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**Idiopathic Distal Sensory Polyneuropathy and Fibromyalgia Syndrome: A Comparative Phenotyping Study**

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### Article

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# Idiopathic Distal Sensory Polyneuropathy and Fibromyalgia Syndrome: A Comparative Phenotyping Study

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## ABSTRACT

**Introduction:** Painful idiopathic distal sensory polyneuropathy (IDSP) and fibromyalgia syndrome (FMS) are cryptogenic chronic pain syndromes. The contribution of small fibre pathology (SFP) in FMS remains controversial. This study aims to quantify small nerve pathology in participants with IDSP and FMS and identify relationships of SFP with sensory phenotypes.

**Methods:** In this study, 73 individuals (FMS: 25, IDSP: 23, healthy volunteers: 25) underwent comprehensive assessment, including neurological exams, questionnaires, sensory tests, and corneal confocal microscopy.

**Results:** IDSP participants displayed lower wind-up ratio (WUR) relative to FMS ( $p < 0.001$ ), loss of function to thermal and mechanical stimuli and elevated neuropathy disability scores compared to FMS and healthy volunteers (all  $p < 0.001$ ). FMS participants demonstrated gain of function to heat and blunt pressure pain

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responses relative to IDSP, and healthy volunteers (heat:  $p = 0.002$  and  $p = 0.003$ ; pressure: both  $p < 0.001$ ) and WUR (both  $p < 0.001$ ). FMS participants exhibited reduced corneal nerve fibre density ( $p = 0.02$ ), while IDSP participants had lower global corneal nerve measures (density, branch density, and length) relative to healthy volunteers (all  $p < 0.001$ ). Utilising corneal nerve fibre length, SFP was demonstrated in 66.6% of participants (FMS: 13/25; IDSP: 22/23). **Conclusion:** Participants with SFP, in both FMS and IDSP, reported symptoms indicative of small nerve fibre disease. Although distinctions in pain distributions are evident between individuals with FMS and IDSP, over 50% of participants between the two conditions displayed both a loss and gain of thermal and mechanical function suggestive of shared mechanisms. However, sensory phenotypes were associated with the presence of SFP in IDSP but not in FMS.

## PLAIN LANGUAGE SUMMARY

In people with painful idiopathic neuropathy (pain related to nerve damage where the cause of nerve damage is unknown), fibromyalgia syndrome (a long-term condition causing widespread pain), and healthy volunteers, the small nerve fibres of the peripheral nervous system, which may be involved in generating pain were assessed. These nerve fibres can be measured at the front of the eye (cornea) which can provide details on whether they are damaged in the

body. The response to temperature, light touch, pressure and pinprick stimuli can also be used to determine if there is a loss or gain of sensation, which may contribute to pain. The aim of this study was to identify the degree of damage to these nerve fibres and to determine whether this damage is associated with a loss (cannot feel or requires more intense stimulus to feel) or gain (stimulus is felt earlier or is painful earlier at lower intensity) of sensory function. The pattern of loss or gain in sensory function is known as a sensory phenotype. It was found that people with painful idiopathic neuropathy had more severe nerve damage, loss of function to temperature and touch, and fewer small nerve fibres in the cornea compared to those with fibromyalgia syndrome and healthy volunteers. People with fibromyalgia syndrome were more sensitive to heat and pressure and had fewer corneal nerve fibres relative to healthy volunteers. The presence of corneal nerve fibre damage was associated with sensory phenotypes (types of sensation felt) in painful idiopathic neuropathy but not in fibromyalgia syndrome.

**Keywords:** Idiopathic distal sensory polyneuropathy; Fibromyalgia syndrome; Small fibre; Corneal confocal microscopy; Quantitative sensory testing; Neuropathic pain; Sensory phenotyping; Pain characteristics

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## Key Summary Points

### *Why carry out this study?*

Painful idiopathic distal sensory polyneuropathy (IDSP) and fibromyalgia syndrome (FMS) are chronic pain conditions with unclear pathophysiology and substantial patient burden.

Corneal nerve fibre deficits may provide objective evidence of a lesion of the somatosensory system.

The contribution of small fibre pathology (SFP) in FMS is controversial, necessitating a detailed investigation to understand sensory phenotypes and their relationship with SFP.

### *What did the study ask?*

This study aimed to quantify small nerve pathology in participants with IDSP and FMS and to identify the relationships between SFP and sensory phenotypes.

### *What was learned from the study?*

IDSP participants were distinguished by pronounced sensory loss and higher neuropathy scores relative to FMS and healthy volunteers, with FMS participants characterised by a gain of function to heat and pressure pain.

SFP was demonstrated in two-thirds of participants using corneal nerve fibre length, with IDSP showing greater corneal nerve fibre loss and FMS exhibiting reduced corneal nerve fibre density relative to healthy volunteers.

Despite distinct pain distributions, half of participants from each condition had both a loss and gain of sensory function, suggesting shared mechanisms.

Sensory phenotypes are associated with the presence of SFP in IDSP but not in FMS.

## INTRODUCTION

Fibromyalgia syndrome (FMS) and painful idiopathic distal sensory polyneuropathy (IDSP) are chronic pain conditions of unclear pathophysiology. The recently updated diagnostic criteria for idiopathic neuropathies published by Freeman and colleagues use IDSP as an umbrella term incorporating idiopathic small fibre, mixed fibre and large fibre neuropathy [1]. The global prevalence of FMS is ~ 2–7% with a predilection for women [2]. FMS is characterised by diffuse regional or widespread pain, while IDSP is typically a length-dependent process, presenting in a stocking and glove distribution, often advancing proximally with time [3]. Pain generation in FMS has traditionally been attributed to abnormal central mechanisms [4]. However, preclinical, and experimental human studies indicate a role for peripheral afferents in spontaneous diffuse pain and tenderness in FMS [5]. Studies have identified small fibre pathology (SFP) in FMS, including reduced intra-epidermal and corneal nerve fibres [6–8]. Similarly, reductions in corneal confocal microscopy (CCM) measures and intra-epidermal nerves have been demonstrated in IDSP [9, 10]. Our meta-analysis demonstrates that SFP occurs in approximately 50% of individuals with FMS [11]. This suggests a possible co-existing peripheral mechanism of pain generation and/or maintenance in a subgroup of participants with FMS. While there is evidence to support a sensory overlap between FMS and idiopathic neuropathy, there is a paucity of data which compare phenotypes and pathophysiology. The aim of this study was to compare sensory phenotypes and small nerve fibre pathology using CCM in people with IDSP and FMS. We hypothesised that there would be significant group differences in corneal nerve fibre metrics and quantitative sensory testing (QST) parameters between individuals with IDSP, FMS, and healthy volunteers. In addition,

we hypothesised that the presence of SFP is associated with the resultant sensory phenotypes in these patient groups.

