Central sensitisation to pain and autonomic deficiencies in fibromyalgia

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Abstract

Objective

Fibromyalgia (FM) is associated with central pain sensitisation, autonomic alterations and neuropathy in small nerve fibres. This study aimed to analyse the association between tonic sweating and central pain sensitisation in FM.

Methods

Fifty-eight FM patients and thirty healthy women were assessed in terms of slowly repeated evoked pain (SREP), as a measure of central sensitisation. Sweating was evaluated by skin conductance (SC), as a sympathetic autonomic measure secondarily indexing possible small nerve fibre peripheral neuropathy. Clinical and psychological factors were evaluated through questionnaire measures.

Results

FM patients displayed smaller SC values than healthy controls, and SREP sensitisation was only observed in FM patients. Pain threshold and tolerance were also lower in the patient sample. Clinical symptoms (pain, fatigue, insomnia) only correlated significantly with SREP sensitisation. SC was inversely related to SREP sensitisation, and this association persisted after statistically controlling for levels of catastrophising and antidepressant use.

Conclusions

These results suggest that central pain sensitisation, proposed as a main pathophysiological mechanism of FM, may depend on sympathetic autonomic deficiencies, suggestive of small nerve fibres neuropathy. Future studies should aim to replicate these results using other central pain sensitisation measures and direct measures of neuropathy or small nerve fibre density.

Key words

fibromyalgia, central sensitisation, small fibre neuropathy, skin conductance, slowly repeated evoked pain, sympathetic activity

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Introduction

Fibromyalgia (FM) is a chronic generalised musculoskeletal pain syndrome with a clear predominance in women over men (8-10:1 ratio) (1). Fatigue, morning stiffness, gastrointestinal problems, insomnia, anxiety, depression and cognitive dysfunctions are other typical symptoms (2, 3). Currently, there is insufficient evidence regarding how early diagnosis might affect the clinical progression of FM; however, it could prevent the requirement for pharmacological treatments over less invasive approaches, such as psychotherapy and physical reconditioning (4). The aetiology of FM is unknown and there are no objective markers to confirm the diagnosis (5, 6). One of the best-supported hypotheses is that the pathophysiology of FM is related to central pain sensitisation processes. Plastic changes in the central nervous system (CNS) can amplify pain in these patients, leading to hyperalgesia and allodynia (7, 8). Recent studies on FM diagnosis introduced the concept of nociplastic pain, which refers to pain arising from altered nociception without evidence of actual or threatened tissue damage, but which is nonetheless capable of activating peripheral nociceptors and altering the somatosensory system (9).

Hyperexcitability of the CNS in FM patients has been widely demonstrated, including augmented pain processing at the brain level, up-regulation of ascending pain pathways and malfunction of inhibitory pain mechanisms (10-13). Another hypothesis regarding the pathophysiology of FM proposes neuropathic features of the disease, based on findings of peripheral small fibre neuropathy (14, 15). Several studies have reported small distal fibre (intraepidermal unmyelinated nerve fibres) neuropathy, a reduction in both dermal unmyelinated nerve fibre bundles and dermal nerve fibre diameter, and even large peripheral nerve fibre neuropathy in distal body parts, all leading to a lower fibre density in comparison with healthy individuals (14-18). The high rate of neurologic and autonomic nervous system (ANS) symptoms, including alterations in heat and cold thresholds, tingling, numbness, etc., seen in FM (19) is congruent with the proposed neuropathy. As additional support for this hypothesis, some studies reported associations between small fibre pathology and the severity of FM symptoms (17). This neuropathy might be mediated by autoimmune and neuroinflammation processes (20).

These two hypotheses about the pathophysiology of FM might be not mutually exclusive. Small nerve neuropathy can promote pain, as normal small nerve fibres have a filtering function according to which they only conduct a small fraction of all incoming discharges evoked by inputs, whereas dystrophic small fibres, having lost this barrier function, unselectively conduct most of the elicited action potentials (21, 22). The increased pain input to the CNS from the altered small fibres can promote the development of central sensitisation to pain. Recent reviews on this topic suggest that FM exists on a continuum between purely peripherally induced (including small fibre neuropathy) and centrally induced pain (23).

