

Online Supplement 1.2

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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 1.2

Historical Context: The Emerging Science of the Stress System

Abstract This online supplement to Chapter 1 provides a brief historical overview of the scientific developments that set the stage for the articulation of the stress-system model for functional somatic symptoms – the model used throughout the book as a means of understanding and treating such symptoms. We focus on one particular thread: the discoveries about the body that have contributed to our understanding about how the body regulates itself and how the body's stress system responds to the challenges of daily living – the stress of life. This historical thread provides us with some preliminary insights into what happens when those challenges – those stressors – are too much for the body to manage, leaving it dysregulated and in disharmony or disrepair, allowing for the potential emergence of functional somatic symptoms.

The body has held close her secrets. The science underlying our modern approach to functional somatic symptoms began to emerge in Europe in the early modern period, when advances in optics, physics, and chemistry led to new methodologies for studying body structure and function. The invention of the microscope in the late 1500s opened up a new, previously

unseen world. While the early images were blurred and obscure, improvements to lenses over the course of the next century enabled Robert Hooke to identify cells in plants (Hooke 1665) and Antony van Leeuwenhoek to visualize bacteria and human sperm.¹ A century and a half later, in the 1830s, Matthias Jakob Schleiden and Theodor Schwann proposed *cell theory*, the idea that both plants and animals were composed of cells (Schleiden 1838; Schwann 1838). Advances in staining techniques brought cells into better focus, and by the late 1800s, the Spanish neuroscientist Ramón y Cajal was able to see the microscopic world of nerve cells and structures ‘clear and plain as a diagram’ (Sherrington 1935, p. 430; Garcia-Lopez et al. 2010). Likewise, electricity, first studied in the 1600s, evolved into a major new research methodology by the 1800s, enabling researchers to use electrical stimulation of the nervous system, alongside dissection experiments and experiments in which nerves were cut, to map out the structure and function of the brain and peripheral nervous system. The establishment of modern chemistry in the 1600s, most notably through the work of Robert Boyle, ultimately led, beginning in the late eighteenth century, to methodologies that used chemical substances to study nerve function. This line of research would, in time, lead to the discoveries that chemical messengers transmit information between neurons and that, more generally, organic molecules play an important role in regulating the body’s many subsystems. In this supplement we highlight some key discoveries about body structure and function that build upon these historical developments and that inform our understanding of how the body regulates itself – discoveries that serve as the foundation for the entire book.

The Body’s Internal Environment

Claude Bernard: The Body’s *Milieu Intérieur*

Claude Bernard (1813–1879), a prominent French physiologist, used what would come to be known as the *scientific method*² – systematic observation, measurement, and experimentation (Bernard 1957 [1865])– to examine the many neurophysiological mechanisms that the body uses to regulate itself.

In his early work, Bernard studied the *physiology* of the gut. He conducted experiments about energy metabolism, including the metabolism of sugar in the liver and the role of pancreatic juices in the digestion of fats. Later on, in experiments that looked at the function of nerves, he discovered that, in animals, the severing of particular sympathetic nerves (the cervical portion of the sympathetic chain) causes vasodilation (redness and increases in temperature on the same side of the face) and that electrical stimulation of the same nerves causes vasoconstriction (paleness and decreases in temperature).³ Still later, he discovered parasympathetic nerves that go to salivary glands and that, when stimulated, cause vasodilation in those glands. Bernard introduced the term *milieu intérieur* – the body’s internal environment – to encapsulate the idea that many neurophysiological processes function to maintain a state of internal stability (Bernard 1994 [1879]). This idea of the body’s internal environment was soon taken up by others, and in an ongoing process of scientific discovery, the mechanisms that maintain this environment have been largely identified. The body’s *milieu intérieur* plays a central role in our book: we see the body as a set of interacting systems that, when working well, regulate the brain-body system and maintain a state of health, harmony, and well-being.

