Published in final edited form as:

Pain. 2007 July ; 130(1-2): 177–187.

Spatial Summation of Mechanically Evoked Muscle Pain and Painful Aftersensations in Normal Subjects and Fibromyalgia Patients

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Abstract

Impulse frequency and number of recruited central neurons are relevant for pain encoding and temporal as well as spatial summation of pain (SSP). Whereas SSP of heat-induced pain is well characterized, mechanical SSP (MSSP) has been less studied. MSSP may be relevant for chronic pain conditions like fibromyalgia (FM) and play an important role in the pathogenesis of this chronic pain syndrome. Our study was designed to determine MSSP in twelve normal controls (NC) and eleven FM subjects. MSSP testing consisted of 5sec suprathreshold pressure-pain stimulations of forearm muscles by up to three identical probes (separated by 4cm or 8cm). The stimulated areas ranged between 0.79cm² and 2.37cm². The subjects rated the pain intensity of mechanical stimuli as well as pain aftersensations. Although MSSP increased monotonically in NC and FM subjects, pressure pain and pressure pain aftersensations were greater in FM subjects and highly associated with clinical pain intensity ($r^2 = .44$ to $.64$), suggesting that spatial and temporal summation factors may contribute to overall clinical pain. However, despite higher experimental pain ratings, the magnitude of MSSP was not statistically different between NC and FM subjects. Furthermore, muscle stimuli elicited more MSSP when separated by 8cm than 4cm and this finding was not different between NC and FM subjects. Thus, mechanisms of MSSP were similar for both FM and NC subjects. The important role of MSSP for pain encoding suggests that decreasing pain in some muscle areas by local anesthetics or other means, may improve overall clinical pain of FM patients.

Keywords

Spatial summation; Aftersensations; Mechanical; Fibromyalgia; Dermatome; Chronic pain

2.0 Introduction

Spatial summation of pain (SSP) relies on central pain mechanisms (Coghill et al., 1993c; Price, 1999) and is important for pain-coding (Price et al., 1989; Douglass et al., 1992; Defrin and Urca, 1996). Whereas most research on SSP utilized thermal stimuli, the spatial summation of

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pressure pain has not been studied in great detail. Both spatial and temporal summation (TSP) are integral mechanisms of pain, particularly in persistent pain conditions (Noordenbos, 1959;Chery-Croze and Duclaux, 1980;Price et al., 1989;Price and Harkins, 1992;Defrin et al., 2002;Defrin et al., 2003). Considerable attention has recently been given to pain summation mechanisms in fibromyalgia (FM), a chronic condition of widespread musculoskeletal pain associated with central sensitization (Staud et al., 2001;Desmeules et al., 2003;Staud et al., 2003a;Staud et al., 2004a;Staud et al., 2004b;Julien et al., 2005;Staud et al., 2006). Compared to pain-free normal control (NC) subjects, FM patients exhibit abnormally enhanced TSP, longer duration of TSP aftersensations, and require lower stimulus frequencies to evoke TSP (Staud et al., 2001). Such abnormalities in TSP have been observed in FM patients with different stimulus modalities including heat and pressure (Desmeules et al., 2003;Staud et al., 2003a). Importantly, greater TSP was elicited by repetitive mechanical muscle (Staud et al., 2003a) than cutaneous heat stimuli in FM compared to NC subjects (Staud et al., 2001). Thus enhanced TSP from muscle stimuli appears to be relevant for widespread pain in FM.

In contrast, there is mixed evidence for abnormal SSP in FM and the extent to which SSP is important for FM pain is uncertain. Using two-minute cold immersions of the forearm, Julien et al. (2005) found that FM patients had abnormally increased SSP, possibly due to inefficient pain inhibitory mechanisms. Another FM study, however, showed no abnormalities of SSP when brief (5 sec) heat stimuli were applied to the hands and forearms (Staud et al., 2004c). Thus, the extent to which abnormal SSP contributes to FM pain is unclear.

A limitation of most published SSP studies in NC and FM patients is the almost exclusive use of cutaneous test stimuli. FM patients, however, report deep-tissue pain far more commonly than cutaneous pain. Thus studies are needed that characterize the role of mechanical SSP (MSSP) from deep-tissue stimulation. The present study was specifically designed to address questions about the central integration of pain and aftersensations (AS) evoked by spatially separate mechanical pain stimuli and to compare these responses in NC and FM patients. In particular, pain AS were of interest to us because 1) we have previously shown that the magnitude of enhanced TSP-AS can predict significant proportions of variance in clinical FM pain ratings (Staud et al., 2003b), and 2) it has been shown that AS-magnitude and duration are strongly associated with the excitability of central nociceptive neurons (Cuellar et al., 2005).

