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Does chronic low back pain modulate the sensory experience?: A case-control study

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Abstract
Chronic low back pain is a highly prevalent condition with unclear pathological underpinnings for majority of the cases. Lack of a mechanistic understanding of the exaggerated pain experience can negatively affect treatment strategies. Over time, quantitative sensory testing has evolved to extend and elaborate on the differential diagnosis of conditions of sensori-neural origin, including chronic pain conditions. Many studies have attempted to classify patients of chronic low back pain using quantitative sensory testing but there are is no protocol or modality that has been standardised to assess the same. A case-control study was designed to test the degree of sensitisation in patients of chronic low back pain in a hospital setting. Gradient of thermal stimuli at the local site (low back region) and the distant site (hand) using method of limits. Series of two-group comparisons were done to compare the study groups. Compared to the pain-free volunteers, patients of chronic low back pain homogenously displayed hyperalgesia at the local and the distant site suggesting widespread sensitisation. Thus, the present study presents a simple and effective quantitative sensory test to capture the ambiguities of sensory changes in chronic low back pain.
Keywords: *Chronic low back pain; Quantitative sensory testing; Hyperalgesia; Allodynia; Thermal pain.*

Introduction

Low back pain is a medically obscure condition[(1-2)] whose prevalence continues to grow at a dramatic rate.[(3)] The physiological underpinning of non-specific low back pain, that can constitute up to 90% of cases, is unknown but believed to be a prismatic of multiple aetiologies and pathologies.[(4)] Though acute low back pain is easily managed without medical attention, only a handful of patients of chronic low back pain respond to traditional treatment options such as physical interventions[(5)] and analgesics[(6)]. Scientists believe that inherent differences of sensitivity phenotypes maybe reflective of different stages of 'sensitisation' that could explain the degree of responsiveness to the

conventional medications.[7] This is easier than done as the (i) transition of various degrees of sensitisation is difficult to define without looking at the properties of the individual neurons,[8] (ii) the episodic nature of low back pain can introduce bias in recall of sensitisation.[9] Given the vast differences in the treatment outcomes, it is plausible that a clearer way of segregation between 'locally/peripherally sensitised' from 'centrally sensitised' may help determine the course of medical treatment.[10]

The application of exogenous sensory stimulus (pressure or thermal) has been a time-tested way to surrogately study the state of sensitisation. Quantitative sensory testing refers to a set of protocols that record the perceptual experience of pain in response to exogenous sensory stimulus applied in a quantifiable and replicable manner.[11] More than a few studies have sensory testing in chronic low back pain. On one hand, studies have reported hypersensitivity.[12–19]On the other hand, studies have found numbness in patients of chronic low back pain[20–23] and others suggesting hypersensitivity.[24] Thus, these studies suggest that the response of patient to quantitative sensory testing has been heterogenous, also the study designs have limitations of proper blinding, and statistical power.[25]At the present moment, there is no clear consensus on which sensory testing protocols would be the most clinically relevant for chronic low back pain.

The aim of the present study was to study how chronic low back pain could modulate the sensory experience. For this, a case-controlled study was designed using a gradient of thermal stimuli delivered at the local site (low back) and at a control site (hand).

Materials and Methods

Study Design and Setup

The study was designed as a cross-sectional, case-control investigation involving a single-time point of assessment. The laboratory measures described below were performed in the Pain Research and TMS Laboratory, Department of Physiology, All India Institute of Medical Sciences (AIIMS), New Delhi. All assessments were performed in a laboratory setup dedicated for the assessment of pain done in a quiet room maintained at a constant temperature and humidity,[26]between 0930 to 1130 hours.[27] Studies have shown that quantitative sensory testing can get affected by menstrual cycle phases,[28,29] tests for female participants were done during the mid-luteal phase. The participants were asked to refrain from taking any rescue analgesics, neuro-active substance, repetitive hand movement, repetitive back movement, or exercises for 24 hours before the investigations.[30]

Participant Recruitment

Chronic low back pain patients visiting the outpatient Department of Physical medicine and rehabilitation were screened for recruitment. Chronic low back pain of non-specific origins was defined as per the report of the National Institute of Health on research standards for chronic low back pain for identifying cases with non-specific pathology.[1] Usual 'red flags' and cases that could be explained by specific pathologies (like cauda equina syndrome and radiculopathy) were ruled out according to the standard clinical guidelines.[2,31] Tests like straight leg raising tests and power were used to rule our neurological symptoms.[32] All patients of chronic low back pain had been prescribed a standard set of exercises at the start of the study as a part of the standard care prescribed by the Department of Physical Medicine and Rehabilitation as a part of their routine outpatient department for chronic non-specific low back pain. Each recruited patient was matched by age- and sex- with a pain-free volunteers. Pain-free state was defined as not having any pain, recurring or resembling chronic pain experience in any way. The inclusion and exclusion criteria for patients and pain-free volunteers are as follows. Right-handed individuals (using Edinburgh handedness inventory)[33] of either sex, aged 18 to 65 years were included after screening. The exclusion

