Programmed Symptoms: Disparate Effects United by Purpose

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Abstract: Central sensitivity syndromes (CSS) share features of similar multiple symptoms, virtually unknown mechanisms and lack of effective treatments. The CSS nomenclature was chosen over alternatives because it focused on a putative physiological mechanism of central sensitization common to disorders such as fibromyalgia, irritable bowel syndrome, vulvodynia and temporomandibular disorder. Increasing evidence from multiple biological systems suggests a further development. In this new model central sensitization is part of an ensemble that includes also the symptoms of widespread pain, fatigue, unrefreshing sleep and dyscognition. The main feature is an intrinsic program that produces this ensemble to guide behavior to restore normal function in conditions that threaten survival. The well known “illness response” is a classic example that is triggered in response to the specific threat of viral infection. The major leap for this model in the context of CSS is that the symptom complex is not a reactive result of pathology, but a purposeful feeling state enlisted to combat pathology. Once triggered, this state is produced by potential mechanisms that likely include contributions of the peripheral and central immune systems, as well as stress response systems such as the autonomic system and the hypothalamic–pituitary–adrenal (HPA) axis. These act in concert to alter behavior in a beneficial direction. This concept explains similar symptoms for many triggering conditions, the poorly understood pathology, and the resistance to treatment.

Keywords: Autonomic, central sensitivity syndromes, fibromyalgia, functional somatic disorders, hypothalamic–pituitary–adrenal axis, illness response, immune, protective homeostasis, purposeful feeling state, stress.

EPIDEMIOLOGY: DIFFERENT DIAGNOSES, SIMILAR SYMPTOMS

Despite the explosive growth in pain knowledge and treatment in the past decades, a group of conditions remain puzzling to pain scientists and an enigma to pain clinicians. There is considerable overlap among these conditions [1]. They share features of chronic widespread pain and/or discomfort, sensitivity to external stimulation, disordered sleep, subjective sense of cognitive dysfunction, stiffness, and fatigue. These symptoms mostly present to varying degrees in conditions that receive different diagnostic labels. These conditions are present in most medical disciplines [1] and include temporomandibular disorder (TMD), irritable bowel syndrome (IBS) and vulvodynia/vestibulitis syndrome (VVS). Fibromyalgia (FM) includes all of these symptoms and can serve as an exemplary prototype for the group. Sensitivity to external stimulation is not a chief component of chronic fatigue syndrome (CFS), but the presence of the other symptoms begs inclusion.

In clinical practice, a patient usually presents with a combination of these symptoms and the clinician must choose among possible diagnoses based on factors such as

regional focus (e.g. IBS, VVS, TMD) or chief complaint such as widespread pain in FM. Patients may often satisfy established diagnostic criteria, such as the ACR 1990 [2], and 2011 [3] criteria for FM or the ROME [4] criteria for IBS. The end result is either a single diagnosis that may include associated symptoms, a predominant diagnosis with recognized comorbidities or dual or multiple diagnoses. This result can be influenced by both the clinician and the patient. The clinician may specialize in a particular disorder, recognizing the symptoms and being familiar with appropriate treatments. A patient may have preconceptions, especially in the modern climate of self-help groups and internet information. For example, a patient may know that the ACR90 criteria for fibromyalgia depended on reports of pain in at least 11 of 18 defined tender points in response to manual 4kg pressure. It is not surprising that “tender point count” may be influenced by conscious or unconscious desire for a physical diagnosis [5, 6].

Overlapping symptoms and comorbidities are not the only defining feature of these conditions. Another feature is the success in treating these conditions, which is modest at best. In FM there is an informal “30-50” rule in which the best treatments provide 30% relief in 50% of the treated patients and 50% relief in 30% of the treated patients in clinical trials. Success of clinical treatments may be less. The search for better treatments is actively ongoing. Considerable attention has been directed towards the concept of patient-

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centered therapy. Predominant symptoms would dictate therapy, such as a choice of a serotonin–norepinephrine reuptake inhibitor (SNRI) in patients with predominant depressed mood, or an anti-epileptic for patients with suspected neuro-pathic symptoms.

Ideally, patient-centered treatment would be mechanistic, focused on identified pathology. Unfortunately, yet another defining feature of these conditions is that the processes that initiate and maintain the symptoms are not known with any certainty. As elaborated below, there is evidence for a variety of mechanisms that range from psychiatric-psychological to genetic-physiological. However, what can be observed is a group of symptoms that lead to multiple diagnoses and comorbidities, and that is poorly understood and poorly treated.

DIFFERENT DESCRIPTIONS, DIFFERENT MEANINGS AND CONNOTATIONS

This “group” could use a label, and several have been applied, including “functional” or “functional somatic syndromes” and “medically unexplained symptoms” [7-10]. “Functional” has a long history and initially was distinguished from “organic.” Disease is closely associated with “organic,” which can imply physical dysfunction at the cellular level or an observable lesion [7]. In contrast, “functional” could imply a physical change in processing at a neural or other level. However, coupling this term with “somatic,” while addressing the physical nature of the symptoms, approaches psychological-psychiatric terminology such as “somatoform disorder,” or “conversion hysteria” [7, 11]. Recognizing the multiplicity and vagueness of the meaning “functional,” Kanaan *et al.* [12] conducted interviews and a survey of British neurologists. Interviews (n=22) described a continuum ranging from nonorganic to bodily dysfunction, altered brain function (including results of modern functional neuroimaging), and psychiatric/conversion disorder. The results of the survey in 319 respondents were similar. The questions were not mutually exclusive and 62% endorsed the meaning of “not organic,” 36% “abnormal brain function,” 30% “a psychiatric problem” and 22% “abnormal body function.” Interestingly, a third of the group reported using more than one meaning at different times. Of the remaining two-thirds, almost all (59% of the entire group) used “functional” strictly to mean “not organic,” without going further.

The neurologists in this survey who took a less rigid approach and chose other and more meanings for “functional” appeared to do so as a clinical utility in which either different meanings or plain ambiguity served a useful communicative purpose. Others have described a use of functional as a temporary term that “is put on the shelf” until the appropriate physiological explanation is found [12]. No mention is made of the duration of the wait, which could conceivably range from days to decades.

“Functional” implies an idea of mechanism, and much of the ambiguity and possible debate is what that function is or should be. In contrast, the term, “medically unexplained symptoms” accurately describes the current state of knowledge about the mechanism. It is not speculative or biased towards any one particular point of view. In some

ways it is the most preferred term because it defines the current state of knowledge and does not go beyond the available evidence. It includes “we don’t know yet,” which acknowledges the steady progression of science and the continual discovery of explanations for what previously was unknown. It describes the amount of available evidence and not a particular direction that the evidence may ultimately lead.

