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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 11.1

The Brain Stress Systems: The Implicit Level of Brain Operations

Synonyms Used in the Neuroscience Literature to Denote the Brain Stress Systems

In clinical practice when talking to children – and throughout the book – we use the simple term *brain stress systems* to denote brain regions that underpin salience detection, arousal, pain, and emotional states. In the neuroscience literature, different scientists use different terms to discuss these brain regions. Examples of alternate terms include the following:

- The limbic brain (MacLean 1955)
- Emotional systems in the brain/ brain emotional systems (Panksepp 1992)
- The *stress system in the brain* (Chrousos 1992)
- The emotional brain (ledoux 1998)
- anterior cingulate cortex (ACC)/limbic motor cortex (Craig 2005)
- The brain as the central organ of stress and adaptation (McEwen 2009)
- Brain structures involved in stress regulation and the stress response (Pervanidou and Chrousos 2011)
- Emotion-processing regions/systems (Vuilleumier 2014)

- Emotion-processing alterations in (specific brain region) (Pick et al. 2018)
- Regions that mediate motivational and affective processing (Cojan et al. 2009)
- Mesolimbic system and emotional limbic brain (Baliki and Apkarian 2015)
- Affective processing or affective motivational processes (Blakemore et al. 2016)
- Mesolimbic system, corticolimbic system, or emotional brain (Vachon-Preseau et al. 2016)
- Neural networks influencing autonomic function (Dum et al. 2016)
- Allostatic-interoceptive system (Kleckner et al. 2017)

Whatever the name used, the common theme is that brain stress systems involve activation of brain systems that underpin salience detection, motivation, arousal, pain, and emotional states; that is, the terms refer to brain regions that are involved in processing motivationally salient information from the body and external environment, and in modulating the body's hormonal, autonomic, and motor response(s) to affective, motivational, or threat stimuli. The following paragraphs describe some of the key regions, anatomically defined:

- Areas involved in salience detection, awareness of body state, and homeostatic feelings (e.g., insula and the nucleus accumbens) and areas involved in limbic motor processing that work in tandem with the insula and that inform motivation and behaviour (e.g., the anterior cingulate) (Craig 2005)
- Areas that make up the default mode network (e.g.: medial frontal areas such as the medial prefrontal cortex [mPFC] and ACC; medial posterior areas such as the posterior cingulate cortex and precuneus; and temporo-parietal regions). While the default mode network's anterior regions are implicated in the processing of salience, its posterior regions are implicated in internal predictions, representations of self, judgment of self-agency in action, and consciousness (Vuilleumier 2014; Voon et al. 2010; Koch 2018).

- Areas that are part of the limbic/paralimbic system and are involved in modulating the body's hormonal, autonomic, and motor response(s) (e.g., ventromedial PFC [vmPFC], ACC, amygdala, cerebellar vermis, hypothalamus, and midbrain and brain stem nuclei mediating HPA-axis activation, autonomic arousal, brain arousal, and reflexive motor programs).
- Areas involved in top-down regulation capacities (e.g., dorsolateral PFC [dlPFC]), in memory, learning, and expectancy (e.g., hippocampus), and in modulating HPA-axis activity (e.g., hippocampus).

For the role of brain stress systems in energy regulation and allostasis, see Kleckner and colleagues (2017); in homeostatic emotions and autonomic system homeostasis, see Craig (2011) and Strigo and Craig (2016); in activating the HPA axis and sympathetic system, see Pervanidou and Chrousos (2018); in functional neurological disorder (FND), see Pick and colleagues (2018), Blakemore and colleagues (2016), Vuilleumier and Cojan (2011), and Vuilleumier (2014); in chronic pain, see Vachon-Preseu and colleagues (2016) and Navratilova and Porreca (2014); in irritable bowel syndrome, see Larsson and colleagues (2012); in chronic fatigue and interoceptive processing, see Finkelmeyer and colleagues (2018); and in brain processes associated with stress-system activation, see McEwen and colleagues (2015).

