**Why does pain spread? An investigation of inhibition in the human brain**

**Protocol**

Background

Defined as pain that lasts longer than three months, chronic pain is one of the leading causes of years lived with disability in the world today [1]. A perplexing dimension of pain is the spatial dimension: why is it that pain so often becomes widespread across the body? The spread of pain to adjacent locations and unaffected body sites may reflect an impairment in the spatial tuning of sensory processing. Until now the intensity of pain has been the focus of investigation: “rate your pain on a scale out of 10”. The spatial dimension of pain, the spread of pain that someone may mark in a body diagram in the waiting room or in a research study questionnaire, has been neglected in comparison. What ought we to do with this important information, and what can it tell us about the function of a patient’s nervous system?

Pain is defined as an unpleasant sensory and emotional experience [2]. In this research project we are interested in the sensory component in particular – how the human nervous system processes and spatially tunes incoming sensory information. No matter the location of the injury, pain is produced by the central nervous system – the brain and spinal cord. (In fact it is crucial to remember that pain can arise in the absence of obvious injury or trauma[3].) Certainly as pain becomes chronic, the relationship between pain and any injury that may have occurred becomes more tenuous. And there are common features across different chronic pain conditions, irrespective of where the pain is felt. These features highlight the crucial role of the brain in chronic pain. For instance, the more traditional physiotherapy treatments – aimed at reducing pain and disability in the affected body part – are not always effective [4]. Second, the spread of pain does not always follow predictable nerve territories but instead occurs in intriguing patterns, for instance in mirroring to the opposite side of the body [5]. Third, pain sufferers have fascinating deficits in their perceptions, not least of all their perception of touch [6]. They are hyper-sensitive – the feeling of their clothing touching their skin elicits pain – and yet at the same time they report that they are clumsy with their sense of touch. They may be poor at recognising something touching their skin; this concept is termed tactile acuity.

Tactile acuity, the ability to precisely interpret touch information on the skin, is commonly measured, in the clinic and in neuroscience research, with the two-point discrimination threshold (TPD). TPD refers to the shortest distance between two points that someone can recognise as two points, and not one, touching the skin. This is a test of so much more than the function of the peripheral nerves or their receptive fields, as investigated extensively by our collaborator Professor Bob Coghill in the USA [7, 8]. After all, simple detection of touch in pain patients is normal, as demonstrated by our research into chronic low back pain (when no interpretation or discrimination of the touch is needed [9]). Furthermore, the latency, i.e. the time taken for the touch message to relay to the central nervous system, is also normal, as we reported in our meta-analysis of chronic limb pain [10]. Poor tactile acuity, the inability to recognise two points close together in space, indicates a problem with the spatial tuning of sensory information further up the neuroaxis – here we discuss the brain.

TPD is known to be poor across painful conditions [6], indicating an abnormality in the nervous system’s ability to inhibit spatial information. Crucially, TPD can be improved with training. An important randomised trial in phantom limb pain trained patients’ tactile acuity with repeated tactile training over the stump [11]. The TPD training led to improved TPD thresholds and importantly a reduction in pain – and reversal of the abnormal brain activation patterns. Importantly, the training program involved instructions on attending to and evaluating the nature of the touch. Tactile stimulation alone did not have the same effects.

If tactile acuity, and arguably the spatial tuning of sensory information, has been found to improve with training, along with a reduction in pain, why then have no therapies been designed specifically to stop the spread of pain across the body? This proposal asks: can TPD be used as a training tool to retune sensory processing and reduce the debilitating spread of pain? And what are the brain mechanisms of this effect?

In trying to understand the role of the brain in chronic pain, it is crucial that we investigate the brain pathway that information must take before it reaches the cortex. A key gatekeeper in this pathway is the thalamus, a structure deep in the brain, where all incoming sensory information, and pain, must pass through. Thalamocortical rhythm describes the recurrent loops of sensory information between the thalamus and the cortex, and this can be read with electroencephalography (EEG). Once simply regarded as a ‘relay centre’, the thalamus is crucial in controlling the incoming information to the cortex and in determining brain rhythms. The importance of the thalamus as a gateway to the cortex has long been known [12]. More recently, we and others have found thalamocortical rhythms to be altered in several chronic pain states [13-15].

