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13. ABSTRACT ***(Maximum 200 Words)***

Several expert panels have concluded that the constellation of overlapping symptoms characterizing PGWI is not due to a single illness or cause. Rather, physical, emotional, and immune stressors are capable of causing these types of non-specific symptoms. The pattern of biological responses from these stressors depends on both properties of the stressor, as well as characteristics of the host. The major components of the stress response include the autonomic nervous system and the hypothalamic pituitary adrenal (HPA) axis,. Alterations of these systems from normal function have been identified in a number of conditions similar to PGWI such as chronic fatigue syndrome (CFS) and fibromyalgia (FM). In this project we have been intensively studying the activity of the biological stress response in individuals with PGWI, to determine if such persons display the same blunting of the stress response noted in FM and CFS. Parts of this project have been incorporated into a newer, more expansive project comparing physiologic alterations in several illnesses presenting with poorly defined, multisystem symptoms. A multidisciplinary team of investigators with established expertise in FM and CFS, and the measurements of neuroendocrine and autonomic function. In the current project a major finding has been in the area of pain response to physical stimuli. We found that stimulation with adequate pressure to cause similar pain in control and FM subjects resulted in 19 regions of increased regional cerebral blood flow in healthy controls and 12 significant regions in FM subjects. Since pain is one of the hallmark symptoms of FM, these data, along with other data collected, strongly suggests an augmentation of pain sensitivity in patients with FM that may be related to alterations in HPA and autonomic function. These studies are significantly expanded in the new project.

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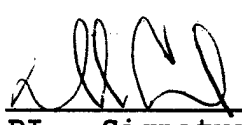

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INTRODUCTION

A significant number of veterans of the 1990 – 1991 Persian Gulf (PG) deployment developed a constellation of symptoms and syndromes which have defied explanation, and have been termed Persian Gulf War Illnesses (PGWI). Several expert panels have been convened to examine the potential causes for these illnesses. There is agreement that this is not a single illness due to a single cause, and that most potential environmental exposures are unlikely to have contributed to this illness.[1, 2] The consensus is that physical, emotional, and immune stressors are capable of causing these types of non-specific symptoms. There are several reasons for the conclusion that "stress" may be responsible for many of the symptoms seen in PGW veterans. Similar illnesses have been noted after nearly every major conflict, although these syndromes have had different names and attributions (e.g. Post Traumatic Stress Disorder [PTSD] and Agent Orange after the Vietnam conflict, "shell shock" after World War I, etc.).[3, 4] More importantly, similar stress-related disorders occur commonly in the general population, with the currently preferred semantic terms being fibromyalgia (FM), chronic fatigue syndrome (CFS), somatoform disorder, and multiple chemical sensitivity (MCS).[5-9] It is therefore plausible that the majority of the symptoms experienced by individuals with PGWI result from exposure to a variety of stressors experienced in conjunction with deployment to the PG. It is also likely that the symptoms noted in PGV fall within a continuum in which FM and CFS would also be included.

The pathogenesis of symptoms in illnesses such as FM, CFS and PGWI is controversial. Some contend that these are primarily psychiatric conditions.[10, 11] Although there are clearly psychological co-morbidities with these illnesses, there are also substantial data suggesting that there is a physiologic basis for the symptoms these individuals experience which may be mechanistically similar to the neurohormonal dysregulation of the human stress response that is common to FM and CFS.

Historical overview of the human stress response.

The human stress system has been the subject of intense study. Historically, Cannon and Selye were particularly instrumental in shaping our ideas regarding the essence of this response. Cannon suggested that "homeostasis" was physiologically achieved by the activation of compensatory and competing systems within the body, although generally avoiding reference to "stress".[12] Selye was the first to popularize the notion that "stress" was a scientifically credible concept, and began to establish the relationship between abnormalities in the stress response, and the development of disease.[16]

Continued research demonstrated that this system is considerably more complex than

originally proposed. Although Selye suggested nonspecificity of the stress response, it is now clear that different types of stressors elicit markedly different biological responses.[17-19] The pattern of biological response depends on both properties of the stressor (e.g., type and intensity), as well as characteristics of the host (e.g., psychological status, novelty and ability to cope with the stressor). We now also recognize that the control of this system is more complicated than originally postulated, with central and peripheral interrelationships between synergistic and competing systems.

Relevant components of the stress response.

The major components of the stress response include the neural and adrenomedullary components of the sympathetic nervous system, the hypothalamic pituitary adrenal (HPA) axis, and the parasympathetic nervous system. Other less prominent components which will not be discussed in this proposal include the vasopressin, renin-angiotensin, and endogenous opioid systems.

The *sympathoneural* system consists of nerve networks which begin in the locus ceruleus and other cell groups in the medulla and pons, and innervate a number of tissues: blood vessels, heart, reticuloendothelial organs, and salivary and sweat glands. The primary neurotransmitter released in this system is norepinephrine. Examples of stressors which lead to a prominent sympathoneural response include exercise and orthostasis.[19] The *adrenomedullary* component of the sympathetic response consists of the cells in the adrenal medulla which release (primarily) epinephrine in response to preganglionic spinal input. The functions of epinephrine have been well-characterized, and include increased heart rate and cardiac contractility, bronchodilation, relaxation of visceral smooth muscle, shunting of blood flow to muscles, and stimulation of the reticular activating system. Activities which elicit prominent adrenomedullary responses include hypovolemia, hypoglycemia, and both pain and emotional distress.[19]

The HPA axis exerts the primary control of the release on glucocorticoids from the adrenal cortex. This response begins with corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) release in the hypothalamus, eliciting corticotropin (ACTH) release from the pituitary, which acts on the adrenal glands. The acute and chronic effects of both steroid deficiency and excess are well described.[15-21] Stressors which have a prominent HPA effect are similar to those that accompany sympathetic adrenomedullary activity.

The parasympathetic nervous system (PNS) can augment the effects of the sympathetic nervous system by withdrawing input, or attenuate sympathetic responses with increased output. This system also controls many vegetative functions. The principal neurotransmitter in this system is acetylcholine. Although the PNS has close interrelationships with the sympathoneural response, the adrenomedullary sympathetic system appears to function fairly autonomously from the PNS.[21]

Central control of the stress systems.

The central control of the stress response is quite complex. Current evidence supports a pivotal role of CRH in coordinating the stereotypical responses to stressors, as noted.[12,20,21] Many factors can raise or lower CRH and thus effect the overall stress response. In addition to the general level overall activity of this system, however, there is "fine tuning" of each of the effector systems that can occur by a number of direct and feedback mechanisms, [12,21,20] and other compounds such a AVP act in synergy with CRH to lead to these changes.[12,21]

Overview of FM, CFS, and related conditions.

Although FM is defined on the basis of chronic widespread pain, and a requisite number of minor symptoms, there is general agreement that there is considerable overlap with other systemic syndromes (e.g. chronic fatigue syndrome, somatoform disorders and multiple chemical sensitivity), and numerous organ-specific conditions such as irritable bowel syndrome, migraine and tension headaches, and a number of regional pain syndromes.[5,7,31-33] Several studies have shown that the symptoms experienced by PGW veterans with unexplained illnesses are very similar to those encompassed within this spectrum of illness, especially when this is viewed in entirety.[34-37] Within this spectrum, FM and CFS are the best studied from a physiologic standpoint.

Accumulated information suggests that the biological stress response is blunted in the chronic phase of FM. The observed changes are consistent with a low central CRH state, although there are many other plausible explanations. The expected biological consequences of a low central CRH state are similar to those seen in FM and the opposite of that seen in acute stress: hypoarousal or fatigue, diffusely increased peripheral and visceral nociception, and decreased sympathetic tone.

