

Online Supplement 4.3

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

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Epigenetics and Functional Somatic Symptoms

Changes in stress-system function are likely to involve, among other things, epigenetic changes and changes in neural and tissue plasticity (Turecki and Meaney 2016; McEwen 2013; McEwen et al. 2015). This online supplement provides the reader with additional information about epigenetic mechanisms and with references pertaining to epigenetics and functional disorders. We note however that the field of epigenetics is a fast-growing area of research. In this context, by the time this book is published – or by the time the reader reads this book – the number of available articles will have increased significantly. Nonetheless, this supplement gives readers a starting point.

Epigenetic Modifications and Pathways

An important current goal of contemporary stress research is to understand ‘the mechanisms by which environmental factors (whether experiential, metabolic, microbiological or pharmacologic) interact with the genome to influence brain development and to produce diverse forms of neural plasticity [and changes in the function of the brain-body stress-system] over

the lifetime’ (Hyman 2009, p. 241; Denk and McMahon 2017). Epigenetic research is central here.

As discussed in Chapter 4, epigenetic processes are those that influence gene expression with no modification to the genetic code itself, typically by increasing or decreasing how the gene is expressed. In other words, epigenetic processes are ones that affect the workings of DNA – that is, gene expression or gene activity in protein transcription – by making changes to structures around the DNA (see Jawaid et al. [2018] for a summary). The *epi* in epigenetics means *around*.

There are three major epigenetic mechanisms that take place at different points of gene expression and protein synthesis (see Bellanti [2020] for a review and for nice visual schematic representations). These epigenetic mechanisms include the following: ‘(1) DNA methylation, (2) posttranslational modifications of histone proteins through acetylation and methylation, and (3) RNA-mediated gene silencing by microRNA (miRNA)’ (Bellanti 2020, p. 379).

In *DNA methylation* the attachment of a methyl group suppresses gene expression by attaching to the DNA. In *histone modification* the attachment of different chemical groups (such as methyl, phosphate, or acetyl groups) to histone proteins, which package DNA, alter gene expression. Histone modification either activates or deactivates gene expression. Finally, RNA (ribonucleic acid) is a nucleic acid present in all living cells. Its key function is to act as a messenger and to carry instructions from DNA for controlling and modulating the synthesis of proteins. *RNA-mediated gene silencing* involves microRNA (miRNA), a small non-RNA molecule that suppresses gene expression by attaching to messenger RNA (mRNA), thereby blocking the transmission of information for protein synthesis.

Some of epigenetic changes may continue to be passed on through all of the cell’s subsequent divisions, and some may be passed down across generations. Nonetheless, despite the molecular changes around the DNA, the DNA itself remains the same.

Epigenetic modifications can affect the functioning of the child’s stress system via numerous pathways (see Yehuda et al. [2016] and Jawaid et al. [2018] for research references).

Epigenetic modifications in parental sexual reproductive cells – sperm in males and egg cells in females – enable stress-related epigenetic changes that have occurred during the life of a parent or even the life of a grandparent to be passed down across generations.

Epigenetic modifications can occur because of stress exposure when the child is still a foetus in utero, also known as *in utero*, *foetal*, or *perinatal* programming (see Online Supplement 4.2).

Epigenetic modifications can occur because of stress exposure when the child is older as a product of inadequate caregiving in the postnatal period, adverse childhood experiences, or adverse experiences during adulthood.

Thus, adverse life events at many different time points, or combinations thereof, can affect gene expression and the reactivity of the child's stress system. For example, in the offspring of Holocaust survivors, epigenetic changes that correlated with parental epigenetic changes were different from those that correlated with a history of physical or sexual abuse in the offspring's own lifetime (Yehuda et al. 2016).

Epigenetic Changes Pertaining to the Stress System and to Functional Somatic Symptoms/Disorders

At the time of writing, many animal and human studies had already identified epigenetic changes on the glucocorticoid receptor gene in response to early-life stress in utero and during the child's early development (Turecki and Meaney 2016; Diez et al. 2020).

In addition, intergenerational transmission of epigenetic changes from human parents – who had been exposed to stress – to their offspring were beginning to be documented (Perroud et al. 2014; Yehuda et al. 2016).

Most relevant for us, a handful of studies have documented epigenetic changes in patients with functional somatic symptoms. With both the science and the language in a state of ongoing change, researchers have been using various terms and concepts to describe the relevant phenomena:

In research on functional neurological disorder (FND), using a trauma-related stress–diathesis model, Diez and colleagues (2020) have described

the changes as involving a complex interaction among environmental, genetic, and epigenetic factors.