In contrast to previous studies, we tested MSSP with three large, spatially separate mechanical probes which are known to elicit predominantly deep-tissue pain sensations (Kosek et al., 1993).

3.0 Materials and Methods

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

3.1 Study Subjects

NC subjects came from the University Health Science Center and the University Campus, Gainesville. Subjects who fulfilled the 1990 American College of Rheumatology (ACR) Criteria for FM were recruited from the Health Science Center Outpatient Clinics and from FM support groups. Prior to testing, all subjects underwent a clinical examination and were excluded from the study if they had abnormal findings unrelated to FM. Continuation of analgesics, including non-steroidal anti-inflammatory drugs (NSAID) and acetaminophen, was not allowed during the study. Therefore, subjects were asked to discontinue analgesics for the duration of five drug half-lives before testing, except narcotics which had to be stopped at least

two weeks prior to study entry. Low dose muscle relaxants and amitriptyline (<15 mg/day) were permissible during the study for treatment of insomnia.

3.2 Ratings of Clinical and Experimental Pain

For ratings of current clinical and experimental pain, a mechanical visual analogue scale (M-VAS) was used (Price et al., 1994) ranging from 0 - 10. The scale was anchored on the left with “no pain at all” and on the right with “the most intense pain imaginable”.

3.3 Tender Point Testing

Nine paired tender points as defined by the ACR Criteria (Wolfe et al., 1990) and two control points (at the center of the right forearm and the right thumbnail) 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/sec. 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 maximal pressure was ≤ 4 kg. If no pain was elicited at ≥ 4 kg the test result was recorded as negative (0).

3.4 Testing Sessions

All subjects underwent one session of MSSP testing. Figure 1 illustrates the locations and different combinations of forearm stimuli used during the experiments. Single probe stimuli were applied to the same three areas of the forearm. Mechanical stimuli were never applied to both forearms at the same time.

3.5 Mechanical Test Stimuli

Three areas were chosen for mechanical testing on the volar surfaces of each forearm 4 cm apart and marked with a pen. Particular care was taken to avoid areas overlying large blood vessels or tendons. The test areas were located between the ulna and radius comprising only soft tissue (i.e. muscles and connective tissues). The pressure applied by each probe was always 2.5 kg to avoid excessive pain in subjects with mechanical hyperalgesia/allodynia. The test stimuli were alternated between three areas of each forearm with at least 1 min between each test stimulus or until all aftersensations had resolved.

Each subject's forearm was placed into an acrylic mold mounted underneath the pneumatic pistons of the testing apparatus and was immobilized by Velcro straps. Mechanical stimuli were applied to the marked areas on either forearm in counterbalanced fashion (Figure 1). To avoid order effects the stimulus applications were counterbalanced by a) number of probes and b) order of stimulation. The distance between the probes varied between 4 cm and 8 cm (two probes could be 4 cm or 8 cm apart; the distance between each of three probes was always 4 cm).

During mechanical stimulation (duration: 5 sec) pressures were increased from 0 to 2.5 kg at a rate of 1 kg/sec, maintained for 2.5 sec, and terminated by immediate retraction of the probe(s) from the forearm (Figure 2). Before each stimulus the probes were positioned several millimeters above the skin surface. If one or two probes were not used during a stimulation trial they were placed 8 cm above the skin surface to prevent skin contact at full piston extension. The mechanical force transmitted to the tissues was measured by an electronic pressure transducer (strain-gage) mounted on one of the probes (see Figure 3). A digital read-out provided real-time measurements of the applied pressures. Because all probes were powered by pressurized air in parallel fashion, the measurement of one probe's pressure was representative for all other probes. The probes were activated by a foot pedal resulting in

simultaneous pressurization of all probes at a preset force. The air pressure was regulated by a pressure valve according to a predetermined value. This experimental design as well as concealing the probes behind a curtain, assisted in blinding of the study subjects regarding the number of probes used during the experiments.