There have been abnormalities have also been noted in most of the hypothalamic-pituitary axes in FM; and, when viewed in aggregate, these findings suggest a low central CRH state and reduced responsiveness of the adrenal glands to ACTH. In CFS there is a blunting of the HPA axis including low 24 hour free cortisol excretion, increased adrenocortical sensitivity to ACTH, and attenuated ACTH responses to CRH. These abnormalities are consistent with a tertiary (hypothalamic) adrenal insufficiency [38,39]. Neuroendocrine studies in FM yield similar results, with a relative hyporesponsiveness of the adrenal glands (decreased production of cortisol in response to CRH or ACTH), low 24 hour urine free cortisol, but an exaggerated pituitary response to CRH.[40,41] Although these data appear to indicate a primary rather than *tertiary* (hypothalamic) adrenal insufficiency as noted in CFS, the aggregate data in FM indicate hypothalamic CRH hyposecretion as well. For example, the normal circadian rhythmicity is disturbed in this condition, indicated by a deficient morning cortisol surge, and supranormal cortisol values are noted during other times of the day.[14,41,42]

Further evidence of a hypothalamic defect of the stress response in FM is found in data examining the response to various stressors in FM. Van Denderen exercised ten FM subjects and controls, and cortisol levels paradoxically fell rather than rose in response to physical exertion.[43] Adler and colleagues found that FM subjects demonstrated statistically significant decreases in baseline ACTH, and an attenuated increase in ACTH in response to hypoglycemia.[44]

Because of the complexity and plasticity of the HPA axis, it is more appropriate to emphasize the similarities between the HPA axis in FM and CFS than to accentuate minor differences: these conditions are both characterized by an underactive and blunted "stress response" at the tissue level. Similar changes in the HPA axis are seen in post-traumatic stress disorder, atypical depression, and seasonal affective disorder [12]. These changes are opposite to those seen in melancholic depression, which is characterized by chronically increased stress system activity.[12,20,45] The reason for these opposite changes in the function of the stress response in clinically similar disorders is not understood. Some have hypothesized that *any* disturbances in stress system activity, be it increased or decreased, can upset homeostasis, and, thus, impair performance [12,46]. Alternatively, subtypes of major depression may have biologically disparate causes [47]. A closer examination may reveal that only certain subtypes of depression are associated with FM and CFS. It is possible that the HPA abnormalities are surrogates for other neurochemical changes that lead to the pain and fatigue seen in these conditions. Other hypothalamic-pituitary axes abnormalities have also been noted. Insulin-like growth factor (IGF-1) has been shown to be low in individuals with FM. This finding is not specific for FM, in that it is also low in a number of other rheumatic diseases such as osteoarthritis and rheumatoid arthritis.[48-50] The defect in IGF-1 synthesis in FM is likely due to a defective hypothalamic response.[50] This is expected as chronic stress leads to suppression of growth hormone and IGF-1 secretion [51] while acute stress typically leads to an elevation in growth hormone (and therefore IGF-1). Additionally, individuals with FM display blunted secretion of thyrotropin and thyroid hormones in response to thyroid releasing hormone (TRH) which once again suggests a blunted stress response.[52]

Abnormalities in autonomic function in FM and CFS.

There have been several studies suggesting that autonomic function is abnormal in FM and CFS. Elam and colleagues studied muscle sympathetic activity and found it to be reduced at baseline in FM [53]. Qiao demonstrated that FM subjects display decreased microcirculatory vasoconstrictor response to both cold and auditory stimulation, and a high baseline skin conductance, both suggesting either diminished sympathetic or elevated cholinergic tone [54]. Bennett and colleagues found that FM subjects had a higher than expected rate of a positive Nielson test (cold induced increased in finger systolic blood pressure), and displayed an increased density of α_2 receptors on platelets [55]. The notion that central sympathetic input is diminished in FM is also supported by data showing that the principal metabolite of norepinephrine (3-methoxy-4-hydroxyphenethylene), is low in the CSF of FM subjects (the metabolite of norepinephrine is measured because the parent compound is undetectable in the CSF)

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Perhaps the most consistent finding regarding autonomic function is that FM subjects have an impaired catecholamine response to a variety of different stressors; in different studies exercise, muscle contraction, and noise led to sympathetic responses which were diminished when compared to control groups [43,53,54]. In the study noted by van Denderen above, submaximal exercise, which induces primarily a sympathoneural response, led to an attenuated norepinephrine response [43]. In the Adler study, hypoglycemia, which is primarily a stimulus for adrenomedullary activation, elicited an attenuated rise in epinephrine in the FM subjects. Martinez-Lavin performed tilt table testing in 19 subjects with FM, and found a decrease in the rise of the low frequency component of heart rate variability, and interpreted this as indicative of a diminished sympathetic response (for further discussion of interpretation of heart rate variability analyses, see Preliminary Data) [57]. Vaeroy and colleagues noted that FM subjects displayed a diminished vasoconstrictory response to a cold pressor test; this stressor elicits primarily a sympathoneural response [58]. Although the autonomic nervous system has not been as extensively studied in CFS, these subjects have been noted to experience a high prevalence of neurally mediated hypotension on tilt table testing, which in turn is felt to be related to autonomic dysfunction [59].

The above information supports the hypothesis that there is blunting of the human stress response in subjects with FM and CFS. The aggregate data suggest abnormalities in both the hypothalamic pituitary axes and the adrenomedullary and sympathoneural components of the sympathetic nervous system. However, the physiologic significance of these changes is not clear. In any of these studies, only a minority of subjects display *abnormal* HPA or sympathetic function. Although there are differences in group means in many of these parameters, there is considerable overlap among the individual values for the FM and control groups.

We have performed a series of studies which have attempted to better delineate HPA and autonomic function in persons with FM and CFS and believe that, given the background information and preliminary studies, that there is blunting of stress response function in FM and CFS which justifies examining these physiologic properties in PGWI.

BODY OF REPORT

Objectives:

The purpose of this proposal was to intensively study the activity of the biological stress response in individuals with PGWI, to determine if such persons display the same types of blunting of stress response function that is noted in FM and CFS. This proposal was

intended to link two DOD-funded groups to offer a unique manner of examining PGWI, integrating the best features of population-based studies, and intensive clinical evaluations. The Klemm Analysis Group was funded to assess the symptoms of 20,000 Persian Gulf and Persian Gulf-era women veterans (The Persian Gulf Women's Health Linkage Study - PGWHLS). The proposed study intended to recruit a representative sample of Persian Gulf women with unexplained illness, and a control group of Persian Gulf women veterans who were asymptomatic but matched for location of deployment, age, and race. These individuals were then to be brought to the Clinical Research Center at Georgetown, and examined with a battery of tests examining function of the human stress response of which most have been shown to be abnormal in individuals with FM and CFS. Both groups would then also undergo a comprehensive clinical and psychological evaluation. This joint effort would significantly strengthen the results of both studies and examine whether objective results validated self-report data on a representative subset of the large cohort. It would also have permitted performance of sophisticated physiologic testing on an unbiased and better matched sampling of cases and controls.

Unfortunately, the PGWHLS from which the cohort for this study was to be drawn was delayed past a point of usefulness to our study. Unable to collect a sufficiently large study group, the grant's original objectives were revised. The original objectives of the grant were to:

1) ***To perform clinical and psychological evaluations on a representative sampling of symptomatic and asymptomatic individuals who were deployed to the GW.***

2) ***To determine if PGWI subjects display evidence of a low central corticotropin releasing hormone (CRH) state***

3) ***To determine if PGWI subjects display evidence of impaired activation of both the adrenomedullary and sympathoneural components of the sympathetic nervous system.***

4) ***To determine if PGWI subjects have evidence of decreased peripheral responsiveness to catecholamines.***

5) ***To determine if significant abnormalities of one or more of these various components of the stress response are present in a statistically significant proportion of individuals presenting with PGWI and whether the nature of the abnormalities predict the predominant clinical symptoms.***

The original objectives are now incorporated in a study comparing physiologic alterations in several illnesses presenting with poorly defined, multisystem symptoms.[98]

That project will be performed by a multi-disciplinary team of investigators with established expertise in FM and CFS, as well as in the measurement of neuroendocrine and autonomic function.

