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# Title Page

# Pain Extent is Associated With Pain intensity but not With Widespread Pressure or Thermal Pain Sensitivity in Women With Fibromyalgia Syndrome


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**Key words**: fibromyalgia, pain extent, pressure pain, sensitization

# Abstract

**Introduction/Objective**: Widespread pain is considered a sign of central sensitization in people with chronic pain. Our aim was to examine whether pain extent, assessed from the pain drawing, relates to measures from quantitative sensory testing in fibromyalgia syndrome (FMS). **Methods**: Thirty women with FMS and no other co-morbid conditions completed pain drawings (dorsal and ventral view) and clinical and related-disability questionnaires. Pain extent and pain frequency maps were obtained from the pain drawings using a novel customized software. Pressure pain thresholds were assessed over the 18 tender points considered by the 1990 American College of Rheumatology criteria for FMS diagnosis and over two additional standardized points. Heat and cold pain thresholds were also assessed on the dorsal aspect of the neck, the dorsal aspect of the wrist, and the tibialis anterior. Spearman's correlation coefficients were used to assess the relationship between pain extent and quantitative sensory testing outcomes as well as clinical symptoms. **Results**: Larger extent of pain was associated with a higher pain intensity (dorsal area: $r_s$=0.461, P=0.010; total area: $r_s$=0.593, P=0.001), younger age (ventral area: $r_s$=-0.544, P=0.002; total area: $r_s$=-0.409, P=0.025), shorter history of pain (ventral area: $r_s$=-0.367, P=0.046), and higher cold pain thresholds over the tibialis anterior muscle ($r_s$= -0.406, P=0.001). No significant association was observed between pain extent and the remaining outcomes. **Conclusions**: Pain drawings constitute an easy and accurate approach to quantify widespread pain. Larger pain extent is associated with pain intensity but not with signs of central sensitization in women with FMS.

**Key words**: fibromyalgia, pain extent, pressure pain, sensitization

# Pain Extent is Associated With Pain intensity but not With Widespread Pressure or Thermal Pain Sensitivity in Women With Fibromyalgia Syndrome

## Introduction

Fibromyalgia syndrome (FMS) is a disabling condition including widespread pain and fatigue, in addition to cognitive, physical and sleep disturbances. The mean worldwide prevalence of FMS is estimated at ~2.7% although it varies depending on the diagnostic criteria applied [1]. Although the etiology of FMS is debated, it is accepted that people with this condition exhibit hyper-excitability of the central nervous system [2].

Pain drawings are used to obtain an illustration of pain location and distribution in people with pain [3]. Several instruments are used to record the pain location and the most common method involves asking the patients to draw where they feel pain on a paper body chart [3,4]. The location of symptoms is heterogeneous in FMS since most patients report that localized pain was present before widespread pain. Some studies have shown through pain drawings that the widespread pain in FMS is formed by multiple regional painful areas and that the intensity of pain is associated with the number of painful body areas [5] and ratings of local pain [6]. Larger pain areas are thought to represent a clinical sign of central sensitization [7]. There is some evidence showing that enlarged pain areas are associated with more persistent and severe pain [8] and higher pressure sensitivity [9] in knee osteoarthritis suggesting that quantification of pain extent can assist clinicians to identify subjects with sensitization. Further, widespread pain was associated with self-perceived disability, depression and self-efficacy in chronic whiplash [10].

No previous study has investigated if larger pain extent is associated with central sensitization in FMS. Therefore, our aim was to examine whether pain extent relates to clinical variables, health status and quantitative sensory test measures in women with FMS.

# Methods

## Participants

Women diagnosed with FMS following the American College of Rheumatology (1990/2010) criteria participated. Since a combination of both ACR 1990 and 2010 criteria is recommended [11], patients were required to fulfill the 2010 ACR Criteria and also needed to present with 11/18 tender points according to the 1990 ACR Criteria [11]. They were excluded if they presented with: 1, co-morbid medical conditions; 2, endocrine disorders; 3, malignancy; 4, psychiatric illnesses; 5, medication drug usage other than analgesics or antidepressants; 6, previous history of surgery or whiplash injury. They were asked to avoid any analgesic or muscle relaxant 24 hours prior to the examination. No change was made to their prophylactic drug treatment. The study was approved by local Ethics Committee of Universidad Rey Juan Carlos (URJC 08-30-2014). All patients provided informed written consent prior to their inclusion.

