Allostatic Load

A REVIEW OF THE LITERATURE

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List of Abbreviations

Abbreviation	Description
ACC	Anterior cingulate cortex
ACTH	Adrenocorticotrophic hormone
ADF	Australian Defence Force
CARDIA	Coronary Artery Risk Development in Young Adults Study
CHD	Coronary heart disease
CMVH	Centre for Military and Veterans' Health
CNS	Central nervous system
CVD	Cardiovascular disease
DHEA	Dehydroepinandrosterone
DSM-IV	Diagnostic and statistical manual – fourth edition
DVA	Department of Veterans' Affairs
GAD	Generalised Anxiety Disorder
GI	Gastrointestinal disease
HPA axis	Hypothalamus-pituitary-adrenal axis
IBS	Irritable bowel syndrome
ICD-10	International classification of diseases – tenth edition
IED	Improvised explosive device
IOM	Institute of Medicine
MDD	Major Depressive Disorder
MEAO	Middle East Area of Operations
MHAT	Mental Health Advisory Team
NVVRS	National Vietnam Veterans' Readjustment Study
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
pACC	Perigenual anterior cingulated cortex
PSNS	Parasympathetic nervous system
PTSD	Post traumatic stress disorder
QBI	Queensland Brain Institute
RMA	Repatriation Medical Authority
SAM	Sympathetic-adrenal-medullary

SES	Socioeconomic status
SNS	Sympathetic nervous system
SOW	Statement of works
VES	Vietnam Experience Survey
WHO	World Health Organisation
WHR	Waist-hip ratio

Summary of Key Terms

The definitions for key terms in the current review are presented (reproduced from Karatsoreos & McEwen, 2009, p. 71).

Key Term	Definition
Homeostasis	Essential parameters of life
Allostasis	Active process of maintaining homeostasis
Allostatic state	Elevated level of mediators (e.g., increased blood pressure, hyper-cortisolemia)
Allostatic load	Cumulative change (e.g., body fat; remodelling of neuronal circuitry)
Allostatic overload	Wear-and-tear, pathophysiology (e.g., atherosclerosis; neuronal damage and cell loss)

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Executive Summary

Introduction

Allostatic load refers to the cumulative effects of chronic and acute stress on the body. It is the process and the product of 'wear-and-tear' on the body and brain. This results from chronic over-activity or inactivity (called dysregulation) of physiological systems that are normally involved in adaption to environmental challenges (McEwen & Gianaros, 2010). The frequency of exposure to these challenges is unique to each individual and individuals accumulate allostatic load at different rates over the life-course. The outcomes of allostatic load can be physiological, psychological, and psychosocial health conditions.

Allostatic load is an evolving model and only one of several models devised to examine and understand the long term health effects of stress. The model cannot explain all causes of ill-health and disease, however it is emerging as a useful model for investigating how stress experienced during military service may impact negatively on health. There are significant opportunities to improve our understanding of measurement tools and the myriad of challenges related to establishing causality between stress and longer term health outcomes. These outcomes include, for example, cardiovascular disease, diabetes, gastrointestinal disorders, and substance use.

There have been few studies which have specifically explored a causal link between allostatic load and adverse health outcomes, and these studies have limitations in design and in consistency of measurement. Consequently this report attempts to draw together evidence from existing studies on *stress* and health outcomes, apply that knowledge to the allostatic load model, and draw some conclusions relevant to the military and veterans' health sector.

Aim

The aim of this review is to provide an overview of the allostatic load model in the context of the human stress response and its potential health outcomes for ADF members and veterans.

The review examines current definitions of stress and the allostatic load model and provides evidence for relationships between military stressors and subsequent health outcomes. It concludes by discussing areas of interest for the Department of Veterans' Affairs (DVA).

Stress

Stress has long been recognised as a major contributing factor to poor health. Much research has focused on the impact of acute traumatic events on mental health, but there are

knowledge gaps regarding the health consequences of chronic or repeated stress. In the short term, the body's stress response is adaptive because it promotes survival. However, this same response can be maladaptive if it is chronic, or repeatedly activated over time. It is the maladaptive aspect of this process that is central to the concepts of allostatic load and overload.

Allostatic load

The allostatic load model describes the process of adaptive functioning of the human biological system in response to stressful stimuli. The model describes the processes that occur when stress is experienced over a long period of time or with repeated stressors (see figure below). Chronic and repeated stressors may be punctuated by acutely stressful incidents. The outcomes are negative health consequences that result from the shift from adaptive to maladaptive functioning.
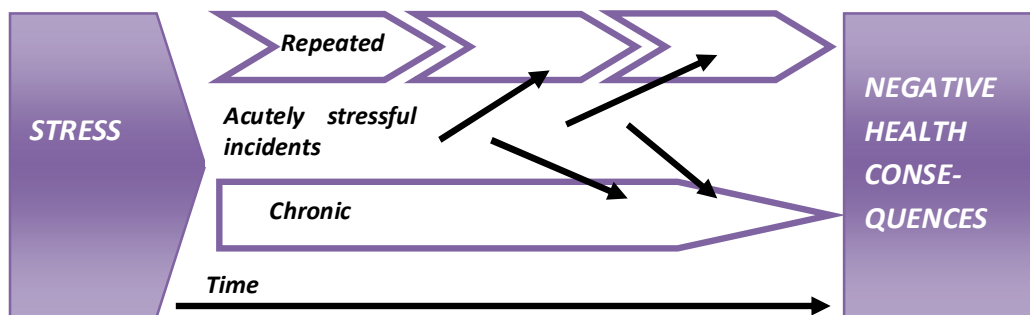
Figure 1. Stress leading to negative health outcomes.

The key to understanding the allostatic load model is 'homeostasis'. *Homeostasis* refers to a person's ability to return to a pre-set steady state of equilibrium following a response to stressful stimuli. It particularly relates to a return to physiological stability in parameters such as body temperature, pH, and heart rate following a stress response typically of the 'fight or flight' kind. It is self-limiting because triggering the response through mediators starts a negative feedback loop, returning the parameters to 'normal'.

Allostasis is an extension of the concept of homeostasis. It refers to the ability of the human regulatory system to *change* a set point and operate at an elevated or reduced level. Allostasis is defined as achieving stability through change (McEwen & Wingfield, 2003). It is the process that maintains homeostasis and actively promotes adaptation. For example, elevated heart rate or cortisol may be needed in the short-term to help us adapt.

Allostatic load takes into consideration the long-term cost of repeated stress and wear-and-tear on the body and brain. This leads to pathology and chronic illness. For example, changes in

brain reactivity and increased production of stress hormones (called biological mediators) may have negative physical, psychological, and social health implications (Fava et al., 2010).

The evidence is that homeostasis maintains the parameters of life, allostasis is the process that allows the body to adapt through change, and allostatic load and overload are the result of cumulative wear and tear on the brain and body.

Allostatic load and adverse health outcomes

There is a considerable body of evidence to suggest that stress has significant effects on health as a result of allostatic load. The research involves, for the most part, correlational analyses of stress with the occurrence of autonomic, cardiovascular, gastrointestinal, and immune system pathology.

The literature indicates that allostatic load, via biological mediators, can contribute to the development of ill-health and disease including: cardiovascular, metabolic, immune, and autoimmune disorders, and is correlated with psychological disorders such as post traumatic stress disorder (PTSD), major depressive disorder, and anxiety. However, disentangling psychological and physiological health outcomes is difficult. For example, although PTSD is a psychological disorder, it is also associated with circulatory, digestive, musculoskeletal, nervous system, and respiratory diseases. Similarly, depression is also linked to physiological outcomes, including cardiovascular disease (CVD) and susceptibility to colds, and indirectly to diabetes, premature aging (including osteoporosis), and mortality (McEwen & Stellar, 1993).

Military stressors

The relationship between stress and illness is enormously complex. However, links between stressors during military deployment and potential negative health outcomes are becoming clearer through research from the United States, the United Kingdom, Australia, and elsewhere. It is the cumulative effect of stressors that define allostatic load. This is particularly pertinent in a military context because even ordinary events, such being separated from family, may become extra-ordinary in certain circumstances, particularly at different points in the deployment cycle. Furthermore, the likelihood of encountering chronic or traumatic experiences may be greater for military personnel compared to their civilian counterpart.

Military personnel can be exposed to a range of stressors across each stage of the deployment cycle, including possible death or injury to oneself, killing or injuring others, poor living conditions, and harsh physical environments. Noncombat stressors may also be experienced by deployed personnel, including being separated from family, friends, and colleagues; loss of or reduction in income; and concern over employment status when deployment ends (O'Toole, Marshall, Schureck, & Dobson, 1999). In addition, military personnel may be exposed to

multiple deployment-related stressors and have multiple exposures to a single stressor, all of which may adversely affect their physical and mental health (IOM, 2008).

Although stress responses and potential long-term consequences differ between individuals, military personnel may experience significant levels of acute, traumatic, and chronic stress which is likely to contribute to allostatic overload.

Deployment and adverse health outcomes

Sufficient evidence for a *causal relationship* between deployment to a war zone and a specific health effect in humans has not been found (IOM, 2008). However, a *consistent positive association* was found between deployment to a war zone and psychiatric disorders, including PTSD, other anxiety disorders, and depressive disorders; alcohol abuse; accidental death in the early years after deployment; suicide in the early years after deployment; and marital and family conflict.

Limited but suggestive evidence of a positive association was found in the case of drug abuse; chronic fatigue syndrome; gastrointestinal symptoms consistent with functional gastrointestinal disorders, such as irritable bowel syndrome or functional dyspepsia; skin disorders; fibromyalgia and chronic widespread pain; increased symptom reporting, unexplained illness, and chronic pain; and incarceration.

Inadequate/insufficient evidence existed to determine whether an association existed between stress and an effect was reached in relation to cancer; diabetes mellitus; thyroid disease; neurocognitive and neurobehavioral effects; sleep disorders or objective measures of sleep disturbance; hypertension; coronary heart disease; chronic respiratory effects; structural gastrointestinal diseases; reproductive effects; homelessness; and adverse employment outcomes.

Therefore, there is growing evidence that deployment (particularly to a war zone which implies considerable stress) is associated with some negative health outcomes, which provides support for the link between deployment and the hypothesised allostatic load model. However, the limitations of these studies make it difficult to draw firm conclusions. Indeed, it is imperative that better designed studies are conducted in order to establish pathways between deployment, stress, and Allostatic Load. At present, the absence of a statistically and meaningfully significant relationship is attributable to poorly designed studies.

Future directions

The allostatic load model has developed a reputation as a meaningful way of interpreting and describing the negative health outcomes associated with repeated or chronic stress. The model explains how activation of the stress response ensures survival in the short-term, but is maladaptive when its activation persists as a result of chronic, severe, or repeated stress.

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The allostatic load model is considered a means of explaining the complex non-linear processes that occur as a result of the accumulation of chronic stress burdens, which often synergise with episodes of acute stress and trauma.

However, it is an evolving model and there are significant opportunities to improve our understanding of measurement tools and the myriad of challenges related to establishing causality between stress and longer term health outcomes. allostatic load has no single, definable outcome that can be easily categorised. Health outcomes are typically heterogeneous and are influenced by many factors. allostatic load can be difficult to measure using current techniques and technology. However, there is a larger scope for measuring secondary and tertiary health outcomes (e.g., blood pressure and cardiovascular disease, respectively). Further research and developments will improve our ability to measure this construct. Future directions will need to:

- Recognise the highly complex and evolving model of allostatic load in an Australian military and veteran context.
- Recognise and understand the significant cross-over between physical, psychological, and psychosocial health outcomes that result from exposure to chronic stress and monitor the prevalence of these.
- Define the model and develop measurement tools in an Australian military and veteran context, which could assist prevention, early intervention, and management.
- Improve measurement of primary mediators and secondary and tertiary outcomes using research designs that aid attribution of causality, e.g. incorporating the broader veteran population and longitudinal designs.

Conclusion

This review confirms the usefulness of the allostatic load model related to the human stress response. It guides our interpretation of the relationship between stressors and negative health outcomes. Whilst the model is dynamic and evolving, it remains an important recent development regarding the way chronic and/or repeated stressors associated with military service and deployment may impact on the health and wellbeing of ADF personnel and veterans. There is an opportunity for past, present, and future research activities to assist the development in our understanding of allostasis and the progression to allostatic load.

PART 1: DEFINING ALLOSTATIC LOAD

This section will summarise the literature on the health effects of chronic and repeated stressors, including the developing model of allostatic load and allostatic overload as predictors of ill health. It does not attempt to draw on all the literature of stress research, but rather to summarise the basis for the model and its potential relevance to the health of military personnel and veterans.

This section will:

- summarise the stress response;
- summarise concepts of allostasis and allostatic load; and
- address the role of allostatic load as a predictor of medical, physical, and psychological decline.

In depth, more technical information about the stress response, allostasis, and the allostatic load model can be found in Appendix A.

Introduction

There has been much focus over recent years on the impact of acute traumatic events on mental health. But there remain knowledge gaps regarding the effects alternative stress patterns (chronic and/or repeated) may have on an individual's psychological, physical, and social health.

Whilst stress has long been recognised as a major contributing factor to poor health, common explanations of stress fail to adequately account for the association between stress and subsequent health outcomes and chronic illness (Logan & Barksdale, 2008). Our accepted understanding is that the body's stress response is adaptive because it promotes survival. Paradoxically, this same response may be maladaptive if it is chronically or repeatedly activated over time. It is the maladaptive aspect of this process that is central to the concepts of allostatic load and overload.

Interpreting stress

One of the earliest steps in the response to stress is the brain's perception that an event is threatening. This will determine how an individual will respond physiologically, emotionally, and behaviourally to the stressor. A stressful stimulus results in changes to physiological systems. The degree of the perceived or real threat determines the magnitude of the consequential stress. Physical stressors may include exertion, environmental demands

(heat/cold), trauma, infection, and inflammation. Psychological stressors may include
(but are not limited to) fear and anxiety, social defeat and humiliation, disappointment (anger,
frustration, etc.), and sometimes even intense joy (McEwen & Stellar, 1993).

The stress response

The stress response enables humans to survive threatening and unsafe conditions through the
'fight or flight' response. Upon interpreting a situation as threatening, the brain immediately
assumes control over the endocrine, cardiovascular, immune, and digestive system. The brain
relies on an elaborate communication network that includes hormones, neurotransmitters,
chemicals associated with the immune system, and other molecular signals. The early response
to acute stress is protective. It enhances immune function, promotes memory of dangerous
events, increases blood pressure and heart rate to meet the physical and behavioural demands
for '*action*', whilst also making fuel readily available so the body can sustain intensified activity
(VanItallie, 2002). Once the threat is removed, the body produces chemicals that return the
body to a normal state of arousal (see Figure 2).
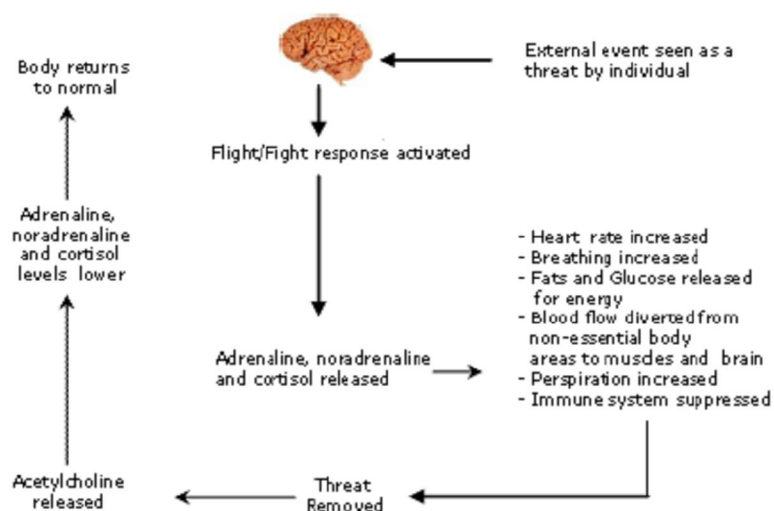
Figure 2. Basic response to stress

Short-term stress response

When the brain perceives a threat, a cascade of physiological changes is activated rapidly in
response. The surge of adrenaline floods the brain and peripheral tissues, subsequently
producing the full-fledged 'fight or flight' response, which includes a faster heart beat, greater
energy, more blood flow to skeletal and cardiac muscle, dilation of the pupils and airways,
higher blood glucose concentration, and so on. Appendix A contains a diagram of the short-
term stress response.

Long-term stress response

Where the challenge or threat is long-term (i.e., days up to years), such as potentially dangerous working conditions during military deployment, recovery of the baseline state may be impeded. It is this long-term continued activation of the stress response, long after the threat has ceased, that potentially poses the greatest risk to human health. Appendix A contains a diagram of the long-term stress response (Figure 2, page 66).

The effectiveness of the stress response is measured by the efficiency with which it mobilises the body's systems to react to a threat (i.e., physiological, neurohormonal, and immunological mechanisms), and how quickly the body's functions return to pre-stress levels. Recovery of the baseline steady state is as important a part of coping, adaptation, and resilience as is the capacity to mount an effective stress response in the first place (Friedman & McEwen, 2004).

The allostatic load model

Homeostasis involves the essential parameters of life and allostasis is the active process of maintaining homeostasis. Within the normal processes of allostasis occur allostatic states. An allostatic state involves a period of time when the body experiences elevated levels of mediators that serve to promote survival, such as increased blood pressure or elevated blood cortisol levels. These processes all occur within the normal range of human functioning. The process of allostasis and the resulting allostatic state may exact a cost on the body. This occurs as a result of chronic stress or when the stress response fails to 'turn off' properly over a long period of time. As a result, allostatic load ensues. This cumulative change may include changes in body fat distribution and remodelling of neuronal circuitry. This then leads to allostatic overload, resulting in pathophysiology, such as atherosclerosis, neuronal damage, cardiovascular disease (CVD), and/or cell loss (Institute of Medicine of the National Academies, 2008).

Homeostasis

Humans survive by maintaining a complex dynamic equilibrium that is constantly challenged by intrinsic or extrinsic disturbing forces or stressors (Craighead & Nemeroff, 2004). In response to a stressor that exceeds a threshold magnitude, an individual changes its behaviour and physiology to maintain homeostasis. Homeostasis refers to stability in various physiological characteristics such as body temperature, pH, and oxygen tension, which are tightly regulated within narrow ranges that promote survival. To maintain steady states, the homeostatic process is self-limiting and incorporates negative feedback loops to return these physiological parameters to a resting state. In emergencies, rapid activation of homeostatic systems preserves the internal environment by producing compensatory and anticipatory adjustments that enhance the likelihood of survival (Goldstein, 2004).

Allostasis and the allostatic state

The concepts of homeostasis and allostasis are integrally linked. Homeostasis is a process that keeps us alive whilst allostasis is a process that helps us adapt. Allostasis refers to the ability of a regulatory system to *change* a set point and operate at an elevated or reduced level, known as an 'allostatic state' (Koob & LeMoal, 2001; McEwen, 1998, 2005, 2007; McEwen & Wingfield, 2003). Through the process of allostasis, the body is able to produce hormones (e.g., cortisol, adrenaline) and other mediators (e.g., cytokines, parasympathetic activity) that help humans to *adapt* to new challenges or situations. This includes both predictable and unpredictable events.

Allostasis is defined as achieving stability through change (McEwen & Wingfield, 2003) and it is the process that maintains homeostasis. It is through mediators of allostasis that the active promotion of adaptation is possible. For example, elevated heart rate, blood pressure, cortisol, or inflammatory cytokines may be needed in the short-term to help us adapt.

Allostatic (or adaptive) systems have much broader boundaries than the homeostatic systems which enables us to respond to our physical states (e.g., awake, asleep, standing, exercising) and to cope with the challenges such as noise, crowding, hunger, extremes of temperature, danger, and microbial or parasitic infection (McEwen, 1998).

The concept of allostasis emphasises that healthy functioning requires ongoing adjustments of internal physiological systems, with fluctuating levels of activity as they respond and adapt to environmental demands. Unlike the homeostasis model, the relevant parameters for allostasis are not constant. Thus, in the allostasis model, mechanisms change the controlled variable from its initial set point by predicting what level will be needed and then overriding local feedback to meet anticipated demand (Sterling, 2004). Thus, short-term allostasis can help to overcome acute challenges and ensure survival by forcing systems to function outside their normal ranges. However, borrowing against a system's long-term integrity assumes that states of indebtedness will be ameliorated quickly once the environment returns to normal. When this does not happen, there are physiological consequences.

Allostatic load

Allostatic load takes into consideration the long-term cost of repeated stress and wear-and-tear on the body and brain (McEwen, 1998, 2006; McEwen & Gianaros, 2010; McEwen & Stellar, 1993; Sterling & Eyer, 1988). The strain on the body produced by repeated 'ups and downs' of physiological systems under challenge, and the changes in metabolism and the impact of wear-and-tear on a number of organs and tissues (including the brain), can predispose an individual to disease. When the mediators of adaptation (e.g., cortisol, inflammatory cytokines) occur chronically, these processes can lead to disease (e.g., hypertension, depression, arthritis, metabolic syndrome) (McEwen & Wingfield, 2010). This is defined as *allostatic load* (e.g., McEwen & Stellar, 1993).

Allostatic load refers to the burden of chronic stress and altered personal behaviours that result from the effects of overuse and dysregulation of the mediators of allostasis. Allostatic load is often manifested by fatigue, anger, frustration, and feeling out of control (i.e., 'stressed out').

This can lead to sleep loss (McEwen, 2006, 2007), anxiety, depression, and such health-damaging behaviours as overeating (Dallman, Pecoraro, & Akana, 2003), smoking, and excessive drinking (Anda et al., 1990; Dube, Anda, Felitti, Edwards, & Croft, 2002). These behaviours can increase and dysregulate the mediators involved in allostasis. When a mediator such as cortisol is present in excessive or insufficient amounts, other mediators are also changed. Over the course of days, weeks, and longer, allostatic load eventually disrupts health, leading to a condition called *allostatic overload* (Institute of Medicine National Academies [IOM], 2008).