Walter Cannon: Anger, Fear, and the Body as a Homeostatic System

In the late 1800s and early 1900s, Bernard’s work served as the foundation for the major advances of Walter Cannon (1871–1945), an American physiologist working at Harvard Medical School. Cannon used X-rays – which had just been discovered – to study swallowing and gastric motility in geese and cats. He became interested in the physiology of the emotions after noticing that stomach movements decreased or even ceased when an animal became angry or frightened. Cannon (1915) discovered that states of anger and fear – later known by the catchy expression *flight or fight*⁴ – involve activation of the sympathetic nerves and secretion of the stress hormones adrenalin and noradrenalin from the adrenal medulla (the adrenal medulla is also stimulated by sympathetic nerves). Through Cannon’s work

it was apparent that emotions (fear, anger, and pain) could induce changes in body state and that these changes were mediated by two interacting body systems: a system made up of nerves and a system made up of hormone-secreting glands. Today the term *sympathetic adrenal medullary* (SAM) *system* is used when referring to the body system that mediates this *fast reaction* to sudden stress. Building on Bernard's idea of the *milieu intérieur*, Cannon introduced the notion of *homeostasis* – namely, that the body is a self-regulating system whose *milieu intérieur* and overall stability are maintained by *interdependent* neurophysiological processes (Cannon 1926).

John Langley: The Autonomic Nervous System

Also in the early 1900s, on the other side of the Atlantic, the English physiologist John Langley (1852–1925) introduced the term *autonomic nervous system* – from the word *autonomy* – to describe the nerve cells and nerve fibres that innervate the *viscera* (the body's internal organs) and to distinguish those structures from the *somatic nervous system*, the nerves that innervate the *soma* (the rest of the body). Langley divided the autonomic nervous system into the sympathetic, parasympathetic, and enteric nervous systems (Langley 1921), with the sympathetic and parasympathetic systems having opposite effects.⁵ The term *autonomic nervous system* is the term that continues to be used today in referring to the sympathetic and parasympathetic systems. It replaced a jumble of other names, including *ganglionic*, *involuntary*, *organic*, *sympathetic*,⁶ *vegetative*, and *visceral*. Langley's autonomic system focused on the motor component of the autonomic system – the efferent pathways from the brain providing motor (*visceromotor*) innervation to the viscera. The afferent (*interoceptive*) pathways from the viscera to the brain were yet to be discovered.

The Stress Response

Hans Selye: The Concept of Stress

Hans Selye (1907–1982), an Austrian-Hungarian endocrinologist who migrated to Canada, introduced the idea of the *stress response* and, with it, the

word *stress* – including *le stress*, *der stress*, *lo stress*, *el stress*, and *o stress* – into our vocabulary across cultures and languages (Selye 1956). According to Selye’s broad definition, stress (or a stressor) is any event (physical, chemical, or psychological) that causes the body to activate an adaptive (or in some cases, maladaptive) response. The stress response includes the many different ways in which the body responds or adapts to the myriad challenges, ranging from the negligible to the catastrophic, that we encounter as part of our daily lives – what Selye called *the stress of life*. Selye highlighted that mild, brief, and controllable states of stress could be perceived as pleasant or exciting, and could function in a positive way to facilitate the individual’s emotional, physical, or cognitive health and subjective well-being (Selye 1974). By contrast, more severe, protracted, or uncontrollable stress – exceeding a tolerable threshold and associated with distress rather than pleasure, excitement, or goal-associated determination – could lead to a protracted stress response that had a negative effect on the individual’s well-being and that, over time, could result in what Selye called *diseases of adaptation*.

Selye’s contributions to stress research were based on his research with rodents. He had observed that the body always responded to stress – or what we now recognize as *chronic* stress – with the same pattern of response: enlargement of the adrenal glands (because they secrete the stress hormones adrenalin/noradrenalin from the adrenal medulla and also cortisol from the adrenal cortex); atrophy of the thymus and lymph nodes (now well-known effects of cortisol on immune cells); and duodenal erosions, or ulcers (secondary to cortisol and other factors). He referred to this pattern as the body’s *stress response*, and he was the first to demonstrate the crucial role of the *hypothalamic-pituitary-adrenal* (HPA) *axis* in that response. Today the term *HPA axis* – of which cortisol (a steroid hormone classified as a glucocorticoid) is the end product – is used when referring to the body system that mediates the *slow reaction* to sudden stress (vs. the fast reaction to such stress via the sympathetic adrenal medullary system). When the HPA axis is activated by stress, cortisol levels increase. Cortisol activates the body and increases energy consumption. And when the stress becomes recurrent or chronic, dysregulation and loss of HPA function (from wear and tear or via complex feedback mechanisms) are likely to result.

Throughout the book we use Selye's idea of stress and the stress response in discussing functional somatic symptoms.

Selye also introduced the idea of wear and tear. At the 'Man Under Stress' symposium, held in mid-November 1963 at the University of California Medical Center in San Francisco, Selye 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' (JAMA 1964).

