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Allostatic load - a challenge to measure multisystem physiological dysregulation

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Allostatic load – a challenge to measure multisystem physiological dysregulation

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Abstract

Allostatic load is a sub-clinical dysregulation state, resulting from the body's response to stress. Allostatic load accumulates gradually over the life course and affects a number of physiological systems. Measuring multisystem dysregulation and changes in it over time is very challenging. In this paper, we discuss composite measures used to capture allostatic load and the challenges involved in deriving and using these measures. Our focus is on measuring allostatic load in later life.

Contents

1. Introduction

In this paper, we discuss the use of composite measures of allostatic load and the problems involved in creating these measures and analysing changes in them over time. First, we introduce the concept of allostatic load as a measure of multisystem dysregulation. Secondly, we review the methods previously used for measuring allostatic load. Third, we discuss the need for longitudinal studies to measure change in allostatic load and its association with predictors and health outcomes. We conclude the paper with a summary of current promising approaches to the measurement of allostatic load. We also discuss future directions in developing measures of allostatic load and changes in allostatic load over time.

2. Allostatic load – a multisystem response to stress

Daily stress and repeated stressful events over the life course can take a significant physiological toll on the body (McEwen & Stellar, 1993). The stress response in itself does not lead to adverse health outcomes, it actually protects the organism from harmful effects. However, each time the stress response is activated, physiological adjustments must be made and over time these adjustments lead to accummulated wear and tear (McEwen, 1998).The theory of allostatic load decribes this accumulated physiological wear and tear and how it may lead to a multisystem dysregulation state and further to poor health . According to this theory, the organism is in a recurrent process of maintaining physiological stability by adapting itself to environmental demands. This process is called allostasis. Allostatic load is the cost of adaptation to cumulative stress. From a biological perspective, stress is chronic activation of responsive physiological systems. However, the extent of activation depends on environmental (number and magnitude of live events) and psychological (evaluation of the stressful events) factors (Clark, Bond, & Hecker, 2007). Due to these different dimensions of stress, there are great individual differences in outcomes. Allostatic load can originate from repeated stress (more stressful events), but may also be a result of lack of adaptation or prolonged or inadequate stress response. Allostatic load is likely to develop when acute stress response becomes chronic. Consequently, health outcomes depend on successful adjustment to the changing demands of the environment: a rapid and promptly terminated stress response facilitates better health.

How does the body react to stress?

Allostasis-adaptation involves nervous, endocrine and immune systems. The immediate response to different stressors is the brain's evaluation of the threat carried out by the amygdala, hippocampus and pre-frontal cortex (McEwen & Gianaros, 2011). This activates the sympathetic-adrenal- medullary (SAM) axis which releases catecholamines such as epinephrine. This is the acute response to the stress. The brain's evaluation activates a sympathetic nervous system response for behavioural fight or flight that prepares the body to react to a stressful situation. It also triggers inflammation, an immune response to prevent tissue damage from pathogen infection. A more long-term response to stress is mediated by the hypothalamic-pituitary-adrenal (HPA) axis which releases glucocorticoids. The activation of the HPA axis supports the increase of metabolic activity to provide enough energy and also manages the parasympathetic nervous system to define the level of physiological arousal. Stress responses can alter health-related behaviours, such as smoking, alcohol use, sleep, diet and exercise, which in turn increase the risk of high allostatic load. How well the physiological system can adapt to the environmental challenges defines the extent of accumulation of physiological dysfunction, allostatic load. If it remains high for a long time, the sub-clinical dysfunction can develop into disease. The pathways to disease may derive from malfunction of several systems. For instance, cardiovascular diseases may result from stress related amygdale hyperactivity, elevation in inflammation and abnormal metabolic functioning. Stress related elevation in inflammation levels and cortisol secretion may on the other hand decrease cell sensitivity to insulin promoting the development of metabolic disorders, such as diabetes. Elevated inflammation levels and cortisol secretion may also promote neurodegeneration, which may lead to cognitive decline and dementia. Inflammation and metabolic abnormalities may contribute to shortening of a region of repetitive DNA at the end of chromosomes (telomere attrition) causing cellular aging (Danese & McEwen, 2012).