Another important aspect of allostasis and allostatic load is the notion of anticipation. Anticipation implies psychological states, such as apprehension, worry, and anxiety, as well as cognitive preparation for a forthcoming event. It is likely that these states result in allostatic load (Schulkin, McEwen, & Gold, 1994).

Allostatic load and allostatic overload are points on a continuum. The pattern, frequency, and duration of stressors are important determinants of the severity of the outcome, as are an individual's response to the stressors. This is presented in Figure 3.
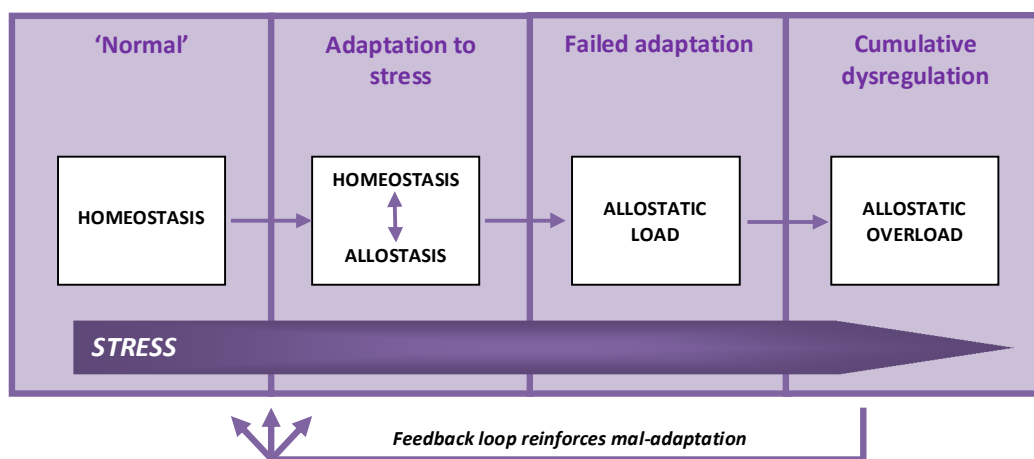
Figure3. The process of allostasis through to allostatic overload, as a product of increasing stress.

Allostatic load 'develops over the life-course, with individuals accumulating allostatic load at different rates. Both the initiation and progression of such dysregulation is postulated to be driven by individual differences in the frequency of exposure to real and perceived challenges and differences in their patterns of physiological responses to these challenges' (Seeman, Epel, Gruenewald, Karlamangla, & McEwen, 2010a), p 227.

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Table 1 provides a summary of the key points on homeostasis and allostasis (Koob & Le Moal, 2004).

Table 1. Homeostasis versus Allostasis

Homeostasis	Allostasis
Normal set point	Changing set point
Physiologic equilibrium	Compensated equilibrium
No anticipation of demand	Anticipation of demand
No adjustment based on history	Adjustment based on history
Adjustment carries no price	Adjustment and accommodation carry a price
No pathology	Potentially leads to pathology

Stress and allostatic load

As previously identified, the human stress response is life-saving in the short-term, and is adaptive when immediate stressors are confronted. However, it can lead to illness or disease when stressors are severe, recurrent, or persistent, and in the long-term is maladaptive. (For a comprehensive discussion on stress and allostatic load, see Appendix A.)

Because of the complexity of the relationship between stress and health outcomes, it is difficult to arrive at an accurate model to describe these links. It is also difficult to measure the impact of stress on the entire range of human biological systems over an extended period of time. Carlson and Chamberlain (2005) suggest the theory of allostatic load could provide a new theoretical orientation for understanding the role of stress in negative health outcomes.

McEwen (2002) proposes four types of physiologic response which lead to allostatic load and overload:

1. Too much 'stress' in the form of repeated, novel events that cause repeated elevations of stress mediators over long periods of time.
2. A failure to habituate or adapt to the same stressor.
3. Failure to shut off either the hormonal stress response, or to display the normal trough of the diurnal cortisol pattern.
4. An inadequate hormonal response that allows other systems such as inflammatory cytokines to become overactive, increasing susceptibility to inflammatory and autoimmune diseases (McEwen & Seeman, 1999)

Three types of allostatic load are represented in Figure 4. The top panel illustrates the normal allostatic response, in which a response is initiated by a stressor, sustained for an appropriate interval, and then turned off. The subsequent panels illustrate four conditions that lead to

allostatic load: repeated 'hits' from multiple stressors; lack of adaptation; prolonged response due to delayed shutdown; and inadequate response that leads to compensatory hyperactivity of other mediators (McEwen, 2004).
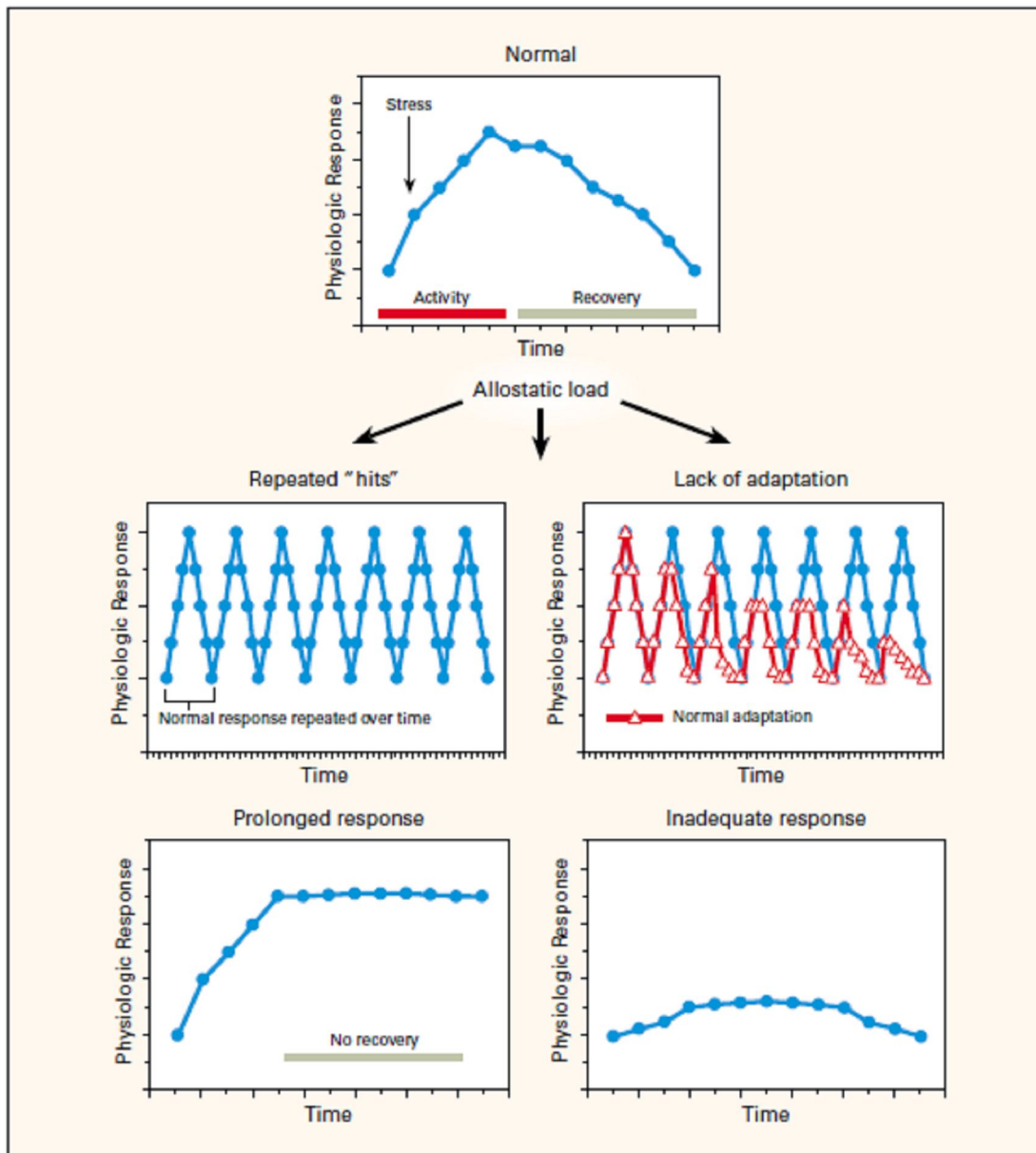
Figure 4. The stress response and development of allostatic load (from McEwen, 2004).

Ongoing debate and refinement

The literature on allostatic load provides for significant academic debate. The debate has essentially been one of semantics regarding what to call processes from homeostasis through to allostatic load. The existence of a significant relationship between stress and negative health outcomes is not under debate. For a comprehensive review, see Day (2005), Romano et al (2009), and McEwen and Wingfield (2010).

'Allostatic load' does not appear in the Diagnostic and Statistical Manual (DSM-IV) or International Classification of Diseases (ICD-10) because at present it is not easily definable and cannot be categorised as an illness diagnosis. It is unlikely to be included in any revisions of those texts in the near future. Diagnoses are often needed for the early identification of health problems and the implementation of treatment and prevention strategies, hence, it may be difficult for organisations to apply the allostatic load model to guide effective health care delivery.

It is important to note that whilst allostatic load is not found in any diagnostic tools, the negative health outcomes (e.g., gastrointestinal [GI] disorders and CVD) *are* measurable and diagnosable. They can be found in the DSM-IV or ICD-10 and therefore represent a potential way forward in what can be measured.

Accepting and implementing the allostatic load model can be difficult because of a lack of evidence in the literature making a direct causal link between primary stressors (effects) and tertiary outcomes. The multifaceted nature of the body and brain are designed to interact in a non-linear manner making these direct causal associations difficult to establish.

Potential relevance to military populations

A link between stressors during the military deployment cycle (i.e., pre-deployment, deployment, and post-deployment) and negative health outcomes for some service personnel is becoming clearer through research from the United States, the United Kingdom, Australia, and elsewhere. Many studies focus on recent deployments, especially to the Middle East. However, the relationship between stress and illness is enormously complex. Individual stressors include ordinary events in daily life as well as major, chronic and repeated challenges (Stressors are discussed in Part 3 of this report). It is the cumulative effect of these stressors that defines allostatic load. This is particularly pertinent in a military context, because even ordinary events, such being separated from family, may become extra-ordinary in certain circumstances, particularly at different points in the deployment cycle. Furthermore, the likelihood of encountering chronic or traumatic experiences may be greater for military personnel compared to their civilian counterpart.

There is a considerable and developing body of literature on the effects of stress and health outcomes for military members. There is strong empirical evidence that allostatic load results from chronic stress, which may be aggravated or accentuated by acute and traumatic stressors. Therefore this suggests that there is indeed a link between primary effects of stress and tertiary outcomes which warrant further investigation. The challenge will be in the identification and management of the lower order secondary outcomes (e.g., common cold, high blood pressure) as this is the area where early intervention would likely have the greatest success.

It is generally agreed that the allostatic load model significantly contributes to a greater understanding of normal and dysregulated biological functioning. Further investigation of the model is warranted, particularly in a military context.

Key points:

- Allostatic load is one of several models devised to examine and understand stress and stress-related disorders.
- The allostatic load model has a growing reputation as a meaningful way of interpreting and describing the negative health outcomes associated with repeated or chronic stress.
- The model explains how activation of the stress response ensures survival in the short-term, but is maladaptive when its activation persists as a result of chronic, severe, or repeated stress.
- Allostatic load is a cumulative phenomenon which develops over the life course, with individuals accumulating allostatic load at different rates.
- The allostatic load model is a means of explaining the complex non-linear processes that occur as a result of the accumulation of chronic stress burdens, which often synergise with episodes of acute stress and trauma. allostatic load is emerging as a useful model for investigating the health effects of stress in a military context.
- Allostatic Load is difficult to measure with current techniques and presents an area for improvement through research.
- Definitions exist for key terms (homeostasis, allostasis, allostatic load, and allostatic overload).

PART 2: THE ADVERSE HEALTH CONSEQUENCES OF ALLOSTATIC LOAD

There have been few studies which have specifically explored a causal link between allostatic load and adverse health outcomes, and these studies have limitations in design and in consistency of measurement. Consequently this report attempts to draw together evidence from existing studies on *stress* and health outcomes, apply that knowledge to the allostatic load model, and draw some conclusions relevant to the military and veterans' health sector.

This section of the review will:

- Discuss the link between chronic stress and specific health outcomes;
- Discuss the relevance of these outcomes to a military and veteran context with particular reference to the Gulf War and Health series (volume 6) Institute of Medicine (IOM, 2008); and
- Conclude with a discussion of potential modifiers to the stress response.

A comprehensive and scientific description of the biological mediators of allostatic load is presented in Appendix B of this report. This section includes information on how mediators of allostatic load impact primary, secondary, and tertiary health outcomes. A detailed description of the link between allostatic load and disease is presented. Neural plasticity is described, including the interaction between stress and key areas of the brain including the hippocampus, amygdala, and prefrontal cortex.

Introduction

There is a considerable body of evidence to suggest that stress has significant effects on health as a result of allostatic load. The research involves, for the most part, correlational analyses of stress with the occurrence of autonomic, cardiovascular, gastrointestinal, and immune system pathology. The literature indicates that allostatic load, via biological mediators, can contribute to the development of ill-health and disease including: cardiovascular, metabolic, immune, and autoimmune disorders, and is correlated with psychological disorders such as post traumatic stress disorder (PTSD), major depressive disorder, and anxiety. However, disentangling psychological and physiological health outcomes is difficult. For example, although PTSD is a psychological disorder, it is also associated with circulatory, digestive, musculoskeletal, nervous system, and respiratory diseases. Similarly, depression is also linked to physiological outcomes, including cardiovascular disease (CVD) and susceptibility to colds, and indirectly to diabetes, premature aging (including osteoporosis), and mortality (McEwen & Stellar, 1993).

The allostatic load model may be a useful way of understanding how military deployment can impact negatively on health. In this model deployment stressors would contribute to the lifetime cumulative effect of stress, thereby leaving the body more vulnerable to disease.

In the Gulf War and Health series (2008), the IOM of the National Academies developed an extremely comprehensive review of the health effects of military personnel in relation to their reactions to deployment to what was defined as a war-zone, and the inherent stressors that this would entail. The IOM has done a thorough review of the available military literature. It is therefore recommended that readers refer to page 115 in Volume 6 (2008) of the series for a *detailed* summary of the health effects research in relation to deployment related stress.

A summary of the link between chronic stress and specific health outcomes in outlined below.

Cardiovascular disease (CVD)

The term *cardiovascular disease* encompasses a wide variety of conditions, the most important of which relate to the development of atherosclerosis in the arteries and high blood pressure. These can lead to coronary heart disease (CHD)—which may be manifested clinically as myocardial infarction (MI), angina, or sudden cardiac death—and to cerebrovascular disease, which may present clinically as a stroke or transient ischemic attack. Most of the features related to CVD are implicated in the allostatic load model.

The three most important risk factors for CVD are blood pressure, blood cholesterol, and smoking. All risk factors are affected by stress and lifestyle.

Hypertension can be regarded both as a type of CVD and as a risk factor for CHD and stroke. These medical conditions and lesser manifestations of CVD, including chest pain and arrhythmia, may be manifestations of CHD but also occur commonly in the absence of any structural disease. Thus, chest pain that occurs in patients without CHD (that is, people who have normal coronary angiograms) tends to occur in younger people who have psychiatric conditions, such as anxiety and depression.

Myocardial infarction is the best-known example of an acute health crisis that is often precipitated by recent physical or psychological stress. An interaction between poor diet and stress promotes endocrine imbalances which alter metabolism and body fat distribution and increase atherosclerosis. This process leads to an increased incidence of myocardial infarction.

The association between deployment and CVD

Self-reports of some cardiovascular symptoms, such as increased heart rate, chest pains and hypertension are greater in deployed than non-deployed veterans (IOM, 2008). There are

consistent findings that deployment to a combat zone is associated with an increase in self-reports of many physical symptoms, however, these symptoms do not necessarily imply any structural heart disease.

There is insufficient evidence that deployment is associated with developing hypertension. Two primary studies (e.g., studies demonstrating methodologic rigor, appropriate control condition, etc.) identified by the IOM, one on Gulf War veterans and the other on Vietnam veterans, used physical examinations for hypertension, both of which produced null findings. Of the six secondary studies (e.g., studies that may be somewhat less rigorous) conducted for hypertension, two found no relationship with hypertension, although four studies did find a relationship. Blood lipids, another important risk factor for CHD, do not appear to be affected by deployment, although PTSD may raise them (IOM, 2008).

Because the follow-up period after the Gulf War is still short (less than 20 years) and the deployed veterans are still relatively young, it is expected that no research findings would exist to suggest that Gulf War veterans are at greater risk for CHD as a result of deployment (IOM, 2008). Symptoms of chest pain are common, but they appear to be part of a nonspecific increase in general symptomatology. This does not imply organic heart disease. Whilst the evidence is not yet conclusive, the increase of reported symptoms indirectly suggests a trend towards greater health problems for veterans, potentially providing support for the allostatic load model.

Veterans of the Vietnam War are now at an age at which heart disease is increasingly prevalent, but again there is no consistent evidence that they are at increased risk as a result of their deployment. Five primary studies assessing CHD in deployed and non-deployed veterans of the Gulf War and the Vietnam War showed no association; two secondary studies were mixed. Apart from nonspecific symptoms, the one long-term medical consequence of deployment in the Gulf War and other wars is a marked increase in the rate of PTSD (IOM, 2008).

Although there may be an increase in resting heart rate, which is a risk factor for both hypertension and cardiovascular events, PTSD does not appear to lead to hypertension. The results for the association of PTSD and CVD are mixed and there is suggestive, but not conclusive, evidence that PTSD increases the risk of CHD (IOM, 2008).

The IOM committee concluded that there was inadequate or insufficient evidence of an association between deployment to a war zone and hypertension. The committee also concluded that there was inadequate or insufficient evidence of an association between deployment to a war zone and coronary heart disease.

Gastrointestinal system

It is well recognised that an association exists between acute and chronic stress and gastrointestinal (GI) dysfunction (Creed et al., 2006; Drossman & Chang, 2003) and stress-induced ulceration of the GI tract has been extensively studied (see McEwen & Stellar, 1993 for references).

Disturbances of GI functioning can result from acute and/or chronic exposure to stress. GI dysfunction can lead to changes in intestinal movements that affect gastric emptying rates and intestinal transit time which in turn cause nausea, vomiting, bloating, diarrhoea, and constipation (IOM, 2008). Psychological distress can also affect sensitivity, which produces abdominal discomfort and pain. Functional GI disorders or syndromes include irritable bowel syndrome (IBS) and functional dyspepsia (IOM, 2008).

Acute stress can produce and activate GI symptoms in people with existing conditions (e.g., Crohn's disease), but the relationship of chronic stress to the onset of disease is difficult to study because onset may take years (IOM, 2008). This is a common consideration in the study of allostatic load and causality. For various forms of inflammatory bowel disease, major life stress events were found to be the most significant indicators of disease activity (Duffy et al., 1991).

There is growing evidence of post-infectious IBS development. In some cases, functional GI disorders are triggered by pathogens, which cause acute gastroenteritis, and the symptoms are then sustained by stressful conditions (Drossman, 1999; Dunlop, Jenkins, Neal, & Spiller, 2003; McKeown, Parry, Stansfield, Barton, & Welfare, 2006).

The association between deployment and GI symptoms

Whilst there are clearly defined links between stress and GI, more research is required in order to understand how this relates to allostatic load, particularly in a military population. The Military Health Outcomes Program (MilHOP) currently underway measures a selection of health outcomes, one of which is GI disorders. Therefore, it is possible that clearer relationships may be established in the future.

Gulf War veterans were found to report GI symptoms more frequently than most other symptoms (Kang, Mahan, Lee, Magee, & Murphy, 2000). It is hypothesised that this is a product of allostatic load. The disorders are then sustained or perpetuated in the presence of psychological comorbidities, including PTSD, anxiety, depression, maladaptive coping style, and impaired social networks (Creed et al., 2006; Drossman et al., 2002; Levy et al., 2006).

The IOM (2008) reported that PTSD was associated with increased GI symptoms in several studies of veterans. In the largest military study, which had the longest follow-up period

(almost 20 years), combat-related PTSD was found to be associated with more frequent later development of GI diseases in Vietnam-theatre veterans compared to Vietnam-era veterans (Boscarino, 1995). Other studies corroborated the relationship between GI disturbances and combat or PTSD (a surrogate for trauma exposure) in veterans of the Vietnam War, Operation Iraqi Freedom (OIF), and of World War II, and the Korean War. This link may provide evidence for the relationship between stress (resulting from and exacerbated by PTSD) and the expression of allostatic load for military personnel.

The IOM committee concluded that there was limited but suggestive evidence of an association between deployment to a war zone (i.e., stressors) and gastrointestinal symptoms consistent with functional gastrointestinal disorders.

Endocrine system

The endocrine system can respond to chronic stress with an array of effects that are often overlapping, interactive, and detrimental. There is currently little research directly linking disorders of the endocrine system with allostatic load.

Endocrine diseases include disorders of the adrenals, pituitary, thyroid, parathyroids, pancreas, gonads, and bone. The most common endocrine disorders are diabetes mellitus and disorders of the thyroid, such as hypothyroidism and hyperthyroidism. Hypothyroidism is characterised by deficient secretion of thyroid hormones either primarily because of a defect in the thyroid or secondarily because of a defect in the pituitary's production of thyroid-stimulating hormone. Many basic metabolic functions are altered by the excess concentrations of cortisol and adrenaline which occur due to chronic stress (McEwen & Lasley, 2002).

Chronic stress can have long-term effects on susceptibility to diseases which are the result of sustained endocrine imbalance. During sustained elevations of cortisol, caused by a high-fat diet or stress, insulin secretion increases to counteract insulin insensitivity produced by the elevated cortisol levels. While the body can cope in the short-term with the stressor, the long-term elevation of cortisol and insulin favour hyperlipidemia and accelerate atherogenesis. This is a condition that can precipitate or exacerbate diabetes.

