Perspectives on Fatigue from the Study of Chronic Fatigue Syndrome and Related Conditions

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Abstract: Fatigue is a symptom whose causes are protean and whose phenotype includes physical, mood, and behavioral components. Chronic fatigue syndrome (CFS) is an illness that has strong biological underpinnings and no definite etiology. Diagnostic criteria established by the Centers for Disease Control and Prevention have helped classify CFS as an overlap of mood, behavioral, and biological components. These include the presence of fatigue for more than 6 months associated with a diminution of functional activity and somatic symptoms, and pain not attributable to a specific diagnosis or disease. Four of the following criteria need to be present: sore throat, impaired memory or cognition, unrefreshing sleep, postexertional fatigue, tender glands, aching stiff muscles, joint pain, and headaches. Many researchers have observed that CFS shares features in common with other somatic syndromes, including irritable bowel syndrome, fibromyalgia, and temporomandibular joint dysfunction. Correlations between inflammation and infection, augmented sensory processing, abnormalities of neurotransmitters, nerve growth factors, low levels of serotonin and norepinephrine, abnormalities of homeostasis of the stress system, and autonomic dysfunction may be hallmarks of CFS. The relative contributions of each of these abnormalities to the profound fatigue associated with CFS need to be explored further to better evaluate and treat the syndrome.

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HISTORY OF CHRONICALLY FATIGUING ILLNESSES

Individuals have been documented as experiencing fatigue, or exhaustion in certain circumstances, since written records have been kept. The earliest medical literature identifies individuals who are chronically fatigued but have no other identifiable medical or psychiatric illness that would account for these symptoms, and these individuals have been described by many different labels over the millennia. In 1869, Beard first coined the term neurasthenia to describe a condition that occurred from depletion of the central nervous system's energy reserves, which Beard attributed to the consequences of aspects of modern civilization. Physicians in the Beard school of thought associated neurasthenia with the stresses of urbanization and the stress experienced a result of an increasingly competitive business environment. Typically, the condition was associated with members of the upper class or professionals with sedentary employment. The term neurasthenia has largely been abandoned, and no evidence suggests that this disorder was one of urbanization.

Many other terms for chronic fatiguing illnesses have arisen, inappropriately, from attributing the chronic symptoms experienced by patients with these illnesses to those of an active infection. For example, terms such as Akureyri disease, Iceland disease, Royal Free disease, and Tapanui flu all have been used first to describe specific outbreaks of patients with chronic fatiguing illnesses and then used more widely to describe others who had demonstrated similar symptoms. These patients, typically affected by severe postinfectious fatigue, may also experience multifocal pain (including in regions such as the muscles, throat, and neck, which are painful during many acute infections), sleep disturbances, memory difficulties, and many other somatic symptoms.

In fact, in the United States, the disorder we now commonly refer to as chronic fatigue syndrome (CFS) largely came about after a potential epidemic of CFS that occurred in the

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practice of a single internist, Daniel Peterson, in Incline Village, Nevada, in 1984 [1]. The patients in this study were extensively evaluated by both the Centers for Disease Control and Prevention (CDC) and several academic groups, and they were found to have immunological abnormalities as well as evidence of elevated antibodies to a number of different viral pathogens, leading to the theory that there was an active viral illness that was causing these symptoms. However, after extensive subsequent investigations of this group of patients, as well as many other clusters of patients initially identified as part of an "epidemic" of fatiguing illness, it became increasingly clear that neither this symptom complex nor any immunological abnormalities identified were specific to any single epidemic, or single pathogen [2-5].

Other terms have been used to describe patients with what we now call CFS. Some of these inaccurately characterized this condition to be the result of a single common pathogen, or ubiquitous organisms, hence, the names chronic Epstein-Barr virus (EBV), mycoplasma, or yeast infections [6-8]. Finally, we will reject the use of terms not supported by pathophysiological evidence, such as myalgic encephalomyelitis. A recurring problem in the history of this illness is that causality has not yet been established but is asserted on the basis of cross-sectional studies or without appropriate control groups. These assertions are almost incorrect, in part because both the symptom complexes and objective "abnormalities" used to infer cause (eg, immunological, neuroendocrine, imaging findings) are very common in the general population [9-11].

We prefer the terms CFS and idiopathic chronic fatigue (ICF) because they are descriptive and do not imply underlying etiologies or triggers. Also, these terms are consistent with the views held by practitioners who treat these patients and researchers who study them that CFS/ICF is a very heterogeneous disorder that, like many other chronic medical illnesses (eg, hypertension, diabetes), has a multiplicity of etiologic and pathogenic factors that contribute to the expression of the syndrome [12,13].

DEFINITION OF CFS AND ICF

A 1994 CDC case definition for CFS requires at least 6 months of persistent fatigue that substantially reduces the person's level of activity. In addition, 4 or more of the following symptoms must occur with fatigue in a 6-month period: impaired memory or concentration, sore throat, tender glands, aching or stiff muscles, multijoint pain, new headaches, unrefreshing sleep, and postexertional fatigue [14]. Medical conditions that may explain the prolonged fatigue as well as a number of psychiatric diagnoses (eg, eating disorders, psychotic disorders, bipolar disorder, melancholic depression, and substance abuse within 2 years of the onset of fatigue) exclude a patient from the diagnosis of CFS. A notable feature of the CDC case definition is that many nonpsychotic psychiatric disorders are not exclusionary for the diagnosis of CFS. Those who do not meet the fatigue severity or symptom criteria can be given a diagnosis of ICF.

EPIDEMIOLOGY

Although the case definition for CFS has been in place for some time [14], there is an unexplainable difference between findings of older epidemiological studies that suggested that this was a very rare (ie, 1% of the population) disorder, and newer studies in which the authors all agree that this occurs in at least 1% to 3% of the population [15]. These data from the newer studies are supported by the 2% to 4% prevalence data reported for fibromyalgia (FM), in which one half of patients meet criteria for CFS [16-18].

Both the prevalence rates of CFS at 1% to 3% and ICF at 5% to 10% are remarkably consistent across many different cultures and countries, including the United States, United Kingdom, Australia, Brazil, and Nigeria [19-22]. The authors of a recent study collected relevant demographic, symptom, and diagnostic data from 33 studies in 21 countries. The subjects had fatigue lasting 1 to 6 months (prolonged fatigue), longer than 6 months (chronic fatigue), or met diagnostic criteria for CFS. Data were obtained from 37,724 subjects (n = 20,845 female; 57%), including from population-based studies (n = 15,749, 42%), studies in primary care (n = 19,472, 52%), and secondary or specialist tertiary referral clinics (n = 2503, 7%). A 5-factor model of the key symptom domains was preferred ("musculoskeletal pain/fatigue," "neurocognitive difficulties," "inflammation," "sleep disturbance/fatigue," and "mood disturbance") and was comparable across subject groups and settings [19].

Although the core symptoms and condition are very similar across countries and cultures, the likelihood of being diagnosed is markedly different in different settings [20,23]. Early reports from tertiary clinics suggested that CFS affected primarily young, white, professionally successful women. Women do appear to be 1.5 to 2 times or more likely to have CFS in population-based studies, but community surveys have found that white men and women have a lower risk of CFS compared with Latino, African-American, and Native American subjects. These disparate findings suggest that the increased prevalence of CFS among white subjects in clinic populations is most likely the result of a disparity attributable to health-care access and use.