The revised objectives of this study are to use functional magnetic resonance imaging (fMRI) to evaluate the pattern of cerebral activation during the application of painful pressure and determine whether this pattern is augmented in patients with fibromyalgia (FM) compared with controls. Although this study does not directly address our initial objective of determining whether a continuum exists in which post-deployment syndromes (represented by PGWI) exists amongst other poorly defined, multisystem syndromes, we believe that the study we conducted is suggestive of means of testing for a possible continuum of functional irregularities amongst the poorly defined, myltisymptom, multisystem conditions commonly found within the civilian population and similarly expressed conditions seen in a subset of military servicemembers returning from stressful deployments. Further, results of our study should lead to future studies which can more definitively define and address this issue. Essentially such studies are likely to have one of three conclusions: stress response function in post-deployment, multisystem symptomatic military subjects is the same as in FM/CFS, normal, or abnormal but different than FM/CFS. If it is demonstrated that stress response function is the same as FM/CFS, this would add considerable credence to the hypothesis that PGWI and other post-deployment syndromes fall within the continuum encompassed by FM, CFS, and related disorders. Although this would not exclude a toxic or environmental exposure as the cause of this symptom complex, it would decrease the likelihood that this is the sole causation. If, on the other hand, we show that stress response function is normal in PGWI subjects or other post-deployment individuals suffering from chronic multisystem complaints, it would seem less likely that this illness is caused by exposure to stressors, and would suggest that this is a different illness than FM/CFS. Finally, if we eventually identify a unique abnormality in stress response function within any of the conditions currently hypothesized to form a continuum, this would be of obvious import, since this would lead to re-examination of the pathophysiology of each condition and of post-deployment conditions, and such findings (of physiologically distinctive processing patterns) would suggest appropriate avenues of research to aid individuals returning with significant multisystem symptomology from future military deployments.

Our current study will, specifically permit a limited testing of the hypothesis that physical evidence of altered physiologic processing in the central nervous system of fibromyalgia patients compared to normal controls can objectively determined. However, results of this study are expected to add to evidence confirming or refuting the hypothesis that a continuum of functional irregularities amongst the poorly defined, myltisymptom, multisystem conditions exists which likely includes post-deployment syndromes (represented by PGWI).

METHODS

Methodology is presented in the attached article: Gracely R, Petzke F, Wolf JM, Clauw

DJ. Functional Magnetic Resonance Imaging Evidence of Augmented Pain Processing in Fibromyalgia. Accepted for publication in volume 46, Arthritis and Rheumatism.

RESULTS

Detailed results are included in the paper noted under "Methods" above. Briefly, results indicated that "stimulation with adequate pressure to cause similar pain in both groups resulted in 19 regions of increased regional cerebral blood flow in healthy controls and 12 significant regions in patients. Increased fMRI signal occurred in 7 regions common to both groups. A common region of decreased signal was observed in ipsilateral primary somatosensory cortex. In contrast, stimulation of controls with the same amount of pressure that caused pain in patients resulted in only 2 regions of increased signal, neither of which coincided with a region of activation in patients. Statistical comparison of the patient and control groups receiving similar stimulus pressures revealed 13 regions of greater activation in the patient group. In contrast, similar stimulus pressures produced only 1 region of greater activation in the control group."

Discussion

The following discussion is reproduced verbatim from our paper (noted under "Methods" above) for the convenience of individuals reviewing this report. "In FM patients, application of mild pressure produced subjective pain reports and cerebral responses that were qualitatively and quantitatively similar to many of the effects produced by application of at least twice the pressure in control subjects. Activation were observed in the contralateral primary and secondary sensory cortices, consistent with findings using brief or tonic thermal stimuli and tonic mechanical stimulation.[102-104] These activations were more pronounced in patients, and the activation in the secondary somatosensory cortex in patients was also observed on the ipsilateral side, suggesting an augmentation of painful input to structures involved in processing the sensory discriminative components of pain. Stimulation sufficient to produce equivalent levels of pain in patients and controls also produced prominent and similar activations in the ipsilateral cerebellum. Other regions with significant activations in both groups included contralateral putamen, inferior parietal lobule, and superior temporal gyrus. Both groups also sowed a common significant decrease in signal in ipsilateral primary somatosensory cortex. The findings of similar activations despite lower amounts of stimulation has also been observed in patients with allodynia caused by cerebral infarction.[105]

The overlap between activations in patients and activations evoked with greater stimulus pressures in control subjects provides one line of evidence consistent with augmentation of pain sensitivity in patients with FM. A second line of evidence is provided by comparison of the similar stimulus intensity conditions.

Application of mild pressure to health controls resulted in 2 areas of significant activation; application of these same pressures to patients resulted in 12 areas of activation overall and 8 areas in common with those resulting from application of greater pressures to control subjects. This difference in the number of overall activations (12 versus 2) and common regions (8 versus 0) provides a second, qualitative line of evidence that pain sensitivity is

augmented in patients with FM. The overlap in the similarly painful conditions and the enhanced response to lower stimulus intensities in patients provide converging lines of evidence for a mechanism involving central augmentation of pain sensitivity rather than simply a change in labeling behavior in the patient population. In terms of the initial experimental question, the result in patients more closely resembles the effects produced by the similar subjective pain magnitude condition in controls than the effect produced by the similar stimulus pressure condition in controls.

The enhanced response in somatosensory primary, secondary, and association areas and in the insula, putamen, and cerebellum contributes to the growing physical evidence of altered physiologic processing in FM. These results are not consistent with simple psychological mechanisms of changed labeling behavior, in which patients establish a more liberal response criterion for reorts of pain threshold and suprathreshold responses. However, it is important to note that proposed attentional mechanisms such as hypervigilance conceivably could have effects on the evoked cerebral response in sensory structures similar to those observed in this study.

Anticipation of a painful stimulus has been shown to increase activity in secondary somatosensory cortex[106], and distraction has resulted in reduced activity in secondary and association somatosensory regions. [107] Hypnotic suggestions have modulated activity in primary sensory cortex[108] and in regions defined as "somatosensory areas" [109]. However, no study of attentional or hypervigilance models has suggested the pattern of augmentation observed in this study, especially because we noted decreased activity in anterior cingulate cortex, which shows increased activity during attention.[110, 111] and anticipation[106, 112] and decreased activity during hypnotic analgesia. [113, 114] Previous studies have also demonstrated findings opposite to those in our FM patients, including increased activity in thalamus during increased attention[111] or suggestions of analgesia[114] and increased activity in insular cortex during anticipation of pain. [106]

Thus, the available evidence suggests that the current results likely reflect the effects of noxious stimulation. The familiarization sessions and repetitive block design with internal control for innocuous stimulation likely minimized the effects of anxiety, and theuse of long-duration stimuli may have minimized the role of anticipation. However, effects attributable to psychological factors such as attention , anticipation, and anxiety are potentially powerful and must always be considered in these types of experiments.

In addition to evidence consistent with augmentation of pain sensitivity in FM patients, the results also show evidence for attenuation of response in the caudate nucleus that was observed in controls; this finding is consistent with the results of resting rCBF evaluation which showed decreased basal flow in the caudate in FM patients. [100] Painful stimulation in control subjects also resulted in significantly increased rCBF in a number of regions in the right and left thalamus; patients with FM showed no thalamic increases. Attenuated thalamic rCBF was also demonstrated in 2 studies of FM,[100, 101] 2 studies of neuropathic pain, [115, 116] and in a study of cancer-related pain. [117] The studies of thalamic activity in FM showed low values of restoring rCBF in the right thalamus and a similar trend in the left

thalamus.

Although the evoked responses observed in the present study are consistent with results of resting rCBF evaluation, this consistency is not expected, nor is it necessary for validational support. Experimental determination of rCBF in the resting state should have little predictive value for evoked responses. Rather, comparing baseline flow with the changes evoked by an intervention may provide more information about underlying mechanisms than can be provided by either result in isolation. For example, reduced flow at baseline could permit a greater evoked response because of the classic physiologic law of initial values, in which the reduced baseline value permits a greater possible response, up to a physiologic ceiling. Alternatively, reduced baseline flow might result from inhibitory processes that also attenuate evoked responses from the same region.

In the current study, findings of an attenuated increase of rCBF in contralateral (and possibly bilateral) caudate and bilateral thalamus inpatients with FM, along with previous findings of lowered resting rCBF in these structures in FM patients, are consistent with a mechanism of tonic inhibition maintained by persistent excitatory input associated with ongoing and spontaneous pain. The viability of this mechanism is supported by the results of 2 studies, which demonstrated decreased thalamic activity in pain attributable to mononeuropathy or cancer.[115, 117] In those experiments, in which pain was localized to a single extremity, analgesic treatment (regional nerve block to patients with neuropathic pain, percutaneous high cordotomy for patients with cancer pain) normalized the reduced rCBF observed in contralateral thalamus, suggesting a process maintained by persistent painful input.