## RESEARCH DESIGN AND METHODS

Participants with IDSP were recruited sequentially from pain clinics at The Walton Centre. Participants with FMS were recruited from fibromyalgia services, musculoskeletal clinics and pain clinics at The Walton Centre and Aintree University Hospital sites. Ethical approval was obtained a priori (North West—Preston Research Ethics Committee – REC reference: 19/NW/0078; South West—Frenchay Research Ethics Committee REC reference: 20/SW/0138) and written informed consent was obtained from each participant and the study conduct adhered to good clinical practice guidelines and the tenets of the Declaration of Helsinki. Data were collected from two separate studies with similar protocols during a similar period of time.

### Study Population

Between 2019 and 2022, 108 participants were screened and 73 adult participants were subsequently recruited (55 women, 18 men; mean age  $49 \pm 13$  years). A total of 35 participants either could not participate or were excluded from the study. Eighteen participants reported being too unwell to participate or encountered logistical problems during the COVID-19 lockdowns in the United Kingdom. Fifteen participants did not meet eligibility criteria such as a diagnosis of diabetes mellitus, systemic disease, or corneal pathology. Participants with painful IDSP ( $n = 23$ ) and FMS ( $n = 25$ ) were recruited sequentially. Participants with a clinical diagnosis by exclusion of idiopathic SFN were included in this study. Participants were excluded if they reported or had a formal diagnosis of diabetes mellitus, systemic disease, corneal pathology, or co-morbid neurological conditions. All

participants underwent laboratory tests as part of the study protocol to exclude other causes of SFP. Participants without a history of chronic pain and all above exclusions were recruited as healthy volunteers ( $n = 25$ ).

### Polyneuropathy Subtyping

The ACTION criteria for IDSP were applied to further classify these participants according to signs and symptoms, QST, point-of-care nerve conduction studies, and CCM [12]. The classification of painful IDSP was accomplished through the utilisation of established and validated pain questionnaires. The diagnosis of primary FMS was based on current or past guideline criteria [13].

### Sample Size Calculation

A sample size analysis determined the minimum sample size required to test the primary study hypothesis regarding participants with IDSP relative to healthy volunteers. The required sample size to achieve 80% power at a significance threshold of  $\alpha = 0.05$  was 17 patients in each group to detect a meaningful group difference in corneal nerve fibre length (CNFL). A post hoc power calculation was performed to account for the inclusion of participants with FMS. A power calculation using the group means and standard deviation of CNFL indicated a 94.6% power at a significance threshold of  $\alpha = 0.05$  with our included cohort.

### Neurological Examination

All participants underwent neurological examination and a detailed assessment of neuropathy using the modified composite system neuropathy disability score (NDS). Vibration perception threshold of the hallux was measured using a neurothesiometer (Horwell Scientific, UK), with readings in millivolts (mV) and an abnormality defined as  $\geq 15$  mV.

## Questionnaires

Neuropathic symptoms, location and pain characteristics were assessed using the Neuropathy Symptom Profile (NSP), McGill Short Form Questionnaire (MPQ), PainDetect (PDQ) and Small Fibre Neuropathy Screening List (SFNSL). The composite scores of the SFNSL and PDQ were used to indicate the probability of small fibre neuropathy (SFN) and a neuropathic pain component, respectively.

## Point-of-Care Nerve Conduction

Sural nerve conduction velocity (SNCV) and amplitude (SNAP) were assessed in the right lower limb using the NC-Stat DPN Check (Neurometrix, Waltham, MA, USA) point-of-care device. Nerve conduction abnormality was determined by  $\geq 1$  measure below threshold (SNCV:  $\leq 44$  m/s; SNAP:  $< 6$   $\mu$ V) [14]. Current perception threshold testing with the Neurometer (MDE Diagnostics, Budapest, Hungary) was undertaken in a subgroup of participants with IDSP and healthy volunteers on the right index finger (C7) at the following frequencies: 2000, 250 and 5 Hz.

## Quantitative Sensory Testing (QST)

All participants underwent QST of the right forearm according to the German Research Network on Neuropathic Pain (DNFS) protocol [15]. Participants with IDSP also underwent QST of the dorsum of the foot. For analysis, raw QST data were logarithmically transformed, followed by a Z-transformation to standardise all values (except paradoxical heat sensations and dynamic mechanical allodynia). This was performed by subtracting the published age and sex reference population mean for each participant's raw scores for every parameter and dividing this value by the reference population standard deviation [16]. A positive Z-score value denotes a gain in function, and a negative Z-score denotes a loss of function in each parameter. This is a standard research methodology allowing

comparisons between participants differing in age and sex.

## Sensory Phenotypes

The frequency of sensory abnormalities and their combinations was characterised using the "LOGO" coding system as described by Maier and colleagues [17]. A loss of function was defined as two standard deviations ( $\leq 1.96$ ) below 0 of the normalised published reference data from the DNFS [18]. Loss of function to thermal stimuli [cold detection threshold (CDT); warm detection threshold (WDT)] was coded as L1; loss of function to mechanical detection threshold (MDT) or vibration detection threshold (VDT) was coded as L2. Gain of function was defined as two standard deviations ( $\geq 1.96$ ) above 0 of the published reference data from the DNFS. Gain of function to cold (CPT) or heat (HPT) pain threshold was coded as G1; gain of function to the mechanical pain threshold (MPT), mechanical pain sensitivity (MPS), dynamic mechanical allodynia (DMA) or pressure pain threshold (PPT) was coded as G2. When both thermal and mechanical abnormalities were present, this was coded as L3 or G3, respectively. Participants without a detected loss or gain were coded as LOG0. These codes were subsequently categorised into one of four patterns: no abnormality detected, loss of function, gain of function, and both loss and gain of function.

