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Fibromyalgia: A Critical and Comprehensive Review

Andrea T. Borchers[1] · **M. Eric Gershwin**[1]

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Abstract Fibromyalgia is a disorder that is part of a spectrum of syndromes that lack precise classification. It is often considered as part of the global overview of functional somatic syndromes that are otherwise medically unexplained or part of a somatization disorder. Patients with fibromyalgia share symptoms with other functional somatic problems, including issues of myalgias, arthralgias, fatigue and sleep disturbances. Indeed, there is often diagnostic and classification overlap for the case definitions of a variety of somatization disorders. Fibromyalgia, however, is a critically important syndrome for physicians and scientists to be aware of. Patients should be taken very seriously and provided optimal care. Although inflammatory, infectious, and autoimmune disorders have all been ascribed to be etiological events in the development of fibromyalgia, there is very little data to support such a thesis. Many of these disorders are associated with depression and anxiety and may even be part of what has been sometimes called affected spectrum disorders. There is no evidence that physical trauma, i.e., automobile accidents, is associated with the development or exacerbation of fibromyalgia. Treatment should be placed on education, patient support, physical therapy, nutrition, and exercise, including the use of drugs that are approved for the treatment of fibromyalgia. Treatment should not include opiates and patients should not become poly pharmacies in which the treatment itself can lead to significant morbidities. Patients with fibromyalgia are living and not dying of this disorder and positive outlooks and family support are key elements in the management of patients.

Keywords Chronic pain · Opiates · Patient support · Trauma · Fibromyalgia · Coping · Stress · Chronic fatigue syndrome

Abbreviations

ACC	Anterior cingulate cortex
ACR	American College of rheumatology
ACTH	Adrenocorticotropic hormone
AGE	Advanced glycation end product
AUC	Area under the curve
AVS	Arteriole-venule shunts
BAI	Beck anxiety inventory
BDI	Beck depression inventory
BMI	Body mass index
BOLD	Blood oxygen level dependent
CAP	Cyclic alternating pattern
CES	D Center for Epidemiologic Studies Depression Scale
CFS	Chronic fatigue syndrome
CML	Carboxymethyllysine
CoQ10	Coenzyme Q10
CRH	Corticotropin-releasing hormone
CSF	Cerebrospinal fluid
CWP	Chronic widespread pain
DLPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
DNIC	Diffuse noxious inhibitory control
DRG	Dorsal root ganglion
DST	Dexamethasone suppression test
ENFD	Epidermal nerve fiber density
FIQ	Fibromyalgia impact questionnaire
FMS	Fibromyalgia syndrome

✉ M. Eric Gershwin
megershwin@ucdavis.edu

[1] Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis School of Medicine, 451 Health Sciences Drive, Suite 6510, Davis, CA 95616, USA

GABA	γ-aminobutyric acid
GHRH	Growth hormone releasing hormone
HADS	Hospital Anxiety and Depression Scale
HPA	Hypothalamic pituitary adrenal
HRV	Heart rate variability
IGF-I	Insulin-like growth factor-I
IBS	Inflammatory bowel syndrome
ICPM	Inhibitory conditioned pain modulation
IL	Interleukin
ITT	Insulin tolerance test
LEP	Laser-evoked potential
MOR	μ opioid receptor
MPQ	McGill Pain Questionnaire
MRS	Magnetic resonance spectroscopy
NAA	*N*-acetylaspartate
NFR	Nociceptive flexion reflex
NMDA	*N*-methyl-D-aspartate
NREM	Non-rapid eye movement
PrelimACR 2010 criteria	Preliminary ACR 2010 diagnostic criteria
PAG	Periaqueductal gray
PBMC	Peripheral blood mononuclear cells
PPT	Pressure point threshold
QoL	Quality of life
RA	Rheumatoid arthritis
RAGE	Receptor for AGE (= advanced glycation end product)
REM	Rapid eye movement
ROS	Reactive oxygen species
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
SSS	Symptom severity scale
TSD	Total sleep deprivation
WPI	Widespread pain index

Introduction

Fibromyalgia has been called everything from an autoimmune to an infectious to a somatic disease. There is in fact no evidence that fibromyalgia is either autoimmune or infectious, but because of its widespread inclusion in these categories and the fact that it is commonly evaluated and treated by rheumatologists makes it an ideal syndrome for discussion in a wide variety of specialties. In this comprehensive review, we will attempt to place fibromyalgia in perspective, including its definitions, its classification, recent research efforts, and an overview of treatment. Although known under a variety of names for at least a century, what is now designated as fibromyalgia or fibromyalgia syndrome (FMS) did not receive its first detailed clinical description until the 1970s [1, 2]. Smythe, in his seminal papers [1, 2], and subsequently other clinicians, proposed diagnostic or classification criteria for FMS, which required widespread pain and a minimum number of tender points (TPs), i.e., anatomic sites that exhibit excessive tenderness upon palpation [3]. Most diagnostic criteria also included non-restorative sleep, fatigue, and morning stiffness. In addition, it was customary to distinguish between primary and secondary fibromyalgia in the absence or presence, respectively, of other medical conditions that might cause, or contribute to, its symptoms. In 1990, a consortium of centers interested in FMS began a multi-center study with the goal of providing classification criteria for this syndrome. A variety of symptom variables were considered, including sleep disturbances, fatigue, morning stiffness, anxiety, irritable bowel syndrome (IBS), headaches, Raynaud-like phenomenon, sicca symptoms, prior depression, paresthesias, and *pain all over*. Nonetheless, the criteria that best distinguished between FMS and other rheumatological and pain disorders were the presence of chronic widespread pain (CWP) and 11 of 18 specific TP sites (see also Table 1). The distinction between primary and secondary FMS was abandoned. These classification criteria were endorsed and published in 1990 by the American College of Rheumatology (ACR) and will be referred to as ACR 1990 criteria in this article [4].

As simple and straightforward as the ACR 1990 criteria may seem, they have nonetheless been interpreted in a variety of ways. The ACR 1990 criteria publication specifically states that "pain in 3 sites (e.g., the right shoulder, left buttock, and the thoracic spine) qualifies as widespread pain" ([4], p. 163). This is correctly summarized as "pain in at least two diagonally opposed quadrants plus axial skeletal pain" [5], but is interpreted as "pain in all four quadrants of the body plus the axial skeleton" in some studies, particularly from Scandinavia, but also from the USA [6–9], as pain in "at least 3 of 4 quadrants" in others, and the axial skeleton sometimes goes unmentioned [10, 11]. Whether it is preferable to perform the tender point examination by digital palpation or dolorimetry also remains a matter of debate [12, 13]. In addition, some clinicians simply ask patients to indicate when the procedure becomes painful; others require a clear expression of pain, such as a grimace, flinch, or withdrawal [7, 14, 15]. These differences in the interpretation of the criteria for CWP and TPs have most likely resulted in considerable heterogeneity between the patient cohorts recruited for individual studies, even though they all fulfilled the ACR 1990 criteria.

It has since become clear that the TP criterion has a variety of problems. TP counts are not very reproducible [16–18], are significantly higher in women [19, 20], and are strongly correlated with various measures of distress and negative affect [20–22]. This biases the patient population toward females and subjects with high levels of psychological distress. Furthermore, the standard assessment of TPs using ascending paradigms is vulnerable to response bias either because the anticipation of a painful stimulus results in heightened pain sensitivity or because the predictability of the stimulus lowers

Table 1 The ACR 1990 criteria for the classification of fibromyalgia [4]

In order to be classified as having fibromyalgia the patient must fulfill the following two criteria:
1) History of widespread pain (present for at least 3 months) with widespread pain defined as pain in the left and right sides of the body, pain above and below the waist and pain in the axial skeleton (cervical spine, anterior chest, thoracic spine, or low back).
2) Pain in 11 of 18 tender point sites on digital palpation (performed with a force of ~4 kg/cm^2 at 9 symmetrical sites that are specified in great detail)

Table 2 The proposed/preliminary 2010 ACR criteria

A patients satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met
1) WPI≥7 and SS≥5 OR WPI 3–6 and SS≥9
2) Symptoms have been present at a similar level for at least 3 months
3) The patient does not have a disorder that would otherwise explain the pain
The WPI is obtained by summing the body areas (out of a possible 19 sites) in which the patient indicates having experienced pain during the preceding week, i.e., it can range from 0–19.
The SSS consists of two parts.
1) The patient grades the severity over the past week of three somatic symptoms (waking unrefreshed, disturbed cognition, and fatigue) on a scale of 0–3, resulting in a maximum score of 9.
2) The physician rates the overall extent of somatic symptoms on a 4-point scale (0 absent, 1=slight, 2=moderate, or 3=severe). A total of 41 symptoms are suggested for consideration, but what number of symptoms corresponds to which of the four categories remains unspecified.
The total possible score for the SSS is 12.

anxiety and thereby reduces the reported pain sensitivity [21]. Even though they are classification, not diagnostic, criteria, the ACR 1990 criteria are used for the diagnosis of FMS. Generally, only rheumatologists are taught how to do the TP examination, yet primary care practitioners should be able to diagnose FMS.

Diagnostic criteria that do not include a TP examination were proposed in 2010 (see Table 2) [23]. These have been approved by the ACR Board of Directors as provisional, but have not been formally adopted [24–28]. They represent a paradigm shift from a syndrome characterized mainly by widespread pain and tenderness to a multi-symptom syndrome in which tenderness is just one of many symptoms. They also introduce a new definition of CWP according to which the pain sites can be confined to a single body quadrant without any involvement of the axial skeleton. Further modifications of these criteria have been proposed in order to make them suitable for use in epidemiological studies by relying exclusively on self-administered questionnaire responses and eliminating the requirement for a physical examination [29]. This makes them a screening tool for FMS-like disorders; nonetheless, contributing authors of the old and new criteria themselves inconsistently and incorrectly refer to patients identified via the survey questionnaires as having FMS [30]. This diagnostic label cannot be applied unless a physician has ruled out other diseases and disorders that could explain the pain. The importance of this provision is highlighted by the finding that even physicians who referred patients to a rheumatologist for suspected FMS missed a diagnosis of inflammatory or degenerative arthritis or soft tissue rheumatism in 45 % of cases [31]. As summarized in Table 3, the prelimACR 2010 criteria were shown to have good specificity (range 91–99 %), but highly variable sensitivity (55–82 %) compared with either a clinical diagnosis or fulfillment of the ACR 1990 criteria [32–35]. Application of the survey criteria in patient cohorts from the US [36], the UK [35], Canada [37], Japan [38], Spain [39], and Germany [40] has yielded very heterogeneous results for both sensitivity and specificity, particularly when using the ACR 1990 criteria as the standard. The discrepancies may partly stem from the different settings and spectra of pain disorders from which the patient samples were recruited and may also reflect true heterogeneity of patients with different ethnic and sociocultural backgrounds. Most importantly, there is very little overlap between the patient groups identified by the different criteria sets or their precursors [35, 41]. This makes the proposition to use the prelimACR 2010 criteria and the ACR 1990 classification criteria side by side untenable if the goal is to identify a homogeneous patient population [23].

Epidemiology

The prevalence of FMS very much depends on the case-finding method(s) and the diagnostic criteria, but even application of the ACR 1990 criteria has resulted in prevalence estimates ranging between 0.4 % (in Greece) and 8.8 % (in Turkey) in population-based studies [35, 42]. In the USA, FMS affects an estimated 2.0 % of the adult population (3.4 % of females and 0.5 % of males). Not surprisingly, the prevalence of FMS-like disorders according to the *survey criteria* is markedly higher in two population-based studies [35, 43], though not in a third [30]. Very limited data are available on the incidence of FMS, which was estimated to be 583/10^5 among Norwegian women aged 20–49 years using ACR 1990 criteria [44], whereas estimates based on ICD-9 codes were 1128 and 688 per 10^5 among female and male adults, respectively, in the USA [45]. There are indications that FMS remains seriously underdiagnosed. Only 12–28 % of subjects identified during population-based surveys as fulfilling the ACR 1990 criteria had ever been diagnosed with FMS [46, 47]. Yet, FMS is also overdiagnosed, which carries

Table 3 Sensitivity and specificity of prelim ACR 2010 and "Survey Criteria" compared to a clinical diagnosis or the ACR 1990 criteria

Country	*n* for patients fulfilling the new criteria	*n* for total sample	Source of the patient sample	Criteria	Standard	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Reference
Iran	n.a.	278	Rheumatology patients: FMS [168] and other rheumatic diseases [110]	ACR 2010	Clinical diagnosis	58.9	92.8	92.5	59.9	72.4	[34]
				"	ACR 1990					79.1	"
Korea	92	98	Rheumatology patients	ACR 2010	ACR 1990	92					[33]
UK (Scotland)	7	32	Population-based sample with or without pain	ACR 2010	ACR 1990	55	99				[35]
Japan	81	137	Rheumatology patients: FMS [94], RA and OA [43]	ACR 2010	ACR 1990	82	91	95	70		[32]
Japan	303	693	Rheumatology patients: FMS [462] RA and OA [231]	survey	ACR 1990	64	96	97	56		[38]
US	173	321	Patients with FMS [135] and various pain disorders	survey	ACR 1990	83	67			74	[36]
Canada	157	451	Rheumatology patients with widespread pain	survey	Clinical diagnosis	90	89.5			89.8	[37]
Spain	511	873	FMS patients [579] from FMS associations and their friends [294]	survey	Clinical diagnosis	88.3	91.8	95.5	79.9	89	[39]
UK (Scotland)	27	32	Population-based sample with or without pain	survey	ACR 1990	64	79				[35]
Germany	108	128	FMS patients from self-help groups and different clinical institutions	survey	ACR 1990					72.7	[40]

the risk of failing to identify and treat conditions that are highly amenable to therapy [31].

Worldwide, females outnumber males by an average of 3:1, but female:male ratios as high as 39:1 have been reported in FMS patients fulfilling the ACR 1990 criteria [42]. Subjects who fulfill the *survey criteria* and subjects with CWP still show a female preponderance, but it is far less pronounced [35, 43]. However, the criteria are not the only reason for the higher proportion of females among FMS patients. There are findings suggesting that differences in healthcare-seeking behavior between men and women along with reluctance of physicians to diagnose FM in men also contribute to the different prevalence estimates in males and females [43]. Whether the clinical expression and impact of FMS differ between male and female patients cannot be determined from the highly conflicting results reported to date [48–52]. In addition to female sex, lower education and other indicators of lower social status have consistently been identified as risk factors for developing FMS and CWP [53–57]. The prevalence is generally low in the youngest age group (~18–30 years of age), but rapidly rises thereafter, with some studies finding peak prevalence rates in the 6th or 7th decade of life [54], whereas others do not observe a peak until 75–85 years of age [42, 58]. While the overall data suggest that there are marked differences in the frequency with which FMS affects specific ethnic groups [42], there are no direct comparisons to support this notion. However, according to community-based data from the USA, FMS may affect African-American and some other minority women significantly more often than women of Hispanic or other European descent [46].

There are several major issues that neither the ACR 1990 nor the prelimACR 2010 criteria address. First, all of the core symptoms of FMS are continuously distributed in both frequency and severity in the general population, and both criteria sets identify the most severe end of this continuum [50, 59, 60]. Second, FMS patients commonly exhibit a variety of symptoms that seem to cluster into syndromes such as chronic fatigue syndrome (CFS), IBS, and other disorders that

are often coined functional somatic syndromes, medically unexplained symptoms, or somatization disorder. In the opinion of some authors, it still remains uncertain whether FMS and these syndromes are all subtly different expressions of the same underlying process or represent distinct entities [61]. A major advantage of the ACR 1990 criteria has been that they have made it possible to explore the association between FMS and comorbidities independent of the diagnostic criteria [28]. In community-based samples, between 23 and 58 % of subjects with FMS or CWP fulfill the criteria for CFS [62–64], with similar values reported in clinical samples [65, 66]. Conversely, 16–37 % of patients diagnosed with CFS also fulfill the criteria of FMS [62, 67, 68]. Between 32 and 80 % of patients with FMS suffer from IBS [61, 69], and 26 to 65 % of patients with IBS also have FMS [70]. In a population-based twin study, twins affected by CWP were >5 times more likely to be affected by IBS compared to the unaffected twins (25.2 vs. 5.4 %) [64]. Other common comorbidities include tension type headaches and migraine, temporomandibular disorder, interstitial cystitis, chronic prostatitis, and vulvodynia.

The Symptoms and Some of Their Objective Correlates

Pain and Hypersensitivity

The core symptom of FMS is CWP. FMS patients report higher pain intensity than patients with rheumatoid arthritis (RA) or ankylosing spondylitis [71]. Yet, they do not necessarily consider pain to be their most bothersome or most severe symptom. Instead, FMS patients ranked the intensity of their pain as lower than the intensity of morning stiffness, fatigue, and non-restorative sleep [72]. Two thirds of FMS patients in the clinical study that resulted in the ACR 1990 criteria endorsed the descriptor *pain all over* [4], and the pain of FMS is often described as diffuse, but drawings of the clinical pain pattern indicate that patients experience pain in numerous localized areas rather than *all over*, with the shoulders, arms, lower back, and buttocks and thighs being most frequently reported as painful [73, 74]. FMS patients use more pain descriptors from the McGill Pain Questionnaire (MPQ) than patients with other rheumatological disorders [71, 75]. Overall, the most frequently chosen words are throbbing, aching, and tender from the sensory subsection and exhausting and wretched from the affective-evaluative subsection [75–77]. Most patients describe their pain as continuous, though of fluctuating intensity with periodical exacerbations [71, 77–79]. In a subset of patients, particularly those with more pronounced hypersensitivity to pressure pain, there may be a distinct diurnal rhythm, with pain, stiffness, and fatigue being highest in the morning and lowest in the late afternoon [80], but this may not become obvious during a limited observation period (e.g., 40 h) [81].

