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Altered psychophysiological reactivity as a prognostic indicator of early childhood stress in chronic pain

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ABSTRACT

There is considerable evidence that early life stress (ELS) can have a lasting impact upon adult physiology. Various childhood (and even prenatal) stressors such as parental separation, neglect, and trauma, can leave an enduring impact upon immune, autonomic and endocrine systems. These changes are increasingly understood to represent vulnerabilities to developing later life medical (and psychological) morbidity. In this article it is hypothesized that these enduring physiological changes may also serve as markers to detect the presence of ELS or rather it's impact upon the individual. Until now, the detection of ELS has relied primarily upon self-report measures that have obvious limitations. If a reliable and objective means of detecting the impact of ELS can be established using physiological means, then one potential application would be in the chronic pain population. At present it remains unclear why for a given injury, some acute pain subjects progress to develop chronic pain, while others make a full recovery. The evidence to date points more to psychosocial factors than nociceptive parameters. The hypothesis proposed in this manuscript that ELS results in altered physiological reactivity may offer in part an explanation for this puzzling variable transition to chronic pain.

Introduction

Developmental plasticity is the differential ability of the developing neonate to respond to various prenatal and postnatal events, offering greater adaptation potential [1]. This capacity to interact with either beneficial or adverse environmental conditions is considered to vary across individuals, and to represent a differential susceptibility that impacts health outcomes [2]. The notion that early life events can interact with this plasticity and be associated with pathological outcomes in adult life was initially formulated from epidemiological research linking coronary artery disease with poor living conditions in childhood [3]. While low birth weight and foetal undernutrition were initially the prime focus of investigation, research has expanded to include other stressors present in early life [4]. There is now also a wide range of adult disease states that are considered to be affected by early life conditions, including obesity, cardiovascular diseases, diabetes mellitus, metabolic syndrome, cancer, migraine and osteoporosis [5–10].

There is considerable evidence that early life stress (ELS) can alter the reactivity of the adult organism to various stressors [11–15] and even alter physiological function in subsequent generations [16–18]. The forms of ELS experienced can be varied, and include maternal separation, infection, food deprivation, trauma, abuse and neglect. The resulting physiological alterations include changes to the autonomic, endocrine, metabolic and immune systems [19–24], certain neural structures [22,25–27] and these changes appear to be stable at least in the short-term [28,29]. This altered responsiveness is not unexpected if one considers that these alterations have the potential to prepare the organism to adapt to subsequent environmental stressors [15,30]. However these alterations may be maladaptive if the organism continues to respond in a manner as if the ELS was still present, when it has ceased to overtly act upon the organism i.e. the organism has been programmed by the ELS [26,31,32]. If the "programming" is such that the organism becomes constantly hyper-responsive to stress, then it is plausible that their systemic physiological responses could be maladaptive in the face of subsequent stressors. The question is then raised whether such maladaptive responses could be used diagnostically to detect the presence of this maladaptive programming or ELS (see Fig. 1). It is the use of these maladaptive responses retrospectively, as opposed to prognostically, that constitutes the first novelty of this proposal.

The concept of ELS is considered here as an universal experience, a continuous (not categorical) variable, that will have an increasingly deleterious impact as it's level increases. Whether

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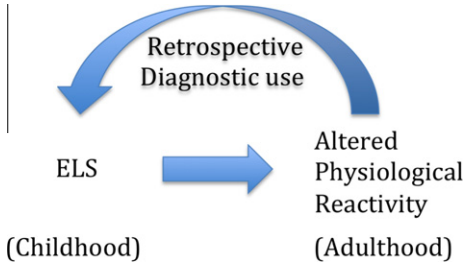

Fig. 1. Can maladaptive alterations in adult physiology be used to reliably detect the presence of ELS?

Table 1
Potential grid for detecting the presence of ELS.

	Duration	Response level	Threshold	Latency
HPA/SAMS				
Inflammatory				
Autonomic				
Metabolic				

HPA: Hypothalamic–Pituitary–Adrenal Axis.
SAM: Sympathoadrenomedullary System.

Table 2
Selection of variables proposed for detecting the presence of ELS.

HPA/SAMS	Cortisol, adrenocorticotropic hormone, dehydroepiandrosterone, noradrenaline, adrenaline
Inflammatory	Interleukin 1β and 6, tumor necrosing factor α, C reactive protein, heat shock protein 70
Autonomic	Muscle sympathetic nerve activity, galvanic skin conductance, skin blood flow, mean arterial pressure, heart rate variability, respiration rate
Metabolic	Body mass index, waist-hip ratio, leptin
Epigenetic	5HTTLPR

HPA: Hypothalamic–Pituitary–Adrenal Axis.
SAMS: Sympathoadrenomedullary System.
5HTTLPR: Serotonin transporter-linked polymorphism.