The increased spatial resolution of fMRI allows characterization of thalamic activations at the nucleic level. In previous studies, activation of thalamus by painful stimuli was assumed to activate ventroposterolateral and ventroposteromedial regions corresponding to the termination of the pain projection system in the spinothalamic tract.[116, 118] The increased rCBF observed in this study localizes a subset of these activations to bilateral ventrolateral nuclei and contralateral ventroanterior nuclei, which are primarily involved in motor function. The presence of these thalamic activations solely in controls may represent an increased motor response that is part of the constellation of affective responses in healthy control subjects, or a number of alternative mechanisms. For example, the lack of activations in the thalamus in FM patients may reflect the lower stimulus intensity delivered to this group, suggesting that, in the presence of pain augmentation, information about stimulus magnitude may be preserved in specific components of the central nervous system. The observed motor activation is also consistent with ipsilateral activation, which could result from suppression of a "swat" response from the opposite upper extremity.

The high-pain conditions in control subjects also resulted in a significant activation in the contralateral anterior nucleus. The anterior nucleus is an essential relay in the classic Papez[118] closed-loop limbic circuit, which involves a sequence of projections form the hippocampal formation to the mammilary bodies to the anterior nucleus. The anterior

nucleus in turn projects to the cingulate cortex, which projects directly back to the hippocampal formation via the entorrhinal cortex or the septal nuclei. The prominent activation of the anterior nucleus in the hig-pain control condition was accompanied by distinct but nonsignificant activations in the anterior cingulate in control subjects and significant difference between the control and patient groups in activations in the anterior cingulate by *t*-test comparison.

There is growing evidence that the anterior cingulate cortex is involved in processing the affective, unpleasant aspects of pain. [99, 111, 113, 120] Activation of a major input to the cingulate cortex solely in control subjects and significantly greater anterior cingulate activation in controls compared with patients, coupled with the unique activations in a variety of regions involved in motor responses (supplementary motor area, caudate, globus pallidus, ventrolateral, extensive cerebellar activations) observed in controls, suggest a state of reduced affective appraisal and responsiveness in FM. Decreased activations have been observed in several studies of chronic pain states. [121-123] The lowered affective reactivity observed in the patient group is consistent with anecdotal evidence that, in the scanner, patients were actually more compliant than controls. In addition, we have observed that a group of 43 FM patients found equally painful stimuli to be less unpleasant than did an age- and gender-matched control group of 28 subjects. [124] These preliminary results and the putative role of the anterior cingulate cortex in processing pain unpleasantness suggest that the reduced response reflects an adaptive mechanism in which chronic pain patients have become so accustomed to persistent pain that the brief, moderate-to-strong pain evoked in the experimental paradigm does not produce the emotional responses observed n those unaccustomed to such pain.

The present evidence of augmentation represents an initial step in the evaluation of the consequences and, ultimately, the causes of chronic pain syndromes such as fibromyalgia. The general augmentation observed in this experiment likely varies among individuals and may be mediated by multiple mechanisms and modulated by numerous factors that have been only partially identified. In addition, the current results can be classified as a static comparison of the consequences of painful mechanical stimulation in FM patients and matched control subjects. This static evidence provides a foundation for new studies that use dynamic designs to further characterize the differences observed in this study. Results from such studies can be used to build on the present data, by evaluating the modulation of the observed differences by factors that influence mechanical pain sensitivity. Future studies can move beyond the necessary documentation of differences in these populations to experiments that elucidate the underlying mechanisms of fibromyalgia and related disorders."

Key Research Accomplishments

Determination of 7 fMRI regions common to patient and control groups under test

conditions.

Determination that subjectively comparable test conditions result in fMRI activation patterns similar in both patient and control subjects.

Determination that objectively comparable test conditions result in fMRI activation of no common regions in patients and controls and produce greater effects in patients.

Conclusion that fibromyalgia patients are differentiated from controls by central nervous system (cortical or subcortical) augmentation of pain processing.

Reportable Outcomes- The following article will be published in volume 46 of Arthritis and Rheumatism in 2002.

Gracely R, Petzke F, Wolf JM, Clauw DJ. Functional Magnetic Resonance Imaging Evidence of Augmented Pain Processing in Fibromyalgia. Accepted for publication in volume 46, Arthritis and Rheumatism.

Conclusions

The fact that comparable subjectively painful conditions resulted in activation patterns that were similar in patients and controls, whereas similar pressures resulted in no common regions of activation and greater effects in patients, supports the hypothesis that FM is characterized by cortical or subcortical augmentation of pain processing.

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Appendices

Functional MRI Evidence of Augmented Pain Processing in Fibromyalgia

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Objective.

Fibromyalgia (FM) is a common rheumatologic syndrome characterized by chronic widespread pain and diffuse tenderness. There is considerable evidence suggesting that the pain and tenderness in FM are due to a central disturbance in pain processing, but the precise mechanism(s) responsible for symptoms remains unclear. Functional MRI (fMRI) can detect changes in regional cerebral blood flow that occur with various tasks. The objective of this study was to use fMRI to compare the pattern of cerebral activation during the application of painful stimuli, to determine whether this pattern differs in FM patients versus controls.

Methods.

Pressure was applied to the left thumb nailbed in 16 right-handed patients with FM and 16 right-handed matched controls. Each FM subject had an fMRI performed while they received moderately painful pressure. The functional activation patterns in the FM subjects were compared to two sets of conditions presented to the controls. In the *stimulus pressure control* condition, control subjects received the same amount of pressure as was delivered to the patients (these were typically rated as "faint" pain by the controls). Each control also received a *subjective pain control* condition, wherein stimuli were increased to deliver the same subjective level of pain experienced by the patients (these pressures were nearly twice the amount required to cause pain in the patients).

Results.

Stimulation with adequate pressure to cause similar pain in both groups resulted in 19 regions of increased regional cerebral blood flow (rCBF) in the healthy controls and 13 significant regions in the patients. Common locations of increased fMRI signal in these two groups occurred in seven regions: contralateral

primary and secondary somatosensory cortex, inferior parietal lobule, inferior frontal gyrus, insula, and putamen, and ipsilateral cerebellum. A common region of decreased signal was observed in ipsilateral primary somatosensory cortex. In contrast, when the same amount of pressure that caused pain in the patients was administered to the controls, there were only two regions of signal increase located in the ipsilateral precentral gyrus and ipsilateral superior temporal gyrus. Neither of these two regions coincided with a region of activation in the patient group. Statistical comparison of the patient and control groups receiving similar stimulus pressures revealed ten regions of greater activation in the patient group: contrlateral primary somatosensory cortex, inferior parietal lobule, insular cortex, anterior cingulate cortex, posterior cingulate cortex; ipsilateral secondary somatosensory cortex; bilateral superior temporal gyrus and cerebellum. In contrast, similar stimulus pressures produced only two regions (ipsilateral medial frontal gyrus and uncus) of greater activation in the control group.

Conclusion.

The fact that the similarly subjectively painful conditions led to similar activation patterns in the patients and controls, whereas similar pressures resulted in no common activation and greater effects in patients, supports the hypothesis that FM is characterized by cortical or sub-cortical augmentation of pain processing.

Fibromyalgia (FM) is characterized by chronic widespread pain (involving all four quadrants of the body as well as the axial skeleton), and diffuse tenderness (1). Population-based studies have demonstrated that approximately 2 - 4% of the population suffers from FM, with the prevalence being very similar in at least five industrialized countries (2;3). The etiology of FM remains elusive, although there is support for the notion that altered central pain processing is a factor in the presentation of this disease. The development of contemporary funtional brain imaging techniques has now provided an opportunity to examine central pain processing in FM.

Although the clinical diagnosis of FM is based on detecting eleven of eighteen "tender points" (regions that are painful when manually palpated with four kilograms of pressure), increased sensitivity to pressure in this condition extends beyond tender points, involving the entire body (4-7). In aggregate, psychophysical studies demonstrate that patients with FM generally *detect* sensory modalities (electrical, thermal, mechanical) at the same levels as normals, but the point at which these stimuli become noxious or unpleasant is lower (8-11).

The subjective nature of FM symptoms has led to a long-standing debate regarding the legitimacy of this condition (12;13), and the predominant mechanism(s) involved in FM (14-16). A generalized increase in pain sensitivity could be due to psychological (e.g. hypervigilance, expectancy) or physiological (e.g., "central sensitization" or other sub-cortical amplification processes) mechanisms. In a clinical setting, the focus is frequently on how difficult these patients are to manage, and on the veracity of their complaints (17;18).