There are two types of diabetes mellitus: type 1, which is a marked deficiency of pancreatic insulin secretion, and type 2, which is a combination of insulin resistance and decreased insulin secretion. Both types lead to increased serum glucose concentrations (IOM, 2008).

Diabetes is a heterogeneous condition and there is evidence to suggest that stressful experiences are a significant risk factor for the onset and exacerbation of diabetes. Currently, there are clearer outcomes for the effects of stress on type 2 diabetes. However, stressful

experiences are also risk factors for the exacerbation of type 1 diabetes as well as for the onset of type 1 diabetes in children.

The IOM (2008) found that acute and chronic stress activated the endocrine system and thereby influenced the immune system, but it was unclear whether those interactions produced endocrine diseases. Potentially confounding variables were considered because stress also increases caloric intake and the hormones released by acute and chronic stress, such as cortisol, can accentuate obesity and lead to insulin resistance, a central feature of type 2 diabetes. There have been several reports that stress, with or without comorbid depression, increased the incidence of type 2 diabetes in non-military populations (e.g., Eaton, Armenian, Gallo, Pratt, & Ford, 1996).

Obesity

Chronic stress has long been associated with obesity (McEwen, 2002; Rosmond, Lapidus, Marin, & Bjorntorp, 1996). Cortisol enhances pathways that lead to increased deposition of fat (adipose tissue) in the abdominal area. An increase in abdominal fat, as opposed to that in the hips and buttocks, is a key risk factor associated with hypertension, diabetes, and CVD (Black & Garbutt, 2002). Obesity is also caused by higher food intake, which commonly occurs with chronic stress, either as a coping strategy or because of sleep deprivation (Dallman, et al., 2003). Sleep deprivation appears to increase hunger through its association with lower concentrations of an appetite-suppressing hormone (leptin) and higher concentrations of an appetite-enhancing hormone (ghrelin) (Spiegel, Tasali, Penev, & Van Cauter, 2004). Increased body-mass index (BMI) is negatively associated with sleep duration, such that people getting less than 8 hours sleep each night exhibit increased BMI (Taheri, Lin, Austin, Young, & Mignot, 2004).

Obesity has serious consequences for the development of diabetes and heart disease because it causes or contributes to insulin resistance (Reaven, Abbasi, & McLaughlin, 2004). Fat is now considered to be the largest endocrine organ in the body, and it is the source of multiple cytokines involved in inflammation and insulin resistance.

The association between deployment and the endocrine system

Two primary studies were examined by the IOM (2008) regarding the association between deployment and diabetes in Vietnam War veterans and Gulf War veterans (Eisen et al., 2005). The authors found no increase in the risk of diabetes in deployed veterans of either war. Several less rigorous studies, one of Vietnam veterans and five of Gulf War veterans, supported the lack of association between deployment to either the Vietnam War or the Gulf War and the presence of diabetes. One study (O'Toole et al., 1996) of Vietnam veterans showed no increase

in diabetes with increasing combat exposure. However, other research conducted on a large sample of male VA veterans found that diabetes may be vulnerable to the effect of PTSD (Trief, Ouimette, Wade, Shanahan, & Weinstock, 2006).

In relation to military personnel and deployment related stress, the IOM (2008) was not able to identify any primary studies (e.g., studies demonstrating methodologic rigor, appropriate control condition, etc.) of obesity in veterans. One secondary study (e.g., studies that may be somewhat less rigorous) by Vieweg et al. (2006) of male Vietnam veterans found that veterans with PTSD were more overweight (82.2% overweight or obese, mean BMI of 30.2) than the general U.S. population (rate of 64.5% overweight or obese). A second found that female veterans with PTSD were more likely to have an eating disorder than those without PTSD (Dobie et al., 2004), while a third found no evidence of eating disorders in Gulf War veterans (Fiedler et al., 2006).

The IOM committee in 2008 concluded that there was inadequate or insufficient evidence to determine whether an association existed between deployment to a war zone and diabetes mellitus. The committee also concluded that there was inadequate or insufficient evidence to determine whether an association existed between deployment to a war zone and thyroid disease.

Immune and autoimmune systems

There is a close interaction between the endocrine and immune systems. Acute stress enhances the immune system to fight infections and to promote wound healing (Dhabhar & McEwen, 2001). However, chronic stress dysregulates the immune system, which can lead to illness, and subsequent allostatic overload over time. Dysregulation of the immune system can have several major health outcomes, including:

- Susceptibility to infection (Cohen, Tyrrell, & Smith, 1991)
- Delayed wound healing (Kiecolt-Glaser et al., 1993; Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995)
- An increase in inflammatory molecules in the circulation (Kiecolt-Glaser et al., 2003)
- Decreased response to immunisation (Glaser, Sheridan, Malarkey, MacCallum, & Kiecolt-Glaser, 2000)

The immune system is highly responsive to behavioural influences and stress. As one example, psychological stress has been found to increase susceptibility to the common cold (McEwen & Stellar, 1993).

Longer-term stress effects on diseases related to the immune system are difficult to document. Increased frequency of negative life events were associated with newly diagnosed Graves'

disease in adults, including a possible interaction between hereditary factors and stress (Winsa et al., 1991). Stressful life events and personality features such as the ability to express anger and irritation have (Glaser, et al., 2000) been implicated as risk factors in women suffering from rheumatoid arthritis in which there was not a family history of the disease. This is strongly suggestive, but is also confounded by the heterogeneity of the disease.

Psychiatric disorders and substance use disorders

McEwen and Gianaros (2010) reported that human neuroimaging studies of the hippocampus indicate that individuals with stress-related psychiatric disorders, such as major depressive disorder and PTSD, show volumetric reductions in the hippocampus. In otherwise healthy individuals, there also appears to be a relationship between chronic stressful experiences and changes in hippocampal morphology. It is possible that pre-existing individual differences in hippocampal and regional brain morphology, which could emerge early in life and which could result from a combination of genetic and developmental influences, could partly increase vulnerability to and decrease resilience against life stress.

DSM-IV defines substance-use disorders as dependence (i.e., tolerance, withdrawal, needing increasing amounts, persistent desire, and unsuccessful efforts to cut down) or abuse (i.e., recurrent use causing domestic, work, interpersonal, or legal problems, or use in physically hazardous situations) of drugs or alcohol.

The most reliable method for determining a history of substance-use disorders is the diagnostic interview. In community and military populations in general, current alcohol problems are often assessed with a screening questionnaire (e.g., CAGE or AUDIT).

It is well established that alcohol use and drug use are comorbid with PTSD and other psychiatric conditions in clinical and nonclinical populations of veterans and non-veterans (Jacobsen, Southwick, & Kosten, 2001; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Mellman, Randolph, Brawman-Mintzer, Flores, & Milanes, 1992). It has been suggested that the high rates of comorbidity between PTSD and substance-use disorders show that they may be functionally related to each other (Jacobsen et al., 2001).

The association between deployment and psychiatric disorders

Psychiatric disorders have long been recognised as a potential consequence of serving in the military during wartime. There is substantial literature on the psychiatric effects of war in general, particularly related to traumatic events. Psychiatric disorders can include, for example, PTSD, anxiety, depression, and substance use disorder.

The IOM committee considered 11 citations on seven primary studies. For all veteran population, those who were deployed to combat zones had a greater prevalence of psychiatric

disorders—particularly PTSD, other anxiety disorders, and major depressive disorder (MDD)—than did veterans who served in the military at the same time but were not deployed to a combat zone. PTSD was also found to be highly comorbid with other psychiatric disorders, particularly generalised anxiety disorder (GAD) and MDD. Furthermore, both the prevalence and the severity of those disorders were associated with the level of combat experienced. The 11 secondary studies, most of them of Gulf War veterans, showed an association between deployment and PTSD, anxiety, and MDD, as well as other psychiatric disorders (IOM, 2008).

The IOM committee concluded that there was sufficient evidence of an association between deployment to a war zone and the development of psychiatric disorders, including PTSD, other anxiety disorders, and depressive disorders.

The association between deployment and substance use disorders
Overall, the IOM (2008) found that troops deployed to Vietnam and the Persian Gulf had consistently higher rates of substance-use problems than the non-deployed controls. Data suggested that deployment was associated with alcohol use, although only the National Vietnam Veterans' Readjustment Study (NVVRS) found a significant association of drug abuse with deployment (IOM, 2008). Two of the three studies of Gulf War veterans (one with Australian veterans) found a higher prevalence of alcohol-use disorders in deployed veteran; a third conducted 10 years after the war, did not. The two studies that assessed drug-use disorders in Gulf War veterans both found an increased prevalence of such disorders in deployed veterans. Results from the secondary studies were also mixed: five of the seven studies found a positive association between alcohol abuse or dependence and deployment, but two studies did not. For drug-use disorders, the results were similarly mixed: two studies showed a positive association, but three did not. The IOM (2008) discuss the limitations of these studies and therefore it is not reproduced here.

The IOM committee concluded that there was sufficient evidence of an association between deployment to a war zone and alcohol abuse. The committee also concluded that there was limited but suggestive evidence of an association between deployment to a war zone and drug abuse.

Central nervous system (CNS)
There is evidence of structural and functional changes to the brain, resulting directly from chronic or severe stress. The changes are associated with alterations of the most profound functions of the brain, in particular memory and decision making. They are also associated with symptoms of fear and anxiety, and they might sensitise the brain to substances of abuse and increase the risk of substance-use disorders (Brady & Sinha, 2005).

CNS - Memory and cognition

A feature that is most refined in humans is the ability to learn from stressful experiences. Humans have the capacity to learn, think abstractly, and subsequently draw on lessons when coping with subsequent exposure to harm (McEwen & Lasley, 2002). The lessons learned are often etched into the brain through measurable structural and functional alterations in nerve cells and networks. It is important to note that human stressors are not only external; they can also be internal, including worry, guilt, or rumination about past or future events. As such, internal and external stressors both contribute to the effects of chronic and cumulative stress (i.e., allostatic load/overload) (McEwen, 2002).

Memory and cognition have been studied extensively in three regions of the brain: the hippocampus, the prefrontal cortex, and the amygdala. The hippocampus is the centre of explicit memory and appears to be particularly vulnerable to chronic stress. Repeated stress has been shown to change the structure and connections between neurons in the hippocampus devoted to receiving signals from other nerve cells (McEwen & Seeman, 1999; Sapolsky, 2003). When hippocampal neurons are remodelled by glucocorticoids working together with some neurochemicals, they lose their plasticity. Plasticity is vital for encoding memories and learning from them. This loss leads to impairment of essential cognitive functions of the brain (Sapolsky, 2003).

The prefrontal cortex integrates information received, such as whether a sudden noise poses a threat, and modulates activity of the HPA axis (McDougall, Widdop, & Lawrence, 2004; Radley & Morrison, 2005). Repeated stress causes structural remodelling of the neurons in the axis that reduce their ability to receive signals from other neurons. As explicated by McEwen et al. (1999) in connection with the structural remodelling in the hippocampus, changes in the prefrontal cortex are most likely driven by increased concentrations of glucocorticoids and by other neurochemicals in the brain that are increased by repeated exposure to stressors (Radley & Morrison, 2005); those changes *impair cognitive flexibility* (Liston, Matalon, Hare, Davidson, & Casey, 2006).

Memories formed in association with stressful life events can be indelible and can be triggered, even years later, by cues associated with the original event. The memories can be triggered by stimuli associated with the original traumatic event (flashbacks) and in some cases, are so intrusive that normal functioning may no longer be possible. In these cases, strong traumatic memories are often expressed as recollections, flashbacks, and repetitive nightmares (McGaugh, 1992). The cause and exacerbation of the memory issues are circular, with stress resulting in the traumatic memory being formed, and then the (often involuntary) recollection, flashback, or nightmares of those memories perpetuating the stress which results in stronger memories of the traumatic event being formed. It is clear that this is a very relevant factor in the relationship between stress and health outcomes (such as PTSD).

CNS - Anxiety and fear

Adrenaline plays a critical role in the encoding of memory for events and stimuli that are arousing, stressful, or fear provoking. The release of adrenaline activates the sympathetic nervous system, amygdala, and HPA axis, therefore creating the link between stress/anxiety and fear.

However, some of the effects of adrenaline being released are inhibitory and act on the prefrontal cortex and PNS, which are the systems that normally keep the sympathetic nervous system in check (via a negative feedback loop) and therefore reduce stress levels after an incident has occurred. Inhibiting the prefrontal cortex favours instinctual responses (e.g., fight or flight) at the expense of more complex thinking and planning (e.g., deciding that the threat is no longer relevant) (Charney, 2004).

The brain has limited capacity to heal itself after damage and if compromised may decline in functionality (McEwen & Stellar, 1993). Adrenal steroid secretion is involved in adaptation to stress and in counter regulating, and in many ways protecting the brain from its own primary neurochemical responses to environmental challenges. Yet, adrenal steroids participate, paradoxically, in damaging effects of long-term environmental challenges on the brain, especially the hippocampal formation.

One factor behind individual behavioural responses to internal or external events is the person's neurochemical makeup, which can bias the way the nervous system interprets and responds to challenge. For example, low serotonin levels have been linked to hostility, increased alcohol intake, violent behaviour (including suicide), and has been found to disinhibit sympathetic activity and lead to increased blood pressure surges that accompany angry and hostile responses. Such an excess of sympathetic reactivity increases vulnerability to adverse health consequences such as myocardial infarction and asthmatic attacks and is an example of allostatic load.

The association between deployment and the CNS

Research suggests that chronic and repeated exposure to stressors can result in physiological changes within the brain and this may influence behaviour. Exposure to chronic or repeated stressors can reduce brain plasticity which is vital for cognitive functioning. Reduced cognitive functioning may limit an individual's capacity to use executive processes to make decisions in a stressful situation and thus influence behaviour. This may have a significant impact on ADF personnel and veterans' functionality and wellbeing.

Memories formed in association with military life stressors can be ineradicable and may be triggered years later by cues associated with the original event. Surges of adrenaline assist military personnel to encode memories for potentially life threatening events. This is an

adaptive process. However, this same process may result in those same individuals identifying cues for danger in 'safe' non-military contexts, such as post-deployment veteran life. When this over-identification of 'dangerous cues' happens, an individual may react in accordance with the remembered threat which may no longer be relevant for saving their lives. Therefore, this would be maladaptive for an individual at this point in their lives.

Research has found that the amygdala undergoes structural changes that are accompanied by an increase in fear conditioning and anxiety-like behaviours (Vyas et al., 2002). Veterans with PTSD who were evaluated with brain techniques have been found to show activation of the amygdala after being exposed to traumatic images.

Chronic stress (e.g., multiple deployments with extended periods of time away from family) increases the activity of the locus coeruleus to produce adrenaline with the same effects as acute stress (i.e., combat exposure) but over longer periods, thereby contributing to chronic anxiety, fear, and intrusive memories as a result of the processes of allostatic load and overload (Charney, 2004). For military personnel, the combination of protracted stressors may contribute to a stress-burden and have negative long-term health outcomes. Chronic stress, impacting on the weight of allostatic load, also contributes to an increase in concentrations of adrenaline outside the brain that can affect other organ systems. As previously mentioned, there is a complex, non-linear interaction of a conglomerate of systems affected by allostatic load.

Potential modifiers of the stress response

It is acknowledged that there are many factors which can alter a person's response to stress, including genetic makeup, early-life history, and the degree to which the stressor can be controlled. There is developing research on epigenetics that may shed light on this issue, however, discussion of this emerging field is beyond the scope of this report.

It is important to consider why some people who experience chronic stress become sick and others do not when under similar degrees and types of stress. In other words, why are some people resilient and others vulnerable to chronic stress? Genes and controllability can play a role in level of resilience.

Genes

Many aspects of the stress response, such as learned and innate fear (e.g., Shumyatsky et al., 2005), reward, social behaviour, and resilience (Charney, 2004), are likely to be under the influence of particular genes. Gene-environment interactions occur and therefore health outcomes will differ between individuals. As such, the observed outcomes of allostasis and allostatic load will differ between individuals, even if exposed to the same stressful circumstances.

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Controllability

One modifier of the stress response is the degree to which a stressor is perceived as controllable (Maier & Watkins, 2005). A sense of control is an important aspect of hardiness (Maier, 1969; Seligman & Maier, 1967; Weiss, 1968). Animal studies demonstrate that stress activates the brainstem nuclei, but activation is inhibited by the prefrontal cortex, a brain structure that appears to be dysregulated in people with PTSD (Amat et al., 2005). A dysfunctional prefrontal cortex in people with PTSD could perhaps exacerbate a feeling of being out of control. Thus the role of one's perception of control in the stress-response process may be particularly important.

Controllability and perception of control are important concepts in a military context. Locus of control is a psychological state, whereby an individual attributes control to internal or external sources. In situations where control is always attributed to external sources, this results in feelings of being out of control and stressed. For military personnel, there are many situations that they will find themselves in that our not directly within their control. This includes being away from family, in combat zones, difficult living conditions, among others. Greater perceptions of control decrease stress which may subsequently result in fewer long-term health consequences as a result of allostatic load. Attributions of control that are made internally is something that can be influenced pre-deployment, during deployment, and post-deployment through resilience training.

Research in this area should focus on attempting to explain the differences in people's vulnerabilities to disease and illness and on ways to increase individual capacity to adapt or adjust in a healthy manner to various strengths or kinds of stress (Logan & Barksdale, 2008). Improved mechanisms for delaying, easing, or preventing allostatic load are required, by identifying causes of differences in individual capacity.

Resilience

Resilience has been defined as the ability to successfully adapt and function proficiently when faced with traumatic circumstances (Fossion & Linkowski, 2007; McEwen, 2002). McEwen (2002) stated that:

> *'resilience is an example of successful allostasis in which wear and tear is minimised, and the brain retains considerable resilience in the face of stress.'*

A resilient person with the ability to adapt to challenging environments will be able to minimise physiological damage and negative long-term health outcomes (Carlson & Chamberlain, 2005). Resilience is an important concept in the allostatic load model, because it has been associated with positive outcomes for individuals, even in situations that could produce pathological conditions (Luthar & Cicchetti, 2000; Masten & Coatsworth, 1998).

The brain perceives stress and produces behavioural and physiological responses to stress. These responses depend on the *interpretations* made by the brain (McEwen, 2002). There are individual differences in how the brain interprets situations produce different behavioural and physiological responses, which can be measured through the functioning of various physiologic systems. The hippocampus plays an important role in memorising and interpreting circumstances and regulating the primary stress mediators for an allostatic state (Sapolsky, 2003). That is, the memory of previous stress influences the ability to anticipate the needed physiological adaptation. Therefore, this provides an explanation as to why vulnerability of many body systems to stress is influenced by experiences from earlier in life (McEwen, 2002).

Key points

This section discussed links between chronic and repeated stressors and various health outcomes in a military and veteran context. Overall, the research suggests that chronic stress is responsible for increasing physiological dysregulation of key biological systems. This then leads to allostatic load and overload.

The literature indicates that allostatic load can contribute to various disorders, including CVD, metabolic, immune, and autoimmune disorders and is correlated to psychological disorders such as PTSD, major depressive disorder, and anxiety. However these links are not always clear and require further research in military and veteran populations.

PART 3: WHAT IT MEANS FOR DVA AND DEFENCE

Introduction

The allostatic load model is continuing to evolve as more research is undertaken and technological advances enhance our understanding of the multiple biological pathways involved in the response to stress. The key challenge for the Department of Veterans' Affairs (DVA) and for Defence will be how best to adapt current thinking and policy to reflect the dynamic role of chronic and repeated stressors in the development of ill health in the physical, psychological, and social domains.

Changing demands from the veteran community for treatment and support services aimed at improving health and wellbeing for disorders claimed to be due to stressful events encountered during service life may present a challenge for DVA, Defence, and other agencies. Stress and the allostatic load model cannot explain all causes of illness and disease. Therefore establishing a link between service-related stressors and subsequent ill health can be difficult for both claimants and the Department. It may be even more difficult if claims are made years after the stressful event occurred.

The increased operational tempo for the Australian Defence Force (ADF), and Australia's involvement in the wars in Iraq and Afghanistan, as well as peacekeeping in Timor-Leste and elsewhere, means that stress-related claims for support and services are expected to increase in the future. In addition to claims made contemporaneously, they are also likely to be made for decades to come. There may also be inter-generational effects. Thus, the true costs of meeting obligations in the provision of support and services in relation to stress-related claims and supporting the wellbeing of veterans as a result of deployment are not easily quantifiable or predictable.

For many Defence members and veterans there is a time lag between when they experienced stress and when they experience health issues that require intervention. This is consistent with the knowledge that stress exposure and the onset of disease are often not immediately temporally linked. If the illness emerges immediately in the aftermath of an event, the causal role of that event logically can be presumed to be more strongly linked than if there is a significant delay between the exposure and the onset of symptoms. The absence of a clear explanation for the prolonged delay between exposure to a stressful event and the onset of disease (e.g., delayed onset PTSD, anxiety disorders, and major depression) may frustrate both claimants and those responsible for determining their support and service requirements.

The allostatic load model is founded on the individuals' response to stress. It is apparent from the literature that the key to understanding allostatic load in the military context is a sound understanding the influence of 'normal' life stressors and an understanding the specific, often unique, stressors associated with military service. The reality is that it may not be entirely possible to disentangle general life stressors from military specific stressors. This provides a challenge in understanding allostatic load within an Australian military context.

An adequate model of stress combined with other adverse exposures and subsequent negative health outcomes is needed in order to account for the delays, differences, and anomalies observed in linking the effects of military life stressors and potential ill health in ADF members and veterans as a consequence of military service or deployment.

