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

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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 ie 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 figure 1) It is the use of these maladaptive responses retrospectively, as opposed to prognostically, that constitutes the first novelty of this proposal.

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

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 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 eg 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 (ie 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)

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

While each of the 4 physiological systems have numerous components that have been identified as being altered secondary to ELS, for instance cortisol or adrenocorticotrophic 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).

TABLE 2: Selection of variables proposed for detecting the presence of ELS .

HPA/SAMS	Cortisol, Adrenocorticotrophic Hormone, Dehydroepiandrosterone, Noradrenaline, Adrenaline
Inflammatory	Interleukin 1 β 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

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 (ie 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.

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.

In figure 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

1) 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 (eg 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 (eg 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).

Hypothesis 1a: That the presence of ELS can be detected by measuring the altered physiological reactivity occurring in response to an acute stressor.

Hypothesis 1b: That ELS occurring earlier in life (<12years old) will leave a different physiological reactivity pattern, to ELS occurring primarily in later teenage years.

Physiological masking

Given that most physiological systems strive to maintain a homeostatic equilibrium, it is plausible that this altered physiological reactivity resulting from high ELS will be masked (or partially so) under low stress conditions. This would mean that baseline values of affected variables, may demonstrate little or no alteration from control group values. So for instance cortisol plasma values may be unaltered at rest, only to reveal significant variation when the organism is acutely stressed. This proposed concealment by a given system may be termed 'homeostatic masking', and may explain in part the variability in results seen across ELS studies (41).

There is also reason to believe that the various systems PNIE (psychoneuroimmuno-endocrinology) are not independent of each other. Endocrine function impacts on the immune system, the immune system on autonomic nervous system and so forth (42-46). What this implies is that in response to an acute stressor, these individual systems could potentially react/compensate in different ways and to different amounts. Thus if monitoring only one system following an acute stressor, then important information may be missed as the other 2 (or more) systems compensate. In other words, what is being proposed is that there may be a level of interaction between the various systems, that has not been generally considered in experimental designs. We don't know for instance, how much the endocrine system

compensates or buffers the immune system for a given stressor. We also don't know if the proposed 'trans-system buffering' is uniform across individuals, or whether it may reflect yet another source of variance in ELS studies.

Hypothesis 1c: That the ELS induced physiological reactivity represents a concerted response between the immune, endocrine, autonomic and metabolic systems.

The idea of multi-system involvement is also pertinent when considering the impact of chronic pain as a stressor (47) in itself.

2) Importance of early detection of ELS in the chronic pain population.

One field where altered physiological reactivity from high ELS levels may have a profound impact is chronic pain. It has been established for many years that chronic pain is not merely an extension of acute pain. The difference between acute and chronic pain is illustrated in the observation that there are a number of other variables that impact upon the development and maintenance of chronic pain, compared to acute pain (48, 49). These include mood and other psychological factors such as resilience and catastrophisation (50). Among these variables, elevated levels of ELS have been observed in subpopulations of patients requiring treatment for chronic pain (51-54).

Many, if not most studies on chronic pain to date assume the chronic pain patient to be physiologically naïve prior to the onset of their pain/treatment, acute or chronic. Any variation in their physiological responsiveness is considered part of the normal distribution in the population concerned. However, if the above assumptions regarding ELS impacting upon physiological reactivity have merit, and elevated ELS levels are present in this population, then the onset of pain may be considered as a subsequent (secondary or tertiary) assault upon a system that having been previously exposed to high levels of ELS, is already "stressed". It has been established for many years that

chronic stress can cause hyperalgesia in animal- models, depending upon intensity and duration of the stressor (55). This idea has a recent corollary in the hyperalgesic priming hypothesis (56), where peripheral nociceptive receptors are considered to have been altered in response to ELS.

It therefore stands to reason that those with high ELS in their past, who subsequently sustain chronic pain from whatever source, will demonstrate an interaction between their premorbid (ie pre-pain) level of ELS and their experience/ tolerance of nociception. So it is hypothesized that those with high ELS might be expected to have lower tolerance and/or greater sensitivity to a given nociceptive input. Whether this speculated alteration in physiological reactivity from high ELS levels results in clinically significant changes to the chronic pain experience remains to be established.

Hypothesis 2a: That chronic pain patients with higher levels of ELS as identified by altered physiological reactivity, will have lower levels of pain tolerance, lower levels of self-efficacy, and score higher on self-report measures that predict poor outcome.

Hypothesis 2b: That acute pain patients who demonstrate a physiological reactivity pattern consistent with high ELS, will have a higher probability of developing chronic pain 12 months later.

Consequences

If chronic pain patients with high ELS did incur a physiological burden in adulthood, it's early objective detection by physiological assessment has a number of possible benefits.

1. It compliments the information gained from paper and pencil forms of ELS assessment with their attendant risks of being manipulated and the patient's fear of being stigmatized that their pain is "all in their head".

2. It will assist in understanding the interactive effects of ELS and adult stressors such as chronic pain. Clinicians attempting to distinguish distress from nociception will appreciate the objectivity of such an assessment.
3. It may offer a means of early identification of those chronic pain patients that would benefit from a more comprehensive treatment package.
4. It has the potential to assist in the early identification of acute pain patients at risk of developing chronic pain.

It is also possible that the objective identification of high ELS will have treatment applications in other fields such as autoimmune and gastrointestinal conditions.

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