After-Sensations and Lingering Pain Following Examination in Patients with Fibromyalgia Syndrome

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Running Title: After-sensations in Fibromyalgia Syndrome

Summary:

In fibromyalgia syndrome, after-sensations following termination of an innocuous brushstroke stimulus persist and are often uncomfortable. This has important implications for patient education and examination.

Abstract

Fibromyalgia syndrome (FMS) is a chronic widespread pain condition with mixed peripheral and central contributions. Patients display hypersensitivities to a spectrum of stimuli. Patients' blunt pressure pain thresholds are typically reduced, and sometimes (~15%) gentle brushstroke induces allodynia. However, after-sensations following these stimuli have not, to our knowledge, been reported.

We examined the perception of blunt pressure and 'pleasant touch' in FMS. Patients were first interviewed and completed standard psychometric questionnaires. We then measured their sensitivity to blunt pressure and perception of pleasant touch including after-sensations; patients were followed for five days evaluating lingering pain from blunt pressure.

We recruited 51 FMS patients and 16 pain-free controls (HC) at a UK Pain Management Centre. Forty-four patients completed the after-sensation protocol. Most patients reported pain after application of less mechanical pressure than HCs; median arm and leg thresholds were 167kPa and 233kPa. Eighty-four percent (31/37) of patients reported ongoing pain at the site of pressure application one day after testing, and 49% (18/37) still perceived pain at five days. After-sensations following brushstroke were common in the FMS group, reported by 77% (34/44) compared to 25% (4/16) of HCs; 34% (15/44) patients, but no HCs, perceived these after-sensations as uncomfortable. For FMS patients who experienced after-sensations, brushstroke-pleasantness ratings were reduced, and skin was often an important site of pain.

Pain after blunt pressure assessment typically lingers for several days. After-sensations following brushstroke stimulation is a previously unreported FMS phenomenon. They are associated with tactile anhedonia and may identify a clinically distinct subgroup.

Keywords

Fibromyalgia, Chronic pain, Painful after-sensations, PAS, Quantitative sensory testing, QST, Lingering Pain

Introduction

Fibromyalgia syndrome (FMS) is a chronic widespread pain condition of uncertain aetiology[1]. FMS pain, associated tenderness[1] and fatigue often have a devastating impact on patients' function, activity, and quality of life[2, 3]. FMS has been classically viewed as a pain state with central amplification[1, 2, 4]. However, there is also mounting evidence of peripheral abnormalities including small fibre pathology with abnormal nociceptor function[5-9] and abnormal thermoregulatory peripheral innervations[10].

In patients with FMS, quantitative sensory testing (QST)[11, 12] demonstrates marked hypersensitivity to a broad spectrum of standardised stimuli; such hypersensitivity is established by registering the patient's evaluation of the stimulus while it is applied[13, 14]. Patients' blunt pressure pain thresholds are typically reduced, termed static mechanical allodynia[15], but gentle brushstroke may only induce pain, or dynamic mechanical allodynia (DMA), in 10-20%[16]. In relation to *noxious thermal* stimuli, (*i.e.,* stimuli that would be painful in normal skin), patients with FMS, similar to patients with other chronic pain conditions, may report painful '*after-sensations'* (PAS), *i.e.,* sensations that persist even though application of the stimulus has ceased[17-19]. In FMS, such PAS occur in up to 83% of cases following noxious thermal stimuli (*e.g.,* 49.5°C - 51.5°C), with the remainder of patients experiencing non-painful after-sensations[20]. Thermal PAS also occur in healthy individuals, at a frequency of 20% to 37% but, aside from being more common, they are more painful and longer-lasting in FMS[20-24]. Following noxious mechanical pressure cuff stimuli, PAS also occur at an increased frequency in FMS, at 50% compared to 12% in controls and are correlated with clinical pain intensity[25].

Anecdotally, other types of skin stimuli may also elicit painful after-sensations in patients with FMS; for example, in our practice, tender point testing required for the 1990 American College of Rheumatology[26] (ACR) diagnostic protocol seems to cause long-lasting pain increases at the testing sites. To our knowledge, no quantitative or qualitative data on after-sensations following brushstroke stimuli have been published. Our goal in this study was to describe, in patients with persistent FMS, after-sensations arising from aspects of mechanical QST assessment and from clinical examination as per ACR 1990, and to characterise subgroups formed based on these phenomena. Here, we report on after-sensations following application of both blunt mechanical pressure and brushstroke in a cohort of patients with FMS.