Stressors in the military

The current review has focused on the development of the model of allostatic load to explain the link between stressors, the biological responses, and the development of subsequent ill health. While military personnel may experience the full range of stressors experienced by those in the general community, there are some key stressors that are considered to be different between the groups. The military literature has focused predominantly on the psychological impacts of military service, particularly deployments, on individual health. This perhaps reflects the relative ease of assigning some causal relationship against diagnostic criteria, such as anxiety and depressive disorders, versus the more difficult physically unexplained or different symptom experiences that may reflect the physical manifestations of response to deployment stressors. This may be why allostatic load and overload has not yet been comprehensively considered in a military environment and instead, primarily psychological disabilities are considered.

Military stressors are generally quite unique (e.g., combat) compared to regular issues of daily living (e.g., traffic) experienced by civilians. Military specific stressors may be responsible for contributing to the burden of allostatic load in this population. Specific deployment-related stressors include all those experienced during actual armed combat, the anticipation of deployment to a war zone, noncombat stressors, military sexual harassment and assault, poor living conditions, and exposure to environmental and chemical stressors. In addition, there are some stressors that have been identified as specific to army reserves, peacekeepers, and women (IOM, 2008).

The psychiatric sequelae of war are well documented (Hotopf et al., 2006). A 2006 IOM report noted that depression, substance use or dependence, and anxiety disorders, especially PTSD, were increased in Gulf War veterans after deployment, and that symptom severity was associated with the level of war stress experienced.

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Conventional combat is considered one of the most potent stressors that can be experienced, but since military conflicts have evolved to include guerrilla warfare and insurgent activities, it is important to broaden the definition of military related stressors to include other potent stressors experienced in a war zone or in the aftermath of combat (e.g., peacekeeping roles) (King, Waghorn, Lloyd, & et al, 2006). Stressors may include an array of physical and psychological events such as constant vigilance against an unexpected attack, the absence of a defined front line, the difficulty distinguishing enemy combatants from civilians, the ubiquity of improvised explosive devices (IEDs), caring for the badly injured or dying, duty on graves registration service, and being responsible for the treatment of prisoners of war (IOM, 2008). In addition to the more obvious combat-related stressors are the noncombat stressors that may be experienced by deployed personnel, including being separated from family, friends, and colleagues; loss of or reduction in income; and concern over employment status when deployment ends (O'Toole, et al., 1999).

The IOM (2008) considered that military personnel deployed to a war zone, even if direct combat was not experienced, have the potential for exposure to deployment-related stressors that might elicit a stress response. The emotional and physical reactions of military personnel to those stressors can vary widely. It is also recognised that factors other than deployment-related stressors can affect the outcome of exposure to potential stressors, including the stress response itself and individual protective and risk factors.

It is this unique combination of stressors (e.g., being away from family and being in a combat zone) that suggest military populations may experience significant levels of acute, traumatic, and chronic stress which is likely to contribute to allostatic overload.

Combat related stressors

Exposure to combat has been described as one of the most intense stressors that a person can experience (Grinker & Spiegel, 1945). For many people who experience combat, it is the most traumatic experience of their life (Kulka, Schlenger, & Fairbank, 1990). The level of combat experienced by military personnel has been found to be the most significant and important determinant of mental health (Mental Health Advisory Team (MHAT), 2006).

Studies on the psychological effects of veterans found that the feature of combat that was uniformly traumatic in three wars – the Vietnam War, the Korean War, and World War II – was being an 'agent' of killing the enemy, rather than just being a 'target' (IOM, 2008). Being responsible for killing someone may be one of the *most pervasive* traumas of war (Fontana & Rosenheck, 1994).

The most frequently reported stressors related to combat veterans include:

- Killing or attempting to kill the enemy (IOM, 2008)
- Being shot at by others (Stretch et al., 1996)
- Threat of danger e.g., being killed, wounded, or being fired on (McGuire et al., 2009a; McGuire et al., 2009b; Stretch, et al., 1996)
- Exposure to dead and wounded comrades, enemy combatants, and civilians (IOM, 2008)
- Being injured (IOM, 2008)

As these findings suggest, it is not only those situations that may be life threatening that are considered stressful for military personnel. The experience of stress and the effects of stressors are experienced uniquely among individuals.

The study by Stretch et al (1996) found that stressors that were most closely associated with PTSD were those related to combat, such as exposure to the killing or wounding of American soldiers by friendly fire, having a friend killed or wounded in action, and exposure to dead or dying people.

What literature there is suggests a strong link between deployment characterised by combat, and a range of health issues. Psychiatric morbidity, for a significant minority of all deployed service members, may result from the deployment of military personnel either to combat zones (Hoge et al., 2004; Jacobson, Ryan, Hooper, & et al, 2008; Wells et al., 2010) or on peacekeeping missions, particularly if atrocities are witnessed (Hodson, Ward, & Rapee, 2003; Ward, 1997).

Noncombat stressors

There are a multitude of stressors associated with military service or deployment that are not necessarily related to combat but instead to what King et al. (1995) described as a 'malevolent environment'. Stressors include:

- Inadequate food, water, weapons or munitions, equipment or supplies (King, King, Gudanowski, & Vreven, 1995; Sutker, Allain, & Winstead, 1993)
- Loss of control, uncertainty, and fear of the unknown (Sutker, et al., 1993)
- Loss of freedom of movement (King et al., 1995)
- Lack of privacy, quiet and personal space (King et al., 1995; MHAT, 2006; Stretch et al., 1996)
- Fear of Scud missile, terrorist, chemical and other military attacks (Sutker et al., 1993; Stretch et al., 1996)
- Being subjected to guerrilla warfare and terrorist actions from civilian insurgents and militias (King, et al., 1995)
- Soldiers needing to be constantly on guard against snipers, IEDs, and suicide bombers (King et al., 1995)

- Viewing all civilians with caution (King et al., 1995)
- Isolation/ separation from family and friends (McGuire et al., 2009a; McGuire et al., 2009b; MHAT, 2006; Sutker et al., 1993)
- Sorting out problems at home (McGuire, et al., 2009a; McGuire, et al., 2009b)
- The behaviour of others (McGuire, et al., 2009a; McGuire, et al., 2009b)
- Lack of leadership (Sutker, et al., 1993)
- Long hours (Stretch et al., 1996)
- Boredom/narrowly restricted outlets for relaxation (MHAT, 2006; Stretch et al., 1996)
- Discomfort with the physical environment e.g. temperature extremes, working in the desert, noise from guns and artillery (IOM, 2008; Stretch et al., 1996; Sutker et al., 1993; McGuire et al., 2009b)
- Risk of vehicle accidents (McGuire et al., 2009a; McGuire et al., 2009b)
- Protracted delays returning home after cessation of hostilities (Sutker et al., 1993)

Uncertainty about the duration of deployment, deployment length, and family separation are consistently identified as major stressors (Bray, 2003; Wright, Marlowe, & Gifford, 1996). Deployment length is also related to increased mental health and marital problems (IOM, 2008). Uncertainty about deployment duration can be related to particular conflicts stages, for example, it was a continuing concern for U.S. troops during the Gulf War, particularly during the early phases of the build-up (Wright, et al., 1996). This sentiment was reflected anecdotally in a recent CMVH Think Tank in 2010[1]. Military personnel and their families indicated that deployment length, particularly if it were for over 6 months, was stressful for ADF members and their families. The greatest stressor for Australian Gulf War-era veterans who had been deployed to areas other than the Gulf was feeling cut off from family members and significant others (IOM, 2008; Sim et al., 2003).

Deployment length tends to be of an even higher concern to soldiers that have been deployed more than once (Bray, 2003; MHAT, 2006). The current length of deployment for Australian ground troops in the Middle East Area of Operations is 8 months.

Interestingly, noncombat related stressors can be rated more highly than combat related stressors. In the East Timor Health Study conducted by McGuire et al. (2009b), the most common stressors, such as threat of danger and risk of vehicle accidents, were typically found to have the highest average stress scores; however, there were some instances where less common stressors were rated as highly stressful, such as 'double standards', 'leadership', 'overload of work,' and 'the Australian military hierarchy.'

Australian Navy Gulf War veterans were surveyed to identify stressors in military units that were not actively engaged in combat or that had little exposure to combat, rather, these personnel served in blockade efforts or provided transport, supplies, or medical support

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[1] Centre for Military and Veterans' Health (2010) Think Tank Report 2010. *Readjustment to 'normal' How can DVA and Defence help?*

(Ikin et al., 2004, 2005; McKenzie et al., 2004). The researchers found that the stressors were similar to those reported by ground forces:

- Being on a ship or aircraft passing through hostile water or airspace (81%)
- Been in fear of artillery, missile, Scud rocket, or bomb attack (71%)
- Felt cut off from family or significant others (67%)
- Feared death, injury, or being trapped as a result of a missile attack or hitting a sea mine (54%)

Bartone et al. (2009) categorise the primary stressors of modern warlike operations as follows (some of these are also relevant to peacekeeping operations – see Table 2 below):

Table 2. Military related stressors and stressor characteristics

Stressor	Characteristics
Isolation	Remote location
	Foreign culture and language
	Far from family/friends
	Unreliable communication tools
	Newly configured units with unfamiliar co-workers
Ambiguity	Unclear/changing mission
	Unclear rules of engagement (ROE)
	Unclear command/leadership structure
	Role confusion
	Unclear norms, standards of behaviour
Powerlessness	Movement restrictions
	ROE constraints on response options
	Policies prevent intervening, providing help
	Forced separation from local culture, events, places
	Unresponsive supply chain – trouble getting needed supplies/repair parts
	Differing standards of pay, movement, behaviour for different units in area
	Indeterminate deployment length
	Do not know/cannot influence what is happening with family at home
Boredom (alienation)	Long periods of repetitive work activities without variety
	Lack of work that can be construed as meaningful, important
	Overall mission/purpose not understood as worthwhile or important
	Few options for play, entertainment
Danger (threat)	Real risk of serious injury or death from:
	Enemy fire, bullets, mortars, mines, explosive devices
	Accidents, including 'friendly fire'
	Diseases, infections, toxins in the environment
	Chemical, biological, or nuclear materials used as weapons
Workload	High frequency, duration, and pace of deployments
	Long work hours/days during the deployments
	Long work hours/days before and after deployments

Primary Stressor Dimensions in Modern Military Operations (table reproduced from Bartone et al. 2009, p 2).

Linking deployment with adverse health outcomes

A literature review on health effects associated with deployment to the Middle East Area of Operations (MEAO) was conducted (Monash Centre for Occupational and Environmental Health and Centre for Military and Veterans' Health, February 2007). Exposures and experiences during deployment are important considerations when investigating predictors of adverse health effects in veterans. The specific findings of the literature review were:

- Anxiety disorders, including PTSD, are the third most common post-war psychological disorder found in Australian Gulf War veterans, after substance abuse disorders and affective disorders. PTSD and major depression were more prevalent in 1990/91 Gulf War veterans than in military comparison group members.

- PTSD was more prevalent for U.S., but not U.K., veterans who had deployed to Iraq and to a lesser extent to Afghanistan compared with those who had not deployed. PTSD and major depression were more prevalent for lower ranks, and those with higher numbers of stressful combat experiences.

- PTSD was associated with increased numbers of sick call visits and work days missed, as well as increased numbers of physical and psychological symptoms, with important implications for attrition from service as well as health service utilisation. The risk of leaving military service has been shown to be highest in the first year after onset of affective disorder symptoms, with important implications for troop retention following deployment.

- In veterans, PTSD is highly comorbid with major depression. Anxiety disorders tended to precede affective disorders, perhaps as a result of PTSD increasing avoidance behaviour which increases depressive symptoms, such as isolation and loneliness.

- U.S. and Australian 1990/91 Gulf War veterans had a higher prevalence of substance disorders than military comparison group members.

- Substance disorders (mainly alcohol disorders) were the most common post-war psychological disorder found in 1990/91 Australian Gulf War veterans and in many overseas veteran groups. Alcohol disorders tend to be more prevalent in lower ranks, younger veterans, and those with higher numbers of stressful combat experiences.

- Research into the relationship between psychological disorders in veterans has shown that alcohol disorders were the first to develop post-Gulf war, and tended to precede affective disorders, but follow anxiety disorders.

- Gulf War veterans have exhibited higher levels of recent self-reported somatic (physical complaints not accounted for by general medical conditions) disorders than comparison group members. Such somatic disorders were related to stressful combat and other experiences in 1990/91 Gulf War as well as in U.K. Afghanistan and U.S. Iraq veterans.

- In studies of social functioning, wives of U.S. Gulf War servicemen reported lower levels of family cohesiveness and their children reported increased levels of anxiety and depression, compared with families of comparison group members.

The authors of the literature review found that the primary limitations of the studies reviewed was the use of cross-sectional study designs and self-report of outcome and exposure data. This has been shown to have poor validity and repeatability. It may also introduce considerable recall bias. This emphasises the need for prospective study designs.

The cross-sectional Australian Gulf War Health Study of over 80% of Australian Gulf War veterans, and a comparison group of subjects who had also been on an active deployment, concluded that the Gulf War veterans were at increased risk of several psychological disorders. They reported more symptoms than the control group, but there was no unique clustering of symptoms and no differences on a wide range of health measures, and thus no new 'Gulf War Syndrome' (Sim, et al., 2003). This is consistent with the allostatic load model, such that the effects of cumulative stressors can result in a range of potential health outcomes, depending on predisposing factors of the individual. The greatest increase in risk was for PTSD, but anxiety disorders, depression, and substance use disorders including problem drinking were also more common in the Gulf War group. Within this group, the risk of psychological disorders increased as the number of reported adverse military experiences related to the Gulf War increased. The increased risk of psychological disorders was only slightly reduced when Gulf War veterans were compared with the control group. The effect of Gulf War service on psychological health, therefore, could not be fully explained as representing a 'deployment effect' (Sim, et al., 2003).

Sufficient evidence for a *causal relationship* between deployment to a war zone and a specific health effect in humans has not been found (IOM, 2008). The guidelines used to assess causality included strength of association, dose-response relationship, consistency of association, and temporal relationship.

A *consistent positive association* was found between deployment to a war zone and psychiatric disorders, including PTSD, other anxiety disorders, and depressive disorders; alcohol abuse; accidental death in the early years after deployment; suicide in the early years after deployment; and marital and family conflict.

Limited but suggestive evidence of a positive association was found in the case of drug abuse; chronic fatigue syndrome; gastrointestinal symptoms consistent with functional gastrointestinal disorders, such as irritable bowel syndrome or functional dyspepsia; skin disorders; fibromyalgia and chronic widespread pain; increased symptom reporting, unexplained illness, and chronic pain; and incarceration.

A conclusion that *inadequate/insufficient evidence existed* to determine whether an association existed between stress and an effect was reached in relation to cancer; diabetes mellitus; thyroid disease; neurocognitive and neurobehavioral effects; sleep disorders or objective measures of sleep disturbance; hypertension; coronary heart disease; chronic respiratory effects; structural gastrointestinal diseases; reproductive effects; homelessness; and adverse employment outcomes.

Most research has focused on the deployment stage, but a broad perspective is needed that integrates the three stages of deployment: pre-deployment, deployment, and post-deployment. Murphy (2003) found that preparation for deployment, in terms of knowledge of probable role, tasks, rules of engagement, and local politics, were highly correlated with satisfaction during deployment and wellbeing at the end of deployment. On multiple indicators, such as psychological distress and state anxiety, the pre-deployment and post-deployment phases have been found to be more stressful than deployment (Murphy, 2003). Factors associated with the homecoming are related to the likelihood of developing PTSD and other stress reactions. A rapid transition from an overseas operational theatre to home may exacerbate existing stress (Murphy, 2003a).

Therefore, there is growing evidence that deployment (particularly to a war zone which implies considerable stress) is associated with some negative health outcomes, which provides support for the link between deployment and the allostatic load model. However, the limitations of these studies once again make it difficult to draw firm conclusions.

Limitations of veteran studies

The IOM (2008) identified a number of major limitations in the literature of the physical, psychological, and psychosocial effects of deployment-related stress on health outcomes. One major limitation was that few studies measured combat exposure directly. For those studies that did assess combat exposure, this was done with questionnaires or scales and often researchers only asked whether the exposure occurred rather than attempting to measure the degree to which the veteran may have found the experience stressful. This would have assisted in making inferences regarding links to the allostatic load model. Furthermore, few studies attempted to determine the effects of repeated or combined exposures, for example, exposure to extreme heat, wearing of chemical protective gear, and shooting at the enemy.

Another limitation in many studies was their retrospective designs. As a result, they have been unable to distinguish whether health effects existed before or were consequences of deployment and therefore potentially attributable to allostatic load. Some studies used self-report questionnaires to assess health effects and exposure, as well as to identify the presence of risk or protective factors. The issue with questionnaires is that they can lead to recall bias with regard to exposures or inaccuracies in reporting health effects. Based on these reasons, the IOM (2008) report relied most heavily on studies that included an examination by a health professional or other appropriate evaluation methods. Studies of psychiatric disorders, such as PTSD, which relied on symptom checklists as outcome measures were weighted lighter than those involving diagnostic interviews by health professionals. The IOM noted that many studies had a selection bias with health effects assessed in veterans already in treatment groups (e.g., inpatients or outpatients at PTSD clinics), or were selected from registries of veterans

established by veteran affairs. Lastly, sufficient time may not have passed since deployment to detect the development of some health outcomes, e.g., cancer or heart disease, particularly in Gulf War, OEF, and OIF veterans.

Methodological issues were noted in a more recent review and meta-analysis of quality-assessed literature on PTSD prevalence related to deployment status across war eras. The studies included deployment to the primary conflict zone during the wars in Iraq and Afghanistan (OIF and OEF), the Persian Gulf War, and the Vietnam War (Magruder & Yeager, 2009). The meta-analysis assessed the impact of military deployment by war era on the odds of PTSD among military veterans. Deployment was associated with a significant (1.5- to 3.5-fold) increase in risk of PTSD, with the odds greatest for Vietnam veterans. The authors suggest reasons to account for differing odds ratios across war eras: different rates of exposure and homecoming experiences, an improvement in quality in later studies, changes in DSM criteria, and length of time since exposure. This outcome lends support to the allostatic load model, such that increased stress (deployment combined with other extraneous variables) are associated with detrimental health outcomes. They concluded however that, 'until truly common study designs and assessments can be undertaken, the explanations for these differences [in odds ratios] are merely conjecture' (p. 788).

Key points

- Establishing a link between service-related stressors and subsequent ill health can be difficult. It may be more difficult when claims are made years after the stressful event occurred.
- Increased operational tempo for the ADF may mean that stress-related claims for support and services will increase in the future.
- An adequate model of stress and negative health outcomes is needed to account for the delays, differences, and anomalies observed when linking the effects of military life stressors and ill health outcomes in ADF members and veterans as a consequence of military service or deployment.
- Military stressors are unique (e.g., combat) compared to regular issues of daily living (e.g., traffic) experienced by civilians.
- Combat is considered one of the most potent stressors. There are also many non-combat related stressors, such as separation from family and significant others.
- Multiple studies have found consistent links between deployment and negative health outcomes.
- There are limitations in the veteran literature, including a lack of direct measurement of combat exposure or the degree to which exposures were experienced as stressful. Other limitations were retrospective and cross-sectional designs, or studies that involved self-reporting symptoms.

PART 4: FUTURE DIRECTIONS (WHAT TO DO ABOUT IT)

Recognising allostatic load in the military

There is a global military interest in the underlying premise of the allostatic load model and this is well summarised in the Institute of Medicine, Gulf War and Health review (Volume 6, 2008). Although it is a model that is increasingly gaining recognition and inspiring discussion and research in a military context, it is not yet recognised by a common or familiar name in Australian military or veteran environments. A major anticipated outcome of this review is to contribute to defining the language of allostatic load in a military literary context and to foster a greater understanding of the construct. A further outcome is to encourage consensus on the development and definitions surrounding a model that could be considered in any future focus on the health and wellbeing of current and ex-serving members.

Whilst a range of research activities have looked at wellbeing related to deployment stressors, there remains an opportunity for DVA and/or Defence to take a leadership role in researching allostatic load in an Australian military context. Our knowledge of allostatic load in the context of ADF members is incomplete and lacks specificity. The MilHOP study is collecting longitudinal health data. This presents an opportunity to design future projects that can collect this data and to use what data has been collected to begin to answer relevant question to unpack this complex relationship. The implication for understanding more about the allostatic load model is broad. The model lends itself to improvement and refinement related to prevention, intervention, and treatment of modifiable factors for health outcomes of ADF personnel and veterans. There is the potential to improve outcomes and reduce the burdens associated with long-term health care for veterans.

Our knowledge of the *long-term* health outcomes related to allostatic load and overload is incomplete. The challenge here is the generally long interval between potential exposures to stressors during military service and the subsequent development of tertiary health outcomes. A further challenge is to understand more clearly the exposure and impact of other, non-military related stressors. It may be that the health issues of older veteran populations can contribute to our understanding in this area. One approach could be to determine illness patterns from health records within the veteran community going back over several decades. Some work exists in this area with cancer and mortality information, but with limited data available for disorders and illnesses identified as relevant in the allostatic load model.

It is probable that there are other indicators of chronic and problematic biological dysregulation. There is both strong and suggestive evidence that some of these indicators

include 'lifestyle' mediators, such as substance abuse and associated negative consequences, such as arrests for driving infringements and violence. Recent CMVH studies involving ADF members indicate that worry about being away from their family is one of the greatest stressors whilst deployed (McGuire et al., 2009). The influence that families and relationships have on ADF members is probably (at least) equal in relevance to those stressors which occur in the 'workplace'. Family and external relationships can also be protective factors for members.

There is evidence from the U.S. Army that an increase in risk taking behaviours (e.g., driving under the influence, starting a fight, etc.) are observed for defence members post-deployment (Adler, A., Mental Health Advisory Committee [MHAT], U.S. Army). These behaviours may be early indicators that individuals are experiencing difficulty coping. It may be that the personnel management tools such as performance appraisals and disciplinary records may contribute to our understanding of military specific outcomes that may relate to the allostatic load model. These are examples of measurable outcomes that may be more likely to occur earlier in the continuum to dysregulation (and are often worse post-deployment). This is relevant for Defence in the immediate term, but important to DVA for veterans' ongoing treatment needs.

