

Somatosensory test responses in children with growing pains

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Purpose: To further the understanding of growing pains (GP), in particular, the nature of this pain disorder.

Methods: This study included 33 children aged 5–12 years who met criteria for GP (cases) and 29 children without GP of similar age and sex (controls). Nineteen controls were siblings of cases. GP was diagnosed by standard consensus questionnaires. A questionnaire addressed characteristics of the pain and family history of GP. Evidence for peripheral neuropathic disorder was tested by somatosensory testing and provocation tests of peripheral nerves. Somatosensory testing by a blinded researcher involved threshold determination and/or response magnitude to nonpainful stimuli including touch, dynamic brush, cold, vibration, and deep pressure applied to limb and abdominal sites.

Results: Distributional, temporal, and quality characteristics of the pain were in accordance with published descriptions. There was no indication of primary musculoskeletal disorder. No evidence was found that GP is a peripheral neuropathic pain syndrome. There were minor but statistically significantly increased responses to cutaneous cold, vibration, and to deep pressure stimuli in cases compared to controls, evident in a wider distribution than the symptomatic lower limbs.

Conclusion: GP is a regional pain syndrome with evidence in this study of mild widespread disorder of somatosensory processing.

Keywords: growing pains, somatosensory testing, case-control study

Introduction

From the time of the earliest descriptions of growing pains (GP) to the most recent reviews,^{1–3} the nature of the prevalent disorder of childhood, GP (benign nocturnal limb pains of childhood), has remained enigmatic. Early etiological theories of GP addressed growth,⁴ relative hyperactivity and fatigue,^{5–8} anatomical/biomechanical factors,^{9,10} and psychogenic factors.^{4,11} However, none of these factors have been shown to be more than potential contributors. The current study was designed to shed light on the question put forward by Naish and Apley, “What is this malady called GP?”⁴

Evidence that GP may be arising from somatic tissues, particularly musculoskeletal structures, in the limbs has not been convincing.^{1,3} The possibility that GP is mediated by peripheral nerve dysfunction has not been definitively tested. Evidence of disordered somatosensory processing in the form of widespread deep pressure allodynia (pain due to a stimulus which does not normally provoke pain)/hyperalgesia (an increased response to a stimulus which is normally painful) has been demonstrated by pain threshold testing by Hashkes et al.¹² This is the only published study of somatosensory

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testing in GP and did not include responses to cutaneous stimuli which are less sensitively elicited in clinical conditions characterized by a widespread deep hyperalgesic state. The hypothesis of this paper is based on Haschkes et al's evidence for deep hyperalgesia, with the aim of confirming this hypothesis and extending the evidence to cutaneous somatosensory responses.

Arising from this background, the hypothesis that GP is characterized by widespread disorder of somatosensory processing was tested. Alternatively, it is a peripheral neuropathic pain syndrome (pain initiated or caused by a primary lesion or dysfunction in the (peripheral) nervous system).⁴³

Materials and methods

Thirty-three children (14 males, 19 females) aged 5–12 years were recruited by advertisement (newspaper, radio, school newsletter, hospital notice board), conscious that the peak age of point prevalence for GP is 4–6 years.⁸ However, symptoms may develop later and continue into adolescence,³⁵ and somatosensory test responses are less reliable under 5 years.²³ The written advertisements were headlined: “Volunteers, children aged 5–12 years, are required for an ethically approved study into the nature of nocturnal limb pain syndrome (GP).” The content included: “This study will be conducted by personnel from the Sydney Children’s Hospital (Pain Medicine Unit) and the University of New South Wales. If your child has aches and pains in the limbs, especially legs and particularly at night, participation in this study would be greatly appreciated. This study is in no way harmful and should not cause distress. We shall also be asking for a volunteer, such as a friend, of similar age and same sex as your child to come along and participate in what will be an interesting study.”

Those who responded were mailed a package containing further information about the study including the planned sensory testing, consent forms, and a GP screening questionnaire,¹³ based on Petersen’s GP criteria (Table 1).¹⁴ With there being no gold standard for the diagnosis of GP, the Petersen criteria have been widely applied in published studies to a point of reasonable consensus.¹⁵ A case selection flowchart is presented as Figure 1. Each participant (cases and controls) was also reviewed by a pediatrician (AY) to consider differential diagnoses of lower limb pain.

