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Fibromyalgia: A Disorder of the Brain?

PETRA SCHWEINHARDT, KHARA M. SAURO, and M. CATHERINE BUSHNELL

This article presents evidence that fibromyalgia patients have alterations in CNS anatomy, physiology, and chemistry that potentially contribute to the symptoms experienced by these patients. There is substantial psychophysical evidence that fibromyalgia patients perceive pain and other noxious stimuli differently than healthy individuals and that normal pain modulatory systems, such as diffuse noxious inhibitory control mechanisms, are compromised in fibromyalgia. Furthermore, functional brain imaging studies revealing enhanced pain-related activations corroborate the patients' reports of increased pain. Neurotransmitter studies show that fibromyalgia patients have abnormalities in dopaminergic, opioidergic, and serotonergic systems. Finally, studies of brain anatomy show structural differences between the brains of fibromyalgia patients and healthy individuals. The cerebral alterations offer a compelling explanation for the multiple symptoms of fibromyalgia, including widespread pain and affective disturbances. The frequent comorbidity of fibromyalgia with stress-related disorders, such as chronic fatigue, posttraumatic stress disorder, irritable bowel syndrome, and depression, as well as the similarity of many CNS abnormalities, suggests at least a partial common substrate for these disorders. Despite the numerous cerebral alterations, fibromyalgia might not be a primary disorder of the brain but may be a consequence of early life stress or prolonged or severe stress, affecting brain modulatory circuitry of pain and emotions in genetically susceptible individuals. *NEUROSCIENTIST* 14(5):415–421, 2008. DOI: 10.1177/1073858407312521

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Fibromyalgia is a syndrome whose main features include chronic, widespread musculoskeletal pain and stiffness in association with fatigue and poor sleep. Fibromyalgia patients may also experience a variety of other symptoms, including emotional distress, depression, decreased motivation, and dyscognition. The American College of Rheumatology 1990 (ARC-90) criteria for the diagnosis of fibromyalgia consist of pain in all four body quadrants in combination with excess tenderness to manual palpation of at least 11 of 18 muscle-tendon sites, in the absence of a clinically demonstrable peripheral nociceptive cause (Wolfe and others 1990). Fibromyalgia has been estimated to affect up to 4% of the general population of industrialized countries (Clauw and Crofford 2003). Although fibromyalgia can affect both genders, females are almost 10 times more likely to be diagnosed with fibromyalgia, and 85% of the fibromyalgia population seeking treatment is female (Wolfe and others 1990). The average fibromyalgia patient uses more medication and outpatient services than other chronic pain patients and costs the health care system more than twice as much as the average health care user (White and others 1999). Treatment success in fibromyalgia, both pharmacologic and nonpharmacologic, is often limited, with

fewer than 50% of patients experiencing adequate symptom relief (Leventhal 1999).

Fibromyalgia is not a recently discovered medical condition; descriptions have been found in the medical literature as far back as the early 17th century. For many years, no objective physical signs could be detected in patients with fibromyalgia. Today, the diagnosis of fibromyalgia is still based on the subjective report of widespread pain and sensitivity to palpation. However, several pathophysiological abnormalities have been revealed in recent years. Current research suggests that altered CNS physiology might underlie the symptoms of fibromyalgia. We present here an overview of psychophysical findings that illustrate the enhanced sensitivity of patients with fibromyalgia, brain imaging data showing cerebral activation patterns in line with the increased subjective pain reports, and evidence of CNS alterations observed in fibromyalgia that could potentially contribute to pain augmentation and other symptoms of the disorder. Finally, we will relate the CNS findings to important factors that might contribute to the etiology of fibromyalgia, namely the stress system and the genetic make-up of an individual.