A younger organism is often better equipped to react to stress and quicker to recover from it than an older one. However, a number of individual factors such as genetic makeup, developmental stage and previous personal experiences play important roles both in how stress is perceived and how the body reacts to and recovers from stressful situations.

The allostasis-adaptation process often follows three stages of stress mediation (see Figure 1). In the first stage, the acute stress response activates the primary mediators including stress hormones (e.g. epinephrine, norepinephrine and cortisol) and anti-inflammatory cytokines (e.g. Interleukin-6). In the second stage, a more long-term stress response results in the secondary outcomes which include changes in metabolic (e.g. insulin, glucose, total cholesterol, triglycerides, visceral fat depositing), cardiovascular (e.g. systolic and diastolic blood pressure) and immune systems (e.g. C-reactive protein, fibrinogen). Finally, the allostasis-adaptation process results in the tertiary outcomes that can be poor health, cognitive decline, cellular aging, diseases, such as cardiovascular diseases and diabetes, and eventually death (Leahy & Crews, 2012; Seeman, McEwen, Rowe, & Singer, 2001). It is not clear how long it takes to develop secondary and tertiary outcomes after primary stress reactions. Characteristic of the allostasis-adaptation process is that the physiological mediators are interconnected, reciprocal and have non-linear effects (Juster, McEwen, & Lupien, 2010; McEwen & Gianaros, 2011).

Allostatic load affects many organ systems highlighting the importance of measuring allostatic load as a multisystem concept. For this reason measurement is based on deriving a composite score based on indicators from a number of different systems. However, developing these composite measures is challenging. Allostatic load accumulates throughout life and therefore the study of processes in longitudinal settings is also needed. Because these processes are often non-linear and reciprocal, the estimation of change may become complex.

Stress mediation	**System**	**Biomarker**
Primary mediators	Neuroendocrine	Epinepherine, norepinephrerine, dopamine, cortisol, dehydroepiandrosterone (DHEAS), aldosterone
Secondary outcomes	Immune	Interleukin-6, tumor necrosis factor-alpha, c-reactive protein (CRP), insulin-like growth factor-1 (IGF-1)
	Metabolic	HDL and LDL cholesterole, triglycerides, glucosylated hemoglobin, glucose insulin, albumin, creatinine, homocysteine
	Cardiovascular and respiratory	Systolic blood pressure, diastolic blood pressure, peak expiratory flow, heart rate/pulse
	Anthropometric	Waist-to-hip ratio, body mass index (BMI)
Tertiary outcomes	Poor subjective health, disability, cognitive decline, cellular aging, diseases, death	

Figure 1. Stress mediation, systems and biomarkers used to measure allostatic load.

3. Measures of allostatic load

The usual approach to measuring allostatic load is through composite measures of a range of *biomarkers*, various measures that are sensitive to subtle changes in the biological state resulting from environmental exposure (see Figure 1).

Which biomarkers should be used to measure allostatic load?

In one of the first attempts to operationalise the definition of allostatic load, 10 biomarkers were used (Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). Four of them were primary mediators: cortisol, epinephrine, norepinephrine and dehydroepiandrosterone sulphate (DHEAS). Six of them represented secondary outcomes: systolic and diastolic blood pressure, waist-hip ratio, high-density lipoprotein (HDL) and total cholesterol ratio and glycosylated haemoglobin. The measures were chosen so that they would cover both primary mediators and secondary outcomes of allostatic load and represent the function of neuroendocrine, cardiovascular, metabolic and fat deposition systems. The allostatic load score was the number of biomarkers where the individual was located in the highest risk quartile.