## Corneal Confocal Microscopy (CCM)

CCM was performed using a standard internationally accepted protocol in both eyes using a laser scanning corneal confocal microscopy device (Heidelberg Retina Tomograph 3 Rostock Cornea Module; Heidelberg Engineering, Heidelberg, Germany) to acquire images of the corneal sub-basal plexus. On average, 6–8 images (3–4 from each eye) were selected in a masked fashion (from group allocation) according to image quality and apical positioning of the central sub-basal nerve plexus. Automated image analysis was undertaken using ACCMetrics in a masked

and randomised manner. The corneal metrics quantified include corneal nerve fibre density (CNFD), corneal nerve fibre branch density (CNBD), and corneal nerve fibre length (CNFL). Published automated corneal nerve fibre thresholds were used to indicate abnormal corneal nerve counts and thus the threshold for SFP [19]. These were: CNFL < 15.3 mm/mm<sup>2</sup>; CNBD < 18.7 branches/mm<sup>2</sup>; CNFD < 16.7 fibres/mm<sup>2</sup>. Participants were considered to have SFP if they were below the CNFL threshold.

## Statistical Analysis

The statistical package R (v.4.0.2) was used for statistical analysis. Data were assessed for normality using quantile–quantile plots and Shapiro–Wilk test. Summary statistics were reported as mean ± standard deviation or median ± interquartile range as appropriate. Groups (IDSP, FMS and healthy volunteers) were compared using a one-way ANOVA followed by a Tukey's HSD test or Kruskal–Wallis test followed by a Dunn's test

**Table 1** Cohort characteristics

Variables	HV, <i>n</i> = 25 <sup>a</sup>	FMS, <i>n</i> = 25 <sup>a</sup>	IDSP, <i>n</i> = 23 <sup>a</sup>
Age (years)	42.4 (13.6)	48 (12.9)	57 (10)
Female <i>n</i> (%)	16 (64)	24 (96)	15 (65)
Years since diagnosis	0 (0–0)	6 (5–9)	6 (2.5–8.5)
Years symptoms prior to diagnosis	0 (0)	4 (2–10)	3 (1–10)
No analgesic medicine <i>n</i> (%)	0 (0)	9 (36)	6 (26.1)
1 Analgesic medicines <i>n</i> (%)	0 (0)	4 (16)	2 (8.7)
≥ 2 Analgesic medicines <i>n</i> (%)	0 (0)	12 (48)	15 (65.2)
BMI (kg/m <sup>2</sup> )	27.2 (5.9)	30.1 (8.2)	32 (8.6)
Waist (cm)	85.9 (11.5)	86.6 (14.9)	100.6 (20.8)
Systolic BP (mmHg)	122.6 (12.2)	126.5 (21.7)	130.7 (22.3)
Diastolic BP (mmHg)	78.7 (9)	76.3 (13.3)	81.1 (15.5)
HbA1c	35.4 (9.5)	36.8 (3.9)	38.8 (3.5)
Fasting glucose pmol/l	4.5 (0.5)	4.9 (0.8)	5 (1.3)
Cholesterol mmol/l	4.7 (0.7)	5.2 (1.1)	5 (1.3)
Triglycerides mmol/l	1.2 (0.4)	1.9 (1)	1.3 (0.4)
HDL mmol/l	1.6 (0.4)	1.6 (0.6)	1.5 (0.4)
LDL mmol/l	2.6 (0.6)	2.9 (0.9)	2.9 (1.1)
eGFR 60 ml/min/1.73 m <sup>2</sup>	83.6 (10)	83.8 (8.9)	76.8 (10.8)

Demographic, anthropometric and biochemistry summary measures of participants with FMS, IDSP and healthy volunteers *BP* blood pressure, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated haemoglobin, *HDL* high density lipoprotein, *LDL* low density lipoprotein

<sup>a</sup>Mean (SD); Median (0.25–0.75) IQR. *n* (%) where stated. The SFNSL is highly sensitive but has low specificity; a score less than 11 indicates a low probability of small fibre neuropathy, scores between 11 and 48 are suggestive of probable small fibre neuropathy, a score greater than 48 suggests that small fibre neuropathy is likely. A PDQ score of greater than 18 indicates a high likelihood of neuropathic pain

for multiple comparisons. For two group comparisons, parametric data and non-parametric variables were evaluated using an independent *t* test or Mann–Whitney *U* test, respectively. For all tests, a *p* value of < 0.05 after corrections for multiple comparisons was considered statistically significant. Categorical data were reported as frequencies and percentages by group. The mode of each item was used to broadly characterise groups as an indication of intensity, severity, or frequency of each descriptor on a Likert or ordinal scale. Fisher's exact test was used to test the association between the presence of SFP and sensory phenotype.

## RESULTS

### Clinical and Laboratory Patient Characteristics

Data from 73 participants were included in this analysis. Participants with IDSP were older relative to healthy volunteers (Table 1). There was a comparable duration in symptoms prior to a formal diagnosis and disease duration after diagnosis in participants with IDSP and FMS. Overall, blood tests and anthropometrics were unremarkable between the three groups. Participants with FMS or IDSP were prescribed 1 (*n* = 6, 12.5%), or ≥ 2 (*n* = 27, 56.3%) analgesic medicines. In this study, participants were on a diverse range of medications, making it challenging to conduct a systematic assessment of how these drugs influenced our findings.

### Neurological Examination and Questionnaires

Participants with IDSP scored higher on the neuropathy disability score relative to participants with FMS and healthy volunteers (Table 2). Participants with FMS and IDSP had higher scores in the SFNSL, MPQ, PDQ and NSP questionnaires relative to healthy volunteers (Table 2). The total scores of NSP and SFNSL were higher in participants with FMS compared to IDSP participants. Pain scores were comparable between the two groups.