Central pain sensitisation in FM patients has been measured using evoked dynamic pain indicators such as temporal summation of pain (TSP), which is significantly enhanced in FM patients (24). However, TSP has also been observed in other pain conditions, and sometimes in healthy controls (12, 25, 26), and is not associated with clinical pain in FM patients (24, 27). Another proposed protocol to assess pain sensitisation in FM is slowly repeated evoked pain (SREP), which displayed better diagnostic accuracy for FM than TSP (25). SREP sensitisation was observed in FM and episodic migraine (both central sensitisation syndromes) patients, but not in patients with rheumatoid arthritis (a peripheral condition) or healthy controls (25, 28). Moreover, SREP sensitisation predicts the level of clinical pain, which supports the hypothesis that it is associated with the underlying pain mechanisms of FM (25, 29, 30). Although SREP sensitisation is also linked to catastrophising (29), its diagnostic advantages are maintained after controlling for that trait (25, 29).

One of the methods used to evaluate the neuropathy of small nerve fibres is measurement of sweating. The eccrine sweat glands are controlled by postganglionic non-myelinated C-fibres from the sympathetic ganglia, which combine with peripheral nerves, travel to sweat glands, and interlace the periglandular tissue with cholinergic terminals (31). Thus, sweating can provide insight into sympathetic innervation of the skin. Sweating can be measured by quantitative sudomotor axon reflex testing (32) or distal electrochemical skin conductance (33). Results obtained using these techniques showed impaired sudomotor function in FM (22, 33, 34). Skin conductance (SC) also measures sweating through a simpler method (sweating reduces the resistance of the skin to the passage of electricity). Using this technique, lower tonic SC levels, as well as reduced SC responses to breathing manipulations, were observed in FM patients compared to healthy controls (35). Furthermore, the absence of associations between SC and state anxiety and body temperature in these patients suggests a breakdown of the adaptive functions of sweating in FM (35). In this study we analyse the association between central sensitisation to pain, as measured by SREP, and sweating, as measured by SC. The relations found in previous studies between clinical symptoms and SREP (29) and SC (35) support such an association. Additionally, a study by Vecchio *et al*. (36) of FM patients with mild loss of peripheral nociceptors in the thigh reported a reduced habituation response, as assessed by laser-evoked potentials delivered to this body location. However, research in this area is scarce and the association between the CNS and ANS dysregulations seen in FM is still unclear (33).

In this context, we hypothesised that alterations in ANS activity, as measured through sweating and secondarily indexing small nerve fibre neuropathy, will be associated with greater central sensitisation to pain. Hence, an inverse association between tonic SC and SREP sensitisation was predicted. A methodological problem here is that a high proportion of FM patients use antidepressant medications, which have anticholinergic effects and can affect sweating (37, 38). Therefore, the effect of antidepressant use was controlled in the analysis.

Methods

Participants

Fifty-eight women with a diagnosis of FM according to the 1990 American College of Rheumatology criteria, participated in the study (29 taking and 29 not taking antidepressants). In total, 22 patients used selective serotonin reuptake inhibitors (75.86%), 14 (48.28%) used tricyclic and 11 (37.93%) used serotonin and norepinephrine reuptake inhibitors (some patients used a combination of drugs). To check for groups differences in SREP sensitisation and SC, 30 healthy women also participated. No significant differences in age or body mass index were observed among the three groups, *i.e*. the two FM subgroups and the controls (Table I). In order to avoid potential confounding due to sex-related differences, and given the greater prevalence of women with FM, only women were enrolled in the study. Patients were recruited from the Fibromyalgia Association of Jaén, Spain, through announcements on social networks. The volunteers were contacted by phone to arrange the date and time of the experimental session, and to check whether they were diagnosed with FM by a rheumatologist. Exclusion criteria for all participants included any kind of cardiovascular disease, metabolic abnormalities, neurological disorders, drug abuse and/or severe psychiatric conditions. Healthy controls were required to be free from any chronic pain condition. The Ethics Committee of the University of Jaén approved the study protocol.