It is suggested that any future work be directed towards creating a comprehensive and inclusive understanding of the relevant secondary health outcomes for ADF personnel. As the allostatic load model is a dynamic one, it is expected that the definitions and resulting measures will evolve over time.

Key points

- There is a need to further understand the allostatic load model and its relevance in the military context
- It is necessary to promote meaningful contributions towards the understanding of health and wellness and the association between exposure and stressors
- There is a need to define the language of allostatic load in a military context and to foster a greater understanding of the construct
- Opportunities exist to promote the existence of the model to improve wellness and long-term health outcomes for current and ex-serving members
- There are challenges involved in attributing causality between military stressors and the development of long-term health outcomes in some cases. This could be overcome by using the broader veteran population to aid research
- Assessment of biological dysregulation needs to include observable behavioural mediators, such as lifestyle, and should include:
  - The families of ADF members
  - Records of appraisals and disciplinary records for objective measures of other indicators of the effects of stress.

Measuring allostatic load in an Australian military context

As previously identified, the challenge of the allostatic load model is that it is currently difficult to provide evidence for direct cause and effect relationships. Whilst animal studies provide strong evidence for causal links between stress and negative health outcomes, in most cases only inferences can be made in human studies. This difficulty is compounded by the fact that individuals may respond differently even under the same or similar circumstances. It may be difficult to define a causal relationship to reflect the model and its influence.

There is an opportunity to improve the identification and measurement of factors that are precursors to allostatic load and to consider what these factors may be in a broad and inclusive manner. It is currently difficult to measure the primary effects of the mediators involved in the allostatic load model (e.g., cortisol levels, glucocorticoids, changes in the amygdala and hippocampus [neurogenesis and atrophy]). However, what we can measure are the secondary (e.g., waist to hip ratio, blood pressure, cholesterol to high-density lipoprotein ratio) and tertiary outcomes (e.g., CVD, decreased physical capacity, severe cognitive declines). The available research on health outcomes for deployment, primarily involving U.S. studies, provides some guidance regarding a starting platform for Australian based research and development.

It is anticipated that it will be challenging to incorporate the allostatic load model into the existing health care and compensation systems, particularly on the strength of the currently known associations. However, there is increasing evidence that allostatic load represents a significant advancement in our understanding of the human stress response. Consideration should be given to developing and refining measurement methods.

A shortcoming of research has been the lack of consistent measurement methods of allostatic load. There are currently areas in the literature that require more development, both in the civilian community and an Australian military context. Identifying the most reliable and valid tools for measuring allostatic load is still be considered 'under development'.

Research suggests that there are limitations in technology which limit our ability to measure some of the mediators of allostatic load, because they are nonspecific and may be affected by other variables that change from one individual to another. For example, the regulation of cortisol, which can be assayed from saliva, plasma, and urine, is highly complex and researchers to date have struggled to define the best approach to obtain a reliable and valid assessment (Loucks, Juster, & Pruessner, 2008). Further research that is focused on the chemical mediators and primary effects would benefit our understanding of biological responses to stress. Emerging technologies related to gene expression to phenotypic outcomes (e.g., metabonomics) may also prove to be promising in advancing research into allostatic load. This type of technology has the potential to assess dysregulation at multiple sites in the metabolic

networks (Singer, Ryff, & Seeman, 2004). Linkages with institutions specialising in endocrinology, immunology, and brain function would likely assist in clarifying our understanding further.

Defining measurement tools for allostatic load may be informed by looking closely at areas that have strong evidence linking military stressors with health outcomes. Because deployment related stress has received the most attention in the military literature, the strongest links have been found to exist between a cluster of stressors and psychiatric disorders (i.e., PTSD, anxiety, depressive disorders), alcohol abuse, accidental death in the early years after deployment (i.e., increase in risk taking behaviours), suicide in the early years after deployment, and marital and family conflict. Continuing to monitor the prevalence of these established outcomes will remain important and provide a potential basis for intervention and evaluation based research.

Therefore consideration should be given to:
- Monitoring the prevalence of these outcomes in an Australian military context
- Evaluating how they link with other measures of stress
- Using existing health data to investigate alternate secondary outcomes as evidence of patterns suggesting dysregulation
- Assessing service-life, including periods of non-deployment
- Assessing civilian life.

Studies should be designed to consider a range of physical testing and survey activities for which there is currently strong evidence of a relationship between stress and allostatic load. Progress and further refinement of the process could then progress from this evidence-based platform.

The best approach would be to model the shared variance among biological systems, rather than measuring the impact of any particular factor in isolation (e.g., exposure to chronic stress or deployment). This approach offers a way to conceptualise and test for cumulative or simultaneous effects of such factors on an array of systems (Seeman et al., 2004). Evidence strongly suggests that measures taken in isolation are not typically reliable measures of allostatic load (i.e., cortisol, blood pressure). There are a range of factors which have been shown to contribute to allostatic load when considered in combination, for example, high fat diet, atherosclerosis, and type 2 diabetes which can contribute to negative health outcomes, such as cardiovascular disease. This approach will improve in strength when current limitations in measurement tools are remedied. More research into improving measurement tools and their application across biological systems is required.

For more information on the operationalisation of allostatic load, as well as measurement and issues associated with this, please see Appendix C of this report for a detailed review.

IOM (2008) recommendations

The following recommendations from the IOM (2008) Gulf War and Health series provide guidance for ensuring the quality of future screening and research activities to support quality data collection related to stress and health outcomes in military and veteran populations:

- Conduct pre-deployment and post-deployment screening for medical conditions, including psychiatric symptoms and diagnoses, and for psychological status to help collect direct evidence about the causal nature of the effects of deployment-related stress.
- Pre-deployment screening would help to identify at-risk personnel who might benefit from targeted intervention programs during deployment and would establish a baseline against which later health and psychosocial effects would be measured after deployment.
- Post-deployment screening and assessment would provide data that could be analysed to determine the long-term consequences of deployment-related stress and would allow Defence and DVA to implement intervention programs to assist deployed veterans in adjusting to post-deployment life.
- Assessments should be made shortly after deployment and should identify those exposures most stressful to the veteran.
- Assessments should be made at regular intervals thereafter (e.g., every 5 years) in order to identify the long-term health and psychosocial effects.
- Any longitudinal assessments conducted should also be conducted in a representative group of non-deployed veterans to allow appropriate comparisons between deployed and non-deployed veterans regarding health and psychosocial effects.
- Australian research may need to go further and have a non-military control group for comparison.

Key points

- Limitations in technology impair our ability to measure some of the mediators of allostatic load and measurement methods to date have not been consistent
- More is to be learned about measuring primary mediators and secondary and tertiary outcomes
- It is difficult to measure mediators, however, there is a larger scope for measuring secondary and tertiary outcomes
- Monitoring the prevalence of health outcomes linked to military stress will remain important and could provide a potential basis for intervention and evaluation based research

- Effective study designs could include a range of physical testing and survey activities that focus on areas for which relatively strong evidence exists, emphasising physical and medical testing and potentially model the shared variance among the various biological systems.
- It is useful for pre- and post-deployment screening to focus on screening for physical and psychological conditions, or risk factors of such, and for data to be analysed to explore causal links and long-term effects

Early-life stress and allostatic load: A challenge

Individual variations in behavioural and biological reactions to stressful situations depend on genetic factors, gender, developmental stage, and physiologic and psychological history (McEwen & Stellar, 1993).

Individuals have some pre-existing load of stressful experiences, which are ultimately reflected in the functioning of their brain and body. Chronic life stressors (e.g., financial problems, work stressors) can affect people by creating a sense of conflict or feelings of lack of control. The result of these types of chronic stressors may be anxiety, depressed mood, and/or a reduction in sleep-quality. Consequently, these psychological and physical changes can lead to self-medication through comfort-eating, consuming an excess of alcohol, smoking, other drugs, and neglecting regular exercise. Coupled with anxiety, depressed mood, and poor sleep, such behaviours dysregulate the normal physiological activities and are responsible for allostatic overload, or a chronic stress burden. The dysregulated stress response involves increased cortisol, insulin, and inflammatory cytokines at night, as well as increased heart rate and blood pressure, and reduced parasympathetic tone. If an abnormal dysregulated state persists (e.g., for months or years), it is likely that adverse health outcomes will result. This may include hypertension, coronary heart disease, stroke, obesity, diabetes, arthritis, major depression, gastrointestinal disorders, chronic pain, and chronic fatigue syndrome (IOM of the National Academies, 2008).

The influence of early-life stressors on longer term negative health outcomes will likely be one of the most ethically challenging aspects in understanding the effects of allostatic load in a military population. Whilst there is significant evidence to suggest that negative experiences as a child, such as neglect and abuse, can have lifelong effects (neurological, physiological, and psychological), the question to consider is how this information could be potentially used in a military context. Options include the screening out of higher risk candidates through to the identification of those that at are at risk and on whom valuable stress response management skills could be focused. Without careful planning and consideration, measuring early-life stress could provide stakeholders with difficulties in managing the key issues of equality, privacy, and opportunity.

Key points

- Negative health outcomes are relatable to early childhood experiences
- There is a need to review entry screening tools to reflect this knowledge
- There are major ethical considerations in how this information should be utilised.

Linking with current programs, studies and initiatives

It is acknowledged that Defence undertakes comprehensive pre- and post-deployment screening, including Return to Australia Psychological Screening (RtAPS) and Post Operational Psychological Screen (POPS), and has contributed considerably to research in deployment related health outcomes for the more recent operational deployments.

The ADF is already implementing programs that are aimed at building resilience, such as BattleSMART (Self-Management and Resilience Training), which is an evidence-based program designed to encourage optimal emotional and behavioural responses to adverse events that are considered to promote resilient psychological functioning for military personnel. Improving wellness for personnel is fundamental as an early intervention to reduce the effects of allostatic load. This could aid in the prevention of associated health outcomes resulting from chronic, repeated, and traumatic stress.

Both Defence and DVA are conducting research which may benefit from reappraisal and potentially re-analysis against the constructs of the allostatic load model. Examples of these include the recent Deployment Health Surveillance Program studies on the Near North Area of Operations, studies of Korean and Vietnam veteran populations' health outcomes, Gulf War studies and the current MEAO Health studies. In the MEAO studies, there is a prospective component which includes physical testing and some biochemical measurements that have largely been based on the current understanding of the model and should contribute in a meaningful way to our understanding of allostatic load in the ADF.

Additionally, DVA has embarked on studies of families of military personnel that were both deployed and not deployed. These are currently focused on the Vietnam and Timor Leste era cohorts that should contribute significantly to our current understanding of the psychosocial mediators, both positive and negative, which are linked to key identified stressors.

It has been identified that brain plasticity, that is changes in the hippocampus and amygdala, result from stress and chronic physiological dysregulation. Therefore, improving wellness for ADF members and veterans at an early stage may also affect brain plasticity to improve health and wellbeing. More research is needed in this area where tangible benefits may flow in terms of enhanced decision-making and modification of the individual stress response.

A positive initiative would be for the ADF to consider how the process towards allostatic load can be modified in a military context. This includes identifying critical points in the process of moving from allostasis (adaptive, healthy) to allostatic load (maladaptive, unhealthy). There also is a need to examine post-deployment re-integration into civilian life and how it may compound, on the one hand, or ameliorate, the adverse effects of deployment and war experiences. This could do much to inform areas where resources and research into modifying factors would provide the ADF with the most immediate benefits. Longer term benefits would be seen for DVA.

Perhaps most importantly, the ability to capture and interrogate health and personnel data needs to be enhanced. The development of the ADF's electronic health record (JeHDI [Joint e-Health Data and Information] program) offers a unique opportunity to develop the data on which a longitudinal approach could be taken, especially in the areas of behaviour mediators and the development of secondary and tertiary health outcomes. Available psychological data from recruitment, clinical incidents, and operational sources would augment the completeness of any health records. This, coupled with surveillance modules which could be developed, offer the opportunity to considerably enhance the understanding of relationships between mediators and longer term health outcomes in ADF members. Additionally, they support the evaluation of interventions aimed at modifying the human stress response in military populations. Similarly, using existing DVA data for claims and health care utilisation would significantly enhance the data on which evaluation of the model could be based.

Key points
- Current and previous research activity could be re-evaluated and research questions developed in line with the current understanding of the allostatic load model
- The development of a longitudinal comprehensive data set should be investigated to reflect the longer term associations between stressors and health outcomes with the model, including those of post-deployment re-integration into civilian life.

Conclusion

This review confirms the usefulness of the allostatic load model related to the human stress response. It guides our interpretation of the relationship between stressors and negative health outcomes. Whilst the model is dynamic and evolving, it remains an important recent development regarding the way chronic and/or repeated stressors are associated with military service and deployment, and how this may impact on the health and wellbeing of ADF personnel and veterans. There is an opportunity for past, present, and future research activities to assist the development in our understanding of allostasis and the progression to allostatic load. DVA is well positioned, in association with initiatives occurring within Defence, to take on a leadership role in order to improve our understanding of military stressors and their short and longer term consequences.

APPENDIX A: STRESS AND THE ALLOSTATIC LOAD MODEL

The word *stress* is used in many contexts and has a variety of meanings. It is often used to describe a situation characterised by real or perceived threats to a person; however it is also commonly used to refer to the body's response to such threats. Thus, *stress* has been used both to describe environmental events (the stressors) that trigger responses and to refer to the resulting changes (stress responses) that occur in the brain and body (McEwen & Stellar, 1993). The following section describes the stress response, including its basic biology and physiology, as well as introducing the concepts of allostasis, allostatic state, allostatic load, and allostatic overload.

Interpreting stress

One of the earliest steps in the response to stress is the brain's perception that an event is threatening. This will determine how an individual will respond physiologically, emotionally, and behaviourally to the stressor. A stressful stimulus results in changes to physiological systems, and the degree of the perceived or real threat determines the magnitude of the consequential stress. Moreover, stressors are heterogeneous and are thus experienced differently by different people. Physical stressors may include exertion, environmental demands (heat/cold), trauma, infection, and inflammation; whilst psychological stressors may include (but are not limited to) fear and anxiety, social defeat and humiliation, disappointment (anger, frustration, etc.), and sometimes even intense joy (McEwen & Stellar, 1993).

There are wide individual variations in behavioural and biological reactions to stressful situations. This depends on genetic factors, gender, developmental stage, and physiologic and psychological history. Some individuals are highly resilient and cope with stress easily; others are highly vulnerable (Rutter, 1985). The response to stressors is also considerably variable, and there are individual differences both physiologically and behaviourally in how a person perceives a challenge. Possible responses include aggression, escape, anxiety, and executive function (a complex set of behaviours).

Early and late phases of the stress response

Table A1. Physiological changes during the stress response

Early Phase of the Stress Response (Duration: minutes to hours)
- Increased heart rate and blood pressure
- Increased respiration
- Mobilisation of energy from liver and body fat
- Sharpening of attention and cognition
- Increased fear conditioning (learning)
- Blunting of pain
- Altered intestinal motility

Later Phases of the Stress Response (Duration: days to weeks)
- Enhanced immune system
- Suppression of appetite and digestion
- Suppression of growth
- Suppression of reproduction
- Persistence of increased heart rate and blood pressure in some cases
- Release of stress hormones

The human stress-response evolved as an acute reaction for coping with a significant challenge or threat, therefore the effectiveness of the response is measured not only by the efficiency with which it mobilises the body's systems in order to react to a threat (i.e., physiological, neurohormonal, and immunological mechanisms), but also by how quickly the body's functions can return to pre-stress levels. Thus, recovery of the baseline steady state is as important a part of coping, adaptation, and resilience as is the capacity to mount an effective stress response in the first place (Friedman & McEwen, 2004).

Short-term stress response

When the brain perceives a threat, a cascade of physiological changes is activated rapidly in response. The stress response is spearheaded by the hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). The sympathetic nervous system can be thought of as the 'on switch' (for the 'fight or flight' mechanism). When the SNS is activated, it uses adrenaline to stimulate the inner regions of the adrenal gland to secrete large amounts of adrenaline and other catecholamines (hormones and neurotransmitters that includes adrenaline and dopamine), into the circulation. The surge of adrenaline floods the brain and peripheral tissues, subsequently producing the full-fledged 'fight or flight' response, which includes a faster heart beat, greater energy, more blood flow to skeletal and cardiac muscle, dilation of the pupils and airways, higher blood glucose concentration, and so on. A diagram of the short term stress response can be seen in Figure A1 (www.worldofbiology.wikispaces.com).

SHORT TERM STRESS RESPONSE

Hypothalamus

Afferent nerve cell

Spinal cord

Efferent nerve cell

Acetylcholine

Adrenal medulla

Norepinephrine an amine hormone

Epinephrine an amine hormone

Increased breathing rate

Increased metabolic rate

Changed blood flow patterns

Increased blood pressure

Increased blood flow to muscle and liver

Decreased blood flow to kidney and intestines

Glycogen broken down to glucose

Increased blood glucose levels

Figure A1. The short-term stress response in humans.
Note. Epinephrine = adrenaline; Norepinephrine = noradrenaline.

Long-term stress response

Where the challenge or threat is long-term (i.e., days up to years), such as potentially dangerous working conditions during military deployment, recovery of the baseline state may be impeded. It is this long-term continued activation of the stress response, long after the threat has ceased, that potentially poses the greatest risk to human health (see Figure A2 from www.worldofbiology.wikispaces.com). This failure to fully return to a baseline state represents a real possibility for the ADF population who may experience extended periods of time in both acute and chronic stress phases during deployment, which can result in longer-term (e.g., months, or longer, after post-deployment) stress response activation. Therefore, this population potentially may be at a greater risk for negative health outcomes.

LONG TERM STRESS RESPONSE

Hypothalamus

Neurosecretory cell

Corticotropin-releasing hormone (CRH)

Anterior pituitary

Adrenocorticotropic hormone (ACTH)

Adrenal cortex

Mineralocorticoids

Glucocorticoids

Retention of sodium ions and water by kidney

Proteins and fats broken down and converted to glucose

Increased blood volume and pressure

Increased blood glucose levels

Figure A2. Long-term stress response in humans.

Allostatic load and overload

Allostatic load and allostatic overload are points on a continuum. The pattern, frequency, and duration of stressors are important determinants of the severity of the outcome, as are a person's response to the stressors. Diagrammatically, this progression has been represented in Figure A3.

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Figure A3. The process of allostasis through to allostatic overload, as a product of increasing stress.

Link between stress, allostatic load and disease outcomes

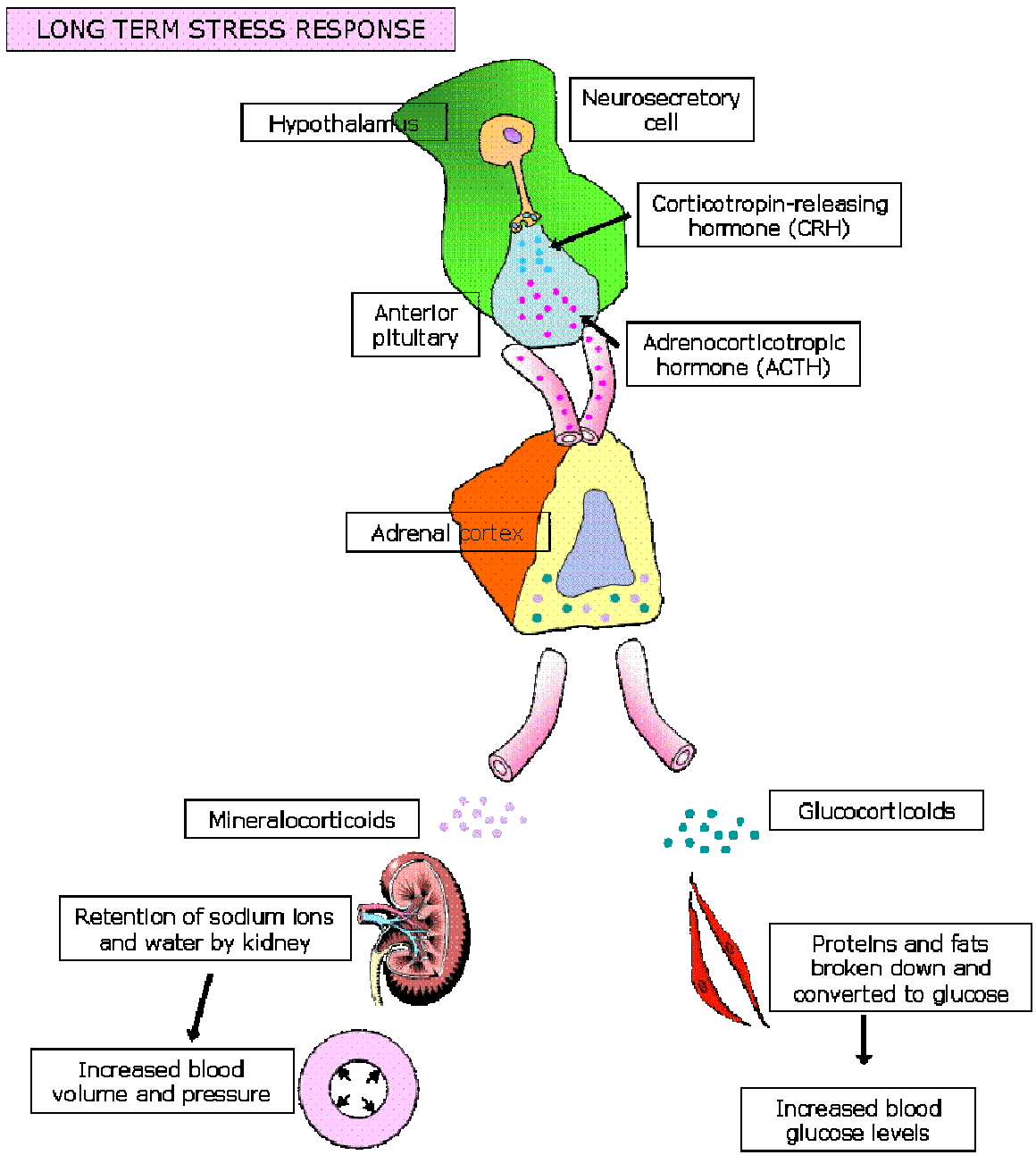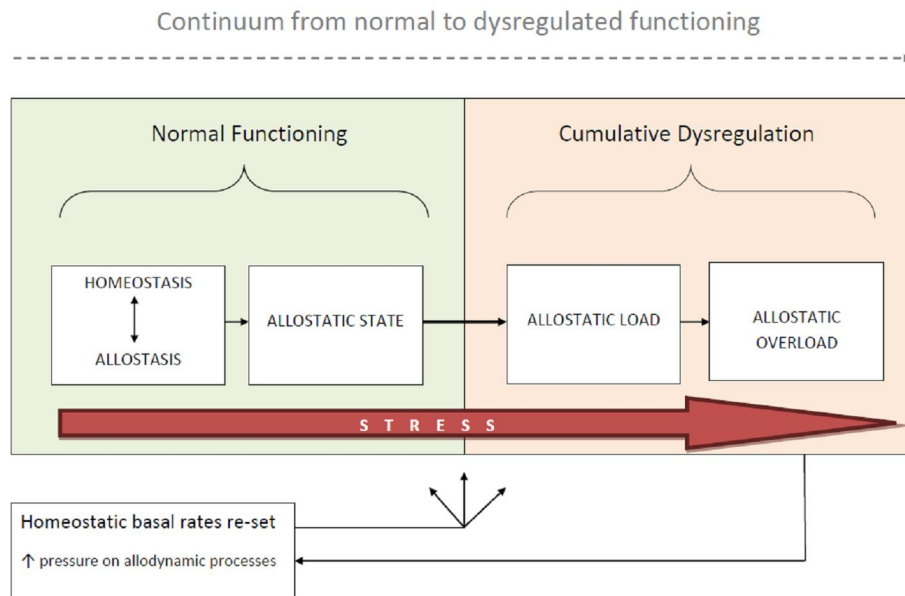Individual variations in behavioural and biological reactions to stressful situations depend on genetic factors, gender, developmental stage, and physiologic and psychological history (McEwen & Stellar, 1993). VanItallie (2002) noted that well-controlled studies in laboratory animals have found robust relationships between a variety of specified, investigator-applied stressors and predictable illnesses. In humans, the direct culpability of stress is not easily established, because the vulnerability of the host is a major pathogenetic consideration, and the duration, repetitive nature, and severity of the stress is often hard to demonstrate. Thus, *'although a growing number of illnesses have been found to be associated with dysregulation of the stress system, the precise role of stress in their causation usually is not clear. Illness itself is often a powerful stressor….In most of the stress-related diseases that affect humans, stress does not appear to be the sole or even the principal causative factor. Rather, it contributes – to a variable degree – to the pathogenesis, precipitation, exacerbation, or prolongation of the illness…there is little doubt that, in many cases, stress plays a critical role in determining clinical outcome'* (VanItallie, 2002, p. 42) (Cohen, Janicki-Deverts, & Miller, 2007).

