EJP
European Journal of Pain

ORIGINAL ARTICLE

Central sensitization as the mechanism underlying pain in joint hypermobility syndrome/Ehlers–Danlos syndrome, hypermobility type

G. Di Stefano[1], C. Celletti[2], R. Baron[3], M. Castori[4], M. Di Franco[5], S. La Cesa[1], C. Leone[1], A. Pepe[1], G. Cruccu[1], A. Truini[1], F. Camerota[2]

1 Department of Neurology and Psychiatry, Sapienza University, Rome, Italy
2 Physical Medicine and Rehabilitation Division, Policlinico Umberto I, Sapienza University, Rome, Italy
3 Division of Neurological Pain Research and Therapy, Universitätsklinikum Schleswig-Holstein, Kiel, Germany
4 Division of Medical Genetics, Department of Molecular Medicine, San Camillo-Forlanini Hospital, Sapienza University, Rome, Italy
5 Rheumatology Unit, Department of Internal Medicine and Medical Specialities, Sapienza University, Rome, Italy

Correspondence
Andrea Truini
E-mail: andrea.truini@uniroma1.it

Funding sources
None declared.

Conflicts of interest
None declared.

Accepted for publication
10 January 2016

doi:10.1002/ejp.856

Abstract

Background: Patients with joint hypermobility syndrome/Ehlers–Danlos syndrome, hypermobility type (JHS/EDS-HT) commonly suffer from pain. How this hereditary connective tissue disorder causes pain remains unclear although previous studies suggested it shares similar mechanisms with neuropathic pain and fibromyalgia.

Methods: In this prospective study seeking information on the mechanisms underlying pain in patients with JHS/EDS-HT, we enrolled 27 consecutive patients with this connective tissue disorder. Patients underwent a detailed clinical examination, including the neuropathic pain questionnaire DN4 and the fibromyalgia rapid screening tool. As quantitative sensory testing methods, we included thermal-pain perceptive thresholds and the wind-up ratio and recorded a standard nerve conduction study to assess non-nociceptive fibres and laser-evoked potentials, assessing nociceptive fibres.

Results: Clinical examination and diagnostic tests disclosed no somatosensory nervous system damage. Conversely, most patients suffered from widespread pain, the fibromyalgia rapid screening tool elicited positive findings, and quantitative sensory testing showed lowered cold and heat pain thresholds and an increased wind-up ratio.

Conclusions: While the lack of somatosensory nervous system damage is incompatible with neuropathic pain as the mechanism underlying pain in JHS/EDS-HT, the lowered cold and heat pain thresholds and increased wind-up ratio imply that pain in JHS/EDS-HT might arise through central sensitization. Hence, this connective tissue disorder and fibromyalgia share similar pain mechanisms.

What does this study add?: In patients with JHS/EDS-HT, the persistent nociceptive input due to joint abnormalities probably triggers central sensitization in the dorsal horn neurons and causes widespread pain.

1. Introduction

Ehlers–Danlos syndrome (EDS) comprises a growing range of hereditary connective tissue disorders primarily affecting skin, ligaments, joints, blood vessels and internal organs. The widely agreed EDS classification identifies six major variants, the most common being the hypermobility type (EDS-HT) (De Paepe and Malfait, 2012). The lack of specific clinical signs and laboratory confirmatory tests makes EDS-HT merely a tentative diagnosis. EDS-HT also shares identical clinical features with the joint hypermobility syndrome (JHS). Some authors therefore consider these two disorders as a unique and indistinguishable condition (JHS/EDS-HT) (Tinkle et al., 2009).

Although patients with JHS/EDS-HT frequently complain of pain (Castori et al., 2012), its underlying mechanisms are still unclear. Some patients suffer from joint-related pain, but in most of them, pain has a complex distribution poorly compatible with joint-related pain. Whereas some studies suggested that patients with this rare disease might suffer from neuropathic pain (Camerota et al., 2011; Rombaut et al., 2014), others, given that pain related to JHS/EDS-HT usually spreads beyond the joints and causes fatigue, suggested that it resembles fibromyalgia (Sendur et al., 2007; Voermans and Knoop, 2011). No study has verified whether patients with JHS/EDS-HT have somatosensory nervous system damage, a prerequisite for neuropathic pain (Truini et al., 2013a), or suffer from central sensitization, an essential feature in fibromyalgia. Knowing more about the mechanisms responsible for JHS/EDS-HT-related pain might help in managing this commonly reported symptom more appropriately.