Psychophysical Findings in Patients with Fibromyalgia

Although the diagnosis is based on the presence of ongoing musculoskeletal pain and increased sensitivity to pressure, fibromyalgia patients report increased pain to a variety of noxious stimuli, including cutaneous heat pain (McDermid and others 1996; Staud and others 2001) and intramuscular hypertonic saline injection (Wood and

From the Alan Edwards Centre for Research on Pain, Faculty of Dentistry (PS, KMS, CB), and the Department of Anesthesia (CB), McGill University, Montreal, Quebec, Canada.

Address correspondence to: M. Catherine Bushnell, PhD, Director, Centre for Research on Pain, McGill University, Room M/19, Strathcona Anatomy & Dentistry Building, 3640 University Street, Montreal, Quebec H3A 2B2 (e-mail: catherine.bushnell@mcgill.ca).

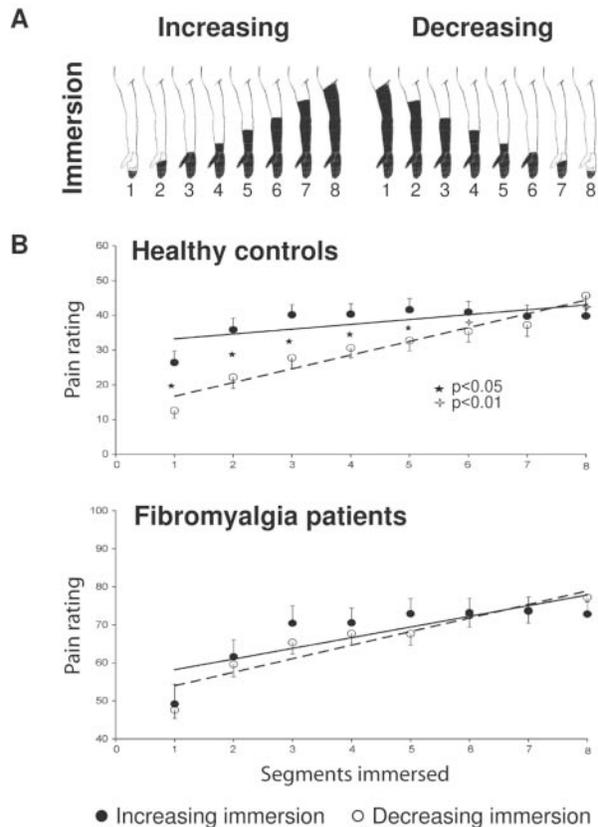


Fig. 1. Fibromyalgia patients show abnormal diffuse noxious inhibitory control (DNIC) mechanisms. Julien and others (2005) used an experimental procedure in which subjects immersed predetermined segments of their arms in noxious cold circulating water for 2-minute periods. During the increasing session (A—left), the immersions started with the fingertips and ended with the entire arm, and during the decreasing session (A—right), the immersions started with the entire arm and ended with the fingertips. The authors hypothesized that the decreasing session would result in the full recruitment of the DNIC mechanisms and result in lower pain ratings than the increasing session, particularly when smaller numbers of segments were immersed. Part B shows that the pain ratings of healthy subjects were lower during the decreasing immersion sessions than during the increasing immersion sessions, supporting the hypothesis. In contrast, fibromyalgia patients did not rate the pain differently in the two types of sessions. Adapted from Julien and others (2005). Modified and used with permission.

others 2007). Other phenomena related to pain perception are also abnormal in fibromyalgia patients. Temporal summation of nociceptive stimuli, in which the perceived intensity of rapidly repeated short noxious stimuli increases throughout a sequence, is enhanced, and diffuse noxious inhibitory control (DNIC), in which one pain inhibits another, is reduced in fibromyalgia (Staud and others 2001; Julien and others 2005; Lautenbacher and Rollman 1997; Fig. 1). Alterations in

