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An investigation of the role of negative affectivity on abnormal pain perception and functional brain activity in the limbic system of women with fibromyalgia (FM).

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AN INVESTIGATION OF THE ROLE OF NEGATIVE AFFECTIVITY ON ABNORMAL PAIN PERCEPTION AND FUNCTIONAL BRAIN ACTIVITY IN THE LIMBIC SYSTEM OF WOMEN WITH FIBROMYALGIA (FM)

by

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Title An Investigation of the Role of Negative Affectivity on Abnormal Pain Perception and Functional Brain Activity in the Limbic System of Women With Fibromyalgia (FM)

Microstimulation of limbic brain system structures and the thalamus is known to evoke acute chest pain, without nociception, in patients with recurrent, non-cardiac chest pain and anxiety disorder (Lenz et al., 1995). This study sought to determine if anticipation of a painful stimulus also evokes pain in the absence of nociceptive stimulation in fibromyalgia (FM) patients with high negative affectivity (NA) and if pain-related anxiety, limbic system activation, or both mediates this effect.

All subjects were women and included 9 FM patients (4 high NA, 5 low NA) and 9 healthy controls (4 high NA, 5 low NA). NA was determined by scores more than 1 standard deviation above and below the adult normative mean on the Positive and Negative Affect Schedule. Subjects were told the study would measure responses to potentially painful transcutaneous electrical nerve stimulation (TENS). On Day 1, subjects completed the Pain Anxiety Symptoms Scale (PASS); underwent sham electromyographic (EMG) recording at four left body sites with preprogrammed, low EMG visual feedback; made visual analog scale ratings of intensity and unpleasantness at each site; and underwent single photon emission computed tomography (SPECT) brain imaging of regional cerebral blood flow (rCBF). On Day 2, subjects received sham TENS stimulation at same

four sites with preprogrammed, high EMG visual feedback; made visual analog scale ratings of intensity and unpleasantness at each site; and underwent SPECT brain imaging. Group differences on all variables were assessed by one-way or repeated measures analyses of variance.

High NA FM patients produced significantly higher PASS scores than all other groups. Only high NA FM patients showed significant increases in pain intensity and unpleasantness and right anterior cingulate cortex rCBF with sham TENS stimulation.

In conclusion, anticipation of pain in FM patients with high pain anxiety may activate pain memories encoded in the anterior cingulate cortex and thus evoke perceptions of increased pain intensity and unpleasantness. This may account in part for the abnormal pain sensitivity and other unusual sensory perceptions often seen in this FM subgroup. Pain anxiety may be an important target for pharmacological and behavioral interventions for FM.

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ACTH	Adrenocorticotropin hormone
ANOVA	Analysis of variance
BIS	Behavioral inhibition system
CBT	Cognitive behavioral therapy
CNS	Central nervous system
CSF	Cerebrospinal fluid
CSQ	Coping Strategies Questionnaire
EEG	Electroencephalography
EMG	Electromyography
FM	Fibromyalgia
fMRI	Functional magnetic resonance imaging
GCRC	General Clinical Research Center
HMPAO	Hexamethylpropyleneamine
HPA	Hypothalamic-pituitary-adrenal
IBS	Irritable bowel syndrome
MRI	Magnetic resonance imaging
NA	Negative affectivity
NGF	Nerve growth factor
PANAS	Positive and Negative Affect Scale

PASS	Pain Anxiety Symptom Scale
PET	Positron emission tomography
PRS	Pain Rating Scale
POMS	Profile of Mood States
RA	Rheumatoid arthritis
rCBF	Regional cerebral blood flow
ROI	Region of interest
SDT	Sensory decision theory
SP	Substance P
SPECT	Single photon emission tomography
TENS	Trancutaneous electrical nerve stimulation
UAB	University of Alabama at Birmingham
Vc	Ventrocaudal nucleus

INTRODUCTION

Fibromyalgia (FM) is a rheumatologic disorder of unknown etiology characterized by chronic, diffuse, musculoskeletal aching and soreness that is often accompanied by poor sleep, fatigue, and morning stiffness (Wolfe, 1986). Beyond the primary muscular pain, FM patients may also report localized articular pain, subjective swelling of the hands and/or knees, as well as numbness or coldness of the extremities (Wolfe, 1986). The disorder most commonly afflicts women between the ages of 25 and 40 (Yunus, Masi, Calabro, Miller, & Feigenbaum, 1981) at a 7 to 1 ratio relative to men (Wolfe, Ross, Anderson, Russell, & Herbert, 1995). Epidemiological studies suggest that FM is a common syndrome, estimating that 3 to 6 million Americans are presently afflicted (Goldenberg, 1987). FM is frequently found among persons who seek medical care. Approximately 15% of patients from rheumatology practices and 5.7% of patients from general medical practices are found to have FM (Wolfe, 1989).

Research has consistently demonstrated that patients with FM display abnormal pain perception with pressure stimulation at a multitude of anatomic sites (Bradley et al., 1995; Gibson, Littlejohn, Gorman, Helme, & Granges, 1994; Granges & Littlejohn, 1993; Lautenbacher, Rollman, & McCain, 1994) but also with other stimulation modalities such as heat (Gibson et al., 1994; Lautenbacher et al., 1994). In addition, there is consistent evidence of altered neurosensory processing of afferent stimuli among persons with FM such that greater sensory information reaches the higher brain centers (Gibson et al., 1994; Bradley et al., 1997). These findings indicate that among persons with FM

there is an alteration in the sensory-discriminative dimension of the pain experience. This is primarily known to be influenced by the rapidly conducting ascending spinal pathways that project to the ventrobasal thalamus and somatosensory cortex of the brain, the latter of which provides perceptual information on the location, magnitude, and spatiotemporal properties of noxious stimuli (Melzack & Casey, 1968).

Our research laboratory has provided behavioral and physiological evidence related to alterations in the sensory-discriminative dimension of pain found in persons with FM. Our behavioral studies involving pain threshold and sensory decision theory (SDT) tasks suggest that dolorimeter pressure stimulation evokes significantly greater transmission of sensory information to higher brain centers in FM patients and community residents with FM who have not sought treatment for their pain (nonpatients) compared to healthy controls (Bradley et al., 1997). Our neuroimaging studies have demonstrated that FM patients and nonpatients with insidious symptom onset, relative to healthy controls, display significantly lower regional cerebral blood flow (rCBF) in the right caudate nucleus and significantly higher cerebrospinal fluid levels of substance P (SP) during resting conditions (Bradley, Sotolongo, Alberts, et al., 1999). Preliminary results of a newly funded study suggest that unilateral painful stimulation produces increases in rCBF in the contra-lateral thalamus and somatosensory cortex in healthy individuals. In patients with FM, the stimulation did not produce increases in the thalamus; however, significant rCBF increases were demonstrated in the right anterior cingulate cortex (ACC) and the somatosensory cortices bilaterally (Bradley, Sotolongo, Alarcón, et al., 1999).

The results of our studies thus far on the sensory-discriminative dimension of pain have led us to conclude that the chronic widespread pain in FM may result from a central sensitization process characterized by release of SP, decreased firing thresholds in peripheral nociceptors and spinal transmission neurons, and inhibited functional activity in the caudate nucleus and thalamus. As a result, these structures show diminished ability to modulate nociceptive transmission from the spinal cord to higher brain structures involved in pain perception.

The affective-motivational dimension of pain is also considered important in the abnormal perceptions of many FM patients who report unpleasant or painful sensory experiences after exposure to low intensity environmental stimuli that are not aversive to healthy persons. We recently used a new behavioral laboratory procedure involving credible sham transcutaneous electrical nerve stimulation (TENS) to study the affective-motivational dimension of pain in patients with FM. In order to maximize affective-motivational pain responses, we chose to study FM patients with high scores on an index of negative affectivity (NA) or the tendency to experience emotional and physical distress in response to a wide variety of stimuli (Watson & Clark, 1984). We found that the FM patients with high NA reported significantly higher levels of pain than low NA patients in response to the sham TENS procedure and preprogrammed, visual, electromyographic (EMG) feedback indicating high levels of physiological arousal (Alexander et al., 1996). That is, high NA patients experienced increased pain when they were led to believe that they were receiving highly arousing electrical stimulation despite the fact that they received no stimulation. Low NA patients actually showed a modest decrease in pain with sham stimulation.

There is a tendency to assume that pain perception in FM patients in the absence of nociceptive transmission is purely an abnormal psychological or cognitive phenomenon that has little or no relationship to alterations in physiological processes. However, we believe that pain in FM patients with high NA in response to sham TENS stimulation may be associated with increased functional activity in limbic structures known to attribute emotional valence and attention to pain (Chapman, 1995). These structures are also known to have links to areas of the brain associated with sleep cycles (Siegal & Rogawski, 1988) and hypothalamic-pituitary-adrenal (HPA) function (Chapman, 1995), both of which are known to be abnormal in patients with FM (Moldofsky, Scarisbrick, England, & Smythe, 1975; Crofford et al., 1994). Thus, it is important to study both the sensory-discriminative and the affective-motivational dimensions of pain in order to better understand the abnormal pain perception found in persons with FM.

This study represents the first use of neuroimaging to measure functional activity (i.e., rCBF) in limbic brain structures (i.e., anterior cingulate cortex, prefrontal cortex) associated with the affective-motivational dimension of pain that may contribute to abnormal pain perception in women with FM. Our specific aim was to perform functional brain imaging on four subject groups at baseline and during a credible, sham (i.e., placebo), TENS procedure that reliably evokes pain in the absence of nociceptive stimulation in FM patients who score high on an index of NA. There were four subject groups: (a) 5 FM patients with high NA, (b) 5 FM patients with low NA, (c) 5 healthy controls with high NA, and (d) 5 healthy controls with low NA.

The background section that follows will first present a discussion of the relevant literature regarding the FM syndrome. This section will focus on issues of classification

and diagnosis, followed by a discussion of current research into the etiology and pathogenesis of FM including current models developed to explain the abnormal pain perception and symptoms found in individuals with FM. The second section will include a brief review of NA, and will focus on the symptom-perception hypothesis and its possible neurophysiological correlates. The final section will present relevant literature regarding functional brain imaging and neurophysiological correlates of the sensory-discriminative and affective-motivational dimension of pain.

Fibromyalgia (FM)

Classification Criteria

FM has been described under a variety of names over the past eighty years, including *fibrositis*, *nonarticular rheumatism*, and *psychogenic rheumatism*, each of which reflected a hypothesized underlying mechanism for a constellation of symptoms that included characteristic tender areas of the body, nonrestorative sleep, and fatigue. However, it was not until 1977 that Smythe and Moldofsky developed the first generally accepted diagnostic criteria for FM. The criteria included five elements: widespread aching, local palpitation-elicited tenderness at 12 of 14 potential points, skinfold tenderness over the upper scapular region, disturbed sleep, and normal laboratory studies and x-rays. Disagreement over the exact nature of these tender points, including number needed to make a diagnosis and location, continued after the criteria were set forth in 1977. Ten out of 25 tender points were proposed by Bennett (1981) and 7 out of 14 by Wolfe (1986) in order to meet requirements for a positive diagnosis of FM.

In 1990, the American College of Rheumatology (ACR) established the currently accepted diagnostic criteria for FM. In a controlled, multicenter study, 293 patients with FM and 265 age- and gender-matched chronic pain controls were compared on more than 300 variables in order to determine the criteria associated with the best sensitivity and specificity (Wolfe et al., 1990). The criteria were comprised of three elements: (a) history of widespread musculoskeletal pain greater than 3 months duration; (b) pain in both the upper and lower and left and right body segments along with axial skeletal pain; and (c) tenderness in response to greater than or equal to 4 kg pressure at least 11 of 18 anatomic locations defined as *tender points*. Specificity of these criteria was found to be 81.1%, sensitivity 88.4%, and accuracy 84.9%. Although, there is some debate regarding how well the criteria represent typical patients seen in clinics who present with a multitude of related symptoms such as fatigue, irritable bowel syndrome, and sleep disturbance (Bennett, 1993), the establishment of reliable and valid criteria has enhanced research efforts in understanding the etiology and pathogenesis of this disorder.

Etiology

Peripheral Mechanisms

Early hypotheses regarding the etiology of diffuse musculoskeletal pain centered on peripheral abnormalities. William Gower (1904) assumed underlying inflammation of the fibrous tissue in these patients and thus referred to the disorder as fibrositis. Many investigations since have focused on muscular abnormalities and changes to account for the pain experienced by individuals with FM.

Several studies have suggested there are histological changes in the muscles of FM patients. The changes, which are consistent with tissue anoxia, include *moth-eaten* and *ragged-red* muscle fibers at tender points (Bartels & Danneskiold-Samsoe, 1986; Bengtsson, Henriksson, & Larsson, 1986). A *rubber-band* morphology of the quadricep muscle was more frequently found in FM patients compared to patients with chronic myofascial pain (Jacobsen, Bartels, & Danneskiold-Samsoe, 1991). It was hypothesized by the investigators that the muscle of individuals with FM may be in an extended state of contraction leading to an energy crisis in the muscle cell.

In the study by Bengtsson, Henrikksson, and Larsson (1986), reduced levels of ATP, ADP, and phosphocreatinine were found in the trapezius muscle of patients with FM as compared to a group of normal controls. Bennett (1993) hypothesized that these findings may reflect continuous muscle microtrauma due to the muscle being in a continuous state of activity. However, in FM patients, no relationships have been found between muscle tension and pain (Zidart, Backman, Bengtsson, & Henriksson, 1990), and electron microscopic evaluation of muscle biopsies do not demonstrate differences between FM patients and controls (Yunus & Kalyan-Raman, 1989).

Recent studies have utilized magnetic resonance spectroscopy to study muscle energy metabolism and activity-induced muscle damage in patients with FM. Jacobsen and colleagues studied the calf muscle of 12 patients with FM and 7 healthy controls with MRS during rest, aerobic and anaerobic exercising conditions, and post-exercise recovery (Jacobsen, Jensen, Thomsen, Danneskiold-Samoe, & Henriksen, 1992). They found that patients with FM have a reduced voluntary capacity for work; however, their biochemical response to work and recovery was normal. Similar results regarding the biochemical

response to work and recovery have been found with the forearm muscles of both the dominant and nondominant arm (Jubrias, Bennett, & Klug, 1994) and the upper trapezius and tibialis anterior muscles (Simms et al., 1994). In addition, results of a recent study using a fatigue-loading task suggest that FM patients have normal structure and neuromuscular function of the leg muscles (Hakkinen, Hakkinen, Hannonen, & Alen, 2000). However, other investigators have shown that FM patients, compared to appropriately matched controls, exhibit significantly lower resting levels of phosphocreatine and adenosine triphosphate, as well as significantly higher levels of adenosine diphosphate, both of which are indicative of an abnormal bioenergetic processes (Park, Phothimat, Oates, Hernanz-Schulman, & Olsen, 1998).

In sum, most well controlled studies have not shown strong evidence that defects in muscle tissue or its biochemical processes are the primary causes of FM. Only a small number of studies suggest that biochemical abnormalities or alterations in muscle function may contribute to FM symptoms. These findings must be replicated in larger independent samples before they can be considered to be reliable.

Central Mechanisms

Recent studies with FM patients have demonstrated generalized tenderness in response to pressure at both the ACR tender points as well as at many other anatomic sites known as *control points* (Bradley et al., 1995; Granges & Littlejohn, 1993; Kosek, Ekholm, & Hansson, 1995). These findings suggest that centrally mediated factors may be involved in the generalized tenderness experienced by persons with FM. Several areas of research including studies on pain perception, HPA axis, metabolic dysfunction related

to sleep disturbances, neurotransmitter functioning, and functional activity of central nervous system structures have supported this hypothesis.

Pain perception. It has been consistently demonstrated that patients with FM display significantly lower pain thresholds not only at the tender points as outlined in the ACR criteria but also at a large number of other anatomic sites known as control points (Bradley et al., 1995; Gibson et al., 1994; Granges & Littlejohn, 1993; Lautenbacher et al., 1994). It has also been demonstrated that FM patients display lower pain thresholds in regards to other modes of stimulation such as heat (Gibson et al., 1994; Lautenbacher et al., 1994) and electrocutaneous stimulation (Lautenbacher et al., 1994). In addition, a significant increase in cerebral evoked potentials with CO_2 laser stimulation at pain threshold and 1.5 times above pain threshold has been found in FM patients compared to healthy controls (Gibson et al., 1994). These studies suggest that there is a diffuse change in pain modulation in FM with a greater activation of central nervous system (CNS) pathways following noxious input.

Nonrestorative sleep. Sleep disturbance and fatigue are often considered a core feature of the FM syndrome. Patients, upon awakening, report diffuse stiffness, aching, and fatigue. They do not perceive their sleep as refreshing and they typically describe it as light or restless. Moldofsky and colleagues (1975) were the first investigators to report an abnormal electroencephalographic (EEG) pattern in FM patients. In a preliminary study of 10 FM patients it was found that each subject demonstrated a fast frequency alpha EEG intrusion onto slower frequency delta EEG during deep, stage IV, non-rapid

eye movement (REM) sleep (Moldofsky et al., 1975). These same investigators demonstrated that muscular aches and pains as well as fatigue could be induced in healthy volunteers if awoken by a buzzer during stage IV sleep; however, the symptoms disappeared after several nights of uninterrupted sleep. A similar study found that disruption of slow wave sleep in healthy women produced decreased pain thresholds and increased discomfort and fatigue as well as an increased inflammatory flare response of the skin (Lentz, Landis, Rothermel, & Shaver, 1999). However, other research has demonstrated that the alpha EEG sleep anomaly is not specific to FM but is also seen in rheumatoid arthritis as well as after febrile illness (Moldofsky, Lue, & Smythe, 1983; Moldofsky, Saskin, & Lue, 1988).

Neuroendocrine and metabolic abnormalities. Metabolic abnormalities in FM patients were first hypothesized following the reports of alpha EEG non-REM sleep disturbance. Previous studies in humans and animals suggested an important role for serotonin in the regulation of non-REM sleep, pain sensitivity, and affective states. Thus, researchers hypothesized that a disturbance in CNS serotonin metabolism may underlie the symptoms of FM (Moldofsky & Warsh, 1978). They studied plasma-free tryptophan, an amino acid precursor of serotonin, in 8 patients with FM symptomatology. Ratings of subjective pain were inversely related to levels of plasma-free tryptophan; however, plasma-free tryptophan was not related to pain threshold levels or mood ratings.

