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Effects of early childhood trauma on hypothalamic—pituitary—adrenal (HPA) axis function in patients with Chronic Fatigue Syndrome

Stefan Kempke[a,*,1], Patrick Luyten[a,b], Sarah De Coninck[c], Boudewijn Van Houdenhove[d], Linda C. Mayes[e], Stephan Claes[d]

[a] *Faculty of Psychology and Educational Sciences, University of Leuven, Leuven, Belgium*
[b] *Research Department of Clinical, Educational and Health Psychology, University College London, London, UK*
[c] *Biological Psychology, Faculty of Psychology and Educational Sciences, Vrije Universiteit Brussel, Brussels, Belgium*
[d] *Department of Psychiatry, University Hospitals Leuven, University of Leuven, Leuven, Belgium*
[e] *Yale Child Study Center, Yale Medical School, Yale University, New Haven, USA*

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Summary
Background: There is a paucity of studies that have investigated the assumption that early childhood trauma is associated with hypothalamic—pituitary—adrenal (HPA) axis dysfunction in Chronic Fatigue Syndrome (CFS). The current study is the first to simultaneously investigate relationships among early childhood trauma, cortisol activity, and cortisol stress reactivity to psychosocial stress in a sample of well-screened CFS patients. We also examined whether self-critical perfectionism (SCP) plays a mediating role in the potential relationship between early trauma and neurobiological stress responses.
Methods: A total of 40 female patients diagnosed with CFS were asked to provide morning saliva cortisol samples (after awakening, 30 min later, and 1 h later) for seven consecutive days as a measure of cortisol activity. In addition, patients were exposed to the Trier Social Stress Test, a well-validated stress test, to investigate the relationship between early childhood trauma and cortisol stress reactivity. Before the start of the study, patients completed the Childhood Trauma Questionnaire-Short form (CTQ-SF) as a measure of early childhood trauma (i.e. sexual, physical

* Corresponding author at: Faculty of Psychology and Educational Sciences, University of Leuven, Tiensestraat 102, 3000 Leuven, Belgium. Tel.: +32 16 325871; fax: +32 16 325920.
E-mail address: stefan.kempke@ppw.kuleuven.be (S. Kempke).
[1] Postdoctoral researcher of the Research Foundation Flanders (FWO).

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and emotional traumatic experiences). SCP was measured with the Depressive Experiences Questionnaire (DEQ). Data were analyzed by calculating several indices of cortisol secretion (i.e. Cortisol Awakening Response and Area Under the Curve).
Results: There was no association between early childhood trauma and cortisol as measured over the 7-day period. However, emotional neglect was significantly negatively related to cortisol reactivity in the TSST. SCP did not significantly mediate this association.
Conclusion: Findings of this study suggest that emotional neglect is associated with blunted HPA axis reactivity, congruent with the assumption that CFS may reflect loss of adaptability of the neuroendocrine stress response system in at least a subgroup of patients.

1. Introduction

Chronic Fatigue Syndrome (CFS) is characterized by chronic, medically unexplained fatigue and physical and/or mental fatigability in response to exertion in particular (Fukuda et al., 1994; Carruthers et al., 2011). It is a highly debilitating condition that most often affects women (Jason et al., 1999) and that is associated with high psychosocial and economic costs (Collin et al., 2011). A considerable proportion of CFS patients also suffers from chronic pain symptoms, and studies increasingly suggest that CFS may be part of a broader spectrum of chronic pain and fatigue disorders (Kanaan et al., 2007; Van Houdenhove et al., 2010; Ablin et al., 2012).

There is accumulating evidence that impairments in stress regulation may play a key role in the development and perpetuation of CFS (Silverman et al., 2010; Luyten et al., 2011; Nater et al., 2011). Most research in this context has focused on hypothalamic–pituitary–adrenal (HPA) axis function in CFS as measured by the stress hormone cortisol. In general, studies have found evidence for reduced cortisol activity and lower cortisol stress reactivity in CFS (Cleare, 2003; Van Den Eede et al., 2007; Papadopoulos and Cleare, 2011; Tak et al., 2011; Nijhof et al., 2014), which may reflect a dysregulation of the stress response system after a prolonged period of chronic physical and/or mental stress (Van Houdenhove and Luyten, 2010; Van Houdenhove et al., 2009, 2013).

However, it is important to note that previous studies on HPA-axis function in CFS have also yielded inconsistent results (for an overview see Papadopoulos and Cleare, 2011). Differences in study results may be in part explained by the fact that CFS is a multi-factorial and etiologically heterogeneous condition (Van Houdenhove and Luyten, 2008). Hence, there is a need to unravel the mechanisms that may underlie HPA-axis alterations in carefully screened CFS patients (Van Houdenhove et al., 2013).

There is a growing body of evidence to suggest that early life stress, and early childhood trauma in particular, may explain in part HPA axis dysregulation in CFS (Luyten et al., 2008; Van Houdenhove et al., 2009; Nater et al., 2011). Both animal and human studies indicate that early adversity, especially during so-called ''critical time windows'', may affect brain structures and the expression of genes that have been shown to regulate the stress system, leading to a neurobiological 'switch' from HPA axis hyperactivity to hypoactivity in the long run (e.g., Heim et al., 2000, 2001; Miller et al., 2007; Luecken et al., 2009; Lupien et al., 2009; Trickett et al., 2010). Congruent with these findings, a number of studies have shown that CFS is associated with a high prevalence of early childhood trauma (for an overview see Borsini et al., 2013; Kempke et al., 2013a; Afari et al., 2014). In a recent study, we found that more than half of the patients with CFS reported a history of childhood trauma (Kempke et al., 2013a), replicating earlier findings in both tertiary care settings and in a population-based study (Van Houdenhove et al., 2001; Heim et al., 2006, 2009). Moreover, we demonstrated that early childhood trauma, and emotional trauma in particular, was associated with the core symptoms of CFS (Kempke et al., 2013a). Thus, research suggests that early trauma is an important risk factor for CFS.

Yet, to the best of our knowledge, only two studies have investigated the relationship between early childhood trauma and HPA axis function in CFS patients. Heim et al. (2009), in a population-based survey, investigated the association between exposure to childhood trauma as determined by the Childhood Trauma Questionnaire Short Form (CTQ-SF) (Bernstein et al., 2003) and cortisol levels after awakening (i.e. between awakening and 60 min post-awakening) as collected on a regular workday. Results showed that only CFS patients with a history of trauma had lower mean cortisol levels after awakening compared with control subjects. This finding is consistent with more basic research demonstrating a relationship between early life stress and reduced cortisol responses (Heim et al., 2000; Carpenter et al., 2007, 2009; Miller et al., 2007). In contrast to these findings, however, Van Den Eede et al. (2008) found that CFS patients *without* a history of early adversity showed lower cortisol responses to a stress challenge test (i.e. dexamethasone/corticotropin-releasing factor test) compared with age- and education-matched healthy controls.

Thus, more research is clearly needed to investigate the effects of early adversity on HPA axis functioning in CFS given the paucity of studies and the contradictory findings in the few available studies. Moreover, as far as we know, there is no study that has simultaneously investigated HPA-axis activity and reactivity in CFS patients. For instance, in a study of depressed patients, Dienes et al. (2013) studied both naturalistic cortisol secretion and cortisol reactivity to a laboratory stressor. There are also no studies that have investigated whether early childhood trauma is associated with impaired HPA-axis reactivity to *psychosocial* stress in CFS. Gaab et al. (2002, 2005) found no differences in cortisol responses to a standardized psychosocial stress test,