Functional neuroimaging can be a useful tool to examine the mechanisms involved in pain processing. A variety of functional imaging techniques consistently reveal a group of brain structures that are activated during painful conditions. Positron emission tomography (PET) and recently functional magnetic resonance imaging (fMRI) show that painful thermal, electrical, chemical and pressure stimulation results in increased regional cerebral blood flow (rCBF) in structures involved in the processing of sensation, movement, cognition and emotion (19-21). Pain stimulation-related neural activity is inferred from this increase in rCBF since focal increases in activity are known to trigger a spatially and temporally localized increase in flow to meet increased neural metabolic demands.

Functional neuroimaging has only recently been applied to the evaluation of conditions such as FM. Single photon emission tomography (SPECT), which evaluates rCBF over a period of 30 minutes, has revealed diminished resting rCBF in bilateral thalami and caudate nuclei in a study of 10 patients with FM compared to 7 control subjects (22). A second study using 17 FM patients and 22 controls replicated the reduced rCBF in the right thalamus and observed a trend for reduced rCBF in the left thalamus. This study also found reduced rCBF in the inferior dorsal pons and in a restricted region of the right lentiform nucleus (23).

SPECT designs provide static, baseline measures of rCBF in patients at rest. As noted by Pillemer et al., measurement problems in patients with FM may be decreased and experimental power increased by dynamic designs that include evaluation of physiologic responses during baseline and stimulation conditions (24). SPECT can be applied to assess the response to an intervention such as a painful stimulus by repeating the 30-minute acquisition after the intervention. Dynamic effects during shorter time periods can be assessed by increasing the temporal resolution of 30 minutes to one minute with PET methodology, and to less then five seconds by using fMRI. Additional features of fMRI such as increased spatial resolution and lack of

radioactive tracers have resulted in the recent rapid application of this method to the investigation of a wide range of clinical conditions.

This study used the spatial and temporal resolution of fMRI brain imaging to characterize the pattern of increased rCBF produced by blunt pressure applied to the thumb nailbed in 16 normal subjects, and compared this response to the pattern evoked in 16 patients with clinical tenderness associated with the diagnosis of FM. The experimental design addressed the simple question, "Does the pattern of brain activation in FM patients match that produced by equally low stimulus pressures in normal volunteers, or match that produced by equally subjectively painful stimuli (produced by significantly greater stimulus pressures) in the normal volunteer group?" A match of equal stimulus intensities is consistent with the hypothesis that the pain complaints in the patient group represent an exaggerated response to an otherwise normal pain-signaling system. A match of equal subjective pain intensities is consistent with a pathological increase in pain sensitivity in the patients.

PATIENTS AND METHODS

Patients and control subjects

Sixteen non-clinically depressed right-handed patients (15 female, 1 male; age 52.6±12.3, range 19-69) meeting the 1990 ACR criteria for FM at the time of the study were randomly recruited from a sample of 165 consecutive clinic patients. Patients were allowed to stay on long-term medications although analgesics were discontinued 12 hours prior to the psychophysical baseline and fMRI sessions. Sixteen healthy control subjects (15 female, 1 male; age 45.8±10.5, range 22-61) were recruited through newspaper advertisements and compensated for their participation. All subjects underwent a history and physical examination to screen

for concurrent illnesses, including screening for depression using the Beck depression inventory (BDI). All subjects gave informed consent prior to testing. The protocol was approved by the Georgetown University Institutional Review Board.

Psychophysical Assessment

In a pre-fMRI baseline session, pressure pain sensitivity was evaluated by subjective scaling of suprathreshold sensations using a combined numerical analog descriptor scale of pain intensity and unpleasantness (25). Discrete pressure stimuli of 5 s duration were applied to the left thumbnail by a 1-cm^2 hard rubber probe attached to a hydraulic piston. A combination of valves and calibrated weights produced controlled, repeatable stimulation that approached a rectangular waveform. Subjects rated the intensity and unpleasantness of pressure pain sensations evoked by an ascending series of stimuli beginning at 0.45 kg/cm^2 and ascending in 0.45/cm^2 kg steps up to tolerance or to a maximum of 9 kg/cm^2. Following the ascending series, seven stimulus intensities (0.45, 0.9, 1.35, 1.8, 2.7, 3.6, 4.5 kg/cm^2) were delivered twice in random order. The inter stimulus interval was 20 sec.

Psychophysical Analysis

Pressure pain thresholds were defined for each subject as the mean of the highest stimulus intensity that received all zero responses during the ascending series and the next highest stimulus intensity that received at least one response of painful. The psychophysical function describing pain magnitude versus stimulus intensity was used to estimate stimulus intensities that would evoke a pain intensity of 11 ("moderate") in the patients and healthy controls (see Figure 2). This method was also used to determine a stimulus intensity

that would evoke a mean pain intensity of 3 ("faint" to "very weak") in the healthy controls. The response value of 3 in the healthy controls was chosen from preliminary data because the stimulus intensity needed to produce this subjective level closely matched the intensities needed to evoke a response of 11 in the patients. These intensities were used in a simulation procedure within 2-24 hours before the actual scan. Pain intensity was recorded every 10 s over complete ten-minute runs following the same 30 s on and off cycles used in the scanner to ensure that subjects were able to tolerate the pressure stimulation and that the evoked sensations were in the desired subjective range.

Functional Imaging

MRI and fMRI scans were performed on a 1.5 Tesla Siemens Vision System. T1-weighted MRI anatomical scans (4 msec TE, 9.7 ms TR, flip angle 12 deg., 256 x 256 matrix, 256 mm FOV, 1-mm cubic voxels, acquired non-interleaved in the sagittal direction) were followed by one or two functional scans using multi-slice echo-planar image (EPI) fMRI acquisition (40 ms TE, 5 s TR, 5 s repetition time (TR), flip angle 90 deg., 64 x 64 matrix, 192 mm FOV, 50 horizontal 3 mm slices). These parameters allowed coverage of the entire brain with 3 mm cubic voxels. A sequence of 128 time points (brain volumes) was obtained per run (one stimulation condition per run). The results of 8 scans (three in the beginning, 5 at the end) were discarded, leaving 120 scans for the analysis. In each stimulation condition, subjects received alternating 30 s of innocuous touch and 30 s of painful pressure for a total of ten one-minute cycles. The onset and offset were coincident with the beginning of a scan and the series was initiated on the third scan. Stimulating pressure was relieved for 0.3 s at 3 s intervals to avoid occlusion of blood flow. These parameters are represented in Figure 1, which shows the time course of a single stimulus cycle and a complete scan.

Imaging analysis

Imaging data were analyzed with MEDx (Sensor Systems, Inc., Sterling Virginia). The functional images were corrected for head motion and intensity differences. Excessive head motion was determined by motion detection software and visual inspection of raw and processed images. Acceptable motion-corrected images were spatially smoothed at 6 mm full-width-half-maximum (FWHM). The 60 scans collected during the touch condition and the 60 scans collected during the pain conditions were compared by t-test. Resultant Z statistical maps were registered into standardized space using the SPM96 EPI template and resliced to 2 mm^3 voxels. Group Z-maps were computed from the sum of individual Z maps divided by the square root of N. Activations were considered significant at $p < 0.05$ corrected for multiple comparisons using the random Gaussian field theory correction (26). This correction recognizes the correlation between neighboring voxels due to spatial smoothing and reduces the number of elements used to calculate the correction to the actual number of independent elements. Two analyses were performed for each condition. An overall analysis searched for activations in the entire brain, including white matter and regions of grey matter not previously implicated in pain processing. The overall analysis was followed by a limited search conducted only in regions broadly identified as contributing to pain processing. The volume for the intial search was defined from the results of a separate study (27, unpublished observations) comparing the effects of the same painful stimulus to no stimulation in two separate scans in 27 subjects. The volume was defined as any region exceeding an uncorrected p value of $p <0.001$ ($Z=3.09$) in either comparisons of "high subjective pain" to "no stimulation" ($n=27$ scans), "low subjective pain" to "no stimulation, ($n = 27$ scans) and both types of pain to "no stimulation" ($n = 54$ scans).

For comparisons between conditions in FM and controls, clusters within a condition were defined as a volume of activations with at least one statistically significant voxel (corrected $p < 0.05$) and adjacent surrounding voxels with an uncorrected significance of $p < 0.005$ or greater. Common activations between different conditions were defined by overlapping clusters or by proximity of maxima within 7 voxels (1.4 cm). Significant differences between conditions were assessed by t-test and the significance level was corrected for multiple comparisons using the random Gaussian field theory correction (26). Separate analyses assessed either the entire brain or a search volume defined as all voxels showing significant activations in any condition. Anatomical regions were identified by inspection of individual functional images superimposed on an individual structural image, and by conversion of the coordinates to the coordinate system of the Talairach and Tournoux atlas and localization using this atlas (28) and automated software (29).

