

# A Review on Experimental Assessments of Pain Threshold in Healthy Human Subjects

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## A B S T R A C T

There are three types of nerve fibers that are involved in the transmission of pain stimuli: C fibers (slower fibers) for thermal, mechanical and chemical stimuli, A-delta fibers for thermal or mechanical stimuli and A-beta fibers for touch stimuli. Clinically, this is crucial in making an accurate assessment of the pain level experienced by a suffering patient, in indicating the appropriate therapy and studying the response to treatment. The threshold is actually the experience of the patient, whereas the intensity measured is an external event. But often pain investigators tend to define the threshold in terms of the stimuli. Pressure, Thermal, Electrical and LASER are some of the pain induction methods that we have discussed in this article.

## 1. Introduction

**P**ain is an unpleasant, subjective experience that consists of sensory and emotional aspects (Rainville, et al., 2002). The sensory one contains the transmission of signals from periphery through lateral thalamus and somatosensory cortices (S1 and S2), as well as the posterior insular cortex (Price, et al., 2002).

The affective-motivational component (i.e. pain unpleasantness or emotional pain) refers to the emotional responses to a painful stimulus and primarily involves the limbic system. It activates the ACC and the anterior insular cortex components of the limbic system (Moisset & Bouhassira, 2007). It has been shown that physiologic responses to pain (changes in blood pressure and skin galvanic response, among other changes) are mediated by neural substrates related to but distinct from the somatosensory aspect of pain (Boggio et al., 2008).

Pain is always subjective. Individuals learn the application of the word through experiences related to injury in early life. Experiences which resemble pain but are not un-

pleasant, e.g., pricking, should not be called pain. Unpleasant abnormal experiences (dysesthesias) may also be pain but are not necessarily so because, subjectively, they may not have the usual sensory qualities of pain (This definition has been reproduced with permission of the International Association for the Study of Pain® (IASP®)).

An accurate assessment of the pain level experienced by a suffering patient is of great importance in making a correct diagnosis, in indicating the appropriate therapy and in studying the response to treatment (Lundeberg, et al., 2001). Here, the uses of experimental pain induction methods are over-viewed with respect to three important areas of clinical pain research. First, developing our understanding of the mechanisms of pain report and response. Second, assessment and prediction of pain report and response. Third, the use of experimental pain as a way to train pain coping skills and to evaluate their effectiveness in cognitive behavioral treatment (Edens, et al., 1995). From a pain treatment perspective, as the pain mechanisms in many diseases are poorly understood, the moderately successful trial and error approach is most often used in the selection of analgesics. Hence, there is a need for new methods in the characterization and treatment of pain (Stahl, et al., 2004).

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## 2. Neurocircuits of Pain Perception

The mechanisms responsible for the sensory component of pain are clear. From peripheral sites around the body such as the skin and visceral organs, sensations are transmitted to the spinal cord and from there to the brain by sensory nerve fibers. Sensory nerve fibers have various functions and come in a variety of sizes. They also vary in how quickly their messages reach the brain. There are three types of nerve fibers that are relevant to our discussion:

- A-delta fibers
- C fibers
- A-beta fibers

Discuss the above three in the same order – i.e. A-delta first, C fibers next and so on – see paragraph below

The synapse site of these afferent sensory fibers is at the spinal cord and then impulses are transmitted up the spinal cord to the brain.

C fibers are referred to as polymodal as they respond to mechanical, thermal and chemical stimulation; they are slower fibers that transmit the thudding, dull pain of injury, inflammation or disease.

The A-delta fibers respond to thermal or mechanical stimulation. They are fast because they are covered in a layer called myelin and warn of impending tissue damage. You can see your response to stimulation of these fibers in your quick reaction when you touch a hot dish on the cooker. The A-beta fibers transmit touch and play a very important role in the sensation of pain. All the fibers travel to the dorsal horn of the spinal cord, which is divided into layers of cells called lamina. The laminae have been numbered according to location. Most of the fibers finish in lamina I and II. The nerves then give off long fibers, which cross to the other side of the cord and ascend to the thalamus and somatosensory areas of the brain cortex. The A-delta fibers end in the ‘thinking’ part of the cortex which is why we can accurately locate where the pain is. Interestingly these fibers are also responsible for pinprick sensation. A patient who has been given a strong dose of morphine for pain will still jump if his or her skin is pricked. This is a protective mechanism and very difficult to abolish unless the patient is deeply anaesthetized or a nerve block is used.

