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# Functional Somatic Symptoms in Children and Adolescents: The Stress-System Approach to Assessment and Treatment

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## Online Supplement 8.1

### Brief Summary of Research Pertaining to the HPA Axis and Functional Somatic Symptoms

In this supplement to Chapter 8, we provide the reader with a brief summary of studies showing various patterns of HPA dysfunction in adults with functional somatic symptoms, children with functional somatic symptoms, and individuals with a history of sexual abuse or maltreatment.

#### **HPA-Axis Dysfunction in Adults with Functional Somatic Symptoms**

Compromised HPA-axis function in individuals with functional somatic symptoms has been most extensively studied (and documented) in adults—especially women—who suffer from fatigue and meet criteria for chronic fatigue syndrome. This body of work has documented five main findings: lower cortisol levels, attenuated diurnal variation of cortisol, enhanced negative feedback within the HPA axis, changed glucocorticoid-receptor sensitivity to cortisol, and blunted HPA-axis responsiveness (see

Papadopoulos and Cleare [2011] for review). Also important to note is that patients with chronic fatigue who engage in physical interventions that improve physical resilience and well-being, or in psychological interventions that address comorbid depression and improve psychological well-being, have improved HPA function (Papadopoulos and Cleare 2011; Rimes and Wingrove 2013).

HPA-axis dysfunction has been documented in adult patients with functional neurological disorder (FND): cortisol levels were found to be elevated in the resting state, where they were correlated with threat vigilance (Bakvis et al. 2009b; Bakvis et al. 2009c), and during a stress test, where they were correlated with abnormal postural behaviour (increased sway and decreased frequency compared to controls) (Zito et al. 2018).

Finally, adults with mixed functional somatic symptoms—various combinations of fatigue, somnolence, nausea, hyperalgesia with varying pains and aches, dizziness, and so on—show HPA-axis dysfunction: circadian rhythm obliteration or a reversal pattern characterized by lower morning and higher evening cortisol levels compared to healthy controls (Tsigos et al. 2015). This patient group also showed increased high-sensitivity C-reactive protein (activation of the immune-inflammatory system) and abnormalities in measures of body composition and tissue health.

Data pertaining to HPA function in studies of adults with different functional symptoms or syndromes are briefly summarized in the Table OS 8.1.1.

## **HPA-Axis Dysfunction in Children and Adolescents with Functional Somatic Symptoms**

HPA-axis dysfunction is also implicated in children with functional somatic symptoms. In a large, prospective study of 2230 Dutch youth—the TRAILS study—adolescents who reported non-neurological functional somatic symptoms (overtiredness, dizziness, headache, stomach pain, vomiting, nausea, or musculoskeletal symptoms [pain in the back, neck, shoulders, arms, or legs]) on the Somatic Complaints scale of the Youth

<b>Table OS 8.1.1</b>	
<b>Studies Documenting HPA Dysregulation in Adults Diagnosed with Different Functional Disorders</b>	
<b>Functional disorder Study</b>	<b>Biological marker</b>
<b>Non-epileptic seizures (FND)</b> Bakvis et al. (2009b)	<p>↑ Basal diurnal cortisol levels (afternoon and evening)</p> <p>No difference in saliva amylase (a measure of autonomic nervous system activity)</p>
<b>Non-epileptic seizures (FND),</b> Bakvis et al. (2009a)	<p>No differences in cortisol before and during Stroop test</p> <p>↓ HRV throughout Stroop test</p> <p>↓ HRV at recovery</p>
<b>Chronic fatigue syndrome (review of the literature)</b> Papadopoulos & Cleare (2011)	<p>↓ Cortisol levels</p> <p>Attenuated diurnal variation of cortisol</p> <p>Enhanced negative feedback within the HPA axis</p> <p>Changed glucocorticoid-receptor sensitivity to cortisol</p> <p>Blunted HPA-axis responsiveness</p>
<b>FND (motor subtype)</b> Zito et al. (2019)	<p>Failure to increase cortisol during stress test</p> <p>A smooth regular movement pattern (compared to controls whose pattern was more complex) during stress test</p> <p>Failure to decrease body sway during stress test</p>
<b>Mixed functional somatic symptoms</b> Tsigos et al. (2015)	<p>Circadian rhythm obliteration or reversal pattern (↓ morning cortisol levels and ↑ evening cortisol levels)</p> <p>↑ high-sensitivity CRP</p> <p>Abnormal measures of body composition and tissue integrity</p>
CRP, C-reactive protein; HRV, heart rate variability.	

Self-Report showed dysregulation of the HPA axis (Janssens et al. 2012). Adolescents within the symptom cluster for overtiredness, dizziness, and musculoskeletal pain had low cortisol levels on waking. And adolescents within the cluster for headache and gastrointestinal symptoms had low cortisol levels during stress exposure (a social-stress task).

Some small studies have identified HPA-axis dysregulation in children with functional abdominal pain, whereas others have not (see Gulewitsch [2017] for review).

Like their adult counterparts, adolescents with chronic fatigue show HPA dysfunction (in particular, lower cortisol secretion) over the circadian cycle (Rimes et al. 2014) and attenuation of the HPA axis—both adrenocorticotrophic hormone (ACTH) and cortisol—during psychosocial stress (Segal et al. 2005). ACTH is produced by the anterior pituitary and is part of the HPA axis. The study by Rimes and colleagues (2014) found that HPA dysfunction resolved with cognitive-behavioural therapy targeting psychological factors (perfectionist striving and high moral expectations) that were associated with low cortisol levels. These data suggest that certain patients activate their stress systems and dysregulate their HPA axis via top-down psychological mechanisms such as perfectionist striving, high moral expectations, catastrophizing, or recurring traumatic memories (see Chapter 12).