Further research has supported a serotonin deficiency hypothesis in FM. A serum amino acid profile was studied in 20 patients with primary FM and was compared to a group of matched normal controls. It was found that patients with FM demonstrated

significantly lower levels of total serum tryptophan as well as six other amino acids relative to the normal control group (Russell, Michalek, Vipraio, Fletcher, & Wall, 1989). In another study, the density of serotonin reuptake receptors on peripheral platelets and serum serotonin concentrations were compared to matched healthy controls (Russell et al., 1992). FM patients demonstrated a lower concentration of serum serotonin than controls, and binding of ^{3}H-imipramine, a measure of serotonin reuptake receptor density, was significantly higher in the FM sample. However, ^{3}H-imipramine binding in FM patients normalized following treatment with ibuprofen and alprazolam. It was suggested that the serotonin metabolism abnormality is different in FM patients than in depressed individuals since depressed individuals typically display reduced ^{3}H-imipramine binding. A follow-up study that compared the levels of serotonin, norepinephrine, and dopamine metabolites in the cerebrospinal fluid (CSF) found that CSF levels of metabolites for all three neurotransmitters were lower in FM patients compared to controls (Russell, Vaeroy, Javors, & Nyberg, 1992).

In addition to neurotransmitter functioning, investigations have looked at CSF levels of SP and nerve growth factor (NGF). Vaeroy, Helle, Forre, Kass, and Terrenius, (1988) were the first investigators to demonstrate elevated levels of SP in the CSF of FM patients. Those results were replicated in a subsequent study that compared CSF SP in FM patients with that of normal controls; however, CSF SP levels correlated only weakly with tenderness on examination (Russell et al., 1994). The most recent investigation found that both individuals who seek treatment for FM and individuals who meet criteria for FM but have never seen a health care professional for their disease-related symptoms, known as nonpatients, display significantly higher levels of CSF SP than normal controls

(Bradley, Sotolongo, Alberts, et al., 1999). Only one study has investigated levels of NGF in the CSF. The results of the study found the patients with primary FM had increased concentrations of NGF relative to healthy controls (Giovengo, Russell, & Larson, 1999).

Other laboratories have demonstrated evidence that FM may be characterized by abnormal functioning of the HPA axis (Crofford et al., 1994; McCain & Tilbe, 1989). The evidence includes hyperactive adrenocorticotropin hormone (ACTH) release and adrenal hyporesponsiveness. In a study of 12 FM patients compared to a sample of age- and sex-matched normal controls, Crofford and colleagues (1994) assessed the basal and ovine corticotropin-releasing hormone stimulated HPA axis function. It was demonstrated that patients with FM had significantly lower 24-hr urinary free cortisol with normal peak and elevated trough plasma cortisol levels. Additionally, there was a significant decrease in net integrated cortisol response to ovine corticotropin-releasing hormone in FM patients indicating adrenal hyporesponsiveness. Griep, Boersma, and De Kloet (1993) had previously demonstrated this adrenal hyporesponsiveness, and also showed a hyperreactive pituitary ACTH response in patients with FM.

Bennett, Clark, Campbell, and Burckhardt (1992) have demonstrated another neuroendocrine axis abnormality in FM patients that may be linked to the disturbed sleep. These investigators measured serum levels of somatomedin C in 70 FM patients and 55 healthy controls. Significantly lower levels of somatomedin C were observed in the FM patients compared with the healthy controls, which could not be explained with concomitant therapy or by weight. Since somatomedin C is mostly secreted during stage IV sleep and plays a critical role in muscle homeostasis and repair, it was hypothesized that

this abnormality may explain the link between disturbed sleep and disposition to muscle pain. Two subsequent reports have confirmed this finding (Ferraccioli et al., 1994; Griep, Boersma, & De Kloet, 1994), while another has not (Jacobsen, Main, Danneskiold-Samsoe & Skakkebaek, 1995).

Functional activity of CNS structures. CNS abnormalities or dysregulation have been hypothesized to contribute to chronic pain conditions; however, attention is just now being devoted to examining these structures among chronic pain populations. Our lab performed the first functional imaging study of CNS structures in women with FM compared to healthy women (Mountz et al., 1995). We used single photon emission computed tomographic (SPECT) brain imaging to measure rCBF in the thalamus and caudate nucleus among these groups. It is well known that the thalamus plays an important role in both pain perception and the integration of pain signals (Chudler & Dong, 1995). Although the role of the caudate nucleus in pain regulation is less understood, it was recently reported that a large number of nociceptive specific and wide-dynamic-range neurons are located in this structure and are involved in signaling the occurrence of noxious events (Chudler, Swigiyama, & Dong, 1993). Indeed, we found that patients with FM, relative to controls, were characterized by significantly lower rCBF to the left and right hemithalami and the left and right heads of the caudate nucleus. These findings were not related to age, education, or self-report measures of anxiety or depression. Subsequent studies from our group have demonstrated decreased rCBF in the left and right heads of the caudate nucleus, relative to healthy controls, among non-patients with FM as well as patients with insidious symptom onset (Bradley, Sotolongo, Alberts, et al.,

1999). However, we observed that patients whose symptoms began with a physical trauma demonstrated decreased rCBF primarily in the thalamus.

The most recent study in our laboratory investigated changes in rCBF in response to acute, painful stimuli among FM patients with insidious symptom onset and healthy controls (Bradley, Sotolongo, Alarcón, et al., 1999). Subjects were presented with phasic, right-sided, pressure stimulation that was tailored to each individual's pain threshold. Healthy controls demonstrated increased rCBF in the left thalamus and left somatosensory cortex, whereas the FM patients failed to show activation in the thalamus. However, they demonstrated increased rCBF in the right anterior cingulate cortex and the left and right somatosensory cortices. It is important to note that prior to entering the study, all subjects were screened for depressive disorders by a structured psychiatric interview. Those subjects who met criteria for any depressive disorder were not allowed to participate in this study. Thus, the differences in functional activity in response to acute pain could not be attributed to depression. In sum, we believe that low levels of functional activity in the thalamus and caudate nucleus probably represent a response to high levels of nociceptive neural input. As a consequence, the modulating actions of these structures on nociceptive transmission are compromised, thereby contributing to the low pain thresholds and other abnormal pain perceptions exhibited by persons with FM.

Neurosensory processing of stimuli. In relation to the dysregulation of functional activity in CNS structures, there has also been evidence of altered neurosensory processing of afferent stimuli among persons with FM. Gibson and colleagues (1994) compared 10 FM patients with 10 age-matched healthy controls with regard to heat pain thresholds

and cerebral event-related potentials following CO_2 laser stimulation. Patients with FM demonstrated significantly lower heat pain thresholds and increased peak to peak amplitude of the cerebral potential evoked by CO_2 laser stimulation at both pain threshold and 1.5 times pain threshold intensity. In short, patients with FM displayed greater activation of CNS structures than did healthy controls in response to a significantly lower intensity level of noxious stimulation than that delivered to the controls. This study further supported the hypothesis that patients with FM display a multimodal generalized change in pain sensitivity that is mediated by changes in the functional activity of CNS structures.

Our research group has performed a SDT analysis in order to better understand the factors that underlie low pain thresholds among persons with FM. A series of 100 dolorimeter stimuli were administered to patients, nonpatients, and healthy controls at 10 tender points and 10 control points. The stimulus intensity varied between 0 kg to pain threshold plus 1 kg and were presented in random order. The subject then rated each stimulus as either *painful* or *non-painful* on a 7-point rating scale. This allowed us to calculate an index of sensory discrimination ability that, according to SDT theory, is associated with altered neurosensory processing of afferent stimuli such that greater sensory information reaches the higher brain centers. When comparing patients, nonpatients, and controls on this index at baseline, 1-year, and 2-year follow-up, it was found that patients and nonpatients, relative to controls, exhibited higher scores on an index of sensory discrimination ability at both assessments (Bradley et al., 1997). Therefore, persons with FM, regardless of health care-seeking behavior, demonstrated greater accuracy than healthy controls at identifying stimuli at pain threshold or above as *painful*

and stimuli below pain threshold as *non-painful*. This suggests that persons with FM demonstrate altered neurosensory processing of afferent stimuli.

Etiopathogenic Models of Fibromyalgia

Currently, three models have been proposed to explain the etiology of FM symptoms, based upon our current understanding of the central and peripheral mechanisms possibly involved in this disorder. The model proposed by Yunus (1992) suggests that a complex interaction between central and peripheral factors is responsible for the pain and fatigue experienced by persons with FM. The model emphasizes the importance of neurohormonal dysfunction in contributing to aberrant pain processing at the central level. These neurohormonal dysfunctions may include deficiencies of inhibitory neurotransmitters such as serotonin and norepinephrine, or an overactivity of excitatory neurotransmitters such as SP, or a combination of both. These neurohormonal dysfunctions may be determined by several factors such as genetic predisposition or stress (i.e., viral infection, mental stress, physical trauma).

Other central and peripheral factors that may contribute to the symptomatology of FM are also included in Yunus' (1992) model. The central factors include sleep anomalies and psychological distress such as depression and anxiety. The peripheral factors that may contribute include muscle microtrauma, physical deconditioning, and spinal stress. However, Yunus stated that the main thrust of future research should focus on central factors in that they are most likely to be important to the development of FM.

Bennett (1993) proposed a model of FM pain resulting from muscle microtrauma that occurs following unusually low levels of exertion and subsequently does not heal

normally. A predisposition to muscle microtrauma may be genetic or may result from disruptions in growth hormone secretion that are produced by stage IV sleep disturbance and HPA axis dysfunction. Psychological contributions are recognized as important in maintaining and perpetuating the sleep anomaly noted above. In addition, the model includes a feedback loop between pain and fatigue that together contribute to inactivity and deconditioning as well as subsequent development of muscle microtrauma. Although not directly seen as important to the development of pain in FM, Bennett recognizes that abnormalities of neurotransmitters such as serotonin and SP may enhance the perception of peripheral pain.

Our research group also developed a model for the etiopathogenesis of abnormal pain perception in FM which maintains that central factors play a primary role in FM pain, including abnormal function of brain structures such as the thalamus and caudate nucleus (Figure 1; Bradley et al., 2000). Within this model, the distal contributory factors for the development of FM may result from a genetic predisposition or from one or more other precipitating events such as physical trauma, infectious illness, or emotional trauma. Physical trauma may directly contribute to abnormalities in muscle tissue and peripheral nerve endings, whereas emotional trauma or infectious illness may alter neuroendocrine functioning and thus lead to dysregulation of HPA axis as well as to abnormalities in muscle tissue. Muscle tissue damage, in turn, produces nociceptive transmission to the spinal cord and increases in neuropeptides involved in pain transmission including CSF levels of SP. Prolonged nociceptive transmission leads to central release of excitatory amino acids, SP, dynorphin, and calcitonin gene-related peptide as well as hyperexcitability of dorsal horn spinal neurons (i.e., central sensitization). This

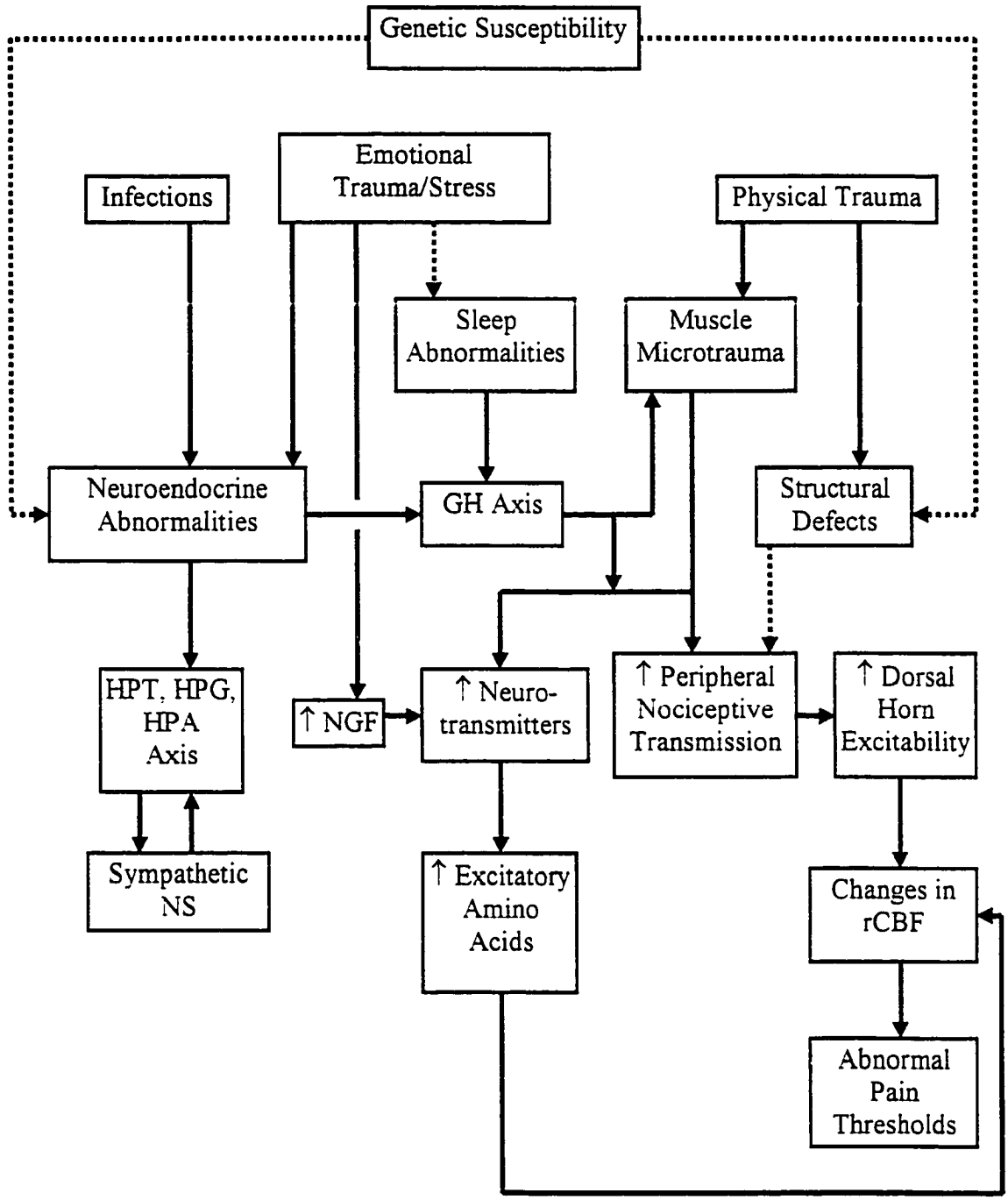

Figure 1. Etiopathogenic model of fibromyalgia (Used by permission of copyright holder).

produces a barrage of nociceptive input to the brain that eventually alters the function of brain structures that process the sensory-discriminative and affective-motivational dimensions of pain. The function of the latter structures is also influenced by and may influence alterations in HPA axis function. Thus, abnormally high levels of nociceptive input to the brain and abnormal pain perception (e.g., decreased pain thresholds and widespread persistent pain) are maintained.

Negative Affectivity

Description of Negative Affectivity

The term *negative affect* (NA) was used by Watson and Tellegen (1985) to describe one of two independent dimensions of mood that had emerged from their studies of psychological distress. NA reflects the extent to which one generally reports experiencing a broad range of negative mood states across different situations. The high end of the dimension indicates emotional arousal and is described by the terms *distressed*, *fearful*, *jittery*, *nervous*, and *hostile*. The low end of the dimension represents a relative absence of emotional involvement and is described by the terms *at rest*, *calm*, *placid*, and *relaxed*.

Watson and Clark (1984) proposed that NA is a construct that accounts for the moderate to high correlations that exist among various measures of psychological distress (i.e., measures of depression and anxiety). The authors performed a meta-analysis of studies that had reported correlations among common personality and psychological distress measures. They demonstrated remarkably high intercorrelations between the instruments purportedly used to measure a diversity of constructs (i.e., anxiety, depression, neuroticism, anger). The authors concluded that the various instruments were better

conceptualized as different measures of the same underlying factor, negative affectivity, or the general tendency to experience and report negative emotional states. In addition, the 12 measures of NA reviewed by Watson and Clark have been found to be relatively stable across time and are therefore considered to reflect trait tendencies.

In sum, NA is a normal personality trait that reflects the extent to which an individual experiences a broad range of negative emotional states and negative self-concept. High NA individuals experience general distress across different situations and maintain a fairly stable negative self-image. The subjective experience of distress includes feelings of anxiety, tension, anger, scorn, revulsion, guilt, self-dissatisfaction, and rejection (Watson & Clark, 1984). On the other hand, individuals low on NA are described as relatively content and secure.

Negative Affectivity and Physical Symptom Reporting

Watson and Pennebaker (1989) reported substantial correlations between self-reported psychological distress and report of physical symptoms (*r*'s from .25 to .62) across six samples of college students and other adults. They proposed the symptom-perception hypothesis as an explanation of the NA-symptom reporting relationship. They argued that NA, rather than being solely a disposition of negative emotionality, is better described as a general trait of *somatopsychic distress*. Thus, the relationship between NA and physical symptom reporting is explained by the fact that they are influenced by the same underlying factors. Indeed, variations in attentional and cognitive processes are thought to be responsible for variations in both physical and psychological symptom report. Specifically, it is hypothesized that individuals high in NA have a hypervigilant

attentional focus on internal processes and sensations and an anxious, apprehensive, threat-focussed cognitive or attributional style with regard to physical and psychological sensations.

Only a few studies have examined the relationship between NA and symptom perception. Cohen, Doyle, Skoner, Gwaltney, and Newsom (1995) performed a prospective study of the relationship between state and trait NA and physical symptom reporting in healthy individuals after induced exposure to a respiratory illness. Baseline state and trait NA were associated with increased numbers of subsequent physical complaints. Individuals high in state NA demonstrated greater objective disease severity that was related to the greater number of physical complaints. However, the association of trait NA and symptoms was independent of objective disease. Therefore, increased complaints among those high in trait NA seemed to be independent of objective illness, whereas increased complaints for people high in state NA were more closely tied to illness.

The symptom perception hypothesis has also received support in studies of chronic disease populations. A study of asthmatic subjects found that high NA was associated with more frequent and severe symptoms than low NA (Priel, Heimer, Rabinowitz, & Hendler, 1994). However, the perception of the severity of asthma symptoms was unrelated to objective disease status measures or clinical assessment. Similar results were found for adolescents with insulin-dependent diabetes (Wiebe, Alderfer, Palmer, Lindsay, & Jarrett, 1994). Those individuals high in NA were more likely than low NA individuals to misattribute non-diabetes-related symptoms to blood glucose levels and to exhibit poorer metabolic control. They concluded that high NA is related to a negative

bias in labeling physiological sensations that eventually leads to poorer disease management.