Methods

Study design and study subjects

Patients participated in an ongoing phenotyping study aiming to correlate clinical with immunological phenotypes (ISRCTN:18414398). They had been identified from a registry of patients assessed for treatment with an interdisciplinary pain management program (PMP), at a tertiary National Health Service hospital in northern England (The Walton Centre). All patients had consented for their names to be entered into this registry; the consenting rate for entry is 98%.

Patients were approached for the phenotyping study by letter, and interested patients attended for a single study visit. Inclusion criteria were FMS of over one year duration, ACR diagnosis 2010[3] or 1990[26] (both were assessed on the day and either qualified), age above 18 years, and an average weekly pain intensity of ≥4/10 on a numerical rating scale (where 0 = 'no pain', and 10 = 'as bad as you can imagine'). The examination for tender points as per ACR 1990[26] was conducted after some training had occurred to achieve a pressure of approximately 4kg/cm^2. Exclusion criteria included pregnancy or breastfeeding and inadequate understanding of the English language.

With regards to after-sensations, drawing from clinical experience, we expected that patients would find both the clinical examination of tender points[26] and examination with the pressure algometer (see below) painful for a prolonged period following the assessment, and we wished to study the duration of that response. Patients were given a pain diary to enter the presence or absence of any lingering pain from the examination of ACR 1990 tender points[26] and algometry test sites on each of days one to five after their study visit, and these scores were communicated over the telephone after this period.

Upon examination with brushstroke, as part of a protocol to assess pleasant touch, initial patients in this phenotyping study unexpectedly reported post-examination after-sensations, which often seemed unpleasant. These initial research subjects further advised that it was challenging for them to clearly identify after-sensations as 'painful', and that the term 'uncomfortable' would best encompass the unpleasant sensation that they experienced. We consequently adapted the study protocol to allow a more in-depth assessment of this phenomenon. We obtained ethics approval to enquire about the

character of these sensations, and to include a pain-free healthy control (HC) comparator group, which was subsequently recruited from university and healthcare staff.

The phenotyping study received ethical approval from Health and Care Research Board Wales: 18/WA/0234. All participants gave written consent, and they were reimbursed expenses up to £30 for their travel and HCs an additional £30 for their time.

Study procedure

Following consent and confirmation of eligibility (see above), patients were asked questions pertaining to their general health and fibromyalgia symptomatology; this included the tissue location of their perceived most intense pains in either 'bones', 'skin', 'muscles', or 'joints'; with multiple answers permitted. Participants also self-completed a set of standardised questionnaires which were then checked for completeness by a member of the team. These included the EQ-5D[27], the McGill Short Questionnaire[28], a Brief Pain Inventory (BPI)[29], the Hospital Anxiety and Depression Scale (HADs)[30], the Pain Catastrophizing Score[31], the Experiences in Close Relationship Questionnaire (Revised) (ECR-R)[32], the Pain Self-Efficacy Questionnaire (PSEQ)[30], the Revised Fibromyalgia Impact Questionnaire (FIQR)[33] and PainDETECT[33]. All patients were then examined for their skin sensitivity (see next section).

QST Procedure

A brief mechanical QST protocol was designed to test patients' mechanical pain threshold and skin sensitivity based on that previously published by Boehme *et al.*[34]. The procedure was performed by RB and AG following training by AM. The tests took place in a quiet, temperature-controlled (21°C) test room.

Pressure pain threshold

Subjects were asked to sit comfortably, and a standardised script read to them (see Supplementary material, Figure S2). The script read:

"I will press this pressure measuring device against one of your muscles. Please immediately say NOW as soon as the usual sensation of pressure changes to an additional sensation which is painful such as

'burning', 'stinging', drilling' or 'aching'. This is not an endurance test, tell us as soon as this becomes painful. This will be carried out a total of 3 times."

Static blunt pressure pain threshold was measured using a pressure algometer (FDN200; Wagner Instruments, Greenwich, CT, USA) with a 1cm^2 rubber tip, which was placed on the skin and a continuous ramp of increasing intensity (approximately 0.5kg/s, corresponding to 50kPa/s using a metronome) was applied until the patient confirmed that the sensation of pressure had changed to an additional one of pain. The patient was not able to see the dial. The pressure pain threshold was determined by the arithmetic mean of three consecutive readings. The test sites were the lateral right arm over brachioradialis and the left leg over vastus lateralis.