### Pain Characteristics

The total cohort frequently reported deep aching pain, burning discomfort, sensitivity to touch and symptoms consistent with paraesthesia, with over half evaluating their experience as punishing or cruel (Fig. 1A–C). Participants with FMS characterised their pain as throbbing and tender, often triggered by slight pressure and overall evaluating the experience as exhausting (Fig. 1D). In contrast, IDSP participants described their pain as stabbing or sharp. Sudden pain attacks and radiating pains were reported by most participants (Fig. 1B, C).

### Pain Location

In participants with FMS, pain was reported more frequently in the shoulders and neck (70.8%), back and upper chest (71%), legs (67%), and lower back and buttocks (63%). In IDSP, all participants reported pain in acral distributions, over a third reported pain in their feet only (39%), both hands and feet (52%), hands only (9%) and over half (57%) also had pain in their legs. Pain in FMS participants was frequently widespread (63%) or regional (38%), encompassing both proximal and distal distributions or two or more proximal sites (Table S1).

### Autonomic Symptoms

Participants with FMS frequently reported muscle weakness, painful arms, muscle cramps, and autonomic symptoms including bowel problems, orthostatic hypotensive and sicca symptoms, and rated hypersensitivity of their legs, hot flushes, and tingling sensations as their most distressing symptoms (Fig. 1G).

### Quantitative Sensory Testing (QST)

Participants with IDSP demonstrated a loss of function to thermal (WDT, CDT and TSL; all *p* < 0.001), tactile (MDT; *p* < 0.001) and wind-up ratio (WUR) (WUR; *p* < 0.001) stimuli relative to FMS and control groups. Participants with FMS had reduced tactile detection thresholds



**Table 2** Neuropathy tests including neurological examination, nerve conduction studies, questionnaires quantitative sensory testing and corneal confocal microscopy of participants with IDSP, FMS and healthy volunteers

Variables	HV, <i>n</i> = 25 <sup>a</sup>	FMS, <i>n</i> = 25 <sup>a</sup>	IDSP, <i>n</i> = 23 <sup>a</sup>	FMS – HV <sup>b</sup>	FMS – IDSP <sup>b</sup>	HV – IDSP <sup>b</sup>
Clinical examination						
NDS	0 (0–0)	0 (0–0.5)	4 (0.5–7)	–	–	–
VPT left	5 (3.9–6.5)	5.1 (4.3–6)	14 (8–36)	–	–	–
VPT right	5.5 (4–6.7)	5.4 (4.3–6.7)	15 (8–38)	–	–	–
SNAP	11 (6–11)	13 (10–16)	5 (4.5–8.5)	–	–	–
SNCV	54 (53–59.8)	55.5 (55–58)	55 (53–55)	–	–	–
Current perception (2000 Hz) <sup>c</sup>	218 (166–250)	–	333 (250–502)	–	–	–
Current perception (250 Hz) <sup>c</sup>	93 (58–126)	–	165 (42–424)	–	–	–
Current perception (5 Hz) <sup>c</sup>	65 (33–78)	–	46 (30–165)	–	–	–
Questionnaires						
NSP (total)	0 (0–1)	20 (18–26)	12 (8–15)	–	–	–
MPQ—pain descriptors (total)	0 (0–2)	28 (21–34)	20 (12–26)	–	–	–
MPQ—VAS	1 (0.8)	68.9 (24.2)	20 (12–26)	–	–	–
MPQ—pain index	0 (0–1)	4 (3–5)	4 (3–5)	–	–	–
SFNSL ≥ 48 indicative of SFN	0 (2–6)	50 (45–59)	24 (12–35)	–	–	–
PDQ current pain	0.5 (1.1)	7 (5–8)	5 (4–7)	–	–	–
PDQ strongest pain in the last month	0 (0–2)	9 (8–9.5)	9 (7–10)	–	–	–
Pain detect average pain	0.7 (1.4)	8 (6–8.5)	7 (5.5–8)	–	–	–
PDQ total	0 (0–1.25)	28 (23–29.5)	22 (16–30)	–	–	–
Quantitative sensory testing						
CDT	– 0.6 (1.2)	– 0.8 (0.9)	– 2.5 (1.5)	0.807	< 0.001	< 0.001
WDT	– 0.6 (1.2)	– 0.8 (1)	– 2.4 (1.3)	0.814	< 0.001	< 0.001
TSL	– 0.6 (1.1)	– 0.8 (1)	– 1.9 (1.3)	0.662	0.005	< 0.001
CPT	0.3 (1.5)	0.5 (1.2)	0.4 (1.4)	0.86	0.933	0.986
HPT	– 0.7 (1)	0.5 (1.5)	– 0.8 (1.2)	0.003	0.002	0.963
PPT	– 0.1 (1.4)	4 (3)	0.3 (1.8)	< 0.001	< 0.001	0.773

**Table 2** continued

Variables	HV, <i>n</i> = 25 <sup>a</sup>	FMS, <i>n</i> = 25 <sup>a</sup>	IDSP, <i>n</i> = 23 <sup>a</sup>	FMS – HV <sup>b</sup>	FMS – IDSP <sup>b</sup>	HV – IDSP <sup>b</sup>
MDT	0.1 (1.3)	– 1.2 (1.7)	– 2.8 (2)	0.017	0.006	< 0.001
MPT	1.2 (1.3)	0.6 (1.1)	0.9 (1.9)	0.398	0.861	0.741
MPS	– 0.1 (1.2)	1.2 (1.6)	0.7 (2)	0.013	0.53	0.182
WUR	– 1.6 (1)	0.3 (1.2)	– 2 (1.1)	< 0.001	< 0.001	0.521
VDT <sup>c</sup>	0.6 (0.56–0.64)	0.56 (0.41–0.61)	0.41 (– 6.9–0.61)	0.138	> 0.9	0.012
DMA <sup>c</sup>	0 (0–0)	0 (0–0.66)	0 (0–0)	0.008	0.543	0.322
PHS <sup>c</sup>	0 (0–1)	0 (0–0)	0 (0–0)	> 0.9	> 0.9	> 0.9
Corneal confocal microscopy						
CNFL	16.7 (4.3)	14.2 (4)	12.1 (3.1)	0.057	0.165	< 0.001
CNFD	27.4 (4.4)	23.7 (7.5)	19.7 (6.4)	0.101	0.075	< 0.001
CNBD	44.5 (20.1)	31.5 (15.3)	26.3 (12.5)	0.02	0.52	0.001