Different Terminologies in the Neuroscience Literature Pertaining to the Brain in a State of Defensive Mode Versus Restorative mode

Different scientists refer to the brain in defensive and restorative mode in different ways. A common theme that connects these ideas is that the neurophysiological systems in the human body function in a hierarchical – evolutionarily determined – order, with brain-body state changing in response to the changing environmental context.

Stephen Porges refers to these different neurophysiological states as *different neural platforms* (Porges and Furman 2011).

Bud Craig talks about the asymmetry in homeostatic activity and representation (Craig 2005; Strigo and Craig 2016), with a bicameral forebrain ‘such that sympathetic activity, negative affect, avoidance behaviour and energy expenditure are operationalized predominantly in the right forebrain while parasympathetic activity, positive affect, approach behaviour and energy nourishment are operationalized predominantly in the left forebrain, with opponent interactions between the two sides’ (Strigo and Craig 2016, p. 3).

Gennady Knyazev (2012) refers to *different functional domains that support different ways of solving adaptive challenges*.

And Amy Arnsten (2015, p. 1376) talks about ‘rapidly flipping the brain from reflective to reflexive control of behaviour’.

When talking to children, we just use the simple terms *restorative mode* and *defensive mode*.

Aberrant Changes in Neural Activation, Glial Activation, and Connectivity

A recurring theme across different functional somatic symptoms is that excessive activation of brain stress systems appears either (1) to *maintain* activation of motor-, sensory-, and pain- processing regions that are associated with and generate specific aberrant motor patterns, sensory symptoms, or complex/chronic pain, or (2) to *disrupt* motor-, sensory-, pain- processing in the brain, generating unusual motor patterns, sensory symptoms, or complex/chronic pain. For the basic science literature on how the excessive activation of brain systems affects patients with chronic pain, see reviews by Vachon-Preseau (2016) and Tanasescu et al. (2016), and study by Kaplan et al. (2019); with fibromyalgia, see Lopez-Sola et al. (2017), Albrecht et al. (2019), and Richard et al. (2019); with FND, see Vuilleumier (2014), Blakemore et al. (2016), and Pick et al. (2018); with tinnitus, see Chen et al. (2017) and Leaver et al. (2011); with functional cough, see Canning et al. (2014); and with chronic fatigue (the literature on which is just emerging), see Shan et al. (2018).

Inefficient Use of Energy Resources

Readers interested in energy regulation may like to explore Picard and colleagues' 2018 review of energy and stress adaptation and Bud Craig's and Timothy Noakes's work about pain and fatigue as homeostatic emotions that help regulate behaviour to ensure the protection of whole-body homeostasis (Craig 2003; Noakes 2012).

Plasticity Changes in the Brain and Epigenetics

Excellent materials are available on brain plasticity, in general (Fu and Zuo 2011; May 2011), and, more specifically, on brain-plasticity changes in children or adults with a history of maltreatment (Pal and Elbers 2018) or chronic pain (Kuner and Flor 2017; Richard et al. 2019). Recent articles also investigate changes in brain function and structure in FND and chronic fatigue – presumably as a result of plasticity changes (Bègue et al. 2019; Kozłowska et al. 2017; Shan et al. 2016; Shan et al. 2017). Studies regarding epigenetic processes in child and adult patients with chronic fatigue are yet to be done. For review articles about the epigenetic processes that shape the reactivity of the stress system and brain-plasticity changes in maltreated children and in children who have experienced chronic or cumulative stress, see Turecki and Meaney (2016) and McEwen and colleagues (2016). For references about epigenetic research in patients with functional somatic symptoms, see Chapter 4 and Online Supplement 4.3.

Stress-Related Wear and Tear

The origins of wear and tear date back to the 1960s. At the 'Man Under Stress' symposium, held 15–17 November 1963 at the University of California Medical Center in San Francisco, Hans Selye (see Online Supplement 1.2) gave the following definition: 'Stress is the rate of wear and tear in the human machinery that accompanies any vital activity and, in a sense, parallels the intensity of life' (Medical News January 4, 1964).