The C fibers are slower than the A-delta fibers in their conduction and are associated with ‘second pain’. That is the dull, burning, aching, throbbing pain which is generally diffuse over a wide area usually after the initial sharp pain. It may occur minutes or hours later.

A-beta fibers, whilst they do not transmit pain sensation, are part of the larger picture. They occur in the skin and are the largest of the three fibers. While they synapse in the dorsal horn they do not cross over in the spinal cord and are the fastest conducting. These fibers are activated by touch and cutaneous stimulation which can be used therapeutically.

Noiceptive inputs from viscera and muscle are poorly localized. This means the sensation of pain is quite diffuse and cannot be pinpointed to a localized area. This is because the synapses from these fibers do not terminate in the substantial gelatinosa (lamina II) but in lamina I and IV (Mann, et al., 2006).

## 3. Classification of Pain Receptors

We have pain receptors present throughout our bodies, especially the skin, surfaces of the joints, some structures in the skull, periosteum and arterial walls. Some organs have less pain receptors (gut, muscle, etc). It is interesting to note that the brain itself does not have any pain receptors. So the brain is insensitive to any potentially painful stimuli inflicted on it. There are three types of pain receptors:

- Mechanical
- Chemical
- Thermal

A mechanical stimulus (touch) would be, for example, high pressure or stretch, and a thermal pain stimulus would be extreme heat or cold. Chemical pain receptors can be stimulated by chemicals in the outside world (e.g. acids), but also by certain products that are present in the body and locally released upon trauma or inflammation or other painful stimuli. (Mann, et al., 2006)

## 4. Pain Threshold

Pain threshold is commonly defined as the least experience of pain which a subject can recognize. Properly defined, the threshold is really the experience of the patient, whereas the intensity measured is an external event. But it is common practice for researchers in the field of pain to define the threshold in terms of the stimulus. However in psychophysics, thresholds are defined as the level at which 50% of stimuli are recognized. In that case, the pain threshold would be the level at which 50% of stimuli would be recognized as painful. The stimulus is not pain (q.v.) and cannot be a measure of pain (International association of studies for pain). Pain threshold assessment is a crucial aspect of any study about pain in human subjects in experimental laboratory settings. In this article we will review four different ways for assessment of pain threshold with

different modalities to induce controlled pain with measurable intensity of stimulation (please re-phrase sentence to make the meaning clearer).

## 5. Experimental Pain Induction

There are four commonly used ways to induce experimental pain in threshold assessment studies: Pressure (mechanical) (Lazarou et al., 2009, Kinser et al., 2009, Ylinen et al., 2007), thermal (Angst et al., 2000, Zhou et al., 2009, Pavlakovic' et al., 2008), electrical (Lee et al., 2009, Norrbrink et al., 2009, DeSantana et al., 2008, Cowan et al., 2009) and laser mediated stimulation of nociceptors. Note that pain in these experimental study designs refers to the somatosensory aspect of pain as noted earlier.

### 5.1. Peripheral Electrical Stimulation Induced Pain Assessment

There are two main aspects regarding the importance of peripheral electrical stimulation in investigation of pain threshold. First, the effect of percutaneous (transcutaneous) electrical nerve stimulation (PENS or TENS) on pain threshold related to other physical parameters (thermal pain threshold, pressure pain threshold) – discussed in a later section. Second, assessment of the threshold of pain generated by electrical pulses. In this section we discuss assessment of the threshold of pain induced by electrical pulses.