3.6 Apparatus Used for MSSP Experiments

Spatial summation studies of deep tissue pain are technically challenging because of varying characteristics of deep tissues at different locations. We resolved this problem by using several mechanical probes powered by air pressure in a parallel design (see Figure 3). Thus our proprietary stimulator not only provided identical pressure stimuli at several different test sites separated by up to 8 cm but also made simultaneous activation of all probes possible. In addition to visual barriers, this latter feature was intended to blind the study subjects to the number of activated probes. Up to three pneumatic pistons were used to apply precisely controlled muscle stimuli during the experiments (see Figure 3). The pistons were part of a pneumatic cylinder mounted on steel bars which were attached to a stainless steel base plate to prevent movement of the cylinders during pressure applications. The cylinders were fastened to the bars by winged screws, thus providing easy maneuverability in the horizontal and vertical axis. The circular foot plate of each piston (diameter: 1cm; area: 0.79 cm²) was covered by acrylic with smooth edges. Hoses from a pressurized air tank were connected to all cylinders in parallel fashion to provide equal pressure to each piston. Controlled by a pressure valve, the pneumatic pistons extended for up to 8 cm (dependent on air pressure and tissue resistance) and actively retracted into the cylinders after each stimulus. This design enabled the simultaneous application of identical pressures at each piston tip regardless of variances in tissue resistance. It also allowed rapid applications of mechanical stimuli without prolonged skin contact.

3.7 Blinding of Study Subjects to Probe Number

Because expectations related to the number of probes used for the experiments could affect each subject's pain ratings, all experiments were performed behind a visual barrier. Thus the subjects were unable to see the testing apparatus, including the number of probes used for each part of the experiments. After each stimulus as well as 15 sec and 30 sec after its termination, the subjects were prompted to rate mechanical pain sensations to assess not only immediate but also after-sensations associated with muscle stimulation. In addition the subjects were asked after each stimulus to provide one verbal descriptor for probe related sensations. Subsequently they were prompted to estimate the number of probes used for each particular trial. All subjects were aware that the number of probes used during the experiments ranged from one to three.

3.8 Data analysis

Statistical analyses were calculated using SPSS 15.0 software (SPSS, Inc., Chicago, IL). A series of mixed model ANOVAs was used for testing of spatial summation of pressure pain with diagnosis and number of probes as independent variables. Wilcoxon signed rank test was utilized for comparisons of subjects' estimates related to number of mechanical probes.

4.0 Results

4.1 Study Subjects

Twelve NC and eleven FM subjects were enrolled in this study. All subjects were female and right handed, and all were Caucasian except for one Asian American and one Hispanic female. The average age (SD) of the NC and FM subjects was 35.6 (14.1) years and 44.6 (15.9) years, respectively. An independent t-test showed that the age of NC and FM subjects was not significantly different ($p > .05$). FM subjects reported moderate overall clinical pain ratings of

3.3 VAS units (see Table 1). The number of tender points was 4.5 and 16.6 for NC and FM subjects, respectively. 45% of FM subjects took low doses of muscle relaxants (mostly cyclobenzaprine) or antidepressants, which were withheld on the day of testing.

4.2 Subject Blinding to Number of Probes Used

Correct estimates of probe numbers by the study subjects during each experiment varied between 26 % and 92% in NC and FM subjects (see Table 2). Most correct estimates were reported during one (83.0 %) and three probe (65.7%) experiments. The least correct estimates were provided by the subjects during two probe experiments (26%). Wilcoxon's signed rank test showed a significantly higher percentage of correct estimates for one and three probe experiments compared to two probe experiments ($p < .03$). However, there was no significant difference between NC and FM subjects' correct estimates noted ($p > .05$).

4.3 Pain Ratings of Mechanical Pain Stimuli at Either Forearm

Because pain ratings of mechanical pain stimuli applied to the right or left forearm were not significantly different (all $p > .05$), the averaged ratings of both upper extremities were used for the analysis.

4.4 Ratings of Mechanical Pain Stimuli Using Single Probes

Pain evoked by single probe stimuli was considerably greater in FM compared to NC subjects. The mean (SD) mechanical pain ratings during 5 sec muscle compression ranged from 0.93 (0.78) to 1.02 (0.76) VAS units and 4.38 (2.50) to 4.59 (2.62) VAS units for NC and FM subjects, respectively (Figure 4). Dependent t-tests did not show significant differences between mechanical pain ratings related to individual probes at any of the three probe locations in either NC or FM subjects ($p > .05$). Independent t-tests, however, demonstrated that FM subjects rated mechanical pain stimuli by single probes significantly higher than NC at every probe location (all $p < .001$).