We were the first to investigate the chemical mechanisms of thalamocortical rhythms. We used EEG, which offers optimal time resolution, to read the rhythms of the brain over the cortex. In an effort to understand the basis of the EEG thalamocortical rhythms, we used magnetic resonance spectroscopy (MRS), the only direct measurement of neurochemistry in vivo, to study the neurochemical levels of the thalamus. Specifically we were interested in the thalamic concentration of gamma-aminobutyric acid, GABA, the human brain’s major inhibitory neurochemical. For the first time we were able to show a relationship between the concentration of GABA in the thalamus and brain rhythms over the cortex in people with pain [13]. The relationship between GABA and the cortical spatial distribution of the rhythms was also different in pain. One of the cortical regions was the sensorimotor region, where the rhythms correlated with pain intensity and pain duration. But the most fascinating thing about this relationship? The relationship did not exist in controls. It seems there is something different about the thalamocortical pathway, this highway for sensory information, when someone is in pain. We now want to look into this further: what does this relationship between thalamic neurotransmitter content (e.g. GABA) and EEG rhythms mean in terms of the spread of pain? Does this relationship change with targeted tactile training aimed at restoring normal inhibition and spatial tuning?

Inhibitory neurons are responsible for far more than simply providing stop signals for activity in the human brain [16]. Inhibitory processes allow for the ‘sculpting’ of neural activity along the pathways of the central nervous system [17]. Such a concept is critical for the sensory system. Accurate recognition of touch on the skin is heavily reliant on an intact system of inhibition. It follows that pain – and its spread – would be heavily reliant on an intact system of inhibition. But this is not known.

Rationale and objective

* A common complaint in chronic pain is its spread. This spatial dimension of pain, the fact that pain spreads unpredictably, is very poorly understood and under-investigated.
* Tactile acuity is poor in people with pain. We know that tactile acuity is reliant on inhibition; tactile acuity can be trained; and improved tactile acuity relates to improved pain levels.
* Pain and touch must travel via the thalamus, which exerts inhibition on incoming information before it reaches the cortex for processing.
* Our work has shown an intriguing relationship between neurotransmitter levels in the thalamus and thalamocortical rhythms – in pain only.
* To date no one has investigated such neuroimaging relationship as a basis for sensory inhibition or spatial tuning, nor are there therapies designed to diminish or eliminate the spread of pain.

We aim to test the efficacy of a tactile discrimination training program on the spread of back pain. We hypothesise that the training program will reduce the spread of pain (boundaries indicated on a body map/photo by participants). We will also assess the efficacy of the training program by reductions in the intensity and unpleasantness of pain, pain-related disability and perceptual abnormalities of the back, and improvements in tactile acuity. We hypothesise that pain will be associated with the neuroimaging measures (eg the thalamic neurotransmitter/thalamocortical rhythm relationship).

Piloting

Prior to commencing this investigation, we will optimise the tactile acuity testing and/or training program conditions in up to 10 participants. This will serve as a pilot to refine operational aspects of the study procedures before we commence the investigation detailed herein. This is important given the novelty of this experiment.

Methods

Participants

This exploration will recruit up to 40 participants with chronic low back pain (i.e. pain duration of 3 months or more). This sample size includes up to 10 participants for piloting. Participants must be aged between 18 and 70 years and be fluent in both written and verbal English language.

Participants will be excluded if: their pain is primarily visceral in origin; they have signs or symptoms of nerve root pain (according to routine clinical assessment); they have evidence of current specific spinal pathology (eg malignancy, fracture, infection, inflammatory joint or bone disease); they are pregnant or less than 6 months post-partum; or they have undergone recent spinal surgery. Participants will be excluded if they suffer a significant mental health disorder and/or health impairment that would interfere with their safe participation and adherence to study requirements. Magnetic Resonance Imaging (MRI) safety contraindications (i.e. pregnancy, metal implants, cardiac pacemaker) and electroencephalography (EEG) safety considerations will apply. For the MRI component of the study, we will require that participants have a general practitioner (GP) who they see on a regular basis. This is a requirement of the MRI facility. The Doctor in our team will refer participants for scanning and then liaise with the participant’s own GP – notifying the GP of their patient’s involvement in our research and communicating any incidental brain imaging findings to the GP for further care.

The sample size of n = 30 has been estimated based on (is larger than most [10]) other pain and neuroimaging studies. The data collected will form a proposal to investigate broader questions on sensory and motor systems in chronic pain, with a larger NHMRC grant. (Application for Category One funding with these data is a requirement of the Raine Grant funding of this current proposal).

Design

“Scan sessions” (EEG and MRS) may be conducted before and after the tactile training program. Scan sessions will include assessment of pain spread, pain intensity and pain unpleasantness. Participants will undergo assessment of two-point and single-point discrimination thresholds, and complete questionnaires. In the first scan session participants will be randomised into either the two-point tactile training program or the one-point tactile training program (control). Both of these will comprise up to 8 training sessions in total. The scan sessions, where possible, will be conducted within a short time frame (or at least the second scanning session will, where possible, be conducted within approximately a week of training completion), in order to maximise chances of a positive training effect on pain (and detection of its effects with neuroimaging). A consistent number of training sessions is administered to the participants, which will involve a progression in difficulty; see below.