In this prospective study, we sought information on the mechanisms underlying pain related to JHS/EDS-HT, verifying whether this symptom depends on somatosensory nervous system damage or central sensitization. To do so, we enrolled 27 consecutive patients with HT-EDS. In all patients, we collected information from clinical examination and pain questionnaires, analysed quantitative sensory testing profiles, recorded responses to a standard nerve conduction study and laser-evoked potentials and compared these diagnostic variables with those for matched healthy controls.

2. Methods

2.1 Study cohort and design

We enrolled 27 patients with JHS/EDS-HT (3 men, 24 women, mean age 35.7 ± 10.9 years). Patients were consecutively recruited in the outpatient clinic for heritable connective tissue disorders at the Physical Medicine and Rehabilitation Unit at Sapienza University, Rome. Inclusion criteria were JHS/EDS-HT diagnosed according to the Villefranche criteria for EDS-HT (Tinkle et al., 2009) and Brighton criteria for JHS (Tinkle et al., 2009) and age older than 18 years. A trained clinical geneticist at the connective tissue clinic at San Camillo-Forlanini Hospital, Rome, confirmed the diagnosis and differentiated JHS/EDS-HT from other partially overlapping disorders. Exclusion criteria were cognitive disturbances and peripheral or central nervous system disorders. We also enrolled 27 healthy volunteers (3 men, 24 women, mean age 35.0 ± 11.1 years), selected among the hospital staff and individually matched for gender and age. These control subjects were assessed with a short medical history and a short neurological examination.

All subjects underwent clinical examination, including the DN4 questionnaire and the fibromyalgia rapid screening tool. DN4 questionnaire was administered to the maximal area of pain. This screening tool consisted of seven items related to symptoms and three related to clinical examination, with a cut-off of 4. Of the 27 patients included in the study, 20 underwent quantitative sensory testing. In all patients, we recorded a standard nerve conduction study, assessing the non-nociceptive afferent fibres, and laser-evoked potentials, assessing nociceptive afferent fibres. Patients did clinical examinations and diagnostic tests at the Department of Neurology and Psychiatry in the University Hospital Policlinico Umberto I, Rome. This research was approved by the local institutional review board and all patients gave their informed consent.

2.2 Clinical examination

Patients underwent neurological examination and detailed sensory profiling using bedside tools. Tactile sensation was tested with Von Frey filaments, vibratory sensation with a tuning fork (128 Hz) and pinprick sensation with a wooden cocktail stick. Muscle strength was evaluated with the Medical Research Council Score. In the clinical examination, we also recorded the number of body areas affected by pain (widespread pain index) and somatic symptoms score as reported in the Preliminary Diagnostic Criteria for Fibromyalgia established by the American College of Rheumatology (Wolfe et al., 2010). Patients completed the DN4, a validated questionnaire aimed at diagnosing neuropathic pain (Bouhassira et al.,

2005), and the fibromyalgia rapid screening tool, a validated self-completed questionnaire for detecting fibromyalgia syndrome (Perrot et al., 2010). Patients were also asked to mark the pain distribution area on a somatic map.

2.3 Quantitative sensory testing

For quantitative sensory testing, we used a thermode (ATS, PATHWAY, Medoc, Israel). The computer-driven PATHWAY system contains a metal contact plate (contact area 30 × 30 mm) equipped with an external Peltier cooler element that cools and heats the plate to target levels. The baseline temperature of 32 °C reached target temperature at a ramp rate of 1 °C/s. Quantitative sensory measures were tested on the left-hand dorsum and the right trapezius region. In 20 patients, we tested the thermal detection thresholds for detecting cold (cold detection threshold) and warmth (warm detection threshold), thermal-pain thresholds for cold (cold pain threshold) and heat stimuli (heat pain threshold). In this study, we also investigated pain summation to repetitive 256 mN pinprick stimuli delivered to the left hand and right trapezius region (wind-up ratio) with the 'Pinprick' equipment, MRC Systems GmbH – Medizintechnische System. This test compares the numerical pain rating (NRS) (range 0–10) given for a series of repetitive pinprick stimuli applied at equal intensity with the NRS for a single stimulus at the same intensity. The 'wind-up' ratio calculated by dividing the arithmetic mean pain intensity rating for the series of stimuli by the arithmetic mean pain intensity rating for the single stimulus. All procedures took place in accordance with the recommendations given by the German Research Network on Neuropathic Pain (Rolke et al., 2006; Magerl et al., 2010). Quantitative sensory testing data in patients were compared with those for gender- and age-matched controls included in the study.