4.5 Spatial Summation of Mechanical Pain

Besides pain ratings, all subjects provided one single most appropriate verbal descriptor of probe related sensations other than pain after each stimulus. The most frequently used verbal descriptors included dull (25.5%), sore (19.8%), aching (18.9%), throbbing (8.5%), tingling (7.6%), and radiating (6.6%). These terms comprised 87% of all used verbal descriptors and were consistent with deep tissue sensations. Chi square tests showed that NC and FM subjects did not differ in their use of verbal descriptors except for "throbbing", which was more frequently used by FM compared to NC subjects ($p < .05$).

4.5.1 Effects of Probe Location on MSSP Using Two Probes—In this experiment the number of probes compressing muscle tissues and their locations on the forearms were varied in several ways (Figure 1 A to C). The distance between probes was either 4 cm for probe combinations A: ●●○ and B: ○●● (see Figure 1 A and B) or 8 cm for probe combination C: ●○● (see Figure 1 C). As shown in Figure 5, regardless of probe combinations, FM subjects' ratings of mechanical pain by two probes were significantly higher than NC. Mean (SD) mechanical pain ratings of NC and FM subjects were 1.64 (1.04) and 5.56 (2.66) (combination A), 1.58 (0.98) and 5.52 (2.63) (combination B), and to 1.95 (1.12) and 5.72 (2.60) (combination C), respectively. A mixed model ANOVA of mechanical pain with diagnostic group (FM vs NC) as between subjects' factor and probe combinations (3) as within subjects' factor showed a significant main effect for diagnostic group ($F(1,20) = 3.99$; $p < .001$) and probe combination ($F(2,40) = 8.51$; $p < .01$). There was no significant interaction effect detected for probe combination $\times$ diagnostic group ($F(2,40) = 0.39$; $p > .05$). The use of simple contrasts showed that probes separated by 8 cm resulted in significantly greater pain ratings than probes

separated by 4 cm in NC and FM subjects ($p < .05$). These results indicate that a) FM subjects rated mechanical pain stimuli higher than NC; and b) mechanical pain ratings of NC and FM subjects were significantly greater when two probes were separated by 8 cm than by 4 cm (see Figure 5).

4.5.2 Effects of Increasing the Number of Probes on MSSP—All three probes in this experiment were separated by 4 cm (see Figure 1D). As shown in Figure 6, MSSP occurred in both NC and FM subjects and mechanical pain ratings were greater for FM than NC subjects. The mean (SD) mechanical pain ratings (VAS units) of 5 sec stimuli during simultaneous activation of three probes were 2.27 (1.14) and 6.15 (2.66) for NC and FM subjects, respectively. Subsequently, the average mechanical pain ratings (VAS units) using one probe (0.97 and 4.47), two probes (1.72 and 5.60) and three probes (2.28 and 6.15) were compared in NC and FM subjects, respectively (Figure 6). A mixed model ANOVA of mechanical pain ratings was performed with diagnostic group (2) and number of probes (3) as independent factors. This analysis showed a significant main effect for diagnostic group ($F(1,21) = 22.48$; $p < .001$) and number of probes ($F(2,42) = 13.0$; $p < .001$). There was no significant interaction effect of diagnostic group $\times$ probe number noted ($F(2,42) = 1.51$; $p > .05$), indicating that increasing the number of probes from one to three did not affect NC and FM subjects' ratings differently. Use of simple contrasts showed that mechanical pain ratings significantly increased with each step-wise addition of probes ($F(1,21) = 55.84$; $p < .001$). These results indicate that FM subjects rated mechanical pain stimuli higher than NC. In addition, mechanical pain ratings increased monotonically with increasing number of probes from one to three (see Figure 6). This effect, however, was not statistically different between NC and FM subjects.

4.6 Correlations of MSSP Ratings with Clinical FM Pain

To test the relationship of mechanical pain ratings with the overall clinical pain of FM subjects, several correlation analyses were performed. Pearson's product-moment correlations of clinical FM pain with mechanical pain ratings were significant for one probe ($r^2 = .47$; $p < .05$), two probes ($r^2 = .47$; $p < .05$), or three probes experiments ($r^2 = .44$; $p < .05$) (Figure 7).

