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Elevated cortisol awakening response associated with early life stress and impaired executive function in healthy adult males

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ABSTRACT

Experiencing early life stress (ELS) and subsequent dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may play a role in the aetiology of mental health disorders. However, the exact mechanisms linking HPA-axis dysregulation with the development of psychopathology have not been fully delineated. Progress in this area is hampered by the complex and often conflicting associations found between markers of HPA-axis function and risk factors for mental health disorders such as impaired executive function (EF) and ELS. This study investigated the association of the cortisol awakening response (CAR) with ELS and EF in a healthy adult male population (n = 109, aged 21–63). As previous inconsistencies in CAR and ELS association studies may be the result of not considering ELS-related factors such as cumulative exposure, type of stressor and developmental timing of ELS, these were also investigated. The main findings were that the CAR was significantly elevated in individuals reporting ELS compared to those reporting no ELS (p = 0.007) and that an elevated CAR predicted poorer problem solving/planning (p = 0.046). Cumulative exposure, type of stressor and developmental timing of ELS were also found to impact significantly on the CAR. These results suggest that ELS is associated with chronic changes in HPA-axis function and that these changes may be associated with impairments in problem solving/planning. Future work should investigate further the neurobiological mechanisms linking ELS, the CAR and EF and their role in conferring risk for the development of mental health disorders.

Introduction

Experiencing stressful life events during childhood or adolescence (early life stress; ELS) is a risk factor for later development of mental health disorders such as depression and schizophrenia (Mandelli et al. 2015; McLaughlin et al. 2010; Read et al. 2001). Although the exact mechanisms have not been fully delineated the hypothalamic-pituitary-adrenal (HPA) axis, the major neuroendocrine regulator of stress responses, likely plays a role in mediating the effect of stressors on the development of psychopathology (Doom and Gunnar 2013). Impaired executive function (EF) may also be a risk factor for mental health disorders. Impairments in EF, a set of higher order cognitive processes that facilitate the attainment of goals (Diamond 2013), are transdiagnostically associated with mental health disorders (McTeague et al. 2016) that are linked with ELS. Indeed, impaired EF may be an intermediate phenotype more closely linked to biological mechanisms than more complex disease states per se (i.e. a cognitive endophenotype; Almasy and Blangero 2001, Gottesman and Gould, 2003) and it may represent a mechanism linking a dysfunctional HPA-axis to mental health problems. Conversely, better EF may protect against the development of mental health disorder symptoms in 'at risk' populations (Davidovich et al. 2016). Consequently, studies that investigate both the effects of ELS on HPA-axis function during adulthood and the relationship between ELS-induced alterations of HPA-axis function and EF may be particularly important for understanding risk phenotypes that may confer vulnerability to psychopathology.

One common method of investigating HPA-axis function is through the measurement of the cortisol awakening response (CAR). Originally described in the 1990's (Pruessner et al. 1997) the CAR refers to a typical rise in cortisol within the first 30 min of waking (Clow et al. 2004; Wust et al. 2000). The CAR has been shown to be associated with mental health disorders, with an elevated CAR predicting subsequent new on-set anxiety (Adam et al. 2014) and depression (Adam et al. 2010), a blunted CAR being found in patients with severe depression symptomology (Veen et al. 2011) and those with first episode psychosis and schizophrenia (Berger et al. 2016). Since the CAR may be a stronger predictor of depression than other measures of HPA-axis activity (Adam et al. 2010) it may be a particularly interesting index of HPA-axis function for investigating risk factors for mental health disorders.

Studies investigating the physiological and cognitive effects of

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experiencing early life stress (ELS) in healthy adults enable investigation of potential risk phenotypes for psychopathology free from confounding factors associated with disease, such as symptoms and medication. Despite this, few studies have been conducted aiming to elucidate how the experience of ELS contributes to dysregulation of the CAR in non-psychiatric populations. Those that have show mixed findings regarding the association of ELS with CAR in adulthood, with both negative (Meinlschmidt and Heim 2005) and positive (Engert et al. 2011) associations reported. It has been suggested that different types of stressor may have differential effects on HPA-axis function as assessed by the CAR (Engert et al. 2011). This is supported by work showing that physical abuse compared to emotional abuse may increase HPA-axis sensitivity to subsequent stressors (Kuhlman et al. 2015a). In addition, experiencing physical abuse is associated with a blunted cortisol response under acute stress challenge even when controlling for other types of ELS (Carpenter et al. 2011) and early physical/sexual abuse, but not other types of early onset maltreatment, has been linked with diurnal cortisol dysregulation (Cicchetti et al. 2010).

Several strands of research suggest that other ELS-related factors may lead to greater or lesser impacts on the functioning of the HPA axis. The allostatic load hypothesis predicts that chronic or repeated exposure to stress leads to a cumulative physiological toll that likely includes dysregulation of the neuroendocrine stress system (McEwen 1998). Indeed previous research with children has found that those who had experienced multiple types of ELS were more likely to show hyperactivity of the HPA axis indexed by elevated morning cortisol levels (Cicchetti and Rogosch 2001). The age that ELS is experienced may also be related to HPA-axis dysregulation. For example, early but not later onset of physical/sexual abuse is linked with diurnal cortisol dysregulation in children (Cicchetti et al. 2010). Furthermore, previous research has found that experiencing stressful life events during younger childhood as opposed to adolescence is associated with greater risk of developing depression or post-traumatic stress disorder (Maercker et al. 2004), and poorer response to antidepressant treatment in depressed patients (Williams et al. 2016).