The impact of stress-related wear and tear on the brain is best documented in children who have been maltreated (Nelson et al. 2014; Blanco et al. 2015; Pal and Elbers 2018) and in adult patients with PTSD (Miller et al. 2018). An emerging literature is looking at structural brain changes – that may potentially reflect wear and tear in patients who have been ill for a long time – in adult patients with FND (Bègue et al. 2019) or chronic fatigue (Shan et al. 2016; Shan et al. 2017).

Predictive Coding

Interested readers may like to read Kleckner and colleagues (2017), who discuss how predictive representations help the brain to predict what will happen and to anticipate energy needs, to regulate body state, and to guide perception and action. They can also read about the application of the predictive-coding model to the understanding of chronic pain (Hechler et al. 2016; Wiech 2016), functional neurological symptoms (Voon et al. 2010; Edwards et al. 2012), and functional somatic symptoms more generally (Van den Bergh et al. 2017). A related literature in sports medicine – pertaining to fatigue – discusses athletes' use of conscious deceptions to influence the brain's predictive representations about energy use during sports events. By modifying the athletes' conscious representations of their remaining energy reserves (which are overestimated), these deceptions allow for further all-out exertion and allay the experience of fatigue (Noakes 2012; St Clair Gibson et al. 2003).

References Pertaining to the Metaphors for Explaining Changes in Brain Function to Children with Functional Somatic Symptoms

Overactive Brain Stress Systems Disrupt Motor Processing

Some of the easier-to-read studies include Voon and colleagues (2011) and Vuilleumier (2014), plus the summary of studies in Blakemore and colleagues (2016) and Pick and colleagues (2018).

Brain regions that lie at the intersection of emotion processing and motor processing include the ACC, supplementary motor area (SMA), basal ganglia, striatothalamocortical circuits, and cerebellum (vermis). For a summary of findings, see Blakemore and colleagues (2016); for discussion of the interaction between salience detection in the insula and limbic motor responses in the ACC, see Craig (2011); and for discussion of emotion and motor processing in the SMA, see Kozłowska and colleagues (2017).

Overactive Brain Stress Systems Disrupt Sensory-Processing Regions

The neuroscience research literature pertaining to patients with functional sensory symptoms – for example, patients with functional blindness, functional deafness, tinnitus, or loss of limb sensation – is more limited (for review, see Vuilleumier [2014, pp. 331–332]). For tinnitus, see Chen (2017) and Leaver (2011).

Studies and Publications Pertaining to Non-epileptic Seizures (NES)

The research domain of non-epileptic seizures is a current area of interest, research, and controversy. Currently, even the terminology for non-epileptic seizures remains a matter of ongoing disagreement. Some epileptologists, for example, use the term *psychogenic non-epileptic seizures* (the term used in DSM-5); others prefer *dissociative seizures* (ICD-11 classifies dissociative disorders with non-epileptic seizures); and yet others prefer *functional seizures* or even *dissociative attacks* or *dissociative convulsions* (the latter is from ICD-10). We use the simple term *non-epileptic seizures* in the book for several reasons:

- Children dislike the term *psychogenic* because many interpret this as meaning that they are *psycho* or mad. The use of *psychogenic* in clinical practice with children is a sure way to destroy the therapeutic relationship.

- We also dispute the term *psychogenic* because in some of our patients, their non-epileptic seizures are a manifestation of innate defence responses – for example, tonic immobility or collapsed immobility – which we share with other mammals, reptiles, and insects. If we tonic immobility is framed as psychogenic when manifesting in a child, it also has to be framed as psychogenic when manifesting in a beetle, lizard, a crocodile, a shark, or in the opossum. This idea is clearly ridiculous.
- We prefer a broader term – such as *non-epileptic seizures* – that also allows us to include non-epileptic seizures that take place in the context of pain, hyperventilation, and hypoxia related to stress-related closure of the airway (see Kozłowska and colleagues, [2018a,b]). Interestingly, in these sister articles, we used the term *psychogenic* non-epileptic seizures because we had experienced significant criticism when we used the term *non-epileptic seizures* without the ‘psychogenic’ from reviewers as part of the peer-review process.