WHAT ARE THE UNIQUE CHARACTERISTICS OF THE FATIGUE ASSOCIATED WITH CFS?

There is nothing unique about the fatigue associated with CFS, except that it is chronic and severe enough to be

functionally disabling. The authors of many studies report that multidimensional measures such as the Multidimensional Fatigue Inventory or Multidimensional Assessment of Fatigue show that patients with CFS experience impairment in all fatigue domains and that no single domain is any more affected that any other in a group of CFS patients [24]. In general, although there are individual studies reporting contrary findings, self-report measures of baseline fatigue (measured in various ways) correlate poorly with objective measures of performance (eg, exercise or cognitive testing), leading many authors to emphasize that "perception" of fatigue seems to be abnormal in subjects with CFS [25-29]. The few neurophysiologic studies performed likewise suggest that there is diminished central activation in patients with CFS [30,31].

The best indicator of whether fatigue is associated with CFS rather than another condition is literally in the company it keeps. In the overwhelming majority of patients with CFS, the fatigue is accompanied by multifocal pain, sleep disturbances, and/or cognitive difficulties. These symptoms are encompassed within the 8 "minor" criteria for the CFS diagnosis. Many patients with CFS also experience anorexia, nausea, night sweats, a subjective sense of fevers, frequent dizziness, and intolerance to alcohol and medications.

OVERLAP WITH OTHER FUNCTIONAL SOMATIC OR CENTRAL PAIN SYNDROMES

Although the core symptom of CFS is fatigue, the 1994 CDC criteria for CFS require that a patient experiences 4 or more (of a possible 8) other chronic symptoms besides fatigue to fulfill these criteria. Five of the eight symptoms required in addition to fatigue are pain-based symptoms (sore throat, tender glands, aching or stiff muscles, multijoint pain, new headaches); therefore, it is virtually impossible for a patient to meet CDC CFS criteria without having pain in at least one body region. In fact, most patients with CFS have prominent pain in multiple anatomical regions, especially if they are queried about chronic pain over the course of their lifetime. In fact, an absence of a history of multiple sites of pain may differentiate this particular subset of CFS patients from the subset that clearly overlaps with FM, irritable bowel syndrome (IBS), and chronic headache patients, for example.

FM, IBS, chronic headaches, and other related syndromes have an interesting history as well. The terms used to describe and label patients with these syndromes are also largely historical and at least initially were viewed through the perspective of the specialist that sees patients with symptoms in a particular region of the body or of underlying pathogenesis (eg, infectious disease, endocrinology). Thus, an infectious disease expert may see a patient and focus on the infectious nature of his or her symptoms, rule out active infection, and use the label CFS. A physiatrist seeing the same patient may focus on the few most severe regions of pain and diagnose myofascial pain, whereas a rheumatologist instead notes that the pain is more widespread and not accompanied by inflammation and diagnoses FM. Historically, subspecialists have used the descriptive terms most familiar to them given their training and patient populations most commonly treated.

When researchers question the etiology of syndromes, for example, that EBV does not cause CFS or autoimmune dysfunction does not cause FM, the syndromes often are renamed. "Chronic EBV syndrome" became CFS when EBV was shown to not be the causative agent. Fibrositis became FM when it was clear there was no diffuse inflammation of fibrous tissue throughout the body and it was demonstrated instead to be a result of central pain augmentation characterized by widespread pain. Spastic colitis similarly became IBS, temporomandibular joint (TMJ) syndrome became temporomandibular joint disorder (TMJD), and interstitial cystitis is well on its way to be renamed painful bladder syndrome, all because of the recognition that central factors rather than peripheral damage or inflammation appear to be driving the pain. Even psychiatrists got into the misnaming game. The terms somatoform disorder and somatization imply that patients have multiple somatic symptoms over the course of their lifetime without any clear "organic" cause. This term also is rapidly losing credibility as it becomes increasingly clear that there are in fact objective neurobiological underpinnings to this spectrum of illness.

There is now unanimity that at least a large subset of patients with CFS have a condition that is much broader than just CFS and has been labeled variously, including "functional somatic syndromes," "medically unexplained symptoms," "chronic multisymptom illnesses," "somatoform disorders," and perhaps most appropriately, "central sensitivity syndromes." Yunus [32] first showed FM to be associated with tension-type headache, migraine, and IBS; this author designed a Venn diagram in 1984 that emphasized the epidemiological and clinical overlaps between these syndromes and primary dysmenorrhea. This diagram helped stimulate research to search for etiological connections among these syndromes [32,33]. Hudson and colleagues [34-36] demonstrated that conditions such as CFS, FM, IBS, and other pain/fatigue syndromes coaggregated in patients and in families. In this review, the more recent term central sensitivity syndrome (CSS) as proposed by Yunus is used because, in the opinion of the review author, it represents the best nosological term at present.

There is also a clear overlap between the CSS disorders and a variety of psychiatric disorders (Table 1). This overlap likely occurs at least in part because the same neurotransmitters (albeit in different brain regions) are operative in psychiatric conditions. The presence of comorbid psychiatric disturbances is somewhat more common in patients with CSS seen in tertiary care settings than primary care settings [37,38]. Figure 1 demonstrates the overlap among FM, CFS,

Table 1. *Clinical entities currently considered parts of the spectrum of central sensitivity syndrome (CSS)*

Clinical Syndromes
Fibromyalgia
Chronic fatigue syndrome (CFS)
Irritable Bowel Syndrome (IBS) and other functional gastrointestinal disorders
Temporomandibular joint disorder (TMJD)
Restless leg syndrome (RLS) and periodic limb movements in sleep (PLMS)
Idiopathic low back pain (LBP)
Multiple chemical sensitivity (MCS)
Primary dysmenorrhea
Headache (tension > migraine, mixed)
Migraine
Interstitial cystitis/chronic prostatitis/painful bladder syndrome
Chronic pelvic pain and endometriosis
Myofascial pain syndrome/regional soft-tissue pain syndrome

and a variety of regional pain syndromes as well as psychiatric disorders and demonstrates that the common underlying pathophysiological mechanism observed in most patients with FM, and large subsets of patients with these other syndromes, is central nervous system pain or sensory amplification.

ETIOLOGY AND PATHOGENESIS OF THESE SYNDROMES

The use of research methods such as epidemiological and twin studies, experimental pain testing, functional imaging, and modern genetics has led to substantial advances in understanding several of these conditions, most notably FM, IBS, TMJD, and CFS. These advances have led to an emerging recognition that chronic central pain itself is a "disease" that very often co-occurs with chronic fatigue, sleep disturbance, and memory difficulties, and that many of the underlying mechanisms operative in these heretofore "idiopathic" or "functional" syndromes may be similar, no matter whether the pain is present throughout the body (eg, in FM), or localized to the low back, the bowel, or the bladder.