Current perception threshold was undertaken in 8 healthy volunteers and 8 participants with IDSP

*CDT* cold detection threshold, *CPT* cold pain threshold, *CNFD* corneal nerve fibre density, *CNBD* corneal nerve branch density, *CNFL* corneal nerve fibre length, *DMA* dynamic mechanical allodynia, *HPT* heat pain threshold, *MDT* mechanical detection threshold, *MPT* mechanical pain threshold, *MPQ* McGill short-form pain questionnaire, *MPS* mechanical pain sensitivity, *NDS* neuropathy disability score, *NSP* neuropathy symptom profile, *PDQ* paindetect questionnaire, *PHS* paradoxical heat sensation, *PPT* pressure pain threshold, *SFNSL* small fibre neuropathy screening list, *SNAP* sural nerve amplitude, *SNCV* sural nerve conduction velocity, *TSL* thermal sensory limen, *WUR* wind-up ratio, *VDT* vibration detection threshold, *VPT* vibration perception threshold

<sup>a</sup>Mean (SD); Median (0.25–0.75 IQR)

<sup>b</sup>Tukey’s HSD

<sup>c</sup>Dunn test (with Bonferroni adjustment)

(MDT; *p* = 0.01) and increased responsiveness to mechanical stimulation (MPS; *p* = 0.01) and allodynia (DMA; *p* = 0.008) at the group level, relative to healthy volunteers (Fig. 2; Table 2). Participants with FMS exhibited gain of function to heat pain (HPT; IDSP: *p* = 0.002; healthy volunteers: *p* = 0.003) blunt pressure (PPT; both *p* < 0.001) and WUR (WUR; both *p* < 0.001) stimuli relative to IDSP and healthy volunteers.

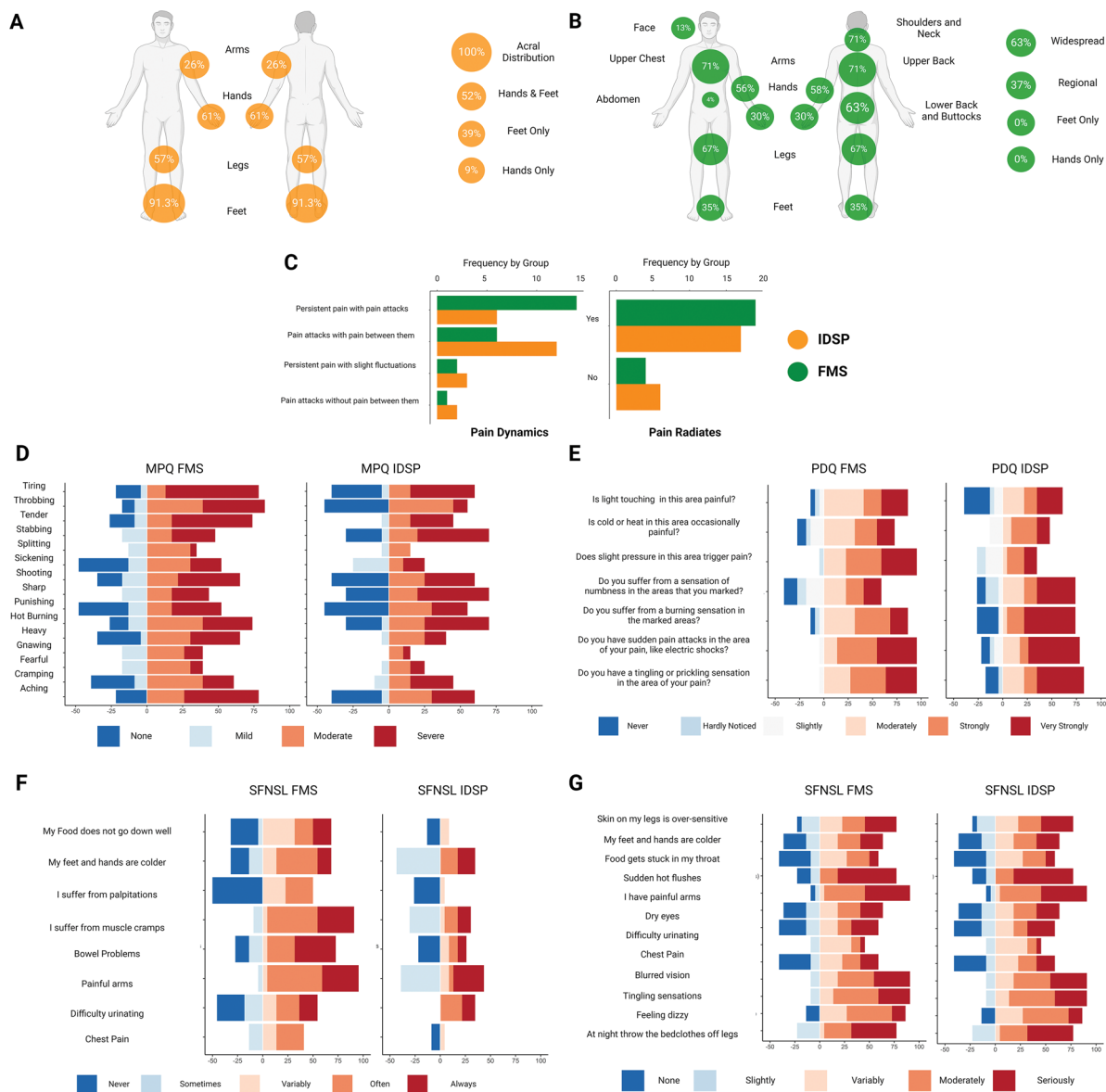
**Corneal Confocal Microscopy**

Corneal sub-basal nerve plexus measures CNFL, CNFD and CNBD were reduced in participants with IDSP relative to healthy volunteers (all *p* < 0.001). In participants with FMS, CNBD was

reduced relative to healthy volunteers (*p* = 0.02) (Table 2; Fig. 2C).