2.4 Neurophysiological examination

All patients underwent a motor and sensory nerve conduction study using surface recording electrodes with standard placement. Methods used matched those recommended by experts at the International Federation of Clinical Neurophysiology (Kimura, 2006). Testing comprised sensory nerve action potentials and conduction velocities recorded from sural, ulnar and superficial radial nerves. We also tested compound motor action potential amplitudes and conduction velocities from peroneal, tibial and ulnar nerve. We did not check isolated mononeuropathies involving the median nerve owing to their high prevalence in the general population. To study laser-evoked potentials, we used a neodymium:yttrium-aluminium-perovskite (Nd:YAP) laser (wavelength 1.34 mm, pulse duration 2–20 ms, maximum energy 7 J) (Truini et al., 2013b). The dorsum of the right foot and left hand was stimulated by laser pulses (intensity, 150–200 mJ/mm^2; duration, 5 ms; diameter, 5 mm) eliciting pinprick sensations. The interstimulus interval was varied pseudorandomly (10–15 s). After each stimulus, the laser beam target was shifted. To determine the laser perceptive threshold, we delivered stimuli in series at increasing and decreasing intensities and defined the perceptive threshold as the lowest intensity at which the subjects perceived at least 50% of laser stimuli. The early, lateralized component, N1, and the main complex, N2–P2, were recorded through disc electrodes from the temporal areas (Tc) referenced to frontal area (Fz) and vertex (Cz) referenced to the nose. From 10 to 20 trials, devoid of artefacts was collected and averaged. We measured peak latency and amplitude (peak-to-peak) of the temporal N1 component and the N2–P2 vertex complex. Neurophysiological data in patients were compared with those for gender- and age-matched controls.

2.5 Statistical analysis

Because some data were non-normally distributed (D'Agostino and Pearson omnibus normality test), we used the Mann–Whitney test to compare differences between patients and healthy subjects. We analysed the correlation between the severity of spontaneous pain and the cold and heat pain threshold at the hand and trapezius region with the Spearman r correlation index. p values <0.05 were considered to indicate significance. All data are reported as mean ± SD.

3. Results

In all patients, neurological examination yielded unremarkable findings and sensory profiling disclosed no sensory deficits. Most patients suffered from axial, left- and right-sided, and upper and lower segment pain (Fig. 1), described as burning, dull and aching sensations combined. Although in several patients pain mainly involved joints, most subjects suffered from widespread pain. In all patients, answers to the DN4 questionnaire argued against neuropathic pain (all patients scored less

