

## Online Supplement 6.1

**Open Access** This content is licensed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits any noncommercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence and indicate if you modified the licensed material. You do not have permission under this license to share adapted material derived from this book or parts of it.

The images or other third-party material in this book are included in the book's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the book's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder.



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

Kasia Kozłowska, Stephen Scher, and Helene Helgeland

## Online Supplement 6.1

### The Autonomic Nervous System

In this supplement to Chapter 6, we provide the reader with a table summarizing studies that document stress-system activation or dysregulation in children diagnosed with different functional disorders. We provide additional information about Stephen Porges's polyvagal theory and our reasons for utilizing a functional rather than anatomical model of the autonomic system, and also about postural orthostatic tachycardia syndrome (POTS).

### **Autonomic Nervous System Dysregulation in Children with Functional Somatic Symptoms and Disorders**

Table OS 6.1.1. summarizes the results of studies that have found autonomic nervous system activation or dysregulation in children, including adolescents, with functional somatic symptoms or disorders.

| Table OS 6.1.1                                                                                                                                                                                |                                                                                                                                                                                                                                   |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| Studies Documenting Autonomic System Activation or Dysregulation in Children Diagnosed with Different Functional Disorders                                                                    |                                                                                                                                                                                                                                   |  |
| Functional disorder (symptom studied)                                                                                                                                                         | Biological marker                                                                                                                                                                                                                 |  |
| <b>Recurrent abdominal pain</b> (pupil size at rest, during a cold pressor task, and during 15-minute recovery)<br>Rubin et al. (1967)                                                        | Compromised recovery: less decrement in pupil size† (constriction mediated by the parasympathetic system) during recovery                                                                                                         |  |
| <b>Recurrent abdominal pain</b> (pupil size at rest, during a cold pressor task, and during recovery)<br>Apley et al. (1971)                                                                  | Compromised recovery: unstable pupil recovery pattern, characterized by recurring dilation and constriction, and pupil sizes that did not return to resting-level size, suggesting a sympathetic dominance                        |  |
| <b>Recurrent abdominal pain</b> (pupil size at rest and following phenylephrine drop in right eye [dilates pupil by stimulating $\alpha$ -adrenergic receptors])<br>Battistella et al. (1992) | Dilatation was greater (presumed increased reactivity of post-synaptic $\alpha 1$ -adrenergic receptors, which are usually activated by sympathetic nerves and which cause contraction of smooth muscle mediating pupil dilation) |  |
| <b>Chronic fatigue</b><br>Wyller et al. (2007)                                                                                                                                                | Sympathetic predominance (increase in LF/HF ratio) of cardiovascular regulation during very mild orthostatic stress                                                                                                               |  |
| <b>Chronic fatigue syndrome</b> (measured during sleep)<br>Boneva et al. (2007)                                                                                                               | Sympathetic predominance and neuroendocrine alterations:<br>Heart rate ( $\uparrow$ )<br>Heart rate variability ( $\downarrow$ )<br>Plasma noradrenalin ( $\uparrow$ )<br>Lower plasma aldosterone                                |  |

|                                                                                              |                                                                                                                                                                                       |
|----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Chronic fatigue syndrome</b> (in the resting condition)<br>Wyller et al. (2008)           | Heart rate ( $\uparrow$ )<br>Diastolic blood pressure ( $\uparrow$ )<br>Plasma noradrenalin ( $\uparrow$ )<br>Mean blood pressure ( $\uparrow$ )<br>Plasma epinephrine ( $\uparrow$ ) |
| <b>Recurrent abdominal pain</b> (resting state of cold pressor test)<br>Dufton et al. (2011) | Heart rate ( $\uparrow$ ) during resting state<br>Heart rate ( $\uparrow$ ) during cold pressor test                                                                                  |
| <b>Chronic fatigue syndrome</b><br>Wyller et al. (2011)                                      | Systolic blood pressure variability ( $\downarrow$ ) during orthostatic stress<br>A sympathetic predominance of baroreflex heart rate control during orthostatic stress               |
| <b>Recurrent abdominal pain</b> (resting state)<br>Sowder et al. (2010)                      | LF/HF ratio ( $\uparrow$ ) (~ sympatho-vagal balance)                                                                                                                                 |
| <b>Recurrent abdominal pain</b> (24-hour ECG)<br>Jarrett et al. (2012)                       | No differences in vagal function (HF power) and LF/HF ratio (~ sympatho-vagal balance) between patients and healthy controls                                                          |
| <b>Chronic fatigue syndrome</b><br>Sulheim et al. (2012)                                     | Heart rate ( $\uparrow$ )<br>Blood pressure ( $\uparrow$ )<br>Total peripheral resistance ( $\uparrow$ )<br>LF/HF ratio ( $\uparrow$ )<br>(~ sympatho-vagal balance)                  |
| <b>Chronic pain</b><br>Tsao et al. (2012)                                                    | Heart rate ( $\uparrow$ ) at baseline (trend level)<br>Heart rate ( $\uparrow$ ) following a cold pain task (trend level)                                                             |
| <b>Chronic pain</b><br>Evans et al. (2013)                                                   | Heart rate variability ( $\downarrow$ )                                                                                                                                               |

