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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 9.1

The Immune-Inflammatory System

In this supplement to Chapter 9, we provide the reader with additional information about the immune-inflammatory system: the cross-talk between the immune-inflammatory system and other components of the stress system; the challenges to studying the immune-inflammatory system, along with the new methodologies that are emerging; the immune-inflammatory cells that reside in the brain; the different ways in which the immune-inflammatory system can respond to stress; a short summary of studies that show that inflammatory markers are elevated in patients with functional somatic symptoms; a discussion of biological processes by which the immune-inflammatory system is thought to activate the stress system; the relationship between chronic fatigue syndrome and other functional somatic symptoms; interesting themes emerging from research pertaining to chronic fatigue syndrome; and the impact of Western living on the immune-inflammatory system

References Pertaining to the Cross-talk Between the Immune-Inflammatory System and Other Components of the Stress System

Readers interested in the detail of the cross-talk between the immune-inflammatory system and other components of the stress system might start by reading the basic science contributions by Chrousos (1995), Elenkov and colleagues (2000), Bellavance and Rivest (2014), McEwen and colleagues (2015), Morris and colleagues (2017), Picard and colleagues (2018), and Agorastos and colleagues (2019).

Methodological Problems in Research Pertaining to the Immune-Inflammatory System

A threshold problem in studying the immune-inflammatory system in functional somatic disorders has been the lack of methodologies that measure small increases in inflammatory markers or that measure the pattern of change in the levels of messenger molecules across the system as a whole. Most of the studies available to date have measured one or a handful of inflammatory markers at a time. This is analogous to measuring the tip of an iceberg, where the size of the tip is used to estimate the size of the ice as a whole, but where the shape or pattern of the underlying iceberg remains unknown. Common markers of inflammation have included C-reactive protein (CRP), cytokines (e.g., interleukin [IL]-6), and tumour necrosis factor- α (TNF- α).

To date, CRP, a large protein that is relatively easy to measure, has been a commonly used marker of immune-inflammatory system activation in both research and clinical practice. CRP is normally not detectable in blood – or detectable only at very low levels – unless immune-inflammatory cells are activated somewhere in the body. Doctors have long used CRP (readings of $>10\text{mg/L}$) as an indicator of infection or possible inflammatory disease. More recently, it has become apparent that low CRP levels ($<2\text{mg/L}$) are associated with health and well-being (Ironson et al. 2018) and that moderate levels ($2\text{--}10\text{mg/L}$) – considered low-grade

inflammation – are associated with ill health, both physical and emotional (Ironson et al. 2018; Wium-Andersen et al. 2013). Given the availability of a high-sensitivity assay and, through the TRAILS study, a normative reference range for adolescents (Jonker et al. 2017), it is now possible to identify and interpret small variations in CRP.

In the future, a new marker of inflammation, soluble urokinase plasminogen activator receptor (suPAR), may be added to CRP, IL-6, and TNF- α , to assess inflammatory status. A recent prospective study of twins suggests that suPAR may improve measurement of stress-related inflammatory burden – that is, inflammation that occurs in the context of adverse childhood experiences (ACEs) (Rasmussen et al. 2019).

An alternate research strategy is the development of methodologies that use mass spectrometry to simultaneously measure multiple proteins – for example, metabolites from cellular processes (Roberts 2016). These more complex technologies – sometimes called *multiplex arrays* – have already begun to be used in research with adults (Montoya et al. 2017; Backryd et al. 2017; Hackshaw et al. 2019). These technologies provide ‘a characteristic chemical “fingerprint” with a unique signature profile’ (Hackshaw et al. 2019, p. 2556). This is analogous to sampling a larger area of the iceberg and measuring the chemical profile to estimate the chemical profile of the ice as a whole (the overall shape or pattern).