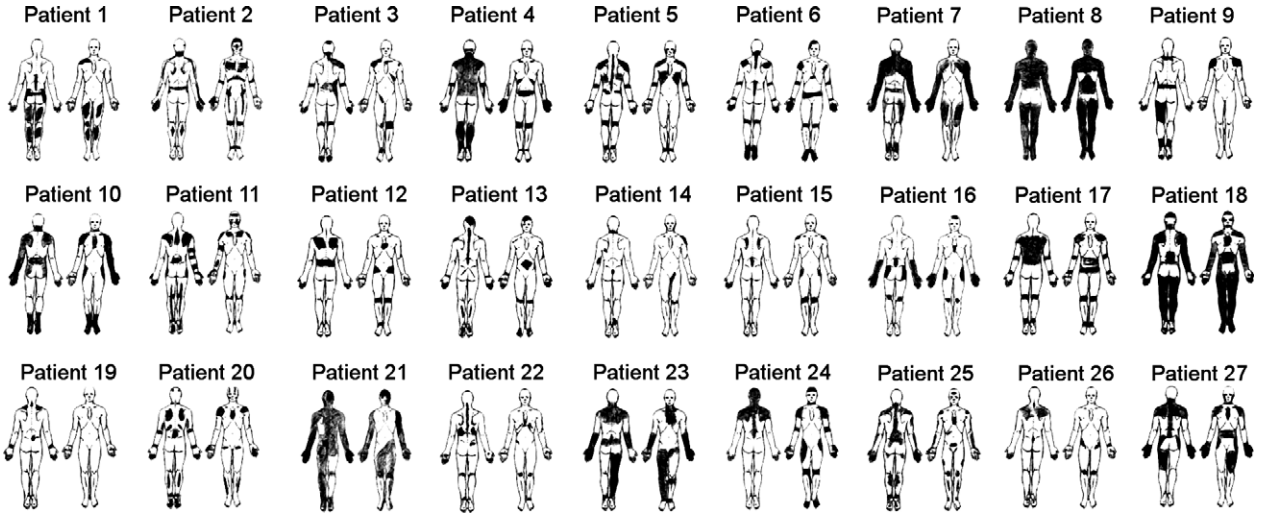

Figure 1 Topographical maps showing the reported pain distribution in the 27 patients with joint hypermobility syndrome/Ehlers–Danlos syndrome, hypermobility type. Patient 19 had a lower widespread pain index and patients 16 and 26 had a lower somatic symptom score than those needed for the diagnosis of fibromyalgia, according the Preliminary Diagnostic Criteria for Fibromyalgia established by the American College of Rheumatology.

than 4). Conversely, in all patients, the fibromyalgia rapid screening tool score was compatible with fibromyalgia, and in 24 of the 27 enrolled patients (Fig. 1), the clinical examination agreed with fibromyalgia diagnosed according to the Preliminary Diagnostic Criteria for Fibromyalgia established by the American College of Rheumatology (Wolfe et al., 2010) (Table 1). These patients complained of widespread pain, cognitive symptoms (thinking or remembering problems), unrefreshed sleep, fatigue and various somatic symptoms, such as muscle pain, irritable bowel syndrome, headache, pain or cramps in the abdomen, dizziness, depression, constipation, ringing in ears and loss of appetite combined. Whereas quantitative sensory testing found no difference in cold and warm detection thresholds between patients and healthy controls, it showed that patients with JHS/EDS-HT had hyperalgesia to cold and heat stimuli, having lowered cold and heat pain thresholds ($p < 0.0001$) and an increased wind-up ratio ($p < 0.001$) (Table 1). The severity of pain (i.e. pain referred to the average spontaneous bodily pain at the time of examination) did not significantly correlate with the cold and heat pain threshold. The correlation between the intensity of pain and the cold and heat pain threshold at the trapezius regions nevertheless approached the statistical significance (cold pain: $r = 0.3902$, $p = 0.08$; heat pain: 0.4364, $p = 0.05$). Nerve conduction study and laser-evoked potential studies found no differences between patients and healthy controls.

4. Discussion

In our prospective study in patients with JHS/EDS-HT, clinical examination, pain questionnaires, quantitative sensory testing and neurophysiological responses disclosed no somatosensory nervous system damage. Conversely, quantitative sensory testing documented hyperalgesia to cold and heat stimuli, and an increased wind-up ratio implied central sensitization. These new findings based on detailed diagnostic tests strongly suggest that rather than reflecting a neuropathic pain condition, pain related to JHS/EDS-HT probably shares mechanisms similar to those underlying fibromyalgia.

All the patients diagnosed as having JHS/EDS-HT we enrolled in this study suffered from pain. This finding is in line with previous studies showing that pain has a high prevalence in patients with this connective tissue disorder, frequently manifesting as the predominant symptom (Voermans et al., 2010; Castori et al., 2012). In all patients, quantitative sensory testing, nerve conduction study and laser-evoked potentials provided objective and reliable information on somatosensory nervous system function. International guidelines indicate these techniques as 'reference standards' for assessing the somatosensory nervous system in patients with pain (Haanpää et al., 2011).

To diagnose neuropathic pain, a challenging task (Baron et al., 2010), and ensure reliable findings on whether JHS/EDS-HT is associated with neuropathic pain, we used the DN4 questionnaire, a highly specific

Table 1 Findings from clinical examination, quantitative sensory testing and laser-evoked potential studies in the 27 patients with joint hypermobility syndrome/Ehlers–Danlos syndrome, hypermobility type.