Brushstroke

Keen to explore gentle touch in greater depth than can be achieved by formal QST, which measures only DMA[11], we chose to focus on slow and fast brushstroke QST, coupling this with the qualitative perception of skin sensation. This was interrogated using a mixed methods approach[35]. Subjects were asked to sit comfortably with their *left* arm supinated on a pillow. Participants were shown the numerical scales before brushstroke examination and instructed that they would be stroked with a soft brush. A 30cm ruler was placed securely alongside their arm. The ruler placement marked the test site and was consistent for all tests. Participants received gentle stroking touch applied manually to the skin of the lateral left forearm in the supinated position at slow (3cm/s) and fast (30cm/s) speeds from proximal to distal (with the hair) over a 10cm length. A QST brush (SENSELab Brush-05, Somedic SenseLab AB Norra Mellby, Sweden) was used to deliver the stimulus and a metronome used to ensure correct speeds. The brushstroke was not obscured from the participants. Immediately following each brushstroke, subjects were asked to rate their perceptions on grounded 5cm numerical rating scales (NRS) for pleasantness, intensity, ticklishness and pain. The anchoring statements are shown in parenthesis and were as follows. Pleasantness was rated from -5 ('very unpleasant') to +5 ('very pleasant'). Participants were then asked to rate the intensity on a grounded NRS of 0 ('no sensation') to 10 ('very intense'). Ticklishness was rated from 0 ('not ticklish') to 10 ('very ticklish'), and pain from 0 ('none) to 10 ('worst possible').

Following the protocol adaptation from participant eight onwards (see above), subjects were additionally asked (after completing these NRS descriptions ~ 30 seconds) about the presence of any brushstroke test sensations that occurred immediately following the cessation of the final stimulus, using a

combination of yes/no, multiple-choice and open-ended questions[35]. Firstly, the subjects were asked: 'After the brushstroke tests, have you felt any lingering sensation?' ('yes or no'). If the subjects confirmed the presence of such lingering sensations, they were asked to describe their quality; 'did this lingering sensation feel like 'pins and needles', 'burning' or 'other'. Subjects were encouraged to report in free text all they felt and were permitted to select or record multiple types of sensations, as relevant. Subjects were then asked whether their sensations following brushstroke were uncomfortable ('yes' or 'no'). We have termed sensations extending beyond the brushstroke tests as 'after-sensations'. For testing protocols, please see supplementary material, Figure S2.

Statistics

Data were collated using Microsoft Excel version 16 (Microsoft Corporation, Redmond, WA, USA) and analysed with GraphPad Prism version 9 (GraphPad Software Inc., San Diego, CA, USA). Normality of data were tested with the Kolmogorov-Smirnov test. For normally distributed data, a paired or unpaired Students T test with Welch's correction for unequal variance was used. For non-normally distributed data, a Wilcoxon matched pairs rank sum test was used for paired data, and a Mann-Whitney test for unpaired data. For comparison of multiple non-normally distributed groups a Kruskal-Wallis test was implemented. For categorical binary data a Fisher's exact test was used. For the non-normally distributed brushstroke tests and pressure pain threshold data a Kruskal-Wallis test was utilised with a Dunn's post hoc test between groups with correction for multiple comparisons. A multiple linear regression model using a least squares approach was used to analyse variability in brushstroke pleasantness, modelling for intercept and main effects only, and residual plots assessed for assumption validity. Correlation was tested with a Pearson's correlation coefficient and, again, residual plots assessed. Odds ratios were calculated for the probability of experiencing after-sensations with FMS. Statistical significance was set at $p<0.05$, and a correction for multiple comparisons was made for each hypothesis (*e.g.,* Bonferroni). All p values under 0.05 were displayed for completeness. We speculated that some aspects of the FIQR were particularly relevant in testing the hypothesis that after-sensations had clinical relevance and, therefore, analysed several FIQR sub-items individually which ranged from 0 (least) to 10 (maximal impact) (Supplementary Table S2).

Results

1. Demographics

Demographic data is displayed in Table 1 for all 51 patients and 16 healthy controls (HC). In the FMS group, there were 46 females with a mean age of 49.4 years (26 to 66) and five males with a mean age of 41.6 years (24 to 58). Prior to recruitment, 32/51 patients had completed a comprehensive, 16 day (>100 hours) interdisciplinary PMP, whereas 19 patients had been assessed for the program but were not treated. FMS patients were noted to have a higher weight and BMI than HCs. Patients had a mean symptom duration of 10.6 years, and both their resting pain and seven-day average pain rating was 7/10. The average HADs scores for anxiety and depression were both 11.7, which is at the clinical threshold for anxiety and depression. The mean PCS, EQ-VAS, and FIQR scores were 24.3, 46.6 and 69.9, respectively. Chronic pain preceding widespread pain was common at 80% (41/51).