Unfortunately, even this seemingly objective term is interpreted negatively. As Yunus aptly articulates, many infer “medically unexplained” not as “not yet medically explained” but rather as “no medical explanation” so therefore it is “all in the head” [7, 13]. If not medically explained, it must be psychiatrically explained. This connotation and the psychiatric uses of “functional” are major reasons that Yunus sought a new term for this group of syndrome/conditions. He chose this new term based both on the explicit meaning of previous terms and on the connotations implied by terms such as “medically unexplained.” This goal and the increasing evidence for the finding of increased sensitivity to stimulation led to the term “Central Sensitivity Syndromes” [11, 14]. It implies a common physiological mechanism among many disorders. Importantly for Yunus, both the meaning and the connotation avoid any type of psychological or psychiatric label.

CENTRAL SENSITIVITY SYNDROMES (CSS) AND CENTRAL SENSITIZATION (CS)

The central feature of CSS is increased sensory sensitivity to both painful and non-painful stimulation. While the main focus has been sensitivity to stimuli that activate nociceptive fibers (pressure, heat, electrical stimulation) there is increasing evidence that the sensitivity extends beyond the nociceptive system to include stimulation such as loud sound [14-18]. This hypersensitivity is the commonality used for the label CSS. These syndromes also share other symptoms such as widespread spontaneous pain, fatigue, and perceived cognitive dysfunction (dyscognition). As noted above, chronic fatigue syndrome is not noted for sensory hypersensitivity, but shares many of these other symptoms.

Thus the term ‘CSS’ implicitly and explicitly connects sensory hypersensitivity to “Central Sensitization” (CS). The concept and definition of CS has evolved over time and usage varies from the accepted definition. We join a number of pain scientists with a very restrictive view of CS that shares both commonalities and differences with CSS. We believe that it is critically important to describe the evolution of the term and the supporting scientific evidence to both avoid confusion and to accurately define what we are talking about.

Winding back the clock, an author of this article was one of seven authors of an extensive examination of a single patient with traumatic neuropathic pain of the foot and lower leg [19]. During a series of diagnostic blocks, an anesthetic block of a peripheral (sural) nerve relieved pain both in that nerve territory and in the territory of a separate peripheral (peroneal) nerve. The mechanisms of relief in the two nerve territories were completely different. All sensations were abolished in the sural nerve territory due to the

anesthetic block. In contrast, the pain vanished in the peroneal nerve territory while the sensations “normalized”; sensations in this region felt completely normal and similar to those on the contralateral side. These results were surprising and puzzling and it took years to fully understand them. In a subsequent series of repeated examinations on 4 patients, the same results were obtained in the upper limb of one patient and in the lower limb of three [20]. Extensive sensory testing supported the concept that focal input from nociceptors produces a spinal process in which pain sensitivity was altered in a large region surrounding the putative locus of painful input. This alteration included an area of pinprick hyperalgesia and an area of mechano-allodynia in which burning pain was evoked by light brushing. Discrete administration of a local anesthetic confined to the painful focus quickly abolished these evoked pain abnormalities and the surrounding skin felt “normal.” Testing revealed several interesting features: 1) The spread of pain in otherwise normal skin crossed nerve territories, suggesting a spinal process, since nerve territories disappear within the spinal cord. 2) The symptoms included cold hyperalgesia, in which even room temperature metal caused pain. 3) The pain to light brushing could represent either lowered thresholds in pain nociceptors or a change in phenotype of A-beta touch fibers that normally do not mediate pain sensations. Testing with electrical stimuli suggested the latter A-beta mechanism which was confirmed with both electrical stimulation and the use of differential blocks. 4) Sensitivity to both deep painful pressure and to heat was found at the “primary” zone at the site of the painful focus but not in the “secondary regions” of pinprick hyperalgesia and mechano-allodynia. 5) The painful secondary areas returned after the block of the primary region waned.

This mechanism of central sensitization is now well understood, resulting in an expansion of symptoms surrounding a natural injury or experimental injury in the laboratory by methods such as a burn or intradermal injection of capsaicin, the active ingredient in chili pepper. At the time, this mechanism defined CS, and we were careful to use other terms such as augmentation [20, 21] to describe symptoms of widespread pain and sensory hypersensitivity in other conditions. As we describe below, the meaning of CS has been broadened by some investigators while others adhere to this original meaning of CS. To be clear, we will refer to this well documented mechanism as “classical CS.”

IMPORTANT DISTINCTIONS BETWEEN CLASSICAL CS AND CSS

The term CSS explicitly links these disorders to CS and implicitly to the evidence-based classical CS. While seemingly similar, there are dramatic differences between CSS and classical CS. Classical CS is regional, with a usually identifiable primary painful focus with symptoms of mechano-allodynia and pinprick hyperalgesia in surrounding secondary zones. The symptoms are largely confined to the somatosensory system; there are no noticeable hypersensitivities to non-somatosensory modalities such as sound. In contrast, the symptoms of CSS are widespread and do not usually include pinprick hyperalgesia, A-beta-mediated

mechano-allodynia or pronounced cold hyperalgesia. The sensory symptoms are not confined to the somatosensory system and are accompanied by other symptoms such as fatigue and dyscognition.

Interestingly, if the well-known features of classical CS are a component of CSS, the CS mechanism would implicate a peripheral rather than central process. The logic is as follows: 1) Sensitivity to blunt pressure (tenderness) and heat are hallmarks of CSS. 2) In classical CS, these abnormalities are found in the primary zone, the painful focus. 3) It is conceivable that CSS could represent a widespread CS in which the whole body is a primary zone, and the painful input from these zones is relatively weak and does not produce any secondary symptoms such as pinprick hyperalgesia, A-beta-mediated mechano-allodynia or cold hyperalgesia. Cytokine sensitization of peripheral receptors may be an example of a widespread primary zone as is the widespread pain of mild sunburn. 4) However, the pain in this case would originate from widespread peripheral sources and represent a peripheral versus a central neural process. CS might be present in this situation but it would not be necessary for the symptoms. The peripherally-mediated symptoms would be present without CS; any CS would only serve to increase them further.

