example of the natural variation in the serotonin transport gene 5-HTT. Anxiety-related personality traits are "mediated by amygdala activation, such that short allele carriers are more sensitive to negative stimuli. Individuals with the short allele of 5-HTT have been repeatedly observed to have significant amygdala activation to emotional stimuli in response to negative stimuli compared to neutral stimuli" (B3, pg. 155). This susceptibility increases an individual's risk for anxiety and depression.

> *There is also evidence for moderation of the stress process by allelic variation in a number of other genes, including the human brain-derived neurotrophic factor gene, the dopamine transporter gene, and the catechol-omethyltransferase gene. While not yet tested in interaction with environmental influences, a number of genes that are linked with HPA axis functioning are also likely candidates for*

other gene–environment interactions relevant for allostatic load, including 363s (single nucleotide polymorphism) and BCl1 (restriction fragment length polymorphism), both of which are linked to cortisol response to stress (B3, pg. 156).

Genetic predisposition to reactivity of the allostatic system has consequences to individual resilience or susceptibility. This was expressed differently across the articles ranging from a discussion of individual differences that influence “genetic liability” (B1, pg. 432), phenotypic presentation of predator avoidance (B2, pg. 107), or protein function and enzymatic activity (B3, pg. 143). These examples play out as differences in the strength or weakness of peripheral systems to bear the burden of high biochemical mediator levels. An individual with a weak cardiovascular system experiencing chronic load would have a higher risk of a heart attack than an individual who is genetically resilient. Genetic predisposition is just as important in influencing the central response. If an individual has a higher baseline of anxiety, he or she might not venture out into society, reducing access to social resources. Finally, if an individual is slower to metabolize cortisol, or any of the allostatic biochemical mediators, this could lead to excess or deficient basal levels of biochemical access for an allostatic response.

Genetic predisposition to differences in biochemical mediator metabolism could also predispose individuals to a higher resilience to damage from chronic stress decreasing the risk of becoming overloaded. Lower levels of biochemical mediators are needed to overcome the stressor, making the individual more likely to have positive outcomes when exposed to a chronic stressor. Conversely, individuals genetically predisposed to over-production of biochemical mediators will have a higher basal level of biochemical exposure leading to a higher level of biologic wear and tear. For these individuals, lower amounts of stress exposure may push internal component systems into dysregulation relative to other individuals.

As behavioral and physiological anticipatory processes relevant to life course stages involve a high degree of gene regulation across multiple systems, a change in gene regulation could fail to terminate an allostatic response and turn a positive stressful situation into a detrimental one.

3c. *Brain Condition and Social Behavior*

The biological sciences acknowledge the brain as the organ not only of stress processing and allostatic activation but also of stress memory.

> *We highlight translational animal and human evidence demonstrating that the brain is the central mediator and target of stress resiliency and vulnerability processes. We emphasize that the brain (a) determines what is threatening, and hence stressful, to the individual; (b) regulates the physiological, behavioral, cognitive, and emotional responses that an individual will deploy in order to cope with a given stressor; and (c) changes in its plasticity both adaptively and maladaptively as a result of coping with stressful experiences.* (B1, pg. 432)

All four articles discussed the concept that the brain ages by exposure to years of chronic stress, through chronic activation of the feedback system by altering cortisol receptor density in the hippocampus. These changes remove the hippocampal brakes on the amygdala. While the hippocampus decreases in ability to engage in the central response, the amygdala becomes hyperactive. In animals, hyperactivity of the amygdala from chronic stress leads to high aggression between animals living in the same cage as evidence of stress-induced plasticity in the amygdala relating to aggression and anxiety (B1, pg. 437). The discourse describes how this dysregulation alters behaviors like pessimism, hostility, negative affect, and depression all potentially affecting mate access and social status. The interaction of high load and social behavior alter individual abilities and the resources available to combat a stressor. With each stressful encounter, a memory of the stressor, behavioral response, and associated outcome carry forward to inform future stress responses. The central response informs individual behaviors to align with those that have been successful in previous encounters.

> *They [previously cites articles] also suggest that even the healthy adult brain may retain physiological markers of stress exposure for lengthy periods, making the brain a living record of stress exposure across the life span. (B3, p.153)*

3d. *Body Condition*

As stated earlier, positive outcomes following a challenging stressor are adaptive and healthy when there is adequate time to recover. To understand how differences between individuals experiencing the same stress leads to different health outcomes, the biological literature focuses on the body's condition. This discourse centers on infection status, disease status, age, and previous injuries. The body's condition is crucial to interpreting individual resilience or susceptibility to load accrual. Previous exposures in each of these categories have the capacity to increase individual susceptibility to overload and thus physiological dysregulation.

One article, B2, focused heavily on the individual life as a context to interpret the salience of the allostatic response to future appraisal/responses. Factors in anticipatory behavioral and physiological changes can increase energy demand to cope with the lifecycle. Such demands could be caused by childhood and adolescent development, fertility cycles, pregnancy, and lactation. This is evidenced by differences in life stage and body condition. Individuals can temporarily alter their sensitivity to stress to respond to the current demand, such as during pregnancy (B2, p.106). Conversely, adolescents experiencing anorexia or bulimia have decreased reproductive function presumed from the body's redirection of energy needs from reproductive organs to maintain necessary caloric levels.

Most of the articles focused on the timing of similar exposures over the life cycle and how differences in exposures over the life course may lead to different health outcomes. For example, adverse childhood environments show an increased risk of morbidity and mortality outcomes in adult years over individuals who experience the same stressors during adulthood. Periods that are more malleable or resistant depending on the maturation of brain circuitry are called "biologically stress-sensitive period[s]" (B3, pg. 160). Earlier life successes and failures shape the memory and response to stressors in the future.

From this section, it is clear the biological literature is very attentive to variation in an individual's capacity to weather repeated or chronic stress exposures. Individual differences can arise from lifestyle choices and behaviors such as smoking and exercise, differences in genetic predisposition of biochemical mediators and allostatic reactivity, brain condition and social behaviors, and the health of the peripheral component systems. As the allostatic response occurs through biochemical messengers acting on component systems, it is important to understand how individual differences in mediators fit into the allostatic model in order to measure and interpret them correctly.

4. Allostatic Load Biochemical Mediators and Component Physiological Systems

The accommodation to external stress required by the brain and body occur via biochemical mediators in related component systems. Accurately capturing biomarker measurements of both the central allostatic accommodation occurring in the brain and the peripheral accommodation in the body is crucial to interpreting outcomes of allostatic measurement. The composite systems involved in the allostatic response are the brain (central response), and the peripheral component systems: metabolic, cardiovascular, immune, and nervous systems.

Theoretically, central and peripheral mediators should reflect how the allostatic states described previously become biomarkers for the measurement of load. That is, true biomarkers would reflect an individual's current allostatic load, and distinguish between an individual who is experiencing high allostatic load and an individual who is experiencing allostatic overload indicative of dysregulation. The articles chosen to represent the biological literature were not focused on employing and interpreting specific biomarkers used to assess allostatic load. Most of the biological articles did reference the seminal paper by Seemen et al. (1997) describing 10 biomarkers identified to capture component system functioning. However, there was no discussion in the biologic articles of the scoring method used to measure allostatic component systems. This is important to note as the social science literature spends little time unpacking and applying different allostatic responses (accommodation, load accrual, overload, and dysregulation) in their interpretation of measured biomarker panels. For this reason, I included the 10 biomarkers from that study in Table 6 when comparing the results from Phase II analysis. We will see, in the second phase of the analysis that the measurement of composite allostatic systems as markers of load and overload is unclear.

Summary of the Biological Literature on Allostasis

The biological literature details how a stressor activates allostatic accommodation through central and peripheral responses requiring altered levels of biochemical mediators. This discourse is direct in describing how physical and social threats activate the brain to muster a biochemical change affecting brain, cardiovascular, metabolic, and immune responses, but sparse in describing why stressors have this ability. The chosen literature focused on resilience factors such as a healthy diet, exercise, and genetic resilience in component physiological systems, and the health of the brain and body in altering behavioral and physical responses to the stressor. These differences impact an individual's capacity to resist stress-induced dysregulation and risk for mental and physical morbidity and mortality.