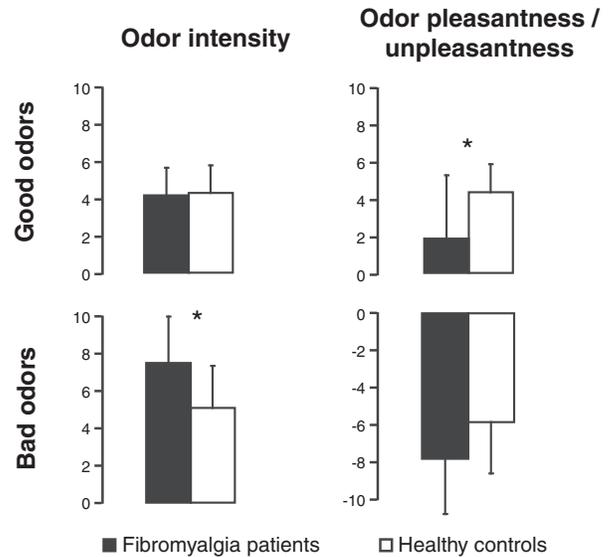


Fig. 2. Sixteen female fibromyalgia patients and 15 age- and sex-matched healthy control subjects were presented with six standardized unpleasant and pleasant odors and rated the intensity and the pleasantness or unpleasantness of each odor. Although fibromyalgia patients and healthy subjects rated the intensity of the pleasant odors similarly, the fibromyalgia patients rated the odors as significantly less pleasant than did the healthy controls ($P < .05$). Fibromyalgia patients rated the unpleasant odors as more intense than did the controls ($P < .05$), with a similar tendency to rate these odors as less pleasant ($P = .13$). Bars represent mean and standard deviation.

temporal summation and DNIC have been presented as evidence that fibromyalgia patients may have dysfunctions of pain modulatory systems at the CNS level (Clauw and Crofford 2003).

Although little has been reported concerning the perception of sensory modalities other than pain, there are indications that fibromyalgia patients have a hypersensitivity to unpleasant stimuli of other sensory systems. For example, one study found decreased noise tolerance in fibromyalgia patients (McDermid and others 1996). Similarly, our laboratory observed altered olfactory perception in fibromyalgia patients. Fibromyalgia patients rated the unpleasant odors but not the pleasant odors as more intense than did control subjects. Furthermore, in rating the pleasantness and unpleasantness of the odors, they rated the positive odors as less pleasant, with a similar tendency for rating the negative odors as more unpleasant (Fig. 2). These types of findings show that the enhanced perception of unpleasant stimuli is not restricted to pain but may be a more general effect involving altered hedonic appreciation of sensory stimuli.

Brain Activation Studies Corroborate Subjective Pain Reports

Laboratory findings of increased sensitivity might be interpreted as exaggerated reporting; however, functional