Variables	Patients	Healthy controls	*p* values
Clinical findings			
Age (years)	35.6 ± 10.9	35.9 ± 10.8	0.9
Gender (F:M)	24:3	24:3	–
Duration of disease (years) (time from diagnosis)	3.0 ± 4.1	–	–
Fibromyalgia rapid screening tool score	5.7 ± 0.7	–	–
Intensity of pain (NRS 0–10 points)	6.7 ± 1.7	–	–
Widespread pain index	11.5 ± 3.3	–	–
Somatic symptom score	5.3 ± 1.2	–	–
Hand thermal-pain detection thresholds			
Cold detection threshold (°C)	29.8 ± 0.8	29.6 ± 0.8	0.5
Warm detection threshold (°C)	34.4 ± 0.9	34.9 ± 1.1	0.3
Cold pain threshold (°C)	18.4 ± 2.5	9.6 ± 3.1	**<0.0001**
Heat pain threshold (°C)	40.6 ± 6.3	45.5 ± 1.5	**<0.0001**
Trapezius thermal-pain detection thresholds			
Cold detection threshold (°C)	29.6 ± 0.7	29.6 ± 0.7	0.9
Warm detection threshold (°C)	34.3 ± 0.7	34.5 ± 0.8	0.4
Cold pain threshold (°C)	20.6 ± 1.8	9.7 ± 3.4	**<0.0001**
Heat pain threshold (°C)	39.8 ± 1.0	45.9 ± 2.5	**<0.0001**
Wind-up ratio			
Hand	1.5 ± 0.8	1.0 ± 0.08	**0.001**
Trapezius	1.46 ± 0.6	1.0 ± 0.07	**0.0001**
Hand laser-evoked potentials			
N1 amplitude (μV)	7.0 ± 3.6	7.0 ± 2.7	0.5
N2P2 amplitude (μV)	35.4 ± 14.1	31.4 ± 8.9	0.8
Foot laser-evoked potentials			
N1 amplitude (μV)	5.4 ± 2.7	6.3 ± 2.8	0.1
N2P2 amplitude (μV)	33.5 ± 12.7	26.4 ± 9.3	0.08

All data are reported as mean ± SD. All comparisons with the Mann–Whitney test.
The intensity of pain refers to the average spontaneous bodily pain at the time of examination.
Statistical significances indicated in bold.

tool (Bouhassira et al., 2005), and undertook objective diagnostic tests investigating somatosensory nervous system function. In all our patients, the DN4 questionnaire argued against neuropathic pain. Accordingly, neurological examination and objective diagnostic tests showed no somatosensory nervous system damage. Given that the widely accepted criteria for a definite diagnosis of neuropathic pain require objective evidence showing somatosensory nervous system damage (Hansson, 2002; Truini et al., 2013a), our data therefore argue against previous studies suggesting that JHS/EDS-HT is associated with neuropathic pain (Camerota et al., 2011; Rombaut et al., 2014). These contrasting results probably reflect the different approaches used for diagnosing neuropathic pain. Because in this study we used the DN4 questionnaire, a highly specific tool for diagnosing neuropathic pain (Bouhassira et al., 2005), and undertook objective diagnostic tests including quantitative sensory testing, nerve conduction study and laser-evoked potentials, we deem our findings valid. A potential limitation of QST and LEPs is that they have been conducted, in some cases, outside the main area of pain; nevertheless, we can reasonably exclude a somatosensory system damage in our patients, being the pain area not consistent with a neuroanatomical distribution, and the lack of sensory deficits, as assessed with the clinical examination and the DN4. Furthermore, QST was conducted in all patients from hand dorsum and trapezius region; the trapezius region, in particular, was one of the most painful area in several patients. The analysis performed separately on this subset of patients did not provide different results in comparison with the sample of patients.