With this in hand, I now move to evaluating how the social science literature has applied the allostatic framework and its measurement to different studies of population health and identifying where there are overlaps and disconnects with the biological definitions of allostasis with the goal of moving towards an integrated framework.

Phase II: Use of Allostasis in the Social Sciences Literature

Capturing the etiology of stress-induced illness using the allostatic framework requires measurement of allostatic load as a biomarker of internal stress response. The biochemical mediators measured to inform the allostatic load biomarker are both a marker of stress exposure and a marker of disease risk. The social science literature is focused on the application of allostatic load measurement to confirm the causal pathway between long-term psychosocial and physical stressors and chronic illness. Though the social sciences have been measuring external societal pressures and their associated risk for illness for over a century, a biomarker of the stress response greatly enables researchers to measure stress response and assess interventions in a real-time fashion. Though this is simple in theory, appropriate measurement and interpretation is crucial to accurate assessment of exposures and interventions.

When comparing themes across disciplines, Table 4 (see next page) indicates where the social science literature is congruent with, extends, or misapplies the subthemes identified in the Phase I analysis. Examples of misapplication include the difference between a central and a peripheral response, and the distinction between high load and overload. Absent from the social science discourse was any discussion of genetic factors impacting individual capacity. Strikingly, none of the social science articles stated the brain was the locus of biochemical mediator regulation. However, while the biologic discourse was sparse in describing external stressors, the social science discourse is rich and enhances this theme with detailed models of causal pathways across the SEM framework.

For ease of comparison, I have followed the same thematic structure as in Phase I with attention directed attention to where the social science discourse either extends the knowledge base or where themes were misapplied.

Table 4 Social science theme comparison overview

Biological Discourse	Application in Social Science Literature		
Themes : Subthemes	Congruent	Extends	Misapplication
Allostatic Response			
○ Allostatic Accommodation: Central & Peripheral			X
○ Load Accrual	X		
○ High Load / Repeat exposure	X		
○ Dysregulation			X
External Threats			
○ Social threat		X	
○ Physical stimuli		X	
Individual Capacity			
○ Lifestyle & Behaviors	X		
○ Genetic Predisposition			X
○ Social Behaviors	X		
○ Brain/Body Condition	X		
Allostatic Load Biochemical Mediators and Their Component Physiologic Systems			
○ Brain & Nervous			X
○ HPA Axis			X
○ Cardiovascular System	X		
○ Metabolism	X		
○ Immune/Inflammatory	X		

1. **Allostatic Response**

In general, the social science articles did not reflect the same depth and breadth of concepts related to allostatic accommodation. Most of the social science literature articles included in this analysis depict allostatic accommodation as originating from the lower brain and brainstem. This presentation bypasses the central response as part of the etiology of the stress response and, in so doing, is a misapplication of this tool to measure behavioral responses and health outcomes.

1a. *Allostatic Accommodation: Central and Peripheral Response*

The social science literature was also prone to exclude the brain as the originating source of allostatic accommodation with most articles depicting social stressors as directly modifying peripheral responses. The language below demonstrates how SS5, SS7, and SS8 fail to fully conceptualize the brain as directing the allostatic response. Though they are nuanced, we will see later how this misapplication is reflected in measurement and interpretation of the biochemical mediators involved in accommodation.

> *Conceptually, allostatic load (AL) refers to the body's ability to adjust physiologically to stressors. SS5, pg. 978.*

> *Allostatic load mainly affects the cardiovascular, metabolic and immune systems by disturbing the release of important biomarkers in the body (i.e., epinephrine, dehydroepiandrosterone sulphate and cortisol) SS7, pg. 144*

> *After a stressor is triggered, the first responders of the allostatic physiological reaction are parameters in the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS). SS8, pg. 1989*

A few articles do acknowledge measures of brain activity leading to downstream peripheral responses, though this acknowledgement does not carry forward in adequate measurement and interpretation later in the article. This leaves interpretation muddied. The next quote confuses the causal pathway from central to peripheral response.

> *Stressors are theorized to be associated with neuroendocrine responses, which can have cascading effects on other systems of the body by increasing blood pressure, immune-responses, cancer, etc.* (SS5, pg. 978).

1b. *Allostatic Load: Load Accrual, High Load, Dysregulation*

The goal of the chosen social science articles was to identify increased biochemical mediator levels in relation to chronic stress exposures. In general, the articles use of various allostatic states focused only on states of high load and dysregulation. This narrow focus results in confusion between the concepts of load accrual, high allostatic load, and overload-induced dysregulation. This is problematic as interpretation of the biomarkers measured to reflect allostatic load require drawing a distinction between load, overload, and dysregulation. The social science discourse interprets the collection of composite biomarker measurements as both an indication of long-term stress exposure and as a risk factor for chronic disease-induced morbidity and mortality. In order for chronic exposure to lead to increased morbidity and mortality, composite systems must first accrue load, become overloaded, and then respond to overload through changes that lead to dysregulation. In discussing dysregulation directly, the concept is implicit but the language use, and later measurement, again muddle the difference between allostatic load (AL) and chronic biochemically-induced dysregulation.

> *The latter [allostatic load] represents the effect of wear and tear on an individual's physiology from repeated exposure to or lack of adaptation to stressors resulting in negative health outcomes. (SS7, pg. 144).*
>
> *Thus, AL is characterized by dysregulation across bodily systems, and markers of AL are derived from multiple regulatory dimensions.* (SS10, pg. 1134)
>
> *Allostatic load represents cumulative dysregulation which eventually develop across multiple interconnected physiological systems as a result of frequently repeated or chronic activation over the life course. (SS10, pg. 117)*

This confusion is further illuminated in SS6, a review article focused on cortisol levels in allostatic load measurements. It reports conflicting results between studies measuring cortisol against similar external stressors. While some of the surveyed articles in SS6 reported that high levels of cortisol are associated with low socioeconomic status (SES) and poverty, others reported non-significant cortisol levels in the exposed leaving the review with conflicting results. The biological discourse tells us the low levels found might be indicative of a flattening of the cortisol diurnal curve. High levels of cortisol would indicate an increased activation of the HPA axis to repeated or chronic stressors while a flattening of the curve would be observed once an individual had been pushed into HPA dysregulation. This blunting effect would reflect dysregulation instead of healthy levels.

In total, the term allostatic load was used to indicate any level of biochemical accrual, from high levels due to chronic stress exposure to states of dysregulation that were outcomes of chronic exposure. In principle this might not be alarming but the implications for research designs and the need to ask the right questions, capture the right variable, and describe results accurately suggest that the lack of clarity in the social science literature opens the door to substantial potential measurement error and highly attenuated results.

2. **External Threats**

The social science literature extends the discourse of allostasis with respect to external threats based upon decades of well-crafted studies designed to measure stressful life experiences across the SEM framework. Where the biological sciences identify broad categories of external stressors (war, trauma, and changes in the sleep cycle), the social science literature expands on these concepts by employing disciplinary knowledge of riskscapes, socioeconomic status (SES), social disparity, minority status, and exposure to adversity. The social science field has employed reliable survey methods for measurements of stressors such as neighborhood perception, daily hassles, pollution concerns, negative life events, multiple disparities, education, income, poverty, culture, social position, violence and criminal acts, discrimination, and perceived stress; all of which meet the biological criteria of representing social and physical threat.

Repeated exposure to stressors, both from the same source and different sources, are captured in the social science concept of double jeopardy (SS5, pg. 979). The double jeopardy framework captures measurement of stressors resulting from multiple power differentials that play out in different contexts across the different levels of the SEM framework. Riskscapes are systems of double-jeopardy where multiple external stressors are acting upon an individual.