Individuals have some pre-existing load of stressful experiences, which are ultimately reflected in the functioning of their brain and body. Chronic life stressors (e.g., financial problems, work stressors) can affect people by creating a sense of conflict or feelings of lack of control. The result of these types of chronic stressors may be anxiety, depressed mood, and/or a reduction in sleep-quality. Consequently, these psychological and physical changes can lead to self-medication through comfort-eating, consuming an excess of alcohol, smoking, other drugs, and neglecting regular exercise. Coupled with anxiety, depressed mood, and poor sleep, such behaviours dysregulate the normal physiological activities and are responsible for allostatic

overload, or a chronic stress burden. The dysregulated stress response involves increased cortisol, insulin, and inflammatory cytokines at night, as well as increased heart rate and blood pressure, and reduced parasympathetic tone. If an abnormal dysregulated state persists (e.g., for months or years), it is likely that adverse health outcomes will result. This may include hypertension, coronary heart disease, stroke, obesity, diabetes, arthritis, major depression, gastrointestinal disorders, chronic pain, and chronic fatigue syndrome (IOM of the National Academies, 2008). Please see Figure A4, adapted from IOM (2008).
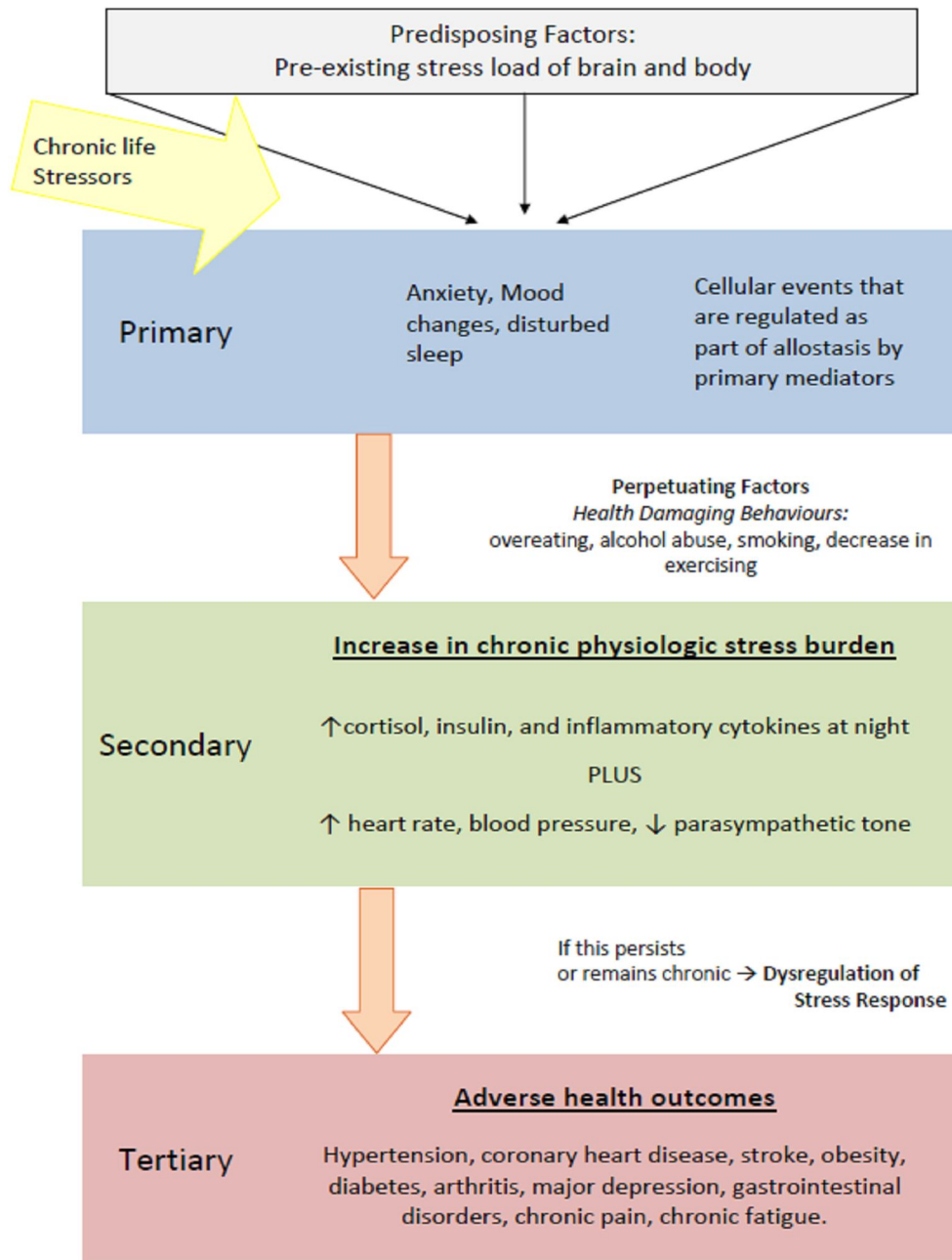
Note. Primary, Secondary, and Tertiary refer to the effects of allostatic mediators on the human body.

Figure A4. Link between stress, allostatic load, and health outcomes

Convincing epidemiological evidence exists that supports the hypothesis that certain acute stressors, such as earthquakes and combat, can precipitate heart attacks or PTSD in susceptible individuals. Further, evidence is accumulating which suggests that chronic stress may give rise to, or indeed worsen, a number of illnesses (e.g., CVD, gastrointestinal disorders, diabetes, obesity). The relationship between stress and disease is represented at Table A2 (adapted from VanItallie, 2002, p. 43).

Table A2 - Mechanisms by which activation of the stress system may increase risk of myocardial infarction, stroke, high blood pressure, cardiac arrhythmia, visceral obesity, and exacerbate diabetes.

Stress Response	Clinical Effect
Adrenaline ↑	↑ platelet aggregation → thrombosis of coronary/cerebral arteries → *myocardial infarction/stroke*
Sympathetic Nervous System (SNS)↑ Noradrenaline ↑ Cortisol Secretion ↑	↑ peripheral vasoconstriction → ↑ peripheral vascular resistance → *hypertension*
Adrenaline ↑ SNS activity ↑	↑ heart rate → ↑ myocardial irritability → ↑ risk of *cardiac arrhythmia*
SNS activity ↑ Adrenaline secretion ↑ Cortisol secretion ↑	↑ insulin resistance + ↑ gluconeogenisis → *impaired diabetes control*
Cortisol secretion ↑ GH/IGF-1 ↓ LH/testosterone ↓ TSH/T_3 ↓	↑ visceral obesity → insulin resistance syndrome → ↑ dyslipidemia → *atherosclerosis*

Note. SNS = sympathetic nervous system; GH = growth hormone; IGF-1 = insulin-like growth factor-1; LH = luteinizing hormone; TSH = thyrotropin; T_3 = triiodothyronine.

APPENDIX B: MEDIATORS

Stimuli from internal inputs from the body and external sensory sources are interpreted and processed in the brain. This parallel processing enables the brain to control and coordinate behavioural and physiological adjustments engendered by internal or external challenges to homeostasis (McEwen & Gianaros, 2010). However, how the brain responds to stimuli may be influenced by or depend upon a number of variables, including genetic make-up, developmental history (i.e., early childhood experiences), current behavioural and psychological states of the individual, and psychosocial factors (McEwen & Gianaros, 2010).

The biological systems that promote adaptation include the hypothalamus-pituitary-adrenal (HPA) axis, the autonomic nervous system, the metabolic system, the gastrointestinal tract, the kidneys, and the immune system. The chief bio-mediators of these systems are cortisol, cytokines, and metabolic hormones (McEwen, 2006).

The central processor

The brain is the central organ of stress processes and allodynamic adaptation and therefore will be discussed in detail throughout this section. The brain determines which of our experiences are perceived as stressful, it orchestrates how we will cope with stressful experiences, and it changes both functionally and structurally as a result of stressful experiences.

The brain circuitry includes the hippocampus, amygdala, and prefrontal cortex which are responsible for coordinating response systems in order to cope with external and internal challenges or perceived threats to homeostasis and wellbeing (McEwen & Gianros, 2010). They also serve important functions in cognition, emotions, and impulse control. They help to interpret events on the basis of current and past experiences whether an event is threatening or otherwise stressful, thus influencing the allostatic response.

Primary mediators of allostasis

Mediators of allostasis help maintain homeostasis. There are four primary mediators, or chemical messengers, that are released as part of allostasis:

- **Cortisol**: a glucocorticoid with receptors present in virtually every tissue and organ in the body, which mediates effects ranging from induction of liver enzymes involved in energy metabolism to regulating the trafficking of immune cells and cytokine production to facilitating formation of fear-related memories.

- The catecholamines **noradrenaline** and **adrenaline**, released by the adrenal medulla and sympathetic nervous system respectively, which produce widespread effects throughout the body ranging from vasoconstriction and acceleration of heart rate, to trafficking of immune cells to targets, as well as enhancement of fear-related memory formation. Adrenergic receptors are widespread throughout the body, in blood vessels and target organs such as the liver, pancreas, and brain (which is not accessible to circulating catecholamines; however catecholamines signal the brain through the sensory vagus and the nucleus of the solitary tract, as in learned fear).
- **Dehydroepiandrosterone (DHEA)**, a functional antagonist of cortisol that may have effects via other signalling pathways. Low DHEA is considered deleterious, as is chronically high cortisol.

The interactions between the chemical mediators and nervous system components of allostasis and allostatic load are depicted in Figure B5.
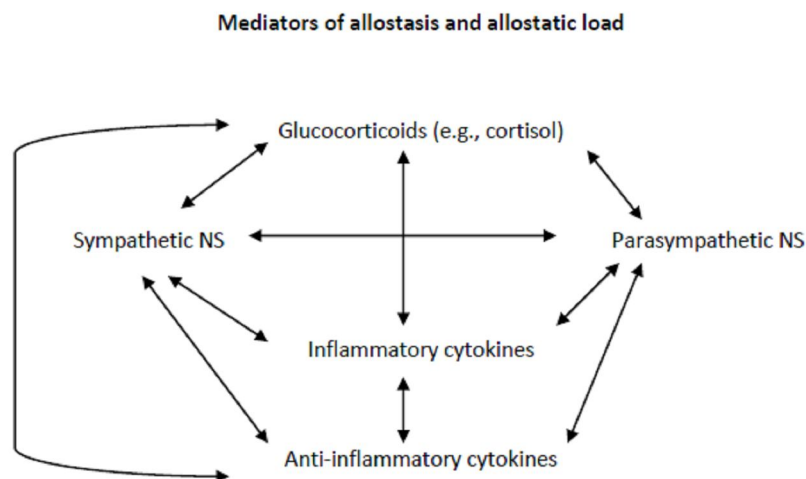
Figure B5. Interacting Mediators of allostasis and allostatic load (McEwen, 2006).

This model demonstrates that each system regulates the others in a reciprocal manner. Moreover, there are multiple pathways for regulation, including positive and negative feedback loops.

Effects of the mediators of allostatic load

The primary mediators of allostasis have both protective and damaging effects on the body. In the short term these mediators are essential for adaptation, maintenance of homeostasis, and survival (allostasis).

Mediators such as glucocorticoids serve the body well in the short term by replenishing energy reserves after a period of activity (e.g. escaping a perceived threat, running away from a predator). However, over longer time intervals the mediators exact a cost (allostatic load) that can accelerate disease processes (McEwen, 2006). The presence of mediators such as glucocorticoids which increase appetite are useful and functionally adaptive when playing sport or doing manual labour, but are unhelpful at times when we engage in certain regular daily activities, such as eating whilst watching television. Subsequently, inactivity and lack of energy expenditure creates a situation where chronically elevated glucocorticoids can impede the action of insulin to promote glucose uptake. This can result in increasing insulin levels, and together, insulin and glucocorticoid elevations promote the deposition of body fat. This combination of hormones also promotes the formation of atherosclerotic plaques in the coronary arteries (McEwen, 2000a).

The primary effects, and secondary and tertiary outcomes of mediators of allostasis represent biological events, or markers, on the continuum from normal to dysregulated functioning.

Primary effects
Primary effects are organ- and tissue-specific cellular events that are regulated as part of allostasis by the primary mediators.

The primary effects of allostatic load are typically not measured; however early in the allostatic load literature, McEwen and Seeman (1999) noted that it would be desirable to study primary effects, because they are the basis for the secondary and tertiary outcomes, which represent the biological progression along the allostasis (normal) to allostatic overload (dysregulated) continuum.

Measuring those primary effects that are known to be the basis for secondary and tertiary outcomes would allow for diseases to be 'intercepted' early (ideally before they became problematic or symptomatic). Subsequently, it would be possible to place preventative interventions into action to prevent resulting negative health consequences (i.e., myocardial infarction, diabetes, etc.).

For example, glucocorticoids regulate gene expression via several pathways which involves interactions with DNA. DHEA is known to antagonise glucocorticoid action in a number of systems. In a prospective cohort analysis of 4255 Vietnam veterans tracked over 15 years, lower DHEA and a higher cortisol ratio to DHEA ratio were associated with an increased risk of

all-cause cancer and other-cause mortality (Phillips, 2010). Therefore, measuring primary effects (e.g., DHEA and cortisol ratio), which inevitably can/will occur much earlier in the average person's life, can provide information to inform the prevention (or reduction in severity) of future diseases developing by addressing at least one of the causes, which may be an imbalanced ratio of mediators.

Secondary outcomes

Secondary outcomes are integrated processes that reflect the cumulative outcome of the primary effects in a tissue/organ specific manner in response to the primary mediators.

Secondary outcomes, all related to abnormal metabolism and risk for CVD, include waist/hip ratio (WHR) index, blood pressure, cholesterol/high-density lipoprotein (HDL) ratio, and HDL cholesterol. Often, secondary outcomes reflect the actions of more than one primary mediator.

The following measures have been used to measure secondary outcomes in the allostatic load literature (Karlamangla, Singer, McEwen, Rowe, & Seeman, 2002; Seeman, McEwen, Rowe, & Singer, 2001; Seeman, Singer, Rowe, Horwitz, & McEwen, 1997; Seeman, et al., 2004), and will be discussed in greater detail below:

- Blood pressure is a primary indication of the allostatic load that can lead to accelerated atherosclerosis as well as insulin resistance.
- Cholesterol and HDL cholesterol are measures of metabolic imbalance in relation to obesity and atherosclerosis.

Tertiary outcomes

Tertiary outcomes refer to the actual diseases or disorders that are the result of allostatic load, which can be predicted from the extreme values of the secondary outcomes and of the primary mediators.

Tertiary outcomes in research on allostatic load (e.g., MacArthur study, discussed in detail below) included CVD, decreased physical capacity, and severe cognitive declines. However, McEwen and Seeman (1999) suggest that cognitive decline should be assigned as a secondary outcome, while Alzheimer's disease or vascular dementia should be considered tertiary outcomes. They also suggested that cancer would be a tertiary outcome, whereas the common cold would be a secondary outcome, because it is an indirect measure, in part, of immune system efficacy.

Adopting this framework would allow for allostatic load measurement at an earlier age and stage in the allostatic load to overload continuum, perhaps enhancing earlier intervention.

Tertiary health outcomes are possibly the most quantifiable outcomes of allostatic load to measure, and have therefore been a major focus of research to date.

Link between allostatic load and disease

Examples of tertiary outcomes include the relationships that exist between allostatic load with both heart disease and diabetes. For the cardiovascular system, repeated surges of blood pressure in response to stress, or the failure to shut reduce pressure surges efficiently, promotes the generation of atherosclerotic plaques, and synergises with metabolic hormones which results in Type II diabetes; thus constituting a form of allostatic load (McEwen & Seeman, 1999). Overactivity of the metabolic system, involving repeated HPA activity in stress or elevated evening cortisol, correspondingly leads to allostatic load in terms of insulin resistance, accelerating progression towards Type II diabetes, including abdominal obesity, atherosclerosis, and hypertension (McEwen & Seeman, 1999). There also seems to be a relationship (although the direction is currently unknown) between diabetes and major depressive disorder. In both conditions, there are overlapping abnormalities in brain morphology and function, with alterations in insulin-glucose homeostasis, immune-inflammatory processes, and oxidative stress mechanisms (McIntyre, Soczynska, & Konarski, 2007). Links have also been found to exist between Type II diabetes and later Alzheimer's Disease. Mechanisms to explain this link include insulin and insulin resistance, inflammatory cytokines, and oxidative stress. Obesity or physical inactivity may also influence Alzheimer's disease through hypertension, insulin sensitivity, or inflammation (Haan, 2006).

The immune system is regulated by neural input from sensory, sympathetic, and parasympathetic nerves, as well as by circulating hormones, of which the glucocorticoids are the most prominent. Although they have been regarded as inhibitors of immune function, adrenal steroids (e.g., glucocorticoids) are now recognised as having a biphasic effect on immune function (McEwen, 2007). Under acute stress, energy reserves are mobilised, vegetative processes and reproduction are suppressed, and the body is made ready for 'fight or flight,' with the possibility of wounding. Thus, the immune defence system acutely gears up to aid in protecting the body from infections and to accelerate wound healing. However, the activation of this process can be ambivalent. Firstly, enhancement of immune function in the case of an autoimmune disease may in fact be deleterious to some individuals, or secondly, when there is indeed a pathogen involved it may be beneficial. Conversely, suppression of the

immune system may be beneficial where an autoimmune disorder is concerned, but may be dangerous where a pathogen is involved. Thus, the immune system exemplifies the contrasting aspects of 'protection' and 'damage' in terms of allostasis and allostatic load (McEwen, 2000a).

Measuring allostatic load via secondary outcomes

Secondary health outcomes reflect the cumulative effects of the primary mediators (often more than one) on a specific organ or tissue. Therefore, measuring allostatic load based on secondary outcomes indicators should enhance early intervention opportunities.

In a military context, monitoring secondary indicators would provide a practical method of providing early treatment for personnel before the symptoms or illness become chronic and more difficult (or ineffective) to treat. For example, treating high blood pressure with medications, diet, relaxation, and exercise is easier and more effective than treating cardiovascular disease.

The role of behaviour in the allostatic load model

Anticipation, or lack thereof, and worry can contribute to allostatic overload. Anticipation is involved in the reflex that prevents us from blacking out when we get out of bed in the morning and is also a component of worry, anxiety, and cognitive preparation for a threat (McEwen & Wingfield, 2000). Anticipatory anxiety can drive the output of mediators such as adrenocorticotrophic hormone (ACTH), cortisol, and adrenaline; thus, prolonged anxiety and anticipation is likely to result in allostatic load. For example, salivary cortisol levels increase within 30 minutes after waking in individuals who are under considerable psychological stress (e.g., work or family stress).

The effects of stimuli on the individual's nervous system (their 'information processor'), is determined, in part, by the genetic makeup, stage of biological development, and also by past learning and social history.