OTHER MEANINGS FOR CS

A large and growing body of evidence identifies and details the mechanisms of classical CS. Indeed, the phenomenon could be accurately described as “evidence-based CS.” However, over time the meaning of CS has broadened to describe a general class of mechanisms that share the CNS hypersensitivity observed in classical CS without the necessity of an initiating and/or maintaining input from nociceptors. The IASP definition embraces this general class of mechanisms, “increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold input” [22]. CS is now a general term that includes the well-documented evidence-based classical CS, which is now referred to as “activity-dependent CS.” It also includes hypothetical cases in which CNS mechanisms enhance nociceptive input by autonomous mechanisms that do not depend on input from C-fiber nociceptors. In addition, it includes CNS mechanisms that have been demonstrated in the laboratory that may apply to clinical populations. One example is the modulation of pain input from descending systems in which the brain inhibits or facilitates pain at the spinal level. Descending analgesic systems are well described and there is clinical evidence for lack of tonic descending analgesia in CSS. However, these findings could also represent the effects of a descending system that is already activated by the widespread pain in these conditions and the failure to observe a descending analgesic effect is due to the fact that these systems are already active and cannot be activated further [5, 23]. Another possibility is increased descending facilitation. Animal studies have identified a circuit from periaqueductal gray (PAG), which receives inputs from multiple brain regions that include the anterior cingulate, insula, amygdala and the hypothalamus. PAG provides the major input to the rostral ventral medulla (RVM) that exerts both inhibitory and excitatory effects on nociceptive afferents in the spinal dorsal horn. [24-30]. Such

horn. [24-30]. Such facilitation could provide a mechanism for sensory hypersensitivity. However, applying the standards of evidence-based medicine, at present, there is insufficient evidence for a descending facilitation mechanism mediating the symptoms of CSS conditions. A final possibility is an autonomous CS that does not depend on maintenance by persistent peripheral input. There is (as yet) little evidence for autonomous CS and a large and convincing body of evidence for CS initiated and maintained by nociceptive input. Thus, the new nomenclature includes classical CS, which is likely minimally involved as a mechanism common to these syndromes. Exceptions include IBS, a regional visceral disorder that appears to involve CS due to peripheral input [31] and possible input from muscles in fibromyalgia [32]. CSS leaves room for further possibilities if demonstrated in the future.

We acknowledge that there can be other, more generalized meanings for the use of “central sensitization.” Our interpretation may be too strict. However, these meanings follow (in time) and overlap with the restricted use of this term. CSS was chosen in part because it did not have any of the connotations of a psychological/psychiatric disorder. We note that it is not free of connotation. It may have little in common with physiological mechanisms of central sensitization but carries a strong connotation of an established physiological mechanism of augmented sensory sensitivity.

CLASSICAL CS HAS A PURPOSE THAT PROMOTES SURVIVAL

We have provided the extended description of classical CS above for another reason. This CS represents a prime example of the purpose behind CSS symptoms. CS has a purpose. Otherwise, why would the body contain mechanisms to make pain worse? Endogenous analgesic mechanisms that attenuate pain make sense. But why exacerbate pain? The answer was emphasized by Wall [33] with an example of a dog struck by a car. The dog first experiences the pain of injury, accompanied by vocalization and fleeing the site of the injury. Pain serves to avoid or minimize injury, adding conscious withdrawal to reflexive withdrawal. This is followed by a second phase in which the dog lies curled and unmoving. CS has exacerbated pain and inhibited movement. It promotes behaviors (or lack of behaviors) that protect and immobilize the injured area, promoting natural healing. CS is recuperative, it maximizes the chance of survival under natural conditions.

Thus, as emphasized by Wall [33], there are two types of pain that are easily distinguished by the interaction of pain and movement. The first is the common pain that most think about and is described by the IASP definition, “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” The second is a recuperative pain that follows injury and promotes healing; in one case pain evokes movement, in another, movement evokes pain. Janig and Levine [34] have used parallel terms of “fast defence” and “slow defence” to describe these complementary types of pain.

THE OVERLAPPING SYMPTOMS OF THESE SYNDROMES ALSO HAVE A PURPOSE THAT PROMOTES SURVIVAL

This is the major thesis of this paper. It has been hinted by many writers but not presented as a formal model. We propose that the overlapping symptoms of widespread pain, sensory hypersensitivity, fatigue, stiffness, unrefreshing sleep and dyscognition are not the direct consequence of a disease state or a pathological process. These symptoms are not reactive. Rather, they are proactive, they are created for a purpose. This purpose is the same as for classical CS, to influence behaviors to promote survival. Like classical CS, this purpose is to *promote quiescence* by inhibiting and limiting the normal range of behavior. Promoted or purposeful quiescence is the common theme that binds these syndromes, and we will use the shorthand “PQ conditions” to describe this group.

In this view, a disturbance of homeostasis that threatens the viability of the organism activates a group of protective physiological responses and also motivates behavior. Behavior is motivated solely by symptoms that have associated feeling states. In normal daily life, these include hunger, thirst and thermoregulation. In terms of these overlapping disorders, quiescence is promoted by widespread pain, physical and mental fatigue, and augmented sensitivity to most forms of stimulation. All of these observed symptoms guide behavior to restore homeostatic balance during conditions of threatened survival.

An important feature of this model is that the observed symptoms are not a direct consequence of pathology. They are activated in concert by a protective program, an intrinsic process activated to promote survival. During our early studies of classical CS, we initially described the spinal effects that cause widespread pain, hyperalgesia and allodynia as “abnormal processing.” We quickly realized that this processing was not abnormal, and relabeled it “altered central processing” [20]. Classical CS represented a normal response to pathological input. Similarly, “abnormal” has been used in the literature to describe the common symptoms in CSS conditions. We propose that the symptoms in these overlapping PQ conditions are not “abnormal” but rather evoked by an intrinsic program that is normally activated by multiple pathologies. It also conforms to the principle that multiple disease states must be represented by a limited repertoire of symptoms [35].

One interesting consequence of this model is that research studies of associations among symptoms are actually studying the program and not the pathology that triggers the program or fails to reset it. Much of the knowledge that has been gained about these disorders may be program related. The pathologies to a large degree remain elusive. The evidence of considerable overlapping symptoms and comorbidities is not only consistent with this model but actually provides supporting evidence.

This model does not exclude unique symptoms that do not overlap across conditions. These may have several logical explanations. The variability can be explained in part by known genetic predisposition and by environmental influence. In addition, the activation of this program does not

exclude simultaneous regional processes and reactive symptoms. It would only be surprising if any mechanism represented the sole source of symptoms.