There is also a conceptual split in literature. Some literature states that the mechanisms of non-epileptic seizures are not known (Sawchuk et al. 2019). By contrast, our own work with children, we have identified a number of innate-, stress-, or pain-related processes – whose mechanisms are already known – that appear to explain the presentations in various subset(s) of our child patients with non-epileptic seizures (Kozłowska et al. 2018a,b).

For reading materials pertaining to non-epileptic seizures, see the following:

Kozłowska, K., Chudleigh, C., Cruz, C., Lim, M., McClure, G., Savage, B., Shah, U., Cook, A., Scher, S., Carrive, P. & Gill, D. (2018a).

‘Psychogenic Non-epileptic Seizures in Children and Adolescents: Part I – Diagnostic Formulations’. *Clinical Child Psychology and Psychiatry*, 23, 140–159.

Kozłowska, K., Chudleigh, C., Cruz, C., Lim, M., McClure, G., Savage, B., Shah, U., Cook, A., Scher, S., Carrive, P. & Gill, D. (2018b).

‘Psychogenic Non-epileptic Seizures in Children and Adolescents: Part

II – Explanations to Families, Treatment, and Group Outcomes’.

Clinical Child Psychology and Psychiatry, 23, 160–176.

Kozłowska, K., Rampersad, R., Cruz, C., Shah, U., Chudleigh, C., Soe, S., Gill, D., Scher, S. & Carrive, P. (2017). ‘The Respiratory Control of Carbon Dioxide in Children and Adolescents Referred for Treatment of Psychogenic Non-epileptic Seizures’. *European Child & Adolescent Psychiatry*, 26, 1207–1217.

Perez, D. L., Dworetzky, B. A., Dickerson, B. C., Leung, L., Cohn, R., Baslet, G. & Silbersweig, D. A. (2015). ‘An Integrative Neurocircuit Perspective on Psychogenic Nonepileptic Seizures and Functional Movement Disorders: Neural Functional Unawareness’. *Clinical EEG and Neuroscience*, 46, 4–15.

Perez, D. L. & LaFrance, W. C., Jr. (2016). ‘Nonepileptic Seizures: An Updated Review’. *CNS Spectrums*, 21, 239–246.

Sawchuk, T., Asadi-Pooya, A. A., Myers, L., Valente, K. D., Restrepo, A. D., L. D. A., Homayoun, M., Bahrami, Z., Alessi, R., Paytan, A. A., Kochen, S., Taha, F., Lazar, L. M., Pick, S., Nicholson, T. R. & Buchhalter, J. (2019). ‘Clinical Characteristics of Psychogenic Nonepileptic Seizures Across the Lifespan: An International Retrospective Study’. *Epilepsy & Behavior*, 102, 106705.

Synonyms for Brain Regions Involved in Processing Pain

Pain-processing regions are also known as the *pain matrix* or *pain network* (Singer et al. 2004), *brain maps for pain* (Doidge 2015), or as *neural representations of pain* or *neurotags* (Butler and Moseley 2013; Wallwork et al. 2016). When talking to children, we use the simple term *pain maps in the brain*.

Historically, the pain matrix was divided into (1) the sensory-discriminative component (lateral thalamus and primary and secondary somatosensory cortex), which was thought to process pain intensity, localization, and quality, and (2) the affective component (anterior insula, ACC, vmPFC), which was thought to process the affective aspects of pain (i.e., how salient and distressing it was to the individual).