[Table 1]

2. FMS patients are more sensitive to mechanical stimuli than HCs and perceive less pleasure from gentle touch (tactile anhedonia)

Figure 1 displays data from the pressure pain thresholds and the brushstroke tests. As expected, the median pressure pain threshold values were significantly reduced in the FMS patients at both the right arm and left leg (Figure 1a). Brushstroke intensity (NRS) was not significantly different between FMS and HC cohorts for either slow or fast brushstrokes (Figure 1b). FMS patients reported both slow and fast brushstrokes as significantly less pleasant (Figure 1c). Within the HC cohort, slow brushstrokes were not more pleasant than fast with our multiple variable analysis (Kruskal-Wallis with Dunn's post hoc test) which is contrary to reported findings[34]. We chose, also, to analyse our data as done in previous studies which have assessed slow and fast brushstrokes QST, in which data were dichotomized by slow or fast brushstroke and tested using a Mann Whitney U test. In this analysis our data recapitulates the observation previously found ($p<0.01$)[34]. In our multiple variable analysis we found a trend towards reduced ticklishness of brushstrokes in the FMS group, which did not reach significance (Figure 1d). Brushstrokes were rarely painful (i.e., there was little dynamic-mechanical allodynia); the median pain intensity during these strokes was zero in both study groups for both slow and fast (Figure 1e). In total 14% (7/51) of FMS subjects reported pain scoring between 0.0 and 4.3/10

for slow brushstrokes and between 0.0 and 3.3/10 for fast brushstrokes. No HCs reported pain. Considering the small number of patients experiencing dynamic mechanical allodynia (n=7), there was no trend regarding this parameter and the perceived anatomical the location of worst pain.

It is conceivable that PMP treatment might alter patients' affective experiences as a result of the psychological interventions provided as part of the program. Subgroup analysis showed that the slow stroke intensity, slow stroke pain, fast stroke intensity and fast stroke pain were significantly less in patients who had previously been treated with this intervention, however, following p value correction for multiple tests, only slow stroke intensity remained significantly reduced. Interestingly, the brushstroke pleasantness ratings were not affected (Supplementary Figure S3).

[Figure 1]

3. Brushstroke pleasantness is negatively correlated with PainDETECT values but not WPI, SSS, PCS or HADS.

[Figure 2]

We identified a fair degree of variability in the pleasantness ratings in the FMS group. To test for associations which might explain the loss of pleasant touch, we performed a multiple regression analysis with a model considering the degrees of pain-widespreadedness and somatic symptoms (WPI, SSS), psychological factors (PCS, HADs A and HADs D), and neuropathic symptoms as measured by PainDETECT, assuming a least squares model. Only PainDETECT values (with higher values indicating more likely neuropathic pain) were significantly (inversely) associated with both slow stroke pleasantness ($p<0.01$) and fast stroke pleasantness ($p<0.0001$) (Figure 2). For slow brushstroke pleasantness, Pearson's correlation coefficient (r) was 0.3951 (95% CI: -0.6405 to -0.0765; $p<0.05$), and for the fast brushstroke r was -0.4866 (95% CI: -0.7028 to -0.1881; $p<0.005$).

4. After-sensations

Patients reported lingering pain at the examination sites (tender-point or pressure algometry) with a frequency of 78.1% (25/31) at day one and 46.7% (14/30) at day five. *Brushstroke after-sensations* were experienced by 77.3% (34/44) FMS subjects (Figure 3a). In almost half (15/34) of these patients (15/44 of all tested FMS patients), the reported sensation was classed as 'uncomfortable'. At a 25% (4/10) incidence, HCs experienced after-sensations with a significantly diminished frequency ($p<0.0005$), which were never uncomfortable. The odds ratio of experiencing after-sensations with FMS was 10.2 (95% CI: 2.5 - 32.4). When considering only patients that experienced dynamic mechanical allodynia, 83.3% (5/6) had after-sensations and in 66.8% (4/6) these were uncomfortable.

[Figure 3]

The qualities of these after-sensations were similar in FMS patients between uncomfortable after-sensations (UAS) and not-uncomfortable after-sensations (nUAS), with 'pins and needles' being the modal response, followed by a lingering sensation that the brushstroke was still taking place (Figure 3b). The median number of reported sensations was one, ranging from one to three. For HCs the after-sensations were 'cool' (1/4) 'brush still there' (1/4) or 'tingling' (2/4).

When stratifying patients by whether they had undergone the PMP treatment, no trend was seen in the presence of brushstroke after-sensations. Of the 25 patients that attended the PMP, 76% (19/25) had after-sensations, and of the 19 that did not attend the PMP, 79% (15/19) had after-sensations.

