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Design, rationale and feasibility of a multidimensional experimental protocol to study early life stress

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ABSTRACT

There is a rapidly accumulating body of evidence regarding the influential role of early life stress (ELS) upon medical and psychiatric conditions. While self-report instruments, with their intrinsic limitations of recall, remain the primary means of detecting ELS in humans, biological measures are generally limited to a single biological system. This paper describes the design, rationale and feasibility of a study to simultaneously measure neuroendocrine, immune and autonomic nervous system (ANS) responses to psychological and physiological stressors in relation to ELS. Five healthy university students were recruited by advertisement. Exclusion criteria included chronic medical conditions, psychotic disorders, needle phobia, inability to tolerate pain, and those using anti-inflammatory medications. They were clinically interviewed and physiological recordings made over a two-hour period pre, during and post two acute stressors: the cold pressor test and recalling a distressing memory. The Childhood Trauma Questionnaire and the Parental Bonding Index were utilised to measure ELS. Other psychological measures of mood and personality were also administered. Measurements of heart rate, blood pressure, respiratory rate, skin conductance, skin blood flow and temporal plasma samples were successfully obtained before, during and after acute stress. Participants reported the extensive psychological and multisystem physiological data collection and stress provocations were tolerable. Most (4/5) participants indicated a willingness to return to repeat the protocol, indicating acceptability. Our protocol is viable and safe in young physically healthy adults and allows us to assess simultaneously neuroendocrine, immune and autonomic nervous system responses to stressors in persons assessed for ELS.

1. Introduction

1.1. Background

Substantial evidence links early life stress (ELS) to a range of medical and psychological outcomes [1]. Children subjected to stressors, such as physical/sexual abuse, harassment, neglect or war, are at greater risk of developing personality changes, suicidal behaviours, depression and other psychiatric problems [2]. Distress in early life can leave a lasting physiological imprint in the form of a dysregulated hypothalamic-pituitary-adrenal (HPA) axis [3]. This has been found when there has been the loss of a parent [4,5], divorce of parents [6], childhood abuse (both physical and sexual) [2,7–9] [10], neglect [11], maternal depression [12–14], low socio-economic status [15,16], parenting style (e.g. anger/control) [17–19] and post-traumatic stress disorder (PTSD) [2].

Almost invariably in these studies, ELS is dichotomised into present/absent categories, or there is a comparison between a clinical (high ELS) and control (low ELS) population against a clinical outcome variable such as dermatitis or drug taking behaviour or vulnerability to PTSD. Within these studies ELS has typically been used as the predictor (usually categorical) of specific or systemic pathophysiology and

Abbreviations: ELS, Early life stress; HPA, Hypothalamic-pituitary-adrenal; ANS, Autonomic nervous system; CTQ, Childhood Trauma Questionnaire; PBI, Parental Bonding Instrument; DASS, Depression, Anxiety and Stress Scale; EPQRs, Eysenck Personality Questionnaire Revised – short form; DS14, Type D Scale; CPT, Cold pressor test; RDM, Recall of distressing memory; PTSD, Post-traumatic Stress Disorder; ECG, lectrocardiogram

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disease risk. An association between ELS and the presence of altered physiology or pathology appears robust [20]. At the end of these studies the limitation of retrospective recall is invariably and appropriately noted. While behavioural descriptors, rather than subjective judgements, of childhood stress can improve the reliability of questionnaires assessing childhood events, factors such as childhood attachment, emotional neglect and parental warmth remain confounded by the current emotional relationship with the parent [21–23]. Is there a way then to avoid, or at least minimise, the reliance upon retrospective recall?

Given the established links between ELS and altered physiology, we propose that these physiological alterations might be able to be collectively combined into a bio-index that would provide a dose-response curve without relying upon retrospective recall. This would entail the ELS-associated physiological alterations being the predictors, and ELS being the outcome variable. Initially we anticipate the physiological markers being associated with a global measure of ELS, with future refinement being able to predict sub-factors (emotional abuse/neglect) of ELS. To create this bio-index, a wide range of potential physiological predictors needs to be measured simultaneously in the same participants. This paper reports on the feasibility of this approach within a university laboratory setting. The protocol deployed used a dual stress-induction method. The feasibility, including safety, acceptability, and the practical logistics of this complex design, were assessed.

1.2. Aims

The aims of this study were: 1) to develop a protocol to investigate neuro-immuno-endocrine responses to stressors that could form the basis of a physiological (biomarker) index of ELS, and 2) to determine the feasibility, including acceptability and safety, of measuring indicators of ELS, as well as mood and psychological traits linked with ELS, prior to measuring autonomic, immune and endocrine parameters before, during and after inducing acute physical pain, and then psychological stress, in young healthy participants.