Skin conductance and central sensitisation measurements

Skin conductance (SC) was recorded using a MP36 Biopac polygraph, Acknowledge 4.2 software (Biopac Systems Inc., Goleta, CA, USA) and Ag-AgCl disposable electrodes (Biopac EL507) with a 1 cm^2 contact area (placed on the thenar and hypothenar areas of the right hand). The recording (in μSiemens, μS) was performed with a constant current of 0.5 v.

Central pain sensitisation was assessed by the SREP protocol, which consists of a single series of nine repeated pain stimuli of 5s duration, with a 30s interstimuli interval, delivered to the third fingernail of the left hand. A pressure algometer (Tracker Freedom; JTECH Medical, Lawndale, CA, USA) with a stimulation surface area of 1 cm^2 was used for this propose. The algometer was inserted into a screw-piston, which was specifically designed to fix and press the fingernails, allowing for reliable maintenance of stimulation pressure. The protocol applies painful stimulation pressure to determine the pain sensitivity of each participant; the pressure (Kg) needed to evoke low-to-moderate pain intensity in all participants is applied. This pressure was calculated through the following formula: Intensity = Threshold + 1.25ET; where ET = (tolerance - threshold) / 4) (39). Threshold and tolerance to pressure pain were obtained previously. Each pain stimulus is followed by a pain intensity rating using a 0–10 visual analogue scale (VAS), where 0 equates to "no pain" and 10 to "maximum pain". The SREP sensitisation index is the difference between the last and first pain ratings among the series of painful stimuli (29).

Clinical and psychological assessment

Clinical pain, fatigue and insomnia, as the three main clinical symptoms of FM, were evaluated to corroborate their previously reported association with SREP sensitisation (40), and to explore their relation to SC. Clinical pain was assessed using the Spanish version of (41) the McGill Pain Questionnaire (42). This 73-item instrument has a Cronbach's α (internal consistency) value of 0.74 (41). The global score of this instrument is reported herein. Fatigue was assessed by the Fatigue Severity Scale (43). This scale comprises nine items scored using 7-point Likert scales (total score range: 9–63), and has a Cronbach's α of 0.88. Sleep was evaluated with the insomnia subscale of the Oviedo Sleep Questionnaire (44), which consists of

Table I. Demographic, clinical, pain and skin conductance variables: comparisons among patients taking and not taking antidepressants, and healthy controls.

Variables	Patients not using anti-depressants (n_{1a}=29)	Patients using anti-depressant (n_{1b}=29)	Healthy controls (n_2=30)	Comparisons between FM subgroups ($n_{1a} - n_{1b}$)		Patients not using anti-depressants vs. HC ($n_{1a} - n_2$)‡	
				t or χ^2	*p*	*t* or χ^2	*p*
Age (years)	50.00 ± 10.71	52.34 ± 7.09	50.37 ± 7,54	-0.98	0.330	-0.15	0.880
BMI	26.65 ± 4.10	28.28 ± 5.22	26.47 ± 3.83	-1.32	0.191	0.179	0.859
SREP sensitisation	1.90 ± 1.50	1.34 ± 1.02	-.03 ± .61	1.63	0.109	6.41	<0.001
Skin conductance (μS)	2.30 ± 2.44	1.27 ± 1.07	4.00 ± 3.79	2.09	0.043	-2.05	0.045
Pain threshold	2.22 ± 1.13	2.54 ± 1.67	3.43 ± 1.00	-0.86	0.394	-4.34	<0.001
Pain tolerance	5.35 ± 2.15	5.56 ± 2.76	6.69 ± 1.80	-0.33	0.744	-2.60	0.012
Catastrophising	17.07 ± 10.40	20.21 ± 12.02	4.33 ± 7.31	-1.06	0.292	5.42	<0.001
Clinical pain	53.28 ± 33.30	66.10 ± 36.66	16.77 ± 11.57	-1.40	0.169	5.59	<0.001
Fatigue	49.48 ± 11.60	51.00 ± 10.49	16.80 ± 13.48	-0.52	0.604	9.97	<0.001
Insomnia	31.62 ± 8.84	34.86 ± 8.01	16.17 ± 8.49	-1.46	0.149	6.84	<0.001
Anxiolytics, n (%)	10 (34.48)	23 (79.31)	5 (16.67)	11.88	0.001	2.47	0.143
Analgesics, n (%)	21 (72.41)	21 (72.41)	3 (10.0)	0.000	1.00	23.03	<0.001
Opioids, n (%)	9 (31.03)	11 (37.93)	0	0.31	0.783	10.99	0.001