4.7 Summation of Mechanical Pain Aftersensations

4.7.1 Summation of 15 sec Mechanical Pain Aftersensations—VAS ratings of MSSP aftersensations (AS) were obtained in NC and FM subjects 15 sec and 30 sec after the end of each set of mechanical stimuli (see Figure 8). Ratings of AS related to mechanical stimuli at 15 sec as well as 30 sec showed spatial summation and were considerably higher in FM as compared to NC subjects. AS ratings obtained 15 sec after the last stimulus increased from 0.12 and 3.47 (one probe) to 0.27 and 3.94 (two probes) and 0.33 and 4.17 (three probes) for NC and FM subjects, respectively. A repeated measures ANOVA of 15 sec AS ratings with number of probes and diagnostic group as independent variables showed a significant main effect for number of probes ($F(2,42) = 20.92$; $p < .001$) and diagnostic group ($F(1,21) = 28.28$; $p < .001$). There was a significant number of probes $\times$ diagnostic group interaction ($F(2,42) = 5.87$; $p < .01$) indicating that the observed increase of AS ratings was greater in FM than NC subjects. Simple contrasts showed that the change from one to two probes significantly increased 15 sec AS ratings in NC ($p < .05$) and FM subjects ($p < .01$). The 15 sec AS ratings associated with the stepwise increase from two to three probes were only significantly different in FM subjects ($p < .05$). This analysis showed that not only mechanical pain ratings of spatially separate pressure stimuli but also their 15 sec AS summated in both NC and FM subjects.

4.7.2 Correlations of 15 sec MSSP-AS with Clinical FM Pain—To evaluate the relationship of 15 sec AS with clinical pain a correlation analysis was undertaken in FM subjects. Pearson product-moment correlations of clinical FM pain with ratings of 15 sec AS

were significant for experiments using one probe ($r^2 = .55$; $p < .05$), two probes ($r^2 = .64$; $p < .05$), and three probes ($r^2 = .60$; $p < .05$) (Figure 9A).

4.7.3 Summation of 30 sec MSSP-AS—Ratings of MSSP-AS at 30 sec likewise were higher as the number of probes increased from one to three, again showing spatial summation (see Figure 8B). NC and FM subjects rated 30 sec AS as 0.03 and 3.12 VAS units for one probe, 0.06 and 3.46 VAS units for two probes and 0.10 and 3.58 VAS units for three probes, respectively. In contrast to 15 sec, NC subjects rated 30 sec AS close to zero during all conditions. Therefore, only the AS ratings of FM subjects were statistically analyzed. A repeated measures ANOVA of 30 sec AS ratings with number of probes as the independent variable indicated a significant main effect for probe number ($F(2,20) = 9.57$; $p < .01$). Simple contrasts, however, showed that only the change from one to two probes significantly increased 30 sec AS ratings ($p < .05$). The 30 sec AS ratings associated with two or three probes were not significantly different ($p > .05$). Thus 30 sec AS summated in FM subjects but this increase was not as robust as seen with 15 sec AS.

4.7.4 Correlations of 30 sec MSSP-AS with Clinical FM Pain—Similar to 15 sec AS the relationship of 30 sec MSSP-AS with clinical FM pain was tested by correlation analysis. Pearson product-moment correlations of clinical FM pain with ratings of 30 sec AS were significant for experiments using one probe ($r^2 = .56$; $p < .05$), two probes ($r^2 = .60$; $p < .01$), and three probes ($r^2 = .59$; $p < .01$) (Figure 9B).

5.0 Discussion

Our experiments demonstrated MSSP for both NC subjects and FM patients. Although FM patients consistently rated pain from mechanical stimuli as more intense compared to NC subjects, MSSP and the factors that influence it were found to be very similar for both study populations. For both NC and FM subjects, MSSP increased monotonically during step-wise enlargement of stimulated tissue areas. Similar summation effects were also found for mechanical pain-AS. Probe separation by large distances (from 4cm to 8cm) resulted in increased MSSP of NC as well as FM patients. Increasing mechanical probe separation, however, did not improve the ability of study subjects to correctly estimate the number of probes as seen in previous experiments using heat stimuli (Price et al., 1989).

5.1 Different Painful Sensations from Skin or Deep Tissues

Almost all previous trials of MSSP have tested spatial summation of skin and/or bone afferents (Greenspan et al., 1997). Most patients with chronic non-malignant pain, however, do not report pain from skin but from deep tissues, including muscles and other soft tissues. Thus testing of MSSP of muscles as in our current study is likely clinically relevant.