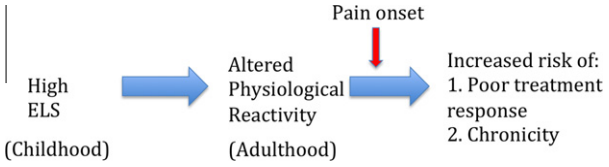

Fig. 2. Maladaptively programmed physiological reactivity, may alter the prognosis following pain onset by increasing the risk of poor treatment response or even the development of chronicity.

there exists any form of clinically meaningful threshold above which the ELS variable exerts a more significant pathological impact remains to be determined. Given the large variety of possible sources of ELS, one (pragmatic) option is to limit the measures of ELS in childhood for the purposes of this study, to childhood trauma and bonding. In addition, other psycho-socio-economic variables can act as covariates e.g. income, education, birth-weight, etc.

It is speculated that there are at least 4 ways that such maladaptive responses could be manifested in the face of new stressors. First the system may have a prolonged response (i.e. take longer to return to baseline). Second the system may have a higher (or lower) level of responsiveness. Third the threshold to respond to a stimulus may be altered such that the system may respond to a lower (or higher) stimulus intensity. Fourth the system may have a longer (or shorter) latency period prior to responding. Taken together with those systems known to be affected by ELS (Hypothalamic–Pituitary–Adrenal Axis (HPA)/Sympathoadrenomedullary System (SAMS), inflammatory, metabolic and autonomic), a detection grid potentially could be constructed (see Table 1).

While each of the 4 physiological systems have numerous components that have been identified as being altered secondary to ELS, for instance cortisol or adrenocorticotropic hormone within the endocrine system [33], it is proposed that measuring a diverse range of components within each system, will enable the reliable identification of an altered physiological reactivity pattern consistent with the presence of ELS (see Table 2 for potential variables to be assessed from several systems).

The second novel element is the possible application of this capacity to detect programming using altered physiology to triage acute and chronic pain patients for more tailored treatment. It is proposed that these purported ELS-induced physiological changes could be used to identify those chronic pain patients who would most benefit from more comprehensive treatment as afforded in a multidisciplinary pain clinic, compared to treatment as usual (i.e. analgesia + physiotherapy). It is also possible that these physiological changes resulting from ELS may assist in the early identification of those acute pain patients who are at greater risk of developing chronic pain.

In Fig. 2 it is proposed that the onset of pain in the adult, is acting as a secondary (or tertiary) stressor in those subjects with high levels of ELS. It is tacitly assumed in most studies that the commencement of pain occurs with an unstressed baseline – be it normally distributed across the population sample. This assumption must be questioned if one considers the possible connection between the impact of ELS on physiological functioning, and our current understanding of the stress-diathesis nature of chronic pain [34].

Hypotheses

Does altered physiological reactivity detect ELS?

It is suggested that in order to detect the anticipated presence of physiological alterations occurring in response to ELS (e.g. prolonged response), it is necessary to take measures of the system(s) under acute stress. It is anticipated that baseline values of those with high ELS will reflect their physiological success (or lack of) at adapting to (masking) their programming. In other words the system is attempting to maintain an equilibrium. Therefore the results from studies that only utilize non-stressed baseline values may mask programmed differences arising from different levels of ELS. The presence of an acute stressor may be required to remove the homeostatic masking (see below) of the ELS system.

If the CNS is considered to be the main driver of subsequent physiological alterations to stress [35,36], then the significance of the stress experienced may play a relevant part in how the organism responds physiologically. For example, not all infants/children will respond to the same stressor, in the same manner or to the same extent [37,38]. This means that attempting to measure ELS like an accounting audit (e.g. level of abuse, number of occasions, duration of deprivation) while important, may fail to reflect the actual impact of the ELS on the individual. Measuring physiological alteration under acute stress may offer an alternate means of objectively assessing the actual impact of the ELS. In addition, developmental windows may represent an additional source of variance with respect to when the ELS occurs [39]. As there is evidence that the HPA response is controlled by social interaction in young children, it has been speculated that the age at which the ELS occurs may be a significant factor in how the HPA system adapts [40].