The Relationship Between Depression, Clinical Pain, and Experimental Pain in a Chronic Pain Cohort

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Objective. Individuals with chronic pain frequently display comorbid depression, but the impact of symptoms of depression on pain processing is not completely understood. This study evaluated the effect of symptoms of depression and/or clinically diagnosed major depressive disorder (MDD) on pain processing in patients with fibromyalgia (FM).

Methods. Results of quantitative sensory testing and neural responses to equally painful pressure stimuli (measured by functional magnetic resonance imaging [fMRI]) were compared with the levels of symptoms of depression and comorbid MDD among patients with FM.

Results. Neither the level of symptoms of depression nor the presence of comorbid MDD was associated with the results of sensory testing or the magnitude of neuronal activation in brain areas associated with the sensory dimension of pain (primary and secondary somatosensory cortices). However, symptoms of depression and the presence of MDD were associated with the magnitude of pain-evoked neuronal activations in brain regions associated with affective pain processing (the amygdalae and contralateral anterior insula). Clinical pain intensity was associated with measures of both the sensory dimension of pain (results of sensory testing) and the affective dimension of pain (activations in the insula bilaterally, contralateral anterior cingulate cortex, and prefrontal cortex).

Conclusion. In patients with FM, neither the extent of depression nor the presence of comorbid major depression modulates the sensory-discriminative aspects of pain processing (i.e., localizing pain and reporting its level of intensity), as measured by sensory testing or fMRI. However, depression is associated with the magnitude of neuronal activation in brain regions that process the affective-motivational dimension of pain. These data suggest that there are parallel, somewhat independent neural pain-processing networks for sensory and affective pain elements. The implication for treatment is that addressing an individual’s depression (e.g., by prescribing an antidepressant medication that has no analgesic properties) will not necessarily have an impact on the sensory dimension of pain.

Major depressive disorder (MDD) is often found in conjunction with chronic pain, with a prevalence of 30–54% among tertiary care patients (1). Hypotheses about the link between MDD and chronic pain include the notion that one causes the other, or that a common underlying diathesis causes individuals to be more susceptible to both MDD and chronic pain (2). Laboratory studies assessing this relationship have yielded inconsistent results, showing increased experimental pain thresholds (3), decreased experimental pain tolerance (4), or no relationship between experimental pain threshold and symptoms of depression (5).

Although the underlying mechanism mediating the comorbidity between MDD and chronic pain is unknown, there is support for a biologic model (i.e., involvement of neurotransmitters such as serotonin, norepinephrine, corticotropin-releasing hormone, and substance P in both chronic pain and MDD), as well as a psychosocial model (i.e., association of sadness or...
maladaptive responses such as catastrophizing or learned helplessness with both chronic pain and MDD).

Pain is a multidimensional experience with both sensory-discriminative and affective-motivational dimensions (6,7). Studies investigating the underlying structure of pain descriptors and pain responses consistently include at least 2 factors that reflect both the sensory and the affective/evaluative dimensions of pain (8).

Stimulation-induced pain consistently increases neural activity in a network of brain structures involved in processing sensation, movement, emotion, and cognition (9–11). Evidence from functional brain imaging and studies of clinical lesions supports a division between brain regions such as the primary and secondary somatosensory cortices (S1 and S2) that process the sensory-discriminative dimension of pain (12), and regions such as the anterior insula and anterior cingulate that process the affective and evaluative dimensions of pain (13,14).

Brain imaging studies in patients with depression have shown reduced cerebral blood flow, specifically in the prefrontal cortex, anterior cingulate gyrus, anterior temporal cortex, caudate, putamen, and thalamus (15–18). The decreased blood flow in specific areas can be reversed with antidepressant therapy (19,20).

Fibromyalgia (FM) is a chronic pain syndrome with a prevalence from 0.5% to 4% in industrialized countries (21). The American College of Rheumatology (ACR) 1990 criteria for the classification of FM require both a history of chronic widespread pain and tenderness to blunt pressure (22). Since these patients often have comorbid depression, FM may be an ideal condition in which to study the relationship between MDD, clinical pain, and experimental pain.

This study evaluated 1) whether higher levels of symptoms of depression (or the presence of comorbid major depression) are associated with increased sensitivity to experimental pressure-induced pain, and 2) which brain areas are involved in mediating the relationship between experimental pain, levels of symptoms of depression, and clinical pain.