Two studies in our laboratory have looked at the relationship between NA and symptom reporting in patients with FM (Alexander et al., 1995, 1996). As previously discussed, FM subjects demonstrate altered neurosensory processing of afferent stimuli as measured by the SDT discrimination ability index. Our laboratory also examined the SDT response bias index and pain thresholds in 80 FM patients classified as low or high in NA (Alexander et al., 1995). Response bias is the characteristic cognitive tendency to frequently label stimuli as painful regardless of their intensity levels and is influenced primarily by psychological factors. In addition, the two groups were also compared on several measures of self-reported psychological and physical distress. Results showed significant group differences in overall psychological distress and self-reported severity of FM symptoms, as well as perceptions of disability. Moreover, FM patients high in NA demonstrated significantly lower pain thresholds and significantly lower scores on the index of response bias at the FM tender points, relative to FM patients low in NA.

We recently used a new behavioral laboratory procedure involving credible sham stimulation with FM patients high and low in NA (Alexander et al., 1996). We found that FM patients with high NA reported significantly higher levels of pain than low NA patients in response to the sham TENS procedure and preprogrammed, visual, EMG feedback, indicating high levels of physiological arousal. That is, high NA patients experienced increased pain when they were led to believe that they were receiving highly arousing electrical stimulation despite the fact that they received no stimulation. Low NA patients actually showed a modest decrease in pain with sham stimulation.

Neurophysiological Model of Negative Affectivity

Gray (1982, 1983, 1987) has proposed that NA is associated with activity in the Behavioral Inhibition System (BIS), which he locates in the limbic system, specifically in the septo-hippocampal area, prefrontal cortex, Papez circuit, and the monoaminergic and cholinergic pathways which innervate these structures. The BIS inhibits behavior, increases nonspecific arousal, and increases attention to and appraisal of aversive stimuli. Gray argues that high trait NA individuals have an overactive BIS that identifies all stimuli as important and thus requires constant checking. This leads to the subjective experience of anxiety or negative affect. Fowles (1994) broadened this perspective and proposed that the BIS is a negative motivational-affective system that is important in both anxiety and depression.

Functional Brain Imaging Studies

Functional brain imaging studies during painful stimulation in both healthy individuals and those with chronic pain have demonstrated the complex nature of pain, involving discriminative, affective, autonomic, and motoric components. Pain-related activation has been found to be widely dispersed across both cortical and thalamic regions (Coghill et al., 1994; Coghill, Sang, Maisog, & Iadorola, 1999). These studies are in accord with pain processing theories that acknowledge that multiple brain regions are likely to play key roles in nociceptive processing (Melzack & Casey, 1968; Price, 1988). The ventroposterior thalamus and the somatosensory cortex are considered to be involved in the discriminative aspect of nociception whereas the medial thalamus and its diffuse projection sites, such as the frontal, cingulate, and insular cortices, are thought to be

involved in the affective aspect of nociception (Melzack, 1986). This review focuses on alterations in brain activity associated with nociception in healthy and chronic pain populations.

Studies of Acute Pain in Healthy Individuals

Most investigations of the effects of painful stimulation on rCBF in healthy individuals have been performed with positron emission tomography (PET); however, similar results have been demonstrated with SPECT imaging procedures. Jones, Brown, Friston, Qi, and Frackowiak (1991) demonstrated that painful phasic heat stimuli produced significant rCBF increases in the contralateral cingulate cortex, thalamus, and lenticular nucleus. Other investigators have demonstrated similar findings with painful phasic thermal stimulation in healthy individuals including significant activation in the contralateral thalamus, cingulate cortex, primary and secondary somatosensory cortices, and the anterior insula (Casey et al., 1994; Coghill et al., 1994; Talbot et al., 1991).

Coghill and colleagues (1994) also found that nonpainful vibrotactile stimulation activated the contralateral and bilateral somatosensory cortices, respectively. In addition, when noxious heat stimulation was compared to vibrotactile stimulation, significant activation in the anterior insula was found during the painful stimulus. The researchers concluded that the primary and secondary somatosensory cortices are primarily involved in the sensory-discriminative processing of pain and that the anterior insula, which is heavily linked to somatosensory and limbic structures, may be involved in integrating nociceptive information with memory in order to appreciate the meaning and dangers of painful stimuli. Both the anterior insula and the anterior cingulate cortex, also implicated

in the affective processing of pain, have been found to be activated with other stimulus modalities including cold pain (Casey, Minoshima, Morrow, & Koeppe, 1996), esophageal pain (Aziz et al., 1997), and intracutaneous injection of ethanol (Hsieh, Stahle-Bäckdahl, et al., 1995).

Recent studies have utilized methodology to directly assess the affective-motivational dimension of pain. Several investigations have provided direct evidence of specific encoding of pain unpleasantness in the anterior cingulate cortex (Craig, Reiman, Evans, & Bushnell, 1996; Rainville, Duncan, Proce, Carrier, & Bushnell, 1997). Rainville and colleagues used hypnotic suggestions to alter the perceived unpleasantness of noxious tonic heat stimuli without altering the perceived intensity. It was found that hypnotic suggestion of increased unpleasantness produced significant increases in rCBF in the contralateral anterior cingulate cortex compared to rCBF during the hypnotic suggestion of decreased unpleasantness. The increase in rCBF in this brain structure was significantly correlated with increases in subjects' perceptions of stimulus unpleasantness. In the anterior insula, rCBF increased with noxious stimulation; however, it was not associated with changes in sensory unpleasantness with hypnotic suggestion.

Another innovative study utilized a thermal grill illusion to induce perceptions of pain without nociceptive input (Craig et al., 1996). In addition to the thermal grill illusion, rCBF was studied with innocuous and noxious cold and heat stimuli. It was found that the anterior insula was the only region activated by both noxious and innocuous stimuli. In contrast, the anterior cingulate cortex was the only cortical region uniquely activated by noxious stimuli. The thermal grill produced significant rCBF increases in the anterior insula and the anterior cingulate cortex. The investigators concluded that because

the anterior insula was activated by both innocuous and noxious stimuli, it was involved in general awareness of the physiological condition of body tissues, which is not dependent on the perception of pain. The anterior cingulate cortex, only activated with nociceptive and nonnociceptive noxious stimulation, was demonstrated to be uniquely involved in affective-motivational component of pain.

Hsieh, Stone-Elander, and Ingvar (1999) demonstrated that rCBF not only in the anterior cingulate cortex but also in the prefrontal cortex responded to psychological variables. Subjects underwent PET imaging during anticipation of an impending predictable and unpredictable pain stimulus. When subjects anticipated an impending unpredictable stimulus, functional activity increased in the anterior cingulate cortex and the prefrontal cortex. In contrast, the anticipation of a predictable pain stimulus resulted in a decrease in rCBF in these two structures. The investigators concluded that this pattern of activation reflects an emotional coping strategy of either vigilance or avoidance during the anticipation of pain and that these two structures are involved in the central modulation of painful distress and attentional arousal.

Studies of Patients with Chronic Pain

Resting State Studies

The first investigation of the effects of chronic pain on functional brain activity was performed on patients with advanced cancer pain (Di Pieró et al., 1991). Compared to normal controls, patients with unilateral cancer pain demonstrated decreased rCBF in the contralateral thalamus. In addition, thalamic rCBF returned to normal levels following complete pain relief with cervical cordotomy. Two subsequent studies of patients

with unilateral neuropathic pain also showed decreased rCBF in the contralateral thalamus (Hsieh, Belfrage, Stone-Elander, Hansson, & Ingvar, 1995; Iadarola et al., 1995). One of these investigations also demonstrated that neuropathic pain was associated with activation of the anterior insula and the anterior cingulate cortex (Hsieh, Belfrage, et al., 1995). This finding supports affective-motivational processing in chronic pain similar to processing involved in acute experimental pain in healthy individuals. However, pain stimulation studies (described below) show a different pattern of activation in the anterior cingulate cortex in different chronic pain populations.

As mentioned earlier in the literature review, our research group performed the first study of rCBF in patients with FM (Mountz et al., 1995). We found that when compared to healthy individuals, patients with FM showed significantly lower resting state rCBF in the left and right hemithalami and the left and right heads of the caudate nucleus. In addition, total cortical blood flow was lower in the FM patients. These findings were not related to age, education, or self-report measures of anxiety or depression. This finding has been replicated in another laboratory (Kwiatek, Barnden, Rowe, & Pile, 1997). Subsequent studies from our group have demonstrated decreased rCBF in the left and right heads of the caudate nucleus, relative to healthy controls, among nonpatients and patients with FM and insidious symptom onset (Bradley, Sotolongo, Alberts, et al., 1999).

Pain Stimulation Studies

Recent investigations have also examined the effects of acute pain stimuli on functional brain activity in patients with chronic pain. One of the first of these studies

evaluated patients with atypical facial pain and controls who were exposed to painful thermal stimuli (Derbyshire et al., 1994). Both patients and controls displayed significant increases in rCBF in the thalamus, anterior cingulate cortex, lentiform nucleus, insula, and prefrontal cortex in response to painful stimulation. However, activation in the atypical facial pain group was significantly greater in the anterior cingulate cortex and significantly less in the ipsilateral prefrontal cortex, relative to controls. The investigators concluded that this altered pattern of response in the atypical facial pain subjects may represent abnormal "supervision" of attentional and emotional schemas for pain. A follow-up study with rheumatoid arthritis (RA) patients demonstrated that, relative to healthy controls, RA patients showed significantly less activation in the anterior cingulate cortex and the prefrontal cortex in response to thermal pain (Jones & Derbyshire, 1997). This pattern was different than that found in the previous study with atypical facial pain patients. The investigators suggested that patients with RA demonstrate adaptive cognitive pain strategies that influence cortical responses to noxious stimuli. In contrast, the patients with atypical facial pain may not utilize adaptive cognitive pain strategies, as indicated by their significantly higher levels of depression.

Hsieh, Hannerz, and Ingvar (1996) studied the effects of inducing cluster headache attacks by sublingual nitroglycerin in patients with a history of cluster headaches. The primary finding was that the provoked cluster headaches activated two areas of the anterior cingulate cortex, the right caudal and the right rostrocaudal; or Brodmann's areas 24 and 32, respectively. The investigators concluded that these two regions of the anterior cingulate cortex are involved in the affective processing of pain and willed attention and

that there is a preferential role of the right hemisphere for attributing emotional valence and attention to the suffering of pain.

Another study examined the effects of acute pain produced by rectal balloon distention in patients with irritable bowel syndrome (IBS) and healthy controls (Silverman et al., 1997). Brain images were obtained by PET at baseline and during both actual and simulated delivery of anticipated painful stimuli. Activation of the anterior cingulate cortex was observed during both actual and simulated delivery of painful stimuli in healthy individuals. Self-report ratings of pain intensity were significantly correlated with anterior cingulate cortex activation in this group. In contrast, no comparable activation was observed in the anterior cingulate cortex in patients with IBS. However, a significant increase in rCBF was seen in the left dorsolateral prefrontal cortex of patients with IBS during both actual and simulated delivery of painful stimuli. It was suggested that activation of the frontal lobes associated with inhibition of the anterior cingulate cortex represents the activation of a vigilance network within the brain that allows the organism to maintain a state of alertness towards expected stimuli.

In contrast, Mertz and colleagues (2000) examined functional brain activity among individuals with IBS and healthy controls during nonpainful and painful rectal distention using functional magnetic resonance imaging (fMRI). Most subjects demonstrated increased activity in the anterior cingulate cortex, prefrontal cortex, insular cortex, and the thalamus. However, individuals with IBS demonstrated greater activation in the anterior cingulate cortex and reported greater pain intensity relative to controls at the same level of stimulation. The investigators concluded that patients with IBS demonstrate a normal pattern of brain activation in response to rectal stimulation; however, patients

with IBS demonstrate heightened pain sensitivity, as evidenced by greater activation of the anterior cingulate cortex and greater reported pain intensity compared to healthy controls presented with an identical stimulus.

As described earlier in the literature review, our laboratory investigated changes in rCBF in response to acute, painful stimuli among FM patients with insidious symptom onset and healthy controls (Bradley, Sotolongo, Alarcón, et al., 1999). Subjects were presented with phasic, right-sided, pressure stimulation that was tailored to each individual's pain threshold. Healthy controls demonstrated increased rCBF in the left thalamus and left somatosensory cortex, whereas the FM patients failed to show activation in the thalamus. However, they demonstrated increased rCBF in the right anterior cingulate cortex and the left and right somatosensory cortices. In addition, the patients' intensity ratings of the pressure stimulation were twice as great as those of controls, even though the patients received significantly lower levels of stimulation than controls. The patients also reported greater use of emotion-focused coping strategies (e.g., praying and hoping) during the stimulation task relative to the healthy controls. All subjects were screened for depressive disorders by a structured psychiatric interview prior to entering the study. Thus, these results could not be attributed to depression.

Purpose of the Current Study

This purpose of this study was to identify changes in activity in limbic brain structures associated with the affective-motivational dimension of pain that may contribute to abnormal pain perception in women with FM. Specifically, the study examined the functional activity of these structures as well as numerical pain ratings in response to a

sham TENS procedure that reliably evokes pain in the absence of nociceptive stimulation in FM patients with high NA. This procedure, then, provides a laboratory model of the abnormal pain perceptions of many FM patients who report unpleasant or painful sensory experiences after exposure to low intensity stimuli that are not aversive to healthy individuals.

The present study examines the responses of four subject groups: 5 FM patients with high NA, 5 FM patients with low NA, 5 healthy controls with high NA, and 5 healthy controls with low NA. The following hypotheses were proposed:

1. FM patients with high NA will report significantly higher levels of pain-related anxiety than all other groups at baseline; high NA controls will report significantly higher levels of pain-related anxiety at baseline than patients and controls with low NA.

2. Only FM patients with high NA will report that sham TENS of four left-side anatomic sites evokes pain at these sites.

3. There will be no significant increases in sensory intensity ratings following sham stimulation among any of the subject groups.

4. FM patients and healthy controls with high NA, relative to FM patients and controls with low NA, will produce significantly greater increases in pain and sensory unpleasantness ratings following sham stimulation.

5. FM patients and healthy controls with high NA will produce significantly higher anxiety-tension ratings on the POMS than FM patients and controls with low NA following sham stimulation.

6. Consistent with ratings of pain and sensory unpleasantness, FM patients and healthy controls with high NA will show significant increases in functional activity (i.e.,

higher rCBF) during sham stimulation in the right anterior cingulate cortex, right anterior insula, and right prefrontal cortex compared to baseline.

7. There will be no significant increases in rCBF in the right somatosensory cortex during sham stimulation among any of the subject groups.

8. There will be no significant increases in rCBF in the left anterior cingulate cortex, left prefrontal cortex, left anterior insula, or left somatosensory cortex during sham stimulation among any of the subject groups

9. FM patients with high NA will report significantly greater use of catastrophizing and praying/hoping coping strategies during sham stimulation than all other groups; high NA controls will report significantly greater use of these coping strategies than FM patients and healthy controls with low NA.

Sample size for the present study was based on a power analysis of the sensory intensity and unpleasantness ratings of 59 FM patients following sham stimulation in a previous study completed in our laboratory (Alexander et al., 1996). It should be noted, however, that the relationships found between NA and subjects' ratings of the sham stimulation were probably diminished by measurement error associated with two factors. One, subjects were divided into high and low NA groups based upon a median split. Two, pain intensity and unpleasantness at paired sites were each measured with only one 100-mm visual analogue scale. The measure of variability used in the present power analysis was estimated by reducing by 25% the standard deviations reported by Alexander et al. This reduction in variability was made given the increased variability of rating scale measurement provided by eight 100-mm visual analog scales at each site, anchored by 4 sensory intensity-related words and 4 unpleasantness-related words, and the classifi-

cation of high and low NA patients based upon a score 1.5 standard deviations above or 1 standard deviation below the mean, respectively. One-tailed comparison of post-stimulation sensory intensity ratings produced by high NA and low NA patients using 5 subjects per group and an effect size of 1.48 was associated with a power of .69 at the .05 level of significance. An identical comparison of poststimulation unpleasantness ratings and an effect size of 2.17 was associated with a power of .93 at the .05 level of significance. It was not possible to perform a power analysis for group differences in rCBF during sham stimulation because there are no similar studies to the proposed investigation. However, it should be noted that most functional brain imaging studies utilize 5 to 10 subjects in each cell, given the sensitivity of assessing changes in rCBF with these methods and the high cost of performing these studies.

METHODS

Design

This study featured a 2 X 2 X 2 repeated measures design with the between-subject variables of subject group (FM patients and Healthy Controls) and NA group (High and Low) and the within-subject group of rating phase (Baseline and Stimulation).

Subjects

Subjects consisted of 20 right-handed women in one of four groups: (a) 5 patients with primary FM and high NA, (b) 5 patients with primary FM and low NA, (c) 5 healthy control individuals without chronic or recurrent pain and high NA, and (d) 5 healthy controls without chronic or recurrent pain and low NA. FM patients were recruited from previous studies in our laboratory and University of Alabama at Birmingham (UAB) Rheumatology Clinic referrals; controls were recruited from previous studies in our laboratory and with newspaper advertisements seeking healthy individuals without recurrent aches and pains. Permission to use human subjects was granted by the UAB Institutional Review Board (Appendix A).

Subjects underwent a three-step screening process. First, subjects were mailed a letter explaining the study. In addition to the letter, subjects were sent the Positive and Negative Affect Scale (PANAS; see description below) and asked to complete and return the questionnaire. Individuals who scored at least 1.5 standard deviations above the adult normative mean of the PANAS Negative Affect Scale (high NA) or more than 1 standard

deviation below the normative mean (low NA) were contacted by phone to complete the screening process. Potential new subjects were then administered a screening questionnaire for FM by phone (Wolfe, Hawley, Cathey, Caro, & Russell, 1985). This questionnaire required individuals to indicate the frequency with which they experience each of 20 FM-related symptoms. FM patients were considered to have passed the screen if they endorsed a specific pattern of major symptoms including nonrestorative sleep and fatigue, generalized aches and pains, and muscle stiffness and aching in the morning. Healthy controls passed the screen if they did not report experiencing any of the major symptoms on a frequent basis (often or always). Previous studies have shown this questionnaire has at least a 70% hit rate in detecting persons with FM (Wolfe et al., 1985). Subjects were also asked several interview questions pertaining to the specific inclusion-exclusion criteria described below. Respondents who failed the telephone screen were excluded from further consideration.

Those who passed the telephone screen were eligible for the final step in the screening process, which involved a comprehensive review of medical records (FM patients only) and clinical examination by a board-certified rheumatologist in the UAB General Clinical Research Center or GCRC (all subjects). This evaluation included an interview and a physical examination. Inclusion criteria for all subject groups were as follows:

1. Subject was a woman between 18 and 65 years of age.

2. Subject passed telephone FM screening questionnaire as either a patient or control (Wolfe et al., 1985).

3. Subject had no known cardiopulmonary problems (e.g., hypertension, asthma, etc.) that might be aggravated by apprehensive anxiety.

4. Subject had no significant medical co-morbidities (e.g., back or neck surgery) or psychiatric illness that might preclude compliance with the study methods, as determined by the rheumatologist.