|                                                                                                |                                                                                                                                                                                                                                                 |
|------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                | Unable to further lower HRV during an acute experimental pain task (loss of capacity to respond to stress)                                                                                                                                      |
| <b>Chronic fatigue syndrome</b><br>Wyller et al. (2014)                                        | Heart rate (↑)<br>Diastolic blood pressure (↑)<br>Mean arterial blood pressure (↑)<br>Heart stroke index (↓)<br>Heart rate variability (↓) in the resting condition<br>HRV indices of sympathetic predominance to an imaginary upright position |
| <b>Irritable bowel syndrome (IBS)</b><br>Stern et al. (2014)                                   | Heart rate variability (↓)<br>Sympathetic dominance<br>Poor vagal tone at rest                                                                                                                                                                  |
| <b>Mixed functional neurological disorder (FND)</b><br>Kozłowska et al. (2015)                 | High heart rate (↑)<br>Heart rate variability (↓)                                                                                                                                                                                               |
| <b>Non-epileptic seizures (NES)</b><br>Kozłowska et al. (2017)                                 | Heart rate (↑)<br>Respiratory rate (↑)<br>Arterial carbon dioxide (↓)                                                                                                                                                                           |
| <b>Chronic pain</b> (8-year follow-up of children with abdominal pain)<br>Walker et al. (2017) | Heart rate variability (↓) in young women with ongoing pain<br>Heart rate variability (↓) in young men with ongoing or remitted pain                                                                                                            |
| <b>Chronic sleep problems</b><br>Alkon et al. (2017)                                           | Heart rate variability (↓) at rest<br>Inability to withdraw vagal/parasympathetic activity (decrease HRV) during task conditions<br>Inability to activate sympathetic system (decrease PEP)* during task conditions                             |

|                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Mixed functional somatic symptoms</b><br>Chudleigh et al. (2018)                                                                                                                                                                                                                                                                                                                                                           | Heart rate (↑)<br>Heart rate variability (↓)<br>Failure to increase HRV with a slow breathing task (vs. controls who showed a robust increase in HRV)                                                                                                                    |
| <b>Chronic/complex pain</b> (resting state)<br>McInnis et al. (2019)                                                                                                                                                                                                                                                                                                                                                          | Heart rate (↑)<br>Skin conductance (↑)<br>Heart rate variability (↓)                                                                                                                                                                                                     |
| <b>Chronic fatigue</b> (6 months post–Epstein Barr virus infection)<br>Kristiansen et al. (2019)                                                                                                                                                                                                                                                                                                                              | Increased sympathetic activity reflected by (↑) plasma adrenalin and (↑) plasma noradrenalin<br>Attenuated LF/HF-response to controlled breathing (less parasympathetic function)                                                                                        |
| <b>Chronic fatigue syndrome</b><br>Nguyen et al. (2019)                                                                                                                                                                                                                                                                                                                                                                       | Increased plasma noradrenalin (hypothesized to help maintain immune homeostasis) as part of neuroendocrine-immune interactions<br>Some alteration in gene-immune pathways (expression of genes involved in encoding proteins that function in adaptive immune responses) |
| <p>* Pupil constriction involves parasympathetic activation, and pupil dilatation involves sympathetic activation.</p> <p>† The pre-ejection period is the time measured in milliseconds between ventricular contraction and the opening of the aortic valve, an indirect measure of sympathetic system activation.</p> <p>HF, high frequency; HRV, heart rate variability; LF, low frequency; PEP = pre-ejection period.</p> |                                                                                                                                                                                                                                                                          |

## Stephen Porges and Polyvagal Theory

As noted in Chapter 6, it is through the seminal work of Stephen Porges (2011) that we are now able to differentiate between the restorative and defensive components of the parasympathetic nervous system. Porges, refers to (1) the *restorative parasympathetic* as the *myelinated vagus* or *smart vagus*, and as the part of the vagus whose *fibres originate in the nucleus ambiguus* (~ restorative parasympathetic), and (2) the *defensive parasympathetic* as the *unmyelinated vagus* or *vegetative vagus*, and as the part of the vagus whose *fibres originate in the dorsal motor nucleus*.