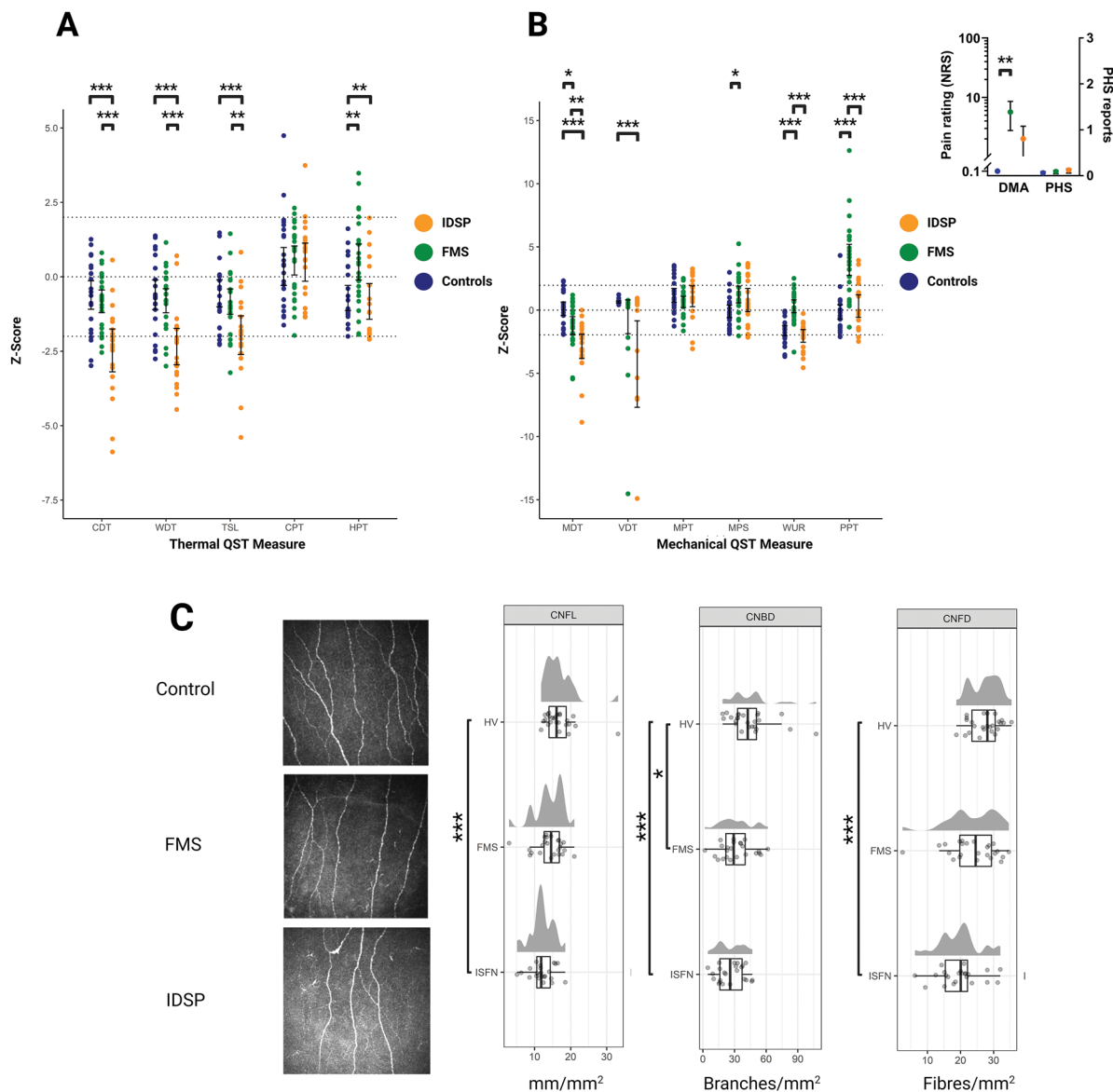
**Sensory Phenotypes**

Half of the participants (FMS: 11/25; IDSP: 16/23) exhibited both gain and loss of function to thermal and/or mechanical stimuli (Table 3). Sensory loss was more frequent in IDSP (IDSP: 6/23; FMS: 1/25), while FMS participants frequently had gain of function only (FMS: 12/25; IDSP: 1/23). According to the SFNSL, over 83% of participants (FMS: 24/25; IDSP: 16/23) had small fibre symptoms (Table 3). Additionally, more than two-thirds (FMS: 21; IDSP: 16; Total: 37/48) were indicated to have a > 90%



**Fig. 1** Summary of self-reported outcomes of participants with Idiopathic Distal Sensory Polyneuropathy (IDSP) and fibromyalgia syndrome (FMS). **A** Participants with IDSP presented with an acral pain distribution which more frequently involved both the feet and hands. **B** Participants with FMS more frequently reported symptoms across three or more regions including distal and proximal regions of the body. **C** Participants with FMS and IDSP reported radiating pains at a similar rate but elected different dynamic descriptors of their pain. The most frequently elected pain dynamic in participants with IDSP was ‘pain

attacks with pain between them’ while participants with FMS commonly elected ‘persistent pain with pain attacks’ to represent their pain. **D** Diverging bar chart showing the McGill Short-Form Pain Questionnaire (MPQ) descriptors of participants with FMS (**left**) and IDSP (**right**). **E** Diverging bar chart showing the Pain Detect Questionnaire (PDQ) responses of participants with FMS (**left**) and IDSP (**right**). **F** Diverging bar chart showing the frequency of SFNSL symptoms reported. **G** Diverging bar chart showing the seriousness of SFNSL symptoms reported