criteria were: presence of any major illness that prevents the participants from adhering to the standard of care (psychiatric, neurological, autoimmune or cardiovascular), contraindications to participation in an upcoming clinical trial (metallic implants, intra-cardiac lines, neuro-active drugs, history of seizures, major head trauma in past six months;[34] history of opioid or substance abuse;[35-37]pregnancy or lactation.

Intensity of Back Pain

Visual analogue scale is a linear continuous scale to quantify pain intensity. It was represented by an 11-cm long line and two anchors, "0" = no pain and "10" = maximum pain experienced. The participants were asked to place a perpendicular line at a position closest to their pain experience in the past month. The distance between "0" anchor and participant's score were measured in cm, resulting in scores ranging from 0 to 10. The internal consistency Cronbach's alpha and test-retest reliability for the scale is excellent for patients of chronic pain[38] and is validated method for chronic low back pain under a variety of settings.[39]

Quantitative Sensory Testing

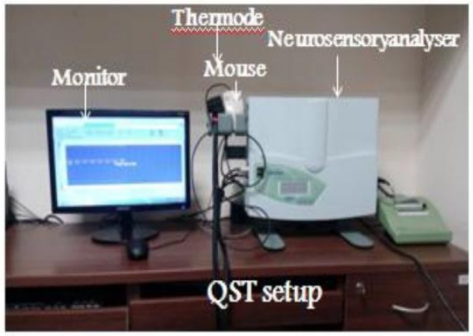
A gradient of thermal gradient was done using the method of limits for three outcome measures (temperature detection threshold, pain detection threshold, pain tolerance threshold), using two stimulating modalities (hot and cold), at two test sites (hand and back). The thermal temperature gradient was controllable by the software setting using the method of limits.[26,38]

An assumption for the method of limits is that there exists an absolute and constant threshold that is discernible by the participants. Figure 1 shows the details of the stimulation paradigm. The present study was performed using Neurosensory Analyzer TSA-II 2000 (Medoc Ltd, Israel). A 30 x 30 mm^2 thermal device connected to Medoc TSA-II was used to deliver all thermal stimuli. It is gel-cooled equipment that controls the temperature of the connected thermode as per the computerized command. It was tied the requires test site with either the attached velcro strap or by using a belt. Before the test, the surface area to be tested was cleaned using alcohol swab. The thermode was tied to the dorsal side of the first dorsal interosseous of the dominant hand. The superior borders of the posterior iliac crests are identified as indicator of L4 spinous process. This was used to locate the L3-L4 inter-osseous space by palpating. A distance of 5 cm was measured lateral from this point box of 3 cm was drawn lateral from the space high points of the iliac crest was palpated used as an indicator of L3-4 inter-osseous space.[39]

For our experiments, the baseline temperature was kept at 32 °C; the thermode was kept tied to the skin surface to allow the skin temperature to adapt to the thermode's temperature. As soon as the responder pad is clicked (as per the instruction), the change in temperature switches direction to go back to the baseline values. The outer limits of the temperature were kept 0 °C (for cold stimuli) and at 52 °C (for hot stimuli) to prevent any tissue damage. In the method of limits, the stimuli are presented in a graduated format, and the participants is required to ascertain the point at which the stimulus switches from non-perceivable to perceivable (separating signal from the noise). The assumption is that the participant would readily indicate this point of detection and click the responder pad immediately. Thus, the method is limited by the time elapsed between the detection and clicking introducing errors on towards the right-side of the measurement. The rate of rise was 1 °C/ sec and rate of fall was 8 °C/ sec. The response could be recorded by clicking on the responder pad (by the participant). The temperature at which the responder pad is clicked appears on the screen before falling back to the baseline. An inter-stimulus interval of 3 to 5 sec was kept for each recording session. Each session consisted of 10 hot and 10 cold stimuli (pseudo-randomized by the system), giving a total of 20 stimuli. Subsequent thermal stimuli are given at an interval of 3 to 5 seconds to sidestep the issue

of anticipation bias.[40] In an eyes closed condition, the participants were asked to indicate the temperature detection threshold by clicking on a response pad connected to the thermode. They were instructed to announce the modality of the stimulus (whether hot or cold) and the intensity of pain felt on an 11-pt visual analogue scale.[41] Prior to the test, sufficient familiarity sessions were given to each participant were given before each assessment to acquaint them with the details of the protocol.