Furthermore, most investigators believe that the neurobiological underpinnings of these conditions undermine the psychiatric construct of "somatization," at least if it is implied that these phenomena are the somatic representation of psychological distress with no "real" pathological basis. Figure 2 shows a theoretical schema for classifying pain syndromes on the basis of their underlying mechanisms. It is important to recognize that even patients with "peripheral" pain syndromes such as osteoarthritis or rheumatoid arthritis will

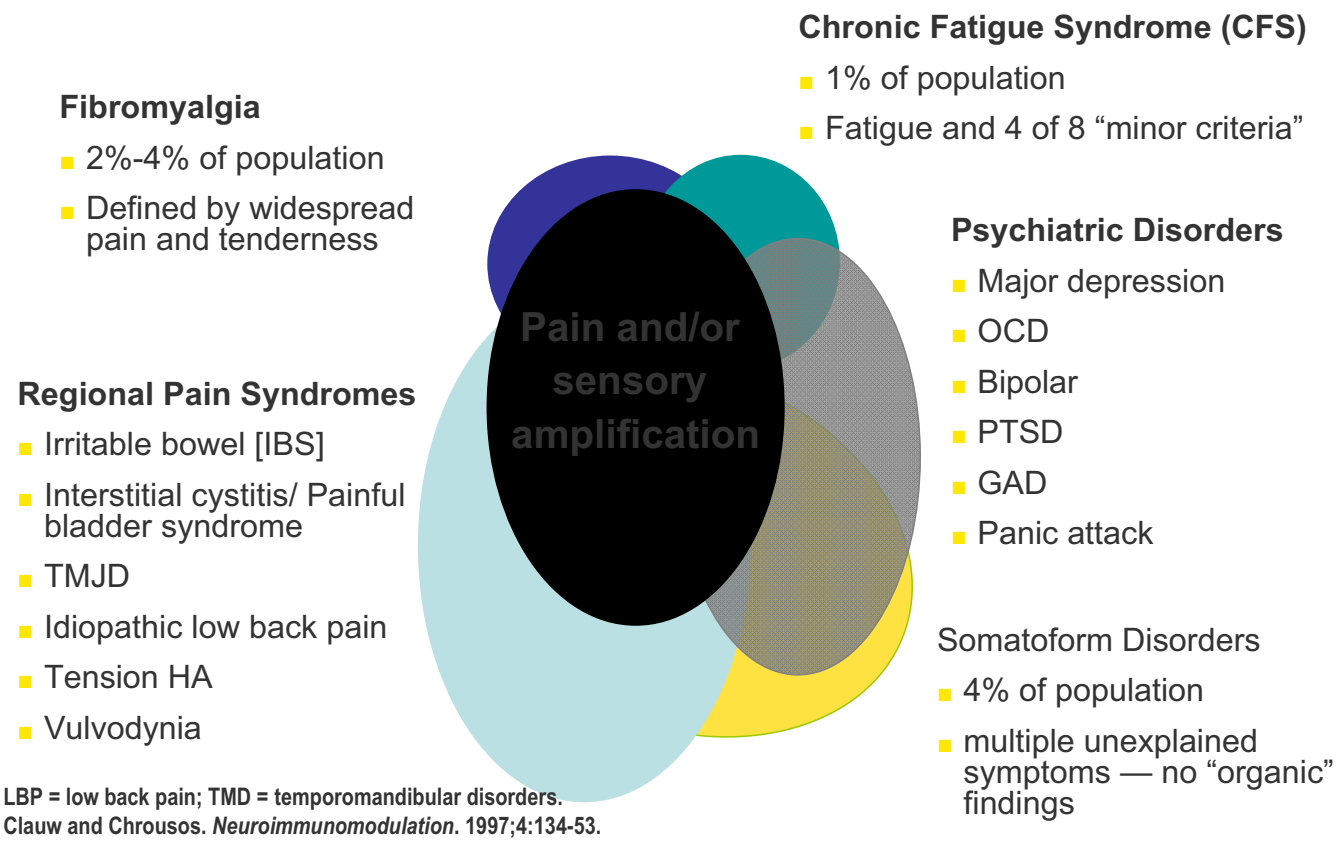

Figure 1. Overlap between systemic syndromes.

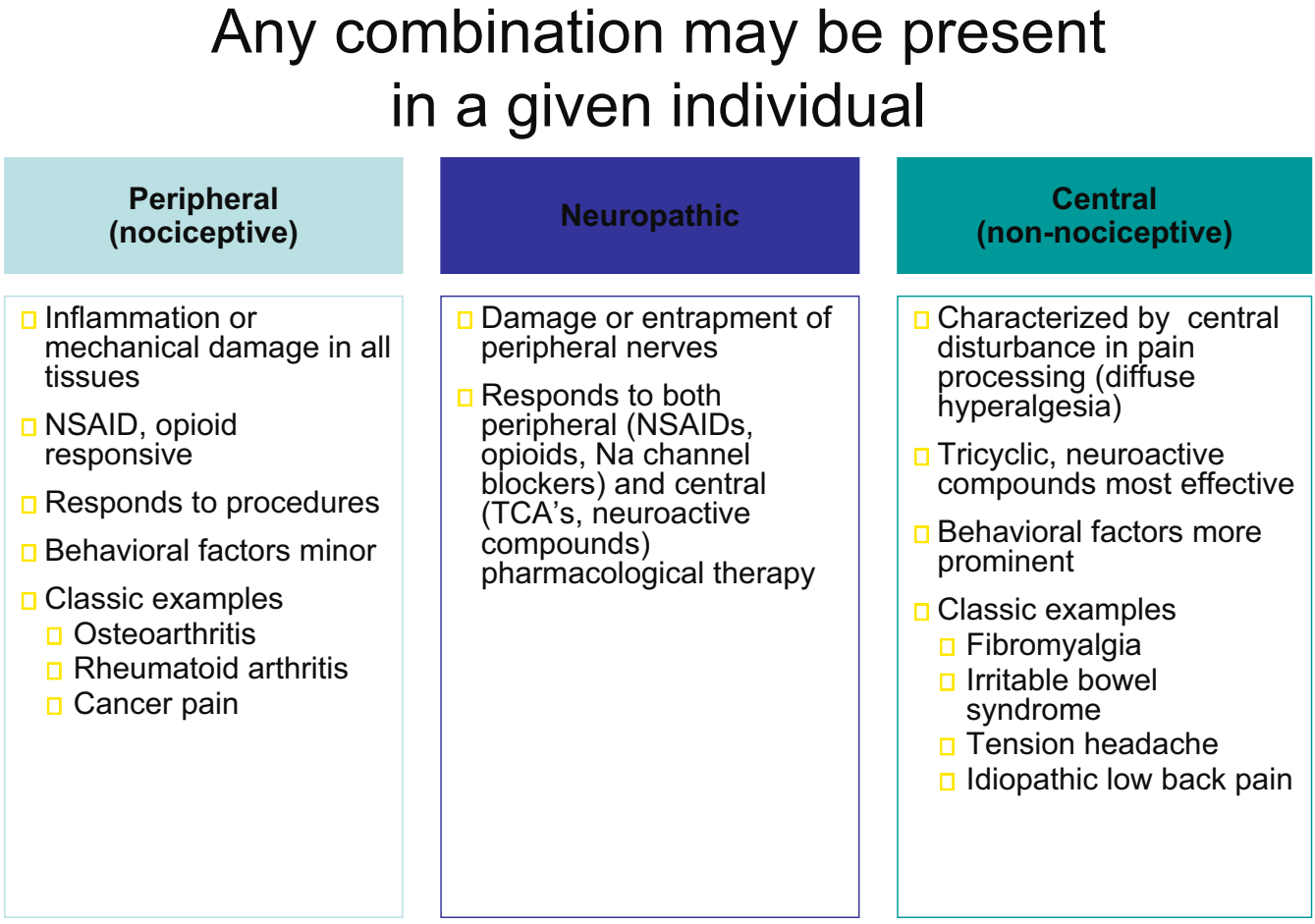

Figure 2. Mechanistic characterization of pain.

often have elements of central pain that need to be treated as such, which is why this construct has moved well beyond simple relevance to functional somatic syndromes.

