Quantitative Sensory Testing for musculoskeletal pain mechanisms; Standard Operating Procedure

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1. Introduction

Quantitative Sensory Testing (QST) is non-invasive testing during which pain sensitivity may be assessed by recording the participant's pain experience in response to a standardised physical stimulus. Pain sensitivity may be an indication of peripheral or central sensitisation of nociceptive neuronal pathways. QST is a form of `psychophysical testing', and combines both subjective and objective components. The measurements from QST are highly dependent on both psychosocial factors (e.g. whether the participant is anxious, whether they feel confident and comfortable in the testing environment, whether the researcher is male or female, etc), and on the nature of the physical stimulus and environment (e.g. the rate at which pressure is increased, the sequence in which test modality are undertaken, anatomical test site, room temperature).

Potential confounding factors need to be eliminated or standardised for QST to be a valid measure of neuronal sensitisation. With standardisation, within and between observer repeatability may be high, and peer reviewed journals will usually require demonstration of high repeatability for each study. Procedures should be done in the same way each time, whoever is the researcher and participant. Following standardised procedures requires skill and practice. Standardisation may enable comparisons or pooling of data between studies, or between assessors.

The Advanced Pain Discovery Platform (APDP) has been resourced to bring together UK expertise and infrastructure for chronic pain research to enable step changes in understanding of pain mechanisms, and develop new ways of treating pain. APDP brings together researchers and people with lived experience of pain across a diverse range of disciplines and conditions. These include people across the age and demographic spectrum with musculoskeletal, neuropathic, visceral or other conditions associated with chronic pain. Participants in APDP have agreed to implement, where feasible, acceptable and scientifically appropriate, standardised protocols for QST, so that data can be compared, shared and combined from across consortia and projects, through the ALLEVIATE data hub. Implementation of standardised protocols and data sharing aims to enable research that might not be feasible using data from any single study, and to compile UK-based normative data. Several QST protocols have been previously described, and QST methodologies continue to be developed. It is intended that APDP protocols be a basis for future improvements, while providing standardisation of core data collection within current and prospective research. These protocols might be a useful introduction to QST for those new to the field, and might help more experienced researchers to navigate perspectives from a range of stakeholders, including patients, researchers, ethics committees and funders.

This Standard Operating Procedure is based on procedures developed and used within Pain Centre Versus Arthritis, derived from previous published protocols, designed to assess central mechanisms of pain hypersensitivity as relevant to musculoskeletal pain (Georgopoulos et al., 2022). Two modalities are described, Pressure Pain detection Thresholds (PPT), and Temporal Summation (TS). Each has been used as a putative index of central pain processing (Rolke, et al, 2006), particularly when the PPT test site is distant or distal to the site of clinical pain (Georgopoulos et al., 2022, Arendt-Nielsen, et al., 2018). It is not possible to definitively distinguish between peripheral and central pain processing using QST in humans, and changes in sensitivity distant to the site of clinical pain, although likely to represent central pain modulation, might also be influenced by systemic or constitutional (e.g. genetic) factors that

have widespread effects on peripheral nociceptive processing. Mechanical stimuli have been selected based on evidence of validity and reliability gained mainly in studies of musculoskeletal diagnoses, where mechanically-induced pain is considered most clinically relevant. It is currently considered that central processing of nociceptive signals might not depend on nociceptive stimulus modality. Forearm has been selected as a standardised test site away from tissue pathology in these protocols. This site is supported by existing data on validity and standardisation of protocols, availability of brachioradialis as a deep somatic tissue, accessibility (e.g. during MRI scanning, or without fully undressing the participant), and low prevalence of local pathology likely to influence pain sensitivity (e.g. neuropathy, musculoskeletal disease). Researchers might wish to describe or confirm absence of local pathology when describing the forearm as a distant/distal test site, evidenced for example by self-reported pain distribution or clinical screening for disease.

2. General preparation

2.1. Testing environment

1. Prepare the study room and equipment. Ensure the equipment is working adequately e.g. by testing on yourself. Ensure that the room is quiet and at a comfortable temperature.

2. Identify what support is available in case you need help.

2.2. Participant preparation

1. Confirm that participant understands and agrees to what they are being asked to do. Be reassuring and do not inadvertently use phrases that might increase anxiety (e.g. `needle,' `hurt').