In contrast to muscles, nociceptors found in the skin originate from small axons that form intraepithelial terminations and so-called glomerular bodies, which are derived from single unmyelinated fibers organized below the epidermis. In somatic tissues, like muscles, this organization varies greatly and may affect the quality of painful sensations (Willis and Westlund, 1997). Thus, compared to well localized cutaneous pain, stimulation of muscle pain fibers produces a diffuse aching sensations and this difference in pain sensations is relevant for MSSP testing. Consistent with such deep tissue pain sensations, our study subjects used verbal descriptors like dull, sore, and aching to characterize pain sensations from mechanical stimuli and MSSP. Although deep tissue pain from mechanical stimulation appears to be independent from skin input (Kosek et al., 1995), we cannot completely exclude contributions from cutaneous nociceptors because they were also activated in our paradigm.

5.2 Spatial Summation of Deep Tissue Pain

The neurophysiological mechanisms of SSP have relevance for the detection of noxious events (Adriaensen et al., 1980; Van Hees and Gybels, 1981; Torebjork et al., 1984), pain coding of central nociceptive neurons (Noordenbos, 1959; Coghill et al., 1991; Coghill et al., 1993b), and identification of pain quality (Chery-Croze and Duclaux, 1980; Defrin et al., 2002). SSP results in decreased pain thresholds (Machet-Pietropaoli and Chery-Croze, 1979; Kojo and Pertovaara, 1987; Defrin and Urca, 1996; Nielsen and Arendt-Nielsen, 1997) and increased perceived pain intensity (Price et al., 1989; Douglass et al., 1992; Defrin and Urca, 1996). Whereas most research on SSP utilized thermal stimuli, the spatial summation of pressure pain has not been studied in great detail. Although several studies showed decreased pressure pain thresholds (PPT) when the stimulation area was increased (Jensen et al., 1986; Greenspan et al., 1997; Polianskis et al., 2002; Defrin et al., 2003), variations in the experimental protocols amongst these studies preclude definitive conclusions on pressure pain characteristics and on differences in responses related to different somatic tissues.

Regardless of minor differences in results across studies (Price et al., 1989), the finding that mechanical and thermal SSP from skin stimuli can take place over wide distances, and thus presumably across spinal segments, supports a pain encoding mechanism that relies on both impulse frequency and number of nociceptive neurons activated. This mechanism has been proposed on the basis of electrophysiological and neural imaging studies of the spinal cord as well as psychophysical testing (Noordenbos, 1959; Price et al., 1978; Coghill et al., 1991; Coghill et al., 1993a; Price, 1999; Defrin et al., 2003). Our results expand these findings for somatic deep tissues. We could demonstrate that progressive increase of mechanically stimulated areas across the forearm results in increasing pain intensity in NC and FM subjects (see Figure 6).

Although our results demonstrate that MSSP is not abnormal in FM, it nevertheless may play an important role for FM pain. There is evidence for the presence of numerous but spatially separate, peripheral pain generators in FM that can contribute to spatial integration of pain (Staud et al., 2006). Indeed, additional support for SSP includes high correlations of number of painful body areas with overall clinical pain intensity in FM (Staud et al., 2004b). Furthermore, interactions of pain facilitatory mechanisms, like SSP and TSP (Staud et al., 2001; Desmeules et al., 2003; Staud et al., 2004c), with pain inhibitory mechanisms, like diffuse noxious inhibitory controls (Staud et al., 2003c; Julien et al., 2005), may play an important role for FM pain.

5.3 Role of Spatial and Temporal Summation for FM Pain

Of possible clinical importance is also the observed spatial summation of mechanical pain-AS, particularly for FM patients (see Figure 8). In contrast to NC subjects, whose mechanical pain-AS were only minor, the AS of FM patients were much higher and increased by spatial summation. Previously, long-lasting enhanced AS have been elicited in FM patients during TSP experiments with heat and mechanical stimuli (Staud et al., 2003a; Staud et al., 2004a). Such enhanced AS are consistent with early mechanisms of central sensitization and represent excellent predictors of overall clinical pain in FM patients (Staud et al., 2003b). Enhanced AS may reflect prolonged afterdischarges of dorsal horn neurons which are detectable during conditions of central sensitization (Cuellar et al., 2005).

