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Biomarkers for assessing population and individual health and disease related to stress and adaptation

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ABSTRACT

Biomarkers are important in stress biology in relation to assessing individual and population health. They facilitate tapping meaningfully into the complex, non-linear interactions that affect the brain and multiple systems of the body and promote adaptation or, when dysregulated, they can accelerate disease processes. This has demanded a multifactorial approach to the choice of biomarkers. This is necessary in order to adequately describe and predict how an individual embedded in a particular social and physical environment, and with a unique genotype and set of lifetime experiences, will fare in terms of health and disease risk, as well as how that individual will respond to an intervention. Yet, at the same time, single biomarkers can have a predictive or diagnostic value when combined with carefully designed longitudinal assessment of behavior and disease related to stress. Moreover, the methods of brain imaging, themselves the reflection of the complexity of brain functional architecture, have provided new ways of diagnosing, and possibly differentiating, subtypes of depressive illness and anxiety disorders that are precipitated or exacerbated by stress. Furthermore, postmortem assessment of brain biomarkers provides important clues about individual vulnerability for suicide related to depression and this may lead to predictive biomarkers to better treat individuals with suicidal depression. Once biomarkers are available, approaches to prevention and treatment should take advantage of the emerging evidence that activating brain plasticity together with targeted behavioral interventions is a promising strategy.

1. Introduction

Until recently, biomedicine focused on the functioning of individual organ systems as they are affected by the genotype and impacted by the physical environment. Each organ system or disorder was viewed, at least from a therapeutic perspective, somewhat in isolation from other systems of the body. Functioning of the brain was left to the separate domains of neurology, neurosurgery, psychology and psychiatry, largely separated from medicine. Furthermore, the biological influences of the social environment, including daily stressors and stressful life events, on brain and body functioning "fell between the cracks". What was investigated in that regard was largely the domain of sociology, social epidemiology and social psychology, with little understanding of the biological and neurobiological implications.

However, this has changed in very significant ways. We now recognize gradients of physical and mental health that are a function of socioeconomic status (SES) and the steepness of the differences between rich and poor in a particular society [1]. This recognition has demanded a closer examination of the mechanisms by which the social, as well as physical, environments, get "under the skin" and affect brain and body health (see pdf downloads in http://www.macses.ucsf.edu/). Furthermore, we

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now recognize that children are particularly vulnerable and that adverse, as well as positive, early life experiences can have a profound and lasting influence on both physical and mental health over the life course. This has demanded that biomedical and social sciences include a life course perspective [2–4].

In addition, the rise of "epigenetics" in its current, as opposed to original, meaning [5] has revitalized the nature-nurture discussion. It has placed a high priority on understanding how experiences and environmental factors regulate gene expression through mechanisms such as DNA methylation, histone modifications, and microRNAs [6]. These operate on allelic variation of genes that are highly reactive, or less reactive, to those influences in terms of the final endophenotype; this has been referred to as "biological sensitivity to context" [7–9].

Moreover, neuroscience has returned to its roots in physiology to go beyond a brain-centric view and incorporate brain–body interactions and elaborate mechanisms by which neuroendocrine, autonomic, immune and metabolic systems communicate with each other and with the brain. The brain has emerged as the central organ of adaptation and maladaptation in response to stressors in the social and physical environments [10,11]. Finally, the existence of developmentally programmed sex differences in many aspects of brain function, along with discovery of subtle sex differences in brain architecture and function, demands that we consider the implications for health and disease of this important example of gene × environment interactions [12–14].

In order to make progress in connecting the mechanistic world of biomedicine with the domains of epidemiology, the social sciences with intervention science and policy, "biomarkers" are needed that tap meaningfully into relevant mediators and primary, secondary and tertiary consequences of their action. This has demanded a multifactorial approach to the choice of "biomarkers" in order to adequately describe and predict how an individual embedded in a particular social and physical environment, and with a unique genotype and set of lifetime experiences [15], will fare in terms of health and disease risk, as well as how that individual will respond to an intervention. "Biomarkers" are also important in population studies to explore how, for example, SES and race and ethnicity impact biological functioning and physical and mental health.

Yet, at the same time, single biological measures can have a predictive or diagnostic value. Moreover, given the importance of the brain as the central organ of stress and adaptation [10], the methods of brain imaging have provided new ways of diagnosing mental health disorders, as will be illustrated for anxiety disorders and depressive illness. This review will provide examples of biomarkers in these various contexts as they pertain to the domain of stress biology, mental health and brain–body interactions. It will, therefore, broaden the more traditional definition of such markers to include measures from brain imaging and gene arrays, as well as biological indicators from other parts of the body, including blood and urine.

2. Criteria for a biomarker

What are the selection criteria for a biomarker? First, biomarkers must be chosen and evaluated in terms of their functional significance in biological pathways, including both primary and secondary mediators and the secondary and tertiary consequences of their actions. Moreover, primary mediators (such as cortisol and adrenalin; see below) show inverted U shaped actions and there are regulatory interactions between the mediators that result in non-linearity [16]. This brings us to the concepts of allostasis and allostatic load that look at the protective, as well as potentially damaging, effects of the mediators of stress and adaptation. This view takes a life course perspective that recognizes the power of the social environment and individual life style [4]; it also considers genetic contributions [9] and recognizes the central role of the brain and the importance of reciprocal brain–body interactions [10]. To adequately describe and analyze these multiple factors and their interactions, biomarkers are needed that tap into multiple interactive systems and look at the brain, as well as systemic physiology.

In the concepts of allostasis and allostatic load [17,18] the goal is to tap into measures of the multiple interacting mediators that affect many body systems concurrently. This is referred to as an "allostatic load battery". These include measures of blood pressure, metabolic parameters (glucose, insulin, lipid profiles, and waist circumference), markers of inflammation (interleukin-6, C-reactive protein, and fibrinogen), heart rate variability, sympathetic nervous system activity (12-hour urinary norepinephrine and epinephrine) and hypothalamic–pituitary–adrenal axis activity (diurnal salivary free cortisol) [18]. In some studies, DHEA and IGF-1 were also used as positive markers of health. Choice of markers is limited by their cost and accessibility in studies involving large numbers of subjects. Telomeres and telomerase have been added as another endpoint of cumulative effect and have shown to be adversely affected by caregiving stress, adverse early life experiences, depression, cardiovascular disease, diabetes and other conditions [19–21] and may be improved by an intensive lifestyle intervention [22].

These biomarkers fall into different classes: primary, secondary, tertiary [23]. Primary mediators include cortisol, sympathetic and parasympathetic activity, pro- and anti-inflammatory cytokines, metabolic hormones and neurotransmitters and neuromodulators in the nervous system. Secondary mediators are those that reflect the cumulative actions of the primary mediators in a tissue/organ-specific manner, often reflecting the actions of more than one primary mediator such as those described above: e.g. those that reflect abnormal metabolism and risk for cardiovascular disease, such as waist-hip ratio (WHR), blood pressure, glycosylated hemoglobin, cholesterol/HDL ratio, HDL cholesterol, as well as telomere length and telomerase activity. As noted by McEwen and Seeman [23], "WHR and glycosylated hemoglobin both reflect the effects of sustained elevations in glucose and the insulin resistance that develops as a result of elevated cortisol and elevated sympathetic nervous system activity. Blood pressure elevation is part of the pathophysiological pathway of the metabolic syndrome, but is also a more 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 and also reflect the operation of the same primary mediators, as well as other metabolic hormones."