Additional Inclusion criteria for FM patients were as follows:

1. Subject's FM diagnosis validated by a rheumatologist using 1990 ACR criteria.

2. Subject was not taking any analgesic, psychotropic, anti-inflammatory, muscle-relaxing, and/or sleep medications from which she could not discontinue for 14 days prior to the study.

Additional Inclusion criteria for healthy controls were as follows:

1. Subject was not currently experiencing any pain symptoms nor had a history of pain lasting longer than 3 months.

2. Subject had not been diagnosed with migraine headaches.

3. Subject was not currently being treated for a major psychiatric disorder with psychotropic medications.

Subjects who satisfied criteria were presented with a more detailed explanation of the study and were asked to sign an informed consent. Subjects were then contacted by phone to schedule an appointment for the study. Once an appointment was made, subjects were sent a letter with instructions for the study, including when to begin discontinuing their analgesic, psychotropic, anti-inflammatory, muscle-relaxing, or sleep medications. Subjects discontinued these medications for 2 weeks prior to beginning the study. A

follow-up phone call was made to remind subjects to discontinue medications and to answer any questions about study procedures.

Measures

Self-Report Measures

Positive and Negative Affect Scale (PANAS)

The PANAS is a brief, 20-item measure of two orthogonal components of mood, positive affect and negative affect (Watson, Clark, & Tellegen, 1988). Each of the two PANAS scales consists of 10 descriptor words such as *distressed* or *enthusiastic* that correspond to the negative affectivity or the positive affectivity construct. Subjects respond to each descriptor by using a 5-point response scale. They were instructed to indicate *to what extent you generally feel this way, that is, how you feel on average.* The PANAS NA score is calculated by summing the scores on the 10 NA items.

High internal consistency (coefficient alpha = .87) and stability (1-year test-retest reliability = .84 to .90) have been demonstrated for the NA scale of the PANAS (Watson et al., 1988). The authors also report evidence of good factorial and convergent validity. For example, the PANAS NA scale has been shown to correlate substantially with commonly used measures of NA and psychological distress such as the Hopkins Symptom Checklist, the Beck Depression Inventory, and the State-Trait Anxiety Inventory.

Only individuals who scored at least 1.5 standard deviations above the adult normative mean for the NA scale were allowed to participate as high NA subjects. Because the adult normative mean is low (M = 18, SD = 6), individuals who scored at least 1

standard deviation below the adult normative mean were allowed to participate as low NA subjects.

Pain Anxiety Symptom Scale (PASS)

The PASS is a 40-item self-report questionnaire of pain-related anxiety (McCracken, Zayfert, & Gross, 1992). Items are rated on a 5-point scale from *never* to *always* to produce a total score and scores on the following 4 subscales: Cognitive Anxiety, Escape/Avoidance, Fearful Appraisal, and Physiological Anxiety. The PASS demonstrates good internal consistency (McCracken, Gross, Sorg, & Edmands, 1993). The validity of the PASS has been supported by positive correlations with measures of anxiety, cognitive errors, depression, and disability (McCracken, Gross, Aikens, & Carmike, 1996) and negative correlations with behavioral performance variables (Burns, Mullen, Higdon, Wei, & Lansky, 2000).

Categorical Pain Rating Scale (PRS)

The PRS is a 7-point categorical scale used in our laboratory with the following categories: 0 = *no sensation*, 1 = *faint sensation*, 2 = *moderate sensation*, 3 = *severe sensation*, 4 = *faint pain*, 5 = *moderate pain*, 6 = *severe pain* (Bradley et al., 1997). Subjects' responses to this scale following sham TENS stimulation were used to determine whether they experienced pain during this procedure.

Numerical-Graphical Rating Scales

A multiple-scale rating system was used to assess pre- and post-stimulation pain intensity, sensory unpleasantness, and sensory intensity. Numerical-graphical rating scales have been used frequently as tools for pain assessment and have demonstrated high degrees of reliability and validity (Jenson & Karoly, 1992). Pain intensity was measured on a 100-mm numerical-graphical rating scale with the anchors of *not at all painful* to *extremely painful*. Scores at each of the four sham stimulated sites were summed to form a total pain intensity score.

Verbal descriptors of sensory intensity and sensory unpleasantness were derived from the Differential Descriptor Scale developed by Gracely and Kwilosz (1988) and utilized in 100-mm numerical-graphical rating scales with each verbal descriptor anchored with *not at all* and *extremely*. Four 100-mm numerical-graphical rating scales with the verbal descriptors of *distressing*, *annoying*, *unpleasant*, and *intolerable* were used to assess sensory unpleasantness. Four 100-millimeter numerical-graphical rating scales with the verbal descriptors of *intense*, *strong*, *severe*, and *tense/tight* were used to assess sensory intensity. Scores from the separate scales at each of the four sham stimulated sites were summed to form a total sensory unpleasantness score and a total sensory intensity score. These scales allowed subjects to accurately describe the intensity and unpleasantness of their sensory experiences, regardless of whether they experienced pain during the sham TENS procedure.

Profile of Mood States (POMS)

The POMS is a list of 65 adjectives related to mood that are rated on a 5-point scale from *not at all* to *extremely* (McNair, Lorr, & Droppleman, 1992). The POMS yields six factors: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment. The POMS demonstrates good internal consistency (coefficient alpha = .90) and test-retest reliability. In addition, adequate concurrent validity has been demonstrated for each of POMS factors with moderate to high correlations with similar types of instruments (r's = .21 to .80). The period to be rated by the subject can be specified by the investigator and can be used to measure the immediate effects of experimental manipulation. For this study, subjects were asked to complete the POMS based upon how they were *currently feeling*.

Modified Coping Strategies Questionnaire (CSQ)

The CSQ is a 50-item self-report instrument designed to assess six cognitive (i.e., diverting attention, reinterpreting pain sensations, coping self-statements, ignoring pain sensations, praying/hoping, and catastrophizing) and two behavioral coping pain strategies (i.e., increasing activity level, and increasing pain behaviors; Rosentiel & Keefe, 1983). The reliability and validity of the CSQ has been examined repeatedly with positive results (Keefe, Salley, & Lefebvre, 1992).

The clinical utility of this instrument has been well established (DeGood & Shutty, 1992), and a situation version of this instrument has been used to assess coping strategy use during painful EMG testing (Buckelew et al., 1990). Similarly, 33 items were reworded to measure coping with the sham TENS stimulation used in this study;

however, all items on the increasing activity level and increasing pain behavior scales, and three items from the praying/hoping scale could not be reworded and were not included. The modified CSQ consisted of five 6-item scales -- diverting attention, reinterpreting pain, coping self-statements, ignoring sensations, and catastrophizing as well as a 3-item praying/hoping scale. Each item was rated on a 7-point categorical scale from 0 (*never did that*) to 6 (*did that the whole time*). The average rating across the items that comprised each scale was calculated for each subject.

Functional Brain Imaging

The acquisition and semiquantification of brain rCBF using SPECT imaging is detailed below in three sections: SPECT Acquisition, Magnetic Resonance Image (MRI) Acquisition, and SPECT Image Data Analysis.

SPECT Acquisition

Subjects were imaged using the Picker PRISM 300XP triple-head Anger gamma camera equipped with high resolution collimators. Prior to imaging, each subject had a 23-gauge heparin lock butterfly needle inserted into a prominent antecubital fossa vein. After needle insertion, the subject was given time to regain composure, the lights were dimmed, and ambient noise was minimized. The subject was given a brief questionnaire to assure she had returned to a baseline resting condition. Once this was determined, the sham TENS baseline or stimulation procedure began. After 1 min of sham TENS procedure, 30 mCi of Tc99m hexamethylpropyleneamine (HMPAO) was injected. The subject remained in the sham TENS procedure for 5 additional minutes to allow for the extrac-

tion and irreversible incorporation of the lipophilic rCBF tracer into the brain. The subject was then taken to the high-resolution triple-head detector SPECT system for scanning. A well-validated reference system device for co-registration of the SPECT brain scan and the MRI scan (described below) was precisely positioned on the subject's head just prior to scanning (Mountz, Wilson, Wolff, Deutsch, & Harris, 1994; Mountz, Zhang, Liu, & Inampudi, 1994).

MRI Scan Acquisition

High resolution T1 and T2 weighted MRI scans were obtained on the 1.5 Tesla GE Signa System. The patient was placed in the scan bed in a comfortable position, and the reference system was precisely aligned on the patient's head in the identical manner in which it was placed for the brain SPECT scan. The patient was placed in the scanner, and image acquisition was performed by obtaining sequential 4-mm-thick sections oriented approximately parallel to and sequentially above the canthomeatal line to include the entire brain. Image data transfer from the MRI scanner was electronically transmitted to the SPECT image scanner. Image data from the two sources were co-aligned with one another by the reference system program to produce sequentially overlapped MRI images of identical orientation and thickness as obtained on SPECT.

SPECT Image Data Analysis

To obtain complete sampling on the SPECT scan, serial regions of interest (ROI) on which the structure is seen on the MRI were delineated, and average counts for the entire number of SPECT sections on which the structure appears was averaged. Cortical

ROI was analyzed using a semi-automated cortical analysis program developed at UAB (Mountz, Deutsch, & Khan, 1993). The algorithm delineated an outer border of 24 annular sectors by determining the 50% maximum counts/pixel threshold and then circumscribed an inner border eight pixels deep. The cortex was then divided into 24 annular sectors of equal annular spacing around the brain to yield cortical ROI for attaining rCBF count data. It is routine to use the 90% count threshold value in each ROI and the reference region for normalization since this produces a highly reproducible sampling of the cortex with minimal statistical variation due to pixel count averaging.

Apparatus

The apparatus used in the sham stimulation-feedback task consisted of a realistic looking electrophysiological recording apparatus (including electrodes, amplifiers, connecting cables) and a computer monitor for providing the bogus EMG feedback. In order to enhance the deception, this apparatus appeared fully functional, with electrical power, working lights, switches and dials. The sham EMG tracings presented on the monitor came from a preprogrammed graphical tracing sequence. Tracing sequences for baseline and sham stimulation were developed using the *AcqKnowledge Version 3.0* electrophysiological recording and analysis software for the Windows 3.1 operating system (1994). The investigator controlled the presentation of these sequences through a control computer connected to the feedback monitor. The simulated electrophysiological recording apparatus, electrode sets, and feedback monitor were placed on a table, facing the subject. The actual control computer was a Gateway laptop computer located on a

separate table outside of a dividing screen to the left of the test area. Control operations were not visible to the subject during the procedure.

Procedure

All subjects underwent the procedures described below, which are also illustrated in Figure 2. The procedures began with a drug washout period. Specifically, subjects were asked prior to beginning the study to forego using any psychotropic, analgesic, anti-inflammatory, sleep, or muscle relaxing medications for 14 days. We have used this procedure in our current neuroimaging studies to reduce extraneous variation in rCBF measurements and have found good compliance among patients and controls. Immediately after the washout was completed, subjects underwent a baseline assessment (Day 1 of Figure 2) in our laboratory at the UAB GCRC. When each subject arrived at the GCRC for her baseline evaluation, a graduate research assistant administered a brief demographic questionnaire that included questions regarding age, education, race, and duration of illness (FM patients only). The assistant seated the subject in a comfortable chair in front of a table which supported the sham TENS stimulation/recording apparatus described above. Next, a trained nuclear medicine technician inserted a small heparin lock butterfly needle into a prominent antecubital fossa vein in the subject's right arm. The assistant then described the baseline sham recording portion of the study, following the EMG instructions for Day 1 (Appendix B). After providing these instructions, the assistant placed an EMG electrode on each of two tender point sites (left trapezius and left second rib at the second costochondral junction) and two control point sites (left mid-ulna and left mid-tibia) as shown in Figure 3. These locations were chosen because they

Flow Chart of Experimental Protocol
Day 1 Baseline Assessment

12:00 p.m.	Subject checked into the General Clinical Research Center (GCRC)
	Procedures reviewed with subject and demographic data collected
12:45 p.m.	EMG electrodes placed on 4 left-side anatomic sites
	Subject underwent 2-minute "test" EMG baseline recording
1:00 p.m.	Subject completed POMS
	Subject completed numerical-graphical rating scales
1:15 p.m.	Needle for HMPAO tracer injection inserted in subject's right arm
1:20 p.m.	Preprogrammed sham EMG baseline recording presented to subject
1:21 p.m.	Tracer injected
1:26 p.m.	Preprogrammed sham EMG recording completed
	Subject completed numerical-graphical rating scales
	Subject completed POMS
1:45 p.m.	Brain SPECT scan performed in the Division of Nuclear Medicine
2:30 p.m.	Subject checked out of the GCRC

Day 2 Sham TENS Stimulation Assessment

12:30 p.m.	Subject checked into the GCRC
	Procedures reviewed with the subject
12:45 p.m.	EMG electrodes placed on 4 left-side anatomic sites
	Subject underwent 2-minute "test" EMG baseline reading
1:00 p.m.	Subject completed POMS
	Subject completed numerical-graphical rating scales
1:15 p.m.	Needle for HMPAO tracer injection inserted in subject's right arm
1:20 p.m.	Sham TENS stimulation and preprogrammed EMG feedback presented to the subject
1:21 p.m.	Tracer injected
1:26 p.m.	Sham TENS stimulation and preprogrammed EMG feedback completed
	Subject completed numerical-graphical rating scales and PRS scales
	Subject completed POMS
	Subject completed manipulation check
1:45 p.m.	Brain SPECT scan performed in the Division of Nuclear Medicine
2:30 p.m.	Brain MRI performed
3:15 p.m.	Subject debriefed regarding the study
3:30 p.m.	Subject checked out of the GCRC

Figure 2. Study flow diagram.

are easily anatomically identified, provide coverage of the whole body, and are well-known and meaningful in FM research. The assistant then told the subject that a *test* baseline recording of muscle activity would be obtained for 2 min to make sure the electrodes were responding to the resting state muscle activity. The subject then completed the POMS to describe her current mood state. The assistant next asked the subject to close her eyes and focus her attention on sensations at the first electrode site (left trapezius) for 15 s and to then rate her perceptions of pain as well as sensory intensity and sensory unpleasantness using the numerical-graphical rating scales. This procedure was repeated for the remaining EMG sites (left second rib, left mid-ulna, and left mid-tibia).

After the baseline ratings were made, the assistant instructed the subject that she would undergo EMG recording of muscle activity at the electrode placement sites without electrical stimulation. The assistant explained to the subject that low amplitude EMG feedback indicates low physiological arousal, whereas higher amplitude EMG levels depict greater levels of physiological arousal. The subject then observed four preprogrammed channels of relatively low amplitude EMG activity, instead of actual feedback, on the computer monitor for a total of 6 min. After the first minute of preprogrammed EMG biofeedback, the technician injected the subject with 25 mCi of Tc-99m HMPAO. The preprogrammed EMG biofeedback continued for another 5 min to allow for tracer uptake into the brain. After the feedback presentation was completed, the assistant asked the subject to again focus on her sensations at each of the four electrode placement sites for 15 s and to rate her perceptions of pain as well as sensory intensity and unpleasantness at each of the four sites by using the numerical-graphical rating scales. The subject then completed the POMS to describe her mood during the sham EMG recording. Fi-

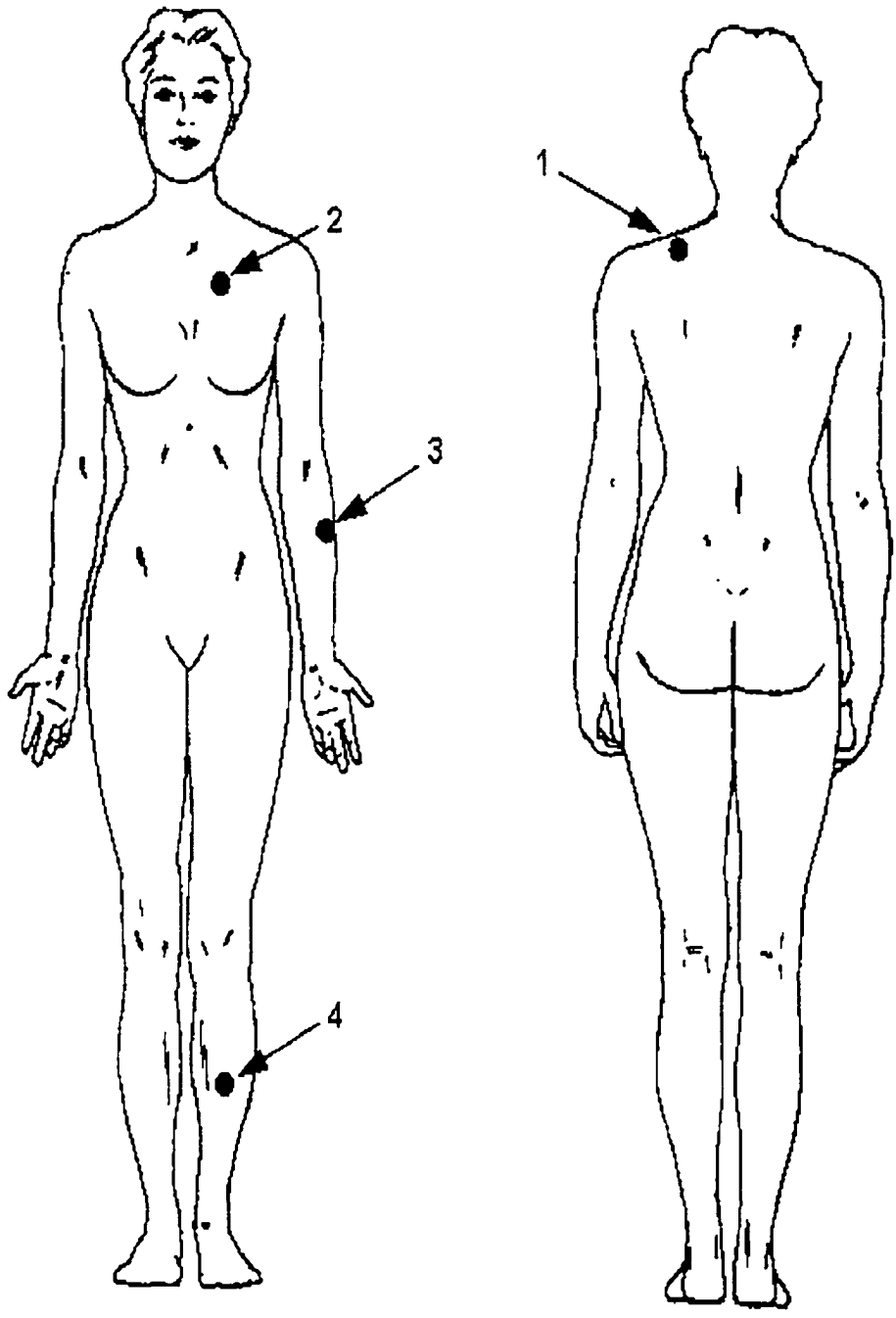

Figure 3. Diagram showing placement of the 4 EMG electrodes used in the sham electrical stimulation task.

nally, the subject underwent SPECT acquisition in the Division of Nuclear Medicine. After imaging was completed, the subject was scheduled to return to the GCRC laboratory in 2 days for the final phase of the research protocol.