See also Agorastos and colleagues (2019) for references on changes in HPA activity in PTSD, depression, and other mental health and physical disorders.

Data pertaining to HPA function in studies of children and adolescents with different functional symptoms or syndromes is briefly summarized in Table OS 8.1.2.

## **HPA Dysfunction in Children and Adolescents with a History of Sexual Abuse or Maltreatment**

As we saw in Chapter 4, many recent studies have confirmed the long-observed association between adverse childhood experiences and functional somatic symptoms and syndromes. If adverse childhood

<b>Table OS 8.1.2</b>	
<b>Studies Documenting Autonomic System Activation or Dysregulation in Children Diagnosed with Different Functional Disorders</b>	
<b>Functional disorder Study</b>	<b>Biological marker</b>
<b>Chronic fatigue syndrome</b> Segal et al. (2005)	↓ Cortisol during synacthen tests (lower mean cortisol levels, lower peak cortisol, reduced cortisol area under the curve, and longer time to peak cortisol)
<b>Non-neurological functional somatic symptoms</b> Janssens et al. (2012)	↓ Cortisol on waking (overtiredness, dizziness, and musculoskeletal pain group) ↓ Cortisol on stress exposure (headache and gastrointestinal symptoms group)
<b>Chronic fatigue syndrome</b> Nijhof et al. (2014)	↓ Cortisol on waking
<b>Chronic fatigue syndrome</b> Rimes et al. (2014)	↓ Cortisol over the day
<b>Chronic fatigue syndrome</b> Sulheim et al. (2014)	↓ Urinary cortisol-to-creatinine ratio
<b>Chronic fatigue syndrome</b> Hall et al. (2014)	Greater Perceived Stress Management Skills related to a greater cortisol awakening response (↑ cortisol), which in turn related to less exertional malaise or, in terms of effect relationships, greater Perceived Stress Management Skills related to less post-exertional fatigue, via a greater cortisol awakening response
<b>Chronic fatigue syndrome</b> Wyller et al. (2016)	↓ Urinary cortisol-to-creatinine ratio Different interrelations between hormones of the HPA axis, sympathoadrenal medullary (SAM) system, and thyroid system in CFS patients and healthy controls
<b>Recurrent abdominal pain</b> Gulewitsch et al. (2017)	↓ Cortisol secretion during social-stress task No change in heart rate variability

experiences are considered in terms of a spectrum, maltreatment – emotional abuse, physical abuse, and sexual abuse—would lie on the more severe end of the spectrum. Studies of individuals with a history of childhood sexual abuse show high rates of functional somatic symptoms across the lifespan (Bonvanie et al. 2015; Paras et al. 2009).

Studies pertaining to HPA function in individuals with a history of maltreatment highlight the role of stress in activating and dysregulating HPA function. Sexually abused girls show a shifting pattern of HPA dysregulation across development: an initial elevation of cortisol in the aftermath of the trauma (overactivation of the HPA axis and too much cortisol), followed by a gradual normalization in early adulthood and, even later, low cortisol secretion (underactivation of the HPA axis and too little cortisol) (Trickett et al. 2010). Sexually abused girls also show (in addition to HPA dysregulation) progressive activation, through adulthood, of both the sympathetic system (elevation of catecholamines) (Trickett et al. 2010) and the immune-inflammatory system (Bertone-Johnson et al. 2012; Baumeister et al. 2016).

A similar pattern of change is found in children who develop PTSD after a motor vehicle accident: an initial elevation of cortisol in the aftermath of the accident is followed by a gradual normalization and, in time, low cortisol secretion along with a gradual elevation of catecholamines (Pervanidou and Chrousos 2012).

Maltreated children also show various patterns of HPA dysregulation in the context of a social-stress test (Harkness et al. 2011; MacMillan et al. 2009).

In some studies, young women exposed to sexual or physical abuse in childhood also show an activated HPA axis (Heim et al. 2000).

Data from the sexual abuse literature in girls/women is also summarized in Table OS 8.1.3.

<b>Table OS 8.1.3</b>	
<b>HPA Dysfunction in Girls/Women with History of Sexual Abuse</b>	
<b>Developmental period following childhood sexual abuse</b>	<b>Biological marker Study</b>
<b>Childhood</b>	↑ Baseline cortisol Trickett et al. (2010)
<b>Late adolescence and early adulthood</b>	Normalized baseline cortisol Progressive increase in catecholamines Immune-inflammatory system activation Trickett et al. (2010) ↑ Cortisol response to stress task (in those with mild or moderate depression) Harkness et al. (2011) ↓ (Blunted) cortisol response to stress task MacMillan et al. (2009)
<b>Later adulthood</b>	↓ Baseline cortisol Progressive increase in catecholamines Immune-inflammatory system activation Trickett et al. (2010), Bertone-Johnson et al. (2012), Baumeister et al. (2016) ↑ ACTH* response to stress task ↑ Cortisol response to stress task ↑ Heart rates to stress task (esp. with comorbid depression) Heim et al. (2000)
* Adrenocorticotrophic hormone (ACTH) is produced by the anterior pituitary and is part of the HPA axis.	

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