2. Ensure that the participant is suitably attired, with test sites fully exposed.

3. Ensure that the participant is rested, relaxed and comfortable. If they have recently undertaken vigorous exercise (e.g. rushing to make their appointment), then wait until they have fully recovered before starting QST.

4. Mark the test sites e.g. with a water soluble marker pen.

5. Enable the participant to adopt the testing position: They will be asked to maintain a relaxed siting position. Pillows and/or foam rollers may be used as needed to help participants maintain a relaxed posture throughout the testing period. The testing position should ideally remain the same throughout the QST assessment.

6. Wash your hands before touching each participant and disinfect equipment that they will come in contact with (ideally in front of them).

7. Proceed to QST modalities in the sequence PPT then TS. Before each modality, explain the procedure and what the participant is being asked to do.

3. Quantitative Sensory Testing Modalities

3.1. Pressure Pain detection Threshold (PPT)

The pressure probe (algometer) consists of a rod with an end the size of a 5p piece (1 cm^2), mounted in a hand-held device connected to a computer by a cable. The force with which the probe is pressed onto the skin is gradually increased until the participant indicates (e.g. by pressing a button) that the sensation has changed from pressure to pain. The probe is then immediately taken off the skin.

3.1.1. PPT Participant Preparation

1. Explain the QST procedure using standardised wording (APPENDIX 1).

2. Ensure the participant is lying comfortably on the couch in a quiet room with exposed test site(s) (e.g., knee and/or forearm).

3. Identify and mark test site(s).

4. Undertake PPT at a `training' test site (e.g., thumbnail) so that the participant knows what to expect, experiences the transition from pressure to pain, and is reassured that the procedure is only mildly and transiently painful.

5. Undertake PPT at the study test site(s) in a standard sequence according to the study protocol. The site of primary interest for the research study should be tested first.

3.1.2. Test Site(s)

1. Thumb or finger nail (`training site') The thumb or finger is positioned relaxed on a flat, firm surface with the dorsal aspect exposed for testing.

2. Brachioradialis (**Figure**1): Forearm loosely flexed and resting on pillow. The test site is approximately 5 cm distal to the lateral epicondyle of the non-dominant forearm, at the brachioradialis muscle. Palpation before testing is advised to ensure that the test will be probing underlying muscle.

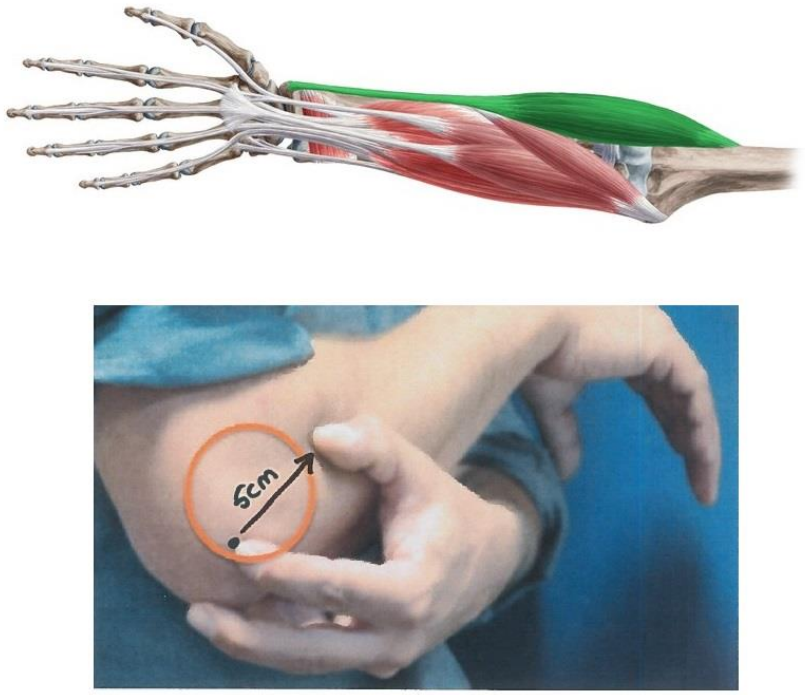


Figure 1. Anatomical site of Brachioradialis muscle and marking site for PPT. The test site is indicated by the model's thumb. (Image downloaded from www.kenhub.com)

3.1.3. Procedure

Record measurements for each site in the standardised sequence stipulated in the study protocol. When repeating on a single site, ensure at least 10 seconds have passed between tests in order to avoid temporal summation.