FMS patients perceive stress, emotional distress, weather changes, cold, sleeping problems, and strenuous exercise as the most aggravating factors for their symptoms in general and pain in particular, while rest, relaxation and warmth are considered helpful by the majority of patients [72, 82]. Importantly, the pain and other symptoms of FMS are invisible, and while they are always present in the majority of patients, they are also quite variable, i.e., their intensity changes from day to day and within the day [83–86]. Their unpredictability along with the difficulty of family, friends and physicians to accept the reality of these symptoms are in themselves further sources of stress and distress for FMS patients. Other factors that strongly influence pain perception are coping styles, in particular catastrophizing and having an external locus of control, which positively correlate with pain and other symptoms, while self-efficacy is associated with reduced pain perception [87–90].

Central Sensitization/Amplification of Pain Signals

Studies in experimental animals and humans have shown that intense or prolonged nociceptive input can result in a protracted increase in the excitability of dorsal horn neurons, designated as central sensitization [91]. Typical manifestations of central sensitization include allodynia (pain resulting from a normally innocuous stimulus) particularly to dynamic mechanical stimuli, hyperalgesia (increased sensitivity to pain) especially to punctate or pressure stimuli, aftersensations, and temporal summation (progressive increase in the response to repetitive noxious stimulation). According to the ACR 1990 criteria, a defining feature of FMS is a decreased pain threshold, i.e., allodynia, for pressure pain at the TPs. The nociceptive flexion reflex (NFR) is a physiological correlate of spinal nociception. The NFR threshold was found to be decreased in FMS patients [92, 93], and to show a strong positive correlation with the pressure pain threshold [93], thereby providing objective evidence for abnormalities in central pain processing. Compared to healthy controls, patients with FMS as a group exhibit enhanced temporal summation of heat and pressure pain [94–96] and of the pain induced by repeated intramuscular electrical stimulation just above the pain threshold [97, 98]. They also show more pronounced and prolonged aftersensations after repeated mechanical and heat stimulation [95, 99, 100]. The evidence for spatial summation of pain is not only more limited, but also more inconsistent, with one study showing spatial summation of cold pain [101], but others finding similar spatial summation of heat pain and mechanical pain in FMS and healthy subjects [96, 99].

The hypersensitivity of FMS patients is not confined to pressure stimuli, but extends to pinprick [5, 102], heat pain [76, 92, 102–111], and cold pain [92, 102, 103, 111]. In

addition, subjects with FMS show decreased thresholds or tolerance for electrical stimulation [76, 104], and auditory stimuli [112–114]. Thus, patients with FMS exhibit many features consistent with central sensitization, but their generalized hypersensitivity and the widespread nature of their pain go beyond the localized phenomenon conceptualized as *central sensitization*, which refers to a specific spinal mechanism. Since other central neurophysiological processes are likely to contribute to the enhanced pain perception of FMS patients the term *central amplification* is considered more appropriate [115].

This heightened sensitivity to noxious stimuli has been interpreted as a manifestation of generalized hypervigilance [112]. Hypervigilance is a theoretical construct that could well prove helpful in understanding the hyperalgesia of FMS patients. Unfortunately, the element of attentional focus on somatic distress signals that was part of the original concept has been lost from many of the redefinitions and operationalizations that have been proposed; these can range from something very similar to hyperalgesia (perceptual amplification) to distractibility [116]. The lack of consensus on the definition of the concept or on its appropriate operationalizations greatly hampers its usefulness in FMS [116–118].

Inhibitory Conditioned Pain Modulation or Diffuse Noxious Inhibitory Control

In healthy subjects, application of a strong noxious stimulus to one part of the body inhibits the perception of another painful stimulus delivered to a distal part of the body. This used to be referred to as diffuse noxious inhibitory control (DNIC) and is now called inhibitory conditioned pain modulation (ICPM). Compared to healthy controls, patients with FMS exhibit deficits in ICPM, as demonstrated using a variety of conditioning stimuli (e.g., tonic heat stimuli [104], immersion of one hand in hot water [119], ischemia [120], or cold pressor test [101, 105, 121–124]) and a variety of outcome measures (pressure pain threshold [120], electrical pain threshold [104], temporal summation of heat pain [119], or thermal pain intensity [101, 105, 121, 124]). It should be noted that DNIC usually requires a painful stimulus to induce an analgesic response, but this system may already be fully engaged in FMS patients, such that further painful stimulation cannot inhibit the perception of additional pain due to a ceiling effect. This is indirectly supported by studies demonstrating that analgesic processes that do not require further pain stimuli are intact in FMS patients, as shown for distraction-induced or expectancy-mediated analgesia [125, 126]. However, in healthy controls, expectations of pain relief or exacerbation affect the extent of ICPM at both the spinal and the supraspinal levels [127]. In contrast, in patients with FMS, such expectations influence only the supraspinal level, whereas the spinal excitability (NFR activity) is actually increased during ICPM regardless of expectations of analgesia or hyperalgesia [126]. On the other hand, it may be more than just a ceiling effect that limits endogenous pain inhibition in FMS patients. Instead, FMS patients seem to have weaker blood pressure increments during the cold pressor test, suggesting that lower baroreceptor activation could play a role in defective ICPM [124], as is supported by other data [128].

Another endogenous pain-modulatory mechanism is activated by aerobic exercise. Yet, while aerobic exercise significantly reduces the magnitude of temporal summation of heat pain sensations in healthy subjects, it may have an enhancing effect in patients with FMS [129]. Similarly, isometric muscle contractions decrease mechanical pain sensitivity over the contracting muscle and contralaterally in healthy subjects, but leave it unaltered or even increase it in patients with FMS [130–133]. The effects of isometric contractions on thermal pain ratings also go in opposite directions in healthy controls and subjects with FMS [133]. This suggests that the pain inhibitory mechanisms involved in exercise-induced analgesia fail to become activated in FMS patients; instead, descending facilitation appears to be recruited. However, some types of pain inhibitory mechanisms may be intact in patients with FMS [96], and there are data raising the possibility that certain DNIC mechanisms may be functional in males only [119], which could then provide a possible explanation for the marked preponderance of females among FMS patients.

In healthy subjects, a noxious mechanical stimulus also enhances corticomotor excitability, measured as an increase in the amplitude of the motor evoked potential (MEP). In contrast, greater MEP amplitudes during noxious stimulation were observed only in those women with FMS who experienced an increase in pain after exercise, whereas MEP amplitudes decreased in those whose pain abated after exercise [134]. Such a decrease in MEP amplitude is consistent with other data showing blunted corticomotor excitability along with alterations in intracortical inhibition and facilitation at rest and during exercise in FMS patients compared to healthy controls [135–137]. Together, these data suggest that the central inhibitory dysfunction of FMS patients is not restricted to pain modulation but extends to corticomotor excitability.

Sleep

Most patients with FMS (between 70 and >90 % in most studies) report poor sleep quality [4, 15, 72, 138–141]. Based on sleep quality questionnaires, patients with FMS take longer to fall asleep, wake up during the night more frequently, sleep fewer hours, and wake up unrefreshed significantly more often compared not only to healthy controls, but also compared to patients with other rheumatic diseases or other pain disorders [142, 143]. Polysomnography partly confirms the poor sleep quality reported by patients with FMS. The most

consistent findings are decreased sleep efficiency (total sleep time/time in bed), higher proportion of sleep time in light sleep, and more time of wakefulness after sleep onset [142, 144]. Increased sleep latency, more frequent stage shifts, and shorter total sleep time have been observed less consistently [144–147]. Remarkably, the poor sleep quality reported by women with FMS was found to be out of proportion to the modest degree of sleep disturbances evident upon polysomnographic assessment [145].

In 1975, Moldofsky et al. [148] observed an increased frequency of α-rhythms during non-rapid eye movement (NREM) sleep in patients with FMS compared to controls. Since α EEG frequencies are usually associated with wakefulness, Moldofsky et al. hypothesized that this increased α activity during NREM sleep was responsible for their nonrestorative sleep pattern in FMS patients. An increased occurrence of α EEG frequencies during deep NREM δ-wave sleep has since been described in patients with FMS compared to healthy controls in several studies [138, 144, 149, 150]. It should be noted, however, that α-wave intrusions into NREM sleep are not specific to FMS, but are seen in patients with a variety of pain syndromes and even in healthy controls, and they may actually represent an indicator of sleep quality rather than disturbance. In addition, α EEG activity is difficult to quantify; therefore it is not surprising that it is observed in highly variable proportions of patients with FMS, and several recent studies did not reveal significant differences in α-δ sleep between patients with FMS and healthy controls, although this may be partly attributable to the much higher interindividual variability in patients with FMS [146, 147]. The cyclic alternating pattern (CAP), a measure of sleep stability/instability, may represent a better marker of sleep quality in FMS since it was found to be increased in frequency in patients with FMS compared to healthy controls, and the CAP rate correlated negatively with sleep efficiency and positively with the TP index [144].

Sleep disorders like obstructive sleep apnea and restless legs syndrome appear to be more common in patients with FMS, particularly in male patients, than in the general population [151–156], and FMS may be more prevalent among patients with sleep apnea than in the general population [157]. The presence of such sleep disorders is associated not only with worse perceived sleep quality, but also with pain, fatigue, and greater symptoms severity (assessed with the Fibromyalgia Impact Questionnaire, FIQ) [151, 156]. Among other predictors of sleep quality, comorbid depression may be an important determinant of sleep difficulties [158], but that is not a consistent finding [139]. Other factors that are associated with self-reported sleep quality include pain, symptom severity, depression, anxiety, perceived disability, levels of perceived stress, and dysfunctional beliefs about sleep, but also physical activity and self-efficacy [141, 159–161]. Symptom severity also correlated with an objective measure of sleep fragmentation [144]. However, none of these factors are consistently identified [162].

The results of longitudinal studies underscore that the association between pain and sleep disturbances in patients with FMS is bidirectional. A night of poor sleep predicts pain intensity the following day and greater pain entails worse sleep, with increased attention to pain being the mediators in both cases [163]. Sleep disturbances may also have detrimental effects on the ability to cope with increased pain or other stressful events [164]. In addition, sleep duration, but not sleep quality, predicted the ability to recover from stressful days, and the effects of several nights of inadequate sleep were cumulative [165]. Both sleep disturbances and pain are also linked to depressive and anxiety symptoms and functional limitations [141, 161, 166], but there is some disagreement over the directionality of these associations. One model shows the path going from disturbed sleep via pain and ineffective coping style to distress and functional limitations [166]. The other shows the path to start with pain and go via sleep quality and self-efficacy to distress and daily functioning [141, 161].

Fatigue

At least 75 % of FMS patients report fatigue [4, 167, 168] and, as mentioned earlier, there is considerable overlap between FMS and CFS in population-based and clinical samples [62–68]. Patients with FMS complain of significantly higher levels of fatigue compared not only to healthy controls, but also compared to patients with other rheumatic diseases [85, 169], but FMS patients show significantly greater day-to-day variability in fatigue [85]. In addition, they rate their fatigue as more severe than their pain [72, 170].

Despite the obvious importance of this symptom, it remains somewhat unclear what exactly patients mean when they talk about their—often-overwhelming—fatigue. Even major initiatives for defining relevant outcome measures for FMS (such as Outcome Measures in Rheumatology, OMERACT, or the Patient-Reported Outcomes Measurement Information System, PROMIS) identify fatigue as an important domain, but fail to provide any definition [171–173]. However, in the context of OMERACT, there has been an attempt to develop a conceptual model of fatigue in FMS by conducting some detailed patient interviews [174]. The descriptors used by the patients indicate that fatigue in FMS is a complex multisystem concept that has physical, emotional as well as mental/cognitive dimensions. The only assessment tool that includes all of these dimensions is the Multidimensional Fatigue Inventory, but in clinical trials the Multidimensional Assessment of Fatigue is also commonly used [175]. In the majority of observational studies, however, FMS patients are simply asked to rate the severity of their fatigue on a visual analogue or numerical rating scale, which completely ignores this complexity.

A wide range of factors have been found to be associated with fatigue [175]. In both cross-sectional and longitudinal studies, pain, stiffness, sleep disturbances, anxiety and depression have shown positive associations with fatigue, while positive affect correlated negatively. In addition, several associations were observed only in longitudinal studies, including negative correlations between fatigue and sleep quality as well as sleep duration, and positive associations between fatigue and emotional distress, negative affect, and negative events. Surprisingly, positive events were associated with decreased fatigue the same day, but increased fatigue on the following day [176]. This underscores how costly an additional boost of energy from positive events can be for FMS patients. Further factors found to be associated with increased fatigue in cross-sectional studies include FMS severity, tenderness, disability, cognitive complaints, and internal as well as external locus of control [175]. Given the lack of a consensus definition or standard way of assessing fatigue in FMS, the meaning of these associations has to be interpreted with great caution.

Cognitive Complaints/Fibrofog

At least 76 % of patients with FMS report concentration difficulties, forgetfulness, mental confusion, or a combination of these complaints [177–180], and almost half of FMS patients rate the severity of these symptoms as ≥6 on a scale ranging from 0 to 10 [181]. FMS patients assess their cognitive performance as significantly worse not only compared to healthy controls but also compared to patients with other rheumatic diseases or chronic pain disorders [179, 182–186]. Some uncertainty remains over whether these subjective complaints reflect truly impaired function or biased perception on the part of the patient. There are data suggesting that patients greatly overestimate the magnitude of their concentration and memory deficits [182, 183]. While global memory complaints were assessed in these studies, questions focusing on self-reported memory and attentional function in a specific daily life context generally reveal correlations between subjective cognitive complaints and certain tests of neuropsychological function [184–186].

One of the most frequently identified aspects of cognitive dysfunction in FMS patients is attention [187, 188]. Unfortunately, this concept has been rather broadly or incompletely defined in many studies. When attention is broken down into processes of alerting, orienting, and executive functioning, FMS patients show deficits in alerting and temporal orienting, but not visual orienting, and in various aspects of executive control [125, 186, 187, 189–192]. Cognitive inhibition, i.e., the ability to keep focused despite distractions, can be conceptualized as a component of executive function and is quite consistently found to be impaired in FMS patients. As a matter of fact, there are indications that cognitive deficits in FMS patients become most obvious in the presence of a distractor or source of stimulus competition, not only in tests of attention but also in tests of working memory [193, 194]. Working memory is another cognitive domain where FMS patients very consistently perform more poorly compared to healthy controls [186, 187, 192, 195, 196]. While addressed in fewer studies, certain measures of semantic memory also show impairments in FMS, including decreased verbal fluency, naming speed, and vocabulary [187, 195, 197]. However, recent data suggest that deficits may be more pronounced in visuospatial than in verbal memory [198, 199]. Inconsistent results have been reported for episodic and implicit memory [187, 195, 200, 201].

Processing speed is of importance in all types of cognitive functions. Significant decrements in processing speed have been documented in FMS patients using a variety of tests [186, 192, 202, 203], even though normal results have also been obtained with certain tasks [204, 205], and occasionally, FMS patients perform even better than controls [202]. However, it is often not possible to clearly distinguish between reduced mental processing speed, decreased psychomotor speed, or a combination of both [206].

It should be pointed out that there are also numerous tests on which FMS patients perform similar to healthy subjects, and that the results for the same tests may not always agree between different investigations [186, 191, 192, 195, 196]. In addition, the comparison of FMS patients to healthy subjects may reveal relatively subtle deficits, even though the patients perform within the normal range compared to normative data. There are only a few reports on the proportion of FMS patients who show impairments when compared with normative values for age- and education-matched controls. Using the Mini-Mental State Examination (MMSE), 58 % of patients with FMS were found to exhibit cognitive deficits in one study [207], but only 15 % in another, even though it used a higher cut-off (≤25 compared to ≤ 24) [208]. In more specific neuropsychological assessments, the frequency of impairment has been reported as 23 % on at least one of several types of memory tests [182], 60 % on the Test of Everyday Attention [188], 49 % on processing speed [202], and up to 40 % of patients reflect deficits on tests assessing various aspects of executive function [186].

Depression or depressive symptoms show associations with some of the cognitive dysfunction in FMS, but they fully explain them in only a few studies, partly explain them in others, and do not show any association in the remainder [187, 191, 192, 198, 200, 206]. These discrepancies may arise because the effects of depressive symptoms appear to be domain- or even task-specific [183, 198, 209] and because different instruments were used for assessing depressive symptoms. Other methodological differences and patient heterogeneity are also likely to contribute to the observed inconsistencies. The lack of association between depression and memory function is somewhat surprising since the

dorsolateral prefrontal cortex (DLPFC) is strongly implicated in protecting from depression [210] and activation of the DLPFC is a typical finding during working memory performance in healthy controls as well as patients with FMS [196, 211]. However, the degree of activation was lower in FMS patients compared to healthy controls, and this difference was largely accounted for by the depressive symptom scores [196]. Consistent with the observation that anxiety ratings were associated with the degree of activation in certain brain areas during working memory tasks [196], anxiety symptoms have been associated with various cognitive variables, including delayed recall, memory, and processing speed [182, 203]. However, others failed to find any correlation with performance on go/no-go tasks [191], and patients with anxiety disorders actually performed better on a mental arithmetic task than those without such disorders [192].

Patient with FMS consider fatigue to have a great impact on their cognitive function [212], and self-reported fatigue is associated with perceived dyscognition [174, 179, 213], but the majority of investigations do not reveal a major impact of fatigue on objective cognitive performance [187, 191, 192, 198, 206]. Daytime sleepiness correlated with a lower rate of correct responses during a mental arithmetic task in the patient group [203], but was not significantly associated with performance on a go/no-go task [191]. Sleep quality would also be expected to affect cognition and was correlated with perceived memory deficits [213]. It was also found to be the only significant predictor of objectively assessed alertness [189], but attention and memory deficits persisted after adjustment for self-reported sleep duration and quality [194], and others did not detect any significant correlations [192].

Pain intensity has been identified as an important determinant of a variety of aspects of objectively assessed dyscognition in FMS [187, 200, 203] and may even account almost entirely for the deficits in processing speed and attention observed in patients with FMS [192, 194]. However, the effect of pain may be task- and domain-specific. In addition, the correlation may only become obvious when pain at the time of neuropsychological testing is assessed rather than average pain over the last week [189]. In partial contrast to the results of objective cognitive assessment, pain ratings were significantly associated with self-reported language deficits, but not with perceived attention or concentration [213]. Many of the brain regions involved in cognitive functions partially overlap areas that play an important role in the cognitive aspects of pain perception and control [211, 214]. Therefore, it has been hypothesized that cognitive dysfunction in FMS arises because brain resources used for pain processing are not available for cognitive tasks [191]. This may be particularly relevant if the pain intensity is high or if patients exhibit high levels of pain-related anxiety or pain catastrophizing, as has been found in patients with FMS [108, 215]. Note, however, that it remains somewhat controversial whether catastrophizing is associated with increased neural responses to painful stimuli [216, 217]. Competition between pain processing and cognitive tasks for a finite amount of brain resources would be expected to affect primarily controlled processes while leaving automatic processes intact, and this is indeed what some of the available data suggest [192, 201].