**PATIENTS AND METHODS**

**Patients and groups.** The study was conducted in the Georgetown University Medical Center General Clinical Research Center, a tertiary health care facility. Written informed consent was obtained from all study participants, and the study was approved by the Georgetown University Institutional Review Board. To be included in the FM cohort, patients had to meet the 1990 ACR criteria for FM (22). Exclusion criteria for all subjects were severe physical impairment, medical conditions that were capable of causing patients’ symptoms (e.g., morbid obesity, autoimmune/inflammatory diseases, cardiopulmonary disorders), uncontrolled endocrine or allergic disorders (i.e., hyper-/hypothyroidism, diabetes, allergic rhinitis), malignancy, severe psychiatric illnesses (e.g., schizophrenia, substance abuse), factors known to affect the hypothalamic-pituitary-adrenal axis or autonomic function (cigarette smoking, daily caffeine intake exceeding the equivalent of 2 cups of coffee), and medication usage other than as-needed analgesics (excluding long-term narcotics) or appropriate dosages of thyroid hormone.

Fifty-three patients (33 female/20 male) and 42 controls (20 female/22 male) were included in the study. The mean ± SD age in the patient group and in the control group was 42 ± 9 years and 38 ± 9 years, respectively. Enrolled subjects were asked to discontinue intake of antidepressant medications 4 weeks prior to the study (depending on the half-life of the drug), but subjects were allowed to take nonsteroidal antiinflammatory medications as analgesics 3 days prior to the study. On day 1 of the study, patients completed self-report questionnaires, underwent the structured clinical interview, and were familiarized with the pain-testing paradigm. On day 2, experimental pain testing and functional magnetic resonance imaging (fMRI) were performed.

**Clinical pain.** Clinical pain was measured using a 100-mm visual analog scale (VAS). The 2 anchors for this VAS were 0 = no pain, and 100 = worst pain imaginable. Patients gave their responses verbally.

**Center for Epidemiological Studies Depression Scale (CES-D).** The CES-D is a 20-item, self-report questionnaire (23) that assesses symptoms of depression in nonpsychiatric adults. This was administered to patients to measure the extent of their symptoms of depression.

**Composite International Diagnostic Interview (CIDI).** The CIDI is a standardized instrument for assessment of mental disorders, with classifications according to the definitions and criteria of the International Classification of Diseases, Tenth Revision and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (24). Trained research assistants administered the 12-month computer version of the CIDI.

**Sensory testing.** Pressure-pain sensitivity was evaluated by subjective scaling of both the pain threshold level and more intense, suprathreshold pressure-pain sensations. Discrete 5-second pressure stimuli were applied to the left thumb-nail by a 1-cm² hard rubber probe. Subjects rated the intensity of pressure-pain sensations using a combined numeric analog descriptor scale (25). During pain testing, a series of stimuli was presented in a predictable, ascending manner, beginning at 0.5 kg/cm² and increasing in 0.5-kg/cm² intervals to tolerance or to a maximum of 10 kg/cm². Following the ascending series, 36 stimuli were delivered at 20-second intervals in random order using the multiple random staircase (MRS) method (26). The MRS method determines the stimulus intensities necessary to elicit faint (0.5 of 20), moderate (7.5 of 20), and slightly intense (13.5 of 20) pain ratings. The MRS provides a relatively pure sensory-physiologic measure of experimental pain sensitivity (27,28).

**Functional imaging.** MRI and fMRI scans were performed on a 1.5-Tesla vision system (Siemens, Munich, Germany). A T1-weighted MRI anatomic scan session (time to echo [TE] 4 msec, time to recovery [TR] 9.7 msec, flip angle 12°, 256 × 256-pixel matrix, field of vision [FOV] 256 mm,
Table 1. Demographic and clinical characteristics of the control subjects and fibromyalgia (FM) patients