A second threshold problem in studying the immune-inflammatory system is the sheer complexity of the system. While most messenger molecules have a clear pro-inflammatory or anti-inflammatory function, some messenger molecules have context-specific roles – either pro-inflammatory or anti-inflammatory – depending on the mode of signalling and the signalling playmates (Scheller et al. 2011). So, for example, while IL-6 normally engages in pro-inflammatory functions in response to stress, its role during exercise is anti-inflammatory: in addition to promoting energy metabolism to ensure sufficient energy resources for muscle, it facilitates secretion of other anti-inflammatory cytokines, with the consequence that its role during exercise is anti-inflammatory (Petersen and Pedersen 2006; Stefanaki et al. 2018). This complexity is challenging from a research perspective.

New Methodologies and Systems Theory Thinking

Researchers are also thinking about biological systems using systems theory – termed *systems biology* or the *network perspective* – and developing technologies to examine biological networks, including protein networks, signalling pathways, and immune-gene networks (Nguyen et al. 2019). Other technologies look at inflammatory markers and associations between body composition and markers that reflect the integrity of body tissues (Tsigos et al. 2015). These methodologies look at patterns of change or patterns of relationship both within and between systems. See for example, Wyller and colleagues (2016), Montoya and colleagues (2017), and Nguyen and colleagues (2019).

References Pertaining to Neuroinflammatory Priming and Immune-Inflammatory Cells in the Brain

Readers interested in more detailed reading about the manner in which immune-inflammatory cells hold memory for past stress can look at articles by Bertone-Johnson and colleagues (2012), Morey and colleagues (2015), Baumeister and colleagues (2016), Frank and colleagues (2016), Brenhouse and colleagues (2018), and Agorastos and colleagues (2019).

Differential Responses of the Immune-Inflammatory System in Response to Stress

In the article entitled ‘Stress, Distress, and Bodytalk: Co-constructing Formulations with Patients Who Present with Somatic Symptoms’ (2017, p. 317), the first author (KK) provided a very short summary pertaining to the differential responses of the immune-inflammatory system to stress. The short summary is quoted here.

The HPA/sympathetic stress system also crosstalks with the immune/inflammatory system; mutual regulation occurs through a complex net of feedback loops on multiple system levels (Chrousos 1995,

2009; Webster et al. 1997). Whether stress activates or inhibits systemic and local immune/inflammatory responses depends on the balance between anti- and pro-inflammatory activity. This balance reflects, in turn, the type and quality of current stressors, the individual's current level of fitness, and the robustness of the individual's HPA axis and parasympathetic functioning, all of which interact with the individual's past history (genetic, epigenetic, relational, and environmental) (Reiche et al. 2004; Chrousos 1992; Dhabhar 2000; Elenkov and Chrousos 2006; Fleshner 2005; Tracey 2002).

Stress can increase the immune/inflammatory response through various mechanisms. For example, stress may, on balance, differentially affect the sympathetic system, leading to increased secretion of tissue CRH by sympathetic nerves and immune cells (which are modulated by sympathetic nerves); local CRH acts to elicit pro-inflammatory responses (Webster et al. 1997; Chrousos 1992). In another scenario, the secretion of norepinephrine by sympathetic nerves may activate release of pro-inflammatory cytokines by immune cells, thereby tipping the balance toward inflammation (Webster et al. 1997; Chrousos 1992). In yet another scenario, in individuals with under-responsive HPA axes – for example, in the wake of chronic childhood stress (as in sexual abuse) – the local release of pro-inflammatory cytokines may fail to adequately stimulate the HPA. As a consequence, cortisone levels are inadequately raised, and the inflammatory reaction in local tissues continues unopposed – representing the failure of a negative feedback loop (Priftis et al. 2009).