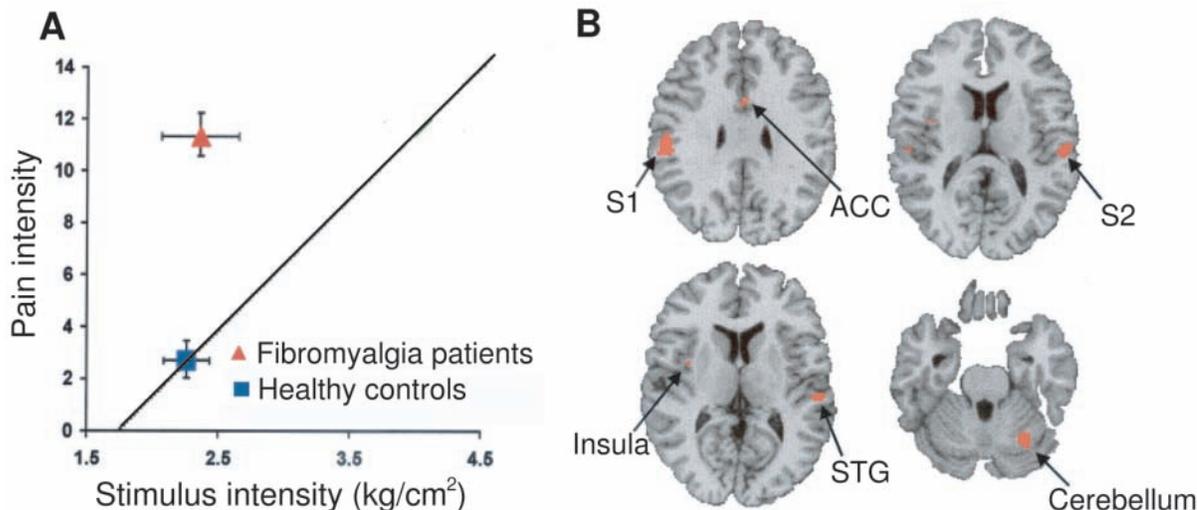


Fig. 3. Gracely and others (2002) showed that an equally intense pressure stimulus was rated as substantially more painful in fibromyalgia patients than in matched control subjects (part A). Correspondingly, using BOLD functional magnetic resonance imaging, the authors showed that the pressure stimulus evoked significantly more activation in fibromyalgia patients than in controls in a number of pain-related brain regions, including primary somatosensory cortex (S1), secondary somatosensory cortex (S2), anterior cingulate cortex (ACC), insula, superior temporal gyrus (STG), and cerebellum (regions displayed in part B). Adapted from Gracely and others (2002). Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

neuroimaging studies show a corresponding augmentation of sensory processing in fibromyalgia patients (Gracely and others 2002; Cook and others 2004; Fig. 3). These studies found that fibromyalgia patients show significantly more activity in response to pressure and thermal stimuli compared to controls in a number of brain regions. Increased activations were observed in structures involved in sensory-discriminative processing, such as contralateral S1 and S2, which argues against the notion that fibromyalgia patients simply report more pain. Instead, it supports the view that neural responses to afferent signals are amplified in fibromyalgia.

Specific Cerebral Dysfunctions Associated with Fibromyalgia

Cerebral Hypoperfusion

Pioneering brain imaging studies of fibromyalgia that measured regional cerebral blood flow (rCBF) at rest using positron emission tomography (PET) or single photon emission computed tomography (SPECT) have shown hypoperfusion in various brain regions of fibromyalgia patients compared to controls (see Williams and Gracely [2006] for review). The specific brain areas with decreased blood flow varied among reports, but at least two studies observed thalamic hypoperfusion. Consistent with the findings of hypoperfusion in the thalamus is a recent structural study reporting decreased gray matter density in the thalamus of fibromyalgia patients (Schmidt-Wilcke and others 2007). Furthermore, a number of studies have

shown thalamic hypoperfusion related to neuropathic pain of both central and peripheral origins (e.g., Garcia-Larrea and others 2006). Thus, although we can only speculate about the implications of thalamic hypoperfusion in fibromyalgia, the current data suggest that this phenomenon may be a substrate of different types of chronic pain.

Neurotransmitter Disturbances

Dopamine

Clinical data provide some evidence that a dysfunctional dopamine system contributes to the symptoms experienced by fibromyalgia patients. Dopamine agonists are effective in alleviating the pain of some patients (Holman and Myers 2005), and the incidence of restless leg syndrome, which is strongly associated with disturbances in dopaminergic pathways, is significantly increased in fibromyalgia (Yunus and Aldag 1996). Moreover, fibromyalgia patients show an augmented prolactin response to the buspirone challenge test, which suggests increased dopamine sensitivity (Malt and others 2003). Indirect evidence for a disturbance of the dopamine system comes from blood flow studies showing decreased rCBF during rest in the caudate nucleus (reviewed in Williams and Gracely 2006), a region that is particularly rich in dopamine receptors. Dopamine is crucially involved for brain functions such as pleasure, motivation, and motor control, and hence, an impaired dopaminergic system could contribute to the affective and motivational symptoms of fibromyalgia patients. However, several lines of

evidence now suggest that dopamine in the basal ganglia also may be important for pain modulation. Results of animal studies using electrical stimulation of dopaminergic structures, such as the striatum, nucleus accumbens, and ventral tegmental area, or administration of compounds leading to increased release or concentration of dopamine in the synaptic cleft (e.g., dopamine reuptake inhibitors) indicate that increased dopaminergic activity can attenuate nocifensive behavior (for review, see Chudler and Dong 1995; Altier and Stewart 1999).

