Overall fibromyalgia pain is predicted by ratings of local pain and pain-related negative affect—possible role of peripheral tissues

R. Staud¹, C. J. Vierck², M. E. Robinson⁴ and D. D. Price²,³

Objectives. Despite variable numbers and intensities of local pain areas, fibromyalgia (FM) patients can provide overall clinical pain ratings. We hypothesized that the overall clinical pain is largely determined by the pain intensity of local body areas. Thus, we assessed the role of local body pains as predictors of overall clinical pain in FM patients.

Methods. Ratings of overall clinical pain intensity and pain-related negative affect (PRNA) were obtained from 277 FM patients. In addition, the patients identified painful body areas by shading a body pain diagram and rated the intensity of each pain area using a mechanical visual analogue scale (VAS). Hierarchical regression analyses were used to examine predictors of overall clinical FM pain intensity including PRNA, number of local pain areas, and maximal/average intensity of local pain areas.

Results. The average overall clinical pain rating of all FM patients was 4.6 (S.D. 2.3) VAS. The PRNA accounted for 19%, number of painful body areas for 9% and maximal/average local pain for 27% of the variance of overall clinical FM pain (P-values < 0.001). The combination of all factors predicted 55% of the variance in overall clinical pain intensity of FM patients.

Conclusion. Peripheral factors (maximal/average local pain and number of painful body areas) predicted most of the variance of overall clinical FM pain, suggesting that the input of pain by the peripheral tissues is clinically relevant. About 19% of the pain variance was predicted by PRNA. Thus, peripheral pain and negative affect appear to be particularly relevant for overall FM pain and may represent important targets for future therapies.

Keywords: Analgesia, FM, Chronic pain, Nociception, Ratings.

Introduction

Pain is one of the most common reasons patients seek medical attention and may be associated with a variety of acute or chronic conditions [1]. Chronic pain syndromes like fibromyalgia syndrome (FM) are a major public-health problem in the US, costing our society billions of dollars annually [2]. Usually, a combination of pharmacological and non-pharmacological methods is used with limited success to treat FM patients. Thus, understanding the mechanisms of FM pain appears extremely relevant for designing effective therapies which may include reduction of painful peripheral stimuli, altering transmission within the central nervous system and changing cortical perception of painful stimuli.

Following tissue damage by trauma, surgery, infection or tumour, a local inflammatory reaction takes place. The inflammatory process includes the release and production of chemical mediators and neuropeptides resulting in peripheral sensitization with repeated and sustained depolarization of peripheral nociceptors (unmyelinated C-fibres and thinly myelinated A-delta fibres) [3, 4]. Any pain that is triggered by acute or ongoing tissue injury can be characterized as nociceptive pain. This pain can originate from somatic structures like skin, periostuem, joints and muscles or from visceral organs. Nociceptors are free nerve endings of thin unmyelinated afferents travelling with sympathetic fibres. Importantly, nociceptive input from deep somatic tissues (e.g. muscle tissues) are well-recognized to result in often profound alterations of the central nervous system pain processing (neuroplasticity) that are likely to result in chronic pain [5].

A large number of reports have described peripheral abnormalities of muscle tissues in FM that might account for pain, including reduced levels of Adenosine triphosphate and phosphocreatine [6], as well as the appearance of ragged red-fibres in the tender points (TPs) of the trapezius muscle of FM patients [7]. These findings may reflect the consequences of muscle microtrauma, which could contribute to activity-related pain and other painful symptoms experienced by these patients [8]. Some investigators have suggested that prolonged muscle tension and ischaemia may account for the painful symptoms of FM [9]. For example, low levels of oxygenation were found in the TPs of the trapezius and brachioradialis muscles of patients with FM [10]. Several studies have shown that the treatment of peripheral pain is relevant for chronic musculoskeletal pain syndromes like FM. Radiofrequency neurotomy of the zygapophysial joints produced complete pain relief in patients with chronic neck pain [11], local anaesthetic blocks abolished mechanical allodynia.
in patients with complex regional pain syndrome (CRPS) [12], hip arthroplasty normalized hip pain as well as mechanical allodynia in osteoarthritis (OA) patients [13], and epidural lidocaine injections completely eliminated pain and tenderness in FM patients [14]. These findings seem to indicate that at least some types of chronic pain are maintained by peripheral impulse input.