Stress can also inhibit the body's immune/inflammatory response through various mechanisms. For example, in a negative feedback loop, elevated levels of glucocorticoids and catecholamines have a wide range of anti-inflammatory and immunosuppressive effects (Chrousos 1995; Webster et al. 1997; Elenkov et al. 2008). Likewise, repeated or chronic stress results in elevated glucocorticoids and catecholamines, mediating a systemic shift in T-lymphocyte type 1 (Th1) versus T-lymphocyte type 2 (Th2) balance and a shift to humoral immunity (a predominantly Th2 response) (Chrousos 1995; Webster et al. 1997). The individual is

consequently less able to eliminate common viral infections and is more vulnerable to inflammatory illnesses, such as asthma and eczema, that can be triggered by viral load.

In addition, more recent data suggest that the health of the microbiota can also modulate the immune-inflammatory system and its response to stress (Bastiaanssen et al. 2020).

Inflammatory Markers Are Elevated in Patients with Functional Somatic Symptoms

A solid body of recent evidence documents increased levels of inflammatory markers in adult patients with chronic pain, fatigue, irritable bowel, musculoskeletal complaints, and other somatization syndromes (Groven et al. 2019; Hackshaw et al. 2019; Montague and Malcangio 2017; Cliff et al. 2019; Slade et al. 2011; Garcia et al. 2014; Hod et al. 2016; Tak et al. 2009; Nicol et al. 2015; Russell et al. 2016; Montoya et al. 2017; Backryd et al. 2017; Bashashati et al. 2017b; Bashashati et al. 2017a; Choghakhori et al. 2017; Tsigos et al. 2015). Likewise, elevated levels of CRP – in the low-grade inflammation range – are present in depression and are found with stress-related symptoms that are often comorbid with it (Raison and Miller 2013; Baumeister et al. 2014; Tabatabaeizadeh et al. 2018).

Studies with children are just beginning to emerge. In the TRAILS study, adolescents reporting non-neurological functional somatic symptoms showed elevated levels of CRP (Jonker et al. 2017). A study that tracked cytokine expression in adolescents diagnosed with infectious mononucleosis found a shift to a pro-inflammatory (defensive) pattern in those who developed symptoms of chronic fatigue versus those who recovered from the illness (Broderick et al. 2012). In the first author's own clinical setting, examination of CRP measures used in the hospital – which does not use the high-sensitivity measure used in research settings – found that as a group, children with FND and children with chronic functional pain displayed an upward shift in CRP levels, suggesting activation of the immune-inflammatory system (Kozłowska et al. 2018; McInnis et al. 2019).

Processes by Which the Immune-Inflammatory System May Activate the Stress System

We can hypothesize how the activation of the immune-inflammatory system might activate the stress system more generally, resulting in diverse patterns of activation and diverse patterns of symptoms. We know that immune-inflammatory signalling molecules produced by cells in the body communicate with the brain via the vagal nerve and via mechanisms in the brain-blood barrier (Karshikoff et al. 2017). Because of these communication routes, activation of immune-inflammatory cells in the body proper – by an infection, a minor injury, or a medical procedure – may also, in some children, lead to activation of glial cells in the brain – the brain’s immune-inflammatory cells.

Alternatively, psychological stress can activate glial cells in the brain in the absence of any physical stressor. We know that stress activates the HPA axis and that cortisol (a glucocorticoid) – the end product of the HPA axis – can promote and sensitize neuroinflammatory processes involving glial cells in the brain (Bellavance and Rivest 2014). In this way, psychological stress can function as an independent trigger factor, as a concurrent trigger factor (e.g., psychological fear about an existing illness or prospective medical procedure), or as a maintaining factor for immune-inflammatory system activation (see Chapter 12 about the mind level of operations).

The same glial cells, activated as above, may work together with interconnected neurons to mediate aberrant changes in the brain stress systems as well as in the HPA axis and autonomic nervous system; any or all of these systems, activated to some degree, may function to maintain symptoms of fatigue, pain, and so on. The activation of these systems may now be independent of the immune-inflammatory system activity that initially activated the glial cells – and act like a runaway horse with nothing holding it in. For a nice, simple discussion pertaining to the glial cells and neuroinflammatory processes, see Lurie (2018).