The current thinking about these overlapping symptoms and syndromes is as follows, and will be reviewed in greater detail:

- The core symptoms seen in patients with these illnesses are multifocal pain, fatigue, insomnia, cognitive or memory problems, and, in many cases, psychological distress [9,39]. Some patients in the population only have one of these symptoms, but more often patients have many, and the precise location of the pain, and the severity and quality of the fatigue, changes over time. Thus, in clinical practice it is useful to evaluate patients with idiopathic fatigue regarding fatigue, pain, and sleep disturbances during the course of their lifetime. It may be that when patients have this pattern of symptoms and past diagnoses, then they have a FM-like central pain syndrome, and if not, then other reasons for fatigue must be more strongly considered.
- The presence and severity of these symptoms vary across populations. All of the diagnostic labels in current use are to some degree arbitrary because there is no objective tissue pathology or gold standard to which "disease" can be anchored.
- These symptoms and syndromes occur approximately 1.5 to 2 times more commonly in women than men. The gender difference appears more apparent in clinical samples (especially tertiary care), however, than in population-based samples [37,38].
- There is a strong familial predisposition to these symptoms and illnesses, and studies clearly show that these somatic symptoms and syndromes are separable from depression and other psychiatric disorders [39-41].
- A variety of biological stressors appear to be capable of either triggering or exacerbating these symptoms and illnesses, including physical trauma, infections, early life trauma, and deployment to war, in addition to some other types of psychological stressors (eg, there was no increase in somatic symptoms or worsening of FM after the terrorist attacks of 9/11) [42,43].

- Groups of patients with these conditions (eg, FM, IBS, chronic headache, TMJD, CFS) display diffuse hyperalgesia (increased pain in response to normally painful stimuli) and/or allodynia (pain in response to normally nonpainful stimuli). Many patients with these conditions also have been shown to demonstrate more sensitivity to many stimuli other than pain (ie, auditory, visual), and data suggest that these patients have a fundamental problem with pain or sensory processing rather than an abnormality confined to the specific body region in which the pain is being experienced. In fact, the expanded relevance of the FM construct relates to the idea that all patients (with and without pain) have different "volume control" settings on their pain and sensory processing. The position on this bell-shaped curve of pain or sensory sensitivity largely determines whether they will have pain or other sensory symptoms during the course of their lifetime and how severe these symptoms will be.
- In addition to pain and sensory amplification, other shared underlying mechanisms that have been identified in these illnesses include: (1) neurogenic inflammation, especially of mucosal surfaces, leading to increased mast cells and the appearance of a mild inflammatory process in the periphery; (2) autonomic nervous system dysfunction; and (3) hypothalamic pituitary dysfunction.
- Similar types of therapies are efficacious for all of these conditions, including both pharmacological (eg, tricyclic compounds such as amitriptyline) and nonpharmacological treatments (eg, exercise and cognitive behavioral therapy [CBT]). Conversely, patients with these conditions typically do not respond to therapies that are effective when pain is attributable to damage or inflammation of tissues (eg, nonsteroidal antiinflammatory drugs, opioids, injections, surgical procedures).

The aforementioned list is meant to be a summary of the findings across the functional somatic or central sensitivity field. CFS is a heterogeneous disorder and likely includes patients who have entirely different pathophysiology, such as those who have an infectious or metabolic condition that has yet to be identified.

Some patients who meet criteria for CFS may not have this spectrum of illness as the root cause for their symptoms.

FINDINGS SPECIFIC TO CFS

Cognitive difficulties have been particularly well-studied in CFS. The authors of CFS studies have suggested that memory problems are a common complaint, but some authors suggest that these subjective symptoms are accompanied by objective abnormalities on neuropsychological testing. However, most did not find good correlation between objective neuropsychological findings or biological markers, and symptoms of dyscognition [44-48].

Some of this disparity likely occurred because the early testing paradigms did not focus on areas that were subsequently shown to be most abnormal in CFS, such as information processing speed, motor speed, working memory, and simple and complex attentional tasks [49]. In more recent studies [50-53], authors have used neuropsychological batteries tailored to the domains that appear to be most impaired. These authors typically identified group differences between CFS and control patients. These effects were independent of and could be differentiated from effects found in frequently comorbid disorders, such as depression, where there is greater psychomotor slowing.

There is a considerable disparity between any patient's self-assessment of his or her cognitive function and the actual cognitive function as measured by neuropsychological batteries in patients with and without disease. The interest in possible brain dysfunction in CFS also led to a flurry of structural imaging studies in CFS. Many studies showed abnormalities in the white matter on structural magnetic resonance imaging scans, but the authors of several well-controlled studies [54-58] failed to replicate these findings, and none of the findings on magnetic resonance imaging were ever found to be sensitive or specific for CFS.

A newer method of assessing brain volumes has gained widespread use in neuroscience and chronic pain states and is just beginning to be applied to CFS. The authors of a recent study [59] have suggested that improvements after CBT were accompanied by increases in brain volume. By the use of functional neuroimaging studies, researchers [60] also have examined changes in blood flow with activity-related tasks, and in CFS the provocation of fatigue has been associated with emotional responses that patients may have difficulty suppressing.

Sleep has also been well-studied in CFS because a logical conclusion might be that chronic sleep deprivation leads to fatigue and other comorbid symptoms found in CFS patients [61-63]. Many sleep abnormalities were noted in a series of studies of CFS patients, but similar to findings in sleep studies of FM patients, none of these findings was found to be sensitive or specific for FM or CFS [64]. Nonetheless, it is becoming increasingly clear that there are very important interrelationships between the symptoms of pain, fatigue, and insomnia and the underlying pathogenesis of these symptoms that are so often shared [64].

Exercise and activity level are as important as sleep in CFS and the entire spectrum of illness. Couch potatoes rarely develop CFS. Several reports document that CFS typically occurs in patients who had high premorbid levels of activity, and, in fact, high premorbid levels of activity and a lower body mass in young adulthood were the strongest predictors of CFS later in life [27,65]. Patients often report excellent preillness physical fitness and energy and an abrupt onset of fatigue. After the onset of illness, patients indicate that physical exertion tends to

exacerbate the fatigue. Glass et al [66] demonstrated that within a group of healthy, young subjects, the ones who developed multiple somatic symptoms after experimental exercise cessation were those that had autonomic and immune profiles resembling those of CFS patients. Recent studies performed by our group further examined the additive and synergistic roles that sleep restriction and exercise cessation have on the development of somatic symptoms in healthy patients and demonstrated that regular exercise seems to buffer some of the adverse effects of sleep on symptom development. Female patients were much more likely to have somatic symptoms when deprived of either sleep or exercise.