The control group comprised 29 children (12 males, 17 females) who did not have limb pain. In view of the difficulties in recruiting volunteers to undergo somatosensory testing, 19 controls were siblings of cases without GP, eight of whom were unaffected twins (three monozygotic; five

dizygotic). The high number of twins was the result of advertisements that, for purposes external to the current study, indicated a particular interest in twins.

A set of clinical somatosensory test procedures was developed based on the standard neurological clinical examination and selected somatosensory tests applicable to children in an office practice to obtain evidence about peripheral neuropathic disorders and/or abnormal central sensory processing. These methods were derived from published protocols.^{16–20} The selection of multimodal-stimulus response measures has been further supported recently by Neziri et al,²¹ who showed that responses to different modalities represent different specific dimensions and should be assessed in combination. The current study however did not use any noxious stimuli (pain provocation in children with a normally functioning nervous system) on request from the South Eastern Sydney Area Health Service Ethics Committee, who approved the final protocol. Thus, there were no pain threshold determinations. The procedures were demonstrated by the researcher (SP), who was blinded as to case or control status. The process was organized by the participating pediatrician so that the blinding was strictly applied.

Taking into consideration the avoidance of quantitative sensory testing apparatus requiring a laboratory base, the related portability and time availability for office/bedside application, and the avoidance of pain thresholds for heat, cold, and mechanical stimuli, the following test stimuli (and responses) were selected and applied to specified sites. Additionally, the cases and controls were assessed for abnormal responses in peripheral nerve or dermatomal distribution. The procedures are summarized in Table 2.^{22–25}

Test stimuli

With focus on the distribution of quantitative or qualitative abnormalities, static light touch was assessed by nonstroking touch of obliquely applied soft brush fibers to lower legs, forearms, and abdomen. This was the first assessment of A-beta peripheral sensory channel, central lemniscal pathway, and a large array of cortical regions.

Calibrated von Frey monofilament stimuli (VF1 Optihair-2 [set of 12 optical glass filaments with force range 0.25–512 mN]; Marstock, Marburg, Germany) enabled fixed graded stimuli to assess static light touch. This procedure also assessed A-beta peripheral sensory channels and lemniscal central pathway. Applied to lower legs, forearms, and abdomen, it provided mechanical detection threshold for touch, pain threshold in states of cutaneous hyperalgesia. For touch

Table I Definition of Petersen's "growing pains,"¹² modified by Evans and Scutter¹³

Pain factors	Inclusion criteria	Exclusion criteria
Nature of pain	Intermittent Some pain free days and nights	Persistent Increasing intensity
Unilateral or bilateral	Bilateral	Unilateral
Location of pain	Anterior thigh, calf, posterior knee – in muscles	Joint pain
Onset of pain	Late afternoon or evening	Pain still present next morning
Physical examination	Normal	Swelling, erythema, tenderness Local trauma or infection. Reduced joint range or motion Limping
Laboratory tests	Normal	Objective findings eg ESR, x-ray, bone scan abnormalities
Limitation of activity	Nil	Reduced physical activity

Note: Reprinted from *The Foot*, 14/1, AM Evans and SD Scutter, Development of a questionnaire for parental rating of leg pain in young children: internal validity and reliability testing following triangulation, Pages 42–48, Copyright 2004, with permission from Elsevier.

threshold, the method of limits was used with the average of threshold estimations from two tests commencing with a subthreshold force (0.25 mN) and two tests commencing with a suprathreshold force (64 mN). Mean stimulus-response determinations from the same sites to von Frey filament

number 9 were determined using the Color Analog Scale (0–10) with upper anchor "very strong touch."

Repetitive dynamic brush stimuli were applied to the limbs and abdomen (as control site) to determine the presence of cutaneous hyperesthesia or dynamic mechanical allodynia.