#### 5.1.1. Electrical Pain Induction Instruments

Percutaneous (transcutaneous) electrical stimulators of nerves and muscles are the most commonly available devices for creating single pulse or trains of pulses needed to generate electrical induced pain. Pain relief, hypoalgesic and analgesic effects, and electro-acupuncture are the often used applications of these devices (Lee, et al., 2009, Norrbrink, et al., 2009, DeSantana, et al., 2008, Cowan, et al., 2009).

These instruments provide constant current high voltage pulses of brief duration for percutaneous stimulation during investigation of electrical activity in nerve and muscle. The output current is more often continuously variable over the range 0 to 100mA or more. Please note that some constant current stimulators are NOT suitable for human subjects. It is recommended to use the FDA approved percutaneous electrical stimulators (e.g. Digitimer DS7A constant current high voltage stimulator Hertfordshire, England) to prevent any unexpected side effects.

#### 5.1.2. Measurement Procedures

In electrically induced pain threshold assessment studies, the primary outcomes are perception threshold and

pain threshold to electrical stimulation. PES should be applied on the target area using an electrical stimulator. Current supply should be started at a defined minimum (0 mA) and be increased in steps (e.g. right index finger with pulse duration of 200  $\mu$ s, using a Digitimer DS-7A Stimulator with increasing levels of 0.1 mA, (Lefaucheur, 2001) until the subject report sensation and then pain. The intensity of current at which the subject first reports perception of the electrical stimulus should be recorded as the perception threshold; the intensity of current at which the subject reports pain should be taken as the pain threshold (Boggio, et al., 2008).

### 5.2. Laser Induced Pain Assessment

Laser evoked potentials (LEP) are often considered as disclosers of subclinical dysfunction of A $\delta$  fibers (small myelinated responsible for thermal-pain sense) and are defined as a sensitive and reliable diagnostic tool for assessing small-fibre function in sensory neuropathies (Truini, et al., 2004).

#### 5.2.1. Laser Pain Induction Instruments:

Thulium doped yttrium-aluminium-garnet (Tm:YAG) laser is the most often used system for laser induced pain assessments. The thulium laser emits near-infrared radiation (wavelength 2000 nm) with a penetration depth of 360 mm into the human skin and allows a precise restriction of the emitted heat energy to the termination area of primary nociceptive afferents without affecting the subcutaneous tissue. To reduce receptor fatigue or sensitization by skin overheating in multi-area studies, you have to stimulate different spots in a specific area. (e.g. 5\_5 cm)

#### 5.2.2. Measurement Procedures

Subjective assessment of induced pain could be verbal: reporting grades of stimulation, from “warm” to “most intensive pain” or also physical, pushing a button, interrupting laser intensity.

### 5.3. Pressure (Mechanical) Induced Pain Assessment

Pressure-pain thresholds (PPTs) occur at the minimum transition point when applied pressure (i.e. force) is sensed as pain (Fischer, et al., 1988). Pressure-pain threshold measures are used in clinical settings for determination of “hot spot” tenderness (Fischer, et al., 1990). Diagnosis of myofascial pain syndrome characterized by tender myofascial trigger points and also diagnosis of myofascial pain dysfunction syndrome (Ohrbach, et al., 1989) and diagnosis of hyperalgesia (Kosek, et al., 1993) have been assisted by PPT measures.

### 5.3.1. Pressure Pain Induction Instruments

Simple handheld pressure algometers (PA) with a spring is commonly used, although more sophisticated electrical devices with a strain or pneumatic pressure gauge have been developed (Ylinen, et al., 2007). Algometers are devices that can be used to identify the pressure and force eliciting pressure-pain thresholds. It has been mentioned in pressure-pain threshold studies that the rate at which manual force is applied should be consistent to provide the greatest reliability (Kinser, et al., 2009).