During clinical examination, when we asked our patients with JHS/EDS-HT to show their pain on a topographical map (Fig. 1), most patients reported that pain simultaneously affected axial, upper and lower segments and left- and right-side, with a wide distribution poorly compatible with joint-related pain. This finding indicates that pain associated with JHS/EDS-HT cannot merely reflect joint abnormalities such as luxation and dislocation, but manifests as a widespread pain. Accordingly, the

Fibromyalgia Rapid Screening Tool and clinical examination in most patients were compatible with fibromyalgia, a condition typically causing widespread pain. Quantitative sensory testing also documented hyperalgesia to cold and heat stimuli and an increased wind-up ratio (i.e. increased responsiveness to repeated pinprick stimuli), signs of central sensitization (Truini et al., 2013a), a common feature in patients with fibromyalgia (Phillips and Clauw, 2013). Our findings on widespread pain and central sensitization in patients with JHS/EDS-HT also agree with a recent study showing that patients with JHS/EDS-HT have hyperalgesia to painful mechanical stimulation (Rombaut et al., 2014). Although our patients suffer from widespread pain, resembling fibromyalgia, several differences between the two conditions should be underlined. Patients with JHS/EDS-HT have acute, repetitive, joint dislocation, a very long duration of chronic pain, with first symptoms and pain starting in the childhood. Probably with time, pain spread beyond joint areas, frequently manifesting as the predominant symptom.

The QST sensory profile in our patients with JHS/EDS-HT might depict the 'irritable nociceptor' phenotype of patients with painful neuropathy (Fields et al., 1998). Most authors attribute this specific pain phenotype to ectopic activity at damaged peripheral nerve endings (i.e. peripheral sensitization) (Truini et al., 2013a). However, in our patients' clinical examination, neurophysiological testing and pain questionnaire showed preserved afferent nerve function. We, therefore, attribute the QST sensory profile in our patients with JHS/EDS-HT to central sensitization phenomenon.

We did not find any significant correlation between the severity of pain and the cold and heat pain threshold. Although this finding might argue against a direct relationship between the central sensitization phenomenon we found and pain, we cannot exclude that the lack of correlation depends on the relatively small sample of patients (the correlation between cold and heat pain threshold at the trapezius region and the intensity of pain approached the significance).

Our study has limitations. Because we enrolled patients in a specialized JHS/EDS-HT outpatient service, we cannot exclude the possibility that we accidentally selected patients with more severe disease; patients with less severe disease might manifest only joint-localized pain, without central sensitization. However, also patients with pain mainly localized to joints exhibited signs of central sensitization.

Concerning our quantitative sensory testing data, it could be argued that we have assessed our control subjects using a short medical history and a short neurological examination, while a recent consensus statement on quantitative sensory testing procedures suggested that validated questionnaires and screening for anxiety and depression should be used for verifying the health status of the control subjects (Gierthmühlen et al., 2015). Nevertheless, because our clinical examinations excluded any health problems and the quantitative sensory testing yielded homogeneous results, we exclude possible bias in healthy control sampling. Another possible limitation is that owing to the limited technical equipment available, not all our patients underwent quantitative sensory testing. Although this limitation might have influenced our results, the seven patients without quantitative sensory testing data and the other patients had similar clinical characteristics making a quantitative sensory testing bias unlikely.

Our findings showing that patients with JHS/EDS-HT suffer from widespread pain and manifest signs compatible with central sensitization also agree with previous studies showing that many patients with rheumatic diseases (e.g. rheumatoid arthritis and osteoarthritis causing nociceptive pain) suffer from fibromyalgia-like, widespread pain and have hyperalgesia to pain stimuli (Im et al., 2010; Lluch et al., 2014). Our findings, therefore, suggest that in patients with JHS/EDS-HT, as well as in many patients with rheumatic diseases, widespread pain might reflect abnormal central processing of the nociceptive input (i.e. central sensitization in the dorsal horn neurons) (Truini et al., 2013a). Given that several studies reported that widespread pain is associated with descending modulatory system dysfunction (Julien et al., 2005; Burgmer et al., 2012), we conjecture that in our patients the persistent nociceptive input due to joint abnormalities might trigger central sensitization in the dorsal horn neurons, possibly involving the descending modulatory system. Accordingly, animal studies showed that dorsal horn neuron sensitization to joint stimuli after experimentally induced arthritis is accompanied by concurrent abnormalities in the descending modulatory system (Danziger et al., 1999).