These concepts of protective homeostasis are summarized in (Fig. 1) and below:

1. Multiple sources of homeostatic imbalance trigger a general program, with the possibility of source-specific input.
2. The triggered program produces a similar core set of symptoms to modify behavior in a beneficial direction.
3. These symptoms may vary according to the source-specific input and vary greatly due to individual genetic and environmental differences.
4. The result in any single individual is a group of symptoms that both overlap and differ from the symptoms in other individuals.
5. These symptoms likely fit multiple diagnostic categories. The categories chosen likely represent the predi-

lection of the clinician, the influence of regional inputs, the motivation and desire of the patient, and random variation in program-evoked symptoms.

ILLNESS RESPONSE, IMMUNE INTERACTION, BEHAVIOR

This concept is certainly not new or completely original. The concept of “sickness behavior” or the “illness response” is well established, describing the behavioral response to infection [36-41]. Two aspects of the illness response expand the concept. Selye [35, 42] focused on stress as a source of dysregulation, utilizing finite biological supplies and ultimately resulting in an exhaustive state that threatens health and survival. Thus the “pathogen” can be any number of conditions that consume limited resources with negative consequences. In addition, regulatory and protective systems championed by Bernard [43] and Cannon [44] suggest that the symptoms in these conditions do not result directly from pathology or a disease process but rather are purposeful and designed to promote behaviors that restore health. In contrast to reactive, “brainless” symptoms arising directly from pa-

Fig. (1). Model of Protective Homeostasis. The center bottom shows the common conception of fibromyalgia and related syndromes in which an individual is predisposed (genetic, environmental events including physical and sexual abuse and other trauma) to the syndrome, which is subsequently precipitated by a stressor, injury or other event. The additional boxes with square corners below the dotted line depict the presence of numerous homeostatic mechanisms that regulate processes such as internal body temperature and blood acid/base balance. The boxes above the dotted line with rounded corners illustrate the model of protective homeostasis. An extreme departure from homeostasis signals a threat to survival. This threat may also be signaled by a smaller departure that is not being corrected by normal physiological and behavioral responses to the imbalance. The survival threat activates an intrinsic program that creates a group of disparate symptoms that have a common purpose. This purpose is to promote behavior that assists physiological responses to the threat. The program evokes symptoms that include enhanced sensory sensitivity to painful and non-painful stimulation, widespread pain, dyscognition and fatigue. Although problematic sleep may be an effect caused by the other symptoms, unrefreshing sleep is also included as a symptom that is different than fatigue or insomnia and likely evoked to also promote desired behavior. These disparate symptoms are united in the effort to promote quiescence and hence survival. The systems that perceive threat, activate the program and generate symptoms are characterized by individual variability due to genetic and environmental influences.

thology, these symptoms are produced by the brain to direct behavior before physiological limits are reached [45]. A prime example is provided by the discomfort experienced during restriction of the airway, such as being forced to breathe through a small drinking straw. The result is a distinct unpleasant feeling that rivals the unpleasantness experienced during altered blood gas concentrations due to insufficient ventilation. Although in this case of restricted ventilation, these concentrations are normal. The effects of true insufficient ventilation are so dire and immediate that the body appears to actually “feed forward” (in time) the distress that would soon follow due to physiological imbalance. The symptoms are experienced before any actual physiological need. This feed-forward provides additional precious seconds to correct the airway obstruction.

The connection between infectious pathology and symptom-guided behavior was provided a half-century ago by Miller [46] who experimentally demonstrated that illness behavior represented a motivational state with specific behavioral consequences. Subsequent evidence for these “purposeful” symptoms was reviewed by Hart [38] a quarter-century ago. Recent evidence has linked the development of illness behavior to the immune response to infection and subsequent release of cytokines, that in turn evoke both physiological responses such as fever and subjective symptoms designed to promote recovery that include sleepiness, lethargy, reduced hunger and thirst [36-40, 47, 48]. As elaborated below, cytokine mechanisms are implicated in increased pain sensitivity. Watkins and Maier [41] provide evidence for a generalized sensitization that is immune rather than neurally mediated. The model presented here extends this concept beyond infection to the many possible imbalances that may evoke symptoms to motivate behavior.

Indeed, this concept of protective homeostasis is gaining traction in multiple fields. It has been explicitly proposed for migraine, chronic fatigue syndrome and for fibromyalgia and related disorders [34, 45, 49]. In some cases this increasing appreciation has taken some time. Noakes [45] points out that the concept of purposeful symptoms in chronic fatigue syndrome was articulated elegantly by Mosso 100 years ago, who stated that fatigue,

“at first sight might appear an imperfection of our body, is on the contrary one of its most marvelous perfections. The fatigue increasing more rapidly than the amount of work done saves us from the injury which lesser sensibility would involve for the organism.”

Noakes [45] further notes that, “It has taken more than a century to confirm Mosso’s idea that both the brain and the muscles alter their function during exercise and that fatigue is predominantly an emotion, part of a complex regulation, the goal of which is to protect the body from harm.”

THE TRIGGERED PROGRAM CAN BE AN ANALOG SYSTEM WITH CONTINUOUS INPUTS AND OUTPUTS.

We have used the concept of a triggered program to describe the homeostatic system. This is a metaphor for a number of possible systems that sense homeostatic imbalance

and provide outputs to direct behavior. The system is likely a neural net with multiple analog inputs and outputs. This system can behave as a triggered system with a robust response, or as a smooth system that increases the behavioral drive signal with increasing homeostatic imbalance. The important feature is a centralized system activated by numerous possible “threats” to normal function that activate a common core of symptoms that influence behavior.

PROGRAM PERSISTENCE

The protective program is normally activated during an acute homeostatic threat and deactivated after restoration of homeostatic balance. For example, spinal central sensitization is evoked after injury to protect and immobilize the injured region until healed. Illness behavior is likewise evoked upon viral threat until the immune system has removed the threat. Similarly, the programmed constellation of PQ symptoms are likely triggered to aid physiological responses to unknown homeostatic threats. In each of these cases, the programs remain active until the acute triggering event (focal nociceptor input, infection) is removed. However, this acute restorative process may not occur due to an ineffective response or to an additional pathology (e.g. neuroma) that essentially breaks the feedback loop. Neuropathic pain due to ectopic discharge from a neuroma is a succinct example of an additional pathology to an initial process (injury) that is not corrected by the programmed responses. The acute condition becomes chronic and the now ineffective physiological responses and programmed symptom responses persist.