Clinically significant musculoskeletal pain is not uniform in intensity and consequent impact on daily activities, and the need for intervention is proportional to its magnitude. Thus, the relative intensity of pain among patients diagnosed with FM is an important predictor for overall clinical pain intensity. Furthermore, FM pain is manifest along a continuum of several factors, including spatial extent, intensity, duration and psychological impact. These factors vary greatly and are presumed to interact in determining the overall pain intensity. In a previous study [15], we have shown that the number of painful body areas and pain-related negative affect (PRNA) can be used as relevant predictors of clinical pain intensity in FM. Our current study expands these findings by asking whether local pain intensity represents an important predictor of overall clinical pain in FM. We hypothesized that local pain intensity would be associated with the magnitude of tonic impulse input from specific tissue sources. Such a pain mechanism is supported by evidence from other conditions like CRPS [12] and irritable bowel syndrome [16]. If ratings of local pain highly correlate with FM patients’ overall clinical pain, this result would provide indirect evidence for the role of peripheral impulse input in FM pain.

Materials and methods

The University of Florida Institutional Review Board approved all the procedures described in this report. Informed consent was obtained from all subjects, and the study protocols conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Study subjects

FM subjects were recruited at the Health Science Center outpatient clinics and from FM support groups. Use of analgesics, including non-steroidal anti-inflammatory drugs (NSAID), tramadol and acetaminophen, was allowed during the study. No subject was taking narcotic analgesics during the trial. Muscle relaxants and antidepressants were the most frequently used medications during the study (64% and 73%, respectively). Levels of physical activity and exercise were not recorded, but subjects were instructed to continue their usual level of activity during the study.

Ratings of clinical pain

A mechanical visual analogue scale (M-VAS) was used for the rating of current clinical pain ranging from 0–10. When pulled by the subjects, the VAS slider reveals a red line that can be used for scaling of painful sensations. The back of the slider displays the subject’s ratings to the nearest 0.1. The scale was anchored on the left with ‘no pain at all’ or ‘no unpleasantness at all’ and on the right with ‘the most intense pain imaginable’ or the ‘most unpleasant sensation imaginable’, respectively [17]. Since pain intensity and pain unpleasantness ratings were nearly identical and highly correlated (R = 0.87 and 0.97 for overall pain and local pain, respectively), only results for pain intensity are reported here. These correlations are similar to those reported previously [18].

Body pain areas and ratings of local pain intensity

All subjects identified currently painful body areas by shading the corresponding areas on a drawing depicting the front and back of the human body, as described before [15]. Subsequently, the M-VAS was used by all subjects to rate the pain intensity and unpleasantness of each shaded area (referred to as pain area). For statistical analysis, the body diagram was divided into 50 standardized areas (26 back and 24 front of body) of similar size (Fig. 1). In case a shaded area included two or more adjacent body areas, only the standardized body area that contained the majority of the shading received a pain-rating score. One investigator (R.S.) was assigned to the task to assure internal consistency of the scoring technique. Local pain ratings were always obtained before TP testing to avoid interference from mechanical stimulation.

Tender point testing

Nine paired TPs as defined by the 1990 American College of Rheumatology (ACR) Criteria for FM [19] and two control points (at the centre of the right forearm and the right thumbnail) [20] were assessed by a trained investigator using a Fischer dolorimeter (Pain Diagnostics, Great Neck, NY). The rubber tip of the dolorimeter was 1 cm in diameter. The dolorimeter was placed on the examination site and pressure was gradually increased by 1 kg/s. The subjects were instructed to report when the sensation at the examination site changed from pressure to pain. Pressure testing was stopped at that moment and the result recorded as positive (1). If no pain was elicited at ≥4 kg, the test result was recorded as negative (0).

Medical College of Virginia Pain Questionnaire

The Medical College of Virginia (MCV) Pain Questionnaire [21, 22] was used to characterize the study subjects (Table 1). The MCV Pain Questionnaire has two domains, consisting of ratings of pain (VAS) and negative emotions related to chronic pain (VAS).