Two recent PET competitive binding studies using the D2/D3 receptor antagonist [^{11}C] raclopride showed that striatal dopamine is released in response to tonic noxious muscle stimulation in healthy human subjects compared to nonpainful stimulation (Scott and others 2006; Wood and others 2007). In contrast, the dopamine response of fibromyalgia patients did not differ between painful and nonpainful muscle stimulation (Wood and others 2007). In the healthy subjects, the amount of dopamine release correlated with the amount of perceived pain, but in fibromyalgia patients, no such correlation was observed (Fig. 4). These findings provide the first direct evidence that fibromyalgia patients may have an abnormal dopamine response to pain.

Dopamine also plays an important role for cognitive functioning. This is interesting because many patients with fibromyalgia complain of problems with memory and concentration, often referred to as “fibrofog.” Although some studies show that perceived memory deficits of fibromyalgia patients are greater than indicated by objective tests, there is clear evidence from neuropsychological testing that fibromyalgia patients do have deficits in cognitive functioning. Fibromyalgia patients perform below average in tests of both working memory and long-term memory (Leavitt and Katz 2006; Park and others 2001). In particular, patients seem to have difficulties with tasks in which competing stimuli are presented and that require, therefore, some degree of stimulus inhibition (Leavitt and Katz 2006). Multiple lines of evidence demonstrate the importance of mesocortical and striatal dopaminergic pathways in memory tasks, perceptual speed, and response inhibition (see Backman and others [2006] for review). Thus, there is an overlap between tasks on which fibromyalgia patients perform poorly and tasks that are related to dopamine functioning, further suggesting that a dysfunctional dopamine system contributes to the symptoms patients with fibromyalgia experience.

Opioids

The dopaminergic system is closely connected to the opioidergic system, which is probably the best described endogenous antinociceptive system. CSF concentrations of endogenous opioids have been found to be elevated in fibromyalgia, suggesting a disturbance also of this neurotransmitter system (Baraniuk and others 2004). A recent PET study investigated the relationship between alterations in the cerebral opioidergic system and pain in fibromyalgia (Harris and others 2007). At rest, patients showed decreased binding potentials for the exogenously administered μ -opioid receptor agonist carfentanil in