Many subsequent studies have also used 10 biomarkers to create the composite score, but the number of biomarkers varies from one study to another (Juster et al., 2010; Seplaki, Goldman, Glei, & Weinstein, 2005). There is a wide range of biomarkers (see Figure 1). Which biomarkers are used varies between studies, depending on the availability of measures. This can make it difficult to compare results from different studies. Although the summary measure of allostatic load is a better predictor of later health than any individual biomarker (Seeman et al., 2001; Seeman et al., 1997) or markers focussed on specific disease such as metabolic syndrome (Karlamangla, Singer, McEwen, Rowe, & Seeman, 2002), it is not clear what is the best combination of biomarkers to use to measure allostatic load. A poor composite score may result from using measures that are not relevant to physiological dysregulation or failing to include measures that are relevant. The inclusion of non-relevant measures would increase measurement error in the summary measure of allostatic load. Exclusion of relevant measures, on the other hand, would weaken the predictive power of the measure. Often the choice of biomarkers is pragmatically dictated by what is available in the data. New data collection involves compromising between what is ideal and what can be collected to maximise the availability of valid data (e.g. the use of non-invasive and inexpensive measures).

Allostatic load score should represent the interplay of different systems (e.g. inflammatory, neuroendocrine, metabolic) and the markers may act as acute (primary mediators) or more long-term effects (secondary outcomes). It is important to take these into account in creating a composite measure (Seplaki et al., 2005). Different systems can be weighted so that the outcome score is representative of multisystem dysregulation. Measures of metabolic and cardiovascular systems (clinical measures) are stronger predictors of later health outcomes than inflammatory and neuroendocrine measures (non-clinical measures) (Goldman, Turra, Glei, Lin, & Weinstein, 2006). Primary mediators representing endocrine system, on the other hand, are more strongly associated with stress than secondary outcomes in inflammatory, cardiovascular or metabolic systems (Clark et al., 2007). The use of both primary mediators and secondary outcomes in the composite allostatic load score also complicates the decision about the optimal time to carry out the data collection. Data are often collected on a single occasion. This may not be an advisable approach for measures that require long-term monitoring. For example, use of cortisol measured on a single occasions has been criticized (Dowd, Simanek, & Aiello, 2009).

Previous results indicate that it is important to distinguish the two levels of mediation in allostatic load measures (Juster et al., 2010). Hence, it may be useful to use separate summary scores for primary mediators and secondary outcomes. The association between the allostatic load measure and health outcome is sometimes not linear, for instance both the top highest and bottom lowest quartiles may represent high allostatic load risk. In this case it may be necessary to allow both high and low values to be counted in the score.

How should the composite score of allostatic load be calculated?

The measure used most often is a simple count score. This comprises a count of the number of biomarkers for which the individual falls into the highest risk quartile of each measure's sample distribution (Seeman et al., 1997). In addition to the upper or lower 25th percentile, the cut off point can be also set to the highest and lowest 10 %. The higher cut-off points produce a measure that is a stronger predictor of health. However, it may lack sensitivity to detect early signs of dysfunction compared to using lower cut-off points. It is also possible to use clinical cut-offs, but until now there are no universally agreed values for cut-offs (Juster et al., 2010; Seeman et al., 2001).

There are also a number of other methods to measure allostatic load: Z-score allostatic load index , bootstrapping, canonical correlations, recursive partitioning, *k*-means cluster analysis, genetic programming based symbolic regression algorithms and grade of membership methods (Juster et al., 2010). The Z-score index reflects an individual's difference from the sample mean in each biomarker included. It is easy to derive but may need adjustment if measures have quadratic associations with health outcomes. Bootstrapping is a resampling technique that makes inferences about population parameters by generating multiple repetitive computations that estimate the shape of sampling distributions. Bootstrapped estimates can then be used as weights for allostatic load markers. Canonical correlation is a multiple correlation method to identify the best set of biomarkers to predict health outcomes. Recursive partitioning uses multivariate reduction to identify the best biomarkers and cut points to predict health outcomes. *K*-means cluster analysis is a multivariate reduction technique to identify homogeneous groups of cases that are then sorted into one of any specified number of clusters. Genetic programming based symbolic regression algorithms use a regression and classification approach to simulate the dependency between the variables in the data.