The following diagram (see Figure B6) is from an early and influential paper written by McEwen and Stellar (1993) on stress and the individual. The flow diagram considers the stimulus within the individual's social context, behavioural reaction, and biological response, leading to allostatic load.
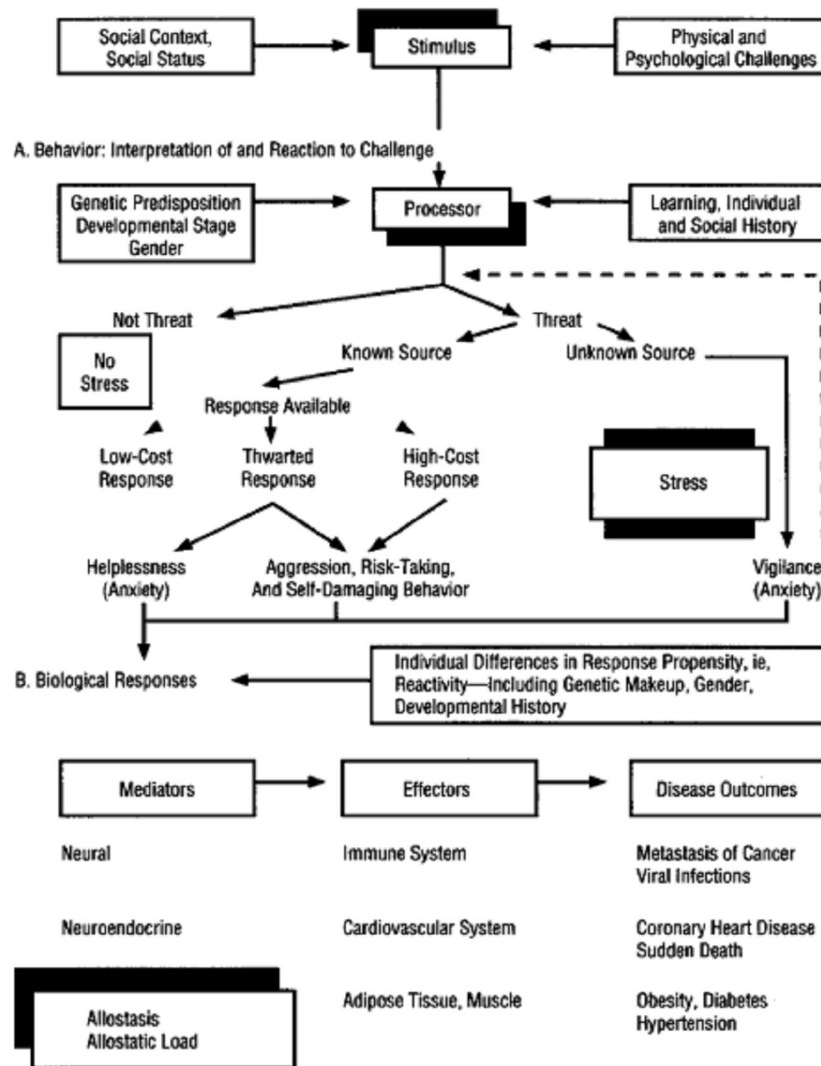
Figure B6. Stimuli, behaviour, the interpretation of and reaction to challenges, and allostatic load (McEwen & Stellar, 1993).

Behaviour and physiologic analysis of allostasis and allostatic load involve somewhat different methodologies and provides different types of information that are often complementary. The notion of allostatic load implies that there is a steady state in which ongoing environmental challenge is balanced by a physiologic response that is elevated above the basal level. Sometimes the environmental challenge is a long-lasting behavioural state brought about by a prior traumatic event, such as occurs in PTSD.

PTSD is an example of behaviour linked to physiologic allostatic load. Physiologically, there are elevated catecholamine/cortisol ratios in individuals with PTSD (see McEwen & Stellar, 1993 for a comprehensive list of references), whereas psychological assessments reveal differences in reactivity in the PTSD patient, involving hypervigilance and other characteristics that may be both the *cause and the result* of the elevated sympathetic neural reactivity (McFall et al., 1990).

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Together, the behavioural and physiological assessments provide a more complete picture of a complex disorder and allow for investigation of pathophysiological processes that may be activated over long term periods.

A summary of biomarkers repeatedly used in allostatic load studies is described by Justers, McEwen, and Lupien (2010).

Neural plasticity: the allostatic load model

The ability to learn, remember, and make decisions may be compromised by chronic stress and may be accompanied by increased levels of anxiety and aggression (McEwen, 2007).

The human stress system consists of the central and peripheral nervous systems, the endocrine system, and the immunological system. As indicated above, the brain is the key organ involved in the response to stress, which is defined as an event or events that are interpreted as threatening to an individual and which elicit physiological and behavioural responses (McEwen, 2000a). The brain both *mediates* allodynamic responses and is a *target* of allostatic load. Thus, the communication patterns are bi-directional.

The brain is responsible for determining what is stressful and decides the health-damaging and health-promoting behaviours and physiological responses. It regulates peripheral allodynamic control systems that feed back to the brain to affect functional and structural neuroplasticity. The hippocampus and amygdala are limbic brain structures that process experiences by interfacing with the hypothalamus and brainstem, as well as with higher cortical areas, particularly the prefrontal cortex (McEwen & Gianaros, 2010). Alterations in brain function caused by chronic stress can therefore have direct and indirect effects on cumulative allostatic overload.

The importance of particular areas of the brain in the allostatic load model

Stress and the hippocampus

Chronically, stress hormones and glucocorticoids in particular, contribute to impairment of cognitive function and promote damage to brain structures such as the hippocampus (McEwen, 2000a). The hippocampus is described as one of the most sensitive and malleable regions of the brain, and as very important for cognitive functioning (McEwen & Gianaros, 2010). The hippocampus participates in verbal memory and is particularly important for contextual memory (i.e., time and place of events that have a strong emotional bias). Impairment of the hippocampus decreases the reliability and accuracy of contextual memories, which may exacerbate stress by preventing access to the information needed to decide that a situation is

not a threat. The hippocampus also regulates the stress response and acts to inhibit the response of the HPA axis to stress.

In animal models, allostatic overload manifests in atrophy of neurons in the hippocampus and prefrontal cortex, brain regions involved in episodic and declarative memory, selective attention, and executive function. Animal studies have also found that hippocampal circuitry shows a plastic remodelling of dendrites and synaptic connections and a limited amount of neurogenesis in response to chronic or repeated stress.

Evidence suggests that the human hippocampus is particularly sensitive to elevated glucocorticoids and severe, traumatic stress and shows greater changes than other brain areas, especially in Cushing's syndrome, recurrent depressive illness, PTSD, schizophrenia, and ageing before overt dementia (McEwen & Magariños, 1997).

The mechanism for stress-induced hippocampal dysfunction and memory impairment is twofold. First, acute stress increases cortisol secretion, which suppresses the mechanisms in the hippocampus and temporal lobe that subserve short-term memory. Stress can impair memory in the short term, but this effect is reversible and relatively short-lived. Second, repeated stress causes the atrophy of dendrites of pyramidal neurons in the hippocampus. Although this is reversible if the stress is short-lived, stress lasting many months or years can kill hippocampal neurons (McEwen, 1998). Whether atrophy of the hippocampus more generally is reversible or permanent is unclear (McEwen, 1998). However, hippocampal atrophy can also occur in the absence of elevated glucocorticoid levels. For example, stress early in post-natal life may result in long-term memory deficits and selective loss of hippocampal neurons (VanItallie, 2002).

McEwen and Gianaros (2010) reported that human neuroimaging studies of the hippocampus indicate that individuals with stress-related psychiatric disorders, such as major depressive disorder and PTSD, show volumetric reductions in the hippocampus. In otherwise healthy individuals, there also appears to be a relationship between chronic stressful experiences and changes in hippocampal morphology. It is possible that pre-existing individual differences in hippocampal and regional brain morphology, which could emerge early in life and which could result from a combination of genetic and developmental influences, could partly increase vulnerability to and decrease resilience against life stress.

Stress and the amygdala

The amygdala is also plastic, but responds to stress differently from the hippocampus. Stress causes dendritic *growth* in neurons in the amygdala, rather than shrinkage, which subsequently enhances amygdala-dependent unlearned fear, fear conditioning processes, and aggression. This means that the fear-response *increases*, which has further implications on stress levels,

perceptions of stress, and therefore allostatic load. Animal studies on the prefrontal cortex (the orbital and medial prefrontal cortex and the anterior cingulated cortex) also show stress-induced changes in neuronal structure and connectivity (McEwen & Gianaros, 2011).

A function of the amygdala in stressor-related processing is the rapid assignment of emotional and behavioural salience to social and environmental information. The amygdala is also critical for regulating the neuroendocrine and autonomic stress-response axes, and is sensitive to early-life stress (McEwen & Gianaros, 2010). It is involved in coordinating stress behaviours and modulating memory consolidation, and is important in memory of fear-producing experiences and generation of aversive behaviour (VanItallie, 2002). Studies investigating the neural mechanisms of fear conditioning across species support the conclusion that the amygdala has a critical function in the acquisition, storage, and expression of conditioned fear (Hartley & Phelps, 2010).

Neuroimaging studies have found that the amygdala is involved in mediating forms of peripheral stress reactivity that have been linked to physical health outcomes. For example, individual differences in amygdala reactivity to emotionally salient stimuli have been shown to co-vary with physiological parameters associated with cardiovascular disease risk, including basal levels of autonomic-cardiac control, stressor-evoked changes in blood pressure, and diurnal variations in the secretion of cortisol. Individuals who express greater amygdala reactivity to threatening social cues (e.g., angry and fearful facial expressions) also exhibit higher levels of preclinical atherosclerosis.

The ability to modify or control the nature of emotional responses as circumstances change is important, and failure to regulate fear responses properly has been associated with psychopathology (Hartley & Phelps, 2010). For example, some anxiety disorders are thought to involve dysfunction in the neural systems underlying the extinction of fear learning. Extinction is a form of regulatory process that can control the physiological, behavioural, and experiential components of affective responses. Functional magnetic resonance imaging (*f*MRI) studies examining extinction learning in humans have found that PTSD may result from a failure to consolidate and retrieve extinction learning, which is consistent with evidence that PTSD patients often improve with exposure therapy.

Stress and the prefrontal cortex
The prefrontal cortex is broadly involved in higher cognitive functions, including working memory and executive control. One of its functions is the top-down regulation of stress and threat-related responding and coping processes, and is mediated by the hippocampus, amygdala, and hypothalamus (McEwen & Gianaros, 2010).

Animal studies have found that chronic stress *causes changes* in neuronal structure and connectivity in the medial prefrontal cortex. The medial prefrontal cortex shows reduced neuronal complexity and loss of synaptic connections as a result of repeated stress, whereas the orbitofrontal cortex (i.e., cognitive processing of decision-making) shows greater neuronal complexity as a result of chronic stress.

Human studies have found the perigenual ACC (pACC) to be specifically linked to several emotions and stress-related processes in neuroimaging studies. The pACC is involved in mediating individual differences in stressor-evoked cardiovascular reactivity, which has been associated with cardiovascular disease. The pACC is involved in the human stress response (McEwen & Gianaros, 2010).

Overall, 'studies on the human prefrontal cortex have revealed an important role for this region and its functional subdivisions...in mediating stress-related behavioural and biological reactivity and regulation' (McEwen & Gianaros, 2010, p. 207). Stress can change brain connectivity which can influence our ability to make reasoned decisions.

The importance of plasticity

The concept of plasticity is important because neural plasticity is amenable to prevention and intervention (McEwen & Gianaros, 2010). For example, targeting the plasticity of the hippocampus in depression and mood disorders may underpin pharmacological and non-pharmacological (e.g., cognitive behavioural therapy and aerobic exercise) treatment efficacy (McEwen & Gianaros, 2011) . McEwen noted that social integration and social support were linked to mental health and related brain-based processes and suggested future research in order to delineate the pathways by which social relationships affect the brain, body, health, and ageing.

The literature on the relaxation response appears to suggest that brain plasticity can produce positive outcomes. That is, if chronic stress, trauma, and dysregulation can cause detrimental changes in brain circuitry over time, then similarly, by inducing repeated states of relaxation, brain plasticity can allow for positive circuitry in the brain to be reestablished. Therefore, relaxation might provide the antidote to allostasis and allostatic load.

Self-esteem and locus of control

McEwen and Gianaros (2010) reported that self-esteem and locus of control (positive psychological attributes that emerge early in life and modify the appraisal of environmental stressors) are associated with hippocampal volume and related changes in HPA regulation in both young and elderly people (citing Preussner et al., 2005). In their study, Preussner et al. referred to earlier work in which self-esteem and internal locus of control had been found to be predictive of people's neuroendocrinological reactions to stressful social situations.

Thus, in a mental challenge task, only the subjects with low self-esteem and low levels of internal locus of control exhibited a significant cortisol response, and these personality variables were also found to predict the ability to habituate to repeated psychosocial stress, such that subjects with low self-esteem and low internal locus of control showed continuously high cortisol stress responses.

Preussner et al. (2005) noted that the relationship between self-esteem, locus of control, hippocampal volume, and cortisol regulation is likely to be 'complex and reciprocal.' However, the correlational nature of the data did not allow for strong causal inferences to be made. They suggested links between personality traits and hippocampal volume based on the likelihood that self-esteem and locus of control have a significant effect on stress perception and subsequently the (cortisol) stress response. Thus, 'when considered over a lifetime, a higher susceptibility for perceiving a situation as stressful, and generating stress hormone release…might have an effect on specific brain structures via the neurotoxic effects of cortisol' (p. 822).

The outcomes of this research suggest avenues for alleviating the effects of chronic stress and allostatic load and can be applied in a military and veteran context through building resilience, locus of control, and hardiness.

Socioeconomic status

SES is an important aspect of life experience that plays a significant role in health and disease. It is well established in the literature that SES is a strong and consistent predictor of morbidity and premature mortality (Adler, Boyce, Chesney, Folkman, & Syme, 1993). Further, it is well documented that individuals lower in the SES hierarchy suffer disproportionately from almost every disease and show higher rates of mortality than those above them (Antonovsky, 1967; Syme & Berkman, 1976). This association has been found with each of the key components of SES, including income, education, and occupational status (Alder et al., 1993). Early research shows that SES and health disparities are greatest in middle age and early old age individuals, compared with earlier and later life (Gould & LeRoy, 1988; Wise & Meyers, 1988; House, Kessler, & Herzog, 1990). The SES-health association parallels the allostatic load model, such that the cumulative effect of stress and dysregulation of multiple physiologic systems culminate in a 'meta-factor' of allostatic overload (dysregulation of multiple systems) over a period of time.

Seeman et al. (2010), in their review of the impact of SES on multiple biological regulatory systems over the life course, concluded that SES-related gradients emerge as early as 5 years of age and persist throughout childhood, adulthood, and older age. Lower SES may also adversely affect neural circuitry via stress-related factors, and the regulation of key allostatic control systems may thus become impaired, leading to allostatic load on the body and brain and

perhaps increased risk for ill health. Lower SES has been linked to greater and faster cumulative dysregulation in nearly all biological systems (Seeman, 2010). For example, recent studies have confirmed that neighbourhood advantage is associated with lower allostatic load (Finch, 2010) and that conversely, living in lower SES neighbourhoods is associated with higher allostatic load (Bird, 2010; Conroy, Sandel, & Zuckerman, 2010).

Behaviours such as smoking, poor diet, and lack of exercise are well known to be associated with health status (Otten, Teutsch, Williamson, & Marks, 1990; Paffenbarger, Hyde, Wing, Lee, Jung, & Kampert, 1993; Wilhelmsen, 1988). Early effects of those behaviours are reflected in risk factors such as cholesterol level, obesity, and blood pressure; longer-term effects can be seen in disease and premature mortality. The behaviours and the risk factors have a linear relationship with SES (Adler et al., 1993) and have been identified as consequences (and contributors) of allostatic load and overload.

Early-life experiences

A major risk factor of allostatic load and overload is early childhood experiences of abuse and neglect. This risk factor has been found to increase allostatic load later in life and lead individuals into social isolation, hostility, depression, and conditions like extreme obesity and CVD (McEwen, 2000). Early-life stress has been associated with increases in cortisol and other markers of increased HPA axis activity (Levine, 1962). Animal models provide evidence of the lifelong influences of early experience on stress hormone reactivity. Whereas, depression, childhood abuse, and neglect tend to be more prevalent in individuals at the lower end of the SES spectrum, cardiovascular and other diseases follow a gradient across the full range of SES, which is also evident for allostatic load (McEwen, 2000).

Research has found that higher cortisol concentrations, which persisted from youth to old age, were associated with stressed animals. At greater ages, the excess secretion of cortisol was associated with structural changes in the hippocampus and with deficits in spatial memory (Meaney, Aitken, van Berkel, Bhatnagar, & Sapolsky, 1988). Normal maternal care was found to lead to lower concentrations of corticotropin and cortisol, which are indications of a less reactive HPA axis (Sapolsky, Krey, & McEwen, 1986). Therefore, maternal care and early life experiences are critical in determining how well adults respond to stress.

Cold or unstable parent-child relationships and abuse in childhood have also been found to lead to behavioural and physical problems that continue throughout adult life. McEwen and Seeman (1999) cited evidence that adverse childhood experiences result in increased morbidity and mortality from a wide variety of common diseases. A history of sexual and physical abuse in childhood is a risk factor for PTSD and for hippocampal atrophy and cognitive impairment in

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adulthood (Bremner, 1997). Other impacts include a substantial increase in substance abuse, depression, and suicide as well as increased incidence of heart disease, cancer, chronic lung disease, extreme obesity, skeletal fractures, and liver disease (Felitti, Anda, Nordenberg, & et al., 1998).

Early childhood experiences are relevant to vulnerability to allostatic load. In the case of ADF members, a profile of early life experiences and SES background may be one means of determining those that may be risk of developing negative health conditions following deployment or in their transition to civilian life.

The New Zealand studies: An example of the influences of mediating variables

In a prospective longitudinal study conducted in New Zealand, members of the Dunedin Multidisciplinary Health and Development Study followed an unselected cohort of 1000 children participants (born in New Zealand during 1972–73) who were assessed at birth and at ages 3, 5, 7, 9, 11, 13, and 15 years. At age 26 years, they assessed these individuals for health outcomes including body-mass index, waist/hip ratio, blood pressure, cardio-respiratory fitness, dental caries, plaque scores, gingival bleeding, periodontal disease, major depression, and tobacco and alcohol dependence, and tested for associations between these variables and childhood and adult SES (Poulton et al., 2002).

Compared with those from high SES backgrounds, children who grew up in low SES families were found to have poorer cardiovascular health. Significant differences were also found on all dental health measures, with a threefold increase in adult periodontal disease (31.1% versus 11.9%) and cavity levels (32.2% versus 9.9%) in low versus high childhood SES groups, respectively. Substance abuse resulting in clinical dependence was related in a similar way to childhood SES (e.g., 21.5% versus 12.1% for adult alcohol dependence). The authors concluded that, 'low childhood socioeconomic circumstances have long-lasting negative influences on adult health, irrespective of what health cache one begins life with, or where one ends up in the socioeconomic hierarchy as an adult. Specifically, the findings document that the social gradient in health—which has been amply documented among middle-aged and older adults— actually emerges in childhood'. Further, upward mobility did not mitigate or reverse the adverse effects of low childhood SES on adult health.

A further prospective longitudinal cohort study found that depressed individuals with a history of childhood maltreatment were twice as likely to have clinically relevant levels of hsCRP (i.e., sensitivity to inflammation) compared with control individuals, even after controlling for correlated risk factors such as depression recurrence, low SES in childhood or adulthood, poor health, or smoking (Danese et al., 2008). The authors concluded that it was possible that a

subgroup of depressed individuals with stressful developmental experiences are at the highest risk of future disease and suggested that routine assessment of maltreatment history could provide clinicians with necessary information to identify depressed individuals with elevated risk of inflammation and potentially poor health. Collecting this type of information would also be particularly useful in a military context in order to collect baseline data and to flag individuals who may be at risk for future health issues.

Military studies: Examples

In a study of Dutch veterans who were resistance fighters in World War II, Falger et al. (1992) found that prolonged financial problems and prolonged familial conflict both in childhood and/or adolescence prior to the war were more prevalent in the family life of veterans who experienced 'current PTSD' than in those without the disorder. This lead the authors to speculate that, 'unfavourable conditions for family socialisation during childhood and adolescence…may sensitise subjects' attention to environmental cues that indicate threat…Thus, it may be hypothesised that the hyperalertness found in a large majority of the veterans with current PTSD, as well as the current prevalence rates of CVD risk factors, are associated with early sensitisation to environmental stressors' (Falger et al., 1992, p. 169). Further, after the war veterans with current PTSD experienced more prolonged marital conflicts and prolonged educational problems with children compared to participants without PTSD.

APPENDIX C: OPERATIONALISATION AND MEASUREMENT OF ALLOSTATIC LOAD

The operationalisation and measurement of allostatic load is an area of particular interest because it represents the potential for practical interventions in the field. There is emerging evidence which suggests positive ways to progress in the measurement of various aspects of allostatic load.

Measurement issues

The process of devising an accurate measure of allostatic load is still in its early stages. Most experimental work on allostatic load and changes in neurocircuitry have used animal models, and therefore much work remains to be done in the form of longitudinal studies to translate these findings to humans. In addition, biological and social approaches to stress research have largely diverged in the past into parallel structures with independent academic research traditions, methodologies and literature, which resulted in no common model for specifying the stress process (Ganzel, Wethington, & Morris, 2010). More work is needed in order to integrate approaches from different disciplines in order to explain the human physiological reaction to environmental challenges.

Recent research confirms the allostatic load model as 'a multisystems index of biological dysregulation' and provides 'initial support for a model of [allostatic load] as a meta-construct of inter-relationships among multiple biological regulatory systems, that varies little across sex or ethnicity' (Seeman et al., 2010b). This emphasis on a meta-factor in the allostatic load model means that rather than measuring the effect of particular factors (e.g., exposure to chronic stress) on individual biological systems, the better approach is to model the shared variance among the various biological systems. Seeman et al. concluded that this meta-factor approach offers a way of conceptualising and testing for more cumulative or simultaneous effects of such factors on an array of multiple systems.