Impaired cognitive function in FMS patients may also stem from altered gray matter morphology [218]. The most direct evidence for such an association in FMS patients comes from the discovery of a significant positive correlation between verbal working memory performance and gray matter values in the bilateral medial frontal cortex, while non-verbal working memory correlated with grey matter values in the left middle frontal gyrus [211]. Note that these data are derived from a cohort of patients for whom re-analysis of the fMRI data yielded a substantially different distribution of gray matter values [219, 220]. However, the middle frontal gyrus and the medial frontal cortex were not among the regions where FMS patients showed decreased gray matter volume compared to healthy controls in either of these analyses. There are studies, however, showing significantly reduced gray matter density in areas involved in higher-order cognitive processes in FMS compared to healthy subjects, including the ACC, the prefrontal cortex, and the insular cortex [218, 221–225]. It should be emphasized that a number of the imaging studies described herein are for research purposes only, without any evidence they should be used individually to diagnose a specific patient. This includes, for example, the use of functional MRI.

A significant minority of patients with FM, particularly of those seeking or receiving disability payments, showed evidence of suboptimal effort in standardized tests designed to detect response bias in neuropsychological assessments [183, 226]. In patients without response bias, verbal memory was not objectively impaired compared to patients with RA (none of whom achieved scores indicative of incomplete effort) [226]. This highlights the importance of accounting for effort, which is not routinely done. Nonetheless, there is little indication overall that low effort or simulation accounts for cognitive impairments in the majority of FMS patients [195, 200, 203]. The fact that FMS patients and healthy controls often do not differ in the accuracy of their performance on cognitive tasks (even if the response times are longer in the patient group) also does not support decreased effort [186, 192, 227]. In addition, the results of some neuroimaging studies suggest that FMS patients use more brain resources in order to achieve the same level of functioning as healthy controls [191, 228]. This has been interpreted as a *rising to the occasion*, i.e., a reflection of greater effort [195]. However, patients do not always rise to the occasion, and when fMRI was performed during tasks where patients performed worse than controls, it did not reveal any brain areas where FMS patients showed increased activations compared to healthy

controls [125, 196]. In addition, the recruitment of additional brain resources may not always be beneficial. The results of functional transcranial Doppler sonography to assess blood flow through the middle and anterior cerebral arteries actually suggest aberrant allocation of resources to task-irrelevant areas [203]. The activation of such task-irrelevant areas may constitute one explanation for the poorer performance of FMS patients on a variety of cognitive processes.

Some of the pharmaceuticals routinely used in the treatment of FMS are likely to influence cognition, but FMS patients are not always required to stop taking their medications before objective cognitive assessment, and discontinuation of medications may introduce its own confounding. Most neuropsychological assessments of FMS patients include only a small number of subjects who are taking a variety of different medications, which makes it difficult to detect a significant effect of any single class of pharmaceuticals and renders it almost impossible to control for medication intake. This may explain the mixed results that have been obtained regarding the influence of FMS medications on cognitive function [185, 192, 194, 229], with the majority of studies not revealing any significant effect [188, 189, 200, 203]. Cognitive function has rarely been among the outcome measures investigated in clinical trials, even though self-assessed improvements in this domain make an important contribution to the Patient Global Impression of Change ratings [230]. In the few clinical trials in which objective neuropsychological testing was included as an outcome measure, medications (milnacipran, duloxetine) did not significantly affect cognitive function [231, 232].

Depression/Anxiety

Based on formal psychiatric interviews for assessment for axis I disorders, FMS patients have a lifetime prevalence of mood disorders, mostly major depression, ranging between 20 and 86 % [66, 233–240], and 13–48 % are diagnosed with current major depressive disorder (MDD) [66, 192, 234, 238, 239, 241, 242]. Somewhat fewer data are available on anxiety disorders, but they are present in 27 to 60 % of FMS patients at the time of the examination [234–236], and the reported lifetime prevalence rates are in a similar range [66, 234]. Given these wide prevalence ranges, it is not surprising that it remains somewhat uncertain whether FMS patients exhibit higher lifetime rates of MDD compared to patients with RA [233, 236, 237, 239–241]. Whether FMS patients show elevated rates of major mood or anxiety disorders compared to healthy controls or the general population also has not been fully established [46, 192, 234–237, 241–243]. In recent years, post-traumatic stress disorder (PTSD) has emerged as one of the most important anxiety disorders in patients with FMS [244], but the reported rates vary considerably, with 3 to 57 % of FMS patients in rheumatology or pain clinics fulfilling the diagnostic criteria of PTSD [235, 242, 245, 246] and 41 to 56 % of patients having clinically significant levels of PTDS symptoms [235, 247]. In a large community-based sample from the USA, the lifetime prevalence of PTSD was 14 % in women with FMS-like symptoms, which translated into a six-fold higher risk compared to subjects without such symptoms [46]. Conversely, 21–49 % of patients with PTSD fulfill the ACR 1990 criteria for FMS [248], compared to 5 % of patients with MDD and none of the healthy controls [249]. There have been only two investigations of personality disorders in FMS patients, and the resulting rates were 47 % (14/30) and 12 % (14/115), respectively [235, 242].

The prevalence and severity of depressive symptoms as measured with a variety of self-report scales are consistently and highly significantly elevated in FMS patients compared to healthy controls [159, 250–253], and the majority of comparisons to patients with other rheumatological diseases or pain disorders also show higher mood symptoms in FMS patients [69, 85, 143, 253–255]. Symptoms of anxiety generally are also more frequent in FMS patients compared to healthy controls [159, 192, 250, 253], whereas comparisons to patients with other rheumatological or pain disorders have yielded heterogeneous results [143, 253–255].

Several possibilities could account for the high rate of comorbidity of major depression and FMS. First, MDD could be a consequence of living with chronic pain and other debilitating symptoms. Data showing higher lifetime prevalence of MDD in FMS patients compared to patients with other comparably painful and debilitating diseases and conditions suggest that this cannot be the only scenario [239–241], but are not consistently obtained [233, 237]. In addition, it remains controversial whether conditions like RA are truly comparable to FMS [256]. Second, FMS could represent an unusual manifestation of depression, with the main symptoms of MDD remaining subthreshold in some patients. Yet, some FMS patients stay free not only of MDD, but even of depressive symptoms, throughout their lives. At least in these patients, FMS is unlikely to be a manifestation of MDD. Finally, there is the possibility that MDD and FMS are part of the same spectrum of disorders and share underlying etiologies. There are several arguments in favor of this hypothesis. Major depression and FMS may have some predisposing genetic elements in common. Several of the genes in the dopaminergic and serotonergic pathways that have been associated with the risk of FMS also have been implicated in MDD [257]. FMS and MDD share some pathophysiological features, such as disturbances in the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system and altered availability and function of a variety of neurotransmitters. At least a subset of FMS patients also

responds to the same pharmacological agents as are used for the treatment of MDD. In addition, several investigations have revealed coaggregation of FMS and MDD within families [66, 240, 241], thereby supporting the hypothesis that FMS is a depression spectrum disorder. The strongest support for this hypothesis initially came from a community-based study that compared the rates of MDD in relatives of probands with FMS with or without MDD and of probands without FMS with or without MDD and provided evidence of familial aggregation of the two diagnoses [258]. However, in a separate analysis of the same dataset, the rates of lifetime MDD were nearly identical in women with and without FMS, although the rate of current MDD was markedly higher in FMS patients, possibly due to greater chronicity of MDD [46]. Data from a very large Swedish twin cohort indicate that the increased risk of MDD and general anxiety disorder in cases with CWP compared to unaffected cohort members was entirely due to family environmental factors, whereas the shared genetic background of monozygotic twins made essentially no contribution [64]. These findings argue against the hypothesis that FMS is a depressive spectrum disorder. Both MDD and FMS are associated with a history of physical or sexual abuse [259, 260]. It is possible that this, and maybe the resulting common disturbances in neuroendocrine systems, provide at least a partial explanation for the comorbidity of FMS and MDD.

The importance of trauma or major stressors in the development of FMS has been questioned based on the failure to show an increased prevalence of FMS-like symptoms after the World Trade Center terrorist attacks in a pre-existing community-based survey sample of women [261]. It is noteworthy, however, that over the period of 19 months that elapsed between the start of the first survey and the end of the second survey, 7.9 % of the women who initially were negative for FMS-like symptoms became positive at follow-up. This rate seems inordinately high compared to the annual incidence rates of 0.5–1 % reported to date [44, 45], even taking into account that the criteria used for "FMS-like" symptoms have a positive predictive value for FMS of only 0.73. However, it is also possible that the World Trade Center terrorist attacks are truly not linked to an increase in FMS-like symptoms because an FMS-triggering stressor has to have a more direct personal impact than a public disaster. For example, we do not discourage patients from exercising and we certainly do not discourage people from participating even in contact sports. There is no evidence that female soldiers carrying large backpacks during tours of duty have any increased evidence of fibromyalgia and there is no evidence that female athletes, including those in contact sports, develop or have an exacerbation of fibromyalgia. In fact, as discussed elsewhere, there is no evidence that trauma of any nature, including automobile accidents, play any role in either the induction or exacerbation of fibromyalgia.

Correlations Between Depression, Anxiety, and FMS Symptoms

The results of correlational analyses indicate that depressive symptoms have the potential to influence not only all of the core symptoms of FMS, such as pain [77, 84, 253, 262, 263], fatigue [176, 264], sleep quality [141, 166, 251, 265, 266], dyscognition [183, 229, 267], and overall symptom severity (FIQ scores) [217], but also physical activity [9, 158], physical and social function [234, 268, 269], labor force participation [270], quality of life [262, 268] as well as coping style, in particular catastrophizing [88, 217] and illness behavior [271]. However, none of these correlations are entirely consistent findings [139, 235, 272], and several investigations showed anxiety disorders or anxiety symptoms, but not depressive symptoms, to be associated with pain and pain interference [235, 252]. Importantly, trait anxiety, but not state anxiety, was associated with current pain intensity, suggesting that anxious mood is not a reaction to the disease but may represent a predisposing factor [252]. However, there is considerable co-linearity between symptoms of anxiety and depression [217, 265, 266], and several investigations show both to be associated with pain, sleep disturbances, symptom severity, poorer perceived health, worse physical function, decreased vitality, and impaired social function [217, 234, 265, 266, 268]. In yet another investigation, both depression and anxiety scores correlated with the sensory and affective components of the MPQ and with pain intensity, but in regression analyses, only the physiological component of anxiety together with helplessness and fear of pain predicted the various aspects of pain, whereas depression was an important component in predicting self-efficacy for pain management and coping with symptoms [89]. Similarly, the presence of PTSD in FMS patients is associated with more severe symptoms (more pain, tenderness, and distress, and greater functional impairment) [245, 247], while FMS has a similar effect on PTSD [248, 249], although that is not an entirely consistent finding [244].

The direction of these interactions cannot be determined from these studies. A secondary analysis of data from patients with FMS and MDD who were treated with duloxetine during four clinical trials showed that improvements in mood accounted for 31 % of the improvement in pain [273]. Conversely, reductions in pain were responsible for 40 % of the improvement in mood symptoms. Consistent with these data, others found that a moderate (30–49 %) or substantial (≥50 %) reduction in the pain intensity of FMS patients was associated with improvements in essentially all measured outcomes, including depression, and anxiety [274]. At the same time, the

response rates for both pain and MDD to treatment with duloxetine were not greatly influenced by their respective baseline severities [273]. This suggests that the interactions between depression and pain are bidirectional. It also underscores that, despite their obvious interactions, pain intensity and MDD in FMS show considerable independence. At the same time, these data lend some support to the hypothesis that at least some of the depressive symptoms in FMS arise as a reaction to the chronic pain. Indeed, pain, helplessness, a passive coping style, and family cohesion were all directly related to depressive symptoms, but pain was also found to make an indirect contribution to depressive mood via its association with helplessness and passive coping [275]. Sleep disturbances are another important element in these pathways, but it remains somewhat uncertain whether they constitute a mediator of the link between pain and distress or exert their effect by increasing pain [141, 161, 166]. In another longitudinal study, an increase in pain predicted a rise in emotional distress, and pain and emotional distress each predicted heightened fatigue, with these increases being small, but statistically significant [84]. Importantly, however, emotional distress did not predict subsequent pain. In partial contrast, some cross-sectional data failed to provide support for any association between pain intensity or pain interference and the diagnosis of anxiety or mood disorders [235, 276]. Instead, depression was more strongly related to coping style and effectiveness and support from significant others in addition to several cohort-specific parameters [235, 276]. Anxiety disorders were independently and positively associated with the number of somatic symptoms, the presence of PTSD-like symptoms, solicitous behaviors by significant others and reduced general activity [235].

Neuroimaging Findings

Brain Structure

Neuroimaging studies have provided vital evidence that there are objectively measurable abnormalities in brain structure and function, in particular pain processing, in patients with FMS. Changes in gray matter volume are a consistent finding in pain disorders and are also observed in patients with FMS [277]. With few exceptions, analyses of gray matter volume by voxel-based morphometry have not found a significant difference in total gray matter between patients with FMS and controls, but have generally detected regional decreases in gray matter density [218, 221, 278]. However, the specific areas identified vary greatly between studies, with some consistency emerging only for the anterior cingulate cortex (ACC), the prefrontal cortex and possibly the insula. A variety of other areas have been identified only in single studies. There is also disagreement over the extent to which affective disorders contribute to the observed decreases in gray matter volume [218, 278]. One occasionally finds these changes discussed in terms of loss or atrophy of gray matter. However, similar changes in gray matter density in patients with chronic hip pain due to osteoarthritis were found to be partially reversible after pain relief through total hip replacement surgery [279]. This indicates that they do not constitute irreversible damage or atrophy. It further suggests that changes in gray matter volume are a consequence of prolonged nociceptive input rather than a morphological difference underlying the propensity to develop chronic pain. However, it remains somewhat controversial whether these structural changes are associated with the duration of pain [221], with the majority of studies not seeing a significant correlation [218, 221, 278]. Once again, these are predominantly useful for research only and not in the diagnosis of a specific patient.

In contrast to reductions in gray matter volume, regional increases in gray matter volume in FMS patients compared to controls have rarely been reported [219]. In addition, reanalysis of the data with non-modulated images left only decreases in gray matter volume, and these became evident in a far greater number of areas than were identified in the original study [220]. Nonetheless, increases in gray matter volume may be revealed when age is taken into account. It was recently reported that older patients exhibited exclusively reductions in gray matter density in various brain regions including the bilateral ACC and various areas of the prefrontal cortex, whereas younger patients showed exclusively gray matter increases, specifically in the left insula/putamen, right putamen/globus pallidus/nucleus accumbens, and VLPFC [221]. In younger patients, there also was an inverse association of gray matter in the insula and nucleus accumbens with pain sensitivity, which was not enhanced. In addition, resting state connectivity was decreased between the insula and the dorsal ACC and increased between the nucleus accumbens and a cluster in the DLPFC and premotor cortex. These findings suggests that the changes in the brain of younger patients are adaptive and aimed at enhancing pain inhibitory processes, but that the aging brain may not be able to maintain these mechanisms.

Brain Function

Regional Cerebral Flood Flow

The first neuroimaging studies in FMS used positron emission tomography (PET) and single photon emission computed tomography (SPECT) and demonstrated reduced basal regional cerebral blood flow (rCBF), indicative of decreased neural activity, particularly in the thalamus and caudate nucleus [280, 281].

Connectivity at Rest

The intrinsic functional connectivity of the brain can be determined by assessing the temporal correlation between spontaneous low-frequency fluctuations in the blood oxygen level dependent (BOLD) signal among brain regions of subjects at rest. Using this technique, patients with FMS were shown to exhibit major disturbances in the functional connectivity between brain regions known to play a key role in pain perception and pain modulation, in particular the somatosensory cortices (SI and SII), ACC, insula, amygdala, hypothalamus, and the periaqueductal gray (PAG) [278, 282, 283]. In addition, hyperconnectivity between the default mode network (DMN), an intrinsic network of brain regions involved in self-awareness, and the insular cortex correlated with greater pain sensitivity [282] and higher levels of spontaneous pain [278, 284]. Reductions in clinical pain were associated with decreased connectivity between the DMN and the insular cortex [284, 285]. Others extended these findings by showing that clinical pain was independently associated with increased connectivity between the parietal operculum and the DMN and with decreased connectivity between the PAG and the anterior insula and with reduced connectivity between the parietal operculum/SII and other sensory cortices [283]. Together, these three levels of processing accounted for 71 % of the variance in pain severity [283]. There are data suggesting that decreased resting state functional connectivity between areas involved in pain perception and pain modulation may be useful in predicting pharmacological treatment responses [284, 286].

Functional Imaging During Painful Stimuli

Pressure or heat stimuli that evoke similar levels of perceived pain in FMS patients and healthy controls are consistently found to result in similar increases in activity in the majority of regions known as the pain matrix, namely contralateral SI, SII, inferior parietal lobule, insula, ACC, and ipsilateral SII and cerebellum [278]. There is, however, some heterogeneity regarding further areas of activation or deactivation in patients or controls depending on the reference condition (no stimulation or innocuous stimulation) and the severity of the pain inflicted by the test stimulus. The duration of the stimulus may also play a role since very brief painful pressure stimuli (2.5 s compared to a stimulus duration of 10–30 s in other studies) resulted in activations in fewer regions of the pain matrix than were reported in other studies, and FMS patients actually exhibited deactivations in the thalamus, rostral ACC, and brainstem, whereas healthy controls showed activations in these areas [6].

