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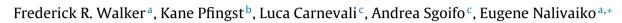


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Review article

# In the search for integrative biomarker of resilience to psychological stress



<sup>a</sup> School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, NSW 2300, Australia

<sup>b</sup> 1st Psychology Unit, Australian Army, Australia

<sup>c</sup> Department of Neuroscience, University of Parma, Via Volturno 39/E, I-43100 Parma, Italy

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### ABSTRACT

Psychological resilience can be defined as individual's ability to withstand and adapt to adverse and traumatic events. Resilience is traditionally assessed by subjective reports, a method that is susceptible to self-report bias. An ideal solution to this challenge is the introduction of standardised and validated physiological and/or biological predictors of resilience. We provide a summary of the major concepts in the field of resilience followed by a detailed critical review of the literature around physiological, neurochemical and immune markers of resilience. We conclude that in future experimental protocols, biological markers of resilience should be assesses both during baseline and during laboratory stressors. In the former case the most promising candidates are represented by heart rate variability and by *in vitro* immune cells assay; in the latter case—by startle responses (especially their habituation) during stress challenge and by cardiovascular recovery after stress, and by cortisol, DHEA and cytokine responses. Importantly, they should be used in combination to enhance predictive power.

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\* Corresponding author.

E-mail address: eugene.nalivaiko@newcastle.edu.au (E. Nalivaiko).

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#### 1. Introduction

Psychological resilience has been variously defined as the process of positive adjustment to adverse events (Fletcher and Sarkar, 2013). In the context of exposure to potentially traumatic events an indicator of resilience would be considered the absence of psychiatric disorder symptoms, such as post-traumatic stress disorder (PTSD). The term "resilience" (or "resilience") was first used in this context by Jack Block in his 1950 doctorate dissertation (Block, 1950); however the concept could be traced back to Sigmund Freud's theory of personality where it had a name of "ego strength" (Freud, 1921). Over recent years, there has been a growing interest in resilience, particularly in its prophylactic properties in at risk populations, most notably first responders and military personnel. Despite the obvious potential, implementation of resilience training and monitoring programs has proven difficult, in large part because of the absence of accurate and rapid tools to assess resilience. Presently, psychometric approaches dominate the research landscape. While these approaches have value, self-report assessments are highly susceptible to self-report bias. This issue is well recognised in many areas of psychometrics but is especially pertinent in populations where low levels of resilience may result in temporary or permanent removal from front-line positions. An ideal solution to these challenges is the introduction of standardised and validated physiological and/or biological predictors of resilience. Such readouts are significantly less prone to subject manipulation and therefore offer the possibility of improved assessment accuracy. Given these facts, the aim of this review will be to provide a brief summary of the major concepts in the field of resilience before providing a detailed critical review of the literature around biological markers of resilience. We initially focus on the significance of assessing resilience; this is followed by a description of psychometric resilience scales and of potential physiological, neurochemical and immune markers of resilience. We conclude by canvassing the multiple pathways for future use of bioanalytic approaches for resilience research.

## 2. Significance of assessing resilience from the public health perspective

Human beings encounter a variety of stressors across the course of their lives, ranging from daily hassles to major life events. Experience of traumatic events has been found surprisingly common across communities, with estimates that most individuals experience a potentially traumatic event in their lifetime (Bonanno and Mancini, 2008; Kessler et al., 1995). There now appears to be compelling evidence to suggest that humans exposed to a common aversive or traumatic experience will exhibit a wide range of responses. Underscoring this point, it has been shown that only somewhere between 10-15% of veterans from the Vietnam conflict (1962–1975) went on to develop PTSD (e.g. (Barrett et al., 1988; Marmar et al., 2015)). While there are likely to be several factors that account for the fractional percentage of veterans that developed PTSD, the figure has widely been interpreted as suggesting that the majority of combat veterans could be characterized as resilient. This phenomenon has further been interpreted as indicating that the principal cause of affective disorders is not the traumatic event per se, but rather the way in which these events are psychological processed by the affected individual.

While cited studies underscore the importance of identifying vulnerable individuals in military servicemen and to enrol them in resilience-enhancing programs prior to deployment, the potential value of resilience measurements is much broader. Firstly, it is directly applicable to occupations associated with real life dangers such as defence or police forces. Secondly, and more importantly, assessing indicators of resilience at early age might appear to be an efficient mean in the prevention of depressive disorders that represent tremendous burden, both for the society as a whole and for individuals suffering from these disorders. Therapeutic strategy for managing these mental illnesses focuses on established cases; it has limited efficacy and high cost. It would be highly advantageous, from both economic and public health perspectives, to identify susceptible individuals prospectively, and to subject them to resilience-enhancing interventions. The major difficulty in this strategy is a lack of means to identify such vulnerable individuals. There are currently no established robust biomarkers of resilience, and all proposed biomarkers do not have discriminative power.

#### 3. Current means for assessing resilience

#### 3.1. Psychometric instruments and their inherent problems

Assessment of resilience has been approached using a number of psychometric tools. Although not exhaustive these include: Ego-Resilience scale (ER89, (Block and Kremen, 1996)), Connor-Davidson Resilience Scale (CD-RISC, (Connor and Davidson, 2003)), Adult Resilience Scale (ARS, (Friborg et al., 2003)), Brief Resilient Coping Scale (BRCS, (Sinclair and Wallston, 2004)), Dispositional Resilience Scale-15 (DRS-15, (Bartone, 2007)), Resilience Scales for Children and Adolescents (RSCA, (Prince-Embury, 2008)) and most recently developed Response to Stressful Experiences Scale (RSES, (Johnson et al., 2011)). Most commonly, these questionnaires determine subjective ratings of psychological factors, such as cognitive flexibility, spirituality, social support, self-efficacy, which lead to positive adjustment (see (Southwick et al., 2005) for a comprehensive review). It has been suggested that currently there is no 'gold standard' psychometric instrument for measurement of psychological resilience (Windle et al., 2011). However, questionnaires such as the Connor-Davidson Resilience Scale (CD-RISC, (Connor and Davidson, 2003)) present a promising approach.

The common problem of all psychometric tests derives from their subjective nature. Their results could be affected by nonintentional or intentional biases, especially in those respondents whose job perspectives and/or career advances depend on their resilience level. Objective measurements are devoid of these flaws, and it will be most advantageous to complement existing psychometric scales of resilience with objectively measurable biomarkers.

#### 3.2. Concept of psychobiological allostatic load

In the review of psychobiological mechanisms of resilience and vulnerability (Charney, 2004) introduced the idea of "psychobiological allostatic load". It is based on the concept of allostatic load and on the knowledge of identified neurobiological factors potentially responsible for stress resilience and vulnerability. In their seminal article, (McEwen and Stellar, 1993) defined allostatic load as "the cost of chronic exposure to fluctuating or height-ened neural or neuroendocrine response resulting from repeated or chronic environmental challenge that an individual reacts to

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