The MacArthur studies: An example

The MacArthur studies on successful aging were conducted in 2007 and were based on a complete data set from a representative community-based cohort of over 700 men and women aged 70-79 at baseline. This was the first major study of its kind to begin with an initial operationalisation of allostatic load (Seeman, et al., 1997). The study identified 10 physiological indicators that were selected as primary and secondary mediators of allostatic load.

They included: the HPA axis, sympathetic nervous system, cardiovascular system, and metabolic processes. The 10 parameters (from McEwen, 2000b) were:

Indices of cardiovascular activity:
1. Systolic blood pressure
2. Diastolic blood pressure

Index of more chronic levels of metabolism and adipose tissue deposition, thought to be influenced by increased glucocorticoid activity:
3. Waist-hip ratio (WHR)

Related to the development of atherosclerosis—increased risks being seen with higher levels in the case of total cholesterol and lower levels in the case of HDL:
4. Serum HDL
5. Total cholesterol

An integrated measure of glucose metabolism over several days time:
6. Blood plasma levels of glycosylated haemoglobin

A functional HPA axis antagonist:
7. Serum dihydroepiandrosterone sulphate (DHEA-S)

An integrated measure of 12-hr HPA axis activity:
8. Overnight urinary cortisol excretion

Integrated indices of 12-hr sympathetic nervous systems activity:
9. Overnight urinary noradrenalin excretion
10. Overnight urinary adrenalin excretion.

Each reflected parameters of functioning across a range of regulatory systems pertinent to disease risks.

Cognitive functioning

It has been hypothesised that increased allostatic load is associated not only with increased development of disease, but with declines in cognitive and physical functioning (Seeman, et al., 1997).

Seeman et al. (1997) used detailed assessments of both cognitive (language, abstract reasoning, spatial ability and memory) and physical performance (balance, gait, chair stands, foot taps, manual ability) at both baseline (1988) and follow-up (1991). This permitted cross-sectional and longitudinal assessments of associations with allostatic load. Cross-sectional correlations between baseline allostatic load and cognitive functioning indicated that higher allostatic load was associated with poorer cognitive performance overall. Higher allostatic load at baseline was also associated with greater risk of decline in memory (especially verbal memory), an association which remained even after controlling for age, sex, race, education, income, baseline health status, physical activity, and prevalent and incident CVD. In a 7 year follow-up study, Seeman et al. (2001) confirmed that the allostatic load measure was indeed a predictor of incident CVD and decline in cognitive functioning, but that the syndrome X components were

largely responsible for the observed effects, offering mixed support for the hypothesis that the comprehensive summary measure of allostatic load would provide the best prediction of outcomes (see below for more detail on measurement issues).

However, Karlamangla et al (2002) claims that while none of the ten indicators of allostatic load exhibited significant associations on their own with health outcomes, the summary measure of allostatic load was found to be significantly associated with all four outcomes, including new cardiovascular events, decline in cognitive functioning, decline in physical functioning, and mortality over both 2.5 and 7 year follow-ups. This analysis indicated that these findings, 'are consistent with the idea that although a modest deviation in the level of activity of a single physiologic system may not be predictive of poor future health, the cumulative toll from modest alterations in several physiologic systems is indeed prognostic of poor health' (Karlamangla et al., 2002, p. 697).

Physical functioning

Seeman et al. (1997) also found that higher allostatic load was associated with poorer physical functioning at baseline and with increased risk of decline in physical performance in the follow-up period of 2.5 years. These results were found to be unaffected by adjustments for potential confounding such as socio-demographic factors, baseline health status, physical activity, and prevalent or incident CVD. In their 7 year follow-up, Seeman et al. (2001) confirmed that the allostatic load measure was a significant predictor of decline in physical functioning. They also found a generally linear and positive relationship between allostatic load and mortality, such that greater allostatic load was associated with greater mortality.

Incident CVD

Elevations in allostatic load have been found to predict CVD (Seeman, et al., 1997). Incidence of CVD was assessed through a summary measure reflecting the occurrence of any of the following: new myocardial infarction, stroke, high blood pressure, or diabetes. The study found increased incidence of CVD in subjects with higher baseline allostatic load. The comprehensive measure of allostatic load provided the best indication of risks for incident CVD (rather than individual risk factors). However, the results from the 7 year follow-up (Seeman, et al., 2001) found that the syndrome X components of the measure were largely responsible for the observed effects.

Limitations of the MacArthur studies

The analyses used secondary data from a convenience (community-based) sample and were thus constrained by the available biological data (i.e., a set of measures not collected specifically to measure allostatic load). Further, the sample was chosen to represent the top third of those aged between 70 and 79 in terms of physical and cognitive functioning.
The question arises as to whether the studies can be generalised to other populations, including a military population, given the nature of the sample used (Seeman, et al., 2001).

Whilst the MacArthur studies demonstrated interesting results for allostatic load, more research within an Australian military population is required. The results of the Middle East Area of Operations (MEAO) study currently underway might be helpful.

Measuring allostatic load

The authors of the MacArthur studies (see above) point out that many of the physiologic parameters used to measure allostatic load have also been characterised as features of 'syndrome X' or 'metabolic syndrome'. However, in a 7-year follow-up of the MacArthur cohort, Seeman et al. (2001) found that the allostatic load measure (which assessed the overall impact of dysregulation across multiple regulatory systems) was a better predictor of mortality and decline in physical functioning than either syndrome X (measured by high systolic and diastolic blood pressure, high ratio of total cholesterol to HDL, high WHR, and high blood plasma levels of glycosylated haemoglobin – an integrated measure of glucose metabolism over several months time) or the non-syndrome X components of the allostatic load measure (i.e., the primary mediators of stress alone [cortisol, adrenaline, noradrenaline, and DHEA]).

In the MacArthur studies, an initial index of allostatic load was constructed by summing the number of parameters for which each individual participant had a value that placed them in the top quartile (or bottom quartile for HDL cholesterol and DHEA-S) of that parameter's distribution within the MacArthur cohort. Seeman et al. noted that that the original set of 10 parameters were not intended to be comprehensive, nor were they offered as a fixed/standard measure of allostatic load. Rather, they were an initial attempt to operationalise allostatic load using available data. Indeed, subsequent work from their research has been able to augment the panel of allostatic load components with additional information on parameters of inflammation (e.g., CRP, interleukin-6) (Seeman, et al., 2010a).

Karlamangla et al. (2002) noted that the construct of allostatic load used in the MacArthur studies was 'necessarily incomplete, [being] an initial operational measure, which was restricted to the biologic measurements that were available in existing data' (p. 708). For example, measurements reflecting activity of the renin-angiotensin system and the inflammatory and immune systems were not included. The authors sought to refine the measure of allostatic load used in the MacArthur studies by posing three questions and providing responses for each (below each question):

1. Does the *magnitude* of the dysregulation in individual systems have predictive ability for future health? *Yes.*
2. Do *different physiological systems contribute differentially* to the relation between allostatic load and health outcomes?
   Yes, different components of allostatic load contribute differentially to future health and function. The best weights for allostatic load components differed, not only across categories of health outcomes (physical decline vs. cognitive decline), but also from one follow-up period to the next (e.g., baseline to 1991 vs. 1991-1995).

The authors concluded that, 'the prognostic information in allostatic load has multiple linearly independent components that are differentially important in predicting different outcomes. However, in all cases, the summary index, reflecting information from multiple systems, was a better predictor of outcomes than individual biological markers' (p. 707).

3. Do components of allostatic load, other than traditional cardiovascular risk factors, contribute to prediction of health risks?

    Yes, the analyses with hormonal allostatic load components (the four components of allostatic load that directly reflect hormonal/endocrine activity, namely urine adrenaline, urine noradrenaline, urine cortisol, and serum DHEA-S) were found to have large and significant associations with functional outcomes, independent of the more standard cardiovascular risk factors, life style and demographic variables. Karlamangla et al. concluded that, 'declines in physical and cognitive functioning in elderly men and women cannot be attributed solely to CVD: alterations in neuroendocrine activity represent additional independent sources of risk' (p. 708).

Overall, allostatic load remains, 'in a fairly early phase of development as a biomarker panel' and, 'in the early stage of biomarker development, there can be reasonable variability in how they are measured between studies. This is currently the case with allostatic load' (Loucks, et al., 2008, p. 526). While the authors characterise allostatic load as, 'a timely, potentially useful tool to measure the degree to which the body's physiological function is outside of its normal range' (p. 528), Loucks et al. express their uncertainties as to its effect on morbidity and mortality outcomes in the diagram below (see Figure C7).
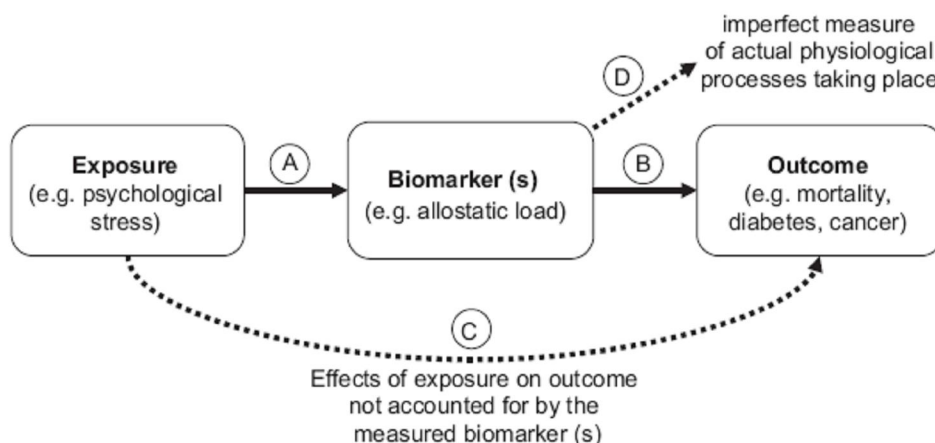

Figure C7. Mediated model of biomarkers (Loucks et al., 2008)

In biomarker (i.e., biomediator) development, perfect biomarkers (i.e., surrogate endpoints) completely mediate the effects of the exposure on the outcome of interest (paths A and B). However, in reality, for most biomarkers, there are unmeasured factors that mediate the

effects of the exposure on the outcome (path C). Finally, almost always, measurement of the biological mediators imperfectly represents the true bioactivity of the mediators (path D) (Loucks et al., 2008, p. 526).

Further, measuring biomarkers/mediators accurately is an issue. For example, the regulation of cortisol, which can be assayed from saliva, plasma, and urine, is 'highly complex, and researchers to date struggle to find the best approach to obtain reliable and valid assessments' (Loucks et al., 2008, p. 527). Singer et al. (2004) noted that there was promise in emerging technologies relating gene expression to phenotypic outcomes such as metabonomics, which deals with metabolic changes in whole organisms and has the potential to assess possible dysregulation at multiple sites in metabolic networks. Current shortcomings in modern medicines ability to measure particular aspects of allostatic load have been cited as a criticism of the model. However, this is not a weakness of the allostatic model per se, rather it is a criticism of our ability to measure it.

An example of the consequences of using different approaches to measuring allostatic load emerged in a review of 26 studies done on the relationship between SES and biomarkers of multiple physiological systems up to June 2009, utilising community-based populations (Dowd, Simanek, & Aiello, 2009). The authors concluded that the findings were mixed, with little evidence that lower SES was consistently related to higher levels of cortisol. Lower SES was more consistently related to higher levels of allostatic load, but primarily via the cardiovascular and metabolic components of allostatic load rather than the neuroendocrine markers. Studies used widely varying approaches to collecting and analysing cortisol levels, which the authors concluded was likely to contribute to inconsistent results. Dowd et al. noted the inclusion of metabolic and cardiovascular markers in allostatic load, which was derived from the theory that HPA and SNS dysregulation affect multiple physiological systems including the regulation of glucose, lipids, and blood pressure. They describe the measurement issues surrounding allostatic load as follows:

> It is nonetheless difficult to interpret findings of SES associations with the 'secondary' outcomes in the allostatic cascade of events while finding no relationships for the 'primary mediators' of cortisol and catecholamines themselves. Especially given the challenges in measuring cortisol secretion, one possibility is that there is less measurement error for metabolic and cardiovascular components of allostatic load that do not have large diurnal variations compared with HPA and SNS markers, increasing the power of empirical tests to identify a significant relationship with metabolic and cardiovascular measures. But since metabolic and cardiovascular markers are by definition 'secondary' outcomes in the cascade of events leading from HPA and SNS dysregulation to poor health outcomes, they are more subject to influence by other physical and behavioural pathways well known to be associated with SES such as diet, physical activity and smoking. Whereas, these behavioural pathways may also ultimately be linked to 'stress', the literature on allostatic load has emphasised the physiological

effects of activation of the HPA axis due to stimuli perceived as stressful. Consequently, while the conceptualisation of allostatic load as dysregulation across multiple physiological symptoms is an important theoretical advance in the study of 'stress' and health, current empirical tests of allostatic load that rely heavily on more general metabolic and cardiovascular measures make interpretation of these results with regards to stress difficult. Combining different physiological systems into a single empirical index rather than taking a system-specific approach involves important trade-offs, and much work remains to bridge the empirical execution of allostatic load with its theoretical underpinnings (Dowd, et al., 2009, p. 1035).

Dowd et al.'s comments highlight the complexity of the issues surrounding the measurement of allostatic load. There is consensus in the theory that, for example, SES is likely related to allostatic load, however, the authors caution that more research is needed to establish causality. This does not preclude using current 'best estimates' to endeavour to measure this construct, for example, continuing to measure secondary outcomes and factors such as SES and early childhood experiences, particularly in a military context. This information is obtainable and may be used to predict or estimate future risk of health outcomes.

Despite continuing work with various methodologies, debate continues about how best to capture the multiple and inter-connected features of allostatic load. This includes questioning the range and scope of physiological measurements that should be included (e.g., which systems and which aspects of these systems), as well as methods for summarising this information into one or more cumulative indices (Seeman, et al., 2010a). In this context, Seeman and colleagues noted that allostatic load differs from more traditional concepts of biological risk in two ways, firstly because it focuses on the sum total of physiological dysregulation across systems (which they view as being closer to reality than a single system focus); and secondly, the inclusion of relatively modest forms of dysregulation (e.g., somewhat elevated blood pressure) in the calculation of biological risk, which are assumed in the allostatic load model to have a significant impact when cumulated across multiple systems, but which would not normally be deemed to have clinical significance in and of themselves.

Clinical criteria for allostatic load

There have been recent proposals for new criteria for determining allostatic overload that could be used in clinical practice. These clinimetric criteria would be based on: (a) the presence of a stressor exceeding individual coping skills, and (b) clinical manifestations of distress (Fava, Guidi, Semprini, Tomba, & Sonino, 2010).

Suggested criteria are presented in Table C3, with both A and B being required (Fava et al., 2010, p. 282):

Table C3. Suggested clinimetric criteria for allostatic load

A	The presence of a current identifiable source of distress in the form of recent life events and/or chronic stress; the stressor is judge to tax or exceed the individual's coping skills when its full nature and circumstances are elevated
B	The stressor is associated with 1 or more of the following manifestations, which have occurred within 6 months after the onset of the stressor: (1) Psychiatric symptoms according to the DSM-IV classification (2) Psychosomatic symptoms according to the DCPR classification (3) Significant impairment in social or occupational functioning (4) Significant impairment in psychological well-being

Fava et al. (2010) suggest that the areas that need to be explored for determining allostatic overload are as follows in Table C4 (p. 282).

Table C4. Suggested clinimetric questions to assess for allostatic overload

Recent life events:	Did any of the following happen to you in the past year: death of a family member or close friend, separation, recent change of job, moving, financial difficulties, legal problems, beginning of a new relationship?
Chronic stress:	Do you feel under pressure at work? Do you get along with your colleagues? Do you get along with your spouse/partner or other family members? Do you feel tension at home? Has any close relative been seriously ill in the past year? Were you subjected to mobbing?
Environmental mastery:	Do you often feel overwhelmed by the demands of everyday life? Do you often feel you cannot make it?
Sleep:	Does it take a long time to fall asleep? Is sleep restless? Do you wake up too early and are not able to go back to sleep?
Somatisation:	Do you feel tired or a lack of energy? Dizziness? Breathing difficulties? Stomach, bowel pain? Other symptoms?
Psychological distress:	Do you feel irritable? Sad or depressed? Tense or 'wound up'?

The MacArthur studies of successful aging (Seeman, et al., 2001) found that although the risk range of each physiologic indicator was not clinically significant, the integrated scores lead to a meaningful allostatic load. The baseline allostatic load score had significant correlations with mortality, incidence of CVD, changes in physical functioning, and changes in cognitive functioning 7 years later. This finding suggests that higher allostatic load is associated with worse health outcomes (Seeman et al. 2001).

Seeman et al. (2004) tried to explain the SES differences in mortality with a cumulative measure of biological dysregulation (the allostatic load). Compared with their previous study, six additional biological components including albumin, interleukin-6, C-reactive protein, peak flow (a measure of lung function), fibrinogen, creatinine clearance (a measure of renal function) were added. Although the cause of death and decreased physical and cognitive functioning were not investigated in these studies, they found that 35.4% of the difference in mortality risk between subjects with higher versus lower educational attainment was explained by the cumulative index of biological risk. Before controlling for the measure of allostatic load, baseline morbidity mediated only 10.4% of the educational differential.

Evans (2003) used six physiological dysregulation indexes (systolic blood pressure, diastolic blood pressure, urine cortisol, adrenaline, noradrenaline, and body mass index) to measure allostatic load. Findings indicated that cumulative risk factors including physical (crowding defined as number of people per room, noise, housing problems) and psychosocial aspects (family separation, family turmoil, violence), and personal characteristics (income to needs ratio, single parent, maternal high school dropout) were associated with heightened cardiovascular and neuroendocrine responses, increased deposition of body fat, and a higher summary index of total allostatic load.

Three analytical strategies can be used to calculate allostatic load scores for individuals (Schulkin, 2004):

1. summation of the number of biomarkers in the risk zone;
2. weighted summation of standardised biomarker scores (through canonical correlation); and
3. recursive partitioning of persons into empirically determined classifications of allostatic load.

Given the complexity of the construct of allostatic load, it is likely that the measurement will involve primary and secondary outcomes (e.g., MacArthur studies), as well as clinimetric criteria. As technology advances, it is anticipated that our ability to measure the nuances of allostatic load will improve. This will unlock important information relating to measurement. However, as it currently stands, we are able to identify and measure allostatic load and should continue to refine our processes. This reinforces the importance of staying abreast of developments in the literature of the measurement and operationalisation of the allostatic load model.

Criticisms of the allostatic load model

The allostatic load model has been criticised in the past. For example, Day (2005) suggested that much of the research conducted on stress neurocircuitry was occurring within a poorly developed conceptual framework. The author suggested that the concept of homeostasis was being 'supplemented' by the concepts of allostasis and allostatic load and that, 'that the concepts of 'allostasis' or 'allostatic load' [do not] offer us anything that was not already apparent, or at least readily derivable, from an accurate reading of the original concept of homeostasis' (p. 1195). Similarly, Romero et al. (2009) proposed that homeostasis and allostasis were almost the same. Their thesis was addressed by McEwen and Wingfield (2010), who noted that any perceived issues relating to homeostasis and allostasis were only a matter of semantics, since the authors of both papers were in agreement about the content, similarities, and differences in the processes being discussed and only disagreed on what it the processes were called, and in which all the concerned researchers are trying to measure.

McEwen [2011, correspondence] indicated that despite criticisms of the allostatic load model, the concept continues to appeal to many people and has helped researchers in epidemiology, health psychology, and ecology. Increasingly it also appeals to biomedical sciences to get a 'handle' on 'stress' as involving consequences not only of the stressful experience, but also the resulting behaviours (i.e., lifestyle). The main problem in some people's minds is measurement and scoring. That is, combining together in one 'score' the measures that tap into both mediators, such as cortisol, ANS activity, and cytokines, and consequences like waist hip ratio, HDL/LDL, glycosylated haemoglobin.

There is also the ambiguity of blood pressure and cortisol as both an acute mediator states and also possibly a sign of an 'allostatic state', i.e., chronic elevation as in hypertension or Cushing's. This is why there is a need for research to define the conditions under which those measures are collected, for example, overnight urine for cumulative output versus salivary cortisol measured four times a day, or during a public speaking challenge. Measures that are taken under ambiguous conditions provide no useful addition to the literature on allostatic load. However, the measures used in the current allostatic load battery (e.g., CARDIA research by Seeman et al., 2010b) are collected routinely and economically in medical examinations. The only complex aspects are measures related to parasympathetic activity. This has led to predictions about health consequences over time and thus has heuristic value as an approximation to what researchers in this field would ideally like to do (i.e., measure in real time, and over time, changes in neuroendocrine, autonomic, immune/inflammatory, and metabolic mediators, which currently is not possible).

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Summary

The concept of allostasis and allostatic load introduced the idea that stress (external challenge) initiates strain on multiple biological systems including organs and tissues, and chronic stress (cumulative risk factors) leads to accumulative physiological wear and tear that can be measured with multiple biomarkers. Although this theoretical model provides a better explanation for the human body's adaptation process to stress and the development of chronic illness, biomarkers used in research to measure allostatic load so far tend to be tied to indicators of CVD. The allostatic load model is predominantly influenced by the sympathetic nervous system, HPA axis, and immune systems, therefore it may be expected that physiological parameters are most suitable to measure allostatic load (which consist of hormones [glucocorticoids such as cortisol] and catecholamines [adrenaline and noradrenaline]). Whilst some of the biological parameters are highly related to cardiovascular risk factors, the complete picture in regards to other morbidities such as diabetes and gastrointestinal disturbances are less clear. Therefore, the next agenda in developing this theory should be to find valid biomarkers to explain the allostatic load of various systems and to verify their prediction of associated chronic diseases through population-based research.

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