Temperature detection threshold was defined as the temperature at which a change from the baseline temperature was first detected. Pain threshold was defined as the minimum temperature at which the first sensation of pain was felt (up till '3' on a continuous 11-point visual analogue scale for pain intensity). Tolerance threshold was defined as the temperature at which a moderate level of pain was felt (from '3' to '6' on a continuous 11-point visual analogue scale for pain intensity). The results of each modality (hot detection threshold, cold detection threshold, hot pain threshold, cold pain threshold, hot pain tolerance threshold, cold pain tolerance threshold) were averaged for each individual at each test site and then pooled for the study groups. Data was imported to an external file and re-analyzed offline by an assessor not involved with the recruitment of participants and recording of the outcome assessment.



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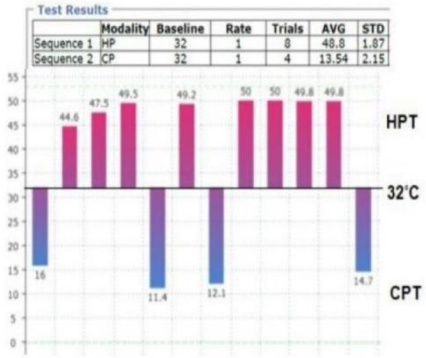

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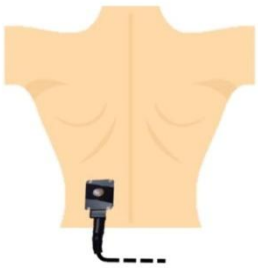

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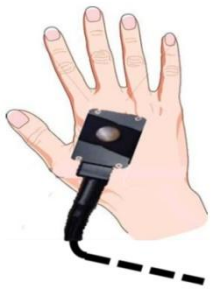

D

E

Stimulation details	
Baseline	32 °C
Rate of ascent	1 °C/ sec
Rate of descent	8 °C/ sec
Inter-stimulus interval	3 to 5 seconds
Number of stimuli	10 /modality
Number of modalities	3
Parameters	Hot detection threshold Cold detection threshold Hot pain threshold Cold pain threshold Hot pain tolerance threshold Cold pain tolerance threshold

F

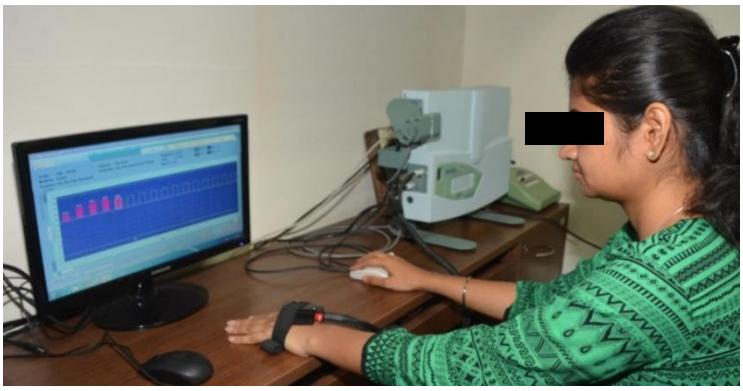

Figure 1 | Setup for assessment of quantitative sensory testing

A. Computer-based Peltier-based thermode Neurosensory Analyser (Medoc Inc, Israel), B. An example of a report generated after a trial run; C. Schematic region being tested at the low back region; D. Schematic diagram showing the site of testing at the dorsum of the hand; E. Parameters of stimulation of delivering thermal stimuli; F. Example of a participant undergoing familiarity sessions for the hot modality at the dorsum of the hand in an eyes-closed conditioned.

Statistical Analysis

Continuous variables were summarized as mean ± standard deviation and compared using unpaired t-test or Mann-Whitney U-rank test. Discrete variables were presented as frequency (percentage) and compared using Chi-squared test. All statistics was analyzed using GraphPad Prism (version 8.0; GraphPad Inc, CA, USA) keeping level of significance at 5%.

Results

We enrolled 123 patients of chronic low back pain and pain-free volunteers. Table 1 depicts the participant characteristics. No significant differences were found for the sociodemographic data like age, sex distribution, working status, or educational status.