FM patients have multiple discontinuous areas of ongoing local pain, suggesting impulse input from multiple peripheral sources (Staud et al., 2006). Continuous impulse inputs from multiple sites could result in sensitization of central nervous system pathways through mechanisms that include TSP/AS. Enhanced TSP mechanisms in combination with normal SSP mechanisms could then contribute to the overall clinical pain in FM. In support of this explanation is the

high correlation of mechanical pain ratings as well as mechanical pain-AS (related to TSP) with FM patients' overall clinical pain ($r^2 = .44$ to $.64$). Additional support for SSP's role in pain coding is provided by previous observations in FM patients that the number of painful body areas predicts the magnitude of overall clinical pain (Staud et al., 2004b).

5.3 Spatial Summation Characteristics are Similar for FM and NC Subjects

This is the first study that evaluated MSSP of NC and FM patients using three relatively large probes which were spatially separated by up to 8 cm. Thus this study was designed to test the relevance of widely separated mechanical stimuli for pain coding. Impulse input from spatially separated areas is particularly relevant for coding of FM pain which is widespread and frequently involves large body areas (Staud et al., 2004b). Our study also indirectly suggests that the increased sensitivity of FM patients to suprathreshold mechanical stimuli (hyperalgesia) may also depend on MSSP. Interestingly the magnitude of MSSP was similar in NC and FM patients. This unexpected finding suggests that the central integrative mechanisms activated by spatially separate muscle nociceptors may not be abnormal in FM patients, including functional inhibitory mechanisms.

5.4 Possible Limitations

Despite our attempts of stimulus concealment (see Methods 3.7), complete blinding is difficult to achieve in studies like ours because experimental pain intensity can cue subjects to the number of activated probes. Conceptually, one would expect the estimated number of activated probes to correlate with low or high pain ratings and be least accurate for intermediate pain. This is exactly what we observed in our study. Both groups of subjects provided their best estimates during low (one probe experiments) as well as high pain conditions (three probe experiments), but estimates of number of activated probes were not better than chance in the two probe trials (Table 2). Thus detection bias is an unlikely explanation for the observed spatial summation of pain as well as painful AS. Although complete blinding of subjects to the number of activated probes was not possible, we do not think that this factor accounts for the main results of this study.

5.5 Conclusions

Our results show that MSSP mechanisms are not abnormal in FM consistent with previously published findings of normal heat SSP in FM patients (Staud et al., 2004c). Several studies, including the present one, have shown that considerable spatial summation of pain takes place within small areas of the hand (Coghill et al., 1993a; Defrin and Urca, 1996), forearm (Price et al., 1989; Douglass et al., 1992), and abdomen (Nielsen and Arendt-Nielsen, 1997). Similar to previous studies of SSP (Price et al., 1989; Douglass et al., 1992) our present study shows that MSSP can take place *within* the forearm of NC and FM patients. Furthermore, our study demonstrates for the first time that MSSP-AS spatially summate over considerable distances suggesting that the widespread pain of FM patients not only reflects integration of temporal but also spatial pain coding mechanisms.

ACKNOWLEDGMENTS

Supported by NIH grants NS-38767, AR053541 and supported in part by Clinical Research Center grant RR00082. The expert technical assistance of Richard M. Cannon, Anwarul Azam, and Myriam M. Lopez is gratefully acknowledged.

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Figure 1.

Location of pressure stimuli applied to the volar surface of the forearms. The surface area of each probe was identical (0.79 cm^2). Three different probe combinations (A, B, C) were utilized for two-probe experiments. Two probe tips were always separated by 4 cm (A, B), except for combination C (8 cm). The locations of individual probes during MSSP experiments with one or three probes are shown in Panel D.

Figure 2.

Time course of mechanical stimuli used for MSSP experiments in NC and FM subjects.

Duration of all pressure stimuli was 5 sec. At the beginning of the stimulus pressures slowly increased at a rate of 1 kg/sec from zero to 2.5 kg, remained at this level for 2.5 sec, and rapidly returned to zero at the end of the stimulus

Figure 3.