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 42)</th>
<th>FM patients (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, no. male/no. female</td>
<td>22/20</td>
<td>20/33</td>
</tr>
<tr>
<td>Age, years</td>
<td>37.9 ± 9.1</td>
<td>42.0 ± 8.9</td>
</tr>
<tr>
<td>CES-D score</td>
<td>6.5 ± 6.6</td>
<td>17.1 ± 10.6†</td>
</tr>
<tr>
<td>Clinical pain VAS score</td>
<td>3.3 ± 10.1</td>
<td>47.5 ± 25.6†</td>
</tr>
<tr>
<td>Pressure-pain intensity, kg‡</td>
<td>1.81 ± 1.47</td>
<td>1.05 ± 0.73§</td>
</tr>
<tr>
<td>MRS low</td>
<td>4.57 ± 2.39</td>
<td>2.96 ± 1.57¶</td>
</tr>
<tr>
<td>MRS high</td>
<td>6.99 ± 2.97</td>
<td>5.15 ± 2.53§</td>
</tr>
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* Except where indicated otherwise, values are the mean ± SD. CES-D = Center for Epidemiological Studies Depression Scale; VAS = visual analog scale; MRS = multiple random staircase (method).
† P < 0.001 versus controls.
§ Low = intensity needed to elicit first pain (pain threshold); medium = intensity needed to elicit moderate pain; high = intensity needed to elicit slightly intense pain.
¶ P < 0.05 versus controls.
§ P < 0.01 versus controls.

1-mm³ voxels, acquired noninterleaved in the sagittal direction) was followed by 2 functional scan sessions using multislice echo-planar imaging fMRI acquisition (TE 40 msec, TR 5 seconds, flip angle 90°, 64 × 64-pixel matrix, FOV 192 mm, 50 horizontal 3-mm slices). These parameters allowed coverage of the entire brain with 3-mm³ voxels. During each functional scan session, the brain was scanned at 5-second intervals. Three initial scans allowed for saturation of the tissue. Starting on the fourth scan, pressure stimuli of 25 seconds’ duration (the “on” condition) were alternated with 25-second resting periods (the “off” condition). Onset and offset of a stimulus was coincident with the beginning of a scan, allowing the acquisition of 5 scans during each of 12 “on” and 12 “off” conditions. During the “on” conditions, stimuli of varying intensities were presented randomly. These stimulus intensities included 3 stimuli calibrated to elicit a rating of 13.5 of 20 (slightly intense pain). The analysis compared the scans acquired during these slightly intense pain conditions to those acquired during the “off” condition.

Figure 1. Outline of study design, including main correlational analysis and group comparisons. FM = fibromyalgia; CIDI = Composite International Diagnostic Interview.

Table 2. Correlation coefficients for associations between evoked pain sensitivity (MRS method), level of symptoms of depression, and magnitude of clinical pain in 53 fibromyalgia patients

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRS pressure-pain intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CES-D score</td>
<td>r</td>
<td>0.20</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.20</td>
<td>0.97</td>
</tr>
<tr>
<td>VAS pain score</td>
<td>r</td>
<td>0.20</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.20</td>
<td>0.26</td>
</tr>
</tbody>
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* Associations are Pearson correlation coefficients. See Table 1 for definitions.

Imaging analysis. Imaging data were analyzed with MEDx 3.4 (Sensor Systems, Sterling, VA). The functional images were corrected for head motion and intensity differences, and were spatially smoothed at 6-mm full width at half maximum.

The brain volumes collected during “on” conditions were compared by t-test to the brain volumes collected during “off” conditions. Resultant Z-statistic volumes and mean differences of the volumes were registered into standardized space using the SPM96 echo-planar imaging template and were then resliced to 2-mm³ voxels.

Results were corrected for multiple comparisons (29). Anatomic 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-Tournoux atlas and localization using this atlas (30) and automated software (31).

Table 3. Association of neuronal activations in brain regions with level of symptoms of depression and clinical pain ratings

<table>
<thead>
<tr>
<th></th>
<th>Coordinates</th>
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<tbody>
<tr>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Contralateral</td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>56</td>
</tr>
<tr>
<td>S2</td>
<td>66</td>
</tr>
<tr>
<td>ACC</td>
<td>8</td>
</tr>
<tr>
<td>Anterior insula</td>
<td>32</td>
</tr>
<tr>
<td>Anterior insula</td>
<td>34</td>
</tr>
<tr>
<td>PFC (BA 10)</td>
<td>32</td>
</tr>
<tr>
<td>Amygdala</td>
<td>18</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>−64</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>−34</td>
</tr>
<tr>
<td>Amygdala</td>
<td>−20</td>
</tr>
</tbody>
</table>

* Associations are Pearson correlation coefficients and Z statistics. Brain areas are mapped to the coordinate system of the Talairach-Tournoux atlas. S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; ACC = anterior cingulate cortex; PFC = prefrontal cortex; BA = Brodmann’s area (see Table 1 for other definitions).
† P < 0.05, corrected for multiple comparisons.
‡ P < 0.001, uncorrected.
Statistical analysis. Correlations between clinical pain, experimental pain sensitivity, and self-reported symptoms of depression were analyzed using Pearson’s correlation coefficients (SPSS for Windows, version 11.0; SPSS, Chicago, IL). For the subset of patients who participated in the fMRI protocol, correlations in the mean difference of neuronal activation between no pain and slightly intense pain at each voxel of the brain and the extent of self-reported symptoms of depression or clinical pain were analyzed using Pearson’s correlation coefficients, corrected for multiple comparisons.