Table I. Participant characteristics: Pain-free volunteers *vs.* Chronic low back pain

	Pain-free volunteers (n = 123)	**Chronic low back pain (n = 123)**	***P*-value**
Age, *mean ± SD*	34.78 ± 7.87	35.98 ± 9.94	0.145
Sex distribution			
Female, *f*(%)	56 (47.15)	58 (47.15)	
Male, *f*(%)	67 (52.85)	65 (52.85)	0.998
Working status			
Working,*f*(%)	90 (68.29)	84 (68.29)	
Not working,*f*(%)	33 (31.71)	39 (31.71)	0.564
Educational Status			
Primary education, *f*(%)	17 (13.82)	25 (20.32)	
Secondary education, *f*(%)	43 (34.95)	42 (34.14)	
Tertiary education,*f*(%)	63 (51.22)	56 (45.58)	

Table showing the demographic characteristics between the groups. Data as mean ±standard deviation or frequency (percentage). Comparisons were made using Mann-Whitney U-rank test, Chi-squared test, or unpaired t-test as appropriate. Level of significance was set at 5%.

Table II. Sensory responses at the local site (back): Pain-free volunteers *vs.* Chronic low back pain

At back	**Pain-free volunteers (n = 123)**	**Chronic low back pain (n = 123)**	***P*-value**
Hot detection threshold at back	34.87 ± 1.23	34.98 ± 1.45	0.666
Cold detection threshold at back	30.75± 0.85	30.43± 1.56	0.455
Hot pain threshold at back	36.60 ± 1.49	36.11 ± 5.07	0.264
Cold pain threshold at back	26.95± 5.04	25.37± 6.62	0.455
Hot tolerance threshold at back	40.78± 1.55	43.22± 2.23	0.004*
Cold tolerance threshold at back	23.95± 6.78	21.08± 8.98	0.005*

Data as mean ±standard deviations. Comparisons were made using unpaired t-test. Asterisk (*) denotes statistical significance at 0.05.

Table III. Sensory responses at the control site (hand): Pain-free volunteers *vs.* Chronic low back pain

At hand	**Pain-free volunteers (n = 123)**	**Chronic low back pain (n = 123)**	***P*-value**
Hot detection threshold at hand	34.42 ± 1.17	34.43 ± 1.43	0.975
Cold detection threshold at hand	31.32± 0.68	30.35± 1.64	0.367
Hot pain threshold at hand	37.57 ± 1.49	37.38 ± 1.41	0.437
Cold pain threshold at hand	27.46± 4.53	23.69± 8.31	0.367
Hot tolerance threshold at hand	40.41 ± 1.48	40.38 ± 1.55	0.911
Cold tolerance threshold at hand	24.54± 5.63	22.78± 6.77	0.027*

Data as mean ± standard deviations. Comparisons were made using unpaired t-test. Asterisk(*) denotes statistical significance at 0.05.

Pain at the time of the test was reported by 30.08% of the patients (37 out of 123 patients); 17 patients reported 1/10 and 20 patients reported pain at 2/10 at the time of time of testing. No differences in sensory threshold were observed between the patients who had pain at time of test and those who did not have pain ($P< 0.05$). No correlation was found for intensity of duration of pain or pain intensity with sensory tests ($P< 0.05$).

Discussion

The present study was aimed at analyzing thermal thresholds in chronic low back pain using quantitative sensory testing. It was observed that sensory responses towards temperature and pain thresholds were comparable between chronic low back pain and pain-free volunteers. Amongst the different intensities of stimulus, moderate pain could capture induce sensory at the local site (low back) and distant sites (hand). The sensory paradigm remained unaffected by characteristics of chronic low back pain.

The main finding of the study was that hyperalgesia at the local site (at the low back region) and at the distant site (at the hand region) was found using thermal stimuli. Augmented widespread sensitivity of the primary afferents afflicts most chronic pain conditions,[42] including chronic low back pain.[25]At the local site, there is some evidence indicating increased inflammatory mediators, sensory innervations, and lowered synaptic efficacy even in non-specific cases of chronic low back pain,[43-45]that could explain the local sensitisation. While at the distant site, the evidence of increased sensitivity at the hand region indicates that a higher centres of the nervous system might also be at play. Central sensitisation, refers to the phenomenon of amplification of neural signalling withing the central nervous system that elicits pain hypersensitivity.[46] In the case of low back pain, recurring acute bouts of pain - often triggered by simply changing postures or walking – sends barrage of nociceptive inputs causing extensive structural and functional change throughout the nervous system.[10,42,46] In line with the notion, evidence from nuclear magnetic resonance[47] and electroencephalography[48] studies shows abnormal activation and organization of the

somatosensory regions in patients of low back pain.