> *[We] explore an interesting new view of allostatic health risk through the concept of overlapping disadvantages, or ''double jeopardy.'' Chronic stressors may influence AL [allostatic load] through less obvious mechanisms, such as being a lifelong member of a disadvantaged group (e.g., being a woman) while experiencing prolonged exposure to an environmental riskscape (e.g., long-term residence in Texas City). (SS5, pg. 985)*

> *Riskscapes themselves are inherently systems of 'double jeopardy', as the individuals living within them are deeply intertwined in unequal geographical processes at multiple levels. This complex system of influences also creates additional inequalities such as the inability to relocate from environmental threats. Such inequalities, in turn, are accentuated for individuals who are members of more than one disadvantaged group (e.g., minority women). Overlapping sources of jeopardy may become too much to cope with, especially without the resources or the power to counter the under-lying macro-level causes of inequality. (SS5, pg.985)*

> *Stress itself may be triggered by multiple environmental factors and life events. Puerto Ricans experience some of these factors, namely high poverty levels, language barriers, cultural changes, negative life events, limited social support, violence and criminal activity, and the strain of perceived or real discrimination. (SS8, pg. 1989)*

The social science literature adds a wealth of knowledge and empirical tools to identify and measure multiple stressors across the levels of the SEM. This presents an opportunity for merging this knowledge with the allostatic model and improving the measurement of community-level stressors that impact health.

3. **Individual Capacity**

The social science literature is also rich with measures of inter-individual variation in potential resilience and susceptibility factors. These measures are important to identifying heterogeneous sub-groups within homogenous exposure populations.

> *External stressors alone do not fully explain the pathway from AL to disease; individual biological differences as well as behavioral responses may alter the way a person responds physiologically to perceived stress.* (SS8, pg. 1989)

> *We examine whether stress, personality, psychosocial variables, coping style, social network, and health behaviors are associated with both SES and AL.* (SS9, pg. 1135)

Table 5 reports the variables identified in the social science literature that correspond to the different subthemes of individual capacity. SS6 is not included in the table because it is a literature review, and as such, did not include specifics about the measures used in the studies included in the review. Of the five articles summarized below, there was little consistency in the choice of variables used to represent lifestyle behaviors, genetic predisposition, social behaviors, and/or body condition. This is reflected in the total column count displayed in Table 5, showing the range of 3-9 variables used in these five studies to measure individual capacity. Details for each of the subthemes are elaborated next.

Table 5 Variables used to represent individual capacity

Subtheme	Individual Variable	SS5	SS7	SS8	SS9	SS10	Total
Lifestyle Behaviors	Smoking	X	X	X			3
	Exercise	X		X	X		3
	Alcohol Use			X	X		2
	Substance Use			X			1
Genetic Predisposition	Gender		X	X		X	3
	Race/Ethnicity		X				1
Social Behaviors and Brain	Perceived Stress	X					1
	Marital Status		X				1
	Place of Birth	X	X				2
Body Condition	Medication Use		X	X		X	3
	Age		X	X		X	3
	Health Ins Status	X	X				2
	Chronic Health	X					1
	Caloric Intake				X		1
	Poor Nutrition			X			1
	Sleep Quality				X		1
	Time btw dental		X				1

3a. *Lifestyle & behaviors*

The social sciences acknowledge the need to account for lifestyle factors, but the five articles varied in their choice of mediators (Table 5). Smoking and exercise were acknowledged in half of the articles, yet all articles missed collecting measures of smoking behaviors. This indicated a loss in translation where there was an acknowledgement that lifestyle behaviors influenced individual resilience to internal stress demands but did not incorporate those measures in their multivariate analysis.

> *Some behavioral stressors have been reported for Puerto Ricans living in mainland US, including smoking, alcohol and substance abuse, low levels of physical activity, and poor nutritional intake. Thus, individual factors and external stressors likely play a role in the observed high prevalence of chronic conditions in Puerto Ricans. (SS8, pg. 1989)*

3b. Genetic Predispositions

There was no discussion in the social science literature of genetics per se as a way to specify diversity between individuals with respect to susceptibility or resilience measures of allostatic load. Race and gender were the two variables that consistently were included that reflect genetics but the two literatures use these concepts to represent different things. In the biological literature, race typically refers to the genetic structure of individual variation in single nucleotide polymorphisms indicative of groups of people whose ancestors originated and evolved together sharing genetic variants through breeding populations. In the social science literature selected, race referred to a self-reported cultural identity of the individual participant. Race in the latter sense is discussed in the context of racism, a clash of cultures.

> *Race/ethnicity was derived from self-identified race/ethnicity and nativity status. Our analysis included non-Hispanic Whites, non-Hispanic Blacks and individuals of Mexican origin. For individuals of Mexican origin, we distinguish between 'foreign-born' and 'US-born'. (SS5, pg. 980)*

> *Because periodontal diseases and other stress-related illnesses tend to be more prevalent in groups who experience higher levels of stress such as minorities, less-educated and low-income individuals, periodontal diseases may be affected by cumulative exposure to socioeconomic disadvantage and racial discrimination. Thus, it is possible that race/ethnicity and socioeconomic position may act as stressors increasing allostatic load that may in turn affect periodontal disease onset. (SS7, pg.144)*

Cultural identification may indicate as much environmental similarity as it does genetic similarity of a population. In some cases, where cultures have a high level of genetic admixture from other ancestral populations, the identity of race may indicate differences associated with environmental exposures and individual capacities (such as lifestyles) more than an indication of genetic susceptibility and risk factors.

Similarly, the identification of gender might encounter the same confusion in translation between biological and social science literature. In the biological literature, sex identifies the hormonal differences between genders. These differences have implications for the baseline levels of biochemical mediators involved in the allostatic system. Additionally, hormonal levels change through the life course in anticipation of reproductive age, during the menstrual cycle, during reproduction, and during post-menopausal years. Understanding the baseline differences in component systems that are activated by an allostatic response assists in understanding gender differences in component dysregulation. Even within the biological literature, B2 referred to gender differences, further confusing the usage of sex verses gender identity:

> *While the stress process literature discusses chronic, life-long stressors and AL, health disparities research may offer some insight into how chronic stressors may be captured in other variables such as gender. In support of our second hypothesis, there were gender differences in the explanatory power of our models and this effect varied by the type of AL outcome assessed. (SS5, pg. 985)*

3c. *Brain condition and social behavior*

While the brain as a whole is absent in the social science literature, it is implicitly present through discussions of the behavioral outcomes from certain neurocognitive processes. These behaviors are not identified as being a product of the allostatic process. Instead behavior changes are measured and discussed as mediating the stress pathway. Below are two examples of how behavior variables were discussed.

> *[Kubsansky et al.] found that measures of hostility partially mediated the relationship between education and AL in this sample.* (SS6, pg. 1304)

> *Many variables associated with increased AL are also associated with SES, suggesting potential pathways through which SES may affect AL. These variables tend to fall into five major domains:*

stress, personality and psychosocial variables, coping styles, social networks, and health behavior. (SS9, pg. 1134)

Personality and psychosocial variables. Hostility, loneliness, depression, social support, emotional stability, agreeableness, surgency, satisfaction with life, optimism, and spiritual well-being were assessed using standard validated scales. (SS9, pg. 1137)

Social behavior was important as well. Two of the social science articles, SS5 and SS7, measured place of origin (whether participants were foreign born vs. U.S. born) but do not comment on why. These studies also measured marital status to indicate some level of inter-personal support.

3d. *Body condition*

Each of the articles comprising the social science literature took a different approach to capturing individual-level differences in physical condition. Though there was little discussion as to why, half of the articles captured measures on age and medication use. Nutritional and health status, and sleep quality were rarely measured.

The analyses in the social science literature did, however, adjust allostatic load scores when individuals were taking a prescribed medication to treat composite dysregulation, which demonstrates understanding that the level of biochemical mediators is lower in dysregulated states than in high load states. I include medications as a variable in this subtheme as evidence of how dysregulated states may be externally adjusted to force reduced arousal of component systems.

To consider the fact that the presence of medication might disguise the development of allostatic load, pharmacological treatment was coded as 2 on the affected physiological system categories (antihypertensive medication on cardiovascular regulation; lipid-lowering medication on lipid metabolism; and diabetes medication on glucose metabolism). (SS10, pg.121)

In total, the inclusion of multiple variables measuring individual capacity in the human environmental context in the social science literature reflects the attempt to capture important variables influencing allostasis. However, there is a lack of consensus within the social science literature about which variables best represent body condition: no article measured everything, and in general, most articles failed to capture a wide range of potential variables. However, the social science literature did attempt to capture variables in each subtheme and brought forward interesting social contexts relevant to individual resilience such as measuring place of birth. The social science literature was most lacking in capturing variation in genetic predisposition.