RESULTS

FM patients displayed significantly lower pressure pain thresholds at the left thumbnail compared to the control subjects determined by either a clinical method of ascending series (1.4 ± 1.1 *vs* 2.7 ± 0.9 kg/cm^2, $t(30) = 3.62$, $p < 0.001$) or extrapolated from the suprathreshold ratings (0.8 ± 0.3 vs 1.1 ± 0.1 kg/cm^2, $t(30) = 4.06$, $p < 0.0001$). The imaging results could not be interpreted in three control subjects in both conditions due to excessive head motion. The data for these three subjects were excluded from further analysis. A fourth control subject showed unacceptable head motion in the low pain condition. These imaging data were excluded but the imaging data from the high pain condition and the psychophysical data were included in the analysis. Differences in thresholds after subject exclusion were still highly significant for the ascending series (1.4 ± 1.1 *vs* 2.7 ± 1.0 kg/cm^2, $t(27) = 3.33$, $p < 0.003$ and for the extrapolated suprathreshold method (0.8 ± 0.3 *vs* 1.1 0.1 kg/cm^2, $t(27) = 3.63$, $p < 0.001$).

Figure 2 shows the relation between conditions, stimulus intensities and pain magnitudes. Patients received a single functional scan with a mean stimulus intensity of 2.4 kg/cm^2 that was sufficient to evoked pain sensations with a mean rating of 11.30 ± 0.90. Healthy controls received a similar functional scan, but a necessarily greater mean stimulus intensity (4.16 kg/cm^2) was needed to evoke pain sensations (11.95 ± 0.94) of the same magnitude as those experienced by the patients. Healthy controls also received a second functional scan with stimulus intensities (2.33 kg/cm^2) similar to those administered to the patients, that produced less-intense pain sensations (mean rating 3.05 ± 0.85).

Tables 1 and 2 show anatomical location, standard coordinates and statistical Z value for the peak voxel activations. The low stimulus pressures delivered to patients resulted in 12 significant regions of increased rCBF. In contrast, these relatively low stimulus pressures failed to produce any significant activations in the control group. Increasing the pressures delivered to the control group to a level sufficient to evoke similar levels of pain experienced by the patients produced 19 significant regions of increased rCBF in the healthy control subjects.

The symbols in Table 1 and 2 and in Figure 2 show overlapping and adjacent activations. High subjective pain delivered to either controls or patients resulted in seven common activations in contralateral (right) primary somatosensory (SI) cortex, inferior parietal lobule (IPL) cortex, a region classified as secondary somatosensory cortex/IPL (SII/IPL), inferior frontal gyrus (IFG), insula, putamen, and in the ipsilateral cerebellum.

The activation patterns are quite close for five of the regions, with peak activations within four or fewer voxels from each other. The activation in the inferior parietal lobule is included since these activations are large with edges within seven mm of each other, and because they occupy a similar functional region associated with sensory association.

In contrast to the results with equivalent pain intensities, applying the low pressure levels used in the patient group to the healthy controls resulted in significant increases in fMRI signal in contralateral superior temporal gyrus at the temporal pole and in ipsilateral premotor cortex. Neither of these activations overlapped with significant increases in fMRI signal evoked by similar levels of stimulus pressure in the patient group.

High subjective pain in the control group also produced increased rCBF in regions that were not observed in the patient group. Table 1 and Figure 3 show activation in a number of regions involved in motor function, including the contralateral supplementary motor area (SMA), contralateral caudate nucleus, and ipsilateral globus pallidus. The prominent, bilateral activations in ventral lateral thalamic nuclei and in the contralateral ventral anterior nucleus are also localized to regions that subserve a motor function. An additional activation is localized in the contralateral anterior nucleus, an integral part of the limbic system. The effects shown in Tables 1 and 2 and in Figure 2 show the effects in the patient group and in the two conditions delivered to the control group, but do not directly compare these effects between groups. These effects were compared by first reducing the results of each scan in each person from a 3-dimensional statistical volume to a 3D volume of mean difference in signal between the on and off conditions for each scan. These mean difference volumes, were compared on a voxel by voxel basis by unpaired t-tests between the patient condition and each of the control conditions. These tests can be classified as a mixed model that

allows generalization of results in the subject sample to the population of control subjects and patients with fibromyalgia. These tests are also relatively conservative, ignoring the statistical information inherent in each scan and attenuated by imperfect normalization to a standard brain shape.

These tests show areas of greater activation in the control group that overlap with the control group activations in ipsilateral cerebellum, contralateral supplementary motor area, medial frontal gyrus, caudate nucleus, and in the bilateral thalamus. Increased activation in controls, in comparison to patients, was also observed in the contralateral inferior parietal lobule, thalamus (pulvinar), posterior cingulate cortex and in the ipsilateral caudate nucleus.

The patient group also showed significant increases in rCBF in bilateral secondary somatosensory cortex and ipsilateral superior temporal gyrus that were not observed in the subjective pain control group. T-tests did not show any significant effects between groups within these regions but did show significantly increased rCBF in comparison to the control group in contralateral posterior and anterior cingulate cortex, parahippocampal gyrus, middle temporal gyrus, and in ipsilateral superior temporal gyrus (Figure 3, Table 4).

DISCUSSION

Mild pressure applied to patients with FM produced subjective pain reports and cerebral responses that were qualitatively and quantitatively similar to many of the effects produced by at least twice the pressure in control subjects. Activations were observed in the contralateral primary and secondary sensory cortex, consistent with findings using brief thermal stimuli and tonic thermal and mechanical stimulation (30-32). These activations were more pronounced in patients and the response in the secondary somatosensory cortex

in patients was also observed on the ipsilateral side, suggesting an augmentation of painful input to structures involved in processing the sensory discriminative components of pain. Stimulation sufficient to produce similar pain in patients and controls also produced prominent and similar activations in the ipsilateral cerebellum (Fig 3). Other regions with significant activations in both groups included contralateral putamen, inferior parietal lobule and superior temporal gyrus. The finding of similar activations despite lower amounts of stimulation has also been observed in patients with allodynia due to cerebral infarction (33).

The overlap between activations in patients and activations evoked with greater stimulus pressures in control subjects provides one line of evidence consistent with an augmentation of pain sensitivity in the patients. A second line of evidence is provided by the comparison of the similar stimulus intensity conditions. Application of mild pressure in the healthy controls did not result in any significant activation while the application of these pressures to patients resulted in 12 overall activations, and seven areas of activation in common with effects produced by greater pressures in the control group. This difference of twelve to zero overall activations and seven to zero common activations provides a second, qualitative line of evidence that pain sensitivity is augmented in FM. The overlap in the similarly painful conditions and the enhanced response in patients to lower stimulus intensities provide converging lines of evidence for a mechanism involving a central augmentation of pain sensitivity rather than simply a change in labeling behavior in the patient population. In terms of the initial experimental question, the result in patients more closely resembles the effects produced by the similar subjective pain magnitude condition in control subjects than the effects produced by the similar stimulus pressure condition in control subjects.

The enhanced response in somatosensory primary, secondary and association areas and in the insula, putamen and cerebellum contributes to the growing physical evidence of altered physiological processing in FM. These results are not consistent with simple psychological mechanisms of changed labeling behavior in which patients establish a more liberal response criterion for reports of pain threshold and suprathreshold responses. However, it is important to note that proposed attentional mechanisms such as hypervigilance could conceivably have effects on the evoked cerebral response in sensory structures similar to those observed in this study. Anticipation of a painful stimulus has increased activity in secondary somatosensory cortex (34) while distraction has resulted in reduced activity in secondary and association somatosensory regions (35). Hypnotic suggestions have modulated activity in primary sensory cortex (36) and in regions defined as "somatosensory areas" (37). However, no study of attentional or hypervigilance models has suggested the pattern of augmentation found in this study, especially since we noted decreased activity in anterior cingulate cortex, which shows increased activity during attention (38;39), and anticipation (34;40), and decreased activity during hypnotic analgesia (41;42). Previous studies have also demonstrated findings opposite to what we noted in the FM subjects, including increased activity in thalamus during increased attention (39) or suggestions of analgesia (42), and increased activity in insular cortex during pain anticipation (34).

