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Review article

Early life stress and cortisol: A meta-analysis

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ABSTRACT

Given the high prevalence of early life stress (ELS) and the potential physiological dysregulation such experiences can lead to, this meta-analysis tested the relationship between ELS and cortisol. Search terms related to ELS and cortisol were entered in to PsycINFO and PubMed. Effect sizes were extracted for four outcomes variables: cortisol awakening response (CAR), baseline cortisol (cortisol at one time point), non-stressed cortisol over time (cortisol captured at two or more time points), and cortisol reactivity to an acute stressor. The articles were additionally coded for potential confounding variables, population-related, ELS-related and cortisol-related moderators. There was no significant relationship between ELS and the CAR ($g = 0.19$, $p = 0.268$), ELS and baseline cortisol ($g = -0.072$, $p = 0.328$), ELS and non-stressed cortisol over time ($g = 0.09$, $p = 0.292$) or ELS and cortisol reactivity ($g = -0.089$, $p = 0.363$). However, there was a significant amount of heterogeneity amongst relationships. Within the ELS-CAR relationship, in those who had experienced ELS that was sexually, physically or emotionally abusive, the CAR was heightened. Within the ELS-Baseline relationship, if blood samples were collected the ELS was associated with a blunting effect of cortisol. The non-significant main effects challenge the commonly held belief in the literature that ELS affects cortisol later in life. However, the high degree of heterogeneity uncovered by this analysis and significant moderators suggest that the literature may benefit from consistent operationalizations of ELS and standardized methods of how cortisol is measured.

1. Introduction

In a study across five states in the United States, 60% of participants reported having experienced at least one instance of early life stress (ELS) as a child (Centers for Disease and Prevention, 2010). Although the term "early life stress" does not have one agreed upon definition, the term is often operationalized by a wide variety of traumas ranging from the loss or death of a parent or close person (Nicolson, 2004) to physical or sexual abuse at a young age (Stein et al., 1997; van der Vegt et al., 2010), to emotional neglect or abuse by caregivers (Buchmann et al., 2014). Given both the extreme nature of these traumas and the high prevalence rate, a further examination of the long-term impacts such stresses may lead to is important.

The hypothalamic pituitary adrenal (HPA) axis is a well-known physiological response system that is activated in acutely stressful situations (Sapolsky, 2004). Activation of the HPA axis triggers the hypothalamus to release corticotropin releasing hormone (CRH) which in turn leads to the release of adrenocorticotropin hormone (ACTH) from the pituitary and finally gluccocorticoids, including cortisol, from the adrenals. Furthermore, the HPA axis functions on a daily cycle. There is an initial boost of cortisol upon awakening known as the cortisol awakening response (CAR), followed by a gradual drop in cortisol levels throughout the day (Corbett and Simon, 2014).

Dysregulation of the HPA axis, whether it is reflected in cortisol levels in stress reactivity or in basal output, has been linked to numerous illnesses. These illnesses are chronic in nature and range from general psychological symptoms of "burn out" (Melamed et al., 1999) to physiological manifestations, such as heart disease and obesity (Chrousos, 2009; Whitworth et al., 2005). Furthermore, cortisol dysregulation has been associated with depression (Herbert, 2013) and anxiety (Vreeburg et al., 2010).

Since the HPA axis is an underlying physiological system both activated and vulnerable to dysregulation by stress, one highly examined area is how ELS can shape activity of the hypothalamic pituitary adrenal (HPA) axis later in life, with cortisol as a primary output (Mello et al., 2009).

1.1. Early life stress and non-stressed cortisol levels

ELS may present a unique threat to HPA axis functioning, as these types of stressors can not only be chronic in nature but also derail normal development during sensitive periods (Shonkoff et al., 2012),

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potentially persisting into adulthood. Studies have found greater likelihood of diurnal cortisol blunting in those who had been sexually abused as children, when controlling for potential confounders (Brewer-Smyth and Burgess, 2008), blunted CAR in those who had been exposed to ELS (Mangold et al., 2010; Meinlschmidt and Heim, 2005), and lower baseline samples pre-stressor in those who reported experiencing severe trauma during development (DeSantis et al., 2011). However, ELS has also been associated with heightened cortisol, such as larger CAR (Lu et al., 2016), and higher cortisol levels throughout the day (Nicolson, 2004). Other studies have not found differences in non-stressed cortisol levels as a function of ELS when daily rhythms were captured (Janusek et al., 2017; Schalinski et al., 2015) or in the CAR (Peng et al., 2014). Trending differences in the effects of ELS were seen in cortisol measured in hair, although only in those individuals who had experienced physical neglect (as opposed to any other types of abuse or neglect; (Fischer et al., 2017). Taken together, the literature is ambiguous as to whether there is an effect of ELS on non-stressed cortisol levels.