1. Disinfect probe head and push button before use with each participant (ideally in front of them).

2. Ensure participant is comfortable and willing to proceed with the procedure.

3. Ask the participant to close their eyes during testing (but not for the training site).

4. Apply the probe perpendicular to the skin and start the graded application of pressure. Apply graded pressure (e.g. following a live graphical representation of pressure on a computer) with a standardised pressure ramp of 50 kPa/sec.

5. As soon as the participant feels that the pressure has changed to pain, he/she should indicate this (e.g. by pressing a hand-held button that gives an audible signal). Immediately withdraw the probe.

6. If the participant has not already indicated transition from pressure to pain, withdraw the probe when a pressure of 1000 KPa is reached.

7. Record the pressure at which the participant indicated transition from pressure to pain.

3.1.4. PPT calculation and interpretation

Measure PPT in triplicate for each test site. PPT for that site for the individual may then be calculated as the arithmetic mean of all 3 values. PPT values within a population are expected to be positively skewed and should be log transformed before parametric analysis. Low PPT indicates greater sensitivity.

3.2. Temporal Summation (TS)

A pen-like, punctate stimulator, featuring a retractable blunt wire, is repeatedly applied to the skin and the participant is asked to rate the severity of pain or discomfort experienced on a 10 cm visual analogue scale (VAS). The punctate stimulator is designed to apply a standard 256mN force.

3.2.1. TS Participant Preparation

1. Explain the TS procedure using standardised wording (APPENDIX 1). Demonstrate the pain Visual Analogue Scale (**Figure 2**).

2. Ensure the participant is lying comfortably on the couch in a quiet room with exposed test site (forearm).

3. Identify and mark test site.

3.2.2. Test site

Brachioradialis muscle of the forearm contralateral to the one used for PPT. Site must not have any obvious skin pathology.

3.2.3. Procedure

1. Ask the participant to close their eyes.

2. Apply the 256mN weighted punctate stimulator perpendicular to the skin. The participant should feel light pricking.

3. Ask the participant “please rate the pain or sharpness you experience on this scale where the left edge indicates no pain or sharpness and the right edge indicates the most intense pain or sharpness imaginable.” Present VAS alongside verbal descriptors (APPENDIX 1).

4. Record the rating.

5. Apply the same stimulator 10 times repeatedly at a rate of 1/second within an area of <1 cm diameter centred on the initial test site.

6. After completing the 10 stimulations, ask the participant to indicate their average pain on the same VAS using the wording; “please indicate on the line how much pain or sharpness you experienced on average during those 10 stimulations, where the left end indicates no pain or sharpness and the right end indicates the most intense pain or sharpness imaginable”. The participant can see their original VAS mark on the same piece of paper when they are giving their average pain.

7. If the participants ask for the test to be discontinued due to severe pain from the punctate stimulation before the 10th stimulation, then the pain and sharpness score is recorded as 10 cm.

8. After a rest period of approximately 5 min repeat procedure 1-6 (Test B).

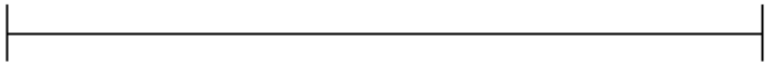
9. Disinfect the punctate stimulator.

3.2.4. TS calculation and interpretation

We recommend use of `wind-up difference', calculated as the rating for the average of the 10 repeated punctate stimuli minus the rating of the single stimulus at the start of the procedure. The arithmetic mean of 2 replicate tests is taken as the participant's TS. High TS values might indicate greater central sensitisation, and might reflect nociceptive processing at the level of the spinal cord.

Pain or Sharpness

Visual Analogue Scale



No Pain/Sharpness Worst Imaginable Pain/Sharpness

Figure 2. 10 cm Visual Analogue Scale for Temporal Summation testing using punctate stimuli.

Ensure when printed that the Visual Analogue Scale measures 10 cm.

Appendix 1: Detailed Verbal Instructions

PPT Verbal Instructions (to be read to the participant)

"I am going to read you the instructions. The reason we read the instructions to each individual is because we want to make sure that the procedure is identical for all participants."