4. **Allostatic Mediators and Composite Systems**

All articles measured allostatic load through a composite scoring system. For this, biochemical mediators active in each component system are scored as high or low, in comparison to levels found in the source population. Those component scores indicate the total load on the body. High component scores are indicative of high levels of dysregulation across body systems.

> *Because biological systems are mutually dependent, challenges to one system may alter multiple set points, and attempts to return one system to a more ideal set point may lead to compensation in others. Thus, AL is characterized by dysregulation across bodily systems, and markers of AL are derived from multiple regulatory dimensions. (SS9, pg. 1134).*

The biochemical mediators measured as part of each composite system clustered differently across the social science literature. This is depicted in Table 6 (see next page) as the color of the biochemical mediator being measured matches the component system identified in each article. I did not label SS6 measures by component systems as component labels were not discussed for each mediator. For reference, I have included a column depicting the original 10 biomarkers identified in work by Seeman et al. and discussed in the introduction above (Seeman, Singer, Rowe, Horwitz, &

McEwen, 1997). The original biomarker panel clustered biomarkers into component systems. The activity involved in regulating each system has the potential to cause wear and tear. For this reason, measurement of these biomarkers is a reflection on the load in the body. Specifically, the 10 markers were grouped as such: systolic and diastolic blood pressure (indices of cardiovascular activity); high-density lipoprotein (HDL) and total cholesterol (indexes of atherosclerotic risk); waist-to-hip ratio and glycosylated hemoglobin (indices of metabolism); dehydroepiandrosterone sulfate (DHEA-S), cortisol, norepinephrine and epinephrine (indices of HPA axis functioning).

Table 6 Allostatic biochemical mediators

Biochemical Mediator	Social Science Articles						Total	Original Biomarkers from Seeman et al
	SS5	SS6	SS7	SS8	SS9	SS10		
Systolic Blood Pressure	X	X	X	X	X	X	6	X
Diastolic Blood Pressure	X	X	X	X	X	X	6	X
Total HDL	X	X	--	X	X	X	5	X
Total Cholesterol	X	X	X	X	X	X	6	X
Glycosylated Hemoglobin	X	X	X	X	X	--	5	X
BMI / WC	X	X	X	X	X	X	6	X
Triglycerides	X	--	X	X	--	X	4	
Fasting Glucose	--	--	--	--	--	X	1	
Epinephrine	--	X	--	X	X	--	2	X
Norepinephrine	--	X	--	X	X	--	2	X
DHEA-S	--	X	--	X	--	--	2	X
Cortisol	--	X	--	X	X	X	4	X
CRP	X	X	X	X	--	X	4	
IL-6	X	X	--	--	--	--	2	
IL-7	X	--	--	--	--	--	1	
IL-10	X	X	--	--	--	--	1	
TNF-alpha	X	--	--	--	--	--	1	
LEBV VCA	X	--	--	--	--	--	1	
EA	X	--	--	--	--	--	1	
EBNA	X	--	--	--	--	--	1	
HSV-1	X	--	--	--	--	--	1	
A1 B	--	--	--	--	--	X	1	
Homocystine	--	--	X	--	--	--	1	
Albumin	--	X	X	--	--	--	2	
IGF-1	--	X	--	--	--	--	1	
Creatine Clearance	--	X	X	--	X	--	2	
Fibrinogen		X					1	

Key – Component Systems (by color):

Cardiovascular	Inflammatory/Immune	Neuroendocrine	HPA	Metabolic

Several comparisons can be made from Table 6. First, when grouping biomarkers into component systems, the social science articles are neither consistent with the Seemen article nor with each other. Blood pressure as a measure of cardiovascular activity was the only biomarker used consistently across articles. Some measure of visceral fat deposits was used as a biomarker in all social science articles but it varied between whether it was a Body Mass Index (BMI) or a waist-to-hip (WH) ratio.

In the social science literature the brain is hardly discussed or recognized as being able to accrue wear and tear. The focus is on peripheral load measurements and resulting chronic dysregulation or disease in peripheral systems. This is displayed in Table 6 by the absence of measurement (represented by the dark boxes) of epinephrine, norepinephrine and partial absence of cortisol measurement across several of the social science articles. As HPA axis activity employs biochemical mediators that have direct function in the brain and are involved in the allostatic feedback loop, measurement of cortisol, norepinephrine, and epinephrine are important to capturing the true load an individual is internally experiencing. Half of the social science articles failed to capture measure of HPA axis functioning demonstrating the de-prioritization of the brain's activity and response involved in allostatic load.

The social science articles also added other biomarkers to represent immune functioning and inflammation.

> *Conceptually, allostatic load (AL) refers to the body's ability to adjust physiologically to stressors. Operationalized as a measure of physiological homeostasis, AL is measured through a diverse set of biomarkers collected from blood, saliva, and other clinical means that reflect cardiovascular, metabolic, inflammatory, neuroendocrine, and immune-related risk.* (SS5, pg. 978)

SS8 and SS9 provided a more comprehensive set of brain mediators that reflected central allostatic load. Specifically, they measured epinephrine, norepinephrine and cortisol. SS5 focused heavily on the immune and inflammatory response by measuring a large number of markers involved in these systems. Though these articles alluded to a central allostatic response, they failed to measure any of the neuroendocrine or HPA-axis mediators. SS7 failed to measure those systems as well. SS8 and SS9 mirrored the original markers most. Though DHEA-S was measured in the early days of allostatic load, it has since been discarded as it provides little insight into the variation of the allostatic response.

The social science articles employed a composite scoring system to measure total allostatic load but used different indicators for determining statistical significance of biochemical mediators, as shown below in Table 7. Assigning a composite load score allows researchers to identify when allostatic load is high, the component system driving the high load. Though this is helpful in associating exposure to outcomes in component systems, such as discrimination with cardiovascular disease, the high variability between articles in identifying the biomarkers used in each composite measurement leads to confusion between studies. In determining what was an extreme biomarker level, articles varied in using a Z-score, a percent cutoff, or a simple summation. I have included sample size numbers to indicate that the composite score method was not associated with sample size.

Table 7 Allostatic Load Composite Scoring

	SS5	SS6	SS7	SS8	SS9	SS10
AL Composite score	Z Score	Varied	Percent Cutoff	Sum	Avg Z Score	Cutoff Values
Sample Size	1072 Residents	7 Articles	3092 Individuals	1116 Individuals	200 Individuals	822 Individuals

Because of the literature choice, only the social science literature employed biomarker measurement with the aim of measuring stress exposure. The social science articles varied in their decision of how to define biomarker overload values. SS5 and SS9 applied a Z score to determine scores that were statistically high. SS7 and SS10 used cut off values for each composite system.

> *Dependent variables included total allostatic load and four components of AL (cardiovascular, metabolic, inflammatory, and immune-related). Traditional composite measures of AL identify ''high risk'' cut-offs for each biomarker and sum the resulting binary scores, similar to a checklist. This approach, however, reduces variation and may not capture the full range of AL. Therefore, we opted for a z-score measure of AL to utilize the interval scores and their variation.* (SS5, pg. 980)

In total, the social science articles varied in their consistency to capture the 10 biomarkers identified in the work of Seemen et al (1997). Though the measurement of DHEA can be excluded from this critique due to lack of utility, measures of epinephrine and norepinephrine were absent from half of the articles. There was additional confusion in what was considered neuroendocrine versus HPA related or what was cardiovascular versus metabolic. In that these systems are highly interrelated and non-linear, variations in the labeling of composite systems might confound cross-study comparisons.

Discussion

The allostatic framework provides the mechanism for understanding how social determinants of health are embodied. There is a demonstrated positive correlation between repeated or chronic physical and social threats and early morbidity and mortality. Social forces occurring at any level of the Social Ecological Model (SEM) can now be traced to increased arousal in the body. In the context of chronic disease, linking causal mechanisms of external stress with those of individual response provides new insights into how health disparities are created and sustained through social structures. The application of measures of allostasis by social science researchers provides evidence for the efficacy of interventions designed to change malleable stress pathways. Understanding what features of an external environment are perceived as stressful, what the dose-response relationship is when experiencing chronic stress, and identifying risk and resilience factors that occur at the individual level will assist future prevention and intervention efforts in addressing chronic illness at a population level.