## Self-reported data

An 11-point numerical point rating scale (NPRS; 0: no pain; 10: maximum pain) was used to determine the current, the worst, and the lowest level of pain experienced the preceding week [12]. The Spanish version of the Fibromyalgia Impact Questionnaire (FIQ) was used to determine related-disability [13]. Higher scores of the questionnaire indicate more negative impact.

## Pain drawing

Participants were instructed to complete a pain drawing by shading, with a pencil, the perceived extent and location of their symptoms on two paper body charts (ventral and dorsal body views). All paper pain drawings were scanned to digital format. The scanned images were manually aligned to a standardized digital body chart and the pain drawings were copied manually by two trained operators using an image analysis software (Inkscape V.0.48.5) [14]. Pain extent, reported as the total number of pixels within the digital encircled pain drawings and inside the body chart, was computed for each digitalized chart [15,16]. Pain extent was expressed as percentage of the total body chart area (ventral: 21577 pixels, dorsal: 145675 pixels, total: 291978 pixels). Pain frequency maps were obtained by superimposing the pain drawings from all participants to illustrate the most frequently reported location of pain across the sample. A color grid was used to indicate the percentage of people that reported pain in a specific area.

**Quantitative Sensory Testing (QST)**

Pressure pain thresholds (PPT) were assessed with an electronic algometer (Somedic AB©, Farsta, Sweden). Patients were instructed to press the "stop-button" as soon as the pressure turned to pain. The mean of three trials on each point was used in the analysis. A 30sec resting period was allowed between trials. The reliability of algometry is high in patients with muscle pain [17]. PPT was measured bilaterally over the 18 tender point areas considered for FMS diagnosis and over the second metacarpal and tibialis anterior muscle in a random order.

Thermal pain thresholds over the dorsal aspect of the neck, the dorsal aspect of the wrist and the tibialis anterior muscle were tested with a Thermotest System (Somedic AB©, Farsta, Sweden). Patients were instructed to press a hand-controlled switch when the sensation change from heat/cold to heat pain/cold pain (heat or cold pain thresholds, HPT/CPT). The mean of 3 trials for each region was used for the analysis. A rest of 5 s was provided between trials.

**Sample size calculation**

Sample size calculation was based on detecting significant moderate correlations ($r=0.6$) between the variables with an alpha level ($\alpha$) of 0.05 and a desired power ($\beta$) of 95%. This generated a sample size of at least 25 subjects.

**Statistical analysis**

Distribution of the data was tested with the Shapiro-Wilk test and non-normally distributed data were observed. Since no side-to-side differences in PPTs, HPTs or CPTs were found, the mean of both sides was used in the analysis. Spearman's correlation coefficients were computed to reveal associations between pain extent with tender point count, pain intensities, related-disability, PPTs, HPTs and CPTs. Correlations were considered weak when $r<0.3$; moderate when $0.3<r<0.7$, and strong when r>0.7. Statistical analyses were performed using SPSS 22 (SPSS Inc, Chicago, IL, USA). The significance level was set at $P<0.05$.

# Results

### Demographic and clinical data of the patients

Thirty women with FMS (age: 49.5±8.1 years) were included. **Table 1** summarizes all data of the sample. The pain extent was 16.2%±3.4%, 13.3%±4.6% in the ventral and 19.3%±6.5% in the dorsal body areas. Pain frequency maps are illustrated in **Figure 1,** whereas correlations between pain extent, clinical symptoms and measures of central sensitization are reported in **Table1**.

### Pain extent and clinical symptoms

Significant negative correlations were observed between pain extent and age (ventral area: $r_s$=-.0544, P=0.002; total area: $r_s$=-0.409, P=0.025) and pain duration (ventral area: $r_s$=-0.367, P=0.046): larger pain extent was associated with younger age and shorter history of symptoms. Pain extent was positively correlated with the worst level of pain (dorsal area: $r_s$=0.461, P=0.010; total area: $r_s$=0.593, P=0.001): the larger pain extent, the higher pain intensity. **Figure 2** illustrates the scatter plots showing the association between pain extent and the worst level of pain. No other association was found between pain extent and clinical features, including tender point count or disability.