5. Patient phenotypes by brushstroke after-sensations

We compared demographics and FMS characteristics between patients with and without brushstroke after-sensations to examine whether this characteristic was associated with a particular clinical phenotype. We found that these groups did not differ in gender, age, FIQR, level of pain, WPI or SSS, pain catastrophising or EQ-VAS (Table 2).

Patients were asked about the perceived tissue location of their most intense pains as either 'bones', 'skin', 'muscles', or 'joints', with multiple responses permitted. Eleven patients (out of n=44 who completed this question) recorded 'skin' as site of their most intense pain, and those with UAS reported 'skin' more often (47%, 7/15) when compared to nUAS (20%, 2/10) or nAS groups (2/19, 11%; $p<0.05$; Supplementary Figure S1).

Those patients who experienced after-sensations rated fast brushstrokes significantly more unpleasant than the other groups (Table 2). Subgroup analyses across the three groups UAS, nUAS and nAS (Supplementary Table S1), indicated slow and fast brushstroke pleasantness measures to be significantly different, with the UAS group rating brushstrokes least pleasant compared to the other groups.

Should patients indeed perceive uncomfortable sensations following gentle stroking of their skin, this may well have deleterious manifestations relevant to their everyday life, such as social interaction within the family. We compared, therefore, the UAS, nUAS and nAS groups with respect to the relevant FIQR sub-items (Supplementary Table S2). No association was found with pertinent individual FIQR measures, e.g., on combing hair, sleep quality or overall pain, although there appeared to be a trend for the parameter 'sensitivity to touch',

[Table 2]

Discussion

In this study we have investigated after-sensations persisting beyond the termination of mechanical stimuli applied to FMS patients' skin. We found that painful 'after-sensations' (lingering pains) are frequently reported several days after study examination, which included application of blunt pressure during the ACR tender point examination (approximately 4kg/cm^2), pressure pain threshold testing and brushstroke QST. Eighty percent (25/31) of patients had lingering pain on day one and 47% (14/30) on day five after examination. The existence of this phenomenon following *blunt mechanical* stimuli has previously been highlighted by others[20] and has often been communicated by patients in our own clinical practice, however, to our knowledge our data provide a first account of its prevalence and duration. The pressure required to generate a noxious stimulus in HCs is typically (200 – 300kpa for the arm and 250 – 450kpa for the leg)[36]. FMS pressure measurements observed in this study are lower than these, representing mechanical hyperalgesia.

This finding also confirms that tender point examination in FMS can regularly cause long-lasting discomfort. A count of painful tender points was part of the now superseded ACR 1990 diagnostic criteria[26]. Although the current diagnostic criteria (ACR 2016)[37] do not include a count of painful tender points, the 1990 criteria are still in wide use, and our results may support diagnosticians in choosing a different appropriate set of diagnostic criteria. These data also support clinical advice to minimise repeat

examination in FMS patients in all settings[38], and our recommendation that patients should be consented to expect increased pain from an examination.

To our knowledge, this is the first report of evoked paraesthesia or, 'after-sensations' following skin-brushstroke testing in FMS. We found that such sensations are common compared with HCs and that patients, but not HCs, often perceive them as uncomfortable. Consistent with the literature, allodynia, defined as pain *during* brushstroke application, was reported by some of our patients (7/51)[36]. This phenomenon in health, however, is not expected to continue after stimulus withdrawal.

Within the FMS group*, reports of uncomfortable, as opposed to non-uncomfortable or no* after-sensations, following brushstroke were associated with reports of reduced pleasantness during brushstroke; on average slow and fast brushstrokes were, in fact, perceived as *unpleasant* by this group. Experience of uncomfortable brushstroke after-sensations was not associated with blunt pressure sensitivity, however, (Supplementary Table S1) and it was particularly frequent in those patients who noted that their skin was the location of their worst pain (Supplementary Figure S1) These features may, therefore, characterise a distinct FMS clinical subgroup in which touch processing is differentially affected.

Reduced brushstroke pleasantness *(i.e., during the brushstroke)* – termed anhedonia, as detected in our study, is consistent with recent reports by Boehme *et al.*[34] and others, although its cause is still unclear[39, 40]. By mapping cortical activity during brush stroking with functional magnetic resonance imaging, Boehme *et al.* found an inverted pattern of insula activity compared to HCs and inferred, therefore, that FMS anhedonia may be related to aberrant central nervous system evaluative processing[34]. Nonetheless, the finding of anhedonia in FMS does not exclude the possibility of abnormal signal processing of input from sensory afferents. Certainly, evidence of small fibre pathology in FMS is mounting[41, 42] with reports of reduced epidermal nerve fibre density[40] and reduced vascular innervation[43]. Bosma *et al.* show that *painful* after-sensations after thermal stimuli are associated with increased activation in the cervical cord dorsal horn in FMS patients[23], pointing, perhaps to continued afferent activity.