The stimulus intensity required to elicit a specific level of perceived pain is significantly lower in FMS patients compared to healthy controls. At equal pressure stimulus intensity, the pattern of activation in FMS patients shows little to no overlap with the pattern observed in healthy controls [278, 280]. This is not entirely unexpected since such a stimulus is experienced as moderately painful by the patients, but as faintly painful by the healthy control group. Most remarkably, however, patients with FMS showed increased activity in several brain areas even after nonpainful warm stimuli [214]. The same study provided some indirect objective evidence for defective descending pain modulation in FMS patients by showing that administration of warm stimuli after heat pain stimuli was associated with significant activations in the PAG in healthy controls, but not in patients with FMS [214]. The PAG is strongly implicated in descending pain modulation [287].

Fewer experiments have been conducted with a tonic rather than a repetitive phasic pain stimulus, namely an incision in the right volar forearm which caused significantly higher pain ratings in subjects with FMS compared to healthy controls [288]. The patient group showed a different temporal pattern of activation in the supplemental motor area, ACC and part of the thalamus. In several other pain processing regions, they exhibited activations when controls presented deactivations and vice versa. Patients with FMS showed a negative correlation between pre-incision activations in the supplemental motor area, mid cingulate cortex and right precentral gyrus and the subsequent pain intensity at incision, whereas the correlations were positive in healthy controls and patients with RA [289]. The area of secondary hyperalgesia, but not of primary hyperalgesia, after an incision was significantly greater in patients with FMS compared to healthy controls [290]. In healthy controls, activation in the DLPFC, and the bilateral sensorimotor cortex showed modest but statistically highly significant negative correlations with the extent of secondary hyperalgesia. In contrast, these correlations were essentially absent (and positive if present) in patients with FMS. This underscores the importance of central, most likely supraspinal, processes in pain perception and modulation of FMS patients.

Since mood disorders are common in patients with FMS, some investigations have attempted to address the influence of distress on pain perception and its imaging correlates. In one study, depressive symptoms did not show any significant associations with clinical pain, experimental pain or pressure pain threshold [291]. However, during pressure stimuli that were perceived as equally painful, depressive symptom scores or the presence of MDD correlated with the extent of neuronal activation in the amygdalae and the contralateral anterior insula during fMRI, suggesting greater affective or emotional responses to pain in patients with depression. Catastrophizing has long been thought to reflect underlying depression, but neuroimaging during blunt pressure pain revealed strong associations between catastrophizing and increased neural activity in a variety of brain areas even after correcting for depression [216]. None of these areas overlapped with those

identified in the previous study [291]. In addition, patients with high catastrophizing scores showed unique activations in the contralateral ACC and in bilateral lentiform. In marked contrast, others did not detect any correlation between the level of depressive symptoms, anxiety, or catastrophizing and the extent of brain activations in response to painful pressure stimuli as measured by fMRI [217]. The discrepancies between the results of these studies may be due to the different methodological approaches, in particular the greater predictability of the stimulus presentation in the two studies that did show an effect of depression or catastrophizing on brain activity [216, 291]. In addition, the patients who had high catastrophizing scores also rated their clinical pain as more intense and scored higher on the sensory, affective and total MPQ short form [216].

Connectivity During Somatosensory Stimuli

Patients with FMS exhibit not only altered resting connectivity, but also show reduced functional connectivity during painful stimulation [278]. This involves regions implicated in descending modulation of pain, more specifically between the rostral ACC and the bilateral hippocampi, amygdala, and brainstem [292]. According to the authors, these findings provide support for the hypothesis that defective descending pain modulation plays a pathologic role in the development of FMS. It should be noted, however, that the volume of the rostral ACC correlated directly with coherence and inversely with disease duration [292]. This would seem to argue that the observed changes are a consequence rather than a cause of FMS. Effective connectivity during temporal summation of heat pain is considered to be fairly similar in FMS patients and controls [278]. Nonetheless, there are several noteworthy differences. In the left hemisphere, FMS patients lack a significant path from S1 to S2 and to the posterior insula and show a substantial increase in the path from thalamus to S2. In the right hemisphere, the direction of the influence between S1 and S2 was reversed and the path from posterior insula to ACC was much stronger in the patient compared to the control group.

A very important consideration that has been insufficiently addressed in the available research is the question of whether, and to what extent, experimental pain reflects clinical pain. The answers to this question have been somewhat mixed, but even in studies showing significant associations between experimental pain parameters and clinical pain, these correlations have been rather modest at best [80, 291, 293, 294]. In addition, patients with FMS differed significantly from healthy controls in the use of catastrophizing and other strategies for coping with their clinical pain, but did not use different coping strategies during the anticipation and actual experience of experimental pressure pain stimuli with or without prior notice of the intensity of the upcoming pain [295]. Together, these findings underscore the major limitations of experimentally induced acute pain in providing insights into the mechanisms of pain perception in FMS.

Neuroendocrine and Cytokine Disturbances

Brain Neurochemistry

Magnetic resonance spectroscopy (MRS) can be used to assess basal or evoked brain activity by determining the concentrations of a variety of metabolites, which are often expressed relative to a standard molecule, most commonly creatine (Cr). Here again, these observations are for research only and not for the treatment of a given patient. One of the more consistent findings in FMS patients has been a reduction of *N*-acetylaspartate (NAA) or the NAA/Cr ratio or both in the hippocampus of FMS compared to control subjects. However, this reduction has been confined to the left hippocampus in two patient cohorts [296, 297], was significant on both sides, but markedly more pronounced in the right hippocampus in another group [298], and was observed exclusively in the right hippocampus in yet another investigation [299]. Unfortunately, no information was provided on the handedness of the patients, the distribution of their pain, or any other features that could explain these discrepancies. Since the levels of NAA are thought to reflect the degree of regional activation, their decrease in the hippocampus of patients with FMS suggests hippocampal dysfunction. The hippocampus is implicated in pain perception, sleep regulation, modulation of the stress response, and also in memory and cognition. Therefore, hippocampal dysfunction may underlie many of the symptoms commonly reported by patients with FMS. Compared to controls, patients with FMS also exhibit reduced connectivity between the hippocampus and other parts of the pain inhibitory network during pressure stimuli perceived as equally painful [292]. This suggests that hippocampal dysfunction may play a key role in the inappropriate pain amplification typically seen in FMS. Indeed, total NAA levels in the left hippocampus negatively correlated with pain intensity and were positively associated with health-related quality of life (HRQoL) and MMSE scores [297]. Others found a negative association between the NAA/Cr ratio in the right hippocampus and FIQ scores [299].

Glutamate (Glu) is another brain metabolite that can be investigated with MRS. Several lines of evidence underscore its potential importance in FMS. First, elevated concentrations of this excitatory neurotransmitter have been detected by HPLC in the cerebrospinal fluid (CSF) of patients with FMS compared to healthy controls [300, 301], even if this is not an entirely consistent finding [302]. Second, administration of

ketamine, a Glu channel blocker, attenuates experimental and clinical pain in a subset of patients with FMS [98, 303]. Since MRS may not accurately measure glutamate (Glu), it is customary to report combined Glu+glutamate (Glx) levels. Greater concentrations of Glx, higher Glx/Cr ratios or both have been detected in a variety of brain regions of FMS compared to healthy subjects [296, 297, 304–306]. Unfortunately, not only the regions investigated with MRS, but also the regions identified as showing elevated Glx levels vary from one study to the next even when performed by the same group of researchers [296, 297, 304–306]. This is regrettable because more detailed knowledge of the localization of increased Glx activity could provide insights into the role of Glu in the pathophysiology of FMS, particularly since elevated Glx concentrations in certain brain areas are associated with clinical pain severity, pain sensitivity, and various other symptoms of FMS [296, 297, 304–306]. After long-term non-pharmacological treatment, the magnitude of the decline in the Glu/Cr ratio of the posterior insula correlated with the magnitude of the decrease in clinical pain and increase of the experimental pressure pain threshold [307].

Other excitatory neurotransmitters and pro-nociceptive compounds, such as substance P, nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF) are all elevated in CSF of FMS patients [301, 308, 309]. In contrast, significantly lower levels of the major inhibitory neurotransmitter of the central nervous system, γ-aminobutyric acid (GABA), were detected in the right anterior insula of FMS patients compared to healthy controls [310]. However, an increase in GABA levels in the ACC only just failed to reach statistical significance. The concentrations of other antinociceptive agents also appear to be reduced, as suggested by the finding that CSF from FMS patients contains lower levels of the metabolites of serotonin, norepinephrine, and dopamine [311, 312]. Platelets are considered to be a good model of neuronal 5-HT uptake, storage and release. From the available data, it remains somewhat uncertain whether the serotonin transporter density on platelets is higher [313], lower [314], or normal [311, 315, 316]. In addition, the results of PET studies indicate that presynaptic dopaminergic activity is reduced [317] and that dopamine release in response to a tonic noxious stimulus is attenuated in FMS patients compared to healthy controls [318]. PET was also used to demonstrate that patients with FMS exhibited significantly decreased μ-opioid receptor (MOR) binding potential in several antinociceptive brain areas [319]. It currently remains unclear whether reduced MOR receptor availability is due to receptor downregulation after prolonged elevations of endogenous opioids, receptor occupancy by endogenous opioids, or decreased MOR functioning. Elevated concentrations of enkephalins have been detected in some FMS patient cohorts [320, 321], but not in others [322].

Stress, the HPA Axis, and the Autonomic Nervous System

At least half of the FMS patients who participated in internet surveys in the USA or Japan felt that their symptoms had been triggered by chronic stress or emotional trauma [72, 167]. The majority of these studies lack proper controls and often lead to misleading or incorrect conclusions. In the US survey, this was followed in frequency by physical injury, surgery, motor vehicle accidents, and emotional or physical abuse as a child or an adult [72]. There is no reliable data that accidents or physical trauma can trigger FMS [323, 324]. There is also no reliable data that accidents or physical trauma can exacerbate or change the natural history of FMS. To what extent FMS is associated with abuse also remains somewhat uncertain because most of the evidence is of low quality and based on highly varying definitions of abuse [259]. However, according to a meta-analysis of the available data (18 case-control studies), FMS is significantly associated with self-reported physical or sexual abuse during childhood or adulthood, but not with emotional abuse. In addition, patients with FMS frequently report greater numbers of major negative life events, higher levels of day-to-day and chronic stress, and more psychological distress compared not only to healthy controls but also to patients with RA [325–330]. The vast majority of patients endorse that emotional distress worsens their symptoms [72]. In a prospective study, stress at the workplace, in particular being bullied, but also having a high work load or low decision latitude, was an independent predictor of the development of FMS during follow-up [331].

Since FMS is considered to be a stress-related disorder, there have been numerous investigations of HPA axis function in patients with FMS. Some investigators consider the available data to be consistent with hypercortisolemia [332]; however, it should not be ignored that the findings are heterogeneous and data consistent with hypocortisolism have also been reported. Hypercortisolemia is characterized by increased circulating concentrations of cortisol, decreased feedback inhibition of the HPA axis, and reduced glucocorticoid sensitivity of peripheral blood mononuclear cells (PBMC) or whole blood, while hypocortisolemia has the opposite characteristics. Tests of feedback inhibition are based on the knowledge that cortisol exerts negative feedback control at the level of the pituitary, hypothalamus and hippocampus to regulate its own plasma concentration. In normal subjects, a dexamethasone dose of 1 mg almost completely suppresses cortisol secretion, while a dose of 0.5 mg allows the identification of increased feedback sensitivity.

The majority of studies show FMS patients to have lower or similar plasma or serum levels of cortisol compared to healthy controls, but a few reports of higher concentrations have also been published [333–339]. Salivary free cortisol output may be similar or higher in FMS patients compared to healthy subjects [333, 340, 341], while the cortisol

awakening response (i.e., the rise in cortisol concentrations in the first hour after awakening) can be normal or diminished [340, 342, 343]. Total and free cortisol concentrations may be dissociated in FMS patients. That is, free cortisol levels and responses to exogenous adrenocorticotropic hormone (ACTH) may be normal even when plasma total concentrations or responses are low [339, 344, 345]. It has been suggested that this dissociation is due to lower levels of corticosterone binding globulin [338], which may represent an adaptation to reduced circulating total plasma cortisol levels, but is not a consistent finding [346]. Urinary excretion of free cortisol may be decreased in FMS patients [333, 338, 347], but is more often similar to control values [145, 146, 334, 348, 349]. For ACTH, the preponderance of the evidence does not support any statistically significant differences between patients and controls, but again, lower as well as higher levels have also been reported [325, 332, 339, 346, 350–353]. The overall circadian variation in ACTH and cortisol values is preserved in patients with FM [332, 340, 354], and when factors that may affect circadian markers are rigorously controlled no differences in the diurnal pattern of plasma cortisol or salivary free cortisol are found between patients with FMS and controls [81]. However, FMS patients may exhibit a flattened plasma cortisol profile, with concentration declining more slowly from the morning peak to the evening trough [332, 346, 347] or starting at lower morning peak values and declining to similar values in the evening [355, 356].

In FMS, both the standard and the low-dose dexamethasone suppression tests (DST) have yielded conflicting results, including impaired, normal, and enhanced feedback inhibition [325, 336, 340, 344, 347, 357]. Some of these discrepancies may be attributable to confounding by depression [341, 357], which is typically characterized by higher basal cortisol levels and decreased cortisol suppression in the DST [358]. Although PTSD possibly shows an even closer association with FMS than MDD [235, 242, 245, 246], it has not been taken into consideration in any of the HPA axis function studies. Yet, there are FMS patients whose HPA reactivity resembles those of the typical patient with PTSD [359], namely lower basal cortisol activity along with increased feedback inhibition of the HPA axis compared to normal controls [325]. Investigations of the expression of glucocorticoid receptors and their affinity for dexamethasone and of PBMC glucocorticoid sensitivity have not provided consistent evidence in favor of hypocortisolism or hypercortisolism either [338–340, 345].

A number of research groups have investigated the reactivity of the HPA axis to exogenous corticotropin-releasing hormone (CRH), ACTH, and physiological or social stressors (summarized in Table 4). The overall results do not allow the identification of an FMS-specific impairment in HPA axis function. In response to CRH, patients with FMS may exhibit increased ACTH, but similar cortisol responses compared to healthy controls [344, 350, 353, 360] or normal ACTH and decreased cortisol responses [346]. This results in an increase in the ACTH:cortisol ratio, which has also been observed after the insulin tolerance test (ITT) [353] and the DST [325], and suggests adrenal hyporesponsiveness in FMS patients [325, 346, 350, 360], in some cases associated with hyperactive pituitary ACTH release [344, 353]. However, cortisol responses to exogenous ACTH may be normal in the same subjects in whom the ACTH:cortisol ratio is increased after exogenous CRH [344]. This argues against an impairment in adrenocortical function and points toward a central mechanism. The investigators who reported these findings suggested decreased sympathetic activity as a possible mechanism [344]; however, FMS is more often characterized by sympathetic hyperactivity in conjunction with hypo-reactivity to stressors [82, 361]. The serotoninergic system regulates HPA function at the level of the hypothalamus, pituitary, and the adrenal cortex [362]. CSF concentrations of the major serotonin metabolite were found to be significantly lower in female FMS patients compared to controls [311, 312]. Therefore, perturbations in the serotoninergic system also represent a potential central mechanism in HPA axis dysfunctions of FMS patients. In contrast to results suggesting adrenal hyporesponsiveness after exogenous CRH administration [346, 353], others observed an attenuated increase of ACTH, but normal rise in cortisol during hypoglycemic clamp, suggesting heightened adrenocortical sensitivity to ACTH [334]. This was, however, not confirmed during graded ACTH infusion, which induced almost identical dose-dependent increases in plasma cortisol levels in FMS patients and controls. In this study, the epinephrine response to hypoglycemia was also significantly decreased, while cortisol, norepinephrine, prolactin, and dehydroepiandrosterone responses were normal [334]. The overall data from this study suggest that there is no generalized impairment in pituitary function, but a diminished ability to activate some part of the hypothalamic-pituitary portion of the HPA axis and the sympathoadrenal system. In yet another study, the more pronounced suppression of cortisol, but not of ACTH, in FMS patients compared to controls during the low-dose DST suggests greater sensitivity of some intra-adrenal control system to glucocorticoid feedback [325]. Finally, the delayed ACTH release in response to systemic administration of interleukin (IL)-6 may indicate a disturbance in the function of hypothalamic CRH neurons [351]. Altogether, the available data suggest that HPA axis function may be disturbed at numerous different levels.