Apparatus used for MSSP experiments in NC and FM subjects. Three cylinders with identical pistons were mounted on a metal frame that allowed adjustments in vertical and horizontal directions. All cylinders were powered by a pressurized air in parallel fashion, thus assuring equal pressures at each piston during the experiments. When controlled air pressure was applied, pistons extended from the cylinders for 5 sec during each trial and actively retracted after each stimulus. All piston tips were circular and flat (surface area: 0.79 cm^2) with smooth edges. The distance between piston tips was always kept at 4 cm except during some of the two probe experiment C (8 cm). One probe was equipped with an electronic pressure transducer connected to a digital read-out. Because identical air pressures were applied to the cylinders during each stimulus trial, pressure readings at one probe were representative for all other probes. Each subject's forearm was stabilized in a plastic mold underneath the probes during the MSSP experiments.

Figure 4.

Average mechanical pain ratings (SD) of NC and FM subjects during mechanical stimulation (2.5 kg) of the forearms using single probes at three different locations (4 cm apart). There was no significant difference between ratings of single probes regardless of location ($p > .05$) in NC or FM subjects. There was, however, a significant interaction effect of diagnostic group ($p < .001$), indicating that FM subjects' mechanical pain ratings were higher than those of NC.

Figure 5.

Average (SD) mechanical pain ratings of NC and FM subjects during mechanical stimulation of the forearms with two probes. Probe positions were varied in three different ways (see Figure 1 A-C) and pressure at each probe was maintained at 2.5 kg during the 5 sec stimuli. mechanical pain ratings of FM subjects were higher than NC regardless of stimulus combination ($p < .001$). MSSP of NC subjects was greater with two probes separated by 8 cm than by 4 cm ($p < .01$) and this finding was not statistically different in FM subjects ($p > .05$).

Figure 6.

Average mechanical pain ratings (SD) of NC and FM subjects during 5 sec mechanical stimuli using one, two, or three probes. There was significant MSSP noted in both groups of subjects ($p < .001$). Although mechanical pain ratings of FM subjects were higher than NC ($p < .002$), the increase (slope) of mechanical pain ratings was not different between diagnostic groups ($p > .05$).

Figure 7.

Correlations of mechanical pain ratings with clinical FM pain. mechanical pain ratings were obtained after 5 sec of mechanical stimulation of forearm muscles with one probe (●), two probes (■), or three probes (▲). Pearson product-moment correlations of clinical FM pain with mechanical pain ratings were significant for one — (r² = .47; p < .05), two probes - - (r² = .47; p < .05), and three probes experiments (r² = .44; p < .05).

Figure 8.

Average ratings (SD) of AS by NC and FM subjects during the MSSP experiments. Pain ratings of AS were obtained 15 sec (Panel A) and 30 sec (Panel B) after the end of 5 sec pressure stimuli using one, two, or three probes on the forearms. mechanical pain-AS were significantly more painful 15 sec and 30 sec after mechanical stimuli in FM subjects compared to NC. Although MSSP-AS seemed to be dependent on number of probes used, this relationship was not consistently seen for three probe combinations. AS15: 15 sec aftersensations; AS30: 30 sec aftersensations; ns: non-significant

Figure 9.

Correlations of mechanical pain-AS with clinical FM pain. Ratings of pain AS were obtained 15 sec (Panel A) and 30 sec (Panel B) after the end of 5 sec forearm muscle stimulation with one, two, or three probes. Clinical FM pain ratings (VAS) highly correlated with ratings of 15 sec and 30 sec AS ($p < .001$). AS = aftersensations

Table 1

Average Ratings (SD) of General Pain as well as Number of Tender and Control Points of NC and FM Subjects.

	NC Subjects n = 12	FM Subjects n = 11
Pain (VAS)	0.3 (0.6)	3.3 (2.1)
Tender Points	4.5 (3.2)	16.6 (2.0)
Control Points	0.1 (0.3)	1.6 (0.6)

n = number; Tender point range: 0-18; Control point range: 0-2; VAS = visual analogue scale (0-10)

Table 2

Correct Estimates of Number of Probes Used during MSSP Experiments by NC and FM Subjects.

	NC Subjects n = 12	FM Subjects n = 11
1 Probe (○○●)	85 %	79 %
1 Probe (○●○)	81 %	74 %
1 Probe (●○○)	90 %	92 %
2 Probes (●●○)	65 %	60 %
2 Probes (●○●)	57 %	49 %
2 Probes (○●●)	40 %	26 %
3 Probes (●●●)	82 %	70 %

n = number; ● = active probe; ○ = inactive probe; order of probes: ●●● = proximal-middle-distal