Though integration of social and biological research on the stress response system holds a great deal of promise in addressing the causes of health disparities, misapplications in measurement of the allostatic response could harm this goal by producing attenuated or null results. For this reason, I attempted to identify and clarify points of disconnect in the translation of the allostatic concept between the biological and social science literature, as it has been employed in recent years. Though very limited in scope, the analysis of these discourses, at one snapshot in time, provides insight into where the biological and social sciences are in sync – and where they are not – with respect to translating the allostatic model into practical measures. Clarity in capturing the allostatic load of an individual as normal, high, or dysregulated has large impacts on findings, as misclassification and measurement error may become too large to capture underlying causal pathways. This error risks stalling the application of the allostatic model in stress research and could misdirect resources intended to move the field of prevention research forward. To illuminate this claim, one could imagine a large prospective study of several thousand participants capturing accurate biomarker measures but interpreting those low measures as healthy instead of in dysregulation or interpreting high levels as an ineffective intervention when in reality the treated population may be reverting from dysregulation into a more stable stage of high load. The complexity of this system requires equal complexity in measurement and interpretation to avoid discarding good interventions as ineffective.

Conversely, integrating the knowledge base the social science literature has amassed through population-wide studies of intricate social relationships is crucial to understanding the allostatic response in humans, something the biological sciences has been slow to absorb into larger models of stress research. Not only are both fields drawing extensively from each other to move their work forward, both are now actively working together in multidisciplinary teams attempting to gain transdisciplinary insight into capturing the entirety of the model, "from neurons to neighborhoods" (Gehlert et al., 2008). Below, I focus on areas of intersection between the biological and the social science literature that may have the greatest impact with respect to integrating these two domains.

The Brain

As individuals age, the stress response can become over-activated causing internal damage and physiologic changes. When the stress response in repeatedly activated, the mediator levels required for restorative, catabolic repair are not achieved. This drives new internal set-points across multiple body systems that lead to dysregulation and poor health outcomes. The biological literature clearly situates the brain as central to making meaning of external stressors, and through appraisal of necessary individual resources, to overcoming those stressors. Stress interpretation as positive or negative begins early in life and is reinforced through the life course with each outcome capable of informing future stress responses.

Missing in the translation of the allostatic framework from the originating field of the biological sciences to the social sciences is the brain. New technologies such as neuroimaging techniques are being employed by the biological sciences to study the brain but are very costly and thus have not been easily applied in large research studies. Understanding central accommodation and dysregulated states in the brain requires real-time measurement of arousal response. This is problematic, as the study of the brain is required to flesh out health outcomes of central allostatic activation and inform how biomarkers in the response pathway lead to illness. However, the social sciences are not merely excluding the measurement of allostatic load in the brain in their analysis; rather they appear to have interpreted the allostatic model as one that assumes dysregulation is happening only in the component systems located elsewhere in the body. In overlooking the role of the brain in measurement of the allostatic system, social science research risks failing to clearly assess stress-related health outcomes in future studies. Even in the article that was the closest in articulating differences between central and peripheral load (SS9), there was a lack of understanding regarding how to measure this load and interpret the relationship to outcomes.

To leave the core emotional regions of the brain out of the causal pathway misses an opportunity to study allostatic response, overload, and dysregulation in the brain. Additionally, component systems are non-linear in their relationship. Researchers cannot assume how measures of high load or dysregulation in one system will affect or co-occur with other systems. In measuring peripheral biomarkers and assuming they are reflecting primary responses, social science researchers are missing an opportunity to both clarify the phenotype measurements and reduce measurement error. The central response directs peripheral systems and therefore a complete measurement of chronic allostatic activation requires measures of brain activity in the allostatic model.

Though this is a by-product of inaccurate translation, it is also an opportunity for the biological and social sciences to work together toward an integrated, interdisciplinary model that could assess and address stress-induced chronic illness. Central to this effort, is the delineation of the difference in application and measurement of allostatic load, overload, and dysregulation. Neuroimaging data may provide the missing link – central allostatic measurement – for use in future studies. Without accurate measurement of central allostatic responses, measurement errors may make it difficult to demonstrate the relationship between exposure to stressors and health outcomes. As component system dysregulation is a non-linear process, a measure of central response, load, and dysregulation would provide a more accurate understanding of the stress response system instead of peripheral secondary measures.

Molecular Epidemiology: Details Matter

The tipping point with regard to when a stressor is adaptive and acute versus when it is maladaptive and chronic may be different between individuals, as we have seen in differences of individual capacity; or between populations, as we have seen in availability of social resources and interpersonal interactions.

Differences between individuals with similar chronic stress exposure must be identified to inform the complex multivariate analysis required for studies of this kind. The theme of individual capacity was identified in both discourses, but the application was diverse. This is another opportunity for multidisciplinary teams to identify and measure those factors contributing to an individual's capacity to withstand chronic allostatic activation. As the measurement of biomarkers is complex and laden with measurement error, I suggest integrating a molecular epidemiologist into these teams to reduce confounding that leads to attenuated results. This specialty field is well versed in the multiple types of intra- and inter-individual error and can identify methods to reduce pre-analytic, measurement, and interpretation error to strengthen the signal of stress response. This is particularly important as differences in individual capacity may impact how individual allostatic measurements are interpreted.

Multiple specialized disciplines will have to work together to inform novel biochemical marker development and validation.

To illuminate the complexity around just one biomarker, of the many used in application of the allostatic model, take as an example the measurement and interpretation of individual norepinephrine levels. Norepinephrine is a neurotransmitter released by the adrenal glands and participates in the fight or flight response process by stimulating the sympathetic nervous systems to increase heart rate, release glucose, and increase blood flow. Levels of norepinephrine vary by hour over the course of the day, so longer windows of measurement over multiple periods are required to accurately capture individual variation for inter-individual comparisons. To increase precision, norepinephrine is usually measured from overnight urinary collections taken from a 12-hour window when basal levels can be measured.

Individuals who are light sleepers and wake through the night show increased basal norepinephrine levels simply due to the act of waking. Thus, without measuring sleep variability, this variable cannot be adjusted for in the analysis. One could imagine an exposure study where some cases may display higher basal levels from non-stress induced sources while some controls may have different sleeping habits that inflate norepinephrine levels. Sleeping habits could be caused by typical stress-related responses, such as a mother waking through the night to attend to her newborn, or non-allostatic pathways such as frequent nightly urination patterns. The latter pathway may be involved in an allostatic response, but unless it is measured and included in the analysis, the causes can be misinterpreted. More importantly, measurement error will confound the choice of threshold value for what is considered high versus normal.

On further reflection, the circumstances underlying differences in individual sleep variation (maternal care or urination frequency) may alter how we interpret which individual characteristics are implicated in the stress response. Sleep disturbance effects on internal norepinephrine exposure for a new mother may be a positive challenge that is accommodated by reliance on her social support network to allow down time the next day, enabling catabolic repair. Conversely, a new mother who is taxed with poor sleep at night, and long hours of physical labor without periods of rest during the day, may tip into a dysregulated state.

The above example was one of biomarker reliability; identifying and reducing measurement variability resulting from biases in collection and lack of precision in distinguishing individual versus inter-individual variation. Such measurement can be accomplished without true interdisciplinary engagement, as the multidisciplinary field of molecular epidemiology has recently filled this translational gap. What will require interdisciplinary participation is biomarker validation in the brain. It is through the new technology of neuroimaging of brain structures that biomarkers of the brain can be validated, moving them from proof of concept to real-time measurement in brain function and response. My next example uses the same biomarker in the context of validating its hypothesized application in measurement of central response, overload, and dysregulation-induced mental illness. The next example will illustrate the need for more research to understand how allostatic biomarkers function in the brain, and how overexposure might lead to mental illness.

Though norepinephrine is also excreted from the adrenal glands, thus implicating it in the peripheral allostatic response discussed above (increasing heart rate, releasing glucose, and increasing blood flow), its relationship to mental illness outcomes derives from its action in the amygdala and hippocampus involving attention and memory. Norepinephrine is a catecholamine that plays a role as a neurotransmitter in the brain and is known to be responsible for brain plasticity during the stress response (McEwen, 2000). It is believed that in an activation of allostatic response, norepinephrine is released, activating the hippocampus, amygdala, and prefrontal cortex, the core emotional regions of the brain (Krugers & Hoogenraad, 2009) and the same regions implicated in anxiety and depression. This activation is in addition to the HPA-axis activation. The norepinephrine mediator of stress memory and neuroplasticity is less known and will require careful validation before we understand its complex role in central allostatic response, how urinary measurement reflects cerebral levels, and how levels change through the load-overload-dysregulation transition.