References Pertaining to Chronic/Complex Pain

See Online Supplement 1.3 (section pertaining to Chapter 9)

Chronic Fatigue Syndrome and Its Relationship to Other Functional Somatic Symptoms

The consensus diagnostic criteria for chronic fatigue syndrome (CFS) include the following: fatigue, sleep dysfunction, joint pain, cognitive dysfunction, headaches, post-exertional malaise, autonomic dysfunction, and symptoms thought to be associated with neuroendocrine manifestations and immune dysfunction (see diagnostic criteria in Cortes Rivera and colleagues [2019]). Having read Chapters 4 to 8, the reader will immediately notice that CFS is highly comorbid with – and overlaps with – the full array of other functional symptoms discussed in this book and with symptoms of anxiety and depression (Rowe 2019; Loades et al. 2019; Strand et al. 2019).

What is also clear is that (1) whether any particular child meets the consensus diagnostic criteria for CFS or not, the child will need treatment for the persisting fatigue and other comorbid symptoms, and (2) the course of treatment is not likely to be much affected by whether the child technically falls within criteria for CFS. For example, in the case of Rudi (Chapter 9) the biopsychosocial intervention would have been similar whether his pattern of symptoms met criteria for CFS or not. Likewise, the internet-based treatment for children and adolescents with chronic fatigue – FITNET – not only resolved fatigue symptoms but also resolved pain symptoms and increased the pain thresholds, even though pain was not formally targeted (Nijhof et al. 2013a). As we saw in Chapter 9, fatigue and pain can both be thought of as homeostatic alarms, and interventions that increase regulation within homeostatic systems and switch off one alarm should also switch off the other.

What is also clear – and what we highlight in Chapter 9 – is that the story of each child will be different and that when functional impairment is significant, each child and family should receive a comprehensive

assessment that identifies all the relevant physical and psychological contributors to the persisting fatigue and other comorbid symptoms. To facilitate healing, the treatment intervention may need to include targeted interventions that address all relevant areas of dysfunction, and on multiple system levels.

Interesting Themes Emerging from Research Pertaining to Chronic Fatigue Syndrome in Adults and Children

Chronic fatigue syndrome can be triggered by an infection or by other physical or psychological stress (Rasa et al. 2018; Chu et al. 2019).

Nice summary articles about the current state of knowledge include the following: Pedersen (2019), Komaroff (2019), Wyler (2019), Missailidis and colleagues (2019), and Cortes Rivera and colleagues (2019). For a broader review of studies about fatigue more generally, see Noakes and colleagues (2012).

In the medical literature, some interesting themes are emerging from brain-imaging studies of adults with CFS (no imaging studies have been conducted in children).

- In studies with experimental tasks – when patients have to muster neural resources to complete the task – patients show a decreased capacity for information processing; to complete the tasks, they need to recruit, compared to controls, a wider set of brain regions, including subcortical regions (for a review of studies, see Shan and colleagues' 2018 fMRI study). The wider recruitment of brain regions uses additional energy resources, thereby contributing (even further) to fatigue.

It is also interesting to consider these findings in the context of the brain in restorative versus defensive mode. Arnsten (2015) suggests that in the context of stress, high levels of noradrenalin impair prefrontal cortex function and increase coupling between the ventromedial prefrontal cortex and subcortical limbic areas. It

is therefore possible that the need to recruit subcortical areas to complete task conditions reflects a shift from restorative to defensive mode – that is, to the recruitment of subcortical areas involved in reflexive action and in baseline survival (Arnsten 2015). This would be consistent with CFS as a shut-down state (see discussion in Chapter 9).

Studies suggest that while adolescents with chronic fatigue also show difficulties with cognitive function – identified in a drop in IQ (Nijhof et al. 2016) – young children are less likely to have cognitive symptoms (Collin et al. 2015).