In this study, we provide the previously unavailable objective finding that the JHS/EDS-HT spares the somatosensory nervous system. Hence, pain due to JHS/EDS-HT cannot be considered a neuropathic pain condition. Our study highlights the heterogeneity of pain pathophysiology in JHS/EDS-HT, with the possibility of a predominance role of central sensitization, possibly associated with descending modulatory system dysfunction, in comparison with nociceptive pain phenomenon. This finding might be relevant for the pharmacological treatment of pain in this rare dis-

ease, because it supports the use of antidepressants, similarly as fibromyalgia patients. Further neuroimaging studies in patients with JHS/EDS-HT might be useful for documenting the descending modulatory system abnormalities and testing the effects induced by antidepressants.

Author contributions

GDS: acquisition and analysis of the data and drafting the manuscript; CC: acquisition of the data; RB: critical revision of the manuscript for important intellectual content; MC: acquisition of the data and drafting the manuscript; MDF: critical revision of the manuscript for important intellectual content; SLC: acquisition and analysis of the data; CL: acquisition and analysis of the data; AP: acquisition and analysis of the data; GC: critical revision of the manuscript for important intellectual content; AT: study concept and design, interpretation of the data and drafting the manuscript; FC: study concept and design and acquisition of the data. All authors discussed the results and commented the manuscript.

References

Baron, R., Binder, A., Wasner, G. (2010). Neuropathic pain: Diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol* 9, 807–819.

Bouhassira, D., Attal, N., Alchaar, H., Boureau, F., Brochet, B., Bruxelle, J., Cunin, G., Fermanian, J., Ginies, P., Grun-Overdyking, A., Jafari-Schluep, H., Lantéri-Minet, M., Laurent, B., Mick, G., Serrie, A., Valade, D., Vicaut, E. (2005). Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* 114, 29–36.

Burgmer, M., Pfleiderer, B., Maihöfner, C., Gaubitz, M., Wessolleck, E., Heuft, G., Pogatzki-Zahn, E. (2012). Cerebral mechanisms of experimental hyperalgesia in fibromyalgia. *Eur J Pain* 16, 636–647.

Camerota, F., Celletti, C., Castori, M., Grammatico, P., Padua, L. (2011). Neuropathic pain is a common feature in Ehlers-Danlos syndrome. *J Pain Symptom Manage* 41, e2–e4.

Castori, M., Morlino, S., Celletti, C., Celli, M., Morrone, A., Colombi, M., Camerota, F., Grammatico, P. (2012). Management of pain and fatigue in the joint hypermobility syndrome (a.k.a. Ehlers-Danlos syndrome, hypermobility type): Principles and proposal for a multidisciplinary approach. *Am J Med Genet A* 158A, 2055–2070.

Danziger, N., Weil-Fugazza, J., Le Bars, D., Bouhassira, D. (1999). Alteration of descending modulation of nociception during the course of monoarthritis in the rat. *J Neurosci* 19, 2394–2400.

De Paepe, A., Malfait, F. (2012). The Ehlers-Danlos syndrome, a disorder with many faces. *Clin Genet* 82, 1–11.

Fields, H.L., Rowbotham, M., Baron, R. (1998). Postherpetic neuralgia: Irritable nociceptors and deafferentation. *Neurobiol Dis* 5, 209–227.

Gierthmühlen, J., Enax-Krumova, E.K., Attal, N., Bouhassira, D., Cruccu, G., Finnerup, N.B., Haanpää, M., Hansson, P., Jensen, T.S., Freynhagen, R., Kennedy, J.D., Mainka, T., Rice, A., Segerdahl, M., Sindrup, S.H., Serra, J., Tölle, T., Treede, R.D., Baron, R., Maier, C. (2015). Who is healthy? Aspects to consider when including healthy volunteers in QST-based studies- a consensus statement by the EUROPAIN and NEUROPAIN consortia. *Pain* 156, 2203–2211.

Haanpää, M., Attal, N., Backonja, M., Baron, R., Bennett, M., Bouhassira, D., Cruccu, G., Hansson, P., Haythornthwaite, J.A., Iannetti, G.D., Jensen, T.S., Kauppila, T., Nurmikko, T.J., Rice, A.S., Rowbotham, M., Serra, J., Sommer, C., Smith, B.H., Treede, R.D. (2011). NeuPSIG guidelines on neuropathic pain assessment. *Pain* 152, 14–27.

Hansson, P. (2002). Neuropathic pain: Clinical characteristics and diagnostic workup. *Eur J Pain* 6(Suppl A), 47–50.

Julien, N., Goffaux, P., Arsenault, P., Marchand, S. (2005). Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. *Pain* 114, 295–302.