Several studies have also focused on the effect of ELS exposure on executive function (EF). Studies typically report deficits in EF following ELS (e.g. Bos et al. 2009; Cardona et al. 2012; Loman et al. 2013). However childhood adversity may not lead to a general impairment in EF and could actually enhance specific aspects (Mittal et al. 2015). A dysregulated HPA-axis, as a consequence of ELS, is likely to affect EF since EFs are subserved by stress-sensitive brain regions that have a protracted development such as the prefrontal cortex (Pechtel and Pizzagalli 2011). This protracted development alongside a high concentration of glucocorticoid receptors make this area vulnerable to both structural and functional changes induced by chronic stress (e.g. Arnsten 2009; Brown et al. 2005; Izquierdo et al. 2006). However, findings from studies examining the relationship between the CAR and EF have been inconsistent with some studies showing positive associations (working memory: Almela et al. 2012; attention switching: Evans et al. 2012; Law et al. 2015), some showing negative associations (error monitoring: Zhang et al. 2015), some showing no association (working memory, attention switching and cognitive inhibition: Franz et al. 2011; working memory: Ennis et al. 2016; Hidalgo et al. 2016) or a more complex U-shaped relationship (working memory: Moriarty et al. 2014).

The primary aims of the current study were to investigate the association of the CAR with both retrospective self-report ELS exposure and with current EF performance (working memory, cognitive flexibility and planning/problem solving) in a healthy adult male population. As gender differences have been reported in the effect of stress and ELS on HPA-axis function (DeSantis et al. 2011; Kudielka and Kirschbaum 2005) female participants were not recruited. Due to the limited and divergent findings in prior research investigating the association between CAR magnitude and ELS in healthy adults (e.g. Engert et al. 2011; Meinlschmidt and Heim 2005) and the mixed findings with the association between CAR and EF (see above) directional hypotheses were not made. Instead, it was hypothesised that experiencing ELS would be associated with an altered CAR and that the CAR would be associated with EF performance. The secondary aim of the current study was to investigate how cumulative exposure (the number of trauma types reported), the type of ELS experienced, and the developmental timing of ELS may impact on the CAR. Based on previous research it was hypothesised that both cumulative ELS exposure and experience of ELS at a younger age would be associated with a more pronounced impact on CAR magnitude. In addition, given previous findings regarding exposure to physical and sexual abuse and HPA-axis dysfunction, it was hypothesised that these types of ELS would be associated with HPA-axis function, as measured by the CAR, when controlling for other types of ELS.

Material and methods

Participants

One hundred and nine healthy adult males (mean age: 34.2 years, SD: 10.6, range: 21–63) from a community sample participated in this research. Participants included were from the first wave of recruitment into a larger study investigating independent and interactive gene and ELS effects on EF (Klaus et al. 2017) from whom we collected saliva samples for cortisol analyses. Participants who self-reported use of steroid based medication or having a current psychiatric diagnosis or a drug or alcohol problem were excluded. There were no additional inclusion/exclusion criteria from the larger study. All participants were assessed for symptoms of psychopathology using the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith 1983) and for current stress levels using a 14-item Perceived Stress Scale (PSS-14; Cohen et al. 1983). Participants had normal to mild levels of anxiety, depression and current stress (means: 6.5 (SD: 3.8), 3.3 (SD: 2.6) and 20.8 (S.D. 8.2) respectively). Participants also completed questionnaires regarding their psychiatric history, demographic information (age, ethnicity and education) and sleep history (waking times and sleep durations). Twelve participants self-reported previous anxiety/depression symptoms and these participants were not disproportionately distributed when grouping participants by previous exposure to ELS. Participants were 94.5% Caucasian and 47.7% held a University level qualification. All participants gave written informed consent to take part and the study was approved by the School of Psychology Research Ethics Committee at the University of Lincoln.

Salivary cortisol collection and measurement

Participants were provided with 4 Salivettes (Sarstedt Ltd., Leicester, UK) for saliva collection and were instructed to wake at their usual times and to collect saliva samples immediately upon awakening and again at 30 min post-awakening on two consecutive week days. Participants were further instructed not to eat, drink, smoke or brush their teeth before providing samples. Across all participants mean second sample collection time was recorded as 30.23 min (SD: 2.02 min) after waking with none later than 45 min post-waking (max: 38 mins) and five cases prior to 30 min. Significant effects were unchanged when analyses were repeated after removing these five participants and so we report analyses for all participants. In order to evaluate adherence to waking sampling a sub-set of participants (n = 13, approximately 12% of the total sample) wore an electronic monitoring device (Actiwatch 2; Philips Respironics, OR, USA). Across both sampling days electronically monitored waking times (mean: 07:14 h) were not significantly different from participant recorded sampling times (mean: 07:15 h, range: 9 min earlier to 12 min later; $t(12) = 1.81$, $p = 0.096$).

Once returned, saliva samples were stored at − 20 °C before being made acellular through centrifugation (716G for 5 min (Beckman