Data analysis

Statistical analyses were calculated using SPSS 13.0 software (SPSS, Inc., Chicago, IL). For clinical measures with high co-linearity, principal component analysis was utilized for factor reduction. Hierarchical regression analysis was used to determine the independent association of overall clinical pain intensity with local pain ratings, number of pain areas and PRNA in FM subjects.

Results

Study subjects

A total of 277 subjects who fulfilled the 1990 American College of Rheumatology Criteria for FM [19] were enrolled in this study. Out of 277 subjects, 17 were male and 260 were female. All subjects were Caucasian except for 15 African-American, seven American Indians and two Hispanic females. The average age (S.D.) of the FM subjects was 48.3 (11.0) yrs. The demographic information of the study subjects is listed in Table 1. Most study subjects did not have other medical illnesses besides FM. However, some FM patients had mild hand OA (30%) diagnosed by physical examination, or mild cervical spondylosis diagnosed by decreased range of motion (15%) or well-controlled hypertension (12%).

Tender point testing, overall clinical pain intensity and areas of local pain

The average TP numbers were consistently high for the FM subjects and similar to those previously reported by other FM studies [23]. FM subjects tested positive at an average of 16.0 out of possible 18 TPs and 1.6 out of two control points. However, similar to previous reports, TP count was not normally distributed in our study population (skewness > 3) [24]. The average (S.D.)
The rating of overall clinical pain intensity of FM patients was 4.6 (2.3) VAS (Table 1). The correlation of TP with overall clinical pain was low (Spearman’s $\rho = 0.2$).

Number of local pain areas

FM subjects’ body drawings identified pain in an average (S.D.) of 20.2 (12.0) body areas. Pain was rated as absent in 30.4 (8.5) body areas. 11.4 (4.6) out of 18 TPs were found to be located in pain areas. The body areas most frequently described as painful included the shoulders (84.3%), arms (48.6%), lower back (64.3%) and thighs (67.4%) (Table 4).

Pain ratings of body areas

The average pain rating (S.D.) across all shaded areas was 4.1 (2.0), the highest pain intensity averaged 6.4 (2.4) and the lowest pain intensity averaged 2.0 (1.7) VAS (Fig. 2). Because we hypothesized that the maximal and average local pain ratings could be reduced to a single variable, an exploratory factor analysis was

**Table 1. Demographic information of 277 FM subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.3 (11.0)</td>
</tr>
<tr>
<td>TPs</td>
<td>16.0 (2.4)</td>
</tr>
<tr>
<td>CPs</td>
<td>1.6 (0.5)</td>
</tr>
<tr>
<td>Overall clinical pain intensity (VAS)</td>
<td>4.6 (2.3)</td>
</tr>
<tr>
<td>Overall clinical pain unpleasantness (VAS)</td>
<td>4.5 (2.5)</td>
</tr>
<tr>
<td>Number of local pain areas</td>
<td>20.2 (12.0)</td>
</tr>
<tr>
<td>Maximal local pain (VAS)</td>
<td>6.4 (2.4)</td>
</tr>
<tr>
<td>Average local pain (VAS)</td>
<td>4.1 (2.0)</td>
</tr>
<tr>
<td>Minimal local pain (VAS)</td>
<td>2.0 (1.7)</td>
</tr>
<tr>
<td>Pain-related depression (VAS)</td>
<td>5.4 (2.9)</td>
</tr>
<tr>
<td>Pain-related anxiety (VAS)</td>
<td>5.3 (2.9)</td>
</tr>
<tr>
<td>Pain-related frustration (VAS)</td>
<td>6.7 (2.6)</td>
</tr>
<tr>
<td>Pain-related anger (VAS)</td>
<td>5.0 (3.2)</td>
</tr>
<tr>
<td>Pain-related fear (VAS)</td>
<td>4.3 (3.1)</td>
</tr>
</tbody>
</table>

TPs, tender points; CPs, control points; VAS, visual analogue scale.