When the subject returned to the laboratory (Day 2 of Figure 2), the assistant again seated her at the table facing the sham TENS stimulation/recording apparatus. The technician then inserted a small butterfly needle in a prominent antecubital fossa vein in the subject's right arm. The assistant carefully explained the sham stimulation/feedback portion of the study, following the EMG instructions for Day 2 (Appendix C). Next, the assistant placed two EMG electrodes on each of the same four anatomic sites used at baseline. The assistant also instructed the subject that a 2-min *test* baseline recording of muscle activity without stimulation would be performed to assure the electrodes were functioning properly. The subject then completed the POMS to describe her current mcod. The assistant next asked the subject to focus her attention on sensations at the electrode placement sites for 15 s and to rate her perceptions of pain and sensory intensity and unpleasantness at each of the four sites by using the numerical-graphical rating scales.

The assistant then informed the subject that she was ready to proceed with the stimulation/recording task. The assistant instructed the subject that low intensity TENS would be delivered through one electrode at each anatomic site. The delivery of TENS stimulation would be signaled to the subject by activation of a red light on top of the apparatus. The assistant also told the subject that EMG recordings from the electrode placement sites would be fed back to her visually on the computer monitor when the red light was turned off. A sham stimulation/recording program, consisting of six stimu-

lus/recording cycles, began immediately after the instructions were given to the subject. Each 1-min cycle consisted of 20 s of sham stimulation, as evidenced by activation of the red light, followed by 40 s of preprogrammed visual EMG feedback activity that showed substantially higher amplitude wave forms than those presented during the baseline assessment on Day 1. The intent was to make the subject believe that the sham stimulation increased muscle fiber activity. After the first stimulation/recording cycle was completed, the technician injected the subject with 25 mCi of Tc-99m HMPAO. The sham stimulation/recording cycle continued for 5 more min to allow for tracer uptake. After the entire sham stimulation/recording program was completed, the assistant asked the subject to again focus her attention on the sensations at each of the electrode placement sites for 15 s and to rate perceptions of pain as well as sensory intensity and unpleasantness at each of the four sites by using the numerical-graphical rating scales. The subject also denoted whether or not she experienced pain at those sites from the stimulation procedure with the PRS and completed the POMS to describe her mood during the sham EMG stimulation. Finally, the subject underwent SPECT acquisition and brain MRI in the Division of Nuclear Medicine.

Immediately following the MRI scan, the assistant escorted the subject to the GCRC and asked her to complete a series of opinion questions that included a manipulation check item to insure the subject believed she had received TENS stimulation. This manipulation check consisted of 10 statements covering a variety of areas related to the subject's personal experience with the study. The subject responded to each statement on a 10-point rating scale (1 = *completely disagree* through 10 = *completely agree*). Nine of the statements were filler or distracters, which discussed the clarity of instructions and the

politeness or sensitivity of the researchers. Statement 4 was the actual manipulation check item on which the subject reported her level of certainty that her muscles were actually stimulated, even if she did not feel any sensations at the electrode sites. If the subject marked a rating of 5 or less on this item, she was considered not to have believed the manipulation. Finally, the subject was debriefed regarding the nature of the study. It should be noted that no subjects suffered physical or emotional distress during the procedures or after debriefing.

Debriefing

Two important considerations were addressed with the formal debriefing. First, due to the deceptive nature of the sham stimulation/feedback paradigm, it was of ethical importance to explain the true nature of the study immediately following completion of the study visit. Second, in order to prevent future subject contamination through shared communication, the assistant asked each subject to refrain from disclosing details of the study until notified that the data collection was completed.

Data Analysis

The first step in the data analysis was to exclude the data from any subject who failed to believe that TENS stimulation actually occurred. As described above, any subject who rated 5 or less on Item 4 of the manipulation check questionnaire was not considered to have believed the study manipulation and, thus, produced invalid data. Examination of the subjects' responses to Item 4 revealed that one of the high NA FM patients met this criterion. In addition, one subject in the high NA healthy control group

failed to complete the MRI and was also excluded from the data analysis. The low failure rate in this study is consistent with the Alexander et al. (1996) finding that 59 of 62 subjects passed the manipulation check. The final analysis, then, was based on the responses of 4 FM patients with high NA, 5 FM patients with low NA, 4 healthy controls with high NA, and 5 healthy controls with low NA.

The second step involved screening the data for violations of statistical assumptions. This process revealed that subjects' responses to the PASS (Cognitive Anxiety, Escape/Avoidance, Fearful Appraisal, and Physiological Anxiety) and the numerical-graphical rating scales of sensory intensity and sensory unpleasantness significantly violated one or more statistical assumptions. The distributions of the PASS scores were successfully adjusted using a logarithmic transformation. Distributions of sensory intensity and unpleasantness ratings were successfully adjusted by using a square root transformation. In addition, the responses on the modified CSQ could not be successfully adjusted using one of the above techniques; therefore, a nonparametric analysis was performed.

The next step involved testing for group differences on demographic variables such as age, education, and time since pain onset that could potentially account for differences in other variables of interest. Since only the patients reported time since pain onset, an independent t-test was performed to detect potential group differences. Differences between the subject groups on age and education were assessed using 2 (patient vs. healthy control) x 2 (high vs. low NA) analyses of variance (ANOVAs). If necessary, group differences were assessed by independent *t* test with Bonferroni correction on those variables for which there was a significant main effect of or interaction between the

independent variables. In addition, expected group differences on the NA scale of the PANAS were assessed using a similar analysis. However, follow-up contrasts among all groups were assessed by independent t-tests with Bonferroni correction.

The final step consisted of evaluating the research hypotheses. Specific hypotheses were tested as follows:

Hypothesis 1 stated that FM patients with high NA will report significantly higher levels of pain-related anxiety than all other groups at baseline; high NA controls will report significantly higher levels of pain related anxiety at baseline than patients and controls with low NA. A 2 (patient vs. healthy control) x 2 (high vs. low NA) ANOVA was performed on subjects' ratings of pain-related anxiety. Group differences were assessed by independent t-tests with Bonferroni correction on those variables for which there were significant main effects or interactions.

Hypothesis 2 stated that only FM patients with high NA will report that sham TENS of four left-side anatomic sites evokes pain at these sites. A Fisher's Exact Test was performed to compare the proportion of subjects in each patient group who reported pain on the PRS following sham TENS stimulation on Day 2.

Hypothesis 3 stated that there will be no significant increases in sensory intensity ratings following sham stimulation among any of the subject groups. A 2 (patient vs. healthy control) x 2 (high vs. low NA) x 2 (pre- and poststimulation) repeated measures ANOVA was performed on subjects' Day 2 ratings of sensory intensity. If significant interactions between the independent variables were found, then follow-up two-tailed, paired *t* tests were performed on subjects' ratings pre- and post-stimulation.

Hypothesis 4 stated that FM patients and healthy controls with high NA, relative to FM patients and controls with low NA, will produce significant increases in pain and sensory unpleasantness ratings following sham stimulation. The same 2 x 2 x 2 repeated measures ANOVA was performed on subjects' Day 2 ratings of pain and sensory unpleasantness. Follow-up one-tailed, paired *t* tests were performed on those variables for which there were significant interactions.

Hypothesis 5 stated that FM patients and healthy controls with high NA will produce significantly higher anxiety-tension ratings on the POMS than FM patients and controls with low NA following sham stimulation. The 2 x 2 x 2 repeated measures ANOVA was performed on subjects' Day 2 ratings of anxiety-tension. Follow-up one-tailed, paired *t* tests were performed on those variables for which there was a significant interaction.

Hypothesis 6 stated that, consistent with ratings of pain and sensory unpleasantness, FM patients and healthy controls with high NA will show significant increases in functional activity (i.e., higher rCBF) during sham stimulation in the right anterior cingulate cortex, right anterior insula, and right prefrontal cortex compared to baseline. A 2 x 2 x 2 repeated measures ANOVA was performed on subjects' rCBF values on Day 1 and Day 2. Follow-up one-tailed, paired *t* tests were performed on those variables for which there was a significant interaction.

Hypothesis 7 stated that there will be no significant increases in rCBF in the right somatosensory cortex during sham stimulation among any of the subject groups. The same 2 x 2 x 2 repeated measures ANOVA as above was performed using rCBF values in

the right somatosensory cortex. If significant interactions were found, then follow-up two-tailed, paired *t* tests were performed.

Hypothesis 8 stated that there will be no significant increases in rCBF in the left pre-frontal cortex, left anterior insula, or left somatosensory cortex during sham stimulation among any of the subject groups. The same 2 x 2 x 2 ANOVA was performed using rCBF values for each of the respective structures. If significant interactions were found, then follow-up two-tailed, paired t-tests were performed.

Hypothesis 9 stated that FM patients with high NA will report significantly greater use of catastrophizing and praying/hoping coping strategies during sham stimulation than all other groups; high NA controls will report significantly greater use of these coping strategies than FM patients and healthy controls with low NA. Mean use of catastrophizing and praying/hoping coping strategies among the four subject groups were compared using the nonparametric Kruskal-Wallis test.

RESULTS

NA Scores and Demographic Variables

Table 1 shows that, as expected, a significant main effect of NA group was found for NA scores on the PANAS, $F(1,17) = 170.10$, $p < .0001$. There was no significant main effect of subject group or significant NA group x subject group interaction. Follow-up contrasts with Bonferroni correction (corrected $\alpha = 0.0125$) demonstrated that the FM patients and healthy controls selected for high NA produced significantly higher NA scores than both the FM patients and healthy controls selected for low NA. In addition, there were no significant main effects or interactions for age or education, and the high and low NA FM patients did not differ in pain duration.

Table 1

Mean (±SE) Values for Demographic Variables and Negative Affectivity (NA) Scores

Variable	FM high NA	FM low NA	HC high NA	HC low NA	*p* value
NA score	38.0 (2.6)	11.6 (0.4)	34.0 (3.3)	11.0 (0.4)	0.0001[a]
Age (yrs)	45.8 (3.3)	43.2 (4.2)	37.5 (4.1)	35.2 (3.5)	NS
Education (yrs)	13.8 (1.0)	14.2 (1.1)	15.5 (1.0)	16.0 (0.7)	NS
Pain duration (mos)	166.5 (38.9)	165.4 (63.4)			NS

[a] main effect for NA group

Hypothesis 1: Differences between Groups on Self-Report of Pain-Related Anxiety

Figure 4 shows there were significant main effects of subject group ($F[1,17] = 13.15, p < .01$) and NA group ($F[1,17] = 16.86, p < .01$) on Total PASS scores. There was also a significant patient group x NA group interaction, $F(1,17) = 6.25, p < .05$, on this measure. Follow-up contrasts with Bonferroni correction (corrected $\alpha = 0.0125$) indicated that FM patients with high NA reported significantly greater pain-related anxiety symptoms relative to all other groups. No other group differences were demonstrated for total scores on the PASS.

Further analyses of the PASS subscales revealed significant main effects of subject group on Cognitive Anxiety ($F[1,17]= 6.99, p < .05$), Fearful Appraisal ($F[1,17] = 12.71, p < .01$), and Physiological Anxiety ($F[1,17] = 24.82, p < .001$). Significant main effects for NA group were also found on the Cognitive Anxiety ($F[1,17] = 28.31, p < .001$), Escape/Avoidance ($F[1,17]= 4.72, p < .05$), Fearful Appraisal ($F[1,17] = 13.82, p < .01$), and Physiological Anxiety ($F[1,17] = 11.20, p < .01$) subscales. A significant interaction was found for Physiological Anxiety, $F(1,17) = 12.80, p < .01$, and a marginal interaction effect was found for Fearful Appraisal $F(1,17) = 3.44, p = .08$. Similar to the results found on the Total PASS scale, follow-up contrasts revealed that FM patients with high NA reported significantly greater scores on Fearful Appraisal and Physiological Anxiety than all other subject groups. In addition, FM patients with high NA reported significantly greater Cognitive Anxiety than FM patients and healthy controls with low NA. Overall, then, FM patients with high NA tended to produce higher scores than the other subject groups on all of the PASS measures except Escape/Avoidance. These results are presented graphically in Figure 5.

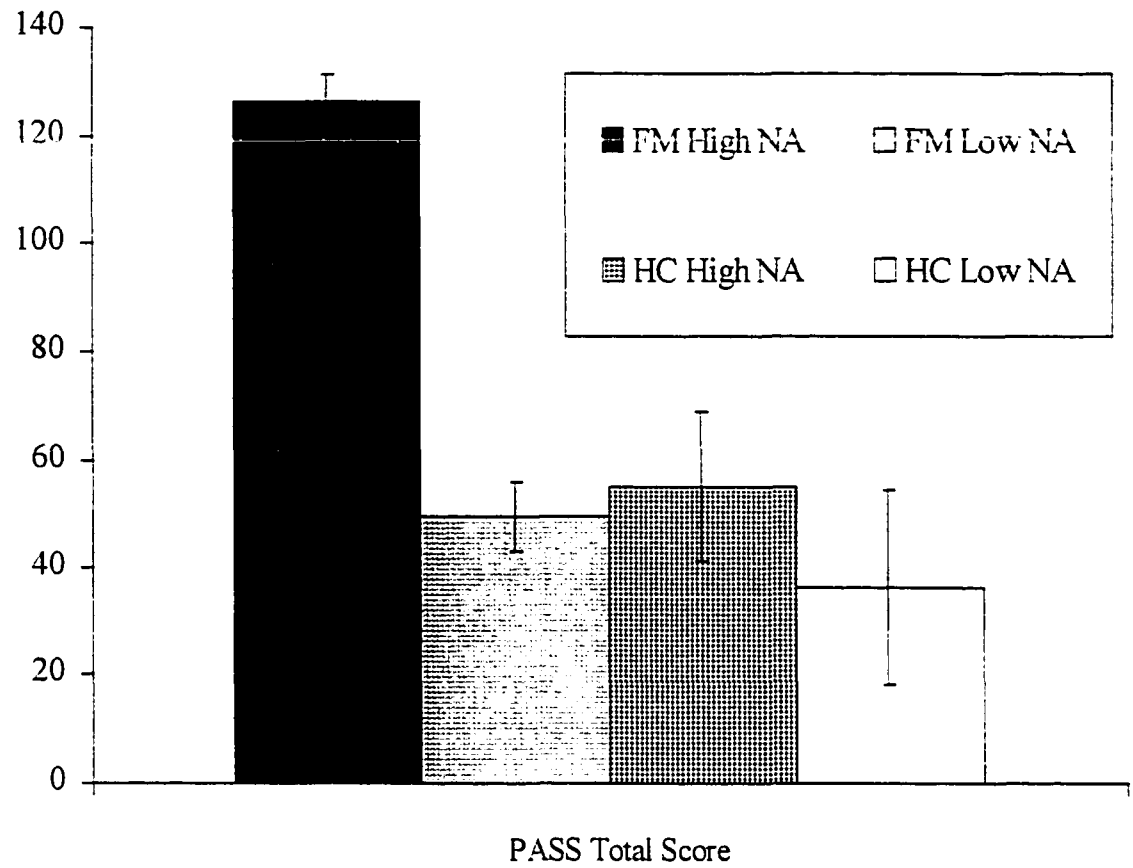

Figure 4. Mean (± *SE*) PASS total score at baseline for FM patients with high and low NA and healthy controls with high and low NA.

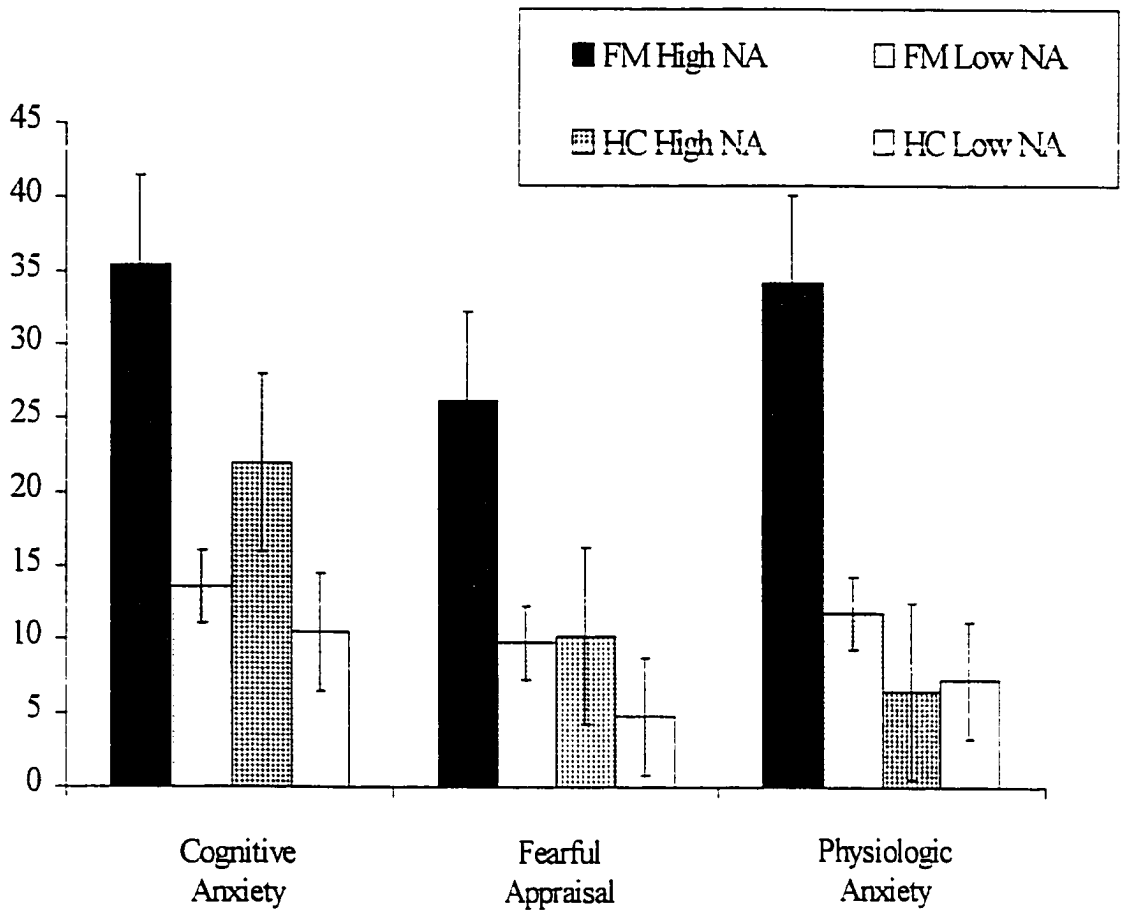

Figure 5. Mean (± *SE*) subscale scores of the PASS for FM patients with high and low NA and healthy controls with high and low NA.