Grade of Membership methods are widely used in creating allostatic load scores (Seplaki et al., 2005). Based on a multivariate reduction technique, this estimates the degree to which each individual displays low, moderate or high values on each of the biomarkers used to a set of individual-specific weights that measure an individual's similarity to each of a certain number of predetermined archetypal profiles (e.g. low vs. high values in primary mediators and low vs. high values in secondary outcomes and the reference profile of having low values in most of the biomarkers). For example, if five archetypes are specified or derived, each individual is given five separate scores. The sum of the four scores (excluding the low risk reference profile) is calculated and this new score is used to measure the dissimilarity from the low risk profile. Although grade of membership is a more fine-tuned approach to detect profiles of allostatic load, the disadvantage is that it is quite complicated to calculate.

While some of the composite scores are relatively simple to create (e.g. z-scores), others require more complex programming (e.g. genetic programming). Some methods, such as canonical correlations and recursive partitioning, although they are intended to measure the multidimensional nature of allostatic load more accurately , are based on information on outcomes. The incorporation of health outcomes into the calculation of allostatic load score can result in models being overfitted so that they cannot be replicated in another context (Seplaki et al., 2005). Another problem is the direction of cause and effect in the associations, especially if the allostatic load measures and health are measured simultaneously.

The comparison of different composite measures of allostatic load has shown relatively little differences in how powerful they as predict ors of health outcomes (Karlamangla et al., 2002; Seeman et al., 2001; Seplaki et al., 2005). There is some evidence that the count-based summary measures that incorporate risk at both high and low tails and measures using continuous properties of the scale (e.g. z-scores) may be slightly better predictors of a wider array of health outcomes than the other measures (Seplaki et al., 2005). The advantage of using the simple count-based and z-score measures is also that they are easy and straightforward to calculate. More comparative studies on different methods are needed.

4. Measuring processes over time in allostatic load

Allostatic load by its definition is a process that develops over time. It is therefore important to choose methods suitable for studying it as a dynamic, changing concept. However, surprisingly very few studies have examined changes in allostatic load or the longitudinal pathways between the different factors associated with allostatic load.

Ageing and individual biomarkers

*S*everal studies (cross sectional and longitudinal) suggest associations between age and particular biomarkers. For example, systolic and diastolic blood pressure gradually increase across the life time until approximately age 70 when the increase appears to cease, see reviews (Fleg & Strait, 2012; Uchino, Birmingham, & Berg, 2010). In a longitudinal study, diastolic blood pressure decreased in later life (Glei, Goldman, Lin, & Weinstein, 2011). Fewer studies have examined age-related changes in neuroendocrine measures. Age appears to be associated with higher levels of norepinephrine, whereas some cross-sectional (Blandini et al., 1992; Esler et al., 2002) and longitudinal (Glei et al., 2011) findings suggest that epinephrine reactivity tends to reduce at older ages. However, not all studies have confirmed these findings , (for a review, see (Piazza, Almeida, Dmitrieva, & Klein, 2010). Higher levels of cortisol and also other adverse patterns in cortisol secretion are more prevalent in older age according to a review (Chahal & Drake, 2007) and some cross-sectional studies (Deuschle et al., 1997; VanCauter, Leproult, & Kupfer, 1996). Some, but not all, studies have found an association between age and greater HPA axis reactivity to stressors (see review by(Piazza et al., 2010). Generally, the immune system is highly effective for the first 40 years of life. After that, some aspects of it start to decline,(for a review see (Aw, Silva, & Palmer, 2007)). The immune reactivity to protect and repair cells generally declines, while systems that promote inflammation such as interleukin-6 and C-reactive protein typically increase in older age, (see review by (Piazza et al., 2010) and two longitudinal studies (Glei et al., 2011; Kizer et al., 2011).