Michael Meaney and Clyde Hertzman: The Embedding of Experience

Beginning in the 1980s, researchers began to recognize that a person's life experiences, especially early life experiences, actually become biologically embedded in the brain and body. Though the term *biological embedding* derives from a 1996 article by Clyde Hertzman (1953–2013) (Hertzman and Wiens 1996; Hertzman 1999), the basic idea comes from the earlier, pioneering work of Michael Meaney and his research team. Meaney showed that rat pups that had been briefly separated from their mothers and handled by experimenters had higher concentrations of glucocorticoid receptors in the hippocampus because the increased licking and grooming by the mother rat following separation caused changes in gene expression and in receptor numbers (Meaney and Aitken 1985; Meaney 2001; Wastell and White 2016). This preliminary work demonstrating that life experiences can alter the expression of genes opened a floodgate of new work, freed from the confines of seeing genes as having a single, unchanging, and unchangeable mode of expression.

As this new work took shape, and as discussed below specifically in relation to stress, it became apparent that life experiences – in the life of previous generations, in utero, during early infancy when the child's *stress system* (see next subsection) was being regulated by maternal care, and during the child's own life trajectory – were embedded into the body via many complex biological mechanisms, both genomic and non-genomic, and that there was a constant interplay between the person's genetic legacy and his or her life experiences, with potential alterations in gene expression. Consequently, when we use the term *biological embedding of life experiences*, we

refer to many different genomic and non-genomic processes, including the following: changes in the operating ranges of neurophysiological systems; changes in the activity of genes involved in regulating the stress response; changes in gene expression; experience-dependent changes in brain structure and function; and wear-and-tear mechanisms within the stress system itself (*allostatic load*; see below). The central point here is that clinicians need to hold in mind the idea that life experiences can cause changes in body function and structure.

George Chrousos: The Concept of the Stress System

At about the same time that Meany was publishing his results on the biological impact of life experiences, George Chrousos and colleagues introduced the term *stress system* in the preface to a collection of research papers entitled *Mechanisms of Physical and Emotional Stress* that had been presented at a 1986 National Institutes of Health symposium (Chrousos et al. 1988). The stress system comprises a set of overlapping and interrelated hormonal, neural (autonomic nervous system), immune-inflammatory, and brain systems involved in mediating the brain-body stress response and underpinning the body's ability to regulate itself in response to the stress of life. Chrousos defined stress as 'a state of disharmony, or threatened homeostasis' (p. 1245) and introduced the term *stress-system disorders* (for Selye's *diseases of adaptation*), which he conceptualized as arising from hyper- or hypo-activation of the stress system (Chrousos and Gold 1992). Over the last 18 years, the stress system has provided clinicians and researchers with an overarching systemic framework for thinking about brain-body systems involved in regulation and the body's response to stress – including those identified by Cannon, Langley, and Selye (Chrousos 2009, 2014). In the book we use the stress system as our overarching framework for understanding functional somatic symptoms. We examine how cumulative stress, uncontrollable stress, and stress that is more than the child can manage can cause dysregulation within the stress system – overactivation, underactivation, loss of circadian rhythm, lack of coherence or harmony within and between stress-system components, and wear and tear – and can manifest as functional somatic symptoms. Because the body systems that

regulate the body – that is, maintain optimal internal milieu – and those that activate in response to stress are one and the same, the terms *body stress system(s)* and *body regulation system(s)* can be used interchangeably.

Robert Haggerty, Peter Sterling, and Joseph Eyer: Illness Patterns in Post-industrial Societies and the Concept of Allostasis

In articles published in 1975 and 1982, the paediatrician Robert Haggerty (1925–2018) took note of the increased incidence of illness patterns involving problems in behavioural, development, and social functioning. He attributed to these phenomena as the *new morbidity* and attributed the increase to day-to-day family stress and ongoing changes in family structure, communities, and the larger society (Haggerty et al. 1975, 1982).

A few years later, in 1988, Peter Sterling and Joseph Eyer – a neurobiologist and an epidemiologist, respectively – published their own, broader analysis of how chronic stress and chronic activation of brain-body stress systems contribute to illness patterns in post-industrial societies. Sterling and Eyer noted that during the course of daily life, many body processes involved in regulation are not stable (contrary to what would be predicted under homeostasis) but are constantly fluctuating (termed *allostasis*). Changes in heart rate, blood pressure, and respiratory rate are examples of these fluctuations. Sterling and Eyer observed that the body anticipates alterations in need and makes the necessary neurophysiological adjustments in advance of the need arising.⁷ To maintain stability of the internal environment in the face of ongoing change, the body either *activates* or *deactivates* regulation systems in response not only to *present* environmental demands (the homeostatic notion) but to *anticipated* ones.