In research on chronic fatigue, Almenar-Perez and colleagues (2019, p. 691) use the expression *gene expression dysregulation*, and Nguyen and colleagues (2019, p. 82) use *deregulated immune gene networks*.

Also in research on chronic fatigue, and in contrast to their 2019 study (see previous paragraph), Almenar-Perez and colleagues (2020, p. 1) refer to *epigenetic and neuroimmune dysregulated pathways*.

Currently, research pertaining to epigenetic processes is being conducted with patients with fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, FND, and other chronic pain more generally. The changes identified include those to genes implicated in the following: the stress response; cellular energy and glucocorticoid metabolism; cellular restoration; DNA repair mechanisms; proteins involved in immune signalling or immune system activation; proteins involved in gut-barrier functions; and neuron morphogenesis and generation, synaptic transmission, and locomotory behaviour/motility (de Vega et al. 2014, 2017; Denk et al. 2014; Enck et al. 2016; Burri et al. 2016; Ciampi de Andrade et al. 2017; Apazoglou et al. 2018; Herrera et al. 2018; Trivedi et al. 2018; Diez et al. 2020). The emerging themes from this body of work are that stress-related epigenetic changes appear to play an important role across functional presentations and that mechanisms that were previously unseen are now coming to light.

Epigenetic References by Topic

For information about epigenetic modifications that can affect the functioning of the child's stress system via various pathways, see research references in Yehuda and colleagues (2016) and Jawaid and colleagues (2018):

Jawaid, A., Roszkowski, M. & Mansuy, I. M. (2018). 'Transgenerational Epigenetics of Traumatic Stress'. *Progress in Molecular Biology and Translational Science*, 158, 273–298.

Yehuda, R., Cai, G., Golier, J. A., Sarapas, C., Galea, S., Ising, M., Rein, T., Schmeidler, J., Müller-Myhsok, B., Holsboer, F. & Buxbaum, J. D. (2009). 'Gene Expression Patterns Associated with Posttraumatic Stress Disorder Following Exposure to the World Trade Center Attacks'. *Biological Psychiatry*, 66, 708–711.

For research articles pertaining to epigenetic changes in patients with fibromyalgia:

D'Agnelli, S., Arendt-Nielsen, L., Gerra, M. C., Zatorri, K., Boggiani, L., Baciarello, M. & Bignami, E. (2019). 'Fibromyalgia: Genetics and Epigenetics Insights May Provide the Basis for the Development of Diagnostic Biomarkers'. *Molecular Pain*, 15, 1744806918819944.

For research articles pertaining to epigenetic changes in patients with irritable bowel syndrome:

Chong, P. P., Chin, V. K., Looi, C. Y., Wong, W. F., Madhavan, P. & Yong, V. C. (2019). 'The Microbiome and Irritable Bowel Syndrome – a Review on the Pathophysiology, Current Research and Future Therapy'. *Frontiers in Microbiology*, 10, 1136.

Enck, P., Aziz, Q., Barbara, G., Farmer, A. D., Fukudo, S., Mayer, E. A., Niesler, B., Quigley, E. M., Rajilic-Stojanovic, M., Schemann, M., Schwille-Kiuntke, J., Simren, M., Zipfel, S. & Spiller, R. C. (2016). 'Irritable Bowel Syndrome'. *Nature Reviews. Disease Primers*, 2, 16014.

For research articles pertaining to epigenetic changes in patients with chronic fatigue syndrome:

Almenar-Perez, E., Ovejero, T., Sanchez-Fito, T., Espejo, J. A., Nathanson, L. & Oltra, E. (2019). 'Epigenetic Components of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Uncover Potential Transposable Element Activation'. *Clinical Therapeutics*, 41, 675–698.

Almenar-Perez, E., Sarria, L., Nathanson, L. & Oltra, E. (2020). 'Assessing Diagnostic Value of MicroRNAs from Peripheral Blood Mononuclear Cells and Extracellular Vesicles in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome'. *Scientific Reports*, 10, 2064.

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- Herrera, S., De Vega, W. C., Ashbrook, D., Vernon, S. D. & McGowan, P. O. (2018). ‘Genome-Epigenome Interactions Associated with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome’. *Epigenetics*, 13, 1174–1190.
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For research articles pertaining to epigenetic changes in patients with FND:

- Apazoglou, K., Adouan, W., Aubry, J. M., Dayer, A. & Aybek, S. (2018). ‘Increased Methylation of the Oxytocin Receptor Gene in Motor Functional Neurological Disorder: A Preliminary Study’. *Journal of Neurology, Neurosurgery, and Psychiatry*, 89, 552–554.

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