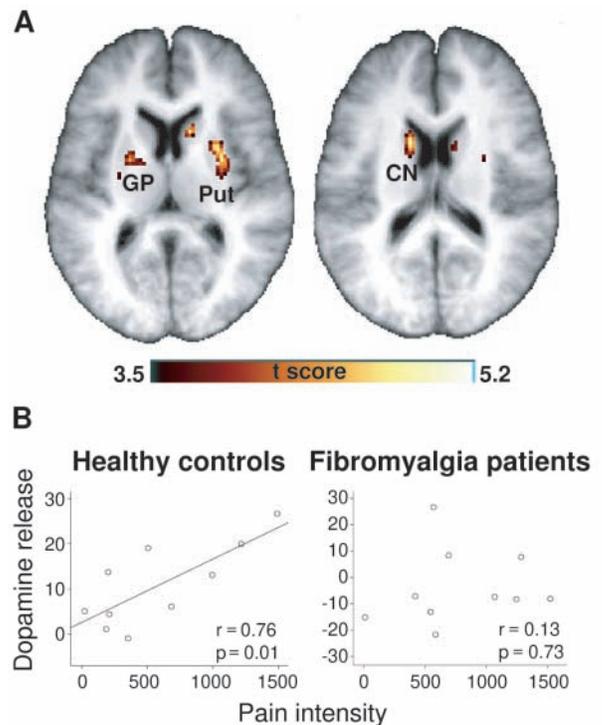


Fig. 4. Wood and others (2007) used a PET competitive binding technique to examine the striatal binding of the D2/D3 receptor antagonist [^{11}C] raclopride during a 20-minute infusion of the hypertonic (painful) or isotonic (nonpainful) saline into the anterior tibialis muscle. Part A shows voxel-based statistical maps of regions of significant reduction in [^{11}C] raclopride binding potential (BP) during administration of hypertonic compared to isotonic saline in healthy control subjects, indicating that healthy subjects released more dopamine in response to painful stimulation. These regions include globus pallidus (GP), putamen (Put), and caudate nucleus (CN). No region showed reduced BP in fibromyalgia patients. Part B shows that in the healthy subjects, the amount of dopamine release correlated with the amount of perceived pain, but in fibromyalgia patients, no such correlation was observed. Adapted from Wood and others (2007). Modified and used with permission.

several brain areas, including the ventral striatum, the anterior cingulate cortex, and the amygdala. These areas are implicated in pain and its emotional modulation, and correspondingly, the binding potentials showed a negative relationship with the magnitude of affective pain scores relative to the sensory scores. Although this type of study cannot inform us whether levels of endogenous opioids were increased or whether receptor availability was decreased, both leading to decreased binding potentials, the findings of Harris and colleagues further substantiate the notion that disturbances in the opioidergic system might be related to pain in fibromyalgia.

An additional area in which decreased binding potentials were observed by Harris and others (2007) has received attention in the context of fibromyalgia. The