What makes the hyperalgesia notable in the present study unique is the uniformity of responses in the recruited participants that is in contradiction to the pre-existing literature.[25] Up till now, the observed heterogeneity of responses to exogenous stimuli is often believed to be reflective of heterogeneity of the underlying pathological changes. This is easily reconciled by the fact that chronic low back pain of non-specific origin, being a diagnosis of exclusion,[1,2] is a 'catch-all' group of patients possessing a myriad of multiple pathologies.[4] However, most evidence of hyperalgesia presented in those investigations have been based on pressure pain[25,49],whose processing differs greatly from thermal pain.[27,50]Alternatively, the uniformity of the findings can also be attributed to the definition of chronicity used for this study. Here, the chronicity was defined as based on a more than six months of symptoms[1]–which is a lengthier time-line than the previous studies. The rational was to circumvent some of the ambiguities associated with the episodic nature of low back pain.[9] Thus, as appealing as it maybe, the homogeneous hyperalgesia noted cannot conclusively be attributed to the selection of the modality. Investigations changing either the duration of symptoms (shorter vs. longer) and choice of modality (pressure vs thermal) might be able to add clarity.

Besides hyperalgesia, the present study found no evidence of allodynia in patients of chronic low back pain. As of yet, allodynia has been reported only in patients with radicular low back pain,[51,52] with only one study focusing on thermal allodynia.[51] In contrast to the reports involving radiculopathy, the participant recruitment for the present study was done after ruling out radiculopathy using straight leg raising tests and other functional maneuvers.[1,2,31,32]Thus, the absence of thermal allodynia could attest to non-radicular phenotype of chronic low back pain patients.[53,54] If thermal allodynia can accurately distinguish between low back pain patients with and without radiculopathy, it could have important prognostic outcomes. Still, the inference remains tentative as radiculopathy (or lack thereof) is a poorly defined description[1,2,31] and requires further work.[32]

That only the moderate intensity of thermalpain stimulus could capture sensory alterations in chronic low back pain–but neither the mild pain nor the innocuous temperature stimuli – requires some elaboration. While the involvement of lateral spinothalamic tract for relaying thermal sensations remains irrefutable, the intensities of these thermal modalities can be differentially encoded in the tract.[55] From what can be gathered from the procedural descriptions of cordotomy is that the sensations of thermal pain and innocuous temperature can be separately targeted,[56,57] implying that the two are distinctly represented within lateral spinothalamic tract.Even at the cortical level, innocuous thermal sensation activates more of primary motor cortex and pregenual anterior cingulate cortex, whereas painful stimuli activates the large swathes of the somatosensory cortex and the insula.[58] Furthermore, a report by Ferretti and colleagues[59] demonstrated that increasing the pain intensity activates anterior portions of insula and the secondary somatosensory. Even more importantly, from ateleological standpoint, different intensities of the stimuli can arouse varying levels of threat to the body. At one side, stronger intensities leads to a greater arousal and evokes a behavioural/ biological avoidance response. While on the other side, milder intensitiesleads to only a lesser arousal and increases the attention/ lowers threshold to incoming stimuli.[60] More inquiries into how our body 'reads' the different aspects of exogenous stimuli could possibly advance our understanding of sensory changes in health and disease.

Since the waxing and waning of pain intensity is a characterising feature of chronic low back pain, it was pertinent to consider the presence of low back pain at the time of testing. A third of the

participants reported mild intensity of low back pain at the time of test. Statiscal analysis found that their sensory profiles were comparable to patients who did not report any low back pain at the time of the test. Thus, the null results confirm the relevance of quantitative sensory tests to examine long-term changes in the somatosensory system, rather than the state of the body the time of testing.[61] Still, the tests with a more severely affected group of chronic low back pain patients. Another possible limitation is that the present study considered a method of limits, wherein the stimulus is ramped-up till the end-point is discernible or ramped-down till the perception returns to the baseline.[62] Threshold estimations based on construction of psychometric curves could refer to a more statistically determined threshold rather than just a perceptual one,[63] but remains to be standardised. Additionally, quite a few successful efforts are also being made to the hardware of the sensory testing devices to make their clinical application more relevant.[64,65] Apart from the benefits of thoughtful recruitment of participants and the choice of modality discussed above, the study may have benefitted from the blinding of the assessors and pre-defined phase of the menstrual cycle of the female participants.[28,29]

Given the current lack of consensus on the optimal battery of sensory testing, we encourage future investigators to pursue the validity and reliability of the sensory paradigms presented in the study. By providing an evidence of centrally-induced thermal hyperalgesia, the present study design may help decode the ambiguities of central sensitization in chronic low back pain, and shed light on better treatment outcomes.

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Declarations

Submissions: The submission has not been previously published, nor is it before another journal for consideration.

Conflict of Interest: No competing or conflict of interests need to be declared by the authors.

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