### 5.3.2. Measurement Procedures

Pressure-pain thresholds provide a quantified force reading of one's "tenderness" and, thus, are very useful in a variety of clinical situations. For example, body locations where unusually low force application elicits pain (possibly in relation to the contralateral body part) may be attributable to an underlying cause that may be hard to quantify by methods other than tenderness. It is possible to quantify recovery (also, speed of recovery) of underlying problems or soreness levels by tracking tenderness levels by PPT. (Kinser, et al., 2009)

Handheld algometers are the most using instruments for PPT measurements. They often have a flat, circular, metal probe measuring in different diameters (Lazarou, et al., 2009). The PPT location that have previously been used successfully in many studies, 10–12 is the first dorsal interosseous muscle, an area innervated by the superficial radial nerve. Pressure should be progressively increased until a discernible sensation of pain is experienced. Participants should be instructed to announce the "stop" verbally at that point and experimenter immediately retracts the algometer. The reliability of the algometers has recently been evaluated in the neck and shoulder muscles of individuals with chronic neck pain, demonstrating satisfactory or good results (intraclass correlation coefficients: 0.78 to 0.93) (Nussbaum, et al., 1998). Handheld pressure algometers have also been found to be highly reliable with repeated measures over time, when tested in pain-free muscles of either the hand or other body regions (Ohrbach, et al., 1989, Isselee, et al., 1997).

In preparation procedures, participants should be instructed in the method of algometer application and

several practice measurements to be taken, using the dominant and nondominant hands in hand area studies. Participants should be requested to remember what the sensation felt like when they indicated their PPT, and report it at the same time point for the following measurements. Gaze straight ahead at a mark placed away during the measurement procedure, makes the participants unable to see either the skin displacement at the application site or the digital display of the algometer, suggesting no participant bias (Lazarou, 2009).

## 5.4. Thermal (Heat) Pain Threshold

Measurement of thermal perception thresholds for heat, cold, heat pain, and cold pain stimuli is an important part of quantitative sensory testing (QST).

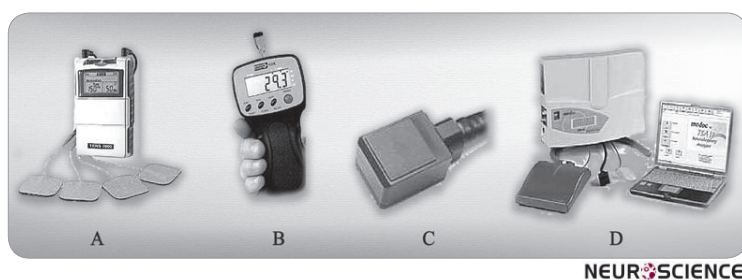
### 5.4.1. Thermal Pain Induction Instruments

Thermal stimuli could be delivered using handheld thermodes (probes) and analyzed by a computer controlled Thermal Sensory Analyzer (e.g. Medoc TSA-2001). (Zhou, et al., 2009) Also new generations of Neurosensory analyzers have been developed that deliver quantitative assessment of small-caliber (A-Delta and C-fiber) sensory nerve function, as well as for large caliber A-Beta fibers. They are also used for identifying thermal pain thresholds in various clinical and research applications (e.g. TSA-II NeuroSensory Analyzer). The TSA-II NeuroSensory Analyzer is a precise, computer-controlled device capable of generating and documenting response to highly repeatable thermal and vibratory stimuli, such as warmth, cold, heat-induced pain, cold-induced pain or vibration. ([www.medoc-web.com](http://www.medoc-web.com))

### 5.4.2. Measurement Procedures

Heat pain threshold (HPTh) and heat pain tolerance (HPTo) should be assessed regarding a cutoff temperature to avoid tissue damage (e.g. 52 °C). Probe temperature should start increasing from a baseline temperature (e.g. 32 °C), at a defined rate until the subject responds verbal or by pressing a button on a handheld device.

Slow rates of rise preferentially activates C-fibers and diminishes artifacts associated with reaction time.



**Figure 1.** Different instruments that are used in pain threshold assessments. A: Transcutaneous electrical nerve stimulator – TENS, B: Digital handheld pressure algometer, C: Thermal sensory analyzer, TSA-II Medoc medical systems, and D: Standard thermode sample.