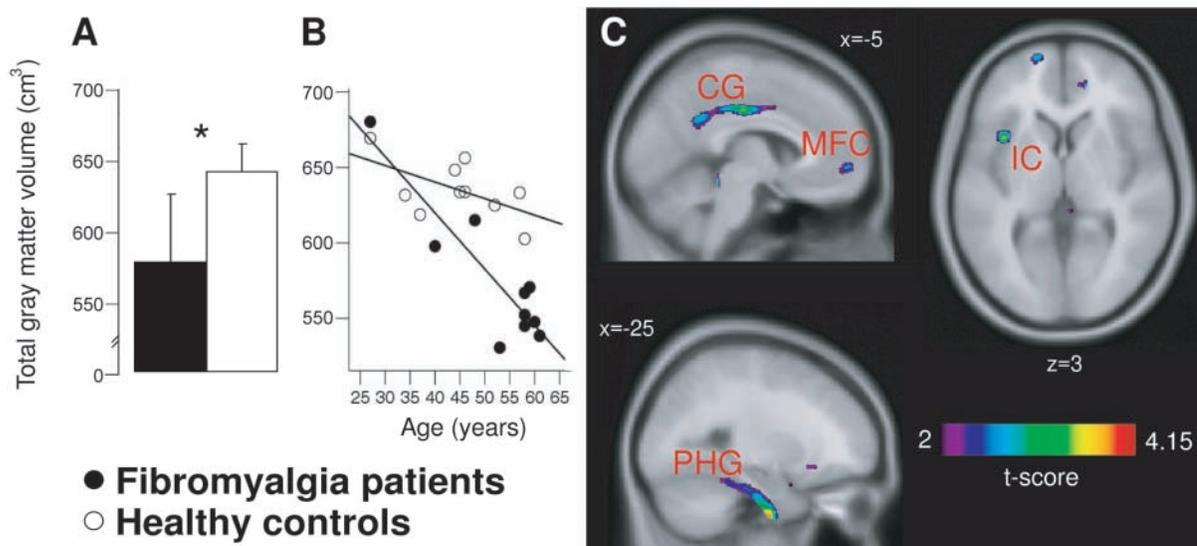


Fig. 5. Kuchinad and others (2007) showed gray matter decreases in fibromyalgia patients relative to healthy control subjects. (A) Total brain gray matter volume in 10 fibromyalgia patients and 10 healthy control subjects. Values are expressed in $\text{cm}^3 \pm \text{SD}$. Including age as a covariate of no interest, fibromyalgia patients had significantly less gray matter volume than did controls. (B) Brain gray matter tissue volume plotted against age. Gray matter volume correlated significantly with age in fibromyalgia patients ($r = -.90$; $P < .001$), with a similar trend in healthy controls ($r = -.57$; $P = .086$). Fibromyalgia patients showed a significantly steeper age-related decline than did controls ($F[1, 18] = 281.57$; $P < .001$). (C) Voxel-wise comparison of gray matter density between fibromyalgia patients and healthy control subjects. Regions showing significantly less gray matter density for fibromyalgia patients than healthy controls included left parahippocampal gyrus (PHG), left and right mid/posterior cingulate gyrus (CG), left insular cortex (IC), and medial frontal cortex (MFC). Adapted from Kuchinad and others (2007). Modified and used with permission. Copyright 2007 by the Society for Neuroscience.

posterior cingulate cortex (PCC) is the only brain region in which resting rCBF has been found to be increased in patients with fibromyalgia (Wik and others 2003). In line with this, activation in this area is decreased when exogenous pain is administered (Wik and others 2006). Furthermore, an analysis of brain gray matter density in fibromyalgia patients and healthy controls (Kuchinad and others 2007—see below) found reduced gray matter in the PCC of fibromyalgia patients. Because the PCC is involved in orientation toward self-relevant sensations, PCC abnormalities in fibromyalgia patients might reflect the ongoing processing of spontaneous pain.

Others

In addition to dopamine and endogenous opioids, other neurotransmitter systems might also be affected in fibromyalgia (see Clauw and Crofford [2003] for review). For example, the serotonergic system has repeatedly been implicated in fibromyalgia. CSF levels of serotonin (5HT) metabolites are decreased in patients with fibromyalgia, as are metabolites of dopamine and norepinephrine. The direct investigation of neurotransmitter systems in humans is achieved using PET, and therefore, the feasibility of such studies is determined by the availability of suitable PET tracers. To date, tracers exist for the investigation of 5HT_{A1} and 5HT_{A2} receptors, and a recent study

showed a relationship between pain sensitivity and 5HT_{A1} receptor binding in healthy volunteers (Martikainen and others 2007). We are awaiting such studies in patients with fibromyalgia.

Structural Cerebral Changes

Recently, there has been accumulating evidence that chronic pain is associated with changes in brain anatomy. Studies so far have focused on changes in the gray matter rather than potential white matter alterations. Although studies have shown both increases and decreases in regional gray matter density, the most commonly observed change is a decrease of gray matter in chronic pain patients. Two studies have examined gray matter density in fibromyalgia patients (Kuchinad and others 2007; Schmidt-Wilcke and others 2007). Kuchinad and others showed that total gray matter volume was less in fibromyalgia patients than in healthy controls, with patients showing a 3.3 times greater age-associated decrease in gray matter than healthy controls (Fig. 5). The longer the individuals had had fibromyalgia, the greater the gray matter loss; each year of fibromyalgia was equivalent to 9.5 times the loss in normal aging. Regional gray matter density analyses revealed gray matter loss in regions associated with pain modulation or stress, such as the cingulate, insular and medial frontal cortices, parahippocampal gyri, and thalamus (Kuchinad and

others 2007; Schmidt-Wilcke and others 2007; Fig. 5). Interestingly, Schmidt-Wilcke and colleagues also found gray matter increases in the striatum and cerebellum.