- In the resting state – when patients’ brains ought to be in restorative mode – patients show dysregulation within the default mode network (part of what we call brain stress systems). Specifically, patients show more irregular BOLD (blood oxygen level–dependent) signals in the posterior cingulate cortex – that is, more irregular activity rhythms – and lower connectivity between anterior and posterior emotion-processing regions within the default mode network (Shan et al. 2018). This dysregulation is likely to compromise the homeostatic processes that support energy renewal, tissue regeneration, and repair functions, thereby contributing to fatigue. Future studies will help clarify whether the brain states of patients with chronic fatigue reflect a shift away from network organization that prioritizes restoration and cortical networks, and toward network organization that prioritizes defence and subcortical networks – that is, a shift from restorative to defensive mode.
- A study looking at changes in brain structure in patients with chronic fatigue found increased grey matter volume in the insula and amygdala – areas involved in interoceptive signals and stress, and part of the brain’s emotion-processing regions – and reductions in white matter volume (Finkelmeyer et al. 2018). Taken together, these data suggest that chronic fatigue may also be associated with maladaptive brain-plasticity changes – including wear and tear – that contribute to maintenance of symptoms.

- A series of studies looking at the relationship between brain structure and autonomic dysfunction in patients with chronic fatigue (increased resting heart rate and blood pressure metrics) points toward dysregulated signalling between subcortical nuclei that are involved in energy regulation and arousal (see Barnden and colleagues [2016] for summary).
- Other data point toward neurophysiological changes associated with energy regulation, arousal, and immune-gene networks (Nguyen et al. 2019); both children and adults with chronic fatigue show dysregulation of the HPA axis and the autonomic system (see Chapter 6).
- Dysregulation of calcium-dependent homeostatic functions – potentially related to dysregulation in energy-regulation systems (including the steroid metabolism pathway involved in glucocorticoid production) – is an area of current research (Nguyen et al. 2017).
- Epigenetic studies in patients with chronic fatigue point toward epigenetic modifications to genes implicated in all of the following: the stress response; cellular energy and glucocorticoid metabolism; cellular restoration; DNA repair mechanisms; and proteins involved in immune signalling (Almenar-Perez et al. 2019; D’Agnelli et al. 2019; de Vega et al. 2017; de Vega and McGowan 2017; de Vega et al. 2014; Herrera et al. 2018; Landmark-Hoyvik et al. 2010; Morris et al. 2018; Trivedi et al. 2018).

As a homeostatic emotion, fatigue, like pain (Wiech 2016), should be subject to modulation by top-down mechanisms. In this context, in adults, studies of top-down cognitive interventions, such as cognitive-behavioural therapy (CBT) or mindfulness, have found the interventions to be helpful (Knoop et al. 2008; Rimes and Wingrove 2013; Nijhof et al. 2012, 2013b; Sollie et al. 2017; Janse et al. 2018).

In children and adolescents, top-down interventions have also been found to be helpful. Of note are studies of the efficacy of internet-based CBT (Nijhof et al. 2012, 2013a,b) and also a study showing that greater

perceived stress management skills related to a greater cortisol awakening response (\uparrow cortisol), which in turn related to less exertional malaise (Hall et al. 2014). These studies suggest that, akin to other functional somatic symptoms and syndromes, top-down cognitive factors play an important role in chronic fatigue. In children and adolescents, internet-based CBT led to recovery in the majority of children and adolescents (Nijhof et al. 2012, 2013a,b).

Impact of Western Living on the Immune-Inflammatory System

In this section we mention some of the common risk factors – or, from the perspective of the body, stressors – that can contribute to the activation of the immune-inflammatory system and that may contribute to the increasing prevalence of chronic inflammation in Western societies, which increases, in turn, the risk for functional somatic symptoms.