### Pain extent and measures of central sensitization

No significant associations were observed between pain extent and widespread PPT or HPT. Pain extent measured from the ventral body chart showed a significant negative correlation with CPT over the tibialis anterior muscle ($r_s$=-0.406, P=0.001): the larger the pain extent, the lower the CPT.

## Discussion

Pain extent was positively associated with the worst level of pain and negatively associated with age and years with pain in women with FMS: a larger distribution of pain correlated with higher intensity of their worst pain, younger age, or shorter history of pain. Pain extent was not associated with tender point count, pressure and thermal pain sensitivity (except CPT over the tibialis anterior) in this sample of women with FMS.

Although it is accepted that individuals with FMS exhibit widespread pain, the evaluation and the quantification of pain drawings in FMS is scarce. Pain frequency maps reported in our study indicate a widespread pain pattern in our sample of women with FMS. In fact, the pain extent values observed in our sample of FMS women were higher than those areas reported in woman with whiplash associated disorders [10]. Further, the pain frequency maps also showed that FMS patients reported pain in neck, shoulder, low back, elbow, or knee areas supporting previous assumptions that the overall widespread pattern suffered by people with FMS is the sum of multiple regional pain areas [5,6]. This hypothesis is supported by current ACR2010 preliminary diagnostic criteria where patients are required to report painful regions rather than widespread pain [18]. Nevertheless, although widespread pain is no longer required for FMS diagnosis according to the ACR2010 diagnostic criteria, most patients (94%) suffered from widespread pain [18]. Therefore, it seems that the symptoms experienced by women with FMS are widespread, but localized in particular areas. Our study is the first to reveal that pain frequency maps show an overlap between the locations of the most frequent pain areas and tender point locations originally proposed and included in 1990 classification criteria for FMS.

Pain extent was associated with younger age and shorter history of pain symptoms. Patient-reported improvements have been also previously correlated with younger age and shorter duration of FMS symptoms at diagnosis [19]. The reduction of pain extent could reflect a natural evolution of FMS where the pain is perceived more widespread during the first years and with time pain tends to become more localized. This hypothesis agrees with long-term studies suggesting that a portion of patients with FMS usually experience improvement in symptoms with time [20,21].

In our study, pain extent was positively associated with the worst pain intensity experienced suggesting that clinical pain is associated with more widespread pain. These results agree with those previously observed in people with knee osteoarthritis where larger pain areas were associated with greater severity of pain [8,9]. The association between pain intensity and pain extent would provide indirect evidence for the role of peripheral input in FMS as previously suggested [5]. Persistent and long-lasting activity from peripheral nociceptive afferents can result in central sensitization that can exacerbate the magnitude of the overall widespread pain [5].

Pain extent was not associated with pressure or thermal pain sensitivity in our sample of women with FMS. We only found that more widespread pain was associated with cold hyperalgesia over the tibialis anterior muscle. Cold pain sensitivity has been previously reported in FMS [22]. Cold hyperalgesia is considered a feature of neuropathic pain as result of peripheral nerve injury and there is evidence suggesting the concept of impaired small fibre function pointing towards a neuropathic nature of the pain in FMS [23]. One possible explanation for our findings may link widespread pain, younger age and shorter history of pain combined with a lower neuropathic involvement.

We explored, for the first time, the utility of the pain drawing to extract pain extent scores in FMS. The software used to compute pain extent eliminates estimation errors; nevertheless, there are some methodological issues that should be considered. First, we collected data from a sample of 30 women, which may be considered a small sample. Second, although the assessment method has shown high reliability [15,16], information on the reliability of pain drawings specifically in FMS are not available. Third, we collected static outcomes of sensitization. We do not know if pain extent would be associated with dynamic outcomes such as wind-up, spatial/temporal summation, or conditioned pain modulation. Finally, we did not investigate the presence of psychological features that can be associated with higher pain extent [10] or abnormal pain drawings in individuals with chronic pain [24]. Nevertheless, a recent review did not support the assumption that unusual pain drawings predict the presence of a disturbed psychological state [25].