There are numerous potential reasons why studies of HPA axis function in patients with FMS have yielded such contradictory results. First and foremost, studies that assess more than a single aspect of HPA axis function in the same group of patients are quite rare, as are studies that evaluate the same HPA response to several different tests [334, 339, 340, 353, 360, 363, 364]. This makes it difficult to discern a response pattern and to pinpoint the precise point within the HPA axis

Table 4 Summary of HPA axis function in patients with fibromyalgia

Test	Study	*n* FMS/C (Male FMS/Male C)		ACTH Responses (for FMS patients compared to healthy controls)	Plasma Cortisol response (FMS compared to healthy controls	Comments
CRH (ovine)	Crofford [346]	12/10 (0/0)	1 μg/kg body weight i.v.	ACTH: similar response Cortisol: decreased response (both AUC)	Decreased	Baseline cortisol levels were significantly higher in FMS patients.
CRH	Griep 93 [353]	10/10 (0/0)	100 μg i.v.	ACTH: Increased response Cortisol: similar response	Similar	
CRH	Griep 98 [344]	40/14 (4/3)		ACTH: Increased	Similar	
CRH	Riedel 98 [360]	16/17 (3/4)	100 μg CRH i.v. (as part of a cocktail containing 3 other hypothalamic releasing hormones)	ACTH: significantly increased 15 min after CRH infusion only	Similar	Baseline cortisol levels were significantly higher in FMS patients.
ACTH	Kirnap [364]	16/16 (3/4)	250 μg		Peak cortisol levels: Decreased	Baseline cortisol levels were also significantly lower
ACTH	"		1 μg		Peak cortisol response: Decreased	"
ACTH	Calis [363]	22/15 (0/3)	1 μg		Peak cortisol response: Decreased	Baseline cortisol levels were similar
ACTH	Wingenfeld [339]	17/24 (0/0)	1 μg		Decreased Salivary free cortisol: Similar	
ACTH	Adler [334]	15/13 (0/0)	0.05, 0.15, 0.5, 1.5 and 5.0 μg/kg		Similar at all doses	
ACTH after overnight DST	Griep 93 [353]	10/10 (0/0)	0.025 or 0.100 μg/kg ACTH body weight		Similar	
Trier Social Stress Test	[339]	17/24 (0/0)			Decreased Salivary free cortisol: similar	
ITT	Griep 93 [353]	10/10 (0/0)	0.1 IE insulin/kg body weight	Increased	Similar	
ITT	Kirnap [364]	16/16 (3/4)	n.a.		Peak cortisol levels: decreased	Baseline cortisol levels were also significantly lower
ITT (Hypoglycemic clamp)	Adler [334]	15/13 (0/0)	Stepped hypoglycemic hyperinsulinemic clamp	Decreased	Similar	
IL-6	Torpy [351]	13/8 (0/0)	3 μg/kg body weight s.c.	Similar, but delayed	Similar	ACTH concentrations took significantly longer to peak in FMS patient
low-dose DST	[325]	15/20 (0/0)	0.5 mg dexamethasone	ACTH suppression: similar	Cortisol suppression stronger	As a result, the ACTH:cortisol ratio was increased
low-dose DST	[340]	12/15 (0/0)	0.5 mg dexamethasone		Salivary free cortisol: Similar, but tended ($p=0.09$) to be higher during the first hour after awakening	

Metyrapone inhibits the 11β-hydroxylase enzyme that catalyzes the conversion of 11-deoxycortisol to cortisol in the adrenal gland and, therefore, results in increased ACTH release from the pituitary [622]

DST dexamethasone suppression test

where the defect occurs. In addition, measurements of a single parameter at one point in time, as performed in most investigations, ignore the complexity of a highly dynamic feedback-controlled system that interacts with numerous other systems on various levels. Recently, HPA axis parameters in patients with FMS, CFS, or both were analyzed using a dynamic model that included ACTH-adrenal signaling, inhibitory feedback and non-ACTH influences [365]. Compared to healthy controls, patients with FMS with or without CFS (designated as pain-predominant) were characterized by blunted inhibitory feedback signaling but normal adrenal sensitivity and decreased non-ACTH inputs during the night [365]. In contrast, the patients with CFS alone (fatigue-predominant) exhibited significantly enhanced nocturnal ACTH-adrenal signaling and marginally increased inhibitory feedback compared to controls. Diurnal parameters did not differ significantly between patients or patient subgroups and controls. Greater production of cortisol per unit ACTH was inversely associated with somatic symptom levels. In addition, sleep disturbances over the previous month correlated with non-ACTH influences on cortisol secretion in controls only, suggesting the loss of some neuroendocrine regulatory factor(s) in patients with CFS/FMS. This study provides a first glimpse of the new insights that could be derived from using dynamic rather than static models. It also highlights that patient selection (in this case the presence of CFS) is likely to be an important contributor to the discrepant results of HPA axis studies in FMS. Most importantly, however, the findings underscore that there is considerable heterogeneity among patients with FMS with regard to the HPA axis disturbance.

Autonomic Nervous Systems

Besides the HPA axis, the locus coeruleus/norepinephrine-sympathetic system constitutes the other major component of the stress response. There are numerous indications that this system is disturbed in FMS patients. There is widespread consensus that the sympathetic nervous system of FMS patients is characterized by basal hyperactivity but hypo-reactivity. However, investigations of basal plasma concentrations and urinary excretion of catecholamines and neuropeptide Y have yielded heterogeneous results but do not generally support sympathetic hyperactivity [334, 351, 366–375]. After exercise and during hypoglycemia, sympathetic responsiveness (noradrenalin release) appears to be normal, but adrenalin release is consistently lower, suggesting adreno-medullary uncoupling [334, 368, 373, 376]. This suggests normal sympathetic responsiveness, but uncoupling of adreno-medullary secretion. In contrast, the response of FMS patients to subcutaneous administration of IL-6 actually was characterized by sympathetic hyperactivity, whereas only a non-significant rise in noradrenalin occurred in controls [351].

Much of the claim that FMS patients show basal sympathetic hyperactivity rests on measurements of heart rate variability (HRV) in order to assess autonomic function [128, 146, 361, 370, 377]. Power spectral analysis can be used to separate HRV into separate frequency components. There is general agreement that the high-frequency (HF) band of the HRV spectrum is of vagal origin and represents a measure of parasympathetic cardiac control. The LF band is frequently interpreted as an index of sympathetic cardiac activation. Yet, this is a fair approximation only under rather specific circumstances in long-term ambulatory recordings [378]. Particularly under resting conditions, however, all of the frequency bands of HRV largely reflect parasympathetic control, and baroreflex activity may be the most important determinant of the LF band [378, 379]. Therefore the interpretation of the LF/HF ratio as an index of sympathovagal balance is also questionable. Yet, it is largely based on the results of HRV studies showing increased LF power and an increased LF/HF ratio that FMS patients are said to exhibit basal sympathetic hyperactivity and blunted autonomic responses to physical and mental stressors [361]. Tak et al. [380] conducted a systematic review and meta-analysis focused exclusively on studies that provided measurements of parasympathetic nervous system influences on HRV during rest (i.e., sitting or supine) in FMS, CFS, and IBS. According to the meta-analysis, parasympathetic nervous system activity was significantly lower in the overall patient group compared to healthy controls. There were no significant differences between the individual syndromes, or between the separate patient groups and the controls. In addition, there was evidence of substantial heterogeneity in the FMS studies. Based on their own thoughtfully constructed scoring method, the authors concluded that the methodological quality of the reviewed studies was poor to moderate in most cases and that the available evidence was insufficient to either accept or reject a definite role for autonomic dysfunction in FMS or related disorders.

Other cardiovascular responses to stressors more consistently are characterized by sympathetic hypo-reactivity [376, 381], although exceptions exist here, too [382, 383] and the responses may go in opposite directions in specific target tissues [367] and after different types of stressors [128, 384]. In addition, FMS patients show an increased prevalence of neurally mediated hypotension during tilt table testing and blunted vasoconstrictor responses to the cold pressor test and to intense auditory stimuli compared to healthy subjects [366, 370]. Such diminished vasoconstriction could be due to either reduced sympathetic or increased cholinergic responses. HRV monitoring during the cold pressor test showed that the HF power reflecting parasympathetic activity was decreased in FMS patients and enhanced in healthy controls [122], suggesting that the blunted vasoconstriction in the FMS group is not due to increased cholinergic responses. However, in contrast to diminished vasoconstrictor responses to the cold pressor

test, 30–53 % of FMS patients exhibit Raynaud-like phenomena, and an increased prevalence of cold-induced vasospasms has also been reported [385]. Yet, there are data suggesting that this might not be due to sympathetic hyperactivity per se, but to α_2-adrenergic receptor upregulation. An alternative hypothesis is agonist-induced β_2-adrenergic receptor desensitization [385].

A reduction in pain and TP counts after sympathetic blockade suggests that increased muscle sympathetic activity plays a role in the muscle pain and fatigue of FMS patients, possibly by enhancing vasoconstriction and impairing microcirculation [366]. There is limited evidence for muscle hypoperfusion [385], but FMS patients were found to exhibit decreased blood flow in the skin above tender points and a reactive hyperemia pattern consistent with increased sympathetic tone [386, 387]. Direct microneurography of the peroneal nerve showed higher muscle sympathetic nerve activity at rest, but a blunted response to tilt table testing in FMS compared to healthy subjects [370]. However, others observed normal sympathetic muscle activity at rest and during static contractions [388].

Growth Hormone/Insulin-Like Growth Factor-I

Growth hormone (GH) is released by the anterior pituitary, and its secretion is primarily regulated by the hypothalamus via the stimulatory growth hormone releasing hormone (GHRH) and the tonic inhibitory somatostatin. The effects of GH are not brought about directly, but are mediated by somatomedins or insulin-like growth factors (IFGs). Stress, exercise, sleep, and relative hypoglycemia induce release of GH through the induction of noradrenalin, adrenaline, dopamine, serotonin and GABA. The original impetus for assessing GH axis function in patients with FMS was twofold: (1) FMS patients often show disturbances in stage 3/4 sleep, the main period of GH secretion, and (2) some of the symptoms of GH deficiency resemble those of FMS, including easy fatigability, reduced exercise tolerance, dysthymia, and impaired cognition.

There is evidence from several large cohorts and various smaller studies that ~ one third of subjects with FMS exhibit low levels of IGF-I [10, 11, 335, 389]. The restriction to a subset of FMS patients probably explains why the difference in group mean levels does not always reach statistical significance in studies including only small numbers of subjects [11, 390]. When measured repeatedly over 12–24 h, GH output is significantly reduced in FMS patients compared to healthy controls, particularly during the night [11]. There are data suggesting that defective GH production is a consequence of FMS, rather than causally involved in its development [390, 391], but these are not consistent findings [392].

While the GH response to the ITT was found to be normal, it was blunted at least in some investigations of all other types of stimuli, including GHRH, exercise, or arginine, suggesting that the disturbance is at the level of the hypothalamus, not the pituitary. However, there are also studies where FMS patients showed greater GH increases than controls in response to ITT or GHRH plus arginine [10, 11]. This suggests that at least some patients with FMS have low GH and/or IFG-I concentrations due to increased somatostatin tone, and there is some indirect evidence to support this [393]. However, somatostatin concentrations in the CSF of patients with FMS were found to be significantly lower compared to controls free of systemic disease [394]. It should be noted that the levels of IGF-1 and GH are often dissociated and they respond differently to various stimuli in FMS patients [11]. This indicates that there may be a disturbance in the HP-GH-IFG-1 axis in the absence of outright GH deficiency and that the exact nature of this perturbation may vary considerably between individual patients [10, 11]. Addition of GH to the standard treatment of FMS patients with low serum IGF-1 levels has been associated with significant reductions in the FIQ and tender point scores, with effects not becoming obvious for at least 6 months [11, 395].

Cytokines

Many of the characteristics of FMS, including hyperalgesia, central sensitization, fatigue, sleepiness, and neurocognitive disorders, resemble those of the sickness response, an orchestrated set of adaptive physiological and behavioral changes occurring in response to infection, tissue trauma or inflammation. It is mediated by the release of peripheral pro-inflammatory cytokines, which then trigger an upregulation of pro-inflammatory cytokine production in the brain, mainly by activated glial cells [396]. Note that a subset of patients with FMS, generally 3–6 % [397–399], but as many as 55 % [400], report that the onset of their symptoms was associated with *flu-like* illness, suggesting some sort of infectious trigger. In addition, an increased prevalence of FMS has been found in patients with hepatitis B virus, hepatitis C virus, HIV, human T cell lymphotropic virus, and *Mycoplasma* infections [401–403]. Conversely, there are some reports of higher seropositivity rates for certain infectious agents in FMS patients compared to healthy controls [401, 404]. It has long been held that Lyme disease increases the risk of FMS, but a recent study showed that the incidence of FMS in patients with culture-confirmed Lyme disease did not exceed that of the general population during long-term follow-up [405]. The results for other infectious agents also are far from consistent [403, 406, 407]. This suggests that, if infectious agents act as triggers for FMS at all, this process is relevant in a subset of patients only.

In experimental animals and humans, both physiological and psychological stress can affect the peripheral as well as the central brain cytokine network, with acute stress sometimes having opposite effects from those observed during chronic stress [408]. Acute stress in humans has been

associated with increased circulating levels of pro-inflammatory cytokines, in particular IL-6, and this appears to be at least partly mediated by the stress-induced activation of the sympathetic nervous system [340, 408, 409]. While acute stress appears to enhance Th1 cytokines, chronic stress may shift the balance toward a Th2-dominant pattern [408, 410]. This would be expected to cause a decrease in pro-inflammatory cytokines, but the results in animal and human studies are mixed. It is becoming increasingly clear that the precise nature of the cytokine response depends not only on the type and severity of stress but also on a variety of individual demographic and psychological factors, such as age, gender, income, mood or emotional state, stress perception, and coping styles. In addition to stress, acute and chronic reductions in the duration or quality of sleep are an important cause of elevations in pro-inflammatory cytokines [409, 411].

In turn, pro-inflammatory cytokines, in particular IL-1β and IL-6, are potent stimulators of the HPA axis. IL-1β, IL-6, and tumor necrosis factor (TNF)α are important modulators of the sleep-wake cycle, generally exerting somnogenic effects [412]. This is observed even after peripheral administration because cytokine signals can reach the brain by various routes and can affect brain regions involved in the wakefulness regulation either directly or by inducing a large variety of mediators. Furthermore, pro-inflammatory cytokines are part of a network of mediators capable of sensitizing peripheral nociceptors [413, 414], including muscle nociceptors [415]. They also contribute to central sensitization, altogether heightening pain responses and contributing to the maintenance of pain [413, 414]. Whereas pro-inflammatory cytokines largely exert algesic effects, anti-inflammatory cytokines generally exhibit analgesic properties.

Since cytokines can play a role in each of the core symptoms of FMS and may in turn be affected by these symptoms, one would expect to find dysregulated cytokine production in FMS patients. However, a systematic review of studies published until 2010 revealed no consistent cytokine pattern in patients with FMS [416], and none has become apparent in more recent investigations. Instead, the available data are highly heterogeneous. For example, higher, lower, or similar group mean concentrations of IL-1β, IL-6, and TNFα have been reported in FMS patients compared to healthy controls [340, 416–424]. Fewer studies have addressed the peripheral levels of Th2 or anti-inflammatory cytokines, but the results have also been quite varied, with mean serum or plasma levels of IL-4, IL-5, and IL-10 being increased, decreased, or not significantly different between FMS patients and healthy controls [416, 417, 425–427]. When plasma cytokines were sampled every 20 min over 24 h, patients with FMS on average released significantly higher IL-10 concentrations during sleep, but not during the daytime [428]. In addition, during the daytime, secretory bursts of IL-10 were synchronized with bursts of pro-inflammatory cytokines (IL-1β, TNFα, and IL-8) in both patients and controls. Yet, the ratios of these pro-inflammatory cytokines to IL-10 during such bursts were significantly lower in FMS patients compared to controls, suggesting a shift toward an anti-inflammatory response in the patient group.

There is increasing evidence that a variety of peripheral chemokines may also be dysregulated in patients with FMS, but do date, there have been few attempts to replicate the reported findings [416, 429]. An exception is IL-8, which was found to be elevated in patients with FMS compared to controls in several studies [335, 416, 420, 421], but similar to controls in others [416, 417, 424]. Plasma concentrations of monocyte chemotactic protein (MCP)-1 were increased not only in FMS patients, but also in their unaffected relatives, compared to healthy controls [430] and correlated positively with changes in pain intensity over time [431]. Constitutive MCP-1 release from cultured monocytes of FMS patients also was significantly higher than in control monocytes [335]. In addition, increased levels of eotaxin have been reported in at least two studies [416, 429] but the results for various other chemokines have been quite heterogeneous [416, 417, 427].

Although correlations have been reported between a variety of cytokines and certain clinical features, very few of them have been replicated. The most consistent finding is a positive association of circulating IL-8 concentrations with pain intensity [431–433], although the association was found to be inverse rather than direct in another study [434]. Other cytokines positively associated with pain intensity are IL-1β [435], TNFα [418], and IL-6 [425], but again there are data suggesting a negative correlation at least in post-menopausal women, whereas no association was evident in pre-menopausal women [433]. IL-1β, IL-6, TNFα and MCP-1 are quite consistently associated with MDD [436, 437], but studies in FMS patients have failed to detect a correlation between depression ratings and IL-6 [420, 422] or other cytokines [427], whereas IL-5 showed a negative relationship [420]. As in MDD, an association between IL-8 and depressive ratings is not a consistent finding [417, 433]. Il-10 would be expected to have anti-algesic effects, yet no association between IL-10 concentrations and pain intensity became apparent in several investigations [425, 438, 439], but it was negatively associated with fatigue [439]. Even more surprisingly, a positive correlation between IL-10 levels and FIQ scores has been observed in at least two studies [425, 438]. It should be noted that none of these correlations is consistently identified, and more often there is a lack of association between clinical features and circulating levels of cytokines [427, 432, 438, 439] or intracellular cytokine production [440].

There are a variety of possible reasons for the observed discrepancies in the results for each of the cytokines and chemokines investigated in FMS patients to date. The multiplex assays that were used in most studies may lack sensitivity, yet neither the detection limit nor the method for dealing

with detectable but not quantifiable results are stated in the majority of publications. Some cytokines show substantial diurnal fluctuations [428], but information on the timing of the sampling and its standardization for all subjects is not always provided. There are a variety of potential confounders that were not given enough consideration in most studies. These include depression and anxiety [425, 441], comorbid CFS [426], pre- or post-menopausal status [433]; and BMI [442, 443]. In addition, the testing of TPs is stressful for patients with FMS and may be associated with a prolonged rise in cytokine production [340], and therefore should not be undertaken on the same day as blood draws for the measurement of basal hormone or cytokine levels. On the other hand, assessing the reactivity rather than basal levels of cytokines may provide more relevant insights into the role of cytokines in the development or maintenance of FMS symptoms. Unfortunately, the only data that suggest differential reactivity between FMS patients and controls were obtained under conditions that induced pain and considerable stress in the patient group only [340].

Most importantly, however, the marked heterogeneity of the available data suggests that there are subgroups of FMS patients with distinct cytokine profiles. Unfortunately, it is rarely reported how many patients have abnormal results, e.g., have cytokine concentrations 2 standard deviations above or below the mean of controls or show values outside of the range detected in controls. Yet, since most studies include such a low number of patients listing all of the individual results in a table could easily be accomplished, as was beautifully illustrated by Dessein et al. [444] for non-cytokine data. In the few studies of cytokines that contain at least graphic representation of individual measurements, one is left with the distinct impression that the majority of patients with FMS falls into the normal range, but that a—more or less substantial—subset of patients exhibits cytokine concentrations that are clearly above or below the range of healthy controls in plasma [425], serum [429, 445], or CSF [420].