**Fig. 2** Quantitative sensory testing (QST) and corneal confocal microscopy measures (CCM) in participants with idiopathic distal sensory polyneuropathy (IDSP) and fibromyalgia syndrome (FMS). **Top** The Z-scores of individual participants by group of thermal (A) and mechanical (B) QST measures represented as a dot plot. The error bars indicate the 95% confidence interval. Idiopathic SFN idiopathic small fibre neuropathy (orange); FMS fibromyalgia syndrome (green); HV healthy volunteers (dark blue). **Bottom** Representative CCM images (C left) from a healthy volunteer, a participant with fibromyalgia syndrome (FMS) and idiopathic distal sensory polyneuropathy (IDSP). CCM measurements from individual participants by group represented

as a raincloud plot. The raincloud plot is a box plot with individual data points with the group distribution represented as a ‘raincloud’. As can be seen, there appears to be a binomial distribution in corneal nerve branch density in the fibromyalgia syndrome group. CDT cold detection threshold, CNBD corneal nerve branch density, CNFD corneal nerve fibre density, CNFL corneal nerve fibre length, CPT cold pain threshold, HPT heat pain threshold, MDT mechanical detection threshold, MPS mechanical pain sensitivity, MPT mechanical pain threshold, PPT pressure pain threshold, TSL thermal sensory limen, VDT vibration detection threshold, WDT warm detection threshold, WUR wind-up ratio

**Table 3** Sensory phenotypes and abnormal findings in participants with FMS and IDSP; *n* (%)

Item	FMS ( <i>n</i> = 25)	IDSP ( <i>n</i> = 23)	Total ( <i>n</i> = 48)
Both loss and gain of function	11 (45.8)	16 (69.6)	27 (57.4)
Gain of function only	12 (50)	1 (4.3)	13 (27.7)
Loss of function only	1 (4.2)	6 (26.1)	7 (14.9)
NCS	1 (4)	4 (17.4)	5 (10.4)
VPT	0 (0)	10 (43.5)	10 (20.8)
CNFL	13 (52)	19 (82)	32 (66.6)
CDT	4 (16.7)	15 (68.2)	19 (41.3)
WDT	3 (12.5)	16 (72.7)	19 (41.3)
TSL	4 (16.7)	9 (40.9)	13 (28.3)
CPT	3 (12.5)	3 (13)	6 (12.8)
HPT	5 (20.8)	4 (18.2)	9 (19.6)
PPT	18 (75)	7 (33.3)	25 (55.6)
MDT	7 (29.2)	14 (63.6)	21 (45.7)
MPT	2 (8.3)	10 (45.5)	12 (26.1)
MPS	9 (37.5)	11 (47.8)	20 (42.6)
WUR	3 (12.5)	9 (40.9)	12 (26.1)
VDT	4 (16.7)	9 (39.1)	13 (27.7)
DMA	5 (20.8)	4 (17.4)	9 (19.1)
SFNSL Likely	24 (96)	16 (69.6)	40 (83.3)
SFNSL Highly probable	15 (60)	3 (13)	18 (37.5)
Neuropathic pain component > 90% Likely	21 (84)	16 (69.6)	37 (77.1)

*CDT* cold detection threshold, *CNFL* corneal nerve fibre length, *CPT* cold pain threshold, *HPT* heat pain threshold, *MDT* mechanical detection threshold, *MPS* mechanical pain sensitivity, *MPT* mechanical pain threshold, *NCS* nerve conduction studies, *PPT* pressure pain threshold, *SFNSL* small fibre neuropathy screening list, *TSL* thermal sensory limen, *VDT* vibration detection threshold, *VPT* vibration perception threshold, *WDT* warm detection threshold, *WUR* wind-up ratio

probability of a neuropathic pain component according to the PDQ.

The presence of SFP presence was significantly associated with sensory phenotypes in IDSP ( $p = 0.017$ ) but not in FMS ( $p \geq 0.9$ ).

### Small Fibre Pathology

Signs and symptoms suggestive of small fibre neuropathy, along with reduced corneal nerve fibre length, were found in 66% of participants (IDSP: 19/23; FMS: 13/25; Total: 34/48).

### DISCUSSION

The primary aim of this study was to identify small nerve fibre abnormalities in participants with IDSP and FMS and to relate those to

neuropathic pain phenotypes. Using physical examination, pain questionnaires and QST, we have demonstrated signs, symptoms, and objective evidence of SFP in over two-thirds of our included participants. Our data demonstrate that sensory loss is more frequently associated with participants with IDSP, although a subgroup of participants with FMS and IDSP exhibit sensory loss concurrent with a gain of function to thermal and/or mechanical stimuli. Despite this, participants with FMS more frequently exhibit increased sensitivity to heat and pressure pain, despite a mild loss of thermal and/or mechanical detection function.

Approximately 50% of participants with FMS showed signs of SFP in either CNFL or CNBD. Our CCM findings broadly agree with findings presented by Klitsch and colleagues of moderate reductions in CNFL and CNFD seen in participants with FMS, and greater decrements in all corneal nerve metrics in participants with SFN [20]. We found participants with IDSP had loss of function in mechanical, thermal and vibration senses. Similar findings in mixed-fibre polyneuropathies and SFN have been reported [21]. Interestingly, participants with SFN exhibited thermal hyperalgesia and mechanical hyperalgesia, while mixed-fibre polyneuropathies were more frequently associated with sensory loss [21]. Unfortunately, there were too few participants with pure isolated SFN to meaningfully test this.

Small fibre damage has been associated with abnormalities in thermal and mechanical parameters [6, 21–23]. A recently published retrospective cohort study identified pathological alterations in corneal nerve fibre metrics, with FMS participants primarily exhibiting differences in branch density [24]. We also identified prevalent thermal and mechanical loss of function in IDSP and found that participants with FMS showed a gain of function to pressure pain. Both IDSP and FMS exhibit a comparable prevalence of mechanical and thermal hyperalgesia. However, mechanical hyperalgesia and sensory loss rarely occur in isolation in IDSP and FMS, respectively. Moreover, we found that SFP was associated with neuropathic pain phenotype in IDSP, but not in

FMS. This is similar to recently published studies which indicates that SFP may not be associated with sensory phenotype in FMS [23].