Some biomarkers have less measurement error and are more reliable, such as body mass index and blood pressure, though even these biomarkers have their own propensity for measurement error. Validation of new biomarkers to understand how neurotransmitters are active in central allostatic response may help distinguish between load, high load, and dysregulation. These new biomarkers could include gene expression panels to understand allostatic changes occurring at the level of gene regulation. This will take input from multiple investigators from diverse disciplines to gain the clarity needed in measurement and interpretation. Interdisciplinary perspectives are needed to reduce measurement error, identify new biomarkers, and to refine our understanding of sources of variation in individual capacity. The field of Public Health Genetics can provide insight into these goals.

Public Health Genetics as a foundation for understanding individual capacity

Plasticity: Resilience vs. Susceptibility

Researchers in the field of neuroimaging situate their work within a concurrent etiology of the psychological state, brain activity, biochemical mediators, and disease outcome (Lane & Wager, 2009). Underlying each of these components are gene-environment interactions and genetic polymorphisms. An understanding of each genetic component is important to measure and interpret the allostatic response. Gene variants may result in differences in protein function (described below) that impact biochemical mediator levels involved in different stages of the allostatic response. Independent or in tandem with gene variants, resilience to overload is modified by the outcomes of stressful experiences, particularly those that occurred during development (birth through adolescence). The adaptive changes that occur in response to previous stressors do so by gene-environment interactions resulting in modification to protein expression and neural remodeling. These changes are indicative of previous exposures, though their complexity cannot be overstated, as dysregulation is a non-linear process. An appreciation of the genetic landscape is required and may be understood by studying interactions of gene variants and changes in plasticity (capacity for allostatic accommodation) from previous environmental exposures and competing internal demands. To this end, I identify below a few targeted areas for further biomarker development and interpretation.

The biological literature has implicated several genetic mechanisms in the stress response that highlight mechanisms involved in the brain's adaptation to stress and the biochemical process of the physical response. Genetic predisposition is just as important in influencing the central response. If an individual has a higher baseline of anxiety, he or she might not venture out into society reducing access to social resources. Finally, if an individual is slower to metabolize cortisol, or any of the allostatic biochemical mediators, this could lead to excess or deficient basal levels of biochemical access for an allostatic response. Genetic predisposition to differences in biochemical mediator metabolism could predispose individuals to a higher resilience to damage from chronic stress decreasing the risk of becoming overloaded. Lower levels of biochemical mediators are needed to overcome the stressor, making the individual more likely to have positive outcomes when exposed to a chronic stress. Conversely, individuals who are genetically predisposed to over-production of biochemical mediators will have a higher basal level of biochemical exposure leading to a higher level of basal load. For these individuals, lower amounts of stress exposure may push internal component systems into dysregulation relative to other individuals.

Genetic variants

5-HTT. Proper serotonergic function impacts individual mood, sleep, and appetite; all are potentially involved in differences in individual capacity as well as in stress-induced dysregulation in the brain. The serotonin transporter gene (5-HTT) has well-studied polymorphisms involving differential outcomes in gene-environment interactions. This genetic interaction involves a heritable change in the DNA sequence that controls the length of this protein. The protein receptor has multiple alleles with short allele/short allele genotype prevalence between 12% and 75% depending on ethnicity (Goldman et al. 2010). Different versions (alleles) of the protein transporter have been differentially associated with decreased serotonin transporter availability resulting in lower reuptake of serotonin in the synaptic cleft. Studies have related the short form of the 5-HTT allele to an increase of depression in adulthood, especially after experiencing childhood mistreatment (Goldman et al. 2010). Because of the varying population prevalence, the impact of stress at a specific developmental stage, and potential susceptibility to individual capacity, incorporating the Serotonin Transporter Gene genotype into studies on the allostatic system is worth investigating.

Brain Derived Neurotropic Factor Protein (BDNF). The biological literature identified interactions between cortisol receptors and expression in BDNF proteins. Protein expression has been shown to predict amygdala and anterior hippocampal responses in anxious and depressed adolescents (Lau et al., 2010). BDNF expression has the possibility of limiting plasticity in the brain. Its activity has been found in the hippocampus, neocortex, amygdala, cerebellum, and hypothalamus making expression studies important for understanding how it is involved in both plasticity and communication between brain structures (Petryshen et al., 2010). Additionally, studies have identified that negative BDNF expression is found in epilepsy while increased levels of expression are found in successful recovery from episodes of depression (Karatsoreos & McEwen, 2011). Other studies have linked BDNF expression with neuronal development, survival, and plasticity (Petryshen et al., 2010). There is global variation in BDNF polymorphisms making this another potential candidate for expression studies in future research involving the allostatic system.

Epigenetic transmission of stress and impact across the life course. Finally, the field of public health genetics can offer insight into the transfer of the effects of external stressors across generations through epigenetic changes during pregnancy. This is a complex process and research is in its infancy, but a clear understanding of epigenetic regulation will add to the etiology of stress-induced mental illness. Recent advances in the fetal origins of disease provide numerous examples that maternal stress during pregnancy increases the risk of depression in offspring while more recent investigation into the regulation of the Human Placental 11B-Hydroxysteriod dehydrogenase 2 enzyme implicates potential regulatory pathways for cortisol transmission through the placenta (Hammen & Brennan 2003; Decker et al, 2012; Reynolds & Seckl 2012).

Any external environment that has the potential of making epigenetic changes in offspring during the perinatal period is important to explore. Epigenetic changes are at the nexus of gene-environment interactions. During the perinatal period, offspring experience an extreme level of epigenetic programming and reprogramming responding to environmental stimuli. The biological literature describes how the allostatic response system is under significant development early in life, and provides insight into the etiology of risk and resilience across the lifespan (Ganzel et al. 2010). During this period, stress experiences and the outcome of the stress response directly impact brain development by changing neural circuits impacting individual response to future stress reactivity (Ozbay et al. 2008). When an infant experiences stressors that are achievable the resulting adaptive stress response that leaves the individual more prepared to overcome future adversity. For each challenge that is positively overcome, the individual experiencing stress is increasingly more resilient to the negative effects of future stressors (Ozbay et al. 2008). Repeated episodes of uncontrollable or overwhelming stress during infancy and childhood, such as child abuse, can lead to ‘learned helplessness' and can cause exaggerated emotional, behavioral, SNS, and HPA axis responsiveness to future stressors, even into adulthood (Ozbay et al. 2008). These early life stressors and the individual's capacity to respond alter physiological set-points in the biological adaptation, setting the developing child on a trajectory toward susceptibility to increased risk to mental and physical illness from life stressors, or resilience to the outcomes of chronic stressors.

Understanding epigenetic regulation is an emerging field focused on the intergenerational translation of the impact of environmental conditions via epigenetic mechanisms in utero. Stressful external environments have the capacity to make epigenetic changes in offspring that limit plasticity and capacity to development in any allostatic component system, and are of particular interest to public surveillance and prevention research.

Limitations

The scope of the study design and methodology were, of necessity, limited to allow completion of a Master's thesis, with direct impact on the generalizability of the findings. The first limitation relates to the way in which multiple disciplines, independent in their own right, were categorized into one of two groups, biological or social sciences. In combining similar disciplines to gain a larger view of the allostatic model, many details were ignored as well as specific perspectives that each discipline has to offer. In making this choice, there was a loss of specificity which was not meant to ignore or disrespect the intricate differences each field has to add to the allostatic model. In addition, in limiting the scope of articles to a three-year window (2009-2012), many interdisciplinary perspectives that are working on understanding the stress response were excluded. Indeed, the multidisciplinary research coming to press in just the past six months is exploding across numerous disciplines, all advocating for and informing future interdisciplinary research. From the onset of this study, my position was situated as a newcomer at the nexus of both the biological and the social science fields. The conversations preceding the start of this work directed the course of research and refined its scope, both of which surely limited the ability to generalize these results across the social science disciplines. As to the biological literature, the specifics of this field are still being worked out while simultaneously being applied to larger population-wide research. Though this work simplifies many of these nuances for broader understanding, it is hoped this simplification will assist in starting interdisciplinary discussions that will be required for large research teams to accurately identify and measure the human stress response in service of reducing the global burden of chronic disease and health disparity.