Finally, the periphery may not be the appropriate compartment for the investigation of cytokine profiles in patients with FMS. To date, the single study of cytokine concentrations in CSF of subjects with FMS patients provides evidence of central inflammation in this group [420]. Elevated concentrations of IL-8, though similar levels of IL-1β, were found in CSF of FMS patients compared to patients who underwent a lumbar puncture for headache, but were free of organic abnormalities. Serum IL-8 levels were significantly higher, but serum IL-1β concentrations significantly lower, in FMS patients compared to healthy controls, and there was no correlation between serum and CSF concentration for either cytokine. This indicates that the elevations in CSF IL-8 were due to localized production. The lack of correlation also underscores that peripheral cytokine levels cannot be used to assess central inflammation. Glial cells are likely to be the source of the elevated CSF IL-8 in FMS patients. It has been proposed that glial cell activation is a crucial step in the induction of chronic pathological pain states since it results in the release of pro-inflammatory cytokines in pain-modulatory regions of the spinal cord, thereby leading to central sensitization, i.e., heightened excitability of the dorsal horn neurons, and ultimately to hyperalgesia [396]. Substance P, glutamate, NGF and BDNF are among the factors capable of activating glial cells and inducing the production of pro-inflammatory cytokines and chemokines like IL-8 [396]. Elevated concentrations of these activating substances have been detected in the CSF of FMS patients compared to normal controls or normative values [301, 308, 309].

Potential Pathogenetic Mechanisms

Genetics and Epigenetics

Genetics

FMS shows strong familial aggregation [240, 446]. Although this may be due to shared environmental or behavioral factors, it suggests that there may be a genetic predisposition to FMS. Indeed, according to data from large adult Swedish and Finnish twin cohorts, genetics account for approximately half of the risk of CWP [447] or of being affected by a cluster of symptoms associated with FMS [448]. Shared family environment was found to have essentially no influence [447]. In marked contrast, in adolescent twins genetics did not make a significant contribution to the risk of widespread pain; instead much of the variation in risk (56 % in girls, 35 % in boys) could be attributed to shared familial and environmental factors [449]. These discrepancies may be partly due to the use of different definitions of chronicity and widespread pain, but the age difference is likely to be another important factor. This would suggest that the genetic risk factors for widespread pain do not develop their full impact until later in life and that widespread pain in childhood/adolescence and adulthood are different entities.

There have been numerous candidate gene studies in patients with FMS, focusing primarily on serotoninergic, adrenergic, and dopaminergic pathways, i.e., genes encoding products that are involved in the transport, signaling, reuptake and deactivation of these neurotransmitters (see Table 5). Some of these gene products are implicated in a predisposition toward pain hypersensitivity, including catechol-*O*-methyltransferase (gene designation: *COMT*) [450], the opioid receptor μ1 (*OPRM1*) [451, 452], and GTP cyclohydrolase (*GCH1*), which may also influence the extent and duration of clinical pain [453–455]. However, in several large European cohorts, *COMT* SNPs and haplotypes did not show any associations with CWP or other chronic musculoskeletal complaints [456, 457] and *GCH1* did not confer any risk of CWP [458]. In one

Table 5 Candidate gene studies in FMS

Encoded protein	Gene	Polymorphism	Ethnic group	n (FM/ controls)	Associations susceptibility	Additional associations	Reference[a]
5-HT transporter	*SLC6A4*	5-HTTLPR[b] S/L	German	62/110	SS (p=0.046)		Offenbaecher et al. [641]
		5-HTTLPR S/L	Jewish	51/497	SS (p=0.024)		Cohen et al. [246]
		5-HTTLPR S/L	Palestinian Arab	48/54	SS (p=0.001)		"
		5-HTTLPR S/L, intron 2 VNTR	Turkish	53/60	n.s.		Gürsoy [637]
		5-HTTLPR S/L	French Canadian	48/50	n.s.		Potvin et al. [643]
5-HT2A receptor (serotonin receptor)	*HTR2A*	T102C	German	168/115	TT protective (p=0.023)		Bondy et al. [634]
		T102C	Brazilian	41/49	TT protective (p=0.028)		[471]
		T102C	Brazilian	51/51	n.s.		[623]
		T102C	Turkish	58/58	n.s.	TT associated with higher levels of psychiatric symptoms	Gürsoy et al. [638]
		T102C (rs6313), rs 6311	Turkish	80/91	n.s.		Tander et al. [645]
Serotonin receptors	*HTR3A*	5 variants	German	48/62	n.s.		Frank et al. [636]
	HTR3B	4 variants	German	48/62	n.s.		"
catechol-O-methyltransferase	*COMT*	rs6269, rs4633, rs4818, rs4680 (Val58Met)	Spanish	113/65	rs4680 AA (Met/Met) (p=0.009) rs4633 TT (p=0.021)	APS (ATCA) and HPS (ACCG) haplotypes were increased in FMS patients (p=0.029)	[624]
		rs4680 (Val58Met)	Spanish	110/110	rs4680 AA (Met/Met) (p=0.048)	Met/Met associated with higher FIQ scores	[625]
		s6269, rs4633, rs4818, rs4680 (Val58Met), rs2097903, rs165599	Spanish	78/80	rs6269 genotype (p=0.015) rs4818 genotype (p=0.001) rs4680 genotype (p=0.023)	ACCG and ATCA haplotypes were associated with FMS susceptibility. GTGA was protective	Vargas-Alarcon et al. [646]
		"	Mexican	57/33	n.s.	Haplotypes were not associated with FMS in Mexican patients	Vargas-Alarcon et al. [646]
		rs4680 (Val58Met)	Brazilian	51/51	rs4680 AA (Met/Met) (p<0.05)		[623]
		rs4680 (Val58Met), rs4818	Brazilian	112/110	rs4680 AA (Met/Met) (p<0.001) rs4818 CC (p<0.001)	rs4680 AA and rs4818 CC associated with highest FIQ scores	[626]

Table 5 (continued)

Encoded protein	Gene	Polymorphism	Ethnic group	n (FM/ controls)	Associations susceptibility	Additional associations	Reference[a]
		rs4680 (Val58Met)	Israeli	209/151 (unaffected relatives)	Met allele (p=0.004)	Met/Met associated with higher number of TPs	Cohen et al. [635]
		rs4680 (Val58Met)	Turkish	61/61	s4680 GG was protective (p=0.04)	The differences in AA and A/G genotypes separately did not reach statistical significance	Gürsoy et al. [639]
		rs4680 (Val58Met)	Turkish	379/290	rs4680 AA (Met/Met) (p=0.016)	rs4680 AA associated with pain sensitivity	[627]
		rs4680 (Val58Met)	Turkish	80/91	n.s.		Tander et al. [645]
		rs4680 (Val58Met)	French Canadian	37/36	n.s.		Potvin et al. [642]
		rs4680 (Val58Met)	Swiss	198/99	n.s.	Met/Met was associated with more severe disease	[250]
Monoamine oxidase A	MAO-A	941G/T	Taiwanese	62/101	n.s.		Su et al. [644]
Monoamine oxidase A	MAO-A	promoter VNTR	Turkish	107/90	n.s.	allele 3 vs. allele 1 is associated with higher FMS risk (p=0.033)	Gürsoy et al. [640]
Monoamine oxidase B	MAO-B	intron 13 G→A	"	"	n.s.		"
α1A-Adrenergic receptor	ADRA1A	rs574584, rs1383914, rs1048101, rs573542	Spanish	78/71	rs1383914 genotype (p=0.01)		Vargas-Alarcon et al. [647]
		"	Mexican	78/48	n.s. for genotypes AGA haplotype protective (p=0.02)		"
β3-Adrenergic receptor	ADRB3	rs4994	Spanish	78/71	n.s.		"
		"	Mexican	78/48	n.s.		"
β2-Adrenergic receptor	ADRB2	rs1042713 (Arg16Gly), rs1042714 (Gln27Glu)	Spanish	78/71	AC haplotype (p=0.05)		"
		"	Mexican	78/48	AC haplotype (p=0.04)		"
		rs1042713 (Arg16Gly), rs1042714 (Gln27Glu)	Hispanic and European Americans	92/57	Arg16Gly protective (p=0.03, p=0.055 after adjusting for age and sex)	No association with the AC haplotype (see above)	[628]
Opioid receptor μ1	OPRM1	A118G (rs1799971)	Turkish	108/100	G-containing genotypes protective (p=0.04)		[629]
Dopamine receptor D4	DRD4	exon 3 VNTR	Israeli	81/458	genotypes with at least one		Buskila et al. [472]

Table 5 (continued)

Encoded protein	Gene	Polymorphism	Ethnic group	n (FM/controls)	Associations susceptibility	Additional associations	Reference[a]
					7 repeat protective (p=0.034), but this was significant only in carriers of the 5-HTTLPR S allele		
Dopamine receptor D3	DRD3	Ser9Gly	French Canadian	37/36	n.s.	Dose–response effect on DNIC efficacy and thermal pain threshold (Ser/Ser<Ser/Gly <Gly/Gly)	Potvin et al. [105]
Dopamine transporter gene	SLC6A3	3′ VNTR	Jewish	87/200	n.s.		Ablin et al. [632]
Substance P receptor	TACR1	1354G/C	"		n.s.		"
a1-antitrypsin	AAT	E342K	"		n.s.		"
Interleukin-4	IL4	intron 3 VNTR	Taiwanese	62/101	n.s.		Su et al. [644]
Endothelial nitric oxide synthase	NOS3	G894T (Glu298/Asp)		96/79	n.s.		Alasehirli et al. [633]
Guanosine triphosphate cyclohydrolase	GCH1	rs3783641 (T/A), rs841 (C/T), rs752688 (C/T), rs4411417 (T/C)	Korean	409/422	n.s.		
					(but possible decrease in the frequency of the protective CCTA haplotype in FMS patients	CCTA was associated with lower pain sensitivity	[630]
Sodium channel Nav 1.7	SCN9	rs4371369, rs4387806, rs4453709, rs4597545, rs6746030, rs6754031, rs7607967, rs12620053, rs12994338, rs13017637	Mexican	73/48	rs6754031 (p=0.036)	rs6754031 GG associated with higher FIQ scores	[470]

[a] References without reference numbers can be found in the review by Lee et al. [631]

[b] 5-HTTLPR=5-HT (serotonin) transporter-linked promoter (or polymorphic) region

of the same cohorts, the T allele of the 5-HT 2A receptor gene was associated with a decreased number of somatic symptoms [459]. This suggests that the T allele could protect from the development of FMS, and this was indeed seen in some studies, but not in others (see Table 5). As summarized in Table 5, significant associations have been reported with these pain-associated and a variety of other genes, but none of them are consistently observed in all populations. A few investigations addressed genetic associations with features of FMS rather than disease susceptibility. In addition to the results summarized in Table 5, there are data suggesting that the Val158Met SNP of *COMT* may be associated with central sensitization [460] and psychological vulnerability in patients with more severe disease [250]. The *COMT* genotype may also modulate the relationship between pain and maladaptive coping [461], and both the *COMT* Val158Met SNP and the rare 118G allele of the *OPRM1* may influence the extent of mood changes in response to elevations in daily pain [462].

In view of the growing evidence that FMS is associated with signs and symptoms of small-fiber neuropathy in a substantial subset of patients [463–467], the *SCN9* gene is of particular interest since 8/28 (29 %) of patients who met stringent criteria for idiopathic small fiber neuropathy were demonstrated to harbor seven different gain of function mutations in this gene [468]. The *SCN9* gene encodes the sodium channel Nav1.7 and has been the target of intense research since the discovery that loss of function mutations result in complete insensitivity to pain, whereas gain of function mutations cause severe chronic pain conditions like inherited erythromelalgia and paroxysmal extreme pain disorder. Since then, the results of animal studies have shown that wild-type Nav1.7 plays an important role in inflammatory and neuropathic pain. Nav1.7 is expressed primarily on dorsal root ganglion (DRG) and sympathetic ganglion neurons [469]. In rats, its expression has been documented both in the central projections and in the peripheral terminals of these DRG neurons with strong immunoreactivity in intra-epidermal nerve fibers [469]. Investigation of ten SNPs in the *SCN9A* gene showed that one of them was associated with severe FMS in Mexican patients [470]. Altogether, these data raise the possibility that a DRG sodium channelopathy could underlie some cases of FMS, particularly those associated with, or presenting as, a small fiber neuropathy.

Overall, no candidate gene has been consistently associated with FMS. This is probably due to the small sample size in most of the studies to date, but may also be due to the failure to consider gene-gene and gene-environment interactions, which may be very strong determinants of the genetic risk of FMS conferred by a single SNP [471, 472]. But, most importantly, a candidate gene approach requires some basic understanding of the pathophysiology of a disease, and such an understanding is largely lacking in FMS.

Several approaches have been adopted to circumvent this problem, including the use of a dedicated candidate gene platform that genotypes>3,000 SNPs in >350 gene [473], the study of genome-wide associations in CWP [474] and FMS [475], and whole exome sequencing with various filters [476]. These failed to confirm any of the associations previously reported in candidate gene studies, and each identified only one or a few genes as showing associations with CWP or FMS, but these genes all differed between studies. In addition, in a genome-wide linkage scan in 116 families with multiple cases of FMS patients a region on chromosome 17 showed evidence of linkage, but this region contains more than 100 genes [477].

The inability to confirm genetic associations in candidate gene studies and the poor success rate in genome-wide SNP analyses, particularly the failure to replicate the detected associations in independent cohorts highlight two issues. (1) If there is a genetic component to FMS, it most likely involves multiple genes, each of which individually makes only a small contribution. (2) The data strongly suggest that FMS is a heterogeneous syndrome not only in its clinical presentation and comorbidities, but also genetically. Hence, efforts should be made to identify more homogeneous patient groups (e.g., those with reduced ENFD, or elevated peripheral concentrations of inflammatory cytokines and other markers of inflammation; or those with clear evidence of HPA axis hypoactivity or hyperactivity) before attempting to elucidate the genetic contribution to FMS.

Epigenetics

Gene expression is determined not only by the DNA sequence itself, but also by epigenetic modification, which in turn reflect developmental and environmental influences. Note that the T102C SNP in the *HTR2A* gene is part of a methylation site that influences the expression of this serotonin receptor. Therefore, some of the discrepant findings concerning the association of this SNP with FMS (see Table 5) may arise from differential methylation and gene expression in carriers of the C allele [478]. In a pilot study, it was recently shown that the genome-wide methylation pattern differed significantly between women with FMS and healthy controls [479]. Of 69 differentially methylated sites, 63 showed a higher degree of methylation in FMS patients. The involved genes included many with potential relevance to FMS because their products play a role in muscle contraction, muscle maturation, neuronal function, inflammatory processes, and response to oxidative stress. In addition, women with FMS had a significantly higher frequency of micronuclei, a measure of chromosomal abnormalities, which may arise from histone alterations.

Central Sensitization

As mentioned earlier, patients with FMS exhibit essentially all of the typical manifestations of central sensitization including allodynia, hyperalgesia, temporal summation, and aftersensations [94–101]. They are hypersensitive not only to pressure stimuli, but also to other mechanical, thermal, electrical, and auditory stimuli [5, 76, 92, 102–114] and the widespread nature of their pain provide further evidence that central mechanism must be involved in the development and maintenance of this syndrome. Since many of these features go beyond what the concept of central sensitization refers to, central amplification of pain may be a more appropriate term.

Nonetheless, it is now widely accepted that central sensitization contributes to the chronification of pain in a variety of diseases and disorders, including FMS [480]. For example, the NFR threshold was found to be decreased in FMS patients [92, 93] and to show a strong positive correlation with the pressure pain threshold, but a negative correlation with current pain intensity, at least in non-depressed patients [481]. This not only provides objective evidence of spinal hyperexcitability in FMS, but also directly ties this hyperexcitability to clinical pain. The enhancement of temporal summation was significantly greater after brief repetitive mechanical stimulation [95] than after repetitive cutaneous heat stimulation [94], suggesting that increased sensitization of deep tissue (i.e., muscle) nociceptors is relevant to the pathophysiology of FMS. The sum of local areas of pain, a score obtained by counting all of the 20 areas on a body diagram that patients rated as painful, was an independent predictor of pain intensity [482]. This suggests that spatial summation of pain might play a role in the pain intensity experienced by patients with FMS.

N-methyl-D-aspartate (NMDA) receptor activation plays an important role in the induction and maintenance of central sensitization. Infusion of the NMDA receptor antagonist ketamine reduced clinical pain and pain hypersensitivity in ~60 % of FMS patients [98, 483]. This also lends support to the hypothesis that central sensitization is a key factor not only in the hyperalgesia but also in the spontaneous pain of FMS. More importantly, however, it indicates that this mechanism is of relevance in a subset of patients only. Further evidence for such subsets comes from the analysis of the spatial distribution of pressure pain hypersensitivity. Some find FMS patients to exhibit such hypersensitivity only at the TPs but not at control sites [78, 484], whereas others report a more generalized hypersensitivity [76, 108, 485, 486]. There are data supporting the existence of both types of patterns in FMS patients [487]. Generalized hypersensitivity is compatible with central pain amplification. Hypersensitivity restricted to TPs is consistent with the hypothesis that FMS is a soft tissue disorder affecting muscles or tendon insertions. This suggests that FMS arises through, or is maintained by, distinct mechanisms in different individuals. This is further supported by the differential responses of FMS patient to various analgesics, which indicate that different pain processing mechanisms are involved in perpetuating pain in individual patients with FMS [483].

The Muscle as Peripheral Nociceptive Input

Muscle Abnormalities

Since FMS patients experience pain deep in their muscles and frequently also complain of muscle fatigue, the muscle has been the target of numerous investigations attempting to identify structural, functional, or metabolic alterations that could explain these symptoms. The results have been inconsistent, but to date no morphological abnormality specific to FMS has been identified, and no signs of inflammation have been detected. Nonetheless, various non-specific alterations have been described with increased frequency in muscle biopsy samples from FMS patients compared to healthy controls [488, 489]. These include an increased occurrence of moth-eaten fibers and ragged red fibers, which reflects the abnormalities in the number, shape, and distribution of mitochondria that becomes obvious during electron microscopy [489–491]. In addition, the fiber size distribution may be altered, although the proportion of type I and type II fibers generally does not differ significantly between FMS patients and controls [490, 492].