Hypothesis 2: Report of Pain at Stimulated Sites in Response to Sham Stimulation

Table 2 shows the number of subjects in each group who reported pain during the sham stimulation procedure. A Fisher's Exact Test demonstrated that FM patients with high NA were more likely to report pain than FM patients with low NA during sham stimulation ($p = .04$).

Table 2

Number of Subjects Reporting Pain During Sham Stimulation

Group	Pain *yes*	Pain *no*
FM high NA	4	0
FM low NA	1	4
HC high NA	0	4
HC low NA	0	5

Hypothesis 3: No Increases in Sensory Intensity Ratings in Response to Sham Stimulation

Table 3 shows the means and standard errors of subjects' sensory intensity ratings at baseline and after stimulation.

Table 3

Mean (± SE) Sensory Intensity Ratings at Baseline and After Stimulation

Subject group	Baseline	After stimulation
FM high NA	1167.5 (64.0)	1432.5 (118.5)
FM low NA	90.2 (42.8)	97.4 (41.8)
HC high NA	165.3 (121.6)	168.3 (106.2)
HC low NA	62.4 (44.0)	64.8 (45.2)

ANOVA demonstrated a significant main effect of subject group ($F[1,14] = 65.75, p < .001$) and NA group ($F[1,14] = 83.28, p < .001$) and a significant subject group x NA group interaction ($F[1,14] = 59.10, p < .001$). There also was a significant main effect of rating phase ($F[1,14] = 14.56, p < .005$) and significant rating phase x subject group ($F[1,14] = 13.44, p < .005$) and rating phase x NA group interactions ($F[1,14] = 12.61, p < .005$). However, these effects were due largely to a significant rating phase x subject group x NA group interaction, $F(1,14) = 12.49, p < .005$). Follow-up paired t tests showed that only FM patients with high NA demonstrated a significant increase in sensory intensity ratings at the stimulated sites following sham stimulation ($t[3] = 5.07, p < .03$). This interaction is presented graphically in Figure 6.

Hypothesis 4: Pain and Sensory Unpleasantness Ratings in Response to Sham Stimulation

We then tested the hypothesis that only FM patients and healthy controls with high NA would report significant increases in pain intensity and sensory unpleasantness ratings in response to sham stimulation. The analyses of the pain ratings are presented first, followed by the analyses for sensory unpleasantness.

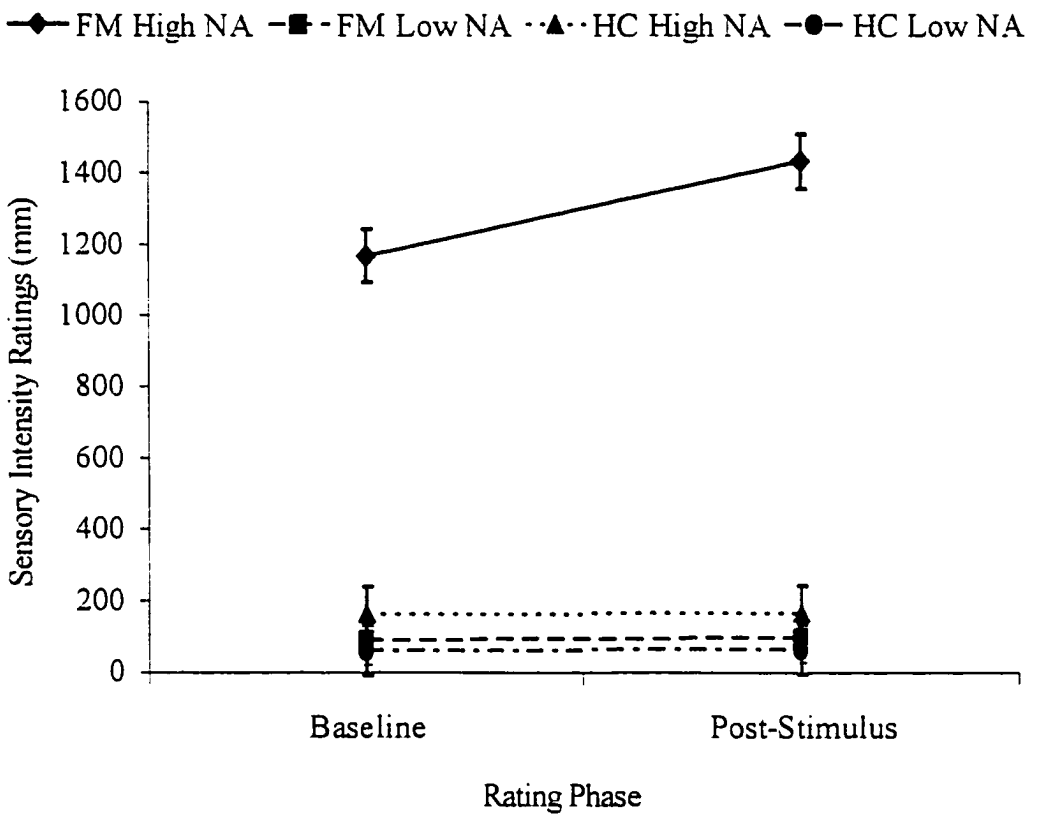

Figure 6. Mean (± *SE*) total sensory intensity ratings at baseline and after sham stimulation for FM patients with high and low NA and healthy controls with high and low NA.

Pain Ratings

Table 4 shows the means and SEs for pain ratings at baseline and after stimulation.

Table 4

Mean (± SE) Pain Ratings at Baseline and After Stimulation

Subject group	Baseline	After Stimulation
FM high NA	299.0 (20.0)	364.3 (32.5)
FM low NA	22.8 (13.3)	31.6 (15.7)
HC high NA	39.8 (25.9)	43.8 (33.4)
HC low NA	8.4 (4.5)	6.8 (3.3)

ANOVA demonstrated a significant main effect of subject group ($F[1,14] = 65.71, p < .001$) and NA group ($F[1,14] = 78.65, p < .001$) and a significant subject group x NA group interaction ($F[1,14] = 50.12, p < .001$). There also was a significant main effect of rating phase ($F[1,14] = 17.60, p < .005$) and significant rating phase x subject group ($F[1,14] = 15.46, p < .005$) and rating phase x NA group interactions ($F[1,14] = 11.59, p < .005$). However, these effects were due largely to a significant rating phase x subject group x NA group interaction, $F(1,14) = 7.79, p < .02$. Follow-up paired t tests showed that only FM patients with high NA demonstrated a significant increase in pain intensity ratings at the stimulated sites following sham stimulation, $t(3) = 5.07, p < .01$. This interaction is presented graphically in Figure 7.

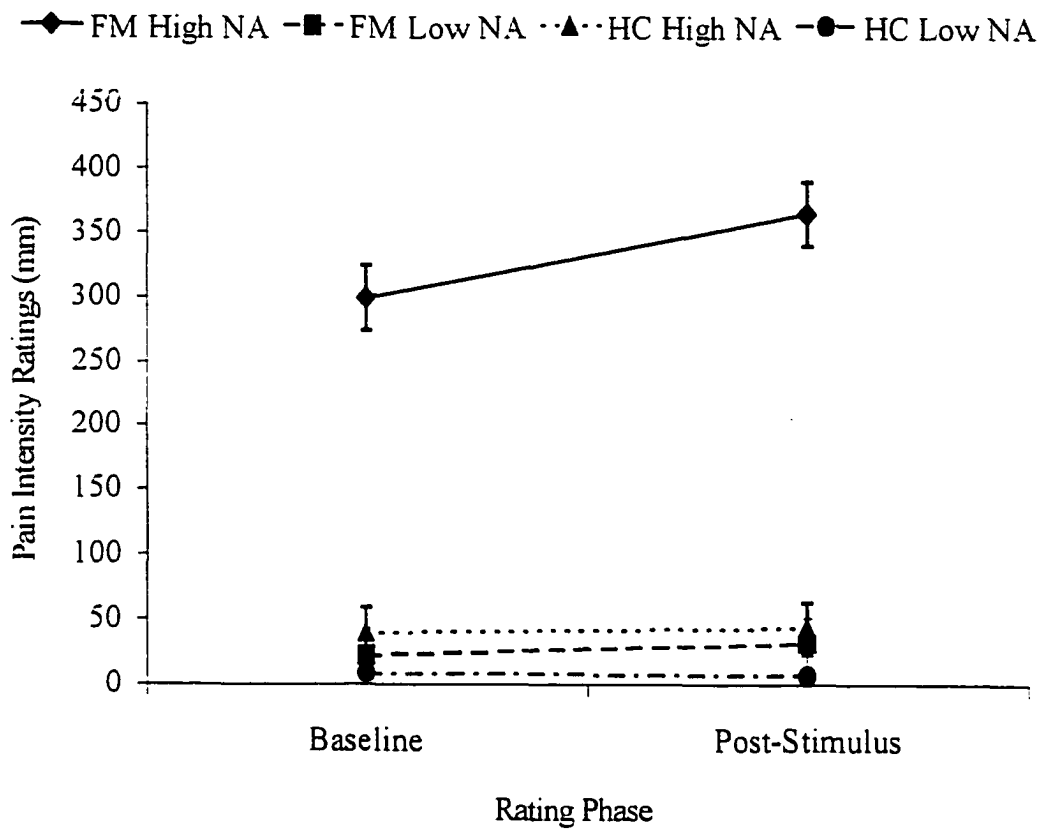

Figure 7. Mean (± *SE*) total pain intensity ratings at baseline and after sham stimulation for FM patients with high and low NA and healthy controls with high and low NA.

Sensory Unpleasantness Ratings

Table 5 shows the means and SEs for total sensory unpleasantness ratings at baseline and after stimulation.

Table 5

Mean (± SE) Sensory Unpleasantness Ratings at Baseline and After Stimulation

Subject group	Baseline	After stimulation
FM high NA	1113.3 (75.2)	1419.5 (131.5)
FM low NA	45.4 (18.9)	76.4 (34.8)
HC high NA	104.3 (61.9)	149.8 (89.3)
HC low NA	32.6 (17.0)	29.8 (13.9)

Results similar to those reported for sensory and pain intensity ratings were found on the sensory unpleasantness ratings. ANOVA demonstrated a significant main effect of subject group ($F[1,14] = 107.07$, $p < .001$) and NA group ($F[1,14] = 133.58$, $p < .001$) and a significant subject group x NA group interaction ($F[1,14] = 97.14$, $p < .001$). There also was a significant main effect of rating phase ($F[1,14] = 17.59$, $p < .005$) and significant rating phase x subject group ($F[1,14] = 10.57$, $p < .01$) and rating phase x NA group interactions ($F[1,14] = 12.76$, $p < .005$). However, these effects were due primarily to a significant rating phase x subject group x NA group interaction, $F(1,14) = 6.28$, $p < .03$. Follow-up paired t tests showed that only FM patients with high NA demonstrated a significant increase in pain intensity ratings at the stimulated sites following sham stimulation, $t(3) = 3.63$, $p < .02$. This interaction is presented graphically in Figure 8.

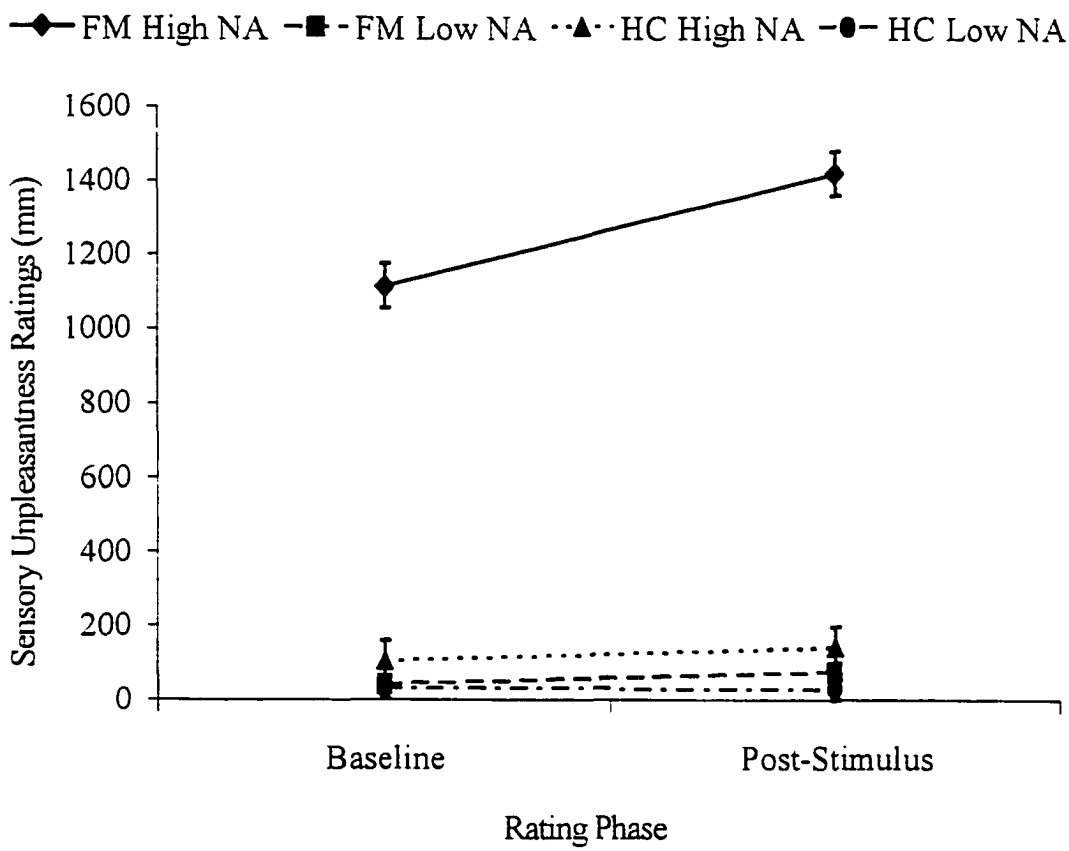

Figure 8. Mean (± *SE*) total sensory unpleasantness ratings at baseline and after sham stimulation for FM patients with high and low NA and healthy controls with high and low NA.

Hypothesis 5: POMS Tension/Anxiety Ratings in Response to Sham Stimulation

We then tested the hypothesis that sham TENS stimulation would produce increases in POMS Tension/Anxiety ratings among FM patients and healthy controls with high NA. Table 6 shows the means and SEs for Tension/Anxiety ratings at baseline and after stimulation.

Table 6

Mean (± SE) Tension/Anxiety Ratings at Baseline and After Stimulation

Subject group	Baseline	After stimulation
FM high NA	41.0 (3.9)	51.5 (6.1)
FM low NA	32.6 (1.4)	31.4 (1.4)
HC high NA	30.5 (0.5)	33.8 (1.9)
HC low NA	30.4 (0.4)	30.6 (0.4)

ANOVA revealed a significant main effect of subject group ($F[1,14] = 15.20, p < .005$) and NA group ($F[1,14] = 15.69, p < .005$) and a significant subject group x NA group interaction ($F[1,14] = 9.92, p < .01$). There also was a significant main effect of rating phase, $F(1,14) = 4.76, p < .05$, and a significant rating phase x NA group interaction, $F(1,14) = 6.37, p < .03$. Follow-up paired, one-tailed, t tests showed that both FM patients ($t[3] = 1.73, p = .09$) and healthy controls ($t[3] = 1.81, p = .08$) with high NA demonstrated a marginally significant increase in Tension/Anxiety ratings following sham stimulation. However, when the mean scores of the healthy controls with high NA are examined, there is very little increase in scores after sham stimulation and the variability among the subjects is extremely low. The scores of the patients with high NA tend

to demonstrate a greater increase in Tension/Anxiety scores following sham stimulation; however, there is greater intersubject variability.

Hypothesis 6: Right Anterior Cingulate, Anterior Insula, and Prefrontal Cortex rCBF in Response to Sham Stimulation

Next, we tested the hypothesis that sham TENS stimulation would produce significant rCBF increases in the right anterior cingulate cortex, right anterior insula, and right prefrontal cortex among FM patients and healthy controls with high NA. The results of these analyses are presented separately below.

Right Anterior Cingulate Cortex

Means and standard errors for rCBF in the right anterior cingulate cortex at baseline (Day 1) and sham stimulation (Day 2) are presented in Table 7.

Table 7

Mean (± SE) rCBF in the Right Anterior Cingulate Cortex at Baseline and During Sham Stimulation

Subject group	Baseline	Sham stimulation
FM high NA	3.52 (0.08)	3.74 (0.07)
FM low NA	3.59 (0.16)	3.50 (0.12)
HC high NA	3.88 (0.13)	3.72 (0.18)
HC low NA	3.68 (0.11)	3.69 (0.07)

ANOVA revealed a significant rating phase x subject group x NA group interaction, $F(1,14) = 8.24, p < .02$. Follow-up paired t tests showed that only FM patients with high NA demonstrated a significant increase in anterior cingulate cortex rCBF in response to

sham stimulation, $t(3) = 2.79$, $p < .05$. For clarity of presentation, this interaction is presented in two graphs. Figure 9 presents rCBF in the right anterior cingulate cortex among FM patients with high and low NA, and Figure 10 presents the same data for high and low NA healthy controls.

Right Anterior Insula

There were no significant main effects or interactions among the independent variables on rCBF in the right anterior insula.

Right Prefrontal Cortex

There were no significant main effects or interactions among the independent variables on rCBF in the right prefrontal cortex.

Hypothesis 7: Right Somatosensory Cortex rCBF in Response to Sham Stimulation

Consistent with our expectations, there were no significant main effects or interactions among the independent variables on rCBF in the right somatosensory cortex.

Hypothesis 8: Left Anterior Cingulate Cortex, Left Prefrontal Cortex, Left Anterior Insula, and Left Somatosensory Cortex rCBF in Response to Sham Stimulation

As we anticipated, there were no significant main effects or interactions among the dependent variables on rCBF in the left anterior cingulate cortex, left prefrontal cortex, left anterior insula, or left somatosensory cortex.