Mean ± SD; BMI: body mass index; FM: fibromyalgia; HC: healthy controls; SREP: slowly repeated evoked pain. No participant in the control group uses antidepressant medication.
‡Comparisons between the patients taking antidepressants and healthy controls also were performed, showing similar statistical differences.

10 items (total score range: 0–50). The Cronbach's α of this questionnaire is 0.77. Finally, pain catastrophising was assessed due to its possible confounding effect on SREP sensitisation. The catastrophising subscale of the Coping Strategies Questionnaire (45) [specifically the Spanish version (46), which has a Cronbach's α of 0.89] was used.

Procedure

First, through an interview, a clinical psychologist obtained sociodemographic, clinical and medication use data. Then, SC was recorded in a sitting position during a 6-minute rest period at 21°C, in the absence of sounds and bright lights. Afterwards, patients were familiarised with the pain stimulation procedure, the concept of pain threshold ("when you feel that pain starts") and tolerance ("when the maximum stimulation pressure that you can tolerate is reached"), and the VAS pain measurement. This practice involved the application of pressure to the second finger of the left hand, increasing at a rate of 1 kg/s. Once patients had been familiarised and trained, pain threshold and tolerance were measured in the third finger of the left hand. Then, the SREP protocol was applied as described above. The order of SC and SREP measurement was counterbalanced within participants, such that in some patients we started with the SC recording, and in others with the SREP protocol. All participants provided written informed consent.

Statistical analysis

No measured variables showed any deviation from normality or homogeneity of variance according to the Kolmogorov-Smirnov and Levene's tests (p>.05), respectively. Student's *t* tests for independent samples were used to compare demographic and clinical variables between groups. Relationships among SREP sensitisation and SC were analysed initially by Pearson's correlations in each FM subgroup (distinguished according to antidepressant use). A bootstrap of 1000 replications was conducted for each correlation. In a second step, multiple regression analyses were performed. To control for the effect of antidepressant use on SC, a linear regression analysis was computed with antidepressant use as the predictor and SC as the dependent variable. Prior to further regression analysis, SC levels were replaced by their unstandardised residuals from this analysis, which were independent of antidepressant use. Finally, a hierarchical linear regression analysis was performed to confirm the association between SC and SREP in the FM sample. Catastrophising was entered as a predictor of SREP sensitisation in the first model and SC (residuals) was entered in the second model. Pearson's correlation was used to examine the associations among SREP, SC (unstandardised residuals) and clinical symptoms in the total FM sample.

Results

Means and standard deviations (SD) of the measured variables for FM patients taking and not taking antidepressants, and the healthy controls, are displayed in Table I. Lower SC levels were observed in patients taking antidepressants in comparison with patients not taking these medications. Furthermore, lower SC levels, but higher SREP and clinical symptoms levels, were found in both subgroups of patients relative to healthy controls. The use of anxiolytics was more frequent in patients taking antidepressants than in those not taking these medications.