Mitochondrial function may also be disturbed as suggested by the finding of decreases in oxidative enzymes [493]. This is further supported by reduced levels of muscular ATP and phosphocreatine, even if they are not consistently observed and even if it is not clear to what extent the physical inactivity and deconditioning of FMS patients contribute to these findings [488, 494–496]. Further evidence of mitochondrial dysfunction comes from PBMC and skin of FMS patients [435, 497, 498]. More specifically, compared to healthy controls, PBMC from FMS subjects exhibited decreased activity of mitochondrial respiratory chain enzymes and reduced mitochondrial membrane potential in conjunction with lower concentrations of coenzyme Q10 (CoQ10) compared to healthy controls. Although respiratory chain enzymes are generally the major source of reactive oxygen species and their activity was lower in FMS patients, there was evidence of increased oxidative stress both in PBMC and plasma. While decreased respiratory chain enzyme activity could explain the lower endurance of FMS patients, it does not explain the muscle pain. However, there are indications that mitochondrial dysfunction induced by CoQ10 deficiency is associated with inflammasome activation and production of IL-1β and IL-18 both in vitro and in vivo, including higher serum levels of both of these cytokines in FMS patients compared to healthy controls [435]. Serum TNFα concentrations were also elevated and the levels of IL-1β and TNFα correlated with pain scores [418]. The

concentrations of CoQ10 in PBMC closely parallel those in skeletal muscle [499]. This suggests that muscle inflammation arising from CoQ10 deficiency-induced mitochondrial dysfunction and oxidative stress could contribute to the muscle pain of FMS patients. Note, however, that circulating concentrations of IL-1β and TNFα are not consistently elevated in FMS patients. Instead, the group means more often are in the normal range or even decreased [416, 419–421, 423]. In addition, no inflammatory changes have been described in muscle biopsy samples from FMS patients. However, it has been reported that immunoreactivity for the advanced glycation end product (AGE), N^{ε}-carboxymethyllysine (CML), is elevated in biopsy samples from the biceps brachii muscle of FMS patients compared to controls [500]. The CML receptor RAGE and its downstream effector, activated NF-kB, along with CD68+ cells (monocytes/macrophages) were detectable in FMS samples, but only rarely could be observed in control samples. These findings suggest that oxidative stress, possibly arising from tissue hypoxia, triggers an inflammatory reaction that could result in the production of pro-inflammatory cytokines, which in turn could contribute to peripheral and central sensitization and pain perception. CML and downstream mediators of inflammation were detected primarily in the interstitial tissue between muscle fibers, i.e., where the fascia are found. The fascia are the major location of muscle nociceptors, and input from muscle nociceptors is highly effective in inducing central sensitization [480]. It has even been hypothesized that fascial abnormalities and dysfunction, rather than irregularities of the muscle cells themselves, play a major role in the pathology of FMS [501].

An abnormal distribution in tissue oxygen pressure suggests that capillary microcirculation is another abnormality of FMS muscle, at least in the area of a TP [502]. This may be a consequence of the reduced capillarization and enhanced thickness of the capillary endothelium that have been described in muscle biopsy samples of FMS patients compared to healthy control samples [489, 490]. In addition, capillary permeability was found to be significantly reduced in FMS compared to healthy subjects, at least in nailfold capillaries [503], where disturbed microcirculation has also been observed [387]. Reduced capillary density and capillary thickening could be either the cause or the result of localized hypoxia, but either way, these results suggest that tissue hypoperfusion could play an important role in the development or maintenance of pain and other symptoms in FMS. There are indications that muscle blood flow is diminished in patients with FMS compared to healthy controls particularly during and after muscle activity, even if the results are not entirely consistent [385, 488, 492]. A major determinant of these discrepancies may be the differential responses of FMS and control subjects to needle insertion trauma, prolonged inactivity or both [492]. However, even non-invasive techniques have yielded conflicting results [504, 505].

Muscle Ischemia

Ischemia has long been hypothesized to be causally involved in the muscle pain of FMS patients [385, 506]. In that case, one would expect FMS patients to exhibit diminished oxygen uptake, decreased anaerobic threshold, and increased lactate concentrations in the muscle and blood during and after exercise compared to matched controls. It is specifically this accumulation of lactate that has been hypothesized to induce muscle pain [506]. Investigations of these issues have yielded inconsistent results, with some finding lower oxygen uptake (VO2 max) after exercise to volitional exhaustion [507–510], but others reporting similar VO2 max in patients and controls [393, 511–513]. Both the lactate threshold and the ventilatory anaerobic threshold were found to be decreased in FMS compared to control subjects [508, 509, 514], i.e., patients reached anaerobic threshold at lower absolute and relative work levels [514]. However, basal and peak circulating lactate concentrations and lactate levels at exhaustion were similar in patients and controls after various types of exercises [368, 508, 515]. Some cohorts of FMS patients actually exhibited significantly lower lactate concentrations after exercise, but this was most likely a reflection of lower effort [510, 513]. Microdialysis studies have yielded heterogeneous results, with resting trapezius muscle containing significantly higher lactate and pyruvate concentrations in FMS patients compared to controls [516], whereas lactate concentrations in the resting vastus lateralis muscle did not differ significantly between patients and healthy subjects [492]. During cycle ergometry, lactate concentrations were significantly increased in FMS patients at the same absolute exercise intensity (30 W), but not at the same relative intensity of 60 % VO2 max. This suggests that FMS patients exhibited higher lactate levels because they had to perform more work in order to keep the exercise intensity at 30 W.

Essentially, the currently available data on muscle blood flow, oxygen uptake and metabolism are inconclusive. Sample sizes are usually very small (<10) to modest, although some studies involved up to 50 patients and 50 controls [509]. Few studies focused on the same muscle, and the exercise protocols differed substantially. In several studies, muscle metabolism was assessed at maximal workload, yet for a variety of reasons (e.g., pain, fear of pain, or deconditioning) many patients with FMS seem to be unwilling or unable to reach a plateau in oxygen uptake or heart rate [507]. This means that the level of performance was limited by symptoms rather than by metabolic factors. But the major issue in all studies of muscle metabolism is the choice of a control group. Matching for age and sex is usually attempted, but few investigators specifically enroll sedentary controls with the same low level of activity and exercise that is typical of many women with FMS. According to their scores on the human activity profile scale, the average activity level of women with FMS

was below the 1st percentile for women in their respective age groups [77].

Due to their inconclusive nature, these data do not provide clear evidence in favor of the hypothesis that ischemia may be a major cause of muscle pain in FMS patients. It should also be noted that lactate accumulation alone is unlikely to be the causal agent. When lactate was applied to the thumb muscle at concentrations that arise during ischemic exercise, it did not cause acute pain [517]. The pain and fatigue ratings rose only when lactate was combined with protons and ATP, possibly because several different types of metabosensitive receptors need to be activated before a pain signal is transmitted. However, these metabolites have not been measured simultaneously in the muscle of FMS patients and controls.

Muscle Fatigue

Patients with FMS often perceive greater levels of exertion at similar or even lower workloads compared to healthy controls [368, 382, 510, 518]. Accordingly, FMS patients exhibited greater electromyographic signs of fatigue during sustained contraction of the trapezius muscle [519] or the quadriceps muscle [510]. Somewhat paradoxically, however, several other investigations revealed decreased electromyographic signs of fatigue in FMS patients compared to controls during voluntary contractions of the biceps brachii muscle [520, 521], deltoid muscle [522], and the vastus medialis muscle [523]. The interpretations of these findings differ substantially. Some think that fewer objective signs of muscle fatigue in FMS patients reflect an altered muscle fiber composition and, therefore, a peripheral phenomenon [523], although no abnormalities in the distribution of type I and type II fibers have been detected in biopsy samples [490, 492]. Others consider their results consistent with abnormalities in the muscle membrane [521], possibly arising from the reported inability of FMS muscles to relax between contractions [524]. This is thought to result in long-lasting depolarization and hyperexcitability, which would then override the electromyographic signs of fatigue [521]. Alternatively, the discrepancy between the patients' higher perceived level of muscle fatigue and lower objective signs of fatigue has been interpreted as a central nervous dysfunction [522]. Only one group of researchers included electrically stimulated contractions in the experimental protocol and found that electromyographic signs of muscle fatigue were decreased in FMS patients only after voluntary contractions, but not significantly different from controls after electrically stimulated contractions [520]. This suggests a different motor recruitment pattern, i.e., an adaptation of the central nervous system.

Other findings lend further support to an altered motor unit recruitment pattern in FMS patients. During sustained contraction of the trapezius muscle, the region of the greatest muscle activity gradually shifted towards the cranial region in healthy controls, while such a shift was not observed in patients with FMS [519]. This appeared to be a consequence of the muscle pain in FMS patients. When muscle pain was induced in healthy controls by the injection of hypertonic saline, the activity distribution within the trapezius muscle greatly resembled that seen in FMS patients, i.e., there was significantly less redistribution of the activity from caudal to cranial regions of the muscle. Others confirmed these findings and extended them by showing that the redistribution of muscle activity in the trapezius muscle is not unidirectional during longer contractions and that the decrease in differential activation in FMS patients was evident at low, but not at high loads [525]. Together, these findings suggest that a peripheral nociceptive stimulus in the form of muscle pain induces adaptations of the central nervous system, i.e., altered muscle control strategies that manifest as a different motor unit recruitment pattern.

Treatment of Peripheral Nociceptors

A peripheral nociceptive input may also be critical in maintaining central sensitization. When lidocaine was injected into the upper trapezius muscle during tonic pressure stimulation, it significantly increased the local pressure pain threshold in FMS patients and controls, whereas placebo injection had no effect [107]. It also attenuated secondary heat hyperalgesia in a remote location (the ipsilateral forearm) in FMS patients, but not controls. This strongly suggests that muscle impulse input plays a role in maintaining secondary heat hyperalgesia and, therefore, central sensitization. Clinical pain intensity was not affected, which was expected since the dose of lidocaine was kept purposely low to avoid systemic analgesic effects.

Other results, however, indicate that persistent peripheral nociceptive input also plays a role in the clinical pain of FMS patients. For example, epidural opioids significantly reduced resting pain and TPs in the lower half of the body, and epidural lignocaine (lidocaine) completely abolished both [526]. Another example comes from the treatment of myofascial trigger points (MTrPs). It has long been hypothesized that MTrPs play a role in the development or maintenance of FMS, but the very validity of MTrPs remains controversial, even though there now are several lines of objective evidence for their existence [527]. The sites of FMS TPs as specified in the ACR 1990 criteria were found to frequently contain both active and latent MTrPs confirmed by intramuscular spontaneous electrical activity [528]. In particular, the epicondyle and the trapezius TP site were associated with active MTrPs in >70 % of FMS cases. Patients with FMS commonly exhibit MTrPs and in much greater numbers than healthy controls [529]. The local and referred pain induced by manipulation of active MTrPs was found capable of reproducing the pattern of clinical pain in women with FMS [74, 529]. The intensity of clinical pain in these patients on the day of the examination

correlated significantly with the mean number of active MTrP [529] and with the area of pain evoked by manipulation of active MTrP [74]. In addition, there was a negative correlation between the number of active MTrP and the pressure pain threshold over several of the FMS TP sites [529].

Importantly, treatment of an MTrP that did not coincide with an FMS TP not only improved the local pain and pain hypersensitivity at the MTrP, but also reduced the overall clinical pain intensity in FMS patients [79]. In addition, such treatment decreased the overall pressure pain sensitivity at TPs and in non-TP muscle and increased the electrical pain thresholds in skin, subcutis, and muscle [79]. Very similar results were obtained with hydroelectrophoretic treatment of painful joints with diclofenac and betamethasone in patients with FMS and joint pain due to microtrauma or osteoarthritis. These findings are consistent with other data suggesting that inactivation of active MTrPs is associated with decreased central sensitization; conversely, sustained manipulation of latent MTrPs in healthy subjects results in an extrasegmental increase in mechanical hyperalgesia, which is indicative of central sensitization [530, 531]. Altogether, these results strongly suggest that both central sensitization and clinical pain in FMS stem from, or are maintained by, persistent peripheral nociceptive input and that treatment of such peripheral pain sources can relieve not only local pain, but can also improve overall pain and diminish central sensitization.

Further Potential Peripheral Nociceptive Input

A considerable portion of FMS patients report neurological symptoms, including paresthesias and dysesthesias, although the proportion varies between 26 and 95 % in different cohorts [4, 15, 168, 532–534]. This has prompted several investigations of epidermal nerve fiber density (ENFD), which may provide objective evidence of small fiber polyneuropathy in patients with clinical signs of small fiber dysfunction. The results demonstrated that ENFD was reduced in a subset of patients with FMS [463–467]. Several other findings in these patients were consistent with a small fiber polyneuropathy, including elevated scores on neuropathic pain questionnaires [464, 535], a high frequency of paresthesias [466], stocking hypesthesia [465], and some abnormal results of sensory testing [463, 467], and autonomic function testing [464]. More specifically, Üceyler et al. [463] provided evidence of deficits in Aδ and C fiber function in the overall cohort of patients they investigated. These deficits included results of quantitative sensory testing indicative of increased thermal and mechanical detection thresholds along with reduced amplitudes of pain-evoked potentials after stimulation with a planar concentric electrode [536]. Note, however, that investigations using laser-evoked potentials (LEPs) rather than planar concentric electrodes have yielded heterogeneous results, with some results being consistent with enhanced Aδ-mediated pain signaling in FMS patients [109, 537, 538], while the largest study to date yielded opposite results [467] and therefore consistent with the findings of Üceyler et al. [463]. In addition, increased thermal and mechanical detection thresholds have very rarely been reported in other groups of FMS patients [5]. The majority of investigations do not reveal significant differences between FMS and healthy subjects for mechanical or thermal detection thresholds [5, 92, 102, 103, 110, 111, 539], and the latter may even be decreased in some patient cohorts [76, 106].

There is disagreement over how reduced ENFD and other signs and symptoms of small-fiber involvement in FMS should be interpreted. Some investigators maintain that such patients exhibit a small-fiber pathology, but that their symptoms are distinct from those with small fiber polyneuropathy [535]. Others assert that they not only showed typical underlying causes of polyneuropathy but also provided both biopsy evidence and results of neurological examination that fully support the diagnosis of small fiber polyneuropathy in these FMS patients [540].

Microneurography of the peroneal nerve revealed abnormal cutaneous C nociceptor function similar to that seen in patients with small fiber neuropathy in 77 % of FMS patients [541]. More specifically, while mechanosensitive type 1A nociceptors functioned normally, a high proportion of the usually silent mechanoinsensitive type 1B nociceptors exhibited spontaneous activity, but also enhanced activity-dependent slowing of conduction velocity, and this distinguished FMS patients from patients with small-fiber neuropathy. Such spontaneous nociceptor activity could well be the pathophysiological basis for the clinical pain of FMS patients. Note, however, that the loss of epidermal innervation and the spontaneous firing of cutaneous nociceptors are somewhat difficult to reconcile with the deep pain that characterizes FMS.

These may be better explained by the findings of another study examining cutaneous innervation, more specifically the arteriole-venule shunts (AVS) from the palmar hypothenar glabrous skin [542]. Compared to healthy controls, the AVS in biopsy samples of FMS patients were significantly enlarged due to an increase of both peptidergic and sympathetic nerve fibers, but with a disproportionately greater increase in vasodilatory sensory innervation. Innervation of arterioles and venules was not altered in FMS patients. AVS play an important role in regulating blood flow to glabrous skin for thermoregulation. In addition, hands and feet act as a reservoir from which blood flow can be mobilized to other tissues, including skeletal muscle, during periods of high metabolic demand. Therefore, it is conceivable that the identified AVS pathology contributes to muscle ischemia and, as a result, to the deep pain characteristic of FMS. In addition, the excessive sensory innervation and the blood flow abnormalities

resulting from it could explain why patients with FMS are so sensitive to cold and why almost two thirds report pain in their hands [543].

The Role of Sleep in Pain

In recent years, it has become increasingly evident that there is a bidirectional relationship between pain and sleep disturbances, but the results of prospective studies suggest a stronger link between insomnia and the subsequent development of pain than between chronic pain and the subsequent development of insomnia [544]. That is consistent with the findings that high scores on the sleep problem scale independently predicted the development of CWP [545], and poor sleep predicted the persistence (vs. resolution) of CWP in population-based studies [546]. In addition, during a 17-year follow-up, self-reported sleep problems at baseline were independently associated with the development and persistence of chronic pain, although the association with progression from chronic pain to CWP lost significance when adjusted for pain during the night [547].

There is substantial evidence that total, partial, or stage-specific sleep deprivation can have hyperalgesic effects in healthy volunteers [544, 548, 549]. Conversely, extended sleep time was associated with decreased heat pain sensitivity in healthy subjects [550], which echoes the observation that recovery after sleep deprivation is associated with significant increases in thermal and pressure pain thresholds compared to baseline even in cases where pain tolerance was not affected by the sleep deprivation protocol [551, 552]. Nonetheless, a significant effect of sleep deprivation on pressure pain or thermal pain thresholds is not a consistent finding [544, 553]. These discrepancies are most likely attributable to the low sample size in most of these studies, the lack of controls groups particularly in earlier investigations, the different sleep disruption or deprivation protocols, and the different outcome measures used for the assessment of hyperalgesia.

In addition, sleep deficits in healthy subjects have been associated with a small, but significant, increase in self-reported spontaneous pain that continues to rise for at least the first 4 days of partial sleep deprivation [411, 554, 555]. Simultaneously, mood becomes more negative and psychosocial functioning declines, but these factors do not explain the increased bodily discomfort after sleep restriction. Similarly, in patients with RA, partial sleep deprivation was associated with a rise in anxiety and depression scores, but these did not explain the increase in self-reported spontaneous pain and number of painful joints [556]. There are data suggesting that sleep discontinuity rather than partial sleep deprivation accounts for this increase in spontaneous pain [557]. Sleep discontinuity was achieved by forcing subjects to stay awake for seven 20-min periods and one 60-min period distributed pseudorandomly during an 8-h sleep opportunity. This is likely to more closely resemble the frequent awakenings reported by subjects with chronic pain. Note, however, that one night of total sleep deprivation was associated with decreased depression and anger scores in patients with somatoform pain disorders [552], indicating that findings in healthy volunteers or specific patient groups cannot be generalized to all patient populations.