1.2. ELS and cortisol levels after stress exposure

Other work has considered the relationship between ELS and cortisol levels after exposure to an acute stressor, producing mixed results as well. For example, studies have reported a blunted cortisol response to the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), an acute psychosocial stressor, as a function of ELS (Carpenter et al., 2007; Carpenter et al., 2011; Elzinga et al., 2008). These negative correlations were observed across types of ELS (i.e. sexual, emotional and physical). On the other hand, other studies reported elevated rather than blunted cortisol responses to acute psychological stress as a function of ELS. For example, Pesonen et al. (2010) observed that participants who had been separated from their parents due to a World War II relocation program displayed heightened reactivity to the TSST in comparison to non-separated controls. Vaccarino et al. (2015) found a positive relationship between ELS and cortisol reactivity to the TSST in healthy controls. Experiencing the death or desertion of a parent in early life was also associated with higher cortisol levels, compared to controls who did not have these experiences, following a suppression of the HPA axis with an acute physiological stressor, the dexamethasone suppression test (DST) and a bolus of corticotropin releasing hormone (CRH) the following day (Tyrka et al., 2008). Finally, some studies reported no correlation between ELS and cortisol reactivity to either a psychological or physiological acute stressor (Andreotti et al., 2015; Phassouliotis et al., 2013).

Overall, a relationship between ELS and cortisol has a sound theoretical basis and some evidence to support it. However, a qualitative examination of the evidence suggests that this effect is not clear and thus requires a more nuanced, quantitative perspective.

1.3. Potential moderators

1.3.1. ELS and psychopathology

Being diagnosed with psychopathology has often been associated with an increased likelihood of having experienced ELS (Green et al., 2010; Nemeroff, 2004). Additionally, the presence of psychopathology is often associated with dysregulation of cortisol production (Herbert, 2013; Vreeburg et al., 2010). Therefore, psychopathology can play an important, confounding role when trying to tease apart the relationship between ELS and cortisol. For instance, Peng and colleagues (Peng et al., 2014) found that depressed patients who had experienced ELS had significantly higher CAR than depressed non-ELS subjects. Patients diagnosed with an Axis I disorder who had experienced ELS displayed heightened cortisol throughout the day and post-DST (Faravelli et al., 2010). Amongst women without major depressive disorder (MDD), experiencing ELS at baseline before the TSST or in reactivity to the TSST was not significantly different; however, those who had experienced MDD concurrent with ELS displayed a heightened cortisol response to the acute stressor compared to MDD/non-ELS participants (Heim et al., 2000; Newport et al., 2004). The same was true in a similarly structured male cohort (Heim et al., 2008). Such findings, in addition to qualitative reviews of the literature (Heim and Nemeroff, 2002), highlight the importance of considering whether the sample has psychopathology when quantifying the relationship between ELS and cortisol.

1.3.2. Design-related moderators: measuring cortisol

A number of different nuances when measuring cortisol, both at non-stressed and post stress levels, emerge across studies. For instance, cortisol is generally at its highest in the morning and lowest at night (Kirschbaum and Hellhammer, 2000), suggesting time of day may add additional variability when quantifying cortisol. Additionally, the type of sample can vary, as cortisol is commonly measured via saliva, blood, urine and hair. These methods capture vastly different time scales. How cortisol is quantified, whether it is sampled at one time point, throughout an experiment, or throughout the day may yield different results (Nicolson, 2008). Furthermore, Khoury et al. (2015) saw a distinction in cortisol quantification methods, with correlations between total cortisol measures (e.g. one time point, area under the curve with respect to ground) and correlations between change in cortisol measures (e.g. area under the curve with respect to increase, difference in cortisol at two time points). Finally, variation in cortisol reactivity to an acute stressor may exist as tasks may range in their efficacy to induce a cortisol response (Dickerson and Kemeny, 2004).

1.3.3. Design-related moderators: measuring ELS

ELS can be quantified by questionnaire or self-report, more in-depth measures such as interviews, or even objective measures such as looking up records or having a parent report on experiences. These methods vary in how accurately ELS may be captured (Monroe, 2008). Furthermore, individual questionnaires may focus in on various types of stressors such as sexual, physical or emotional ELS or, in terms of neglect, abuse or loss. Distinguishing between stressor types is important, as findings are inconsistent, with some stressors eliciting varying levels of cortisol dysregulation (Mello et al., 2009). Finally, the age that the abuse begins, the maximum age of what is considered “early” life stress and the severity of the abuse all may have a role in the relationship between ELS and cortisol.

1.3.4. Population related moderators

In addition to the way a study is designed, the sample population may vary. Numerous studies have noted gender differences both in the occurrence of certain types of ELS (May-Chahal, 2006) and in cortisol levels (Almeida et al., 2009; Kirschbaum et al., 1992; Van Cauter et al., 1996). The age of the population studied may have particular importance as theories on allostatic load (McEwen, 1998), with stress accumulating over time, may change HPA axis functioning and therefore cortisol levels (Almeida et al., 2009; Van Cauter et al., 1996). In order to accurately assess the relationship between ELS and cortisol, population-related parameters need to be addressed as well.

1.4. Purpose and hypotheses

Thus far a number of literature reviews have been conducted to assess the role of ELS. For instance, de Carvalho Tofoli et al. (2011) suggested that ELS might impact the HPA axis, the dysfunction of which is a symptom of depression. Grassi-Oliveira et al. (2008) concluded that ELS might be disruptive to the HPA axis as well as a number of other biological symptoms, which in turn may impact the formation of brain structures including the hippocampus and amygdala. These reviews suggest a commonly held belief that ELS has pervasive and long lasting consequences. However, to our knowledge no quantitative analysis has yet examined the effects of ELS on cortisol stress physiology in an adult population. Such an examination is critical to determine whether there