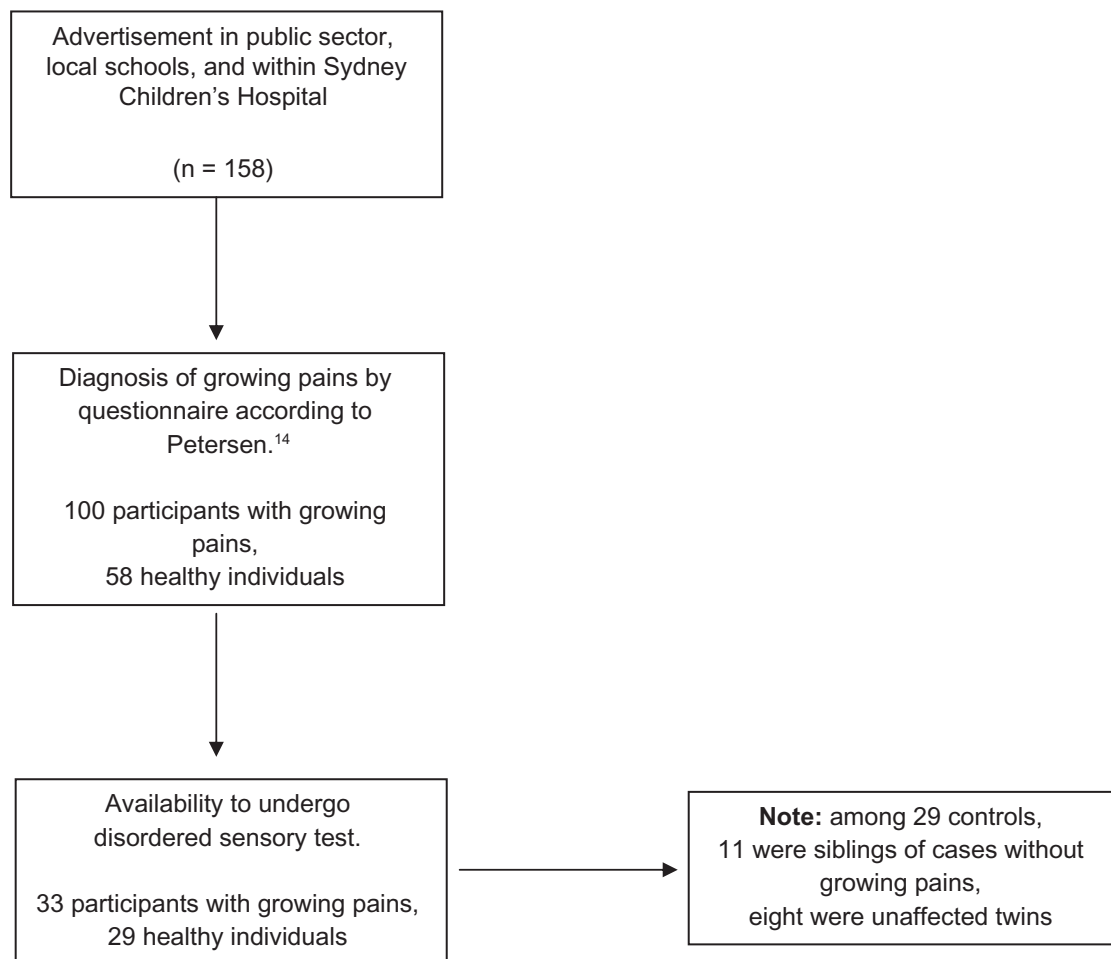
**Figure 1** Case selection flowchart.

Table 2 Somatosensory testing applications applied²²⁻²⁵

Stimulus	Principal receptors	Peripheral nerve activated	Instrument	Method (application to lower legs, forearms, abdomen)	Response measured
Touch, static threshold	Meissner's pacinian	A β	VFI OptiHair-2 von Frey filaments (0.25–512 mN)	Threshold by method of limits	Mechanical detection threshold for touch. Abnormally increased responses indicate hyperesthesia or allodynia.
Touch, static mapping	Meissner's pacinian	A β	Soft artist's brush	Static touch stimuli to legs	Semi-quantitative and qualitative responses to light touch to rule out peripheral nerve dysfunction
Brush, dynamic	Meissner's pacinian	A β	Soft artist's brush	Brush at 60°. Repeat stroke 1/second \times 20.	Increased, decreased, or qualitatively abnormal. Record if pain or unpleasant. Persistence (seconds) of after-sensation. Hyperesthesia, allodynia, prolonged after-sensations interpreted as centrally mediated.
Punctate static, blunt	Merkel Ruffini	A β Some A δ	von Frey filament (number 9)	Pressure until filament bends. Mean = 3 on Color Analog Scale: no to very strong touch.	Mean stimulus-response 0–10. Responses in pain regions can be low, normal or increased (hyperesthetic, hyperalgesia, through central sensitization)
Cool/cold	Unencapsulated	A β and A δ	Thermo Roll at 22°C	Three 3-second rolls in each region. Responses on Color Analog Scale: not cold to ice-cold.	Mean (= 3) responses 0–10. Mechanism of increase response uncertain.
Vibration	Pacinian	A β	Rydell-Seiffer graduated tuning fork 64 Hz	Response magnitude to maximal vibration 5 seconds. Mean = 3 using Color Analog Scale: no buzz to very strong buzzing.	Threshold 0–8. Response magnitude 0–10. Uncertain central mechanisms.
Deep pressure	Intramuscular afferents	Type III, IV	Fischer Dolorimeter (pressure algometer)	Response magnitude to midrange stimulus 2.0 kg/cm ² over 3 seconds. Color Analog Scale 0–10: very strong push.	Response magnitude to single stimulus 0–10. Increased response interpreted as deep allodynia/hyperalgesia, reflecting central sensitization, and/or dysfunction of descending pain modulation.