Our data demonstrate that participants with FMS report burning pain and paraesthesia, with 84% of participants likely to have a neuropathic pain component. These findings agree with previous studies [7, 8]. However, the certainty of the evidence for using the PDQ for the likelihood of a neuropathic pain component is deemed to be low by the Special Interest Group of the International Association for the Study of Pain [25]. This might also clarify why a neuropathic pain component was considered likely in only 70% of participants with painful IDSP. Indeed, symptoms alone are unreliable for a diagnosis of small fibre neuropathy and require an objective test such as abnormal intra-epidermal nerve fibre density (IENFD) at the distal leg [26]. The Besta criteria propose that such clinical signs and symptoms be used in conjunction with QST and IENFD for a reliable diagnosis. The proposed IDSP criteria by ACTION provide a more comprehensive framework for subgrouping using symptomatology, neurological examination, exclusion of other conditions, together with QST and IENFD to delineate small from mixed-fibre polyneuropathy [12].

Notably, both FMS and idiopathic IDSP groups showed a trend towards reduced tactile detection and increased mechanical pain sensitivity, a characteristic noted in previous studies [27, 28]. Participants with IDSP exhibited reduced pain summation while participants with FMS retained sensitivity to pressure pain suggestive of differing pathophysiology. Overall, participants with IDSP and FMS with SFP demonstrated similarities.

Both sensory loss and hyperalgesia can co-occur after neuronal injury [29], leading to both ascending and descending alterations along the neuroaxis [30]. Sensory characteristics associated with neuropathic pain have been successfully replicated in studies involving healthy volunteers through experimental neuropathic pain models [31]. These characteristics seem to align with proposed models explaining the generation and persistence of pain [32]. Importantly, the use of neuropathic pain phenotypes

enables the categorization of individuals into different response groups regarding analgesic medications [33]. Indeed, surrogate models of central sensitisation, including those induced by capsaicin, heat, and electrical stimulation, have demonstrated pharmacological profiles that exhibited greater responsiveness to antihyperalgesic medicines [34].

Widespread FMS pain is accompanied by tenderness and deep aching pain of the muscles. Interestingly, lidocaine injections increased local pain-thresholds and decreased secondary thermal hyperalgesia in participants with FMS [5, 35]. These data suggest pain generation and maintenance through peripheral afferents and descending pain inhibition. Indeed, abnormal spontaneous activity of peripheral c-nociceptors have been demonstrated in FMS and SFN [36]. After-sensations and anhedonia in response to c-afferent stimuli have been reported in participants with FMS, suggesting peripheral c-fibre pathology may contribute to hyperalgesia and FMS pain [6, 8, 37, 38]. Furthermore, both IDSP and FMS are characterised by chronic nociceptive input which worsens at night and disrupted sleep which are implicated in central sensitisation and pain amplification [39, 40]. An immune mediated mechanism has been suggested to be a cause in some individuals with FMS, since passive transfer of IgG from participants with FMS was demonstrated, resulting in peripheral sensitisation of nociceptive afferents in mice [41]. Indeed, a potential incipient pro-inflammatory insult may instigate both peripheral and central sensitivity in participants with FMS and IDSP, representing a possible shared mechanism [30, 42].

A potential limitation of the present study is the sample size, which was further reduced in subsequent exploratory sub-group analyses. Further, the selection of the right forearm for QST may not be reflective of small fibre function of other dermatomes. This is important considering the widespread and regional nature of sensory disturbances and pain reported by participants with FMS and the contrasting stocking and glove distribution seen in participants with IDSP. Additionally, contrasts between participants with FMS and IDSP may be

more pronounced at the dorsum of the foot. The lack of formal nerve conduction studies of the peroneal, tibial, radial, median, and ulnar motor and sensory nerves would facilitate a more precise delineation between small and mixed-fibre neuropathies. Furthermore, a pure sample of participants with small fibre neuropathy would require a formalised screening protocol performed close to the date of testing within one dedicated laboratory to limit sample testing variability. Reductions of cutaneous innervation are evidenced in SFN and are recommended for the diagnosis of neuropathic pain [25]. While CCM has shown utility in the diagnosis of peripheral neuropathy, structural deficits of intra-epidermal nerves in IDSP and FMS would have strengthened our findings. However, evidencing a lesion or disease of the somatosensory system using CCM in patients with an irregular distribution of pain could prove useful considering the lack of established normative thresholds for intra-epidermal nerve fibre density in proximal or regional distributions.

## CONCLUSION

We have demonstrated SFP in most participants with IDSP and half of participants with FMS. Despite clinical heterogeneity, the presence of SFP is broadly associated with sensory loss in IDSP but not in FMS. While there is overlap in the symptomatology of IDSP and FMS, the presence of SFP does not appear to be associated with the sensory phenotype in FMS. These findings highlight the importance of refining diagnostic criteria. Future studies should include longitudinal multi-modal imaging of the neuroaxis and peripheral nervous system to delineate the precise pathophysiology of these conditions, enabling more targeted treatments and improved clinical outcomes.

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**Data Availability.** The data that support the findings of this study are available from the corresponding author upon reasonable request but may require data transfer agreement and associated costs.

## Declarations

**Conflict of Interest.** All authors; Jamie Burgess, Anne Marshall, Leandros Rapteas, David Riley, Kohei Matsumoto, Cheng Boon, Alia Alchawaf, Maryam Ferdousi, Rayaz A. Malik, Andrew Marshall, Stephen Kaye, David Gosal and Bernhard Frank declare that they have no competing interests relevant to the current publication. Uazman Alam has no direct conflict of interest but discloses the following: honoraria received from Procter & Gamble, Viatrix, Eli Lilly, Grunenthal, and Sanofi for educational meetings; investigator-led funding from Procter & Gamble; and sponsorship for travel to an international conference from Daiichi Sankyo.

**Ethical Approval.** Ethical approval was obtained a priori (North West – Preston Research Ethics Committee—REC reference: 19/NW/0078; South West—Frenchay Research Ethics Committee REC reference: 20/SW/0138) and written informed consent was obtained from each participant and the study conduct adhered to good clinical practice guidelines and the tenets of the Declaration of Helsinki. Data was collected from two separate studies.

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