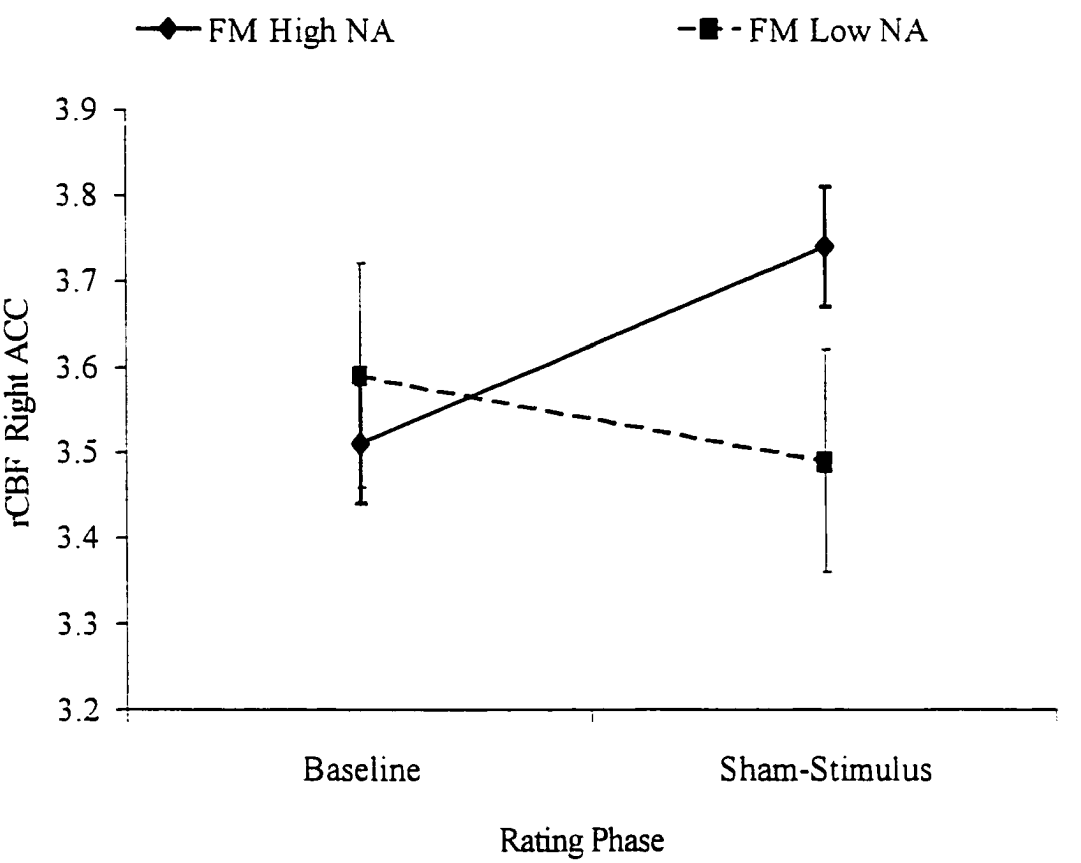

Figure 9. Mean (± *SE*) rCBF in the right anterior cingulate cortex at baseline and during sham stimulation for FM patients with high and low NA.

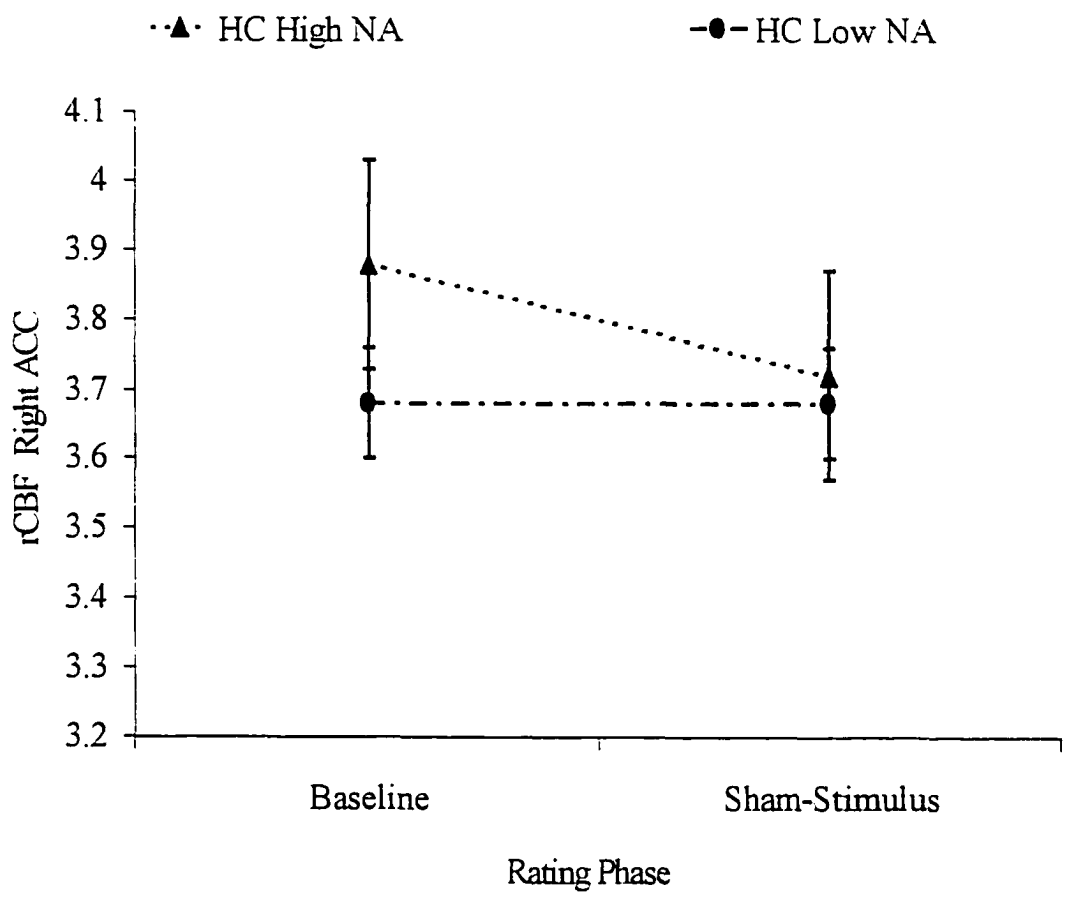

Figure 10. Mean (± *SE*) rCBF in the right anterior cingulate cortex at baseline and during sham stimulation for healthy controls with high and low NA.

Hypothesis 9: Use of Coping Strategies During Sham Stimulation

We used nonparametric Kruskal-Wallis tests to evaluate the hypotheses that FM patients with high NA would report significantly greater use of catastrophizing and praying/hoping coping strategies during sham stimulation than all other groups and that high NA controls would report significantly greater use of these strategies than FM patients and healthy controls with low NA. No other hypotheses were made concerning the other scales of the CSQ; however, to help us interpret the data, the remaining scales were analyzed. Table 8 shows the means and SEs for the catastrophizing, praying/hoping, and coping self-statement scales.

Table 8

Mean (± SE) Scores on Catastrophizing, Praying/Hoping, and Coping Self-Statement Scales During Sham Stimulation

Subject group	Catastrophizing	Praying/Hoping	Self-Statements
FM high NA	0.75 (0.48)	2.75 (1.11)	1.96 (0.85)
FM low NA	0.00 (0.00)	0.00 (0.00)	0.30 (0.30)
HC high NA	0.00 (0.00)	0.00 (0.00)	0.29 (0.17)
HC low NA	0.00 (0.00)	0.27 (0.27)	0.00 (0.00)

The Kruskal-Wallis analysis of catastrophizing scores revealed that FM patients with high NA strongly tended to engage in catastrophizing more frequently than the other subject groups in response to sham stimulation, $X^2 = 7.41$, $p = .059$. Moreover, FM patients with high NA were significantly more likely to use praying/hoping, $X^2 = 13.65$, $p = .003$, and coping self-statements, $X^2 = 10.12$, $p = .017$, during sham stimulation than all other groups. There were no significant effects on the remainder of the CSQ scales.

DISCUSSION

This was the first investigation to employ neuroimaging procedures to study the verbal and physiologic responses of women with FM and healthy controls who believed they might experience pain during exposure to sham TENS stimulation. It was found that FM patients with high NA and high pain anxiety levels reported significant increases in sensory intensity and unpleasantness as well as in pain intensity in response to sham stimulation. Neuroimaging revealed that this group of FM patients also showed a significant increase in rCBF in the right anterior cingulate cortex during sham stimulation. These effects were not found among FM patients with low levels of NA and pain anxiety or among healthy controls with high or low NA and low pain anxiety. In addition, the patients with high NA and high pain anxiety levels, compared to the other subject groups, more frequently reported using praying and hoping as well as coping self-statements as coping strategies during sham stimulation.

These results are consistent with preliminary findings produced by our experimental paradigm (Alexander et al., 1996). That is, the present findings replicate Alexander et al.'s (1996) initial report that women with FM and high NA produce significant increases in ratings of pain intensity and unpleasantness in response to sham TENS stimulation and preprogrammed visual EMG feedback indicating high levels of physiologic arousal. Similarly, both the present study and Alexander et al. found that women with FM and low NA show no changes in sensory intensity or unpleasantness during sham stimulation and high arousal feedback. Alexander et al. (1996) originally

suggested that high NA may predispose both patients and healthy individuals for the development of a hypervigilant, threat-focused, cognitive style. Therefore, high NA individuals are more inclined to perceive novel or ambiguous stimuli as threatening and, thus, report unpleasant sensory experiences in response to sham stimulation and high arousal feedback. However, neither the high NA nor the low NA healthy controls in the present study reported changes in their sensory experiences following sham stimulation. This suggests that individuals do not report altered sensory experiences in this experimental paradigm unless they suffer from persistent pain and high levels of pain anxiety.

Relationship Between Anxiety and Responses to Experimental Stimulation

Two recent investigations have documented the important role of pain-related anxiety in altering the responses of patients with chronic pain to experimental stimulation. For example, Peters, Vlaeyen, and van Drunen (2000) examined associations among NA, pain-related anxiety, and detection of a weak, gradually increasing electrical current applied to the skin during a dual attention task in persons with FM and healthy controls. It was found that neither status as an FM patient nor high NA alone was associated with the time required to detect the electrical stimulation. However, the FM patients with high pain-related anxiety did show decreased reaction times for detecting the electrical stimulation. Similarly, Crombez, Eccleston, Baeyens, van Houdenhove, and van den Broeck (1999) reported that the best predictor of chronic pain patients' responses on an attention-related task was high levels of both pain intensity and pain anxiety.

Rhudy and Meagher (2000) recently compared the effects of pain anxiety and pain-related fear on pain thresholds for radiant heat in healthy men and women. Similar to the methods used in the present study, pain anxiety was induced by instructing one group of subjects that they might receive painful electrical shocks from surface electrodes attached to one index finger prior to the radiant heat threshold procedure. However, no shocks actually were delivered. In contrast, pain fear was induced in another subject group by instructing them that they might experience pain and then delivering three painful electrical shocks prior to assessing the radiant heat pain thresholds. It was found that pain anxiety was associated with relatively low pain thresholds for radiant heat whereas pain-related fear decreased pain reactivity. The investigators suggested that fear induction may have activated descending pain inhibition systems, whereas anxiety induction may have enhanced subjects' attention to the radiant heat stimulation (i.e., produced hypervigilance for noxious stimulation).

To summarize, laboratory investigations of patients with chronic pain as well as healthy controls indicate that pain-related anxiety is associated with increased sensitivity to both painful and non-noxious stimuli. However, this literature has not explicated the physiologic processes that might underlie the association between anxiety and sensitivity to stimulation. The results of the present study suggest that, in highly anxious FM patients, the expectation of painful TENS stimulation may have led to altered sensory experiences and use of pain coping strategies in response to sham stimulation through activation of the right anterior cingulate cortex. Indeed, one might speculate that the expectation of an acute pain stimulus may evoke vivid memories of unpleasant pain experiences in persons with a history of chronic pain and pain-related anxiety that are

mediated by activation of limbic system structures. The following discussion examines several studies regarding the role of anterior cingulate cortex activity in pain anticipation and pain-related learning experiences.

Associations Among Anterior Cingulate Cortex Activity, Pain Anticipation, and Pain-Related Learning

Price (2000) recently reviewed a large number of studies that indicate that the anterior cingulate cortex plays an important role in processing the affective dimension of pain. The anterior cingulate cortex and other limbic structures receive direct spinal and thalamic inputs that may contribute to several aspects of pain affect such as arousal, autonomic and somatomotor activation, as well as directing attention and assigning response priorities (Price). In addition, the anterior cingulate cortex receives serial input from a somatosensory-limbic pathway that contributes cognitive evaluation to pain affect. Moreover, interactions between the anterior cingulate cortex and posterior cingulate cortex are involved in long-term emotional memory processes (Maddock, 1999). Indeed, recall of emotion-related memories produces the highest levels of anterior cingulate cortex activation among persons who report high levels of emotional awareness (Lane et al., 1998).

Several investigations have shown that the anterior cingulate cortex is involved in pain processing in healthy persons and in patients with FM. For example, Lenz et al., (1998) recently showed that, among healthy persons, painful cutaneous stimulation of the face with a CO_2 laser produced the largest evoked potentials over the contralateral anterior cingulate cortex and superior frontal gyri. With regard to FM patients, preliminary neuroimaging data from two independent laboratories indicate that patients, com-

pared to controls, show relatively low levels of activation in the contralateral thalamus and relatively high levels of activation in the right anterior cingulate cortex in response to painful pressure stimulation (Bradley, Sotolongo, Alarcón, et al., 1999; Petzke, Clauw, Wolf, & Gracely, 2000). Conversely, Wik, Fischer, Bragess, Finer, and Fredrikson (1999) recently studied the effects of hypnotic analgesia on brain activation in 8 patients with FM. They reported that hypnotic analgesia produced significant decreases in rCBF bilaterally in the anterior cingulate cortex and the posterior cingulate cortex; hypnotic analgesia also produced significant increases in rCBF bilaterally in the orbitofrontal and subcallosial cingulate cortices as well as significant activation in the right thalamus, and the left inferior parietal cortex.

The anterior cingulate cortex also is activated by expectations of pain as well as pain-related learning. For example, studies of primates and healthy humans indicate that anticipation of unpredictable, painful stimulation increases anterior cingulate cortex activity (Hsieh et al, 1999; Koyama, Tanaka, & Mikami, 1998). Similarly, repeated pairings of painful electric shocks and a neutral light stimulus produces a learned response in which the light stimulus alone reliably evokes increases in galvanic skin response levels and anterior cingulate cortex activity (Knight, Smith, Stein, & Helmstetter, 1999). The Hsieh and colleagues (1999) study is particularly relevant to the present study since it was found that anticipation of pain activated the right anterior cingulate cortex only when subjects could not predict the onset of the noxious stimulus and, thus, probably experienced relatively high levels of pain anxiety. In contrast, anticipation of predictable, painful stimulation led to decreased activity in the anterior cingulate cortex.

In the present study, sham TENS stimulation led to reports of pain and activation of the right anterior cingulate cortex in FM patients with high levels of pain anxiety.

A small number of studies have examined associations between activation of cortical or subcortical brain structures and pain-related learning or memory among patients with chronic pain. Lutzenberger, Flor, and Birmbaumer (1997) exposed patients with chronic back pain and healthy controls to acute experimental pain and later asked them to recall that pain experience as well as two additional, personally relevant, episodes of pain and stress while undergoing EEG. The chronic pain patients displayed a higher EEG complexity value for recall of personally relevant pain episodes than did the controls. However, the patients and controls did not differ in EEG complexity in the other experimental conditions, including those that were equal to the personally relevant pain episode in subjects' ratings of vividness and unpleasantness. The investigators concluded that associative learning may have connected many previously neutral stimuli to the experience of pain in the patients with chronic back pain. Moreover, these learned associations may have created a rich cortical network for pain that could be activated by multiple stimuli. Thus, chronic pain patients may be prone to experience pain in the absence of nociceptive input due to activation of the entire pain-related cell assembly by normally innocuous stimuli that are associated with pain memories.

Two recent case studies have shown that clinical pain experiences may be reproduced in persons with a history of recurrent or chronic pain in the absence of noxious stimulation. Lenz and associates (1994) delivered electrical stimulation to the thalamic ventrocaudal nucleus (Vc) of a man with a history of unstable angina and pain secondary to arachnoiditis. Stimulation of the Vc elicited chest pain identical to that associated with

previous episodes of angina. Importantly, the stimulation-evoked pain was not associated with electrophysiologic, biochemical, or clinical evidence of myocardial strain or injury. Lenz and colleagues (1995) subsequently reported that electrical stimulation of the Vc reproduced the affective and sensory dimensions of chest pain in a man with a history of chest pain associated with panic attacks. The investigators also noted that additional studies in their laboratory indicated that thalamic stimulation reproduced pain with a strong affective dimension only in patients with a history of spontaneous pain with a strong affective component. This may be because thalamic stimulation in patients with chronic pain also activates the anterior cingulate cortex (Davis et al., 2000) and thus, may evoke memories of affect-laden pain experiences.

The literature reviewed above indicates that the anterior cingulate cortex plays an important role in processing the affective dimension of pain in healthy persons and individuals with chronic pain syndromes such as FM. Anterior cingulate cortex activation also is associated with anticipation of unpredictable stimuli, evocation of pain-related memories and clinical pain experiences by electrical stimulation of the thalamus, as well as the development of learned associations between pain and environmental stimuli. Therefore, it is reasonable to conclude that in the present study, activation of the right anterior cingulate cortex mediated the pain responses of the FM patients with high levels of pain anxiety. Moreover, the results of the present study have important implications for understanding and modifying abnormal pain sensitivity in patients with FM.

Implications for Abnormal Pain Sensitivity in Fibromyalgia

Mechanisms of Abnormal Pain Sensitivity

It has been shown in numerous studies that persons with FM report pain in response to low intensity stimuli that are perceived by healthy persons as innocuous (Bradley & Alarcón, in press). Investigators have tended to offer explanations of abnormal pain sensitivity in FM that have emphasized either physiological constructs such as central sensitization (Weigent, Bradley, Blalock, & Alarcón, 1998) or psychosocial processes such as hypervigilance (McDermid, Rollman, & McCain, 1996). The results of the present study suggest that both physiological and psychosocial factors underlie the reports of unpleasant and painful sensory experiences of patients with FM and high levels of NA and pain anxiety during exposure to non-noxious stimulation. That is, high NA represents a characteristic tendency to experience negative emotions in response to a wide variety of stimuli. These individuals, then, may be especially likely to develop pain associated with a strong affective component, numerous learned associations among environmental events, and increased anterior cingulate cortex activity (Knight et al., 1999; Lane et al., 1998; Lutzenberger et al., 1997). An important consequence of this process may be high levels of pain anxiety as these individuals may come to expect to experience negative affect and pain in a wide variety of situations that are not aversive to FM patients with low NA or healthy persons regardless of their NA status. In the present study, the expectation of painful stimulation from the TENS unit may have evoked activation of the right anterior cingulate cortex (Hsieh et al., 1999) as well as encoded pain memories and learned pain responses (Lenz et al., 1995; Lutzenberger et al., 1997) in the FM patients with high NA and pain anxiety and thus led to their verbal responses

of pain during sham stimulation. Indeed, a similar process of activation of the anterior cingulate cortex, pain memories, and learned pain responses may underlie the hypervigilant responses of some FM patients to stimuli such as white noise and low intensity somatic stimuli described by McDermid and colleagues (1996). It is also reasonable to speculate that this process may also be involved in some FM patients' reports of chemical and environmental sensitivities (Clauw & Chrousos, 1997). Therefore, the experimental paradigm used in the present study may be a laboratory model of hypervigilance and thus account, in part, for the abnormal pain sensitivity of patients with FM and high levels of NA and pain anxiety.