**Fig. 1.** The body diagram used by FM patients to indicate local pain comprised of 50 standardized areas. FM patients were asked to shade painful body areas and provide present pain ratings using a mechanical VAS (0–10).
undertaken. A principal components analysis was conducted which yielded one factor with an eigenvalue greater than one (eigenvalue = 2.4) that accounted for 82% of the variance in local pain ratings. The two pain variables loaded positively on this factor with factor loadings of 0.98, supporting our hypothesis that maximal/average ratings represented a unidimensional factor of local pain. We therefore used the factor regression scores from this analysis in subsequent regressions.

**Pain-related negative affect**

Using a VAS (0–10), FM subjects rated frustration as the highest negative emotion (6.7 VAS). Moderate negative emotions included pain-related depression (5.3 VAS), anxiety (5.3 VAS), anger (5.0 VAS) and fear (4.3 VAS). The mean (s.d.) VAS ratings of these pain-related emotions are listed in Table 1.

An exploratory factor analysis was conducted to reduce these affective variables to what was hypothesized to be a single latent variable of PRNA. To this effect, we performed a principal components analysis which yielded one factor with an eigenvalue greater than one (eigenvalue = 3.8), that accounted for 77% of the variance in affective ratings. All of the affect variables loaded positively on this factor, with factor loadings ranging from 0.84 to 0.90. This was supportive of our hypothesis that these ratings represented a unidimensional factor of PRNA. We, therefore, used the factor regression scores from this analysis in subsequent regressions to examine the influence of negative affects on clinical pain.

**Regression analysis**

A hierarchical regression analysis was performed using overall clinical pain-intensity ratings as the predicted variable with the factor regression scores of PRNA, the number of painful body areas, and the factor regression score of maximal and average pain ratings as predictor variables, entered in separate blocks (Table 2).

TP count was not used for this analysis because the distribution of TPs was skewed (skewness > 3, kurtosis > 10) and could not be normalized by mathematical transformations. In addition, the limited range of TP counts (60% of subjects had 18 TPs), resultant from the inclusion criteria, insured that it would not account for a significant portion of variance. The regression analysis was utilized to test the independent and incremental variance accounted for by a particular variable entered into the prediction equation. Each step of the hierarchical regression represented the amount of variance predicted by a variable, after controlling for the variables in previous steps of the analysis. Results of the regression indicated that 55% of the variance in overall clinical pain intensity was predicted by the linear combination of PRNA, number of painful body areas, and maximal/average pain ratings [F(1,258) = 103.7, P < 0.001]. All predictor variables captured unique variance in overall clinical pain intensity with PRNA accounting for 19%, number of painful body areas accounting for 9% of the variance and maximal/average pain ratings accounting for 27% of the variance (P-values < 0.01) (Table 2). However, because PRNA was correlated with all pain measures (R = 0.2–0.6), it was no longer a unique predictor in the regression analysis when the number of pain areas was entered in the final model.

A second hierarchical regression was performed using maximal peripheral pain ratings as the predicted variable with the factor regression score of PRNA and number of painful body areas as predictor variables, entered in separate blocks (Table 3). Results of the regression indicated that 26% of the variance in maximal pain intensity was predicted by the linear combination of PRNA and number of painful body areas [F(1,260) = 81.5, P < 0.001]. All predictor variables captured unique variance in maximal peripheral pain intensity with PRNA accounting for 25% and number of painful body areas accounting for 1% of the variance (all P-values ≤ 0.01) (Table 3).

![Fig. 2. Scatter plot of overall clinical pain of 277 FM patients and (A) number of painful body areas (left panel) or (B) maximal local pain (right panel). The correlation (Pearson’s R) of overall clinical pain with number of painful body areas and maximal pain is 0.39 and 0.72, respectively.](image-url)
Table 3. Results of regression analysis for prediction of maximal/average local FM pain

<table>
<thead>
<tr>
<th>Block</th>
<th>Variable</th>
<th>$R^2$ change</th>
<th>F change</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PRNA</td>
<td>0.25</td>
<td>87.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>Number of pain areas</td>
<td>0.01</td>
<td>56.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Full model</td>
<td>PRNA</td>
<td>0.50</td>
<td>9.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Number of pain areas</td>
<td>0.37</td>
<td>7.5</td>
</tr>
</tbody>
</table>

Beta (standardized) $t$ $P$

Full Model: $R^2 = 0.26$, $F = 81.5$, $P < 0.001$. PRNA = pain-related negative affect.