In addition to evidence consistent with FM augmentation of pain sensitivity, the results also show evidence for attenuation of responses in FM in comparison to controls. The patients did not show the increased response in bilateral caudate nucleus observed in the control subjects, a finding consistent with the results of resting rCBF that showed decreased basal flow in the caudate in FM (22). Painful stimulation in the control subjects also resulted in significantly increased rCBF in a number of regions in the right and left thalamus, while patients with FM showed no thalamic increases. Attenuated thalamic rCBF has been observed also in

two studies of FM (22;23) in two studies of neuropathic pain (43;44) and in a study of cancer-related pain (45). The studies of thalamic activity in FM observed low values of resting rCBF in the right thalamus and a similar trend for the left thalamus.

Although the present evoked responses are consistent with results observed in the resting state, this consistency is neither expected nor necessary for validational support. Experimental determination of rCBF in the resting state should have little predictive value for evoked responses. Rather, comparison of both baseline flow and changes evoked by an intervention may provide more information about underlying mechanisms than can be provided by either result in isolation. For example, reduced baseline flow could permit a larger evoked response due to the classic physiological law of initial values, in which the reduced baseline permits a larger possible response up to a physiologic ceiling. Alternatively, reduced baseline flow might result from inhibitory processes that also attenuate evoked responses from the same region. The present findings of an attenuated increase of rCBF in contralateral (and possibly bilateral) caudate and in bilateral thalamus in patients with FM in this study along with previous findings of lowered resting rCBF in these structures in FM patients are consistent with a mechanism of tonic inhibition maintained by persistent excitatory input associated with ongoing and spontaneous pain. This mechanism is supported by the results of two studies reporting decreased thalamic activity in pain due to painful mononeuropathy or cancer (43;45). In these experiments in which the pain was localized to a single extremity, administration of analgesic treatment (regional nerve block to patients with neuropathic pain, percutaneous high cordotomy for patients with cancer pain) normalized the reduced rCBF observed in contralateral thalamus, suggesting a process maintained by persistent painful input.

The increased spatial resolution of fMRI allows characterization of thalamic activations at the nucleic level. In previous studies, activation of thalamus by painful stimuli was assumed to activate regions in VPL and VPM corresponding to the termination of the pain projection system in the spinothalamic tract (44;46). The increased rCBF in this study localizes a subset of these activations to bilateral ventral lateral (VL) nuclei and contralateral ventral anterior (VA) nuclei, which are primarily involved in motor function. The presence of these thalamic activations soley in controls may represent an increased motor response that is part of the constellation of affective responses in the control subjects, or a number of other alternative mechanisms. A motor activation is also consistent with ipsilateral activation, which could result from suppression of a "swat" response from the opposite upper extremity.

The high pain condition in the normal controls also resulted in a significant activation in the contralateral anterior nucleus (AN). The AN is an essential relay in the classic Papez (46) closed-loop limbic circuit, which involves a sequence of projections from the hippocampal formation to the mammilary bodies to the AN. The AN in turn projects to the cingulate cortex which projects directly back to the hippocampal formation via the entorrhinal cortex or the septal nuclei. The prominent activation of AN in the high pain control condition was accompanied by distinct but non-significant activations in the anterior cingulate and significant difference in the activations in the anterior cingulate in the t-test comparison between the control and patient groups. There is growing evidence that the anterior cingulate cortex is involved in processing the affective, unpleasant aspects of pain (19;39;41;48). The activation of a major input to the cingulate cortex solely in control subjects and a significantly greater anterior cingulate activation in controls in comparison to patients, coupled with unique activations observed in controls in a variety of regions involved in motor responses (SMA, caudate, globus pallidus, VL, extensive cerebellar activations), suggests a state of reduced affective appraisal and responsiveness in FM. Decreased activations have been observed in several

studies of chronic pain states (49-51). Lowered affective reactivity in the patient group is consistent with anecdotal evidence that the patients were actually more compliant in the scanner than the control group. In addition, we have observed that a group of 43 FM patients found equally painful stimuli to be less unpleasant than an age and gender matched control group of 28 subjects (52). These preliminary results and the putative role of the anterior cingulate cortex in processing pain unpleasantness suggests that the reduced response reflects an adaptive mechanism in which chronic pain patients have become so accustomed to persistent pain that the brief, moderate to strong pain evoked in the experimental paradigm does not produce the emotional responses observed in those unaccustomed to such pain.

Further studies are necessary to replicate and extend these findings. In our study as well as others, the significant differences between groups of subjects are matched by equally impressive within-group differences in cerebral responses to painful stimuli. Thus, although previous functional neuroimaging studies have typically employed small numbers (< 10) of subjects, future studies will need to include larger groups and improved experimental designs to precisely delineate how pain is processed in normal persons, and in patients suffering from chronic pain syndromes.

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Table 1.

Significant Increases in rCBF: Subjective Pain Control Condition (High Pressure, High Pain)
Stimulus Pressure Control Condition (Low Pressure, Low Pain)

Side	Region		Coordinates (x y z)			Z-score
Sensory Cortex:						
Contralateral	Primary Somatosensory Cortex		54	-20	44	4.25*
Ipsilateral	Primary Somatosensory Cortex		-52	-22	52	-4.58*
Contralateral	Secondary Somatosensory Cortex/IPL		54	-30	26	3.66
			64	-26	22	4.04*
Contralateral	Inferior Parietal Lobule		52	-52	48	4.06
			48	-54	38	5.00*
Contralateral	Insula		38	4	0	3.79*
Ipsilateral	Insula		-48	12	-2	4.28
Frontal Cortex:						
Contralateral	Inferior Frontal Gyrus		54	16	2	4.07*
Motor Cortex:						
Contralateral	Supplementary Motor Area		12	2	68	4.51
Contralateral	Supplementary Motor Area		2	2	58	5.35
Ipsilateral	*Precentral Gyrus*		*-46*	*2*	*8*	*3.72*
Subcortical Motor:						
Contralateral	Caudate Nucleus		14	4	20	4.32
Contralateral	Putamen		28	6	-2	5.51*
Ipsilateral	Globus Pallidus		-12	0	2	4.90
Thalamus:						
Contralateral	Ventral Anterior Nucleus		12	-8	12	4.71
Contralateral	Anterior Nucleus		6	-4	6	5.04
Contralateral	Ventral Lateral Nucleus		12	-14	2	4.90
Ipsilateral	Ventral Lateral Nucleus		-12	-12	6	6.03
Temporal:						
Contralateral	Superior Temporal Gyrus	BA22	60	12	-6	5.23
Ipsilateral	*Superior Temporal Gyrus*	*BA22*	*54*	*10*	*-4*	*3.89*
Cerebellum:						
Ipsilateral	Anterior Lobe		-24	-48	-30	6.61*
			-36	-44	-38	5.75
Ipsilateral	Posterior Lobe		-50	-58	-36	4.56
Contralateral	Posterior Lobe		28	-70	-32	6.34

* matches activations in the Patient Condition

Table 2.

Significant Increases in rCBF for the Patient Condition (Fibromylagia Patients - Low Pressure, High Pain)

Side	Region	Coordinates (x	y	z)	Z-score
Sensory Cortex:					
Contralateral	Primary Somatosensory Cortex	52	-16	44	4.58*
Ipsilateral	Primary Somatosensory Cortex	-48	-24	52	-4.16*
Contralateral	Secondary Somatosensory Cortex	52	-20	16	5.22
Ipsilateral	Secondary Somatosensory Cortex	-58	-24	14	5.40
Contralateral	Secondary Somatosensory Cortex/IPL	54	-20	30	4.22
		64	-32	24	4.14*
		60	-30	30	4.11
Contralateral	Inferior Parietal Lobule BA40	58	-38	36	4.10*
Contralateral	Insula	36	6	6	3.70*
Frontal:					
Contralateral	Inferior Frontal Gyrus	62	10	2	4.68*
Subcortical:					
Contralateral	Putamen	26	2	4	3.64*
Temporal:					
Ipsilateral	Superior Temporal Gyrus	-70	-28	16	3.68
Cerebellum:					
Ipsilateral	Posterior Lobe	-28	-60	-30	4.30
Ipsilateral	Anterior Lobe	-20	-54	-32	4.21*

* matches activations in the Subjective Pain Control Condition

Table 3.