RESULTS

Fifty-three patients with FM and 42 controls provided complete self-report data and participated in the experimental pain testing. The data from fMRI were collected on a subset of 30 patients with FM (18 female/12 male), with a mean age of 42 ± 10 years. The demographic and clinical data are shown in Table 1, and the study design is shown in Figure 1.

Associations between the magnitude of clinical pain, experimental pain sensitivity, and symptoms of depression for the patient group are shown in Table 2. The magnitude of clinical pain showed only weak correlations with self-reported symptoms of depression (r = 0.26, P = 0.06) and experimental pain (r = −0.18 to −0.30, P = 0.26–0.054). Pressure-pain thresholds at all pain intensity levels (i.e., mild, moderate, severe pain) were unrelated to self-reported symptoms of depression.

Results of the correlational analyses of self-reported symptoms of depression and neuronal activations are shown in Table 3 and Figure 2. Correlations...
with neuronal activations in cortical areas that process the sensory-discriminative dimension of pain (S1 and S2) were not significant. However, CES-D scores were significantly correlated with neuronal activations in the amygdalae and contralateral anterior insula.

Similar to the trends observed with the CES-D scores, clinical pain VAS scores reported by the subset of 30 FM patients did not correlate with neural activity in the S1 or S2 brain regions. The clinical pain scores, however, did correlate significantly with pain-evoked neural activity in the contralateral primary somatosensory cortex, secondary somatosensory cortex, and anterior insula (Table 3 and Figure 3).

Self-reported symptoms of depression cannot be used to definitively diagnose MDD. In our sample of 30 FM subjects who underwent fMRI, a subset of 7 subjects met the full criteria for comorbid MDD by structured clinical interview (i.e., the CIDI). Therefore, in a second analysis, we compared fMRI patterns of neuronal activation in these 7 patients with those of 7 age- and sex-matched FM patients without MDD, and with 7 age- and sex-matched healthy control subjects (Figure 1). Consistent with previous studies in FM, both groups of FM patients, those with and those without MDD, required significantly less pressure to cause slightly intense pain as compared with the healthy controls (FM patients with no major depression 4.7 kg, FM patients with MDD 5.2 kg, controls 6.9 kg; P < 0.001 for both FM groups.
versus controls) (32,33). These equally painful stimuli resulted in similar neuronal activations in the cortical areas that code for stimulus intensity in all 3 groups, and resulted in unique neuronal activations in both the amygdalae and the contralateral insula in the patients with MDD, thus confirming the results of the correlational analysis involving symptoms of depression, and extending the findings to the clinical diagnosis of MDD (Figure 4).

**DISCUSSION**

In a cohort of patients with chronic pain who had a confirmed diagnosis of FM, the level of symptoms of depression or presence of MDD was not associated with either subjective pressure-pain sensitivity or neuronal activations in regions of the brain that are implicated in processing the sensory-discriminative dimension of pain (i.e., S1 and S2). In contrast, the presence of MDD or symptoms of depression was associated with neuronal activation in brain regions implicated in processing the motivational-affective dimension of pain (i.e., the amygdalae and anterior insula). Clinical pain was related to both the sensory and the affective domains, in that it weakly correlated with sensory testing results and with the magnitude of neuronal activations in brain areas associated with affective/integrative aspects of pain processing (i.e., the insula bilaterally, the contralateral anterior cingulate cortex, and the prefrontal cortex).

These sensory testing and functional imaging data are consistent with the findings of a number of other studies suggesting that pain has at least 2 dimensions: a sensory-discriminative dimension that identifies its intensity, quality, and spatiotemporal characteristics, and an affective-motivational dimension that processes its negative valence and unpleasantness (6,7). These data also provide additional evidence that the anterior insula may play a critical role in integrating sensory and emotional experiences, since this was the only region associated with both symptoms of depression and the clinical pain report (34,35).