Because of their frequent co-occurrence, psychiatric and psychological abnormalities have also been very well-studied in CFS. With the advent of a better understanding of the neurobiology of these illnesses, investigators who once staunchly viewed CFS as a psychiatric condition have significantly tempered their views, now acknowledging that these conditions are clearly separable from, and often occur independently of, psychiatric disorders [67,68]. As noted previously, both epidemiologic and twin studies have shown that CFS and other CSS are clearly separate from conditions such as anxiety and depression [39]. Patients with psychiatric conditions earlier in life have a 2 to 3 times greater risk of developing CFS than those who do not have premorbid psychiatric diagnoses, but this still means that most patients with CFS in the general population neither had or have a diagnosable psychiatric condition [69].

Studies have not found personality disorders to be more prevalent in people with CFS. This finding dispels the misconception that these are type A individuals who become dissatisfied with their inability to perform tasks that others also cannot perform. More recent studies, however, did show that a personality trait, neuroticism, was associated with more severe symptoms in those with CFS [69,70]. It is best to think of psychological and psychiatric symptoms similarly to sleep or cognitive disturbances in CFS, that is, as a domain that is important to evaluate in patients with CFS because abnormalities can often be identified. When these comorbidities occur, they often add to the functional burden of the illness, because depression in addition to CFS is likely to be associated with disability and fatigue [71].

POTENTIAL UNDERLYING MECHANISMS IN CFS

Although the CSS conditions all were originally thought to be autoimmune or inflammatory diseases, CFS is one condition in which there are still a sizable number of clinicians and investigators who believe that ongoing infection and/or inflammation plays a significant role in some patients.

The Role of Infections in Triggering CFS and Related Syndromes

One of the reasons that CFS had long been considered an infectious disease is that it is very clear that this symptom complex can be triggered by a variety of infections, including the EBV, Q fever, and Lyme disease, among others [72]. Just recently, infections with unusual or newly discovered pathogens such as the West Nile virus, severe acute respiratory syndrome (ie, SARS), and the H1N1 flu have all been shown to lead to the development of CFS [73-75].

A broader examination of the role of a variety of stressors in triggering this symptom complex helps put this phenomenon in perspective. Arguably the best set of studies examining the underlying mechanisms that are operative in postinfectious CFS are from a large longitudinal study in which the authors analyzed the long-term consequences of infection with 3 different pathogens: the Ross River virus (the cause of epidemic polyarthritis), *Coxiella burnetii* (the cause of Q fever), and EBV and the development of CFS [76]. In this prospective epidemiological study, patients experiencing acute infection with these disparate pathogens were recruited, followed for 12 months, and monitored for the development of fatigue, muscular pain, cognitive dysfunction, and mood disturbances. The symptom complex developed in 12% of the patients at 12 months.

Although these infections cause markedly different acute presentations, a very stereotypical chronic syndrome (characterized by pain, fatigue, and memory difficulties) occurred at a remarkably similar rate after each infection. Demographic, psychological, or microbiological factors during the acute infection did not predict the development of this symptom complex [77]. None of the psychiatric measurements assessed in this study, which included the presence of a premorbid or intercurrent psychiatric disorder, the neuroticism score, and the locus of control score, was significantly predictive of the development of chronic symptoms. As with the studies of emotional stress triggering pain in the population, although distress per se did not predict the chronicity of symptoms after infection, the presence and severity of somatic symptoms (ie, the degree of "somatization") during the acute infection was closely correlated with the subsequent development of chronic fatigue (and pain).

The relationship between acute infection and the development of chronic regional pain and other somatic symptoms has been noted in a number of other conditions related to FM. For example, in a meta-analysis summarizing the results of 8 different studies, Halvorson et al [78] noted that approximately 10% of patients developed postinfectious IBS after an episode of acute infectious gastroenteritis, regardless of the viral or bacterial pathogen that caused the acute illness. Similarly, an episode of acute urinary tract infection is evident in a proportion of women who develop interstitial cystitis/painful bladder syndrome. In fact, in a recent study,

Hamilton and associates [79], who were among the first to investigate this issue across syndromes, found that episodes of gastroenteritis in diagnosed in primary care were risk factors for IBS, whereas viral infections increased the risk for subsequent development of CFS. They again found that premorbid psychiatric disorders such as depression only modestly increased the risk of this occurring.

These results imply that various forms of acute infection are capable of triggering syndromes such as CFS and FM, with multifocal or regional pain; chronic pain most typically occurs in the body region initially affected by the infection. There are often accompanying somatic symptoms such as fatigue, memory, and mood difficulties. The risk of this symptom complex occurring with various infections is consistently found to be approximately 5% to 10%. The reason for this consistency is not clear. Evidently, the inciting infection must be of sufficient severity and duration because the increase in occurrence of chronic symptoms is not observed after common viral infections of short duration. This lack of specificity regarding the triggering effect of infection may well be associated with an underlying genetic predisposition, activated in a similar manner by various pathogens, and/or in patients with a set of "maladaptive" behavioral responses that could lead to symptoms, such as cessation of routine exercise or sleep.

At present, there is one active research area of investigation focused on a potential infection that may be causing CFS: the XMRV virus [80]. Although the study demonstrating both antibody and culture evidence of this virus in a high proportion of CFS patients was methodologically sound, albeit with very few controls, this field has "been here" repeatedly. These results need to be replicated by another group because the institute that performed this study was ostensibly created to identify the infectious or immune underpinnings to CFS, and then longitudinal studies need to demonstrate causality rather than association, as we have learned from previous studies in CFS.

Role of Cytokines

There is an expansive literature on this topic, with the authors of many studies identifying differences in cytokine levels in CFS populations (usually in highly selected tertiary care patients) and others finding normal levels. Antoni, Klimas, and colleagues [81] have arguably been the most active group studying subsets of CFS patients with elevated levels of cytokines, and they have shown that some but not all cytokines are elevated in their cohort of CFS patients compared with control patients. However, other groups have recently published studies in which there was superior methodology, including matching of case and control subjects, such as with population-based approaches, or twin studies. These studies failed to find any specific differences between CFS patient and control subjects, but the population-based studies do show that inflammation is a nonspecific finding in patients with "unwellness" and is also affected by conditions such as obesity [5,82].

In addition, recent findings regarding the role of glial cells, astrocytes, and other neural elements formerly understood to be support structures has led to a critical reexamination of whether subtle inflammatory changes in the central nervous system may be responsible for some of the symptoms observed in conditions such as FM. Immunological cascades have a role in the maintenance of central sensitivity and chronic pain, which is enhanced through release of proinflammatory cytokines by central nervous system glial cells; thus, the traditional paradigm of inflammatory versus noninflammatory pain may gradually be understood as less dichotomous.

COULD CFS (IN PART) REPRESENT A BIOLOGICALLY BASED PERCEPTUAL AMPLIFICATION PROBLEM AS THE RESULT OF AUGMENTED SENSORY PROCESSING?

As briefly discussed, a major pathophysiological finding in all related syndromes that share overlapping clinical and pathogenic features with CFS, such as FM, IBS, chronic headache, and interstitial cystitis, is that these conditions are characterized by hyperalgesia and allodynia, both on experimental pain testing as well as functional neuroimaging. The authors of early studies typically used dolorimetry to assess pressure pain threshold and concluded that tenderness was in large part related to psychological factors because these measures of pain threshold were correlated with levels of distress [83-85].