Comparison of groups: Control Conditions Significantly Greater than Patient Condition

Subjective Pain Control Condition (Normal Volunteers - High Pressure, High Pain)
or
Equal Stimulus Pressure Control Condition (Normal Volunteers – Low Pressure, Low Pain)

Side	Region	Coordinates (x	y	z)	Z-score
Motor Cortex:					
Contralateral	Supplementary Motor Area	6	6	56	3.77
Contralateral	Medial Frontal Gyrus	2	26	46	3.53
Frontal Cortex:					
Ipsilateral	*Medial Frontal Gyrus*	*-10*	*64*	*16*	*3.02*
Subcortical Motor:					
Contralateral	Caudate Nucleus	14	0	20	4.01
Ipsilateral	Caudate Nucleus	-18	-6	22	3.45
Limbic Cortex:					
Contralateral	Anterior Cingulate Cortex	2	26	30	3.69
Ipsilateral	*Uncus*	*-20*	*6*	*-42*	*3.61*
Thalamus:					
Contralateral	Ventral Anterior Nucleus	16	-8	12	3.17
Ipsilateral	Ventral Lateral Nucleus	-16	-12	12	3.80
Cerebellum:					
Ipsilateral	Anterior Lobe	-20	-44	-24	3.53
Contralateral	Posterior Lobe	22	-34	-42	5.10
Ipsilateral	Posterior Lobe	-36	-78	-46	4.45

Table 4.

Comparison of groups: Patient Condition Significantly Greater than Control Conditions

Patient Condition (Patients - Low Pressure, High Pain)
versus

Subjective Pain Control Condition (Normal Volunteers - High Pressure, High Pain)
or
Equal Stimulus Pressure Condition (Normal Volunteers – Low Pressure, Low Pain)

Side	Region	Coordinates			Z-score
Sensory Cortex:					
Contralateral	*Primary Somatosensory Cortex*	*55*	*-18*	*29*	*3.15*
Contralateral	Secondary Somatosensory Cortex	54	-26	18	3.22
Contralateral	Inferior Parietal Lobule	52	-40	38	3.09
Contralateral	*Inferior Parietal Lobule*	*52*	*-40*	*38*	*3.43*
		58	*-28*	*28*	*3.02*
Contralateral	Insular Cortex	36	4	6	3.17
		36	-2	12	3.01
Contralateral	*Insular Cortex*	*36*	*4*	*6*	*3.09*
Ipsilateral	Secondary Somatosensory Cortex		-58	-24	-14 3.87
Ipsilateral	*Secondary Somatosensory Cortex*		*-58*	*-24*	*14 3.93*
Ipsilateral	Inferior Parietal Lobule	-62	-40	44	3.29
Ipsilateral	Insular Cortex	-40	–12	10	3.01
Temporal:					
Contralateral	Superior Temporal Gyrus		62	-10	8 3.31
Contralateral	*Superior Temporal Gyrus*		*46*	*-54*	*10 3.56*
		64	*-52*	*18*	*3.03*
Contralateral	Middle Temporal Gyrus	46	-56	12	3.86
Ipsilateral	Superior Temporal Gyrus		-65	16	-12 4.11
Ipsilateral	*Superior Temporal Gyrus*		*-54*	*-2*	*0 3.19*
Ipsilateral	Middle Temporal Gyrus	40	-70	16	3.75
Limbic Cortex:					
Contralateral	Anterior Cingulate Cortex		1	8	32 3.11
Contralateral	*Anterior Cingulate Cortex*		*1*	*8*	*30 3.25*
Contralateral	*Posterior Cingulate Cortex*		*12*	*-56*	*6 3.05*
		4	*-46*	*40*	*3.05*
Contralateral	Posterior Cingulate Cortex		4	-46	40 3.27

		4	-70	8		3.11
Motor Regions:						
Contralateral	*Cerebellum*		*18*	*-60*	*-32*	*3.31*
Ipsilateral	Cerebellum		-32	-62	-22	3.15
Ipsilateral	*Cerebellum*		*-30*	*-62*	*-26*	*3.86*
Occiptal:						
Ipsilateral	Lingual Gyrus	-4	-90	-10		3.89
Contralateral	Middle Occipital Gyrus	54	-64	-8		3.22

FIGURE LEGENDS

Figure 1. Sequence of events during a single scan. The top panel shows a single stimulation cycle. Stimulus pressure is increased to a level that evokes innocuous tactile sensations for 30 s and increased to a painful level for 30 s. Both types of stimuli are relieved for 0.3 sec at 3 sec intervals to avoid occlusion of blood flow. Functional images of the entire brain are obtained at 5 s intervals resulting in 6 functional volumes for each 30 s stimulus. The bottom panel shows that the cycle is repeated 10 times for a total of 120 volumes collected over 10 min. Three additional scans delivered at the beginning of the series are not analyzed to allow for equilibration of the fMRI signal, and 5 scans at the end of the sequence are not analyzed.

Figure 2. Top left: Experimental conditions. This figure shows mean pain rating plotted against stimulus intensity for the experimental conditions. In the *patient* condition, a relatively low stimulus pressure (2.4 kg/cm^2) produced a high pain level (11.30 ± 0.90), shown by the red triangle. In the *stimulus pressure control* condition, shown by the blue square, administration of a similar stimulus pressure (2.33 kg/cm^2) to control subjects produced a very low level of rated pain (3.05 ± 0.85). In the *subjective pain control* condition, shown by the yellow square, administration of significantly greater stimulus pressures to the control subjects (4.16 kg/cm^2) produced levels of pain (11.95 ± 0.94) similar to the levels produced in patients by lower stimulus pressures. The *patient* condition and the *subjective pain control* condition are identified by red and yellow in all subsequent figures.

Top middle, right and bottom: Common regions of activation in patients (red) and in *subjective pain control* condition (yellow), in which the effects of pressure applied to the left thumb sufficient to evoke a pain rating of 11 (moderate) is compared to the effects of innocuous pressure. Significant increases in the fMRI signal resulting from increases in regional cerebral blood flow (rCBF) are shown in standard space

superimposed on an anatomical image of a standard brain (SPM96). Images are shown in radiological view with the right brain shown on the left. Overlapping activations are shown by orange. The similar pain intensities, produced by significantly less pressure in the patients, resulted in overlapping activations in contralateral primary somatosensory cortex (SI), secondary somatosensory cortex and inferior parietal lobule (SII/IPL), inferior frontal gyrus (IFG) and putamen, and in ipsilateral cerebellum. Near overlapping activations were observed in contralateral IPL and insula. Stimulation of healthy controls by the pressure levels used in the patients evoked significantly less pain and no significant increases in rCBF in comparison to innocuous pressure.

Figure 3. Top Panel: Unique activations in the subjective pain control condition. Significantly increased rCBF indicated by the fMRI signal is shown in red for patients and in yellow for the healthy control subjects as in Figure 3. The results of unpaired t-tests between the mean difference in signal between pain and innocuous touch for each group is shown in blue, with the significance level adjusted for multiple comparisons at a one-tailed $p < 0.05$. Regions in which a significant t test between the conditions overlaps with activation in the control condition are shown in green. The healthy controls showed significant activations that were significantly different from the activation in patients in contralateral supplementary motor area (SMA), medial frontal gyrus (MFG), superior frontal gyrus (SFG), anterior cingulate cortex (ACC); in ipsilateral cerebellum; and in bilateral thalamus and putamen. The activations in the caudate nucleus appear to be bilateral although the ipsilateral activation (left brain, right side of figure) could represent a movement artifact.

Bottom Panel: Unique activations in the patient group. Significantly increased rCBF is shown in red for patients and in yellow for the healthy control subjects as in Figure 3. The results of unpaired t-tests between the mean difference in signal between pain and innocuous touch the patient condition compared to the

control condition is shown in blue, with the significance level adjusted for multiple comparisons at a one-tailed $p < 0.05$. Regions in which a significant t test between conditions overlaps with a significant activation in patients are shown in purple. The patients showed significant activations that were significantly different from the activation in the healthy controls in contralateral SI, SII/IPL and insula, and ipsilateral SII and cerebellum. The regions of white in contralateral SII/IPL and in ipsilateral cerebellum identify locations in which 1) both the patient and control groups show a significant increase in signal during painful stimulation and 2) this effect is significantly greater in the patient group.