Conclusion

The intersection of biological and social science research is illuminating the causal pathway between societal stressors and chronic disease. At a population level, comprehensive research on the etiology of stress using the allostatic model provides insights into new methods of measuring exposure differences between populations and in identifying pre-clinical states for early intervention. The intersection of external pressures and internal responses provides a research opportunity for interdisciplinary investigation into complex research questions. To accomplish this, an exchange of knowledge is occurring between the compendium of biological investigation into individual physiologic responses and the social sciences in search of intermediate measures of the consequences of long-term exposures to stressors from across the levels of the SEM. In the biological literature, there is an ongoing discussion of the complex role that the brain plays in mediating between the stressor and the physical arousal that results from exposure. Additionally, the detail of the allostatic concept in the biological literature allowed for differences between individuals in a state of high load and those in dysregulation. The details of the brain's involvement and direction in the allostatic response were not well represented in the social science articles, nor was there a clear understanding of the difference between high load and dysregulation. Conversely, the social science literature was informative in clarifying the detail and complexity found in the variety of pathways chronic stress may take, including identifying concepts such as double jeopardy and riskscapes. Both bodies of literature identified characteristics of individuals in a population that may change resilience to stress arousal; combining these characteristics and their measurement enhances more comprehensive approaches to studying the allostatic model. Future research investigating population-specific stress pathways in the pursuit of decreasing chronic health conditions will require interdisciplinary efforts from both the social and biological sciences with clear research aims and a common language.

Bibliography

Abbott, A. (2012). Stress and the city: Urban decay. *Nature, 490*(7419), 162-164. doi: 10.1038/490162a; 10.1038/490162a

Aneshensel, C. S. (2009). Toward explaining mental health disparities. *Journal of Health and Social Behavior, 50*(4), 377-394.

Ayres, L., Kavanaugh, K., & Knafl, K. A. (2003). Within-case and across-case approaches to qualitative data analysis. *Qualitative Health Research, 13*(6), 871-883.

Birks, Melanie, & Mills, Jane. (2011). *Grounded theory: A practical guide*. London: SAGE Publications Ltd.

Borrell, L. N., & Crawford, N. D. (2011). Social disparities in periodontitis among US adults: The effect of allostatic load. *Journal of Epidemiology and Community Health, 65*(2), 144-149. doi: 10.1136/jech.2009.098269

Braveman, P., Egerter, S., & Williams, D. R. (2011). The social determinants of health: Coming of age. *Annual Review of Public Health, 32*, 381-398. doi: 10.1146/annurev-publhealth-031210-101218

CDC. (2011). Mental health: Data and statistics. Retrieved July/1, 2012, from http://www.cdc.gov/mentalhealth/data-stats.htm

CDC. (2012). Social determinants of health: Publications. Retrieved October/14, 2012, from http://www.cdc.gov/socialdeterminants/Publications.html

Dekker, M. J., Tiemeier, H., Luijendijk, H. J., Kuningas, M., Hofman, A., de Jong, F. H., . . . Lamberts, S. W. (2012). The effect of common genetic variation in 11beta-hydroxysteroid dehydrogenase type 1 on hypothalamic-pituitary-adrenal axis activity and incident depression. *The Journal of Clinical Endocrinology and Metabolism, 97*(2), E233-7. doi: 10.1210/jc.2011-0601

Dick, D. M. (2011). Gene-environment interaction in psychological traits and disorders. *Annual Review of Clinical Psychology, 7*, 383-409. doi: 10.1146/annurev-clinpsy-032210-104518

Dohrenwend, B. P., Levav, I., Shrout, P. E., Schwartz, S., Naveh, G., Link, B. G., . . . Stueve, A. (1992). Socioeconomic status and psychiatric disorders: The causation-selection issue. *Science (New York, N.Y.), 255*(5047), 946-952.

Dowd, J. B., Simanek, A. M., & Aiello, A. E. (2009). Socio-economic status, cortisol and allostatic load: A review of the literature. *International Journal of Epidemiology, 38*(5), 1297-1309. doi: 10.1093/ije/dyp277

Economou, M., Madianos, M., Theleritis, C., Peppou, L. E., & Stefanis, C. N. (2011). Increased suicidality amid economic crisis in greece. *Lancet, 378*(9801), 1459. doi: 10.1016/S0140-6736(11)61638-3

Editorial. (2012). Life stresses. *Nature, 490*(7419), 143.

Ganzel, B. L., Morris, P. A., & Wethington, E. (2010). Allostasis and the human brain: Integrating models of stress from the social and life sciences. *Psychological Review, 117*(1), 134-174. doi: 10.1037/a0017773

Gee, J. P. (Ed.). (2005). *An introduction to discourse analysis: Theory & method* (2nd ed.). New York: Routledge.

Gee, J. P. (Ed.). (2011). *An introduction to discourse analysis: Theory & method* (3rd ed.). New York: Routledge.

Gehlert, S., Murray, A., Sohmer, D., McClintock, M., Conzen, S., & Olopade, O. (2010). The importance of transdisciplinary collaborations for understanding and resolving health disparities. *Social Work in Public Health, 25*(3), 408-422. doi: 10.1080/19371910903241124

Gehlert, S., Sohmer, D., Sacks, T., Mininger, C., McClintock, M., & Olopade, O. (2008). Targeting health disparities: A model linking upstream determinants to downstream interventions. *Health Affairs (Project Hope), 27*(2), 339-349. doi: 10.1377/hlthaff.27.2.339

Goldman, N., Glei, D. A., Lin, Y. H., & Weinstein, M. (2010). The serotonin transporter polymorphism (5-HTTLPR): Allelic variation and links with depressive symptoms. *Depression and Anxiety, 27*(3), 260-269. doi: 10.1002/da.20660

Gustafsson, P. E., Janlert, U., Theorell, T., Westerlund, H., & Hammarstrom, A. (2012). Social and material adversity from adolescence to adulthood and allostatic load in middle-aged women and men: Results from the northern swedish cohort. *Annals of Behavioral Medicine : A Publication of the Society of Behavioral Medicine, 43*(1), 117-128. doi: 10.1007/s12160-011-9309-6

Hackman, D. A., Farah, M. J., & Meaney, M. J. (2010). Socioeconomic status and the brain: Mechanistic insights from human and animal research. *Nature Reviews.Neuroscience, 11*(9), 651-659. doi: 10.1038/nrn2897

Hammen, C., & Brennan, P. A. (2003). Severity, chronicity, and timing of maternal depression and risk for adolescent offspring diagnoses in a community sample. *Archives of General Psychiatry, 60*(3), 253-258.

Hawkley, L. C., Lavelle, L. A., Berntson, G. G., & Cacioppo, J. T. (2011). Mediators of the relationship between socioeconomic status and allostatic load in the chicago health, aging, and social relations study (CHASRS). *Psychophysiology, 48*(8), 1134-1145. doi: 10.1111/j.1469-8986.2011.01185.x; 10.1111/j.1469-8986.2011.01185.x

Holmes, J. H., Lehman, A., Hade, E., Ferketich, A. K., Gehlert, S., Rauscher, G. H., . . . Bird, C. E. (2008). Challenges for multilevel health disparities research in a transdisciplinary environment. *American Journal of Preventive Medicine, 35*(2 Suppl), S182-92. doi: 10.1016/j.amepre.2008.05.019

Hsieh, H. F., & Shannon, S. E. (2005). Three approaches to qualitative content analysis. *Qualitative Health Research, 15*(9), 1277-1288. doi: 10.1177/1049732305276687

Hughes, V. (2012). Stress: The roots of resilience. *Nature, 490*(7419), 165-167. doi: 10.1038/490165a; 10.1038/490165a

Institute of Medicine of the National Academies (Ed.). (2002). *The future of the public's health in the 21st century* The National Academies Press.

Johnson, J. G., Cohen, P., Dohrenwend, B. P., Link, B. G., & Brook, J. S. (1999). A longitudinal investigation of social causation and social selection processes involved in the association between socioeconomic status and psychiatric disorders. *Journal of Abnormal Psychology, 108*(3), 490-499.