SREP sensitisation correlated inversely with SC levels in the two subgroups of FM patients, but the correlation only reached significance in patients not using antidepressants (Table II). The regression analysis in the whole sample of FM patients, with catastrophising and the residuals of SC (after partialling out the effects of antidepressants) used as predictors, revealed in the first model a positive association between catastrophising and SREP sensitisation

Table II. Correlations between SREP sensitisation and skin conductance in the subgroups of FM patients taking and not taking antidepressants. Confidence intervals calculated from the bootstrap procedure are also included.

	No anti-depressant use FM patients			Anti-depressant use FM		
	r	95% CI		r	95% CI	
		Lower	Upper		Lower	Upper
Skin conductance	-0.46*	-0.72	-0.11	-0.17	-0.45	0.15

SREP: slowly repeated evoked pain. *p<0.05.

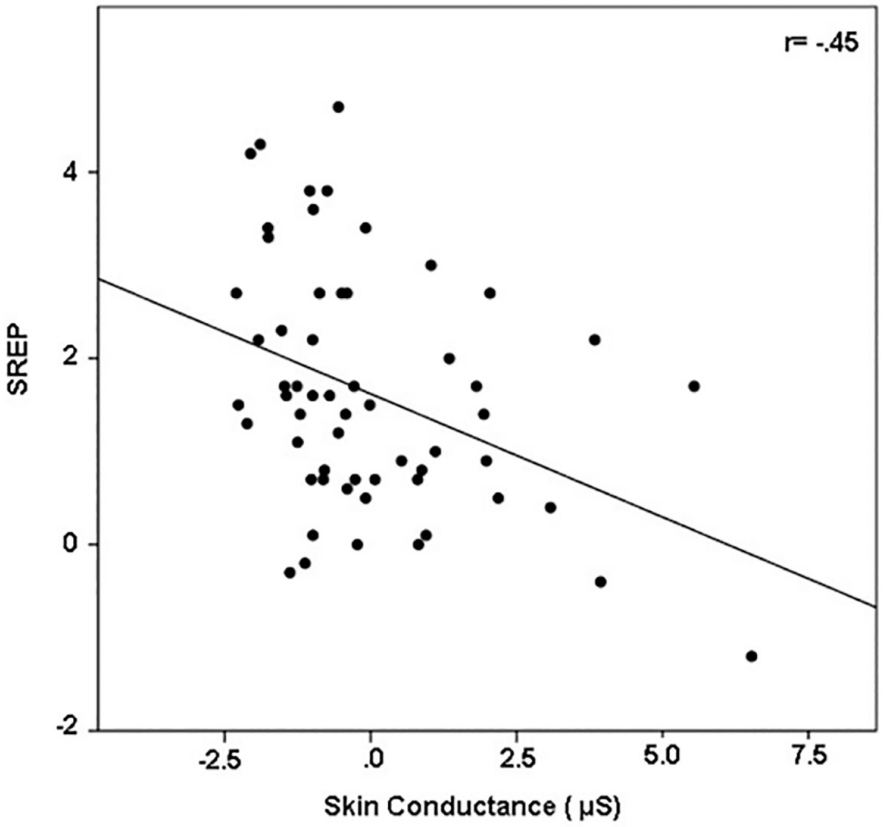

Fig. 1. Scatterplot and regression line for the association between SREP sensitisation and skin conductance (unstandardised residuals) in FM patients.
SREP: slowly repeated evoked pain.

[β=0.33, t(56)=2.65, p=.010, r^2=0.11]. In the second model, SC was a negative predictor of SREP sensitisation [β=0.34, t(56)=2.94, p=.005 for catastrophising; β= -0.38, t(55)= -3.31, p=0.002 for SC; r^2=0.26]. Figure 1 displays a scatterplot of the inverse association between SC (residuals) and SREP sensitisation in the whole patient sample.

