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Early-life stress and recurrent psychological distress over the lifecourse predict divergent cortisol reactivity patterns in adulthood

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Summary Early-life stress (ELS) is associated with substantially increased lifetime risk for recurrent psychological problems, with evidence indicating that dysregulation of the physiological stress reactivity system may be partly responsible. However, some ELS-exposed people remain psychologically resilient. Although two distinct patterns of hypothalamic—pituitary—adrenal axis (HPA) stress reactivity have been observed in ELS-exposed samples (hyper- and hypo-reactive), the hypothesis that these patterns may be associated with long-term history of psychological problems has not been explored. We used healthy Whitehall II study subjects (n = 543) who participated in the 2008 Heart Scan Study (HSS) to assess salivary cortisol responses to a cognitive stressor, ELS exposure, and other psychosocial factors. Mean age of the sample at the HSS was 63 years. HSS data were linked to nearly 20 years of participants' Whitehall data, including repeated measures of psychological distress (GHQ-28). Piecewise growth curve analyses revealed that ELS-exposed persons with a history of recurrent psychological distress in adulthood had significantly blunted cortisol reactivity compared to non-ELS-exposed participants, while ELS-exposed persons with little or no history of distress had significantly elevated baseline cortisol, prolonged responses, and greater total cortisol production. Our findings indicate that for ELS-exposed individuals, different trajectories in psychological health over their adult lifetimes predict different cortisol reactivity patterns. These findings have important implications for our understanding of ELS-related mental health risk and treatment of these disorders.

1. Introduction

Exposure to inadequate caregiving or other early-life stress (ELS) is one of the strongest predictors of recurrent psychological problems in later life, particularly mood and anxiety disorders (Kessler and Magee, 1993; Felitti et al., 1998;

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Widom et al., 2007; Scott et al., 2010). Worldwide, psychological disorders and ELS experiences are both highly prevalent (Menard et al., 2004; Cohen et al., 2006; Kessler et al., 2007; Danese et al., 2009), and some estimates suggest that more than 50% of depression and nearly 60% of suicide attempts may be attributable to ELS, particularly among women (Felitti and Anda, 2009). ELS-associated psychological disorders are also more likely to be early-onset, comparatively severe, and highly recurrent (Kessler and Magee, 1993; Gilman et al., 2003; Heim et al., 2004; Widom et al., 2007). However, many ELS-exposed people remain psychologically resilient throughout their lives, never experiencing the disorders otherwise common in this group (Silk et al., 2007). We need to identify mechanisms through which such divergent outcomes emerge.

Theoretical and empirical research based on the developmental programming paradigm indicates that suboptimal early-life environments can encode vulnerability to later-life psychological impairment through permanent alterations of organ systems and functioning (Hales and Barker, 2001; Raikkonen and Pesonen, 2009). Alterations in the physiological systems that regulate individuals' reactivity to stress — particularly the hypothalamic–pituitary–adrenal (HPA) axis and its end-product, glucocorticoids — appear to play an especially important role (Lupien et al., 2000; McEwen, 2000; van Harmelen et al., 2010), although many biological processes are implicated (Kiecolt-Glaser et al., 2011; Gunnar and Quevedo, 2007; Eisenberg et al., 2010; Jackowski et al., 2011; Pechtel and Pizzagalli, 2011). Atypical glucocorticoid stress responses have been extensively documented in persons with mood and anxiety disorders (e.g., Burke et al., 2005a,b; Yehuda, 2009; de Rooij et al., 2010). A range of studies examining ELS-exposed individuals have also consistently reported significant alterations in cortisol reactivity when compared to non-ELS-exposed controls (Heim et al., 2000, 2002, 2008; Girdler et al., 2003; Taylor et al., 2004; Carpenter et al., 2007, 2009; Elzinga et al., 2008; Gordis et al., 2008; Rao et al., 2008; MacMillan et al., 2009; Engert et al., 2010).