In both respects allostasis differs from homeostasis, which is understood as primarily oriented toward *activation* and *deactivation* in response to *present* demands (and their subsequent withdrawal). Sterling and Eyer also highlighted that the neurophysiological systems within the body, rather than activating and then returning to a single constant state (as in standard homeostasis [see Figure 4.3 Frame A in Chapter 4]), are constantly adjusting up and down to meet new levels of demand, whether higher or lower,

whether anticipated or current. The result is, in effect, different, ever-changing levels of relative homeostasis that allow the body to adjust its level of activity to meet, as needed, the demands of daily life. They also noted that after a period of chronic stress, the body's regulation systems sometimes fail to return to baseline and that they stay activated indefinitely, resulting in a new, higher *set-point* against which the body responds to new stressors (see Figure 4.4 in Chapter 4). The concept of allostasis – and allostatic load (see below) – continues to inform current research (Schenk et al. 2018). Throughout the book, when we are talking about set-points and changes in set-points in the context of functional somatic symptoms, we are using Sterling and Eyer's concept of allostasis.

Bruce McEwen: The Concept of Allostatic Load

Via a series of articles – the first being 'Stress and the Individual', published in 1993 – Bruce McEwen, a neuroscientist with a long-standing interest in the body's stress system, brought Sterling and Eyer's concept of *allostasis* into mainstream thinking and also elaborated that notion in further detail (McEwen and Stellar 1993; McEwen 1998, 2000a, 2000b). McEwen emphasized that chronic stress places a strain on body systems and that this state of chronic activation had a biological cost, termed *allostatic load* or *allostatic overload*. The initial biological cost is increased energy expenditure – like a switch that is turned up too high – because activation of the body's stress system increases energy use in every system of the body. The medium-term biological cost, if the system continues to be overworked, is a change in set-points – like a switch thermostat/control switch being turned to a higher setting – so that the system never returns to its original baseline function (allostasis). The long-term cost of chronic overworking of the system is 'wear and tear', resulting in a damaged stress system; it can no longer activate robustly to respond to stress or is dysregulated because the balance between its different components is disrupted (see also Brenhouse et al. [2018] or Miller et al. [2018] for the manner in which chronic and sustained inflammatory response can also lead to excitotoxicity and prevent typical brain development or cause wear and tear).

This shift from a healthy stress system – in which all components activate in response to environmental challenges, and all components deactivate once the environmental challenge has passed – to a malfunctioning system is a risk factor for ill health. *Allostatic load* was originally applied to illnesses in which ‘wear and tear’ could be easily measured or seen – for example, hypertension, diabetes, and plaque within arteries. We will be applying the concept of allostatic load to *functional* illnesses in which changes in structure and function are more subtle; such differences become apparent only through studies using group-level analyses (comparing groups of patients to healthy controls) (see, e.g., Chapter 4).

Predictive Models, the Bayesian Brain, and Allostasis

On Bayesian approaches to brain function, which build on Bayesian statistics, the brain organizes sensory data about the world (including about the body itself, the internal world, via interoception) into internal models; the brain uses these models to make predictions about diverse dimensions of the world; and it then uses these predictions to assess and update its internal models of the world. Such models, some of which are available to conscious processing and some of which are not, can shape how information is processed and how the body responds. This Bayesian approach has been applied in several ways that are relevant, for our purposes, to (1) the concept of allostasis and the body’s efforts both to anticipate the body’s energy needs in an efficient manner and to prepare to meet those energy needs before they arise (Kleckner et al. 2017); (2) body states (including those that are maladaptive) and the way that biological systems try to maintain a limited number of states (low entropy) in the face of the natural tendency to disorder (Karl 2012); and (3) the way in which ideas, beliefs, and social knowledge shape perception, motor control, and action (Friston 2010; Otten et al. 2017).

For the application of predictive models – predictive representations and predictive coding – to functional somatic symptoms, see Chapters 9 and 11. For additional reading see references provided in Online Supplement 11.1.