An alternate way to look at pain-processing regions is to consider them as a fluid system made up of a set of interacting networks, or matrices. These networks accomplish processing at different levels: baseline processing in the periaqueductal grey nucleus (PAG) in the brainstem and in the thalamus (which receives input from spinothalamic afferents that run in the spinal cord); processing in the insulae and ACC that allows for the subjective experience of pain and for motor response; and higher-order processing in the PFC. The PFC network enables (1) the subjective experience of pain while viewing the pain of another, (2) the pain-relieving effects derived from placebo, and (3) changes in pain perception as a function of strong beliefs.

See Craig (2003) for a summary of how spinal afferents are represented in the insulae, Garcia-Larrea and colleagues (2013) for a detailed summary of the different levels of processing, and Wiech (2016) for brain regions involved in cognitive processes that modulate pain perception.

Overactive Brain Stress Systems Maintain and Amplify Chronic Pain

An easy-to-read article pertaining to the role of the brain stress systems in chronic pain is by Etienne Vachon-Preseau and colleagues (2016), entitled ‘The Emotional Brain as a Predictor and Amplifier of Chronic Pain’.

In addition, Kragel and colleagues (2018, Figure 4, p. 287) provide a nice visual representation showing the overlap between brain stress systems (regions progressing negative emotion) and pain-processing regions.

Simons and colleagues (2014) examine the increased connectivity between brain stress systems (amygdala) and pain-processing regions in a study of children with chronic pain. Malinen and colleagues (2010) show increased resting-state activation of brain stress systems (the insula and ACC) in patients with chronic pain. Napadow and colleagues (2010) demonstrate that increased resting-state connectivity between attention-processing regions and brain stress systems (default mode network and the insula, which are involved in salience detection and pain processing) correlates with pain intensity in fibromyalgia syndrome. Baliki and

colleagues (2014) show increased activation of brain stress systems (medial PFC of the default mode network) and increased connectivity between the medial PFC and the insula across pain conditions. Lee and colleagues (2018) show increased activity in brain stress systems within the default mode network – activated by catastrophizing statements – and a correlation between activation of brain stress systems (the posterior cingulate cortex) and clinical pain severity.

Overactive Brain Stress Systems Maintain and Amplify Fatigue

Unlike research pertaining to chronic/complex pain, research about other homeostatic emotions – for example, fatigue and fatigue-processing regions in the brain – is still in its infancy. Nonetheless, fatigue-processing regions overlap with those that process pain and body state more generally (Boksem and Tops 2008). In addition, a study by Hilty and colleagues (2011) found that the increased perception of effort during exercise and the associated decisions to terminate motor tasks because of fatigue appear to involve activation of brain stress systems (the insula and ACC). In another study, the same group showed increased communication between the mid anterior insular (part of the brain stress systems) and the motor cortex at the end the exercise, when subjects' fatigue was the greatest. In other words, the communication between those regions increased with fatigue (Hilty et al. 2011). For a nice review of the literature, see Noakes and colleagues (2012).

In this context we have hypothesized – in our fatigue metaphor for children – that akin to chronic/complex pain, activated brain stress systems can maintain and amplify the subjective experience of persisting fatigue.

Problems with Memory and Concentration

For the impact of stress on cognitive function, readers may want to read Arnsten (2015), Oei and colleagues (2010), and Kane and Engle (2002); for a discussion of high glucocorticoid levels and memory, Tatomir and colleagues (2014); for the role of other neurochemicals (endogenous

opioids, endogenous cannabinoids, and other anaesthetic neurochemicals) in stress-related disruption of brain functions, Lanius and colleagues (2014); and for the link between exercise and memory, Suwabe and colleagues (2018) and Roig and colleagues (2013). For references pertaining to sleep, see Chapter 5.

For problems with cognitive function in FND, see Kozłowska and colleagues (2015); in chronic pain, Weiss and colleagues (2018); and in chronic fatigue, Nijhof and colleagues (2016) and Collin and colleagues (2015).

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