The inverse correlation of brushstroke pleasantness in our FMS cohort with the PainDETECT score may further signal small fibre pathology as one mechanism of anhedonia in FMS. Should the former be

true, and brushstroke testing predict small fibre pathology, then using brushstroke testing to diagnose small fibre pathology would be much preferable to a painful skin biopsy[41]. In summary, anhedonia could be a consequence of abnormal afferent input, altered spinal processing or altered brain processing.

It is, tempting to speculate that at least the 'early' (i.e., ~15 seconds[20]) brushstroke after-sensations may be mediated by slowly conducting C fibres. One such candidate is the CT fibre, a low threshold afferent which discharges maximally with a slow (1–10 cm/s) brushstroke and elicits a pleasant sensation in subjects[44]. These CT fibres, which are suited to respond to a 'gentle caress', are thought to provide the 'neurobiological substrate for the affective and rewarding' aspects of touch[45]. This 'social' touch is clearly important for physical and social wellbeing[45] and its loss, tactile anhedonia, is a clear feature of FMS[34]. Because CT fibres fire preferentially after stimuli with brushstroke speeds of 1-10 cm/s, one might expect after-sensations to be more strongly associated with slow rather than fast brushstroke pleasantness. However, we note that this would suppose that CT firing is normal in FMS – an assumption that has yet to be confirmed. CT afferent firing in health has a propensity to exhibit after-discharges upon cessation of an innocuous tactile stimulus[9] which further points to a potential role in the development of after-sensations. A further way to investigate this would be a comparison between brushstrokes and vibro-tactile stimuli, the latter of which strongly activate A-fibre low threshold mechanoreceptor afferents but only weakly excite CT afferents[9, 45]. However, it is important to note that brush stroking will activate A-beta and A-delta fibres, as well as the CT afferents, which may all integrate centrally. There are, of course, other explanations, such as reverberating circuits in the CNS or the aforementioned after-discharging afferents.

Intriguingly, patients that had attended our PMP treatment had reduced slow brushstroke intensity ratings. Brushstroke pleasantness ratings were not altered, however. This data might provide the first evidence of PMP treatment potentially affecting selected sensory characteristics in FMS. However, given that all patients in this study had been assessed for the suitability of PMP treatment, it is alternatively possible that the entrance criteria for our PMP also selected for patients with a distinct sensory phenotype. A prospective study in PMP participants would shed more light on these issues.

Dynamic mechanical allodynia and dysesthesias are noted in several neuropathic pain conditions (*e.g.,* post herpetic neuralgia pain)[46] as well as fibromyalgia[16]. We note that DMA was also present in our study at a 10% incidence. The cohort of patients with after-sensations also had a higher incidence of DMA.

The PainDETECT questionnaire was validated as a tool to predict the relative contribution of neuropathic pain in neuropathic and nociceptive (*e.g.,* osteoarthritis) conditions. Fibromyalgia patients were excluded from the validation process, although PainDETECT has been increasingly used in this population. It has been proposed that fibromyalgia should not be considered as a neuropathic pain state[47], however, with mounting evidence that FMS has a peripheral component[5-9] it is, perhaps, unsurprising that fibromyalgia patients experience similar sensory phenomena as patients suffering from neuropathic conditions[47]. In this study, it is curious that although tactile anhedonia is associated with the PainDETECT score, pain intensity, fibromyalgia severity (FIQR), measures of "widespreadedness" (WPI, SSS) or cognitive qualities, such as pain catastrophising, are not. Regardless of the underlying mechanism, be this neuropathy or something else, it seems plausible that tactile anhedonia points to a distinct phenotype.

The German Research Network on Neuropathic Pain (DFNS)[11] has generated a robust and reproducible QST protocol for assessing patients with neuropathic pain. Whilst a thorough, useful, and widely accepted approach, the experimental protocol does not account for the assessment of sensations that linger following stimulus withdrawal. We suggest, therefore, that the DFNS protocol may have been failing to capture a common and germane clinical sequela of chronic pain.