In this example of neuropathic pain the programmed responses become maladaptive, producing now chronic aversive symptoms that serve no useful purpose. The symptoms may be ineffectual in alleviating the program triggers, and maladaptive to varying degrees, depending on whether the persistence is due to a robust triggering pathology or a broken feedback loop.

VULNERABILITY

The maladaptive effects of program persistence could potentially cause a new threat to survival. In the natural state, activation of these protective programs that promote quiescence could leave an animal vulnerable to predators or prevent sufficient self-care, especially if the acute condition becomes chronic. This maladaptation does not invalidate the model. The potential for maladaptation is true for both the proposed model and for the well-established examples of central sensitization and the illness response to infection. However, there are a number of factors that may mitigate this increased vulnerability. For example, the programmed behavior itself may induce safety. A rodent may be most vulnerable to predators while foraging for food and water. Such foraging is inhibited during injury-induced central sensitization and consequent immobility, and likewise reduced during viral assault. Interestingly, in this latter case of the illness response, inhibition of foraging has been attributed to conservation of energy needed for increased metabolism to support fever. This behavior may also promote survival by reducing exposure to predators.

Vulnerability may be reduced also by competing protective programs. There is considerable evidence for a hierarchy

of homeostatic and protective behaviors and the action of one may supersede others. For example, a rat in a hyper-thermic environment will starve to death while looking at a pile of food within easy reach. The thermoregulation program protecting against protein denaturation amongst other things inhibits appetitive behavior. Likewise, flight-or-fight mechanisms may completely inhibit perceived pain and motor inhibition during a predator attack. In these cases, survival is maximized by these shifting program priorities. Similarly, it is expected that the behavioral consequences of the proposed programmed-symptoms may be overruled by a more significant survival threat.

Social factors also mitigate vulnerability. Humans and animals may live in isolation, but many are members of social networks that provide protection and care during program activation.

IMPLICATIONS

The presence of programmed symptoms has implications for both research and clinical care. In research studies, associating symptoms may provide information about the program but inform little about the triggering pathology. Multiple pathologies likely trigger a similar symptom complex [35]. The same masquerade afflicts clinical diagnosis; the programmed symptoms may interfere with diagnosis (IJ Russell, personal observation). Following diagnosis, the challenge is to treat the cause in addition to the symptoms. The modest effects of available treatments is consistent with the concept that symptoms created for a programmed purpose, are likely very resistant to modification by a palliative treatment.

No mechanisms exist in isolation, and multiple factors likely contribute to clinical presentations. The proposed model need not explain all features, but the presence of ubiquitous homeostatic programs cannot be ignored. Such programs provide parsimonious and coherent explanations for overlapping symptoms and comorbidities. On a broader scale, they suggest a reconsideration of symptom origin. Symptoms can be more than a brainless reaction to pathology. Symptoms are created by the brain to provide behavioral assistance to physiological regulation and survival.

PRESENT EVIDENCE

Adoption of this conceptual framework leads to several questions. One question is which events lead to program activation in which individuals? A full-scale infection triggers the program in almost every individual, presumably because program activation is highly adaptive, allowing energy conservation required to generate an immune response aimed at eliminating the stressor, i.e. the infective agent. Although previous infection is a risk factor for Chronic Fatigue Syndrome [50, 51] and might have initially triggered the program, patients with CFS do not have an acute infection, indicating that persistent program activation in these individuals does not contribute to elimination of the stressor. The inciting pathogen might no longer be present or, alternatively, persist in low quantities [52-55]. In either case, the original purposeful activation of the program has become maladaptive. Compared to post-infection CFS, which is quite widely accepted to constitute a sub-set of patients with CFS,

the role of infection in FM is less clear. Viral (hepatitis B and C virus, human T-lymphotropic virus type-1 (HTLV-1)) as well as bacterial infections (Lyme borreliosis) have been associated with an increased prevalence of FM in some studies but not in others [56-58]. Lyme borreliosis can be well treated with antibiotics whereas antibiotics are ineffective in treating fatigue, musculoskeletal pain, and neurocognitive difficulties in patients who have had Lyme borreliosis, again indicating that patients' symptoms are not caused by the infective agent. Similar to infections, other potential risk factors for FM have been found in some studies but not in others. Although this is disappointing within a biomedical framework of cause and effect, this is exactly what is expected from the conceptual framework that FM symptoms are generated by activation of a program that can be initiated by different triggers. Despite the relative heterogeneity of potential risk factors for fibromyalgia, high quality cohort studies have identified several risk factors to develop FM or chronic widespread pain (questionnaire-based studies typically assess CWP rather than FM). The identified risk factors can be grouped into at least four categories: genetic, somatic, psychological, and stressful events. Heritability of FM is approximately 50% [59]. The genetic polymorphisms that have thus far most reliably been identified as to be related to FM/CWP are located in pathways that have been implicated in FM in other lines of research, specifically the adrenergic and serotonergic system. 'Somatic' risk factors include dysfunction of the HPA-axis, a high number of allergies, obesity, local pain disorders, and smoking. Depression has been identified as a psychological risk factor. In the 'stress' category, we group work-related psychosocial risk factors, namely mobbing, high pressure, and low level of decision-making possibilities as well as childhood trauma (e.g. physical and sexual abuse, maternal death) and physical and sexual abuse in adulthood. In addition, several studies identify the reporting of many somatic symptoms as a very important risk factor. Interestingly, genetic variants of the serotonergic system associated with FM, specifically the 5HT2A-receptor (HTR2A) have been associated with personality and affective traits such as somatic awareness, depression and anxiety [60]. Thus, the risk factors for somatic symptoms as well as depression might share considerable overlap with the genetic risk factors. Alternatively, reporting of somatic symptoms could also be an early indication of program activation.

In sum, it appears that some stressors are more effective in activating the program than others. Acute infections lead to program activation in almost every individual, systemic inflammatory conditions such as rheumatoid arthritis do so in a sizable subset, and a variety of other stressors activate the program only in vulnerable individuals. Vulnerability is partly genetically conferred but environmental exposures, such as stressful life events, contribute to vulnerability. Environmental exposures might have a cumulative effect over time and their risk might be modified by gender.