The brushing activates A-beta peripheral sensory channel and lemniscal sensory pathway. The dynamic repetitive stimuli test for temporal summation effects which correlate better with neuropathic pain states than single static stimuli. A standardized camel hair brush (SENSE Lab™ Brush-05; Somedic, Horby, Sweden) exerting a force of approximately 200–400 mN was applied with a single stroke of approximately 2 cm in length over the skin in runs of ten per test site.

Rydel-Seiffer graduated tuning fork (64 Hz, 8/8 scale; US Neurologicals, Poulsbo, WA) was applied to bony prominences, tibial tuberosities, olecranons, and skin over soft tissues (lower legs, forearms, and abdomen). Vibration assessed the A-beta peripheral sensory channel and central lemniscal pathway. Vibration threshold was determined as a disappearance threshold (method of limits). A mean stimulus-response determination for the maximal vibration intensity was determined on a 0–10 scale using an adapted Color Analog Scale with upper anchor “very strong buzzing.”

The assessment of somatosensory responses to cool stimuli was determined by a metal thermoRoll (Marstock). Cool/cold stimuli activate A-beta and A-delta peripheral sensory channels and spinothalamic central pathways. Three rolls of 3 seconds were made at each limb and abdomen site. The roller was allowed to equilibrate with room temperature set at 22°C. The upper anchor of the Color Analog Scale (0–10) was “ice cold.”

Responses to blunt deep pressure stimuli were assessed by application of the Fischer pressure algometer (FDK 10; PDT Inc, NY) to consistent sites over deep somatic tissues (middle lower legs posterolaterally, middle forearms posterolaterally, abdomen, tibial tuberosities, and olecranons). This device has been used in children.^{12,26} Blunt deep (muscle) pressure, as it increases, activates intramuscular afferents Type III and IV and the spinothalamic central pathway. Responses to deep force reaching 2 kg/cm² over 3 seconds, a level comfortably below the mean pain threshold in healthy children, were obtained using the Color Analog Scale (0–10) with adapted anchors, the upper being “very strong push.”

The Color Analog Scale²⁷ was applied with anchors modified in accordance with the type of stimulus. The Color Analog Scale has been shown to be reliable and valid in pain contexts in children as young as 5 years.^{28–30} Generally, visual analog scales have also been used in diverse nonpain applications.

Children were assessed for abnormal mechanosensitivity of peripheral nerves with a stretch by straight leg raising³¹ and brachial plexus provocation tests.³²

Student's *t*-tests for independent samples were performed to compare cases and controls for all sensory testing measures. For each sensory modality, each tested site was analyzed as well as the mean across all tested sites.

Results

There were no significant demographic or anthropometric differences between cases and controls (Table 3). In the GP case sample (*n* = 33), pain was present in the knee region and lower leg in all cases, additionally in the upper leg in eight cases (24%), and in the arms in three cases (9%). Pain was described as aching in 30 cases (94%), deep in 13 (39%), and there were accompanying pins and needles in nine (27%). Episodes occurred daily in six cases (19%), weekly in nine (28%), monthly in eleven (34%), and less frequently in six (19%). The most common duration of a pain episode was 30–60 minutes. Pain intensity was minimal in the mornings and maximal at night. A total of 24 parents (72%) of children with GP reported that their child experienced pain of sufficient severity to wake the child and 22 (66%) reported that the pain induced crying.