Much has been made of the overlap and similarities between pain and symptoms of depression, but these and other data suggest it is also important to identify pain-processing mechanisms that are independent of mood. For example, this and other functional imaging studies in FM suggest that there is objective evidence of amplification of the sensory dimension of pain that is totally independent of mood or emotion (32,36,37). Similar findings of allodynia/hyperalgesia that are not explained by psychological factors occur in other “central” pain syndromes, such as irritable bowel syndrome, temporomandibular disorder, and idiopathic low back pain (33,38).

The notion that sensory and affective aspects of pain may be independently processed is not just of theoretical interest. Dissimilar pharmacologic therapies may differentially influence the sensory and affective dimensions of pain (25). Within the class of antidepressants, some are relatively efficacious analgesics (e.g., tricyclic compounds), whereas others do not function in this manner (e.g., highly selective serotonin reuptake inhibitors) (39). The effects of antidepressants on pain also appear to be independent of mood, since 1) antidepressant effects and analgesic effects frequently occur independently of each other in clinical trials, and 2) doses of antidepressants necessary to produce analgesia are, in many cases, lower than the those required to treat MDD (40–44).

These data are consistent with a neuromatrix model of pain that applies concepts from cognitive neuroscience network theory (45). In this model, dimensions of the pain experience are the output of a neural network program, or neuromatrix, which is determined by genetic influences as well as sensory, cognitive, and affective experiences unique to each individual. This theory maintains that the neuromatrix operates through parallel distributed processing carried out by somatosensory (sensory dimension), limbic (affective dimension), and thalamocortical (evaluative dimension) modules that produce distinct, but related dimensions, which contribute to a unified pain experience.

The present results support the independence of multiple processing networks and confirm that specific cortical regions, particularly the anterior insula, may integrate the output of these separate networks and serve to process an individual’s overall sensory/emotional experience. The term interoception has been used to describe an afferent neural system that is representative of “the material me” that may underlie feelings, emotions, and self-awareness (34). Neural activity in the anterior insula has consistently been observed in studies of pain processing (12,46,47). When lesions of the insular region are present, the affective dimension of pain is altered, whereas the sensory-discriminative dimension is spared; this encompasses a disconnection syndrome called asymbolia for pain (13). Altered neural activity in the insula has not been reported in neuroimaging studies of patients with depression, but it has been observed consistently in emotional tasks with negative affective components, such as tasting salt (48) and viewing faces of disgust (49). This func-
tional characterization is consistent with insular projections to the anterior cingulate and amygdalae, and also consistent with the finding that these regions were associated with clinical pain in the present study (50).

This study identified the mediating processes between symptoms of depression or MDD and pain, and their anatomic correlates in the brain. The design could not determine the independent influence of either chronic pain or depression on each other. The ideal way to address the causality between chronic pain and depression in future studies is to evaluate patients with chronic pain as they transition between depressed and nondepressed states. The few existing longitudinal studies suggest that there is, at best, only a weak relationship between improvement in MDD and improvement in chronic pain, and that this relationship diminishes once the influence of other disease-related variables are controlled (51,52). Any preliminary findings on this topic need replication and extension. In addition, in future studies it may be preferable to utilize a longitudinal, within-subject design to examine neural-activation patterns in the same individual over time, as they move from a depressed to a nondepressed state, or vice versa.

Another potentially fruitful series of studies would examine how different types of drug or nondrug therapies impact upon pain processing. For example, previous studies using experimental pain paradigms have suggested that benzodiazepines and opioids may differentially affect sensory or affective-motivational components of pain, but functional imaging has not been used to study similar phenomenon (25).

Finally, it is not clear if the findings of the current study apply only to FM or might be seen more broadly in other chronic pain conditions. It is possible that all chronic pain conditions that have a prominent central element, i.e., characterized by hyperalgesia/allodynia (e.g., irritable bowel syndrome, low back pain, vulvodynia), may show similar features. It is also possible that this phenomenon of neural activation in pain processing might also be noted in more classic peripheral, nociceptive pain conditions such as osteoarthritis or rheumatoid arthritis.

In summary, chronic pain, MDD, and other forms of these conditions frequently coexist. Although it is tempting to lump these constructs together because they can co-occur and may have common mechanisms, it may not be prudent to extrapolate this concept to individual patients. It appears as though there are different and easily distinguished sensory and affective elements to each individual’s pain experience. There are strong data suggesting that these elements are somewhat independent of one another and respond differentially to both pharmacologic and nonpharmacologic interventions. Evaluation of these sensory and affective dimensions in patients with chronic pain is likely to improve diagnosis, choice of treatment, and treatment efficacy.

REFERENCES