In the FM sample, SREP sensitisation correlated positively with clinical pain (r=0.26; p=0.050) and fatigue (r=0.42; p=0.001) and showed a trend toward an association with insomnia (r=0.25; p=0.063). Unstandardised residuals of SC were marginally associated with clinical pain (r= -0.24; p=0.064), but not significantly with fatigue neither insomnia in the patients. No significant associations between values of SREP sensitisation and SC with pain threshold and tolerance respectively were found.

Discussion

As expected, the use of antidepressant medication, through secondary anticholinergic effects, interferes with the transmission of the input from the non-myelinated sympathetic C-fibres to the cholinergic terminals in the sweat glands (47), which can reduce sweating in FM patients using this medication. Antidepressant medication also interferes with the relation between SC and SREP sensitisation. Levels of SC were lower in our FM patients not using antidepressants in comparison with healthy controls, which corroborates previous studies (33, 35). In patients not taking antidepressants, and in the whole patient sample after statistically controlling for antidepressant use, a clear relationship between central sensitisation to pain (enhanced response to SREP protocol) and sweating, as indexed by SC, was observed in FM. Lower SC levels predicted greater SREP sensitisation, even after statistically controlling for catastrophising.

SREP sensitisation was positively associated with clinical symptoms of FM patients (pain, fatigue and insomnia), but not significant associations were found with pain threshold and tolerance, which corroborates previous findings (29, 40). SC levels only showed a marginal association with clinical pain. These differences could be explained due to fatigue and insomnia may be mainly related to central sensitisation; they are both typical symptoms of various central sensitisation conditions (7, 13). In future studies, it would be instructive to assess additional symptoms more specifically associated with peripheral neuropathy.

Our observation that lower SC levels predict the development of greater pain sensitisation, which is a putative underlying mechanism of FM pain, suggests that both autonomic dysfunction and small nerve fibre neuropathy could be involved in the central pain hyperexcitability of these patients. No studies until now have reported associations between dynamic evoked pain protocols and autonomic measures in FM.

Regarding SREP sensitisation, we previously found almost no associations with several autonomic cardiovascular parameters, both sympathetic and parasympathetic (inter- beat interval, high-frequency heart rate variability, blood pressure variability, pre-ejection period, etc.). The only exception was an inverse association between blood pressure and SREP sensitisation in

FM patients (30). This association is a manifestation of the known phenomenon of blood pressure-related hypoalgesia (*i.e.* higher blood pressure leads to lower pain perception), by which increases in blood pressure exerts an inhibitory influence on pain processing in the CNS (48, 49). The fact that autonomic cardiovascular parameters did not correlate with SREP sensitisation, whereas SC did, might suggest an interpretation of that association is terms of the presence of neuropathy. Neuropathy is more frequently observed in small nerve fibres in peripheral locations (like the small sympathetic nerve terminals innervating the sweating glands) than in more central and larger nerve fibres, such as those innervating the sinus node and myocardium (50). Additionally, authors propose a link between sympathetic activity and FM pain based on the existence of sympathetic hyperactivity in FM (51-54). However, our results showed reduced tonic sympathetic activity, as indexed by lower SC levels. Further research is need to clarify the association between SREP sensitisation and other autonomic parameters for different body locations and organs.

Several studies observed signs of central pain sensitisation (10, 12, 13, 24, 28), altered autonomic activity (35, 50, 53), and impaired small nerve fibres in FM patients (22, 33, 34, 56). More than half of all patients with painful sensory neuropathy report associated autonomic symptoms, in addition to demonstrating abnormalities in sweat function (57). How these alterations interact is still under discussion, and is important for a better understanding of pain chronicity in FM.