Ageing and the composite score of allostatic load

Very few studies have investigated changes in allostatic composite scores over time. Reasons for this include practical difficulties as collecting data and analysing a complex composite measure over time is time consuming and demanding. Participants have to be willing to be repeatedly tested on various measures, many of them invasive. Secondly, analysis of blood or tissue samples requires standardised laboratory settings. Thirdly, changes over time in complex composite measures are not easy to analyse. Because of the use of counts, complex distributions and non-linear associations, they cannot be easily modelled by traditional statistical techniques that assume linear associations between predictors and outcomes. Most previous studies have used quite simple approaches, such as difference scores, to analyse change over time.

The few longitudinal studies undertaken generally show that increase in allostatic load is associated with higher levels of stress and poorer health outcomes. In the MacArthur Studies, change in allostatic load was studied over a period of 2.5 years. Those older people whose allostatic load scores increased were found to be at higher risk of death (Karlamangla, Singer, & Seeman, 2006). In a study among older caregivers, allostatic load score increased over a two-year follow-up (Clark et al., 2007). The change was mainly due to increases in primary mediators of allostatic load. The increase was evident only among caregivers, and not non-caregivers. In a very small study of older adults, allostatic load increase over a three-year period was associated with increases in depressive symptoms (Juster et al., 2011). However, when adjusted by age and gender the association disappeared. The small sample size reduced further over the follow-up.

Some studies have also examined associations between allostatic load and its predictors and health outcomes in a longitudinal setting. For instance, Goldman and her colleagues studied allostatic load and later health outcomes in the Taiwanese older population over a three-year period (Goldman et al., 2006). The results suggested that allostatic load provides early warning signs of later poor health. The authors also highlight the importance of studying the associations longitudinally, as in cross-sectional setting baseline health cannot be controlled. Initial allostatic load level predicted frailty in a three-year follow-up among older people (Gruenewald, Seeman, Karlamangla, & Sarkisian, 2009). A number of other long-term pathways between the predictors and allostatic load have also been suggested, such as early parent-child relationships (Taylor, Karlamangla, Friedman, & Seeman, 2011), and adverse childhood experiences (Danese & McEwen, 2012; McEwen, 2003).

5. Future directions in measuring allostatic load

As allostatic load being a complex multisystem concept ,measuring it is challenging. The factors closely related to allostatic load, -stress and health-, are not simple, unitary concepts either. It is important to disentangle the primary mediators and secondary outcomes from tertiary outcomes (Goldman et al., 2006). Primary mediators are more related to stress, whereas secondary outcomes are more indicators of loss of functioning and health problems. As allostatic load is about long-term effects on physical dysregulation, it is important to use markers measuring chronic stress (not dependent on how stressful one's day has been). More studies are needed on the dynamic, cumulative nature of allostatic load, based on repeated measures. A number of papers discuss the importance of measuring physical dysregulation longitudinally (Goldman et al., 2006; Juster et al., 2011; Piazza et al., 2010) but few such studies exist. Concerns have also been raised about the reliability of measures based on one single measurement occasion. For instance, cortisol measures are highly dependent on the time of measurement, even a half an hour's delay may make a big difference in the values obtained (Dowd et al., 2009). The use of repeated measures over a number of days may help obtain more reliable values. Use of daily diaries may also give additional information on changes over time. A combination of data sources and follow-up over a longer period makes it possible, for instance, to compare an individual's biomarker levels on stressor days to stressor-free days (Piazza et al., 2010).