Our present study is limited as it was not designed to interrogate after-sensations in detail, which were a surprise finding. We did not record their duration nor examine whether their qualities were the same for both slow and fast brushstrokes. It should be noted that we did record a significant reduction in pleasantness between slow and fast brushstrokes in HC and not in FMS, which has been previously noted and underpins the C-fibre tactile theory, although it failed to meet significance in our study in all analyses. The control group was small and was restricted to females, and it did not, therefore, match the FMS group in this regard. Although the proportion of male FMS patients included was small (n=3) it is conceivable that after-sensations had some gender bias: in our FMS cohort, all males on which we

have data, had after-sensations. The HC group also differed by age, BMI, and weight which were potential confounders.

It is important to note that in this present study we measured both brushstroke QST and pressure algometry, and we performed tender point examination. It is not possible, therefore, to extract the relevant contributions of each of these in relation to persisting after-sensations (lingering pain). We further note that the pressure algometry, unlike the tender point examination stopped exactly at the point of painfulness and involved two points on the body (the tender point examination involved 18 points), therefore, we assume that the tender point examination was responsible for most of the lingering pain, however, this study was not designed to confirm this.

We did not record data on the presence or absence of after-sensations in the HC group following pressure pain threshold detection and this is a clear limitation. HCs have been reported to experience painful after-sensations following blunt pressure mechanical stimulus, though the frequency was low at 12% and of an unknown duration[25]. FMS patients are probably heterogenous in sensory phenotypes[48] and it is true that such variability would hamper our ability to distinguish between groups. As an exploratory study, we were not powered to tease out subtle relationships between after-sensations and psychometric data. A larger study is warranted for this. Our cohort was obtained from a tertiary referral centre and may not, therefore, have been fully representative of all patients in the community. Albeit, using this pilot data, it would now be possible to adequately power a study to test the hypothesis that the uncomfortable after-sensation group is more sensitive (as suggested by the association with reduced brushstroke pleasantness), possibly with respect to social measures, such as assessed by TEAQ[49]. In addition to these measures, biochemical changes might also be investigated, for example cortisone or endorphin levels locally or systemically. We placed emphasis on the bothersome-ness of patient symptomatology and, in this regard, further work might look to investigate the presence and character of itch and how this is related to ticklishness. Examinations for atypical allodynia and paraesthesia can easily be done in the clinical setting and understanding patient phenotypes in terms of these may be clinically useful, therefore.

Conclusion

Here we report, for the first time, the presence of after-sensations following the cessation of an innocuous light touch stimulus in a cohort of fibromyalgia patients. When present, these after-

sensations are often uncomfortable. We also report on the prevalence of lingering pain following pressure examination. We suggest that these findings have key implications for clinicians examining patients and ramifications for experimental trajectories. Their recognition may provide assuage to patients and inform the advice and education given. Further research is, of course, needed to investigate these phenomena in FMS and other chronic pains. In this regard, we note that medical efficacy is contingent upon placing patients at the centre of diagnostic formulations and the interrogation of aetiologies.

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Figure Legends

Figure 1: Quantitative Sensory Testing Results

*Boxplots display medians, quartiles, and ranges; (a) pressure pain threshold and (b-e) tactile quantitative sensory testing. Abbreviations: SS = slow brushstroke; FS = fast brushstroke; RA = right arm; LL = left leg. For brushstroke tests, statistical significance tested with Kruskal-Wallis with a Dunn's post hoc test corrected for multiple analyses. **** p<0.0001; *** p<0.001; ** p<0.01; * p<0.05;.n.s. not significant.*

Figure 2 – Scatter Plots of Brushstroke Pleasantness Against PainDETECT Scores

Linear regression lines for average slow brushstroke in red for slow brushstroke and in blue for fast. Correlation was tested with Pearson's correlation coefficient. Significance stated pertains to the test for a non-zero slope of the linear regression line. Significance was set at p<0.05.

Figure 3 – After-sensations Following Brushstroke

(a) Percentages of subjects reporting sensations at the site of brushstrokes, following application of a series of 6 brushstrokes (3 slow and 3 fast) delivered in an alternating order to the left arm, are shown as a pie chart. Abbreviations: nAS = no after-sensations; nUAS = non-uncomfortable after-sensations; UAS = uncomfortable after-sensations. (b) The character of the after-sensations; patients were able to report any number of sensations. The p value pertains to a Fisher's exact test for the presence of after-sensations between HC and FMS. Significance was set at p<0.05.