Autonomic alterations affect pain experience and can promote pain. Nociceptive and autonomic afferents fibres usually act together and can influence each other (53, 58). For example, increased sympathetic activity can influence pain experience (hyperalgesia) in chronic conditions, like severe chronic pancreatitis (53), and complex regional pain syndrome (60, 61). In FM patients, deficiencies in baroreceptor reflex function could explain some of the alterations seen in autonomic cardiovascular control, and are also associated with the severity of clinical symptoms (62-74). The coexistence of some neuropathic features in FM, and the emerging hypothesis of small fibre neuropathy, raises the question of whether FM pain could be explained by a neuropathic-like phenomenon (18, 65). The higher frequency of neurologic symptoms in FM patients, some of which are autonomic in origin (*e.g.* dizziness and orthostatic intolerance, dry mouth and eyes, urine incontinence and bladder discomfort, burning feelings, constipation, dyspnoea, palpitations, sexual dysfunction, difficulty swallowing, decreased sweating, skin discoloration, etc.) (19), may be taken as supportive of that hypothesis. Furthermore, FM sometimes onsets after a trauma like a car accident, neck injury, surgery, etc. (3, 66). Pain is characteristic of neuropathies that involve small myelinated fibres and type-C unmyelinated fibres; however, some small fibre neuropathies are not painful and others, especially those involving large fibres, cause pain (67). In neuropathies, neurons can be sensitised and spontaneously triggered (67). The spontaneous discharges of sensory C-fibres promote sensitisation in the dorsal horn neurons (central sensitisation), which increases their excitability to such an extent that they ultimately respond pathologically to normal stimuli as if they were painful stimuli (68). However, this hypothesis may be plausible for only a subgroup of FM patients, given that most studies only found small nerve fibre neuropathy in subgroups of FM patients (17, 22, 34, 56). This limits its ability to explain the central sensitisation seen in this population. All of this supports the consensus regarding the heterogeneity of the disorder, and the possible existence of different clinical clusters (69). For example, Thieme and Turk (70) reported different psychophysiological patterns among subgroups of FM patients with high, moderate and low SC responses. The largest psychophysiological subgroup was characterised by reduced heart rate, diastolic and systolic blood pressure, and low muscular activity and SC levels, all of which support the idea of an autonomic deficiency in most FM patients. The lower SC levels observed in our study in FM patients supports this suggestion.

This study had several limitations. The first concerns the use of antidepressant medication by a half of our FM patients (and these patients also take more anxiolytics medication). Through its anticholinergic effects, these medications inhibit sweating. In order to avoid confounding due to this effect, only patients not taking anti-antidepressants were included in some analyses, which decreased the statistical power of our study. However, the fact that associations were maintained after the bootstrap procedure and statistically controlling for antidepressant use shows the reliability of our results. Secondly, the mechanisms underlying SREP sensitisation are still unclear, and studies using other central sensitisation measures are needed. However, SREP has displayed good ability to assess pain sensitisation, and to discriminate FM patients from healthy individuals and patients with other pain disorders, suggesting that its mechanisms are likely explained by a central sensitisation process (27, 28-30). Third, SC in not a marker of neuropathy. However, considering that the degeneration of small nerve fibre terminals is a common characteristic of both small fibre neuropathy and autonomic sweat gland dysfunction (33), SC levels (as a surrogate of sweating) might be partially associated with the magnitude of small fibre neuropathy. Thus, our results should be considered preliminary. In order to achieve conclusive findings, they require replication in further studies including larger samples and direct measures of neuropathy, like distal electrochemical SC, quantitative sudomotor axon reflex testing or skin biopsies.

Further studies are also needed to confirm the existence of small fibre neuropathy in FM, where previous studies only revealed the presence of marked differences in the number and morphology of small nerve fibres in this population (71). Future longitudinal studies could clarify the role of neuropathy and reduced small fibre density in the development of FM pain.

In conclusion, our results suggest that the central pain sensitisation processes involved in the pathophysiology of FM could be related to alterations of sympathetic activity in the sweat glands, suggestive of small nerve fibre neuropathy or reduced fibre density.

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