To minimize the biases associated with "ascending" (ie, the individual knows that the pressure will be predictably increased) measures of pressure pain threshold, Petzke and colleagues [86-89] performed a series of studies using more sophisticated paradigms, including random delivery of pressures. These studies showed that: (1) the random measures of pressure pain threshold were not influenced by levels of distress of the individual, whereas tender point count and dolorimetry examinations were; (2) patients with FM were much more sensitive to pressure even when these more sophisticated paradigms were used; (3) patients with FM were not any more "expectant" or "hypervigilant" than control patients; and (4) pressure pain thresholds at any 4 points in the body are highly correlated with the average tenderness at all 18 tender points and 4 "control points" (the thumbnail and forehead).

In addition to the heightened sensitivity to pressure noted in FM, other types of stimuli applied to the skin are also judged as more painful or noxious by these patients, including heat [88,90-92], cold [91,93], and electrical stimuli [94]. These same findings of hyperalgesia and allodynia have been noted in most of the other conditions acknowledged to be

part of this continuum, including CFS, IBS, TMJD, tension type headache, idiopathic low back pain, vulvodynia, and interstitial cystitis [95-99]. Brain imaging studies also demonstrate the existence of central pain augmentation in FM, IBS, low back pain, and several other conditions [100-102].

Finally, recent studies have suggested that FM and other chronic pain states are not just characterized by hyperresponsiveness to painful somatic or visceral stimuli but that they also exhibit a "left-shift" in noxiousness or unpleasantness of other sensory experiences, such as the brightness of light or loudness of auditory stimuli [103,104]. Geisser and colleagues [105,106] used an identical random staircase paradigm to test FM and CFS patients' threshold to the loudness of auditory tones and to pressure. They found that a measure of sensory sensitivity that combined stimulus:response results for both pressure pain and auditory unpleasantness was increased in both CFS and FM patients compared with controls, was independent of psychiatric status, and was strongly correlated with symptoms as well as functional status in both CFS and FM patients.

The notion that FM and related syndromes might represent syndromes in which there is biological amplification of all sensory stimuli has significant support from functional imaging studies that suggest that the insula is one of the most consistently affected regions. This region has been noted to play a critical role in sensory integration, with the posterior insula serving a purer sensory role and the anterior insula associated with the emotional processing of sensations [107-109].

Because self-report of both central and peripheral fatigue are determined on the basis of the patient's "perception," it is conceivable that sensory amplification may be playing a fundamental role in the pathogenesis of CFS and may play a role in other fatigue states. No studies have directly assessed this hypothesis in CFS by demonstrating a similar "left-shift" in many stimulus:response functions, but nearly all studies that have examined the fatigue response to any single stimuli (eg, work performed on exercise or cognitive testing) have noted a similar left-shift to what has been observed with other sensory experiences throughout this spectrum of illness [25,110].

The Potential Role of Specific Neurotransmitters

Overall, the analogy of an increased "volume control" or "gain" setting on pain and sensory processing in conditions such as FM and CFS is supported by studies from a variety of sources and probably is largely responsible for the acknowledged overlap between these conditions and "multiple chemical sensitivity," which is a misnomer because these patients also experience a left-shift in noxious threshold to many sensory stimuli. Similar to essential hypertension in which a variety of root causes can lead to elevated systemic blood pressure, these disorders may in part represent "essential hypertension of pain and sensory processing pathways."

In FM there has been extensive study of neurotransmitters levels that tend to be pronociceptive (ie, Figure 3, left) or inhibit pain transmission (ie, Figure 3, right), have a tendency to increase the volume control. Drugs that block neurotransmitters on the left or augment activity of those on the right will typically be found to be effective treatments, at least for a subset of patients with this spectrum of illness.

The arrows on Figure 3 indicate the direction of the abnormalities in neurotransmitter levels (either in the cerebrospinal fluid [CSF] or other parts of the brain) that have been identified to date in FM. As noted, in FM there is evidence for increases in the CSF levels of Substance P, glutamate, nerve growth factor, and brain-derived neurotrophic factor, and low levels of the metabolites of serotonin, norepinephrine, and dopamine. Any of these could lead to an "increase in the volume control" and augmented pain and sensory processing [111-114]. The only neurotransmitter system that has been studied to date and not found to be out of line in a direction that would cause augmented pain transmission is the endogenous opioid system. Both CSF levels and brain activity by functional neuroimaging appears to be augmented, not reduced (as would cause augmented pain processing) in FM, which may be why opioidergic drugs do not work well to treat FM and related pain syndromes [115,116].

It is of note that nearly all of these neurotransmitters that are known to affect pain and sensory transmission also have profound effects on energy level and alertness, sleep, and other related homeostatic functions. Therefore, it is quite conceivable that imbalances of neurotransmitters in brain neurotransmitters that are believed to be playing roles in pain transmission may be similarly leading to central fatigue and sleep disturbances when these same imbalances between excitatory and inhibitory neurotransmitters occur in brain regions that control these functions in CFS.

Function of the Stress Systems in CFS and Related Conditions

Because of the fact that disparate "stressors" can trigger the development of these conditions, the human stress response has been closely examined for a causative role. These systems are mediated primarily by the activity of the corticotropin-releasing hormone nervous system located in the hypothalamus and locus-ceruleus-norepinephrine/autonomic nervous system in the brain stem. Recent research suggests that although this system in humans has been highly adaptive throughout history, the stress response may be inappropriately triggered by a wide assortment of everyday occurrences that do not pose a real threat to survival, thus initiating the cascade of physiologic responses more frequently than can be tolerated [117]. The type of stress and the environment in