Throughout the book, we have kept our descriptions of the autonomic nervous system entirely functional to sidestep controversies about anatomy (Grossman and Taylor 2007; Grossman 2016) and to include the components of the parasympathetic system that do not run in the vagus nerve or that do not originate in the nucleus ambiguus or the dorsal motor nucleus. For example, parasympathetic fibres also run in cranial nerves – oculomotor, facial, and glossopharyngeal – other than the vagus and in nerves in the pelvis (e.g., pelvic splanchnic nerves) that innervate the uterus, bladder, rectum, and sex organs. These pelvic nerves have preganglionic cell bodies that originate from the lateral horn (lateral column of cell bodies) of the sacral segments of S2 to S4 (not from brain stem nuclei such as the nucleus ambiguus and dorsal motor nucleus).

Both the cranial and sacral/pelvic parasympathetic nerves are involved in the production of functional somatic symptoms.

For more on Stephen Porges's seminal contribution to our understanding of the parasympathetic system in a historical context, see Online Supplement 1.2.

## Postural Orthostatic Tachycardia Syndrome (POTS)

As noted in Chapter 6, orthostatic intolerance/postural orthostatic tachycardia syndrome (POTS) is a common functional presentation in children and often presents alongside other functional somatic symptoms.

In the daily clinical practice at the first author's (KK's) hospital, the POTS diagnosis is used when, on the Standing Orthostatic Tolerance Test (SOTT), children (1) show an increase of  $\geq 40$  heart beats per minute within ten minutes of assuming an upright posture (2) experience no drop in blood pressure and (3) experience or demonstrate any of the following symptoms or signs (regardless of time frame): heart palpitations, chest discomfort, shortness of breath, tremulousness (shaking), light-headedness, nausea, and syncope (fainting).

Some adult criteria for POTS require a duration  $\geq 6$  months. When the symptoms are secondary to deconditioning or prolonged bed rest, some clinicians suggest that the diagnosis should be excluded (Raj 2013; Garland et al. 2015), but other clinicians disagree (Kizilbash et al. 2014; Wells et al. 2018; Stewart 2012). In this context, some clinicians would use the diagnosis of *orthostatic intolerance* in these circumstances because POTS technically requires that, on the SOTT, (1) to (3) persist for at least six months. Nevertheless, in clinical paediatrics, the terms *orthostatic intolerance* and *POTS* are often used interchangeably. Terminological differences notwithstanding, in research settings the duration of the symptoms would need to be carefully documented.

For discussions of consensus criteria, the reader might find that Freeman and colleagues (2011) and Kizilbash and colleagues (2012) are especially useful.

## References

- Alkon, A., Boyce, W. T., Neilands, T. B. & Eskenazi, B. (2017). 'Children's Autonomic Nervous System Reactivity Moderates the Relations Between Family Adversity and Sleep Problems in Latino 5-Year Olds in the Chamacos Study'. *Frontiers in Public Health*, 5, 155.
- Apley, J., Haslam, D. R. & Tulloh, C. G. (1971). 'Pupillary Reaction in Children with Recurrent Abdominal Pain'. *Archives of Disease in Childhood*, 46, 337–340.