Contemporary Methodologies and the Rise of the ‘Data Mountain’

By the turn of the century, the brain came to be seen as the central organ of stress and adaptation (McEwen 2009). In the same way that the microscope had opened up a new world, advances in molecular biology, electrophysiology, and brain-imaging technologies during the second half of the twentieth century opened up many new worlds. Molecular methods allowed researchers to look at the body from the molecular level of genes, receptors, transporters, and proteins. The electroencephalogram (EEG) and brain-imaging technologies (scans using computed axial tomography [CT] and magnetic resonance imaging [MRI]) allowed the visualization of both brain structure and functional patterns of activity in the brain (and body) by looking at electrical, magnetic, and other biological signals. This burst of research activity generated a vast amount of new information about the brain and body, resulting in the emergence of a ‘data mountain’ (p xxiii) (Sterling and Laughlin 2015). It became apparent that every component of the body’s stress system either was regulated by the brain, connected to it, or communicating with it in some way. Each new piece of information highlighted the sheer complexity of the body’s regulation systems and how much was still unknown.

Neuroscientists interested in the autonomic nervous system saw the brain as one of its key components (Westerhaus and Loewy 2001; Critchley 2005; Strigo and Craig 2016). Bud Craig mapped out the missing interoceptive component of the autonomic system – the afferent *sympathetic* and *parasympathetic* pathways carrying information from body tissues to the brain (Craig 2003). Like Langley (see above), he highlighted that autonomic-system regulation involves a balance between the sympathetic and parasympathetic brain-body systems (Craig 2005; Strigo and Craig 2016). Activation of the brain’s *sympathetic* regions, operationalized predominantly in the right forebrain (the right anterior insula and anterior cingulate cortices), is predominantly associated with a defensive brain-body state (negative affect, avoidance behaviour, and energy expenditure), whereas activation of the brain’s *parasympathetic* regions, found predominantly in the left forebrain (the left anterior insula and anterior cingulate cortices), is

associated with a restorative brain-body state (positive affect, approach behaviour, and energy nourishment) (Strigo and Craig 2016).

Stephen Porges, another contemporary neuroscientist, extended the contemporary model of the autonomic system one step further. Using electrophysiological data, he provided evidence that the parasympathetic system has two functional arms. The *restorative arm* functions in antagonism to the sympathetic system (as noted by Langley and Craig), but the other, *defensive arm* mediates defensive responses in the gut and heart, and can, in some circumstances, be activated alongside the sympathetic system (Porges 2011).

We use and represent all these important ideas in the autonomic component of the stress-system model that we use in the book to understand functional somatic symptoms (see Chapter 6).

Neuroscientists interested in hormones began to see the brain as an endocrine gland when they discovered that the hypothalamus secretes hormones into the hypothalamic-pituitary portal system (blood vessels) (Wade 1978; Sapolsky 2015).

Over time, it also became evident that the brain and body are subject to regulation by glucocorticoids, including but not limited to cortisol. Some ten years after Selye's discovery that as part of the stress response, cortisol is secreted by the adrenal cortex, the chemical structure of glucocorticoids was identified by the 1950 Nobel Prize winners, Philip Hench and colleagues. From then on, glucocorticoids became the focus of much research activity and the life work (as discussed above) of prominent neuroscientists such as George Chrousos, Bruce McEwen, and the many researchers they have inspired. It is now known that glucocorticoids act on cells throughout the body and that they are involved not only in responding to stress but in regulating of the body's energy resources, synchronizing day-night rhythms (the body's circadian clock system), restoring a homeostatic state (following stress), and mediating changes in gene expression and the brain's experience-dependent plasticity (Chrousos and Gold 1998; Nader et al. 2010; McEwen et al. 2016).

More recently, the focus has broadened to look at the way that stress and sex hormones affect gene expression and brain function. This body of work is especially relevant to women because female sex hormones work

alongside glucocorticoids to mediate stress-related changes in the brain, making women more vulnerable to stress-related illnesses than men.