A second key question is how program activation leads to patients' symptoms, or, in other words, what is the (neuro-) biology underlying widespread muscle pain, mental and physical fatigue, and waking unrefreshed? There have been numerous attempts to answer this question and many pathophysiological changes have been described but at present the relevant mechanisms are unknown. Similarly to the hetero-

geneity of risk factors, it is plausible that different mechanisms could be more or less important in different individuals and that it would therefore be difficult to find 'the' pathophysiological mechanism. Instead of summarizing all alterations in various physiological systems, we use FM as an example and take a different approach in the following: our starting point is the conceptual framework of (inappropriate) program activation by a stressor and we examine its pathophysiological implications. If the framework is correct, several biological pathways ought to be implicated: the sympathetic system, the HPA-axis, and the immune system. Importantly, there is an intricate interplay between the neural, endocrine, and immune systems in regulating the body's response to stress and the maintenance of homeostasis. Dysregulation of any of these stress systems can lead to dysregulation of multiple physiological and behavioral systems [61-64].

SYMPATHETIC SYSTEM

Several lines of evidence support an involvement of the sympathetic system. Genetic variants affecting the sympathetic system have been repeatedly associated with an increased risk to develop CWP or to have fibromyalgia. Genetic variants have been found in the β 2-adrenoreceptor *ADRB2* and in the enzyme Catechol-O-methyltransferase (COMT), which was shown in a series of elegant studies to be related to pain sensitivity via a β 2/ β 3-adrenergic-dependent mechanism [65]. COMT regulates catechol neurotransmitter levels in the nervous system, i.e. epinephrine, norepinephrine, and dopamine, and could therefore play an important role in regulating homeostasis in response to physical and psychological stressors. Interestingly, the adrenergic pathway genes *ADRB2* and *COMT* have been associated with numerous endophenotypes associated with FM, including autonomic dysregulation [66], alterations in pain processing and modulation [67, 68], sleep dysfunction [69, 70], and anxiety [66, 71].

Autonomic dysregulation is frequently found in patients with FM. There is growing evidence for both increased baseline sympathetic activity and a blunted autonomic response to stressors such as exercise or postural challenges [72, 73] and for possible sub-groups with different response patterns [74]. A key question is whether a dysregulated sympathetic system contributes to patients' symptoms. The sympathetic system, especially via β -adrenergic receptors, has an essential role in regulating blood flow to muscles, which is not only important to supply nutrients but also to eliminate metabolites, including protons, likely contributing to muscle fatigue and pain [75]. Interestingly, it has been shown that mRNA levels (in leukocytes) of receptors responding to protons are elevated in patients with FM [76], possibly contributing to symptoms of muscle pain and fatigue, especially if metabolite elimination was compromised by a dysregulated β -adrenergic system. However, in stark contrast to patients with CFS, exercise did not further increase mRNA levels in spite of symptom increases [76], indicating that other mechanisms contribute to patients' symptoms.

Animal studies show that the chronic stress of unpredictable noise can lead to chronic hyperalgesia in response to the pro-nociceptive mediators prostaglandin E(2) and epineph-

rine [77, 78]. Initiation of hyperalgesia, which developed more than a week after exposure to stress, required concerted action of glucocorticoids and catecholamines at receptors located in the periphery on sensory afferents [77] whereas catecholamines seem to play the key role in maintaining the hyperalgesia at later stages [78]. This animal model implicates stress systems and, in particular, the adenosympathetic system in hyperalgesia to exogenously administered pronociceptive mediators. There are some indications for increased catecholamine levels in patients with FM, at least in some subgroups [79-81], which could possibly act as nociceptive stimuli in a sensitized system. Nevertheless, questions remain regarding the relevance of this mechanism in FM. First, baseline mechanical pain thresholds were not altered in the animal model [77]; it is unclear whether animals had spontaneous pain. Further, systemic levels of epinephrine were lower in the sound-stressed animals than the doses administered to provoke hyperalgesia [77, 78], leaving it unanswered whether stress-induced increases in epinephrine are sufficient to provoke hyperalgesia and/or pain via nociceptor sensitization [77, 82].

Another possibility is that activation of the sympathetic nervous system contributes to patient symptoms via interactions with the immune system. Beta2 adrenergic receptor activation stimulates pro-inflammatory cytokine production in macrophages [83]. Recently, β -adrenergic receptor antagonism was shown to block stress-induced trafficking of macrophages into the brain and block microglial activation in rodents subjected to social defeat stress [84, 85]. In the same studies, anxiety-like behavior was reduced, indicating that immune activation by the sympathetic system was behaviorally relevant. The role of immune system activation, and of microglia activation, in particular, will be discussed in more detail below.

In sum, there are several potential mechanisms, including indirect ones via the immune system, through which the sympathetic system might contribute to symptoms including widespread pain, muscle fatigue, and affective disturbances.

HPA-AXIS

Different genetic variants affecting HPA-axis function have been associated with CWP/FM, although these findings have not been consistently replicated (reviewed in [86]). Nevertheless, evidence from a prospective study demonstrates that a dysfunctional HPA axis (blunted circadian rhythm, decreased feedback sensitivity) is a risk factor for the development of CWP in individuals already at risk based on their psychosocial profile [87]. Thus, a dysfunctional HPA stress system, be it genetic or acquired, predisposes for the development of FM/CWP, at least in individuals already at risk. Interestingly, childhood adversities such as maternal separation alters HPA-axis function (reviewed in [88]) and thus HPA-axis function might mediate the risk of childhood stressors for developing FM/CWP. Results for the specifics of HPA-axis dysfunction are somewhat mixed but the predominant picture appears to be a blunted response to stressors, possibly with increased cortisol levels at rest (reviewed in [73]), reminiscent of the changes to the sympathetic stress system [89]. In women with FM a relationship between cortisol levels upon awakening and pain symptoms has been

observed although in this particular study, cortisol levels in FM patients did not differ from those in controls [90]. Further, the amount of pain in patients with FM has been found to be correlated with cerebrospinal fluid (CSF) levels of cortisol-releasing-hormone (CRH), which were higher than literature values for healthy subjects [91]. However, it has to be emphasized that these data do not inform about causality; increased pain might conceivably activate the HPA-axis, leading to the above.

Hypocortisolism has also been described in FM (reviewed in [73]) and might be predominant in CFS [92]. It has been suggested that an overactive HPA-axis, indexed by increased cortisol levels, exhausts over time and results in hypocortisolism in a later stage [73, 93], which would at least partly explain the mixed findings in patients. A meta-analysis of the cortisol awakening response (CAR) might support this idea by showing that the CAR is positively related to perceived stress levels and negatively to fatigue, burnout, or exhaustion [94]. In addition, etiological subgroups might be associated with different alterations of the HPA-axis. For example, childhood trauma is associated with both hypocortisolism and FM, and co-morbidities such as depression can also contribute to different HPA-axis dysfunctions [91, 95-97].