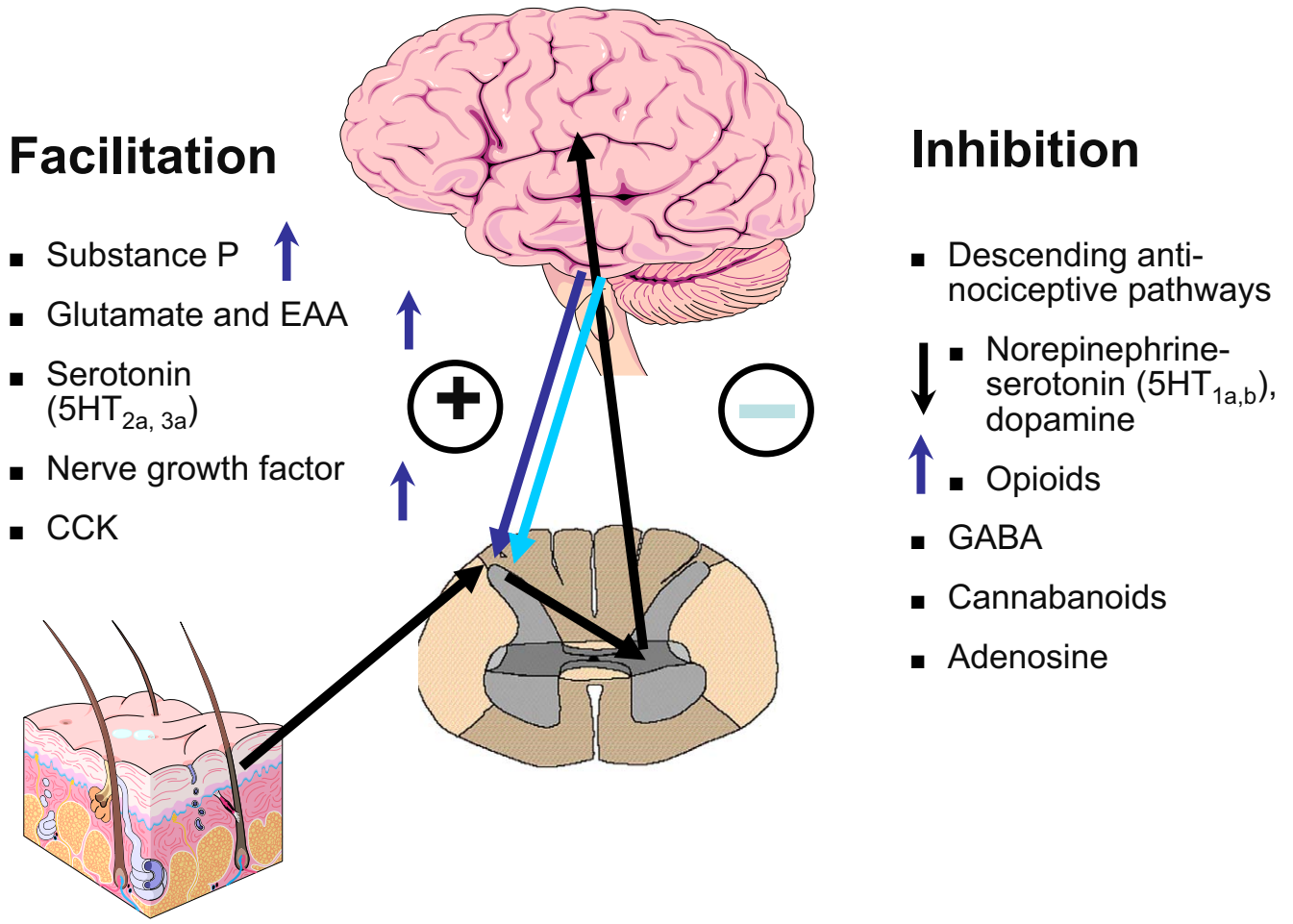

Figure 3. Neural influences on pain and sensory processing.

which it occurs also have an impact on how the stress response is expressed. It has been noted that victims of accidents experience a greater frequency of FM and myofascial pain than those who cause them, which is congruent with animal studies showing that that the strongest physiological responses are triggered by events that are accompanied by a lack of control or support and thus viewed as perceived as inescapable or unavoidable [118]. In humans, daily "hassles" and personally relevant stressors seem to be more capable of causing symptoms than major catastrophic events that do not personally impact the individual.

The authors of 2 studies performed in the United States just before and after the terrorist attacks of 9/11 point out that not all psychological stress is capable of triggering or exacerbating fatigue, pain, or other somatic symptoms. In one study performed by Raphael and colleagues [43], no difference in fatigue, pain, or other somatic symptoms was seen in residents of New York and New Jersey who had been surveyed before 9/11 and then just after the terrorist attacks on the World Trade Center. In another study performed in the Washington, DC, region (near the Pentagon) during the same time period, patients with FM had no worsening of pain or other somatic symptoms after the attacks compared with just before the attack [42].

Recent reviews regarding the role that "stressors" (eg, infections, physical trauma, emotional stress) or catastrophic events may have in triggering the development of CFS, FM, or related conditions have identified several factors that may be much more important than the intensity of the "stressor" in predicting adverse health outcomes. Female gender, worry or expectation of chronicity, lack of control of the stressor, intensity of the initial symptoms, and inactivity or time off work after the stressor make it more likely to trigger the development of pain, fatigue, or other somatic symptoms [119]. Naturally occurring catastrophic events such as earthquakes, floods, or fires are much less likely to lead to chronic somatic symptoms than similarly stressful events that are "human-made," such as chemical spills, or war [120]. Being exposed to a multitude of stressors simultaneously, or during a period of time, may also be a significant risk for

later somatic symptoms and or psychological sequelae. Intensely stressful events can lead to permanent changes in the activity of both mouse and human stress response systems [117,121].

This link between exposure to "stressors" and the subsequent development of CFS and FM led to studies of human stress systems in this condition. These studies have generally shown alterations of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system in CFS and related conditions [122-127]. Although these studies often note either hypo- or hyperactivity of both the HPA axis and sympathetic nervous system in patients with FM and related conditions, the precise abnormality varies from study to study. Moreover, these studies only find "abnormal" HPA or autonomic function in a very small percentage of patients, and there is tremendous overlap between patients and control patients in these studies.

The best recent studies of the HPA axis in CFS provide continued support for enhanced glucocorticoid negative feedback and/or a reduced central HPA axis drive in groups of patients with CFS, but they point out a very important confound in studying HPA function: early life stress. Heim and others have shown that early life stress may lead to permanent changes in HPA functions in humans, and recent studies have suggested that the presence or absence of early life stress was a potent predictor of HPA function in both CFS and population-based studies [128,129]. Similar findings have been noted with FM patients, demonstrating that the presence or absence of early life stress influenced CSF levels of corticotropin-releasing hormone more strongly than any other factor [130]. Studies in FM suggest that HPA function is related to levels of pain but not fatigue [131]. In fact, HPA findings in groups of patients with CFS have not been found to be related to levels of fatigue.

Changes in baseline function of the stress response that may occur after a stressor earlier in life have been shown to predict which symptom-free patients without chronic pain or other somatic symptoms are more likely to develop these somatic symptoms. This has been noted both in population-based studies and in experiments in which healthy young adults are deprived of regular sleep or exercise [66,132].

This theoretical link among stress, changes in stress axis activity, and subsequent susceptibility to develop fatigue or other somatic symptoms or syndromes is also supported by studies demonstrating that patients with FM and related conditions may be more likely than nonaffected patients to have experienced physical or sexual abuse in childhood [133-136]. This appears to profoundly influence HPA function in CFS, and recent studies in CFS have established that early life stress is similarly a major determinant of the abnormal HPA findings in a group of CFS patients versus controls. This pattern of HPA hyporesponsiveness was predictive of a lack of response to CBT, demonstrating the importance of identifying subsets of patients before treatment [128,137].

Role of Autonomic Dysfunction

Heart rate variability at baseline, and with tilt table testing, has been evaluated in patients with CFS and FM as a surrogate measure of autonomic function. Findings have been somewhat inconsistent, especially with tilt table testing [138]. Some of these findings may be indicative of uncovering a diathesis to stress, or a response to deconditioning. For example, several experimental studies have shown that alterations in heart rate variability similar to those in CFS or FM populations may actually represent a diathesis as a marker of autonomic tone that places patients at risk for developing CFS, FM, or related illnesses [66,132,139], possibly identifying patients at risk.