2. Methods

2.1. Study design

The study involved a 4-stage process (Fig. 1): i) Online eligibility screening and completion of questionnaires; ii) Clinical interview and recall of distressing memories, paper-based questionnaire, and laboratory familiarisation; iii) Experimental session involving recording of physiological parameters and collection of blood samples during application of stressors; and iv) Completion of a follow-up questionnaire 1–2 weeks after the testing session. The study was approved by the University's Human Research Ethics Committee, approval No. H-2010-1274.

Key feasibility measures were recruitment of participants, acceptability of the screening and experimental protocol, and safety of both the recall of distressing memories and physiological measurement procedures. The Childhood Trauma Questionnaire and the Parental Bonding Index, which are commonly used to measure ELS but rarely concurrently in the same individuals, were both used. Mood and psychological traits linked with ELS were also measured by questionnaires. In the experimental session, physiological parameters that reflect autonomic function, such as electrocardiogram (ECG), blood pressure, ventilation and sudomotor activity were measured simultaneously. Blood samples were obtained for later analysis of stress (neuro-endocrine) and immune markers. These parameters were chosen because of established or probable links to ELS (32).

2.2. Participants

Young adults with no physical or psychotic condition were recruited using posters placed around a University campus. The posters indicated that the study was investigating childhood stress and psychophysiological reactivity, as well as pain. Interested participants were emailed an ID code which enabled them to log on to an intranet website with detailed descriptions of the study, and to access online screening questions to assess their eligibility based on a priori inclusion/exclusion criteria (Table 1). There was no requirement for a history of ELS. If participants provided a response that deemed them ineligible, they were thanked for their interest in the study and no further questions were provided. Participants were informed that they could withdraw from the study at any stage.

2.3. Stage 1: Online screening and questionnaires

Following the eligibility screening and having read the detailed description of the study, participants signified their consent by ticking a box. Participants then completed a series of online questionnaires to provide demographic, health, lifestyle and social data. Questions included their birth weight, the number of addresses they lived at during childhood and the maximum number of children living in their home during their childhood (Table 2). Participants then completed the following standardised questionnaires that measure attachment, mood and personality characteristics. The PBI and CTQ (see 2.3.1 and 2.3.2) were used as predictor variables to measure ELS. On completion of these questionnaires, participants used their unique ID code on the online portal to schedule a meeting time for Stage 2.

2.3.1. Parental Bonding Instrument (PBI)

The Parental Bonding Instrument consists of 25 items using a 4-point Likert scale and is a retrospective recall of the first 16 years of parental experience that is categorised into the two dimensions of Care and Control. These two dimensions usually yield Cronbach alphas > 0.85 and result in four diagnostic categories: High/Low Care x High/Low Control. Factor analysis of the PBI has repeatedly shown the care dimension to be robust, but three-factor solutions can split the control dimension (also labelled overprotection) suggesting a reduced stability [24]. Instruments used to measure parental attachment or bonding tend to fall into one of two categories: self-report or structured interview. In general, the structured interview instruments require training to conduct, may require inter-rater validity checks, are time-consuming to administer and score. By contrast, the self-report instruments are quick to administer and score, and require no specific training. All parental attachment instruments tend to measure related elements of attachment, which can be categorised into secure/insecure avoidant/insecure pre-occupied/and insecure fearful [25]. The PBI used in our study offers a well validated [24,26], stable [27], easy to use option that is considered comparable to the more labour intensive Adult Attachment Interview in normal populations [28].

2.3.2. The Childhood Trauma Questionnaire (CTQ) short form

This questionnaire was administered offline, during Stage 2, due to the publisher's constraints on its use. The CTQ was originally a 70-item questionnaire that is now widely used in a shorter 28 item format. Each of the 28 items are scored on a 5-point Likert scale (1 = never true to 5 = very often true), yielding scores between 5 and 25 for each question. Of the 28 questions, three are used to assess bias towards minimisation of childhood trauma. The CTQ has been found to contain 5 factors – 3 forms of abuse (emotional, physical, sexual) and 2 forms of neglect (emotional, physical) in clinical and non-clinical populations [29,30]. The five factor structure of the CTQ has been replicated repeatedly across many ethnic groups showing good validity and test-retest reliability, though the physical neglect subscale has been challenged for lack of homogeneity [31] which would need to be