Interestingly, medical conditions characterized by hyper- or hypocortisolism share symptoms with FM. For example, hypercortisolism due to increased release of adrenocorticotrophic hormone (ACTH) (Cushing's syndrome) and hypocortisolism due to adrenocortical deficiency (primary or secondary to ACTH deficiency) are both associated with fatigue, irritability as well as joint and muscle pain [98]. In chronic adrenocortical deficiency, the main symptom is fatigue, probably because of cortisol's regulatory role in energy metabolism. This might explain why hypocortisolism seems to be more commonly found in CFS compared to FM. Other symptoms of adrenocortical deficiency that are similar to FM or CFS symptoms include nausea and ill-defined abdominal pain [99], possibly caused by decreased gastric motility due to decreased cortisol levels. Interestingly, decreased detection thresholds for gustatory, olfactory and auditory stimuli have been observed for patients with adrenocortical deficiency, and hypothesized to be related to increased neural excitability (reviewed in [100]). Increased supra-threshold sensitivity to these types of stimuli has been observed in fibromyalgia [14-18], although it is currently unclear whether FM patients show decreased detection thresholds. Increased cortisol levels, as in Cushing's syndrome, are associated with headaches, backaches, memory problems, and sleeping problems. Muscle weakness can occur (steroid myopathy). Putative mechanisms for this myopathy include abnormalities of carbohydrate metabolism and negative protein balance [98].

Of course, hormone alterations in FM/CFS must be subtle, otherwise other medical conditions would be suspected. Thus, although dysfunction of the HPA-axis can produce symptoms similar to those found in FM/CFS, it is currently unknown whether the subtle hormonal changes detected in FM and CFS are sufficient to produce the clinical picture.

In sum, there is convincing evidence that HPA-axis alterations occur in FM and that they represent a risk factor for development of CWP. Altered HPA-axis function could con-

tribute to the symptoms that patients are experiencing although it seems unlikely (at least to the authors of this article) that subtle alterations in cortisol levels are sufficient to explain patients' symptoms. Nevertheless, the HPA-axis influences many physiological functions, including neurotransmitters, and closely interacts with the sympathetic and immune systems. Thus, HPA-axis dysfunctions might indirectly contribute to FM symptoms.

IMMUNE SYSTEM

Genetic variants affecting immune function have been associated with CWP/FM, although these findings have not been consistently replicated. But other risk factors also suggest involvement of the immune system. Smoking tobacco has been found in a cohort study of over 3000 females to more than double the risk to develop FM after 25 years [101]. Of course, smoking impacts many physiological pathways but a pro-inflammatory state is common (reviewed in [102]). In the same study, the presence of allergies increased the risk of developing FM 4-fold, which is among the highest for any non-psychosocial risk factor, again implicating a disturbed immune system. Also, being overweight or obese has been found to predispose to developing FM in a population-based cohort study of over 15,000 individuals [103]. Similar to smoking, obesity is associated with many different pathophysiological changes but activation of the immune system has been linked to several of the co-morbidities, including rheumatic and cardiovascular diseases (reviewed in [104]). Psychosocial stressors promote inflammation and immune dysfunction [105, 106], supporting the conceptual framework presented here that program activation represents a relatively stereotypical response to a stressor even for stressors that cannot be eliminated by program activation. In these cases the negative feedback loop can be considered to be broken, leading to persistent symptoms.

Prerequisite for the diagnosis of FM is that patients' symptoms are 'medically unexplained'. The purpose of physical examination and laboratory investigations is to rule out alternative diagnoses, and thus, standard laboratory tests are normal. A full blood count, erythrocyte sedimentation rate, C-reactive protein, creatine phosphokinase, and thyroid stimulating hormone are tests recommended by diagnostic guidelines for FM [107] as well as CFS [108]. However, when investigated in research studies, evidence for low grade systemic inflammation can be detected in many patients with PQ conditions. Several publications have reported systemic immune activation in patients with CFS [109, 110]. Also in FM, several studies have found a pro-inflammatory profile of circulating cytokines [111, 112] or reductions of anti-inflammatory cytokines [113].

Pro-inflammatory cytokines are known to cause changes in behavior that closely resemble FM symptoms, fatigue, psychomotor retardation, anhedonia, hyperalgesia, lethargy, muscle aches, cognitive dysfunction, and depressed mood [37, 114, 115]. In the context of infection, this set of symptoms has been termed 'cytokine-induced sickness behavior' (reviewed in [116]). Widespread hyperalgesia can be caused, at least partly, by peripheral or systemic immune activation. Cytokines, as well as other inflammatory molecules, either directly activate nociceptors, act indirectly via activating

inflammatory cells to release algogenic agents, or sensitize nociceptors [117]. Similarly, there is evidence that at least one of the receptors involved in signaling muscle fatigue, i.e. the ASIC-3 receptor, is sensitized by nerve growth factor (NGF), released during inflammation [118]. Further, it has been suggested that sensory muscle afferents that signal fatigue are sensitized by cytokines [119]. Although peripheral systemic inflammation is important in heightening nociception, immune mediators in the central nervous system, at least in the spinal cord, contribute to nociceptive hypersensitivity by modulating excitatory and inhibitory synaptic transmission [120]. Further, many of the other symptoms, including mental fatigue, anhedonia, and increased sense of cognitive effort, require a central component, indicating that neuroinflammation might contribute to patients' symptoms. In CFS, the pro-inflammatory molecules IL-6 and TNF have indeed been found to be elevated in CSF [121, 122]. Increased levels of markers of the innate immune system were observed in two independent cohorts of patients with CFS, FM, or Persian Gulf War Illness [123]. Recently, the chemokine interleukin-8 (IL-8) was shown to be elevated in the CSF of FMS patients [124].

Activated microglia provide an important source of brain cytokines. Evidence shows that microglia mediate stress-induced neuroinflammation and enhanced release of pro-inflammatory cytokines in the rodent brain [125]. Psychological stressors that have been shown to activate microglia include repeated social defeat and repeated restraint [125, 126], which has been combined with water immersion, a stressor with a physiological quality [127]. As discussed above, alterations of stress response systems as well as psychological stressors are known risk factors that predict the development of functional somatic symptoms, and it is thus conceivable that patients with PQ disorders show stress-induced neuroinflammation. In addition, cross-sensitization between the neuroinflammatory sequelae of psychological and immune stressors occurs [128], sensitizing the brain to subsequent stressors, and hence, inducing a state of increased stress vulnerability. This could be key in the context of PQ disorders because this mechanism could explain how seemingly 'benign' infections or other small insults lead to neuroinflammation and accompanying symptoms.