Treatment of Pain in Patients with Fibromyalgia

Cognitive-behavioral therapy (CBT) represents the primary nonpharmacologic treatment for patients with FM. Although numerous uncontrolled studies suggest that CBT produces reliable improvements in pain and psychological status in patients with FM, the three well-controlled studies of CBT efficacy in FM have all produced negative findings (Bradley & Alberts, 1999; Bradley & Alarcón, in press). It is important to note, however, that none of the treatment protocols used in these controlled studies included a component for managing pain anxiety. Given that trait anxiety is one of the best predictors of treatment seeking in persons with FM (Kersh et al., 2000), it is highly likely that a substantial number of FM patients who entered these intervention studies were characterized by high levels of NA and pain-related anxiety. Thus, it may be that inclusion of a treatment component for pain anxiety would improve the patient outcomes produced by CBT.

Vlaeyen and Linton (2000) recently described treatment strategies that may benefit individuals with chronic pain and high levels of pain anxiety. They suggest that, consistent with usual CBT practice, treatment providers should provide an educational component with the aim of revising the patient's view that she suffers from a condition characterized by uncontrollable pain and distress to the belief that she can effectively manage her pain and anxiety (see McCracken, Spertus, Janeck, Sinclair, & Wetzel, 1999 for specific strategies that may be used in this component). Next, it is necessary to identify the stimuli that elicit anxiety in each patient (e.g., specific activities, repetitive movements, environmental events) as well as the negative expectations associated with each stimulus. The treatment provider and patient then must develop graded hierarchies for these stimuli that range from those that produce little anxiety or discomfort to those that the patient believes are well beyond her ability to experience without anxiety and pain. The final treatment component consists of graded exposure to the stimuli in patients' hierarchies so that patients may learn that they are capable of managing their anxiety when presented with these stimuli. For example, a patient may believe that riding a bicycle on a bumpy road will produce spinal compression and increased levels of pain. A graded exposure hierarchy, then, might include riding a stationary bicycle in the physical therapy setting before riding outdoors so that the patient may learn to manage her the anxiety and pain evoked by the act of bicycle riding before attempting to ride outdoors.

Vlaeyen and Linton (2000) noted that a graded exposure intervention is similar to graded activity treatments that are frequently used in behaviorally oriented, chronic pain treatment programs to help patients increase their activity levels. However, a preliminary

study suggests that a graded exposure intervention for patients with pain anxiety produces significantly greater reductions in pain anxiety, use of catastrophizing, and functional disability than a graded activity treatment (Vlaeyen, deJong, Geilen, Heuts, & van Breukelen, in press).

Graded exposure interventions may also improve the outcomes of pharmacological therapies for patients with FM and high levels of pain anxiety. It should be noted that although treatment with tricyclic antidepressants and other psychotropic medications (e.g., cyclobenzaprine, alprazolam) generally is superior to placebo in reducing pain or pain sensitivity at tender points, they produce little improvement in functional disability (Bradley et al., 2000). Similar to the controlled trials of CBT, it may be that the potential effects of pharmacotherapy on patients' daily activities are limited by pain anxiety. That is, FM patients with high levels of pain anxiety may be reluctant to engage in activities that they expect to increase their distress and pain even if they experience reductions in pain sensitivity with pharmacotherapy. In fact, pain anxiety is negatively related to physical capacity measures in chronic pain patients even after controlling for NA, depression, and pain severity (Burns et al., 2000). Thus, provision of graded exposure interventions with pharmacotherapy may produce greater improvement in these patients' quality of life than pharmacotherapy alone.

Directions for Future Research

The major shortcoming of the present study is the small number of subjects assigned to the four experimental conditions. The use of 18 subjects made it necessary to evaluate changes in rCBF and other variables within each condition rather than between

these conditions. In addition, the small sample size limited the generalizability of the reported results. It is important, then, to attempt to replicate the results of the present study with a greater number of subjects. Nevertheless, it should be noted that the present findings regarding the relationship between high NA and FM patients reports of pain and unpleasant sensory experiences during sham stimulation are in accord with findings reported by Alexander et al. (1996), who used a sample of 30 FM patients with high NA and 29 FM patients with low NA. In addition, the present findings regarding the relationship between high NA and pain anxiety and changes in anterior cingulate cortex activity among these FM patients during sham stimulation are consistent with previous studies regarding the effects of pain expectancies and classical conditioning of pain on activation of the anterior cingulate cortex (Hsieh et al., 1999; Knight et al., 1999).

Future studies might also be performed that further elucidate the mechanisms underlying the responses of FM patients with high pain anxiety to sham stimulation. For example, the Knight et al. (1999) investigation suggests that FM patients with high pain anxiety levels may also display physiologic responses indicative of autonomic arousal during exposure to sham stimulation or other stimuli that tend to evoke learned pain responses. Thus, attempts to replicate the present results should also evaluate heart rate, blood pressure, or similar variables during resting conditions and sham TENS stimulation. Similarly, future studies of the effects of stress and noxious stimuli on the verbal and physiologic responses of FM patients and controls would benefit from measurement of pain anxiety. Unpublished pilot work indicates that recall of personally relevant stressful episodes enhances FM patients' reports of pain unpleasantness during exposure to noxious thermal stimulation (L. A. Bradley, personal communication, June 2000). It

may be that FM patients with high levels of pain anxiety are especially likely to display this verbal response and to show activation of the right anterior cingulate cortex due to the activation of pain memories or pain-related learning.

Finally, the limited benefits of pharmacotherapy and CBT for patients with FM strongly suggests that future outcome studies should determine whether the effects of these interventions are associated with patients' levels of NA or pain anxiety. If significant relationships are found between patients' outcomes and these measures, it will be necessary to assess whether inclusion of anxiety-reduction treatments, such as that described by Vlaeyen and Linton (2000), may enhance the effects of both pharmacotherapy and CBT treatments for FM.

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APPENDIX A

INSTITUTIONAL REVIEW BOARD APPROVAL FORM

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Office of the Institutional Review Board for Human Use

Form 4 IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

The Institutional Review Board for Human Use (IRB) has an approved Multiple Project Assurance with the Department of Health and Human Services and is in compliance with 21 CFR Parts 50 and 56 and ICH GCP Guidelines. The Assurance became effective on January 1, 1999 and the approval period is for five years. The Assurance number is M-1149, identification number 01.

Principal Investigator	BRADLEY, LAURENCE A
Protocol Number:	F970501029
Protocol Title	*Role of Limbic Brain System in Abnormal Pain Perception in Fibromyalgia (FM)*

The IRB reviewed and approved the above named project on 6/9/99. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received FULL COMMITTEE review.

IRB Approval Date: 6/9/99

Date IRB Approval Issued: 6/9/99

Ferdinand Urthaler, M.D.
Ferdinand Urthaler, M.D.
Chairman of the Institutional Review Board
for Human Use (IRB)

Investigators please note:

The IRB approval consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.

The University of Alabama at Birmingham
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APPENDIX B

DAY 1 EMG INSTRUCTIONS

ELECTROMYOGRAPHY INSTRUCTIONS - Day 1

Experimenter:

The purpose of this task is to evaluate relationships between muscle fiber activity, your bodily sensations, and brain activity. This equipment is an electrophysiological recorder/stimulator. Using surface electrodes, like these, placed at various locations on your body we can detect minute changes in the electrical activity of groups of muscle fibers that correspond to changes in muscle tension and relaxation. The electrodes collect these signals and send them to this unit where they are amplified and recorded in that computer for future analysis. We call this type of recording ELECTROMYOGRAPHY or EMG. Have you ever heard of it? The EMG activity can also be displayed graphically on this monitor. See each of these lines corresponds to one electrode channel.

This equipment is even more specialized because, as I mentioned, it is also an electrophysiologic stimulator. It can deliver low levels of pulsed electrical stimulation through these same electrodes. This setup allows us to experimentally stimulate body areas with low levels of electricity, then record the response of your muscle fibers, and ask you to report changes in sensation. While the stimulator is capable of delivering a substantial shock, the levels of stimulation we use are low. However, today I will only be recording activity of your resting muscles and NOT delivering any electrical stimulation. Do you have any questions before we hook you up?

(PROCEED WITH ELECTRODE PLACEMENT)

(Gently wipe each site with alcohol pad) This alcohol pad cleans away any surface oil so that the electrode can make good surface to surface contact. These adhesive collars will hold the electrodes firmly in place and yet allow them to be easily removed.

(PLACE ELECTRODES OVER LEFT 2ND RIB, LEFT MID ULNA, LEFT MID TIBIA, AND LEFT UPPER BORDER OF TRAPEZIUS - SEE DIAGRAM)

OK, are you comfortable? We are now ready to begin the session. First, I need to verify that the contacts are good, and the recording equipment is functioning properly. Again, there will be no stimulation of your muscles today. I will only be recording your resting muscle activity. Please sit straight with your back against the chair back, feet flat on the floor, and place your arms on the table in front of you; palms down like this. It is important to hold very still since any movement can introduce erroneous signals. Ready?

(BEGIN TO DISPLAY SHAM BASELINE "TEST" RECORDING - 2 MIN DURATION)

See these squiggly lines? These represent your baseline muscle activity. We'll let it record for two minutes to make sure the recording equipment is working properly.

(TURN OFF SHAM EMG BASELINE "TEST" RECORDING AND PLACE LAMINATED MANNEQUIN DIAGRAM AND BASELINE RATING SCALES AND A SHARP PENCIL IN FRONT OF SUBJECT)

You can relax now. The actual task today will be identical to what you just experienced. Again, we are just assessing your resting muscle activity WITHOUT any stimulation.

We now need to establish your initial levels of sensation and feelings. First I want you to complete a questionnaire about your current feelings (ADMINISTER THE POMS). Next, we will use this diagram as a guide to the areas I want you to focus on which correspond to where we attached the electrodes.

Let's start with area 1 (POINT TO 1 ON MANNEQUIN DIAGRAM). I want you to close your eyes and focus on any sensations you are experiencing in this area. Continue to focus on your sensations until I tell you to stop (TIME 15 SEC). OK, open your eyes. See the rating scales each identified with a different word in front of you? Take the pencil and place a vertical mark on each line at a point that best represents your sensations at this point. Very good! Now let's go to point 2 (POINT TO 2 ON MANNEQUIN). Close your eyes and focus on any sensations at this point. Remember, continue to focus on your sensation until I tell you to stop (TIME 15 SEC). OK, open your eyes. Now, look at the rating scales that correspond to this point. Place a vertical mark on each line at a point that best represents your sensations at this point. Great! Now let's move to points 3 .....

(CONTINUE TO FOLLOW SAME PROCEDURE THROUGH ASSESSMENT OF TWO REMAINING POINTS. WHEN FINISHED, MOVE MANNEQUIN AND SCALES AWAY FROM THE FRONT OF THE SUBJECT)

Thank you. We will now begin the 6 minute recording procedure. As I mentioned earlier, this experience will be just like the "test" recording. I will not be delivering any stimulation to your muscles only recording what your muscles are doing at rest. During the recording procedure the nuclear medicine technologist will deliver the radioactive tracer so that we can determine the resting state brain activity. You probably will not feel anything while the tracer is being injected.

OK, please sit straight up in the chair, feet flat on the floor, and arms on the table in front of you, palms down just like before. Remember to hold very still during the recording process and focus on the sensations in the muscle areas being recorded.

(BEGIN TO DISPLAY SHAM BASELINE RECORDING - 6 MIN TOTAL DURATION)

(TURN OFF SHAM EMG RECORDING AND PLACE LAMINATED MANNEQUIN DIAGRAM AND RATING SCALES AND A SHARP PENCIL IN FRONT OF SUBJECT; COMPLETE RATING SCALES AS DESCRIBED ABOVE)

APPENDIX C

DAY 2 EMG INSTRUCTIONS

ELECTROMYOGRAPHY INSTRUCTIONS - Day 2

Experimenter:

The purpose of the today's task is to evaluate relationships between muscle fiber activity, your bodily sensations, and brain activity during low level electrical stimulation of your muscles. To remind you this equipment is an electrophysiological recorder/stimulator. Using surface electrodes, like these, placed at various locations on your body we can detect minute changes in the electrical activity of groups of muscle fibers that correspond to changes in muscle tension and relaxation. The electrodes collect these signals and send them to this unit where they are amplified and recorded in that computer for future analysis. We call this type of recording ELECTROMYOGRAPHY or EMG. The EMG activity can also be displayed graphically on this monitor. AS before, each of these lines corresponds to one electrode channel.

This equipment is even more specialized because, as I mentioned, it is also an electro-physiologic stimulator. It can deliver low levels of pulsed electrical stimulation through these same electrodes. This setup allows us to experimentally stimulate body areas with low levels of electricity, then record the response of your muscle fibers, and ask you to report changes in sensation. While the stimulator is capable of delivering a substantial shock, the levels of stimulation we will use today are low. Do you have any questions before we hook you up?

(PROCEED WITH ELECTRODE PLACEMENT)

(Gently wipe each site with alcohol pad) This alcohol pad cleans away any surface oil so that the electrode can make good surface to surface contact. These adhesive collars will hold the electrodes firmly in place and yet allow them to be easily removed.

(PLACE ELECTRODES OVER LEFT 2ND RIB, LEFT MID ULNA, LEFT MID TIBIA, AND LEFT UPPER BORDER OF TRAPEZIUS - SEE DIAGRAM)

OK, are you comfortable? We are now ready to begin the session. First, as before, I need to verify that the contacts are good and the recording equipment is functioning properly. There will be no stimulation of your muscles during this "test" recording. Please sit straight with your back against the chair back, feet flat on the floor, and place your arms on the table in front of you; palms down like this. It is important to hold very still since any movement can introduce erroneous signals. Ready?

(BEGIN TO DISPLAY SHAM "TEST" EMG - 2 MIN DURATION)

As before these squiggly lines represent your baseline muscle activity. We'll let it record for two minutes to make sure the recording equipment is working properly.

(TURN OFF BOGUS EMG BASELINE AND PLACE LAMINATED MANNEQUIN DIAGRAM AND BASELINE RATING SCALES AND A SHARP PENCIL IN FRONT OF SUBJECT)

You can relax now.

We now need to establish your initial levels of sensation and feelings. First I want you to complete this questionnaire about your current feelings (ADMINISTER POMS). Next, we will use this diagram as a guide to the areas I want you to focus on which correspond to where we attached the electrodes.

Let's start with area 1 (POINT TO 1 ON MANNEQUIN DIAGRAM). I want you to close your eyes and focus on any sensations you are experiencing in this area. Continue to focus on your sensations until I tell you to stop (TIME 15 SEC). OK, open your eyes. See the rating scales each identified with a different word in front of you? Take the pencil and place a vertical mark on each line at a point that best represents your sensations at this point. Very good! Now let's go to point 2 (POINT TO 2 ON MANNEQUIN). Close your eyes and focus on any sensations at this point. Remember, continue to focus on your sensation until I tell you to stop (TIME 15 SEC). OK, open your eyes. Now, look at the rating scales that correspond to this point. Place a vertical mark on each line at a point that best represents your sensations at this point. Great! Now let's move to points 3 .....

(CONTINUE TO FOLLOW SAME PROCEDURE THROUGH ASSESSMENT OF TWO REMAINING POINTS. WHEN FINISHED, MOVE MANNEQUIN AND SCALES AWAY FROM THE FRONT OF THE SUBJECT)

Thank you. We will now begin the stimulation and recording procedure. As I mentioned earlier, the device will deliver low levels of pulsed electrical stimulation through each electrode. It will then record the resulting EMG activity. I want to reassure you that this type of stimulation causes no physical damage or permanent alterations. Any sensory changes you experience should dissipate within 1 to 2 hrs.

Each stimulus/recording cycle will consist of 20 sec of electrical stimulation followed by 40 sec of EMG recording. When stimulation is occurring, the red light on top of this box (POINT TO LIGHT) will be on; and the EMG lines will all be flat. After the 20 sec of stimulation, the EMG recording will begin. During recording, the red light will be out; and you will see the recorded EMG activity here (POINT TO MONITOR). In general, the bigger the squiggly lines, the greater the muscle fiber activity. Remember, it is extremely important for you to hold very still during the stimulus/recording cycles. As before, the nuclear medicine technologist will deliver the radioactive tracer so that we can determine your brain activity while your muscles are being stimulated. You probably will not feel the tracer being injected.

During the stimulus/recording cycles, we want you to focus on your sensations. You may feel changes in sensation at the areas immediately surrounding the electrodes and also at

other locations throughout your body. Some individuals find these changes to be uncomfortable while others do not. We are interested in your unique sensory experiences. After we complete the stimulation and recording cycles, we will ask you to complete another set of sensory ratings like the ones you just finished.

I know this is a complex and possibly, confusing procedure. It's really important that you completely understand it, so, please tell me in your own words your understanding of the procedure and what you expect to occur.

OK, please sit straight up in the chair, feet flat on the floor, and arms on the table in front of you, palms down just like before. Remember to hold very still during the stimulus/recording process and focus on your body sensations.

(BEGIN TO DISPLAY SHAM STIMULATION EMG - 6 MIN TOTAL DURATION)

(TURN OFF SHAM EMG STIMULATION AND PLACE LAMINATED MANNEQUIN DIAGRAM AND STIMULATION RATING SCALES AND A SHARP PENCIL IN FRONT OF SUBJECT; COMPLETE RATING SCALES AS DESCRIBED ABOVE BUT ADD THE DIRECTIONS FOR THE PRS BELOW)

Next, I want you to identify the type of sensation you experienced at each of these points during the stimulation procedure. Circle the best word to describe your experience (ADMINISTER PRS).

GRADUATE SCHOOL
UNIVERSITY OF ALABAMA AT BIRMINGHAM
DISSERTATION APPROVAL FORM
DOCTOR OF PHILOSOPHY

Name of Candidate Kristin R. Alberts

Graduate Program Psychology

Title of Dissertation An Investigation of the Role of Negative Affectivity on Abnormal Pain Perception and Functional Brain Activity in the Limbic System of Women with Fibromyalgia (FM)

I certify that I have read this document and examined the student regarding its content. In my opinion, this dissertation conforms to acceptable standards of scholarly presentation and is adequate in scope and quality, and the attainments of this student are such that she may be recommended for the degree of Doctor of Philosophy.

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Date 1/11/2001