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#### 5.4.2.1. HPT<sub>h</sub>

“When the sensation first become painful” should be defined as the HPT<sub>h</sub> point for subjects to press the button.

The average of multiple trials at each site should be computed for HPT<sub>h</sub>. In order to avoid either sensitization or habituation of cutaneous receptors, the position of the thermode should be altered slightly between trials. In addition, suitable interstimulus intervals should be maintained between successive stimuli.

#### 5.4.2.2. HPT<sub>o</sub>

“When the sensation was no longer tolerable” should be defined as the HPT<sub>o</sub> point for subjects to press the button. Multiple trials of HPT<sub>o</sub> have to be performed at each site to reach the average, computed as for HPT<sub>o</sub>.

In order to avoid either sensitization or habituation of cutaneous receptors, the position of the thermode should be altered slightly between trials. In addition, suitable interstimulus intervals should be maintained between successive stimuli.

### 6. Considerations in Assessment of Pain Threshold

#### 6.1. Considerations on Pressure Pain Threshold Assessment

Studies have investigated the effect of TENS on result of pressure pain threshold (PPT) assessment. Some of these studies show increasing effect of high-intensity TENS on PPT (Lazarou, et al., 2009). Also, there are some others investigated effects of TENS parameter manipulation on mechanical pain thresholds (Chesterton, et al., 2002).

About PPT it should be mentioned that tenderness may vary greatly in painful body parts and there are often several sensitive sites.

Although a quantitative measure, it is nevertheless a subjective measure, as it is based on patient report of pain. Moreover PPT may be influenced subconsciously by the tester while compressing the PA. Thus, blinding is recommended in studies (Ylinen, et al., 2007)

#### 6.2. Avoiding Auditory Artifacts in Laser Stimulation

Avoiding auditory artifacts due to laser stimulation has been looked at in some studies. Participants' ears are plugged and white noise is presented during the measurements to avoid this disturbance (Antal, et al., 2008).

#### 6.3. Influence of Thermode Pressure on Thermal Pain Threshold

It was previously suggested that the pressure of the thermode on the skin could influence measurements. Also, Pavlakovic, et al., (2008) performed a study and conclude that the pressure with which the thermode is attached to the skin does not significantly affect the intra- and inter subject reproducibility of the thermal sensory threshold measurements.

### 7. Discussion

In summary it is clear that the assessment of pain threshold and sensation parameters are crucial aspects of pain studies and have important clinical implications. In pain studies, we assess and follow up improvement, prognosis and treatment outcomes of central and peripheral neural system defects that affects pain induction and perception pathway. For example, hyperalgesia (enhanced pain perception) due to central and peripheral effects of drugs, mainly opiates, is a serious clinical concern, could substantially affect treatment outcome and abstinence duration, and is one of the topics of interest in the pain studies.

There is hope that with modification of central nervous system, mainly motor cortex and its associated areas, with Non Invasive Brain Stimulation (NIBS) techniques such as transcranial Direct Current Stimulation (tDCS) or repetitive Transcranial Magnetic Stimulation (rTMS) we could obtain clinically significant outcomes in reduction of pain perception. But for quantitative assessment of therapeutic effects, an active pain assessment setting is needed, and it seems that merely relying on patients' self reports on Visual Analogue Scale (VAS) is not sufficient. As has emerged from this review there are various pain assessment paradigms and settings and selecting the most sensitive and less cumbersome technique is the matter of expertise of scientists working in this field.

Therapeutic and behavioral effects of different non-invasive brain stimulation methods are being assessed in patients with neurocognitive deficits (especially heroin addicts) at the Neurocognitive Laboratory of Iranian National Centre for Addiction Studies, Tehran University of Medical Sciences. Studying hyperalgesia in opioid dependent patients and its significance in addiction treatment failure, and also the effects of NIBS on its modification are other important strands of work we are pursuing at our centre. We aim to be able to optimize the effect of brain stimulation methods on pain management in combination with our experimental pain threshold assessment settings in opioid dependent patients with pain disorders.

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