"The idea of this test is to look at pain thresholds. The pain you feel will only be fleeting, as the test will be stopped as soon as you indicate that you have started to feel pain. You will hold this push button in your dominant hand and I will start to apply a graded pressure initially to your fingernail and later to your leg and forearm. You will feel pressure as the probe is pressed down and the pressure will be gradually increased. As soon as the pressure starts to change to pain, you should press the button and I will withdraw the probe."

"The first test will be on one of your fingernails and it is just a practice to let you know how it feels. I will then do the same 3 times on each site on your most painful knee, your lower leg and on your forearm. There will be a few seconds in between each test. If you require more time between the tests we will wait until you feel ready. Feel free to have your **eyes open** and observe the procedure for the first test on your finger but, in order for us to have as accurate measurements as possible, it is important to have your **eyes closed** for the subsequent tests."

*"Please bear in mind that we are **NOT** looking at how much pain you can tolerate, simply at what point you start to feel pain."*

"If, for any reason, you want to stop, let me know straight away."

"Do you have any questions?"

TS Verbal Instructions (to be read to the participant)

"This is a test of how you feel 'Sharpness' or 'stinging.' I will use a blunt metal bristle in this special pen for this test. This stimulator will be pressed gently against the skin on your forearm. It is only applied for 1 second at a time, so the sensation of sharpness will be temporary. It usually feels like a fine wire bristle. The pen is designed not to puncture your skin and is disinfected before we use it with each participant. I will first show you how it feels on your hand, then test once on your forearm, ask you to rate what it feels like, and then with 10 repeated stimulations and ask you to rate what they felt like."

- **Demonstrate how the equipment works on your own arm and then disinfect.**

"Are you happy for me to apply it once to the back of your hand to show you how it feels?"

- **Demonstrate once on their participant's hand.**

- **Show participant the Visual Analogue Scale.**

*"Please use this scale to mark the pain or sharpness you experienced on this line, where **the left edge** of the line indicates no pain or sharpness and **the right edge** of the line indicates the most intense pain or sharpness imaginable."*

"Now I would like you to close your eyes while I will perform the test on your forearm."

- **Test over brachioradialis x 1.**

- **Participant makes a mark on the VAS.**

"I would now like to apply the same stimulator at the same site 10 times repeatedly at a rate of once per second. After completing all 10, I will ask you to mark again on the scale, this time to mark the average pain or sharpness you experienced with the 10 stimulations. Are you happy for me to go ahead? Please close your eyes again."

- **Test over brachioradialis x 10.**

- **Show participant the Visual Analogue Scale.**

"Please indicate on the line how much pain or sharpness you experienced on average during those 10 stimulations, where the left end indicates no pain or sharpness and the right end indicates the most intense pain or sharpness imaginable."

- **After a rest period of approximately 5 min, during which other assessments may be completed:**

"I would now like to repeat the test of how you feel 'Sharpness' or 'stinging in your forearm and again will ask you to indicate on the scale the pain or sharpness that you felt. Will that be alright?"

- **Repeat single and 10x repeated tests over brachioradialis at the same site as above.**

Appendix 2: Disinfection

Before using the algometer and pinprick devices with a participant, they should be always disinfected. The following disinfection protocol is recommended.

Check if all necessary materials are available:

- 2% Chlorhexidine in 70% Alcohol Disinfectant Swipes

Steps for disinfection:

a. Ensure you remove the protective wrapping paper with clean hands without damaging the swipe.

b. Apply the swipe on the surfaces of the equipment that are going to be come into direct contact with the participants skin and rub meticulously until the entire surface has been cleaned.

c. Allow solution to dry for at least 30 seconds before storage or application on a participant.

d. Discard protective wrapping and used alcohol swipe in the appropriate bin.

e. Wash hands if necessary.

Appendix 3: Participant Record Form Template

Pain Pressure Threshold (kPa)

Test site	Right / Left *(Encircle side tested)*			
	Test 1	**Test 2**	**Test 3**	**Average**
Brachioradialis *5cm distal to lateral epicondyle*				

Temporal Summation (VAS)

Testing site	Forearm	Test 1	Test 2	Average TSP Score
	Right / Left	**Pain or Sharpness**	**Pain or Sharpness**	
5cm distal to lateral epicondyle	**Single measure (S)**			(Test 1+Test 2)/2
	Repeated measure (R) *(score for average pain/sharpness)*			
	TSP Score (R-S=)			

References

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