Table 4. Twenty body areas most frequently rated as painful by FM patients

<table>
<thead>
<tr>
<th>Body areas</th>
<th>FM patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R shoulder-posterior</td>
<td>81.16</td>
</tr>
<tr>
<td>L shoulder-posterior</td>
<td>80.43</td>
</tr>
<tr>
<td>R chest-posterior</td>
<td>73.19</td>
</tr>
<tr>
<td>L chest-posterior</td>
<td>73.19</td>
</tr>
<tr>
<td>R lower back</td>
<td>70.29</td>
</tr>
<tr>
<td>L shoulder-anterior</td>
<td>65.22</td>
</tr>
<tr>
<td>L lower back</td>
<td>64.49</td>
</tr>
<tr>
<td>R head-posterior</td>
<td>61.59</td>
</tr>
<tr>
<td>L head-posterior</td>
<td>61.59</td>
</tr>
<tr>
<td>R shoulder-anterior</td>
<td>60.87</td>
</tr>
<tr>
<td>L shoulder-anterior</td>
<td>60.87</td>
</tr>
<tr>
<td>R buttock</td>
<td>58.70</td>
</tr>
<tr>
<td>R buttock</td>
<td>57.97</td>
</tr>
<tr>
<td>R knee</td>
<td>53.62</td>
</tr>
<tr>
<td>L leg-posterior</td>
<td>52.17</td>
</tr>
<tr>
<td>R leg-posterior</td>
<td>50.00</td>
</tr>
<tr>
<td>R arm</td>
<td>48.55</td>
</tr>
<tr>
<td>L chest-anterior</td>
<td>47.83</td>
</tr>
<tr>
<td>L arm</td>
<td>47.83</td>
</tr>
<tr>
<td>L head-anterior</td>
<td>45.65</td>
</tr>
</tbody>
</table>

R = right; L = left.

Discussion

Most FM patients complain of local pains at the shoulders, arms, thighs or lower back, and pain originating from these body areas appears to play an important role in overall chronic FM pain. Our study demonstrated that the combination of maximal/average local pain ratings and the number of painful body areas was highly predictive of the overall clinical pain of FM patients. The combination of these two factors explained 36% of the variance in overall clinical FM pain ratings. When negative pain affect (PRNA) was added to our statistical model, more than half (55%) of the variance in ratings of overall clinical FM pain could be predicted. Thus, the results of our study supported our hypothesis that ratings of local pain and PRNA provide powerful predictors of overall clinical pain of FM patients.

Role of peripheral tissues in overall pain

The important role of peripheral input in chronic musculoskeletal pain is demonstrated by studies that reduced or abolished peripheral pain transmission by local lidocaine injections [25], local anaesthetic block [12] or radiofrequency neurotomy [26]. These findings indicate that at least some types of chronic pain are maintained by peripheral tonic input. Although the exact source of clinical pain remains unidentified in the majority of FM patients, some studies have described muscle changes, including abnormal microcirculation [27], abnormal metabolites [6], histochemical changes [28], segmental muscle fibre necrosis, DNA fragmentation [29] and abnormal mitochondria [30] as possible reasons.