Microglial activation following stress, as well as upon immune challenges, is at least partly dependent on redistribution of peripheral macrophages to the brain [129, 130]. It has been convincingly demonstrated in rodents that resident microglia together with recruitment of primed peripheral macrophages to the brain play a key role in the expression of anxiety-like behaviors induced by repeated social defeat stress [125]. The next section will explore how effects of activated microglia and associated pro-inflammatory cytokines on symptoms might be mediated by the effects on neurotransmitter systems.

CYTOKINE-INDUCED NEUROTRANSMITTER ALTERATIONS

The effects of cytokines on monoamine transmitters have received the most attention but glutamate, GABA, and acetylcholine transmission are also altered [131]. Brain cytokines impact synthesis, re-uptake, and release of serotonin,

norepinephrine, and dopamine, typically with the net effect of decreasing monoamine availability in the brain (reviewed in [131]). Pro-inflammatory cytokines have also been shown to stimulate the release of glutamate from astrocytes and reduce astrocytic expression of glutamate transporters, thereby contributing to excessive glutamatergic signaling and potentially leading to increased glutamate excitotoxicity [132, 133].

Similar to the effects of cytokines on monoamines, levels of dopamine, noradrenaline, and serotonin are decreased in the CSF of patients with FM [134, 135]. Also, using positron emission tomography (PET), altered monoamine function has been observed in a study we conducted in FM [136], and in CFS [137, 138] and other functional pain syndromes [139, 140]. Studies using proton magnetic resonance (MR) spectroscopy suggest that FM is associated with increased glutamate levels [141, 142]. In patients undergoing treatment with the cytokine interferon alpha (INF- α) [143], glutamate increases in the left basal ganglia were correlated with decreased motivation, consistent with inflammation-mediated enhanced glutamatergic neurotransmission. Evidence for fatigue as a symptom of cytokine-induced neurotransmitter alterations derives mainly from work on systemic inflammation, which can be transmitted to the brain via various routes (reviewed in [144]) and can activate local production of cytokines and activate inflammatory signaling pathways, thereby propagating neuroinflammation. Therapeutic administration of INF- α has been used to study the putative mechanisms behind cytokine-induced fatigue. This work suggests that impaired dopaminergic neurotransmission in the basal ganglia is related to behavioral fatigue. Administration of INF- α was associated with increased uptake and decreased turnover of the PET tracer F-DOPA in the basal ganglia, indicating reduced dopamine synthesis and/or impaired release of newly synthesized dopamine [145]. F-DOPA uptake and turnover were significantly correlated with symptoms of mental fatigue, measured by the Multidimensional Fatigue Inventory [145]. In the same study, dopamine function before treatment correlated significantly with several symptoms, including the development of INF- α -induced mental fatigue, reduced motivation as well as sickness symptoms and cognitive symptoms. Interestingly, dopaminergic neurons in the substantia nigra, projecting to the basal ganglia via the nigrostriatal pathway, are particularly sensitive to inflammation [146], which is related to the high density of microglia in this region.

Neuroinflammation-induced changes in neurotransmitters might not only explain fatigue but also the cardinal symptom of chronic widespread pain in FM. The decreased central levels of dopamine, serotonin, and noradrenalin that have been observed in human CSF [134, 135] result in reduced muscle pain thresholds in rats [147]. Previously, it has been shown that intracerebroventricular injection of cytokines results in hyperalgesia [148], which was postulated to be mediated via descending control of nociception. Descending pathways originating in the brain stem play a key role in determining the 'gain' of ascending pain pathways [149]. As we describe above, the PAG and the RVM are key relay structures [150]. Neurochemically, noradrenalin, dopamine, and serotonin are important transmitters for descending pain inhibition [151-153], although serotonin can also be facilitat-

tory when binding to the 5HT₃-receptor [154]. Psychological stressors as well as systemic inflammation have been shown to induce microglia activation in the PAG [127], which could potentially be related to decreased descending pain inhibition.

CONCLUSION

A group of problematic medical conditions share features of similar multiple symptoms, virtually unknown mechanisms and lack of effective treatments. At the same time, overwhelming evidence indicates the presence of many simple to complex biological mechanisms that regulate processes to maintain optimal functioning. These include many protective processes that respond to threats to survival. These processes activate physiological systems, such as vasoconstriction and shivering to maintain core temperature in cold environments, and vasodilation and perspiration to maintain core temperature in hot environments. However, the effects of behavior can be much more powerful than the physiological response; it is far more efficient to stand near the fire when cold, and sit in the shade when warm. Behavior is motivated by feeling states, such as thirst, hunger and fatigue. These states are evoked by many regulatory systems. In most cases, feelings and consequently behaviors, are produced with a safety margin. Behavior is directed early in the process of disturbed regulation before a real threat to survival. For example, the threat to survival of viral infection evokes both a physiological response of fever and a behavioral response to conserve energy by bed rest and avoiding foraging for food or water.

We propose that the multiple symptoms of PQ conditions are logical examples of a similar system that evokes feelings of widespread pain, motor stiffness, fatigue, unrefreshing sleep, dyscognition and sensitivity to stimulation. These are produced as an ensemble by a protective program to ensure survival by promoting quiescence. Like other feeling states, they are produced by intrinsic systems and not directly by some pathology. The system can be evoked by multiple triggers and the output is a collection of multiple symptoms designed for the same behavioral purpose. This concept explains the similar symptom complex for many triggering conditions, the undiscovered pathology and the resistance to treatment.

Although the pathologies remain elusive, accumulating evidence provides likely paths for program inputs and outputs. We describe mechanisms in the sympathetic nervous system, the HPA axis, the immune system, cytokine release and microglial activation. The components are there.

These syndromes have been termed “Central Sensitivity Syndromes” because of evidence for the symptom of hyperalgesia and the fact that central neurons can become sensitized as demonstrated by the effects of persistent nociceptive input. This term has admirably focused attention to the physiological basis of these syndromes. This has been an important step in a process that we believe can be extended further. The role of central sensitization in these syndromes is debated but does not influence the model. The crucial mechanism is activation of an intrinsic program that produces symptoms that guide restorative behavior. This is the fundamental mechanism behind what can be called “Recu-

perative Syndromes” or many other terms for the brain informing us to pull back and take it easy. Augmented sensory sensitivity is one of many symptoms produced by this process.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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