	Healthy pain free subjects *n = 16*		Fibromyalgia *n = 51*		
	Mean	**95% CI**	**Mean**	**95% CI**	
Females %	100%		90%		n.s.
Age	41.2	*35.6 - 46.8*	48.7	*45.7 - 51.6*	<0.05
BMI	25.9 [15]	*22.9 - 28.9*	33.5 [43]	*31.1 - 35.9*	<0.01
Height	1.64 [15]	*1.61 - 1.67*	1.65 [47]	*1.62 - 1.67*	ns.
Weight	69.3 [15]	*62.3 - 76.3*	90.0 [47]	*83.5 - 96.5*	<0.01
Symptom duration (years)	-	-	10.6	*8.9 - 12.3*	-
Current Resting Pain	-	-	7.0	*6.5 - 7.6*	-
Pain in last 7 days	-	-	7.3	*6.8 - 7.8*	-
HADs Anxiety	-	-	11.7	*10.4 - 12.9*	-
HADs Depression	-	-	11.7	*10.6 - 12.9*	-
PCS	-	-	24.3	*20.5 - 28.1*	-
EQ-VAS	-		46.9	*41.7 - 52.0*	-
FIQR	-	-	69.9	*65.6 - 74.2*	-

Table 1 – Demographics of healthy controls and patients and FMS disease characteristics

Values displayed as means with 95% confidence intervals. Where group size varied this is displayed in square brackets. Abbreviations: PCS = Pain catastrophising scale rating; EQ-VAS - EuroQual visual analogue scale; FIQR = Fibromyalgia impact questionnaire revised. Statistical significance tested with a Mann Whitney U test. Uncorrected p value set at 0.05, following Bonferroni correction p<0.01, n.s., not significant.

	Brushstroke After-sensations (AS)	No Brushstroke After-sensations (nAS)	
Group size	n = 34	n = 10	
Females (%)	91.2	100.0	n.s.
Age (years)	46.7 (42.3– 50.6)	49.1 (44.5 – 53.7)	n.s.
BMI (kg/m2)	33.3 (30.1 – 36.4) [31]	38.2 (35.1 – 41.3)	p<0.05
Duration (years)	10.3 (8.5 – 12.1)	12.5 (6.5 - 18.5)	n.s.
FIQR Total	71.3 (66.0 – 76.6)	66.6 (54.4 – 78.9)	n.s.
FIQR Level of Pain	7.8 (7.2 – 8.4)	7.9 (7.1 – 8.7)	n.s.
WPI	13.1 (12.1 – 14.1)	15.0 (12.5 – 17.5)	n.s.
SSS	10.1 (9.5 – 10.7)	9.5 (8.1 – 10.8)	n.s.
Slow stroke pleasantness (NRS)	0.2 (-0.5 – 0.9)	1.3 (0.1 – 2.6)	n.s.
Fast stroke pleasantness (NRS)	0.0 (-0.5 – 0.5)	1.1 (-0.1 – 2.2)	p<0.05
Slow stroke pain (NRS)	0.3 (-0.1 - 0.6)	0.2 (-0.2 – 0.5)	n.s.
Fast stoke pain (NRS)	0.3 (0.0 - 0.5)	0.2 (-0.2 – 0.5)	n.s.
Arm pain threshold (kPa)	176.1 (158.3 – 194.0)	162.2 (126.5 – 197.9)	n.s.
Leg pain threshold (kPa)	245.2 (217.2 – 273.2)	243.7 (190.0 – 297.4)	n.s.
PCS	25.1 (20.3 – 29.9)	20.7 (11.3 – 30.1) [9]	n.s.
EQ-VAS	47.3 (40.9 – 53.7)	52.4 (37.5 – 67.4) [9]	n.s.
Pain DETECT	25.0 (21.5 – 28.5) [14]	21.3 (16.8 – 25.9) [6]	n.s.
Lingering Pain at 1 Day (%)	82.3 [19/23]	75.0% [6/8]	n.s.
Lingering Pain at 5 Days (%)	47.8 [11/23]	42.9% [3/7]	n.s.

Table 2 – Descriptive Quantitative Sensory Testing (Brushstroke) Data

Pleasantness is displayed on a numerical rating scale (NRS) -5 [very unpleasant] to 5 [very pleasant], pain on an NRS of 0-10. Lingering pain is the pain felt at the examination site post examination. Mean values are represented with 95% confidence intervals in parenthesis. Where group size varied this is displayed in square brackets. Abbreviations: FIQR = Fibromyalgia impact questionnaire revised; WPI = Widespread pain index; SSS = Symptom severity score; PCS = Pain catastrophising scale rating; EQ-VAS - EuroQual visual analogue scale rating. Statistical significance tested with a Mann Whitney U test. Uncorrected p value set at 0.05; n.s., not significant. A Bonferroni correction was made for multiple tests in the hypothesis; after 15 tests p<0.003).