Peripheral and central sensitization

One obvious source of nociceptive input for FM pain would be peripheral sensitization resulting from intense or continuous activation of nociceptors during tissue inflammation following injury. Multiple chemical mediators are released at the site of inflammation, including prostaglandins, tachykinins, cytokines, nitric oxide, serotonin and excitatory amino acids that evoke and sustain persistent activity in the sensory afferents innervating the injured or inflamed tissue [31–34]. These events result in multiple translational and transcriptional changes within the nociceptive neurons, effectively lowering their activation thresholds [35]. Thus, in contrast to the acute pain response, injury leads to persistent activity in populations of small afferents and may also activate afferent populations that are excited only in the presence of local factors generated by the injury (e.g. silent ‘nociceptors’) [36]. Persistent activity in peripheral nociceptive afferents also results in central sensitization that can exacerbate the magnitude of both the local and overall pain [37]. Electrophysiological studies have shown that the persistent activation of spinal wide-dynamic-range (WDR) neurons by small, but not large, afferents will lead to a progressive enhancement of the WDR response to each subsequent input and the enlargement of the peripheral receptive field to the spinal neuron will respond [38]. Thus, if effects of abnormal peripheral impulse input of FM patients are amplified further by a state of central hypersensitivity, as previously shown in several studies [23, 39, 40], preventing or treating central hypersensitivity is expected to reduce painful symptoms. One way of attenuating hypersensitivity would be to reduce impulse input to the spinal-cord neurons by pharmacological or other interventions. Other approaches include pharmacological interventions that target central sensitization or the combination of peripheral and central therapies.

Contributions of peripheral pain and PRNA to overall FM pain

We previously provided evidence that a considerable amount of the variance of clinical FM pain ratings can be independently predicted by the sum of local pain areas (SLPA) and PRNA [18]. In that study, SLPA accounted for 16% of the variance in clinical FM pain intensity and thus was superior to previously published predictors, including TPs [41, 42]. However, the combination of maximal/average local pain, as used in our current study, was superior to SLPA for the prediction of overall clinical FM pain (27% vs 16% of the variance) and furthermore, its contribution to the overall pain was independent of the number of pain areas (Table 2). Similar to our previous study, PRNA accounted for a substantial part of the variance in ongoing pain intensity (19%). Thus, both the studies highlight not only the important contribution of local pains but also of PRNA to clinical pain intensity. This relationship emphasizes the multidimensional nature of clinical pain and is consistent with a large body of evidence showing significant correlations between negative mood and clinical pain intensity in the general population [43, 44] as well as FM patients [41, 45–47]. In addition, negative mood and somatic focus also seem to contribute to the persistence of chronic widespread pain [48]. Community studies have shown that widespread pain resolves within 1 yr in almost half of the subjects except those who display these features [49]. Thus, PRNA may also play a role in the persistence of chronic widespread pain.

These results also suggest the need to investigate the potential causal links between tonic peripheral impulse input and PRNA.
There are good theoretical and empirical reasons to think that spatiotemporal peripheral factors, central sensitization, and the organization of pain-related pathways and brain regions foster sensory-to-affect interactions [50, 51]. Because these interactions can occur in both directions, interventions like cognitive behavioural therapy that are designed to not only decrease peripheral tonic impulse input but specifically reduce PRNA may be useful, thus characterizing the relationship of negative affect to the number and intensities of local pains.

Conclusions

FM patients' overall clinical pain appears to be largely dependent on local body pains. Our study, however, was not designed to determine the direction of this relationship, i.e. whether painful input is necessary for clinical FM pain or vice versa. The number of peripheral pain areas and the intensity of peripheral pain are better predictors of overall FM pain than number of TPs, thus suggesting their relevance for FM pathogenesis. Future attempts to improve on the 1990 ACR criteria for FM may also benefit from the inclusion of these factors. The lack of uniformity of FM body pains argues strongly for peripheral contributors to overall FM pain. Thus, tonic impulse input from peripheral tissues may play an important role in FM pain. In addition, other factors including negative affect seem to make separate and unique contributions to overall clinical FM pain. Thus, future studies are needed to further characterize the source of peripheral impulse input and their role for FM pain.

Key messages

- Overall clinical pain of FM patients is dependent on local body pains.
- FM pain is not uniformly distributed across the body but most prevalent in the shoulders, chest and lower back.
- Maximal peripheral pain and pain-related negative affect predict most (55%) of FM patients' overall clinical pain.
- Treatment of local pain and negative affect may reduce overall clinical pain in FM.

Acknowledgements

This work was supported by NIH grant NS-38767, the American Fibromyalgia Association, and supported in part by Clinical Research Center grant RR00082. The expert technical support of Myriam M. Lopez and Patricia A. Hilliard is gratefully acknowledged.

The authors have declared no conflicts of interest.

References