Also, a recent study showed that heart rate variability was normalized after exercise therapy, suggesting that some of these findings may be an epiphenomenon caused in part by deconditioning [140,141]. However, there clearly is a subset of patients with prominent autonomic dysfunction within this spectrum of disorders, and the authors of a recent study [142] suggest that deconditioning plays a role, and a subset of individuals with low cardiac output. Recent studies have pointed out that some of this autonomic dysfunction may be due to deconditioning, and that in some individuals with CFS this may be severe enough to lead to lead to low cardiac output. Peripheral fatigue is likely to contribute to the fatigue picture in these patients with CFS and FM.

It is likely that these neurobiological alterations are shared with other syndromes known to be associated with HPA and/or autonomic function such as depression or posttraumatic stress disorder. A model of susceptibility and developmental aspects of these disorders that takes into account both genetics and personality as risk factors is illustrated in Figure 3. This recognizes the critical importance of stressors in resetting stress response systems, as well as other factors, including (1) the role of behavioral adaptations to these stressors such as cessation of routine exercise and (2) whether an individual is in an environment characterized by control or support.

Twin Studies in CFS

Twin studies have been very instructive in determining key clinical features as well as estimations of the roles of genetics versus environmental factors. Kato and colleagues [39,143,144] have performed a series of studies by using a very large Swedish twin registry and have determined that CFS, FM, IBS, and headache share key symptoms of fatigue, multifocal pain, insomnia, and memory difficulties and that they can be clearly distinguishable from depression and anxiety. In aggregate, these studies suggest that approximately half the risk of developing these illnesses is genetic and the other half environmental.

A series of elegant twin studies performed by Buchwald and colleagues [18,145-149] with identical twins discordant

for CFS has generally shown very few objective differences in coping strategies, sleep, and a number of other measures. They have suggested that genetic factors may be playing a more significant role in male than female patients with these illnesses, and the authors suggest that perceptual abnormalities in sensory symptom expression may represent the biggest difference between affected and nonaffected twins.

Similar Treatments Work for Many of the CSS Entities

There have been very few randomized controlled trials of drugs for CFS, but several drug and nondrug therapies have been shown to be effective for nearly any of the functional somatic or central sensitivity disorders, further reinforcing that this may well be a large overlapping disorder rather than several separate ones. Among classes of drugs, substantial data suggest that tricyclic compounds are effective for treating most of the conditions noted [150-152]. Newer serotonin-norepinephrine reuptake inhibitors such as duloxetine and tramadol have similarly been shown to be effective across a broad range of these conditions [153], and interestingly duloxetine had much earlier been shown to be helpful in treating the pain associated with depression, which is not surprising. The alpha-2-delta ligands such as pregabalin and gabapentin also are being shown to be efficacious in a wide range of these entities [154].

The overall average improvements in fatigue noted with these classes of drugs in FM is not as great as the average improvements in pain, in part because fatigue is a relatively common adverse effect of all of these drugs, leading to less impressive overall effects. However, when patients with FM and CFS have a favorable clinical response to these medications (generally noted in approximately one-third of patients) there is typically a global improvement in all symptoms, including fatigue as well as pain [154-156]. This observation would support the notion that similar neurotransmitter disturbances can lead to many somatic symptoms, including both pain and fatigue.

Figure 4 lists the classes of drugs and their level of evidence in FM. Those drugs with the greatest level of efficacy in FM are also being shown to work in subsets of patients with CSS. More importantly, drugs such as duloxetine are being shown to be effective in conditions such as osteoarthritis and low back pain, demonstrating the these central mechanisms that are "front and center" in patients with syndromes such as FM may be also playing prominent roles in conditions heretofore thought to be peripheral pain syndromes. However, we have known for some time that hyperalgesia and manifestations of central factors, as well as various other indicators of a wide range of "fibromyaglia-ness," are present in conditions such as osteoarthritis and low back pain.

Any one of these classes of drugs only works well in approximately one-third of patients, a fact entirely consistent

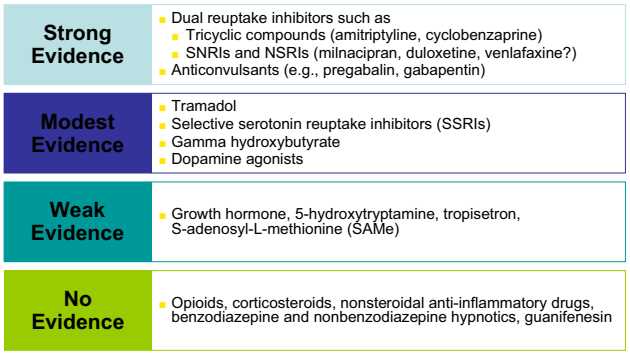

Figure 4. Pharmacological therapies.

with findings supporting the strongly genetic, but polygenic, disorder. Thus, clinicians will need different treatments for different patients. Going back to the "essential hypertension of pain processing pathway" analogy, just as we use 8 to 10 classes of drugs acting in different body systems and at different molecular targets to control hypertension, and patients may respond very well to one class of antihypertensive drug but not another, the same is true of CSS syndromes. Patients may only respond to one of these classes of drugs or may often be in several classes of centrally acting analgesics (eg, a low dose of cyclobenzaprine at bedtime, pregabalin or gabapentin either just at bedtime or twice daily, and a serotonin-norepineprine reuptake inhibitor such as duloxetine or milnacipran during the day). However, our current pharmacological armamentarium is not nearly as well-developed for central pain as for essential hypertension, which is likely one of the reasons that these syndromes are often still difficult to treat.

Figure 4 also points out that classes of drugs that are quite effective for "peripheral" pain as the result of damage or inflammation in peripheral tissues, such as nonsteroidal antiinflammatory drugs and opioids, are not effective analgesics in central pain states. There are even data suggesting that administering opioids to patients with central pain states could worsen their pain by leading to opioid-induced hyperalgesia, which could augment and worsen the baseline hyperagesia that may be playing a central pathogenic role in these conditions.

Just as many pharmacological therapies work across all or most of these conditions, similarly, nonpharmacological therapies such as education, exercise, and CBT have been demonstrated to be effective across nearly all of the CSS conditions [157-159]. Both exercise and CBT have wide acceptance and are supported by RCTs in CFS.

When prescribing exercise in CFS, it is important to realize that these patients are different than healthy ones. The physiological cost of walking is significantly greater for people with CFS compared with healthy subjects. The reasons

for these greater energy demands for walking in those with CFS have yet to be fully elucidated, but research suggests the physiological need for very slow, graded exercise programs to treat CFS and other related conditions [160,161]. Light and colleagues have recently demonstrated that after moderate exercise, CFS and CFS-FMS patients show enhanced gene expression for receptors detecting muscle metabolites and for sympathetic nervous system activation [162]. This finding supports the need for a "start low, go slow" therapeutic approach to exercise in CFS, especially because exacerbations after overactivity are very common.

CONCLUSION

In the past few decades, our understanding of CFS has evolved significantly, as has our understanding of related conditions. CFS is a condition that has strong biological underpinnings and shares pathogenic features and response to treatment with many other syndromes characterized by clusters of multifocal pain, fatigue, and other somatic symptoms. A better understanding of the underlying mechanisms and most effective treatment for this spectrum of illnesses is critical to support clinicians treating these very common conditions. There are clearly subsets of patients with CFS that have differing underlying reasons for their symptoms, and current efforts are focused on identifying subsets that would preferentially respond to therapies directed at root causes.

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