## Conclusions

This study showed that an expanded distribution of pain area was correlated with greater pain intensity, younger age, shorter history of symptoms and cold hyperalgesia detected over the tibialis anterior muscle in women with FMS. Pain extent was not associated with tender point count, pressure or heat hypersensitivity. Pain drawings may constitute an easy and accurate approach for quantification of widespread pain although their ability to identify central sensitization in FMS is questionable.

## Disclosures

M Barbero, C Fernández-de-las-Peñas, M Palacios-Ceña, C Cescon and D Falla, authors of this manuscript, have no conflict of interest to declare.

## Legend of Figures

**Figure 1:** Pain frequency maps generated by superimposing the pain drawings of all women with fibromyalgia syndrome (n=30). The colour bar represents the frequency of coloured areas. Dark red indicates the most frequently reported area of pain

**Figure 2**: Scatter plots of correlations between the total (A) and dorsal (B) are of pain extent with the worst pain experienced the preceding week (NPRS, 0-10) in women with fibromyalgia syndrome (n=30). Note that several points are overlapping. A positive linear regression line is fitted to the data.

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**Table 1**: Spearman's correlation coefficients between the pain extent, computed from pain drawings and quantitative sensory testing outcomes and clinical symptoms for women with fibromyalgia syndrome (n=30).

| | | **Median (IQR)** | **Correlation with Pain extent ($r_s$)** | | |
|---|---|---|---|---|---|
| | | | Ventral | Dorsal | Total |
| | Age (years) | 52 (12) | -.544** | .035 | -.409* |
| | Pain duration (years) | 8 (4.5) | -.367* | .336 | -.017 |
| | FIQ (0-100) | 58.3 (13.5) | .262 | -.147 | .060 |
| | Tender point count (0-18) | 16 (4.25) | .031 | .007 | .016 |
| NPRS (0-10) | Mean pain intensity | 6 (2.0) | .110 | .198 | .272 |
| | Worst level of pain | 9 (1.0) | .212 | .461* | .593** |
| | Lowest level of pain | 4 (1.5) | -.008 | .324 | .215 |
| PPT (kPa) | Suboccipital area | 192 (53.5) | .056 | -.196 | -.118 |
| | Mastoid process | 205 (42.5) | -.005 | -.197 | -.218 |
| | Trapezius muscle | 185 (39) | -.159 | .103 | -.019 |
| | Levator scapulae muscle | 244 (50.2) | .127 | -.151 | -.065 |
| | Posterior iliac crest | 280 (64.5) | -.091 | -.116 | -.214 |
| | Greater trochanter | 275.5 (78.5) | -.040 | .009 | -.098 |
| | Sternocostoclavicular joint | 181.5 (46.7) | .055 | -036 | -.38 |
| | Wrist extensor muscles | 225.5 (49.7) | .217 | -.066 | .053 |
| | Knee (internal part) | 205.5 (22.7) | -.168 | -.040 | -.233 |
| | Second metacarpal | 254.5 (55) | .082 | .013 | .044 |
| | Tibialis anterior muscle | 290.5 (57.7) | -.084 | -.169 | -.190 |
| HPT (ºC) | Cervical Spine | 38.7 (2) | .190 | -.192 | .006 |
| | Dorsal aspect of wrist | 39.2 (2.3) | .206 | .021 | .124 |
| | Tibialis anterior | 40.4 (2.1) | .244 | .047 | .258 |
| CPT (ºC) | Cervical Spine | 24.5 (5.1) | -.199 | .153 | -.006 |
| | Dorsal aspect of wrist | 23.9 (4.6) | -.360 | .095 | -.215 |
| | Tibialis anterior | 24.5 (4.5) | -.406* | .226 | -.147 |

NPRS: Numerical Pain Rating Scale; FIQ: Fibromyalgia Impact Questionnaire;
PPT: Pressure Pain Threshold; CPT: Cold Pain Threshold; HPT: Heat Pain Threshold
IQR: Inter Quartile Range; $r_s$: Spearman's rho

* Significant at the 0.05 level (2-tailed)
** Significant at the 0.001 level (2-tailed)