Because fibromyalgia has often been described as a stress-related disorder (Staud 2007), the observation of decreased gray matter density in the perihippocampal gyrus is of particular interest. Similar neuroanatomical abnormalities have been reported in other stress-related disorders, including chronic fatigue syndrome and post-traumatic stress disorder (PTSD; e.g., Okada and others 2004; Villarreal and others 2002). It has been suggested that atrophy of the hippocampus and other brain areas, such as the amygdala and prefrontal cortex, occurs following elevated glucocorticoid levels (McEwen 2000). Importantly, sustained stress levels of adrenal steroids are probably not required to produce structural changes in the hippocampus; rather, elevations associated with the diurnal rhythm and stressful experiences might be sufficient in susceptible individuals (McEwen 2000). The functional significance of gray matter atrophy in fibromyalgia might include a decreased capacity for endogenous pain inhibition and impaired cognitive functioning in fibromyalgia. The idea that gray matter atrophy might be related to decreased cognitive function is supported by studies of patients with chronic back pain that show both gray matter decreases in frontal cortex and impaired performance on a task of frontal lobe functioning (Apkarian, Sosa, Sonty, and others 2004; Apkarian, Sosa, Krauss, and others 2004).

Fibromyalgia—A Disorder of the Brain?

This review presents substantial evidence of alterations in CNS anatomy and physiology in patients with fibromyalgia. The nature of these alterations, such as neurotransmitter dysfunctions and gray matter changes, argues against the notion that fibromyalgia patients simply report more pain or are merely hypervigilant toward exteroceptive and interoceptive stimuli. However, does this evidence support the idea that fibromyalgia is a primary disorder of the brain, or could all the changes in the brain be driven by physiological alterations outside the brain? The CNS findings support but do not prove the idea that modulatory systems are impaired in fibromyalgia, leading to an imbalance of facilitation and inhibition. Consequently, the processing of environmental stimuli and stimuli that arise from within the body might be augmented, contributing to the heightened perception of pain and other unpleasant stimuli. Similarly, the affective processing of both pleasant and unpleasant stimuli might be altered. Hence, the CNS alterations offer a compelling explanation for the core symptoms of fibromyalgia, such as widespread pain and affective disturbances. However, fibromyalgia might not be a primary disorder of the brain, in the sense that CNS alterations might not be at the beginning in the chain of events leading to fibromyalgia. Fibromyalgia is often regarded a stress-related disorder, based on the report of many patients that the symptoms occur after physiologic or psychological stress and that the symptoms are exacerbated during stress (Staud 2007). This is shared by many other disorders that show a substantial comorbidity with

fibromyalgia, such as depression, irritable bowel syndrome, and chronic fatigue. Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, which can indicate that an organism was subjected to early life stress or severe or prolonged stress, is a strong predictor for the development of chronic, widespread pain (McBeth and others 2007). This substantiates the notion that stress is related to the development of fibromyalgia. The structural and neurochemical changes in fibromyalgia that we have outlined in this article could all be caused by stress exposure of vulnerable individuals. The susceptibility of individuals to develop chronic widespread pain following stress exposure is likely related to their genetic make-up. A large Swedish study of twins reported that genetic factors accounted for approximately 50% of the total variance in chronic widespread pain (Kato and others 2006). Thus far, genetic polymorphisms in serotonergic, dopaminergic, and catecholaminergic systems have been related to fibromyalgia (see Ablin and others [2006] for review). These genetic variations might determine how susceptible specific neurotransmitter systems and CNS structures are to the deleterious effect of stress (stress responsiveness itself might of course also vary among individuals). The exact combination and the degree of impaired CNS systems might then lead to the mosaic of symptoms with which fibromyalgia patients present. Importantly, the spectrum of endophenotypes (Ablin and others 2006) could explain why some fibromyalgia patients respond to, for example, dopamine agonists, whereas others get better with serotonergic agents. The possibility of diagnosing a patient's endophenotype in the future will greatly enhance the ability to tailor treatment individually.

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