- Battistella, P. A., Carra, S., Zaninotto, M., Ruffilli, R. & Da Dalt, L. (1992). ‘Pupillary Reactivity in Children with Recurrent Abdominal Pain’. *Headache*, 32, 105–107.
- Boneva, R. S., Decker, M. J., Maloney, E. M., Lin, J. M., Jones, J. F., Helgason, H. G., Heim, C. M., Rye, D. B. & Reeves, W. C. (2007). ‘Higher Heart Rate and Reduced Heart Rate Variability Persist During Sleep in Chronic Fatigue Syndrome: A Population-Based Study’. *Autonomic Neuroscience*, 137, 94–101.
- Chudleigh, C., Savage, B., Cruz, C., Lim, M., McClure, G., Palmer, D. M., Spooner, C. J. & Kozłowska, K. (2019). ‘Use of Respiratory Rates and Heart Rate Variability in the Assessment and Treatment of Children and Adolescents with Functional Somatic Symptoms’. *Clinical Child Psychology and Psychiatry*, 24, 29–39.
- Dufton, L. M., Dunn, M. J., Slosky, L. S. & Compas, B. E. (2011). ‘Self-Reported and Laboratory-Based Responses to Stress in Children with Recurrent Pain and Anxiety’. *Journal of Pediatric Psychology*, 36, 95–105.
- Evans, S., Seidman, L. C., Tsao, J. C., Lung, K. C., Zeltzer, L. K. & Naliboff, B. D. (2013). ‘Heart Rate Variability as a Biomarker for Autonomic Nervous System Response Differences between Children with Chronic Pain and Healthy Control Children’. *Journal of Pain Research*, 6, 449–457.
- Freeman, R., Wieling, W., Axelrod, F. B., Benditt, D. G., Benarroch, E., Biaggioni, I., Cheshire, W. P., Chelmsky, T., Cortelli, P., Gibbons, C. H., Goldstein, D. S., Hainsworth, R., Hilz, M. J., Jacob, G., Kaufmann, H., Jordan, J., Lipsitz, L. A., Levine, B. D., Low, P. A., Mathias, C., Raj, S. R., Robertson, D., Sandroni, P., Schatz, I., Schondorff, R., Stewart, J. M. & Van Dijk, J. G. (2011). ‘Consensus Statement on the Definition of Orthostatic Hypotension, Neurally Mediated Syncope and the Postural Tachycardia Syndrome’. *Clinical Autonomic Research*, 21, 69–72.
- Garland, E. M., Celedonio, J. E. & Raj, S. R. (2015). ‘Postural Tachycardia Syndrome: Beyond Orthostatic Intolerance’. *Current Neurology and Neuroscience Reports*, 15, 60.
- Grossman, P. (2016). *After 20 Years of “Polyvagal” Hypotheses, Is There Any Direct Evidence for the First 3 Premises That Form the Foundation of the*

*Polyvagal Conjectures?*

[https://www.researchgate.net/post/After\\_20\\_years\\_of\\_polyvagal\\_hypotheses\\_is\\_there\\_any\\_direct\\_evidence\\_for\\_the\\_first\\_3\\_premises\\_that\\_form\\_the\\_foundation\\_of\\_the\\_polyvagal\\_conjectures](https://www.researchgate.net/post/After_20_years_of_polyvagal_hypotheses_is_there_any_direct_evidence_for_the_first_3_premises_that_form_the_foundation_of_the_polyvagal_conjectures)

- Grossman, P. & Taylor, E. W. (2007). 'Toward Understanding Respiratory Sinus Arrhythmia: Relations to Cardiac Vagal Tone, Evolution and Biobehavioral Functions'. *Biological Psychology*, 74, 263–285.
- Jarrett, M., Heitkemper, M., Czyzewski, D., Zeltzer, L. & Shulman, R. J. (2012). 'Autonomic Nervous System Function in Young Children with Functional Abdominal Pain or Irritable Bowel Syndrome'. *Journal of Pain*, 13, 477–484.
- Kizilbash, S. J., Ahrens, S. P., Bruce, B. K., Chelimsky, G., Driscoll, S. W., Harbeck-Weber, C., Lloyd, R. M., Mack, K. J., Nelson, D. E., Ninis, N., Pianosi, P. T., Stewart, J. M., Weiss, K. E. & Fischer, P. R. (2014). 'Adolescent Fatigue, POTS, and Recovery: A Guide for Clinicians'. *Current Problems in Pediatric and Adolescent Health Care*, 44, 108–133.
- Kozłowska, K., Palmer, D. M., Brown, K. J., McLean, L., Scher, S., Gevirtz, R., Chudleigh, C. & Williams, L. M. (2015). 'Reduction of Autonomic Regulation in Children and Adolescents with Conversion Disorders'. *Psychosomatic Medicine*, 77, 356–370.
- 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 and Adolescent Psychiatry*, 26, 1207–1217.
- Kristiansen, M. S., Stabursvik, J., O'Leary, E. C., Pedersen, M., Asprusten, T. T., Leegaard, T., Osnes, L. T., Tjade, T., Skovlund, E., Godang, K. & Wyller, V. B. B. (2019). 'Clinical Symptoms and Markers of Disease Mechanisms in Adolescent Chronic Fatigue Following Epstein-Barr Virus Infection: An Exploratory Cross-sectional Study'. *Brain, Behavior, and Immunity*, 80, 551–563.
- McInnis, P. M., Braund, T. A., Chua, Z. K. & Kozłowska, K. (2020). 'Stress-System Activation in Children with Chronic Pain: A Focus for Clinical Intervention'. *Clinical Child Psychology and Psychiatry*, 25, 78–97.