Somatosensory thresholds usually do not change after total sleep deprivation in healthy volunteers [548, 549, 558] or patients with chronic pain [552, 559]. Nonetheless, healthy subjects perceived heat stimuli as more painful after sleep restriction compared to unrestricted sleep [548, 553, 560]. Yet, the same subjects exhibited decreased LEP amplitudes [548, 560], or an increased LEP threshold after sleep deprivation [553]. This suggests that increased pain perception after sleep deprivation is not mediated by sensory amplification, but rather by cognitive or perceptual amplification or by impaired descending pain control distinct from classical descending inhibition [560]. Nonetheless, decreased efficacy of classical ICPM has been observed in healthy volunteers, with evidence that sleep discontinuity rather than partial sleep deprivation accounts for the effect [557]. Not only do FMS patients exhibit less efficient ICPM [104, 105, 119, 120], but the Pittsburgh Sleep Quality Index score, in particular sleep efficiency and sedative medication use, was the only clinical variable that was significantly associated with ICPM efficacy [121]. Together, these findings underscore how important it will be in the future to pay more attention to the potential impact of the sleep disturbances that almost all FMS patients experience on essentially every one of the other core symptoms of FMS.

Stress and the Stress Response Systems in FMS

In laboratory animals and humans, experimentally induced short-term stress can have analgesic effects, but can also be associated with hyperalgesia and allodynia, depending on the nature and strength of the stressor and the physiological state of the animal [561]. Exposure to chronic stress is more likely to result in stress-induced hyperalgesia or allodynia [561, 562], possibly by inducing hypocortisolism that allows upregulation of pro-inflammatory cytokines, which then can sensitize nociceptors. Indeed, there are experimental human data suggesting that cortisol levels are causally involved in modulating pain sensitivity [563, 564].

As mentioned earlier, patients with FMS often associate both the onset and the exacerbation of their symptoms with stressful experiences [72, 167]. Indeed, there is experimental evidence that acute stress increases pain hypersensitivity and the level of spontaneous pain in patients with FMS, but not in controls [565–567]. The results of a prospective study from northwest England not only showed that the development of CWP was associated with high levels of psychological

distress but also provided the first evidence that the somatization of distress preceded the onset of CWP [568], which was later confirmed in a larger cohort [545]. In addition, among subjects who were pain-free at baseline but at increased risk of developing CWP because of their psychosocial profile, dysfunction of the HPA axis predicted the development of CWP over a 15-month follow-up, and this was independent of psychological and physical risk factors [569, 570]. Specifically, failure of feedback suppression was the most consistent and significant influence, but blunting of the diurnal cortisol rhythm also contributed. In further support of the hypothesis that abnormal stress responses are somehow involved in the development or maintenance of the pain in FMS, CRH concentrations in the CSF of FMS patients correlated significantly with pain as assessed with the MPQ, particularly with the sensory component of the score [571]. This correlation was independent of depressive symptoms. In addition, a flattened diurnal cortisol profile due to decreased morning peak, and similar evening trough, cortisol values appears to be strongly associated with a history of abuse [355, 356]. These, along with other similar data provide support for the theory that childhood trauma resulting in hypocortisolism may constitute one of the pathways leading to the development of FMS [572]. Altogether, it appears that disturbances in a variety of different pathways could result in symptom profiles consistent with FMS. It seems most likely that several of them play a role in the development of this syndrome in each patient, but that the precise extent of the contribution and the precise nature of the combination varies between patients. In any such observations, the possibility of secondary gain should always be entertained.

Treatment and Outcome

Treatment

There is general agreement that treatment of FMS patients requires a multimodal approach, consisting of education, cognitive behavioral therapy, exercise, and pharmacological therapy [573–575], even if the optimal nature of the individual components has not been fully established [576]. We discourage the use of opiates at any level in the treatment of patients with FMS. Further, there is no substitute for education and for encouraging appropriate nutritional and physical therapy support. Patients are not dying of FMS; they are living with FMS and they should not be turned into a poly pharmacy. The first step in the education process is telling the patient that (s)he has FMS. It has been a matter of intense debate whether receiving the diagnostic label of FMS provides reassurance or teaches people to become a patient with FMS. There is some support for both hypotheses in the available data since there have been reports of either increased or decreased health care utilization in the year immediately after the diagnosis of FMS [577–581]. Even if there is an initial decrease, however, the number of office visits, diagnostic tests, and prescriptions begins to rebound after a year or two [577–579].

It is generally recommended that any therapy of FMS patients include cognitive behavioral therapy in order to enhance effective coping and to promote self-efficacy. It should also include some form of aerobic exercise, which is quite consistently shown to improve pain and generally results in larger effect sizes than pharmacotherapy at least on global well being and physical function and affects more different domains [582]. The best type of exercise, particularly whether it should be land-based or water-based, has not been firmly established [583]. In any case, the exercise regimen needs to be carefully tailored to the individual patient who should be encouraged to choose a form of exercise that is low-impact, enjoyable, affordable and easy to adhere to. Even then, patients with FMS often report that exertion exacerbates their symptoms of pain and fatigue [382, 518, 522], sometimes to the point where they have to make a choice between exercise and other activities since they are unable to do both on the same day [584]. Alternating between strenuous exercise and rest may alleviate the acute pain arising from muscle activity in FMS patients [585], and maybe a similar approach could be found to help prevent excessive fatigue during exercise.

The standard pharmacological armamentarium in FMS includes analgesics, antidepressants, anticonvulsants, and muscle relaxants. Patients with FMS frequently use NSAIDS, but clinical studies have failed to demonstrate their effectiveness. There are also no data supporting the use of opioids. The results of randomized controlled trials have demonstrated that tricyclic antidepressants [586, 587], anticonvulsants [588], and serotonin norepinephrine reuptake inhibitors (SNRI) [587], but not selective serotonin reuptake inhibitors (SSRI) [589], are able to beneficially affect one or more of the core symptoms of FMS. Pregabalin and the SNRI duloxetine and milnacripran have been approved by the US FDA for the treatment of FMS, though not by the European Medicines Agency. It is important to recognize, however, that each of these pharmaceuticals will provide clinically meaningful improvement without any major adverse events for a relatively small subset of patients only. In many other patients, the benefits do not outweigh the adverse effects, while the remainder do not experience any symptom improvement or even get worse. This variability in the response to pharmaceuticals should not come as a surprise since the underlying mechanisms of FMS are sill poorly understood and are likely to differ between patients. This would necessitate an individualized approach based not only on the symptom profile, but also on biomedical parameter. To date, however, the necessary scientific basis for such an approach is lacking.

Patients with FMS are frequently overweight or obese [590, 591]. In the general population, obesity is associated not only with an increased risk of chronic pain disorders but also with almost every biomedical abnormality or disturbance observed in subjects with FMS [590]. Similar correlations have emerged in FMS patients [590, 591]. There is growing evidence that weight loss may be an important component of the treatment of FMS patients and can be associated with significant improvements in overall symptom severity, pain, depression, and HRQoL [443, 590].

Outcome

Much of the data on the outcome of FMS comes from patients seen at tertiary referral (rheumatology or pain) clinics, and their prognosis is poor [592], although exceptions have been reported [593–595]. Even in FMS patients recruited from various types of community practices in the USA and Europe, the burden that the disorder imposes is substantial and increases with increasing symptom severity [180, 596]. The vast majority of patients are unlikely to experience remission. As such, claims of exacerbation following trauma such as automobile accidents are not medically plausible. For most patients, the natural history of fibromyalgia indicates that the pain and other symptoms are permanent but fluctuate in intensity. As a result, patients with this disorder experience substantial functional impairment and their global health and HRQoL are markedly lower compared to healthy subjects and similar or worse compared to other chronic diseases and conditions [592]. Patients estimated that being completely pain free would increase their overall health rating by ~24/100 points [180, 596]. Subjects with FMS often become unable to work, i.e., qualify for disability payments, lose their employment or have to retire early, and many of the remainder have to cut back on the hours worked [180, 592, 596]. Many patients report restrictions in activities of daily living and recreational activities. We encourage patients to become as active as possible. Placing patients on disability often leads to worse outcomes. Often times, just a gradual increase in exercise can enormously help patients' well being. Becoming active in community affairs, serving as volunteers and even just having a pet, can be positive influences. There are some data suggesting that FMS patients from the community have a better prognosis compared to those seen in rheumatology and pain clinics, with remissions occurring in 24 % and a substantial portion having regional pain only [594, 595]. However, these findings are based on small numbers and should be replicated in larger cohorts. FMS per se does not represent a heightened mortality risk, but patients with FMS show an increased risk of death from suicide and accidents compared to the general population [597].

Concluding Remarks

It has long been known that FMS as defined by the ACR 1990 criteria is at the end of a severity spectrum of symptoms that are continuously distributed in the general population [20, 50, 59]. This raises the question of whether FMS is a distinct entity. By statistical means, it has been shown that both the ACR 1990 criteria [50] and a precursor of the *survey criteria* identify a distinct subgroup of patients within the severity continuum of FMS symptoms [60]. This was thought to provide some justification for considering FMS a separate entity. It may be justified, but is it meaningful? Is it not the purpose of a diagnosis, and of diagnostic criteria, to identify a group of patients whose signs and symptoms point to a specific disorder or disease that has one (or a finite number of related) pathogenetic mechanism(s) and, therefore, responds to a specific type of treatment? This certainly has not been achieved in FMS yet. Instead, everything points to considerable heterogeneity among patients who fulfill the ACR 1990 criteria—not only in the number, types, and severity of symptoms, but also in every single biomedical parameter that has been investigated to date and, most importantly, in the response to essentially every therapeutic regimen.

One possible approach to improving the classification and treatment of FMS patients could be to determine the existence of subgroups of patients. Although it has been most common to compare only group averages of FMS patients and controls, subgroups have indeed been identified based on such disparate parameters as IGF-1 levels [391], ENFD [464–466], serotonin metabolism [598], sensitivity to heat and cold pain [111], pain processing mechanism [483], or acute responses to pharmaceuticals [483]. Turk et al. [599] were the first to use cluster analysis in order to derive subgroups of subjects with chronic musculoskeletal pain based on the Multidimensional Pain Inventory, and to subsequently classify FMS into one of the three resulting subgroups, labeled dysfunctional, interpersonally distressed, or adaptive coper [599]. These subgroups differed in their responses to a multidisciplinary pain management program [600, 601]. Since then, there have been a variety of attempts to identify subgroups of FMS patients by using cluster analyses (see Table 6). These were based on features of central sensitization alone [487], in combination with psychological distress and coping style [602], or combined with sleep disturbances and depressive symptoms [534]. Other approaches were founded on the core symptoms of FMS themselves [603] or symptom groups obtained via factor analysis [604, 605] and in various combinations with comorbidities. Personality and FIQ scores have also formed the basis for cluster analyses [606, 607]. Symptom groups themselves have been the targets of additional cluster analyses [181, 604, 608].

It seems unlikely, however, that an almost exclusive focus on symptomatology will result in any advances in the treatment of FMS patients because it does not provide much

Table 6 Attempts at cluster analyses to identify patient subgroups based on specific phenotypes

Study	Wilson et al. [487]	Giesecke et la [602]	Torres et al. [606]	de Souza et al. [607]	Docampo et al. [605]	Vincent et al. [603]	Wilson et al. [604]	Rehm et al. [534]	Loevinger et al. [572]
n	1,443	97	874	61	1,446	581	2182 participants in an internet survey	3,035	107
Basis	Scores of TP factors (derived from factor analysis of pain severity ratings during palpation of 18 TP and 3 control points)	Experimental pain sensitivity at TP, Psychological distress, Coping style	Personality	FIQ	Symptomatology, familial and personal comorbidities	Symptoms (pain, fatigue, sleep problems, cognition, stiffness, anxiety, depression)	Symptoms (symptom factor scores derived from factor analyses of physical and cognitive/psychological symptoms)	Self-reported sensory symptoms, comorbidities (Sleep disturbances, depressive symptoms)	Psychological (childhood trauma, current perceived stress, anxiety, mood) biomedical (BMI, metabolic markers, hormones, inflammatory/immune markers)
Group characteristics	1) High severity ratings at all TP and control points	1) Moderate distress, moderate catastrophizing and pain control, low tenderness	1) Higher neuroticism, lower extraversion than cluster 2	1) Low anxiety, depression, morning tiredness scores	Low/low	1) Low levels of all symptoms	1) High physical-high cognitive/psychological	1) Marked hypersensitivity to thermal stimuli, moderate comorbidities	1) "Maltreated" (highest probability of childhood maltreatment, high psychological distress)
	2) Moderate severity rating at all TP and low rating at the control points	2) High distress, high catastrophizing, low pain control, high tenderness	2) All personality dimension scores in the central part of the reference range	2) High scores on all subscales (pain, fatigue, stiffness, morning tiredness, anxiety, depression	High/high	2) Mostly moderate symptoms, low anxiety and depression scores	2) Moderate physical-high cognitive/psychological symptoms	2) Prickling sensation, but normal or below normal sensitivity; moderate sleep disturbance and depressive symptoms	2) "Dysregulated Biology" (high psychological distress, highest levels of physiological dysregulation, high pain, fatigue, disability)
	3) Low severity rating at all TP and control points	3) Normal distress, low catastrophizing, high pain control, extreme tenderness			High/low	3) Mostly moderate symptoms, but high anxiety and depression scores	3) Moderate physical-low cognitive/psychological symptoms	3) Very high pressure pain sensitivity, but otherwise normal sensitivity; lowest sleep disturbance and depressive symptoms	3) "Normal Biology" (high psychological distress, largely normal physiological results, intermediate pain severity)
						4) Highest levels of all symptoms	4) Low physical-low cognitive/psychological symptoms	4) Severe pain attacks, strong pressure pain sensitivity; moderate sleep disturbance and depressive symptoms 5) Slight sensory symptoms, highest sleep disturbance and depressive symptoms	4) "Positive Outlook" (lowest psychological distress, lowest pain, highest global functioning)

insight into the underlying pathogenetic mechanism. Loevinger et al. [572] were the first, and to date only ones, to group FMS patients according to a much larger variety of both psychological and biomedical aspects. Psychological assessments included childhood trauma along with current perceived stress, anxiety, and mood. Biomedical measures consisted of BMI and metabolic markers, several hormones, and inflammatory/immune markers. Four clusters provided the best fit for the data. The most salient features of these subgroups are aptly subsumed under the group labels, namely *Maltreated* (high frequency of childhood trauma and hypocortisolism), *Dysregulated Biology*, *Normal Biology* (but high anxiety), and *Positive Outlook*, with the latter subgroup resembling the adaptive copers described by Turk et al. [599] and possibly also the psychologically highly resilient subgroup identified by others [602]. This underscores that psychological distress is one of the factors that most clearly differentiates the patient subgroups identified by cluster analysis. Nonetheless, the study by Loevinger et al. [572] represents a major advance for having gone beyond psychological distress and for having highlighted possible associations between distress and biomedical parameters.

FMS is a spectrum disorder in a double sense. It is not only part of a symptom frequency and severity spectrum, it may also belong to a larger spectrum of syndromes such as CFS, IBS, and other disorders often subsumed under names like functional somatic syndromes, medically unexplained symptoms, or somatization disorder. Patients diagnosed with any of these syndromes not only share symptoms such as myalgia, fatigue, and sleep disturbances, but they may even fulfill the diagnostic or classification criteria for one or more of the other syndromes [61]. This may partly be due to the fact that the case definitions for each of the syndromes also show substantial overlap. However, this cannot be the only explanation since conditions that do not share any classification criteria still frequently co-occur in the same patient. In addition, all of these disorders are associated with depression and anxiety [609], and actually it has been suggested that they all are part of an even more encompassing *affective spectrum disorder* [610]. Furthermore, the same treatments have shown some efficacy in subsets of these patients, and there is increasing evidence that the individual syndromes and disorders may share pathophysiological mechanisms as well.

A variety of statistical approaches have been used to clarify whether functional somatic symptoms and the symptom complexes used to define syndromes form many distinct groups or a single homogeneous construct, and whether they cluster into a continuous/dimensional or a categorical structure [67, 611–618]. The results have provided some support for each of these aspects. Importantly, latent class analysis of somatic symptoms in >28,500 twins provided evidence that the question should not be *one or many* (syndromes) but *single or multiple* [619]. In this study, a five-class solution provided the best fit for the data. One class largely consisted of healthy subjects; three classes contained high proportions of individuals with specific symptoms (e.g., recurrent abdominal discomfort and CWP were each present in 100 % of individuals in class 3 and class 4, respectively), and one class included mostly subjects who endorsed a high proportion of all symptoms [619]. There is growing agreement among researchers that all functional somatic syndromes share a common underlying susceptibility, but that individual, possibly environmental, factors determine what form the functional somatic syndrome takes in a specific patient and why two or more of them manifest in some of the same subjects. Overall, there is growing evidence that both the similarities and dissimilarities of individual syndromes need to be considered. These dissimilarities include biochemical or biomedical aspects [332, 365, 620, 621], which have been mostly ignored so far in statistical analyses.

There are other, largely neglected, aspects of FMS and overlapping syndromes that should be considered in future investigations. These patients show abnormalities in a variety of systems, e.g., the HPA axis, the autonomic nervous system, the various neurotransmitters involved in the regulation of pain perception, and the immune system. All of these systems are highly dynamic, and their regulation is very intricate, involving not only negative feedback, but also facilitating or inhibitory influences from a variety of other systems. As a result, not only the systems themselves, but also their interactions are characterized by a high degree of complexity. For example, there is extensive cross-talk between the HPA axis not only with the sympathetic system, but also with other neuroendocrine systems and the immune system, which all interface with each other. Studies to date have examined one—or at best, a few—components of a single one of these systems and have largely ignored the dynamic processes occurring within the system and the myriad of interacting systems. It would be highly desirable for future studies to begin to address the complexity of these interactions in patients with FMS and other related syndromes.

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