There was no clinical evidence of a peripheral neuropathic pain syndrome with there being no indication of sensory impairment in peripheral nerve or dermatome distribution, no neurological motor deficits, and no abnormal mechanosensitivity of peripheral nerves according to sciatic and brachial plexus stretch maneuvers.

There were no significant differences in somatosensory test responses between cases and controls in the lower leg

Table 3 Clinical characteristics of participants

	Cases (N = 33)	Controls (N = 29)	t-value	P
Age (years) mean ± SD	7.9 ± 2.3	8.0 ± 2.2	0.05	0.96
Sex (male/female)	14/19	12/17	0.08	0.94
Height (cm) mean ± SD	131 ± 15	129 ± 12	0.65	0.52
Height percentile mean ± SD	75 ± 25	70 ± 24	0.69	0.49
Weight (kg) mean ± SD	30 ± 10	28 ± 8	0.73	0.47
Weight percentile mean ± SD	75 ± 23	73 ± 19	0.39	0.70
BMI (kg/m ²) mean ± SD	17 ± 3	17 ± 2	0.15	0.88

Abbreviations: BMI, body mass index; SD, standard deviation.

sites (except for pressure response magnitude at the lateral calf [$P = 0.04$]), nor in the upper limbs or abdominal site.

Table 4 shows the somatosensory test results averaged across all sites. Response magnitudes to cold, vibration, and deep pressure stimulation were significantly greater in cases than controls while for static punctate tactile magnitude the apparent greater sensitivity in the cases did not reach statistical significance. There were no significant differences between cases and controls in touch threshold and vibration threshold. There was a nonsignificant trend to prolonged brush-induced after-sensations in cases.

Discussion

The study was designed to investigate the nature of the pain, specifically to determine whether there was regional (lower limb) or widespread disorder of somatosensory test responses, in children with GP. The diagnosis of GP is based on history, examination, and the exclusion of identifiable musculoskeletal/orthopedic, neurological, or other causes of limb (especially leg) pains. The features are characteristic of, and are reflected in, the criteria derived from Petersen.¹⁴ Criteria have been determined by gradually acquired consensus but with there being no gold standard for diagnosis, specificity has not been adequately validated. Because patients were accrued by advertisement, the extent to which their features would be similar to a random sample cannot be determined and thus extrapolation to the population of children with GP requires caution.

Consistent with previous studies and reviews,¹⁻³ and consistent with the criterion-based, widely-applied GP definition,¹⁴ there was no evidence for a musculoskeletal/somatic tissue disorder. Further, the essentially negative responses to the neuropathic pain questionnaire, the absence of sensory impairment in peripheral nerve or dermatomal distribution, and the lack of abnormal mechanosensitivity to

brachial plexus and lumbosacral nerve root (sciatic) provocation provided no support for the interpretation of a peripheral neuropathic pain syndrome.^{33,34}

The investigator-blind somatosensory testing covered a range of stimulus modalities. Although the lower leg cutaneous testing showed consistent trends to more sensitive responses in cases than controls, these differences did not reach statistical significance. However, the greater response to deep pressure in the soft tissues of the lower legs in children with GP compared with responses in control children was statistically significant, consistent with previous evidence of deep pressure allodynia/hyperalgesia in children with GP.^{12,35} The overall greater sensitivity of responses averaged across all sites (statistically significant for response magnitude to cutaneous cold, vibration, and deep pressure) suggests a mild widespread disorder of somatosensory processing.

The reference values for children in the relevant age range for face, hand, and foot sites, applying the German Research Network on Neuropathic Pain protocol,²⁰ were reported in detail by Blankenburg et al.²³ The present somatosensory test protocol was in accord with procedures in the Blankenburg et al study²³ and in studies which the authors cited, however, it was simpler, avoided pain threshold, and added response magnitude tests. These investigators found that the younger children (6–8 years) were generally less sensitive to thermal and mechanical detection stimuli but more sensitive to pain stimuli than older children (9–12 years), who in turn were similar to adolescents (13–17 years). The sample size was insufficient to permit valid subset analysis. The response magnitude estimations to subpain stimuli using the Color Analog Scale were novel. These punctuate pressure (blunt, static), vibration intensity, and deep (blunt, static) stimulus procedures were used in general by those investigators, but not in the stimulus response manner the present study applied to avoid pain threshold testing.