Sleep. Sleep deprivation, disrupted sleep, or a disrupted circadian cycle in relation to the earth's day-night rhythm is stressful to body systems and activates the immune-inflammatory system, as well as the HPA axis and sympathetic system (Vgontzas et al. 2002; Floam et al. 2015; Koch et al. 2017). When such sleep problems are chronic – as found in shift workers – then a state of low-grade inflammation can ensue, increasing the individual's risk for functional somatic symptoms, anxiety, depression, and a range of other physical health disorders (see Chapter 5 about the circadian clock).

Diet. An unhealthy diet – one that fails to maintain a healthy, diverse microbiota (the colony of microorganisms in the gut) – also contributes to activation of the immune-inflammatory system. A healthy microbiota population plays a key role in maintaining the integrity of the intestinal wall, maintaining low levels of immune-inflammatory cell activation within the gut, and preventing the proliferation of unwanted microbes there, and it also helps to modulate immune-inflammatory pathways and to regulate homeostatic immunity within the body as a whole (Zinocker and Lindseth 2018; Belkaid and Harrison 2017). When the diet is unhealthy – with too few fruits, vegetables, and fermented and unprocessed foods – it fails to

support a healthy microbiota population or causes the microbiota population to be stressed, and all of these functions are compromised. Both the microbiota and the gut's immune-inflammatory cells will consequently signal threat and modulate immune-inflammatory pathways in a pro-inflammatory direction (see Chapter 10 for more about the microbiota–gut–brain axis). For the association between a pro-inflammatory diet and depression, see Lucas and colleagues (2014).

Weight. Being significantly overweight, which involves an excess of white fat, is stressful for the body and contributes to low-grade inflammation. White fat functions both as an energy reservoir – white fat cells expand and contract with weight gain or weight loss – and as an endocrine organ that produces about 30% of the body's IL-6, a pro-inflammatory cytokine (Mohamed-Ali et al. 1997; Stefanaki et al. 2018). It also produces other pro-inflammatory signalling molecules (IL-1 β and TNF- α) involved in body regulation, including body weight, vascular function, and sex hormones such as oestrogen (Gomez-Hernandez et al. 2016). White fat contains macrophages, white cells, fibroblasts, cell progenitors, and endothelial cells, which secrete various other proteins involved in immune-inflammatory responses or tissue healing.

Sympathetic nerves innervate white fat; working together, the two systems play a central role in regulating the use of available energy stores. This ongoing interplay is especially important in responding to and modulating stress (Bartness et al. 2014). In healthy-weight individuals, white fat functions predominantly in restorative mode and preferentially secretes anti-inflammatory signalling molecules. By contrast, in obese individuals, white fat functions predominantly in defensive mode and preferentially secretes pro-inflammatory signalling molecules (Makki et al. 2013). Importantly, chronic activation of the stress system during development – involving increased secretion of cortisol and catecholamines, which interact with other regulators of energy expenditure (insulin and leptin) – promotes obesity later in life (Pervanidou and Chrousos 2011, 2012; Stefanaki et al. 2018). Starvation and being significantly underweight are also associated with low-grade inflammation (Solmi et al. 2015).

Psychological stress. Psychological stress is known to activate the immune-inflammatory system. For example, catastrophizing before a pain task results in greater levels of IL-6 (Edwards et al. 2008). The many potential brain-body mechanisms by which psychological stress may activate different components of the stress system, which then activate components of the immune-inflammatory system, are being investigated and progressively identified (Gianaros and Wager 2015; Frank et al. 2016). The ongoing psychological burden of sexual abuse may be one of the reasons why victims show long-term increases in plasma IL-6 and other inflammatory markers such as CRP and TNF- α (Baumeister et al. 2016), alongside long-term changes in HPA function and progressive activation of the sympathetic system. Dysregulation of the immune-inflammatory system – a pro-inflammatory state in adulthood – may be one of the mechanisms by which childhood trauma, maltreatment, and early-life stress confer higher risk for functional somatic symptoms and other physical and emotional disorders across the lifespan.

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