Juster, R. P., McEwen, B. S., & Lupien, S. J. (2010). Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neuroscience and Biobehavioral Reviews, 35*(1), 2-16. doi: 10.1016/j.neubiorev.2009.10.002

Karatsoreos, I. N., & McEwen, B. S. (2011). Psychobiological allostasis: Resistance, resilience and vulnerability. *Trends in Cognitive Sciences, 15*(12), 576-584. doi: 10.1016/j.tics.2011.10.005

Karlamangla, A. S., Singer, B. H., McEwen, B. S., Rowe, J. W., & Seeman, T. E. (2002). Allostatic load as a predictor of functional decline. MacArthur studies of successful aging. *Journal of Clinical Epidemiology, 55*(7), 696-710.

Keller, R. (2005). Analysing discourse. an approach from the sociology of knowledge. *Forum: Qualitative Social Research, 6*(3)

Kieling, C., Baker-Henningham, H., Belfer, M., Conti, G., Ertem, I., Omigbodun, O., . . . Rahman, A. (2011). Child and adolescent mental health worldwide: Evidence for action. *Lancet, 378*(9801), 1515-1525. doi: 10.1016/S0140-6736(11)60827-1

Krugers, H. J., & Hoogenraad, C. C. (2009). Hormonal regulation of AMPA receptor trafficking and memory formation. *Frontiers in Synaptic Neuroscience, 1*, 2. doi: 10.3389/neuro.19.002.2009

Lane, R. D., & Wager, T. D. (2009). The new field of brain-body medicine: What have we learned and where are we headed? *NeuroImage, 47*(3), 1135-1140. doi: 10.1016/j.neuroimage.2009.06.013

Lau, J. Y., Goldman, D., Buzas, B., Hodgkinson, C., Leibenluft, E., Nelson, E., . . . Ernst, M. (2010). BDNF gene polymorphism (Val66Met) predicts amygdala and anterior hippocampus responses to emotional faces in anxious and depressed adolescents. *NeuroImage, 53*(3), 952-961. doi: 10.1016/j.neuroimage.2009.11.026

Lund, C., De Silva, M., Plagerson, S., Cooper, S., Chisholm, D., Das, J., . . . Patel, V. (2011). Poverty and mental disorders: Breaking the cycle in low-income and middle-income countries. *Lancet, 378*(9801), 1502-1514. doi: 10.1016/S0140-6736(11)60754-X

Mair, C. A., Cutchin, M. P., & Kristen Peek, M. (2011). Allostatic load in an environmental riskscape: The role of stressors and gender. *Health & Place, 17*(4), 978-987. doi: 10.1016/j.healthplace.2011.03.009

Manenschijn, L., Koper, J. W., Lamberts, S. W., & van Rossum, E. F. (2011). Evaluation of a method to measure long term cortisol levels. *Steroids, 76*(10-11), 1032-1036. doi: 10.1016/j.steroids.2011.04.005

Mattei, J., Demissie, S., Falcon, L. M., Ordovas, J. M., & Tucker, K. (2010). Allostatic load is associated with chronic conditions in the boston puerto rican health study. *Social Science & Medicine (1982), 70*(12), 1988-1996. doi: 10.1016/j.socscimed.2010.02.024

McEwen, B. S. (2000). The neurobiology of stress: From serendipity to clinical relevance. *Brain Research, 886*(1-2), 172-189.

McEwen, B. S. (2012). Brain on stress: How the social environment gets under the skin. *Proceedings of the National Academy of Sciences of the United States of America, 109 Suppl 2*, 17180-17185. doi: 10.1073/pnas.1121254109; 10.1073/pnas.1121254109

McEwen, B. S., & Gianaros, P. J. (2011). Stress- and allostasis-induced brain plasticity. *Annual Review of Medicine, 62*, 431-445. doi: 10.1146/annurev-med-052209-100430

McEwen, B. S., & Wingfield, J. C. (2010). What is in a name? integrating homeostasis, allostasis and stress. *Hormones and Behavior, 57*(2), 105-111. doi: 10.1016/j.yhbeh.2009.09.011

McLaren, L., & Hawe, P. (2005). Ecological perspectives in health research. *Journal of Epidemiology and Community Health, 59*(1), 6-14. doi: 10.1136/jech.2003.018044

Mendel, C. M. (1989). The free hormone hypothesis: A physiologically based mathematical model. *Endocrine Reviews, 10*(3), 232-274.

Ozbay, F., Fitterling, H., Charney, D., & Southwick, S. (2008). Social support and resilience to stress across the life span: A neurobiologic framework. *Current Psychiatry Reports, 10*(4), 304-310.

Paradies, Y. (2006). A review of psychosocial stress and chronic disease for 4th world indigenous peoples and African Americans. *Ethnicity & Disease, 16*(1), 295-308.

Petryshen, T. L., Sabeti, P. C., Aldinger, K. A., Fry, B., Fan, J. B., Schaffner, S. F., . . . Sklar, P. (2010). Population genetic study of the brain-derived neurotrophic factor (BDNF) gene. *Molecular Psychiatry, 15*(8), 810-815. doi: 10.1038/mp.2009.24

Plazas-Mayorca, M. D., & Vrana, K. E. (2011). Proteomic investigation of epigenetics in neuropsychiatric disorders: A missing link between genetics and behavior? *Journal of Proteome Research, 10*(1), 58-65. doi: 10.1021/pr100463y

Reynolds, R. M., & Seckl, J. R. (2012). Antenatal glucocorticoid treatment: Are we doing harm to term babies? *The Journal of Clinical Endocrinology and Metabolism, 97*(10), 3457-3459. doi: 10.1210/jc.2012-3201; 10.1210/jc.2012-3201

Rorty, A. (Ed.). (1996). *Essays on aristotle's rhetoric*. Berkeley, California: University of California Press.

Seeman, T. E., Singer, B. H., Rowe, J. W., Horwitz, R. I., & McEwen, B. S. (1997). Price of adaptation-allostatic load and its health consequences. *Archives of Internal Medicine, 157*, 2259-2268.

Seeman, T. E., Singer, B. H., Ryff, C. D., Dienberg Love, G., & Levy-Storms, L. (2002). Social relationships, gender, and allostatic load across two age cohorts. *Psychosomatic Medicine, 64*(3), 395-406.

Smith, J.A., Flowers, P., Larkin, M. (2009). *Interpretive Phenomenological Analysis: Theory, Method and Research*. Thousand Oaks: Sage Publications Ltd.

Stalder, T., & Kirschbaum, C. (2012). Analysis of cortisol in hair--state of the art and future directions. *Brain, Behavior, and Immunity, 26*(7), 1019-1029. doi: 10.1016/j.bbi.2012.02.002; 10.1016/j.bbi.2012.02.002

Sterling, P., & Eyer, J. (1988). Allostasis: A new paradigm to explain arousal pathology. In S. Fisher, & J. Reason (Eds.), *Handbook of life stress, cognition, and health* (pp. 629-649). Chichester, England: Wiley.

Stewart, J. A. (2006). The detrimental effects of allostasis: Allostatic load as a measure of cumulative stress. *Journal of Physiological Anthropology, 25*(1), 133-145.

Thoits, P. A. (2011). Mechanisms linking social ties and support to physical and mental health. *Journal of Health and Social Behavior, 52*(2), 145-161. doi: 10.1177/0022146510395592

Uher, R. (2009). The role of genetic variation in the causation of mental illness: An evolution-informed framework. *Molecular Psychiatry, 14*(12), 1072-1082. doi: 10.1038/mp.2009.85

WHO. (2012). Commission on social determinants of health: Key concepts. Retrieved October/14, 2012, from http://www.who.int/social_determinants/thecommission/finalreport/key_concepts/en/index.html

WHO. (2012). Social determinants of health: Social determinants Retrieved October/14, 2012, from http://www.who.int/social_determinants/en/

Wolkowitz, O. M., Epel, E. S., Reus, V. I., & Mellon, S. H. (2010). Depression gets old fast: Do stress and depression accelerate cell aging? *Depression and Anxiety, 27*(4), 327-338. doi: 10.1002/da.20686