Changes in gene expression, mentioned above, fall into the new field of *epigenetics*, the study of biological mechanisms that switch genes on and off (Felsenfeld 2014; Bellanti 2020). Epigenetic research has shown that gene expression and the reactivity of many components of the stress system – for example, the hypothalamus – can be modified by life experiences via the processes of *DNA methylation*, *histone modification*, and *RNA-mediated gene silencing* (Meaney and Aitken 1985; Meaney 2001; Bellanti 2020). What this epigenetic research tells us is that life experiences that have occurred in the lifetime of a parent or grandparent, during the child’s prenatal development, or during the child’s life can alter the expression of genes and can change set-points within the brain-body stress system, thereby increasing the reactivity of the child’s stress response (Miska and Ferguson-Smith 2016). For example, subsequent to the World Trade Center Attacks in New York, lower cortisol levels were observed in both mothers and babies of mothers who developed posttraumatic stress disorder in response to September 11 than in mothers who did not develop PTSD and their babies (Yehuda et al. 2005). In adult offspring of Holocaust survivors, lower cortisol levels have been linked with vulnerability to PTSD. This means that both the child’s life story and the child’s family story in past generations are relevant to the child’s presentation in the here and now. Knowing the story can give us hints as to how the child’s stress system may have been shaped by past events.

The brain’s role in the stress response has recently become a focus of attention for neuroscientists interested in the immune-inflammatory system (Tian et al. 2012; Brenhouse and Schwarz 2016). *Glial cells*, the immune-inflammatory cells of the brain (Fields 2009), hold immunological memory for past stress and can both activate and proliferate in response to stress (Brenhouse and Schwarz 2016). Because the activation of neurons, glial cells, and blood vessels is interconnected, it seems likely that stress-induced plasticity processes that take place in the brain, such as the forging, strengthening, weakening, or severing of neural connections, also involve the brain’s glial cells. In an effort to bring attention to the important role played by the brain’s non-neural cells – which outnumber neurons – the

neuroscientist Douglas Fields refers to these non-neural cells as the *other brain* (Fields 2009).

The complex interactions between the brain and body in responding and adapting to stress have also received attention from neuroscientists studying the *enteric nervous system* – an intricate sock-like tapestry of neurons that surrounds the gut; the enteric system has been nicknamed the *second brain* (Gershon 1998). Current research is bringing into focus the complex bilateral relationship between the gut and the brain, and suggests that humans, like all other animals, exist in symbiosis with other creatures and that the gut microbiota – the community of bacteria and other organisms in our gut – may be involved in brain development, modulation of our immune system, and a range of neurodevelopmental and stress-related disorders (Dinan et al. 2018; Rea et al. 2017; Cowan et al. 2018). In this way, it seems not only that the health of our bodies and our minds depends on many interconnected systems but that the health of each depends upon the health of the other and also upon the world outside, including the bacteria that inhabit our bodies.

Notes

1. Antony van Leeuwenhoek did not publish. His discoveries were recorded in letters to the Royal Society – the President, Council, and Fellows of the Royal Society of London for Improving Natural Knowledge – which was founded in November 1660 by King Charles II.
2. The scientific method began to be systematically used by researchers beginning in the 1800s. It involves systematic observation, measurement, and experiment, along with the formulation, testing, and modification of hypotheses (abridged summary from the *Oxford English Dictionary*).
3. Charles-Édouard Brown-Séquard (1817–1894), a Mauritian-born physician, conducted the same experiments and made the same discoveries while working in the United States.

4. The concept of ‘fight or flight’ was firmly established in the first, 1915 edition of *Bodily Changes in Pain, Hunger, Fear and Rage*, where Cannon wrote that ‘the emotion of fear is associated with the instinct for flight, and the emotion of anger or rage with the instinct for fighting or attack’ (Cannon 1915, p. 187). In both the first and second (1929) editions, Cannon referred to these two instincts in a variety of ways: ‘struggle or flight’ (1915, p. 202), ‘flight or conflict’ (1915, p. 205), ‘fighting or flight,’ (1915, p. 211), and ‘fighting or escape that accompany or follow distress or fear or rage’ (Cannon 1915, p. 202). The present authors are unsure when and by whom the catchy expression *fight or flight* was introduced when referring to Cannon’s earlier work. In ‘Fear and the Defense Cascade: Clinical Implications and Management’ (2015), the first author (KK) and her co-authors used *flight or fight* because it better captures the tendency of most mammals to flee, rather than to fight.
5. For example, the sympathetic nerves operate to increase heart rate, and parasympathetic nerves to decrease it. For more on these two systems, see Chapter 6.
6. The idea was that organs were interconnected via mutual sympathy. In this older sense, the sympathetic system included the vagal nerve, which is now not considered part of that system.
7. The ideas that the brain makes predictions about future needs is an important concept in neuroscience (Bubic et al. 2010; Pervanidou and Chrousos 2018). For example, Klecker and colleagues (2017) have developed this thinking and used contemporary research methodologies to look at how the body anticipates the need for energy resources – the process of allostasis.

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