Table 4 Somatosensory test responses (all sites combined)

Sensory stimulus test	Mean (SD)		t (60)	P	95% CI	ES
	Cases (N = 33)	Controls (N = 29)				
Touch threshold (mN)	8.02 (13.96)	8.86 (17.50)	-0.21	0.83	(-8.84, 7.16)	0.03
Vibration threshold (0–8)	7.45 (0.56)	7.51 (0.41)	-0.46	0.65	(-0.31, 0.19)	0.06
Brush after-sensations (seconds)	2.51 (3.85)	1.41 (2.65)	1.29	0.20	(-0.61, 2.80)	0.16
Punctate tactile magnitude (0–10)	4.74 (1.75)	4.18 (1.74)	1.25	0.22	(-0.33, 1.45)	0.16
Cold response magnitude (0–10)	6.37 (1.30)	5.52 (1.86)	2.07	0.04*	(0.03, 1.69)	0.26
Vibration response magnitude (0–10)	4.90 (1.21)	4.17 (1.47)	2.15	0.04*	(0.05, 1.41)	0.27
Pressure response magnitude (0–10)	5.96 (1.06)	5.12 (1.76)	2.25	0.03*	(0.09, 1.60)	0.28

Note: *Significant at $P < 0.05$.

Abbreviations: CI, confidence interval; ES, effect size; SD, standard deviation.

Based on published evidence and results from this present study, GP does not appear to be a somatic/nociceptive (ie, musculoskeletal pain) syndrome, nor is it a peripheral neuropathic pain syndrome. The widespread distribution of sensory disturbances within this sample suggests the likelihood that underlying spontaneous pain is central sensitization of nociception³⁶ and/or disordered descending pain modulation in the central nervous system.³⁷ The authors suggest that, on the basis of this and the authors' previous studies, and other published studies, GP can be provisionally allocated to the group of idiopathic pain disorders as defined by Diatchenko et al³⁸ and to the functional pain syndromes as defined by Mayer and Bushnell.³⁹ These disorders are characterized by an absence of definable somatic disease, by comorbid associations with other idiopathic pain syndromes, by indicators of disordered central processing of nociception, genetic influence, often neuroendocrine dysfunction, and by psychosocial associations. As a group they are prevalent, eg, 1-year prevalence of any syndrome in 5–7 year old children of 23.2%.⁴⁰

There are a number of limitations in this study. Given the modest sample size, the multiple statistical comparisons should be acknowledged as a point of caution regarding extrapolation. The diagnosis of GP was based on consensus criteria and the exclusion of other conditions. This is a limitation in all studies on GP at present. An important objective of future studies is to work towards improved phenotype definition. The sample was pragmatically obtained rather than derived from a random survey. There was potential for selection bias based on severity and greater parental awareness. The controls included siblings, of whom a disproportionate number were twins; however, the reasonable expectation is that such selection would tend to reduce contrast in somatosensory responses in cases and controls.

The somatosensory test methods used in this study are relatively novel and have only recently been applied to children. The somatosensory test procedures were conservative in that they involved the quantification of responses to subpain threshold stimuli whereas quantitative sensory testing has been used most extensively in the assessment of pain thresholds or the quantification of responses to suprathreshold stimuli.⁴¹ Suprathreshold measures (tolerance) are believed to be more clinically relevant than threshold measures.⁴² Temporal summation, a dynamic psychophysical measure, is thought to better capture the pain modulatory ability of the central nervous system as compared to state measures, such as threshold and tolerance that only measure a single point in the pain processing continuum.⁴³ Thus, for most of the measures, the contrast in responses between cases and controls were

relatively minor although the direction consistently favored greater sensitivity of cases for all modalities. A greater contrast between cases and controls would be expected from deep repetitive pressure stimuli testing for temporal summation, radiation, and persistent after-sensations.

Conclusion

The current study has shown that the prevalent pain syndrome of childhood, GP, is characterized by widespread mildly disordered (relatively sensitive) cutaneous and deep somatosensory responses to several stimulus modalities. The perspective of the authors is that although GP has been considered an “end-organ” pain syndrome, an idiopathic/functional pain syndrome concept is favored.³⁹

Disclosure

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