- Nguyen, C. B., Kumar, S., Zucknick, M., Kristensen, V. N., Gjerstad, J., Nilsen, H. & Wyller, V. B. (2019). 'Associations Between Clinical Symptoms, Plasma Norepinephrine and Deregulated Immune Gene Networks in Subgroups of Adolescent with Chronic Fatigue Syndrome'. *Brain, Behavior, and Immunity*, 76, 82–96.
- Porges, S. W. (2011). *The Polyvagal Theory: Neurophysiological Foundations of Emotions, Attachment, Communication, and Self-Regulation*, New York, Norton.
- Raj, S. R. (2013). 'Postural Tachycardia Syndrome (POTS)'. *Circulation*, 127, 2336–2342.
- Rubin, L. S., Barbero, G. J. & Sibinga, M. S. (1967). 'Pupillary Reactivity in Children with Recurrent Abdominal Pain'. *Psychosomatic Medicine*, 29, 111–120.
- Sowder, E., Gevirtz, R., Shapiro, W. & Ebert, C. (2010). 'Restoration of Vagal Tone: A Possible Mechanism for Functional Abdominal Pain'. *Applied Psychophysiology and Biofeedback*, 35, 199–206.
- Stern, M. J., Guiles, R. A. & Gevirtz, R. (2014). 'HRV Biofeedback for Pediatric Irritable Bowel Syndrome and Functional Abdominal Pain: A Clinical Replication Series'. *Applied Psychophysiology and Biofeedback*, 39, 287–291.
- Stewart, J. M. (2012). 'Update on the Theory and Management of Orthostatic Intolerance and Related Syndromes in Adolescents and Children'. *Expert Review of Cardiovascular Therapy*, 10, 1387–1399.
- Sulheim, D., Hurum, H., Helland, I. B., Thaulow, E. & Wyller, V. B. (2012). 'Adolescent Chronic Fatigue Syndrome; a Follow-Up Study Displays Concurrent Improvement of Circulatory Abnormalities and Clinical Symptoms'. *Biopsychosocial Medicine*, 6, 10.
- Tsao, J. C., Evans, S., Seidman, L. C. & Zeltzer, L. K. (2012). 'Experimental Pain Responses in Children with Chronic Pain and in Healthy Children: How Do They Differ?'. *Pain Research & Management*, 17, 103–109.
- Walker, L. S., Stone, A. L., Smith, C. A., Bruehl, S., Garber, J., Puzanovova, M. & Diedrich, A. (2017). 'Interacting Influences of Gender and Chronic Pain Status on Parasympathetically Mediated

- Heart Rate Variability in Adolescents and Young Adults'. *Pain*, 158, 1509–1516.
- Wells, R., Spurrier, A. J., Linz, D., Gallagher, C., Mahajan, R., Sanders, P., Page, A. & Lau, D. H. (2018). 'Postural Tachycardia Syndrome: Current Perspectives'. *Vascular Health and Risk Management*, 14, 1–11.
- Wyller, V. B., Barbieri, R. & Saul, J. P. (2011). 'Blood Pressure Variability and Closed-Loop Baroreflex Assessment in Adolescent Chronic Fatigue Syndrome During Supine Rest and Orthostatic Stress'. *European Journal of Applied Physiology*, 111, 497–507.
- Wyller, V. B., Fagermoen, E., Sulheim, D., Winger, A., Skovlund, E. & Saul, J. P. (2014). 'Orthostatic Responses in Adolescent Chronic Fatigue Syndrome: Contributions from Expectancies as Well as Gravity'. *Biopsychosocial Medicine*, 8, 22.
- Wyller, V. B., Saul, J. P., Amlie, J. P. & Thaulow, E. (2007). 'Sympathetic Predominance of Cardiovascular Regulation During Mild Orthostatic Stress in Adolescents with Chronic Fatigue'. *Clinical Physiology and Functional Imaging*, 27, 231–238.
- Wyller, V. B., Saul, J. P., Walloe, L. & Thaulow, E. (2008). 'Sympathetic Cardiovascular Control During Orthostatic Stress and Isometric Exercise in Adolescent Chronic Fatigue Syndrome'. *European Journal of Applied Physiology*, 102, 623–632.