By definition, allostatic load is a multisystem concept and from the beginning of the use of the concept, it has included biomarkers that have different functions. Representing multisystem dysregulation, allostatic load should be measured with more than one measure, representing more than one system (Seeman et al., 2001). Interestingly, despite the wide variation in the composite measures used, the summary scores present similar patterns of increase with age. Although allostatic load tends to cumulate over time, flattened variability may also be an indicator of poor handling of stress (e.g. reduced heart rate variability and cortisol level changes). Both rapid recovery and higher variability may result in better health (Epel, McEwen, & Ickovics, 1998). It is important to take into account these different patterns in responses in modelling change.

Applying developmental theories may help to gain a deeper understanding of the processes and identifying early and late trajectories. In this it would be useful to use path models based on longitudinal data. To understand the mechanisms of accumulation of [physical wear and tear over time, it is necessary to study ageing organisms, but include data on early development (at least from midlife and preferably from childhood). It is important to remember that the use of linear models may be limiting: stress effects may interact with behaviour.

This leads to the challenge of measuring cumulative allostatic load and the variability in individual trajectories. What is adaptative and what maladaptive depends on the context. One system may benefit from a certain intervention while it may be detrimental to another. Generally, studies of allostatic load are interested in chronic stress measures and may compare populations exposed to chronic stress to ones not so exposed. Such stressors may accumulate over a number of years, for instance the effects of maltreatment in childhood, teenage childbearing, care giving and low socio-economic status. However, a question raised by some previous studies (Dowd & Goldman, 2006) is: is it stress that is the underlying mechanism or is it something else? To find answers to these questions it is important to distinguish the role of intermediate factors such as health-related behaviours and possible interactions, e.g. self-esteem, psychological adaptation strategies and social support may be associated with better well-being only among those with low socioeconomic position (Chen, Miller, Lachman, Gruenewald, & Seeman, 2012; Seeman et al., 2001). Individual differences in allostatic load may result from differential exposure, reactivity and recovery from stressors. This calls for examining factors that promote successful recovery from stress and detailed information on life events themselves. It is also important to investigate the role of intermediate factors, such as social support, health-related behaviours and resilience factors, such as coping and mastery. Stress exposure may result in both vulnerability and resilience (curvilinear function, inoculation to stress) (Parker & Maestripieri, 2011) . The inclusion of genetic information to understand individual differences in why some people respond the circumstances in a different way from others would be also useful (Seeman et al., 2001).

From a methodological point of view, the use of long follow-ups, investigation of mediators or moderators and using a varying combination of biomarkers inevitably leads to a number of questions and problems. One is attrition and dealing with declining number of participants over long follow-ups. The average trajectory of physiological dysregulation may be biased because of selection due to mortality or poor health which in turn may be associated with allostatic load itself (Karlamangla et al., 2006; Leahy & Crews, 2012). It is important to take into account attrition and hidden heterogeneity in longitudinal models. A second question is the required power and sufficiency of the sample size to investigate interactions and complex models. Unfortunately this is rarely achieved: collecting data on biomarkers requires more resources than an ordinary

survey and often inevitably leads to small sample sizes and fewer repeated measurement occasions. However, some relatively inexpensive and user-friendly data collection methods are available (such as saliva collections) that can be carried out by participants and returned by post (Adam & Kumari, 2009). This may make it easier to study larger samples and collect repeated measurements. The third question is the generalisation of the findings to other populations. At the moment, the count measures of allostatic load are based on sample distributions (Juster et al., 2010). The cut-off points for the counts vary from one population to another and can make it difficult to compare the findings. Finding universal cut-off points is however challenging, as the populations may not be comparable. In general, normative data concerning biomarkers and health outcomes are needed. Normative data concerning especially older people are very scarce (Nilsson et al., 2003), most of the studies include only people up to middle age. The task gets more difficult in old age, as it is harder to differentiate what is normative and what is pathological. To take into account the effect of medication and other medical interventions in composing allostatic load score also becomes an increasingly important question when studying older populations.

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