Im, J.S., Li, X., Kotwal, N., Sumner, D.R., van Wijnen, A.J., Davis, F.J., Yan, D., Levine, B., Henry, J.L., Desevré, J., Kroin, J.S. (2010). Alteration of sensory neurons and spinal response to an experimental osteoarthritis pain model. *Arthritis Rheum* 62, 2995–3005.

Kimura, J., ed. (2006). *Peripheral Nerve Diseases, Handbook of Clinical Neurophysiology*. (Amsterdam: Elsevier).

Lluch, E., Torres, R., Nijs, J., Van Oosterwijck, J. (2014). Evidence for central sensitization in patients with osteoarthritis pain: A systematic literature review. *Eur J Pain* 18, 1367–1375.

Magerl, W., Krumova, E.K., Baron, R., Tölle, T., Treede, R.D., Maier, C. (2010). Reference data for quantitative sensory testing (QST): Refined stratification for age and a novel method for statistical comparison of group data. *Pain* 151, 598–605.

Perrot, S., Bouhassira, D., Fermanian, J., Cercle d'Etude de la Douleur en Rhumatologie. (2010). Development and validation of the Fibromyalgia Rapid Screening Tool (FiRST). *Pain* 150, 250–256.

Phillips, K., Clauw, D.J. (2013). Central pain mechanisms in the rheumatic diseases: Future directions. *Arthritis Rheum* 65, 291–302.

Rolke, R., Baron, R., Maier, C., Tölle, T.R., Treede, R.D., Beyer, A., Binder, A., Birbaumer, N., Birklein, F., Bötefür, I.C., Braune, S., Flor, H., Huge, V., Klug, R., Landwehrmeyer, G.B., Magerl, W., Maihöfner, C., Rolko, C., Schaub, C., Scherens, A., Sprenger, T., Valet, M., Wasserka, B. (2006). Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. *Pain* 123, 231–243.

Rombaut, L., Scheper, M., De Wandele, I., De Vries, J., Meeus, M., Malfait, F., Engelbert, R., Calders, P. (2014). Chronic pain in patients with the hypermobility type of Ehlers-Danlos syndrome: Evidence for generalized hyperalgesia. *Clin Rheumatol* 34, 1121–1129.

Sendur, O.F., Gurer, G., Bozbas, G.T. (2007). The frequency of hypermobility and its relationship with clinical findings of fibromyalgia patients. *Clin Rheumatol* 26, 485–487.

Tinkle, B.T., Bird, H.A., Grahame, R., Lavallee, M., Levy, H.P., Sillence, D. (2009). The lack of clinical distinction between the hypermobility type of Ehlers-Danlos syndrome and the joint hypermobility syndrome (a.k.a. hypermobility syndrome). *Am J Med Genet A* 149A, 2368–2370.

Truini, A., Garcia-Larrea, L., Cruccu, G. (2013a). Reappraising neuropathic pain in humans–how symptoms help disclose mechanisms. *Nat Rev Neurol* 9, 572–582.

Truini, A., Biasiotta, A., Di Stefano, G., La Cesa, S., Leone, C., Cartoni, C., Leonetti, F., Casato, M., Pergolini, M., Petrucci, M.T., Cruccu, G. (2013b). Peripheral nociceptor sensitization mediates allodynia in patients with distal symmetric polyneuropathy. *J Neurol* 260, 761–766.

Voermans, N.C., Knoop, H. (2011). Both pain and fatigue are important possible determinants of disability in patients with the Ehlers-Danlos syndrome hypermobility type. *Disabil Rehabil* 33, 706–707.

Voermans, N.C., Knoop, H., Bleijenberg, G., van Engelen, B.G. (2010). Pain in ehlers-danlos syndrome is common, severe, and associated with functional impairment. *J Pain Symptom Manage* 40, 370–378.

Wolfe, F., Clauw, D.J., Fitzcharles, M.A., Goldenberg, D.L., Katz, R.S., Mease, P., Russell, A.S., Russell, I.J., Winfield, J.B., Yunus, M.B. (2010). The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken)* 62, 600–610.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Duration and intensity of pain, analgesic use in the 27 patients with joint hypermobility syndrome/Ehlers–Danlos syndrome, hypermobility type.