Theoretical research indicates that two (or more) different patterns of atypical HPA axis reactivity — in particular, blunted or heightened responses — may be encoded in the aftermath of ELS (McEwen and Seeman, 1999; Boyce and Ellis, 2005). These different stress-response patterns may, in turn, promote differential susceptibility to lifetime psychological disorder (Carpenter et al., 2007; Miller et al., 2007; Gunnar et al., 2009). Therefore, distinct cortisol reactivity patterns may be one of the mechanisms underlying the divergent long-term mental health outcomes observed in ELS-exposed populations.

Research in this field has mostly been characterized by small cross-sectional samples, with participants' long-term histories of psychological problems generally left unexamined. These samples are usually restricted such that participants are either currently psychologically healthy or have a current mood disorder; in both situations, depression symptoms are treated as a statistical confounder. In this literature, blunted cortisol reactivity has been reported in ELS-exposed but currently psychologically healthy adults and adolescents (Girdler et al., 2003; Taylor et al., 2004; Carpenter et al., 2007, 2009; Elzinga et al., 2008; Gordis et al., 2008; MacMillan et al., 2009; Engert et al., 2010), while those with a history of ELS and current major depression have exhibited exaggerated cortisol responses to stress (Heim et al., 2008; Rao et al., 2008).

Two cross-sectional studies have examined cortisol reactivity among ELS-exposed persons with different levels of current psychological disorder (Heim et al., 2000; Harkness et al., 2011). In the first study, adult women with a history of childhood abuse and current major depression exhibited significantly higher cortisol responses compared to abused women without current depression, as well as compared to non-abused women with current depression and non-abused, non-depressed control women (Heim et al., 2000). In the second study, the opposite effect was found: adolescents with a history of childhood maltreatment and current moderate-to-severe depression exhibited blunted cortisol stress responses, while those with a history of maltreatment but only minimal (or no) current depression symptoms exhibited higher and more prolonged cortisol responses (Harkness et al., 2011).

The explanation for these conflicting results is not clear. However, the design of previous studies may have resulted in the misclassification of study participants with respect to their long-term vulnerability to psychological disorder. High levels of depression symptoms among ELS-exposed participants are often reported even in studies where they are required to be free of psychiatric disorder. Additionally, age of onset for mood disorders is typically between 20 and 30 years in ELS-exposed persons (Kessler et al., 1997; Widom et al., 2007), but many of these studies used adolescent (<18 years) (Gordis et al., 2008; Rao et al., 2008; MacMillan et al., 2009; Harkness et al., 2011) or young adult (<30 years) (Elzinga et al., 2008; Engert et al., 2010) samples, leaving their participants' future lifetime psychological vulnerability unclear. Although examining the relationship between early-life stress and cortisol reactivity in young populations has many advantages, including the ability to assess cortisol functioning in those with early-onset psychological disorder at a crucial period of development, investigations in older populations that can incorporate measures of their *long-term*, recurrent psychological disorder are also needed.

Functioning of the HPA axis is known to change over the lifecourse, although evidence regarding the impact of age on cortisol reactivity is conflicting. In a review, Kudielka et al. (2009) reported no significant differences between younger and older adults' cortisol responses to psychosocial stress challenges, but other studies have reported comparatively heightened cortisol responses among older adults (e.g., Almela et al., 2011; Carpenter et al., 2009; Otte et al., 2005). No studies have examined the impact of early-life stress and recurrent psychological distress on cortisol reactivity among older adults.

We used data collected as part of an ancillary study to the ongoing Whitehall II cohort to examine the joint relationships of ELS exposure, psychological history, and cortisol reactivity among a group of older adults for whom long-term recurrence of psychological distress symptoms could be established. We hypothesized that cortisol reactivity patterns observed in the ELS-exposed adults would differ from those observed in non-ELS-exposed adults, but that the patterns would be differential according to psychological history: namely, that the non-ELS-exposed participants would exhibit a median response, while ELS-exposed adults *without* a history of