Electroencephalography (EEG)

Participants will be seated comfortably at a table so that an EEG cap can be fitted to their heads, to measure resting brain rhythms. An EEG cap containing premeasured electrode sites according to the 10–20 system will be fitted to each participant. Chest and eye electrodes may be fitted to monitor cardiac activity, and eye/facial muscle contractions, respectively. EEG data will be acquired in a quiet room for a period of up to ten minutes, with the subject relaxed. The CI is experienced in EEG data acquisition and analysis. The procedure is safe and pain-free.

Magnetic Resonance Spectroscopy (MRS)

An MRI scanner will be used to conduct spectroscopy to assess neurochemistry. MRI will take place at Perth Radiological Clinic (Subiaco). With each subject relaxed and at rest, a head coil and ear protection (ear plugs and/or ear muffs) will be fitted to the participant. A whole-brain high resolution anatomical scan will be acquired for each participant. A whole-brain resting state functional scan (fMRI) or conductivity map may be collected. For the MRS, the anatomical scan will be used as a guide, such that a single voxel (3D pixel) can be placed on the region of the thalamus contralateral to the site of the participant’s (most severe) pain. Spectroscopy will be performed on this voxel, to quantify neurochemistry, for instance glutamate, a major excitatory neurotransmitter. The CI is experienced with the process of MRS acquisition and analysis.

Total scan time should not exceed 60 minutes. Scans may be omitted if it is deemed as appropriate by the investigator or the participant (eg if the participant experiences discomfort). Omission of any of the procedures does not impact participant safety or risk.

As for MRI scanning, EEG procedures may be omitted if deemed optimal by investigators or participants, eg for patient comfort. Such an omission would not impact participant safety or risk.

Two-point tactile training program

Testing and training may take place at spatial locations remote from the pain, at spatial locations adjacent to the region of pain, and/or at spatial locations in the site of pain if the participant will tolerate it. TPD is the smallest distance between two points that someone can recognise as two points touching their skin, and not one. Thus this test of one’s ability to identify separate stimulus areas relies heavily on inhibition. Stimulation will be conducted using highly precise, pain-free callipers placed on the skin until the very first blanching of the skin appears [18]. The distance between the two calliper tips will be gradually increased and decreased repeatedly, and the two-point discrimination threshold will be deemed as the distance at which participants consistently report two points instead of one touching the skin. One-point stimuli trials will be used to serve as a control condition. Participants will be informed of correct and incorrect responses to each stimulus.

We have introduced criterion-based progression to the training program, for consistency across participants, and importantly to increase participants’ motivation and interest in the program – and ultimately improve the likelihood of an improvement in pain. Progression is through stages, as indicated below.

Stage 1:

* delivery of sets of two-point stimuli (approximately 25 stimuli per set; sets containing pre-determined, pseudo-randomised lists of stimuli)
* the distances delivered will be based on the individual’s own TPD threshold
* as well as judging whether one or two points are felt on the skin, participants will be asked to judge whether two-point stimuli are wider or narrower than the preceding stimuli
* all responses by the participants will be met with feedback from the researcher
* progress to Stage 2 – after a minimum of two sessions in Stage 1.

Stage 2

* -as well as judging whether one or two points are felt on the skin, participants will now be asked to show the researcher the distance they believed they received. They will be presented with a (visual) choice of the distances they are receiving in the set.
* all responses by the participants will be met with feedback from the researcher
* after a minimum of two sessions, progress to smaller increments of distance between the two points.

One-point (control) tactile training program

Participants will undergo a single-point training program at the same sites, and with consistent timings of stimulation, as the condition above. Probes of different sizes will be used: a small diameter probe (approx. 1 – 5 mm) and a large diameter probe (approx. 6 – 50 mm). Placing the single points of differing diameters will ensure that the stimuli are still novel and changing, and therefore engaging and holding the participants’ attention. Prior to placing any probes on the skin a brief instruction will be given to the participants. Participants will be told the broad concept that the processing of sensory information occurs both at a conscious and a sub-conscious level; and that they are in the 'subconscious processing' arm of the study. The researcher will notify the participants that as the objects are placed on their skin they need to focus their attention on the objects as they touch their skin, even though in this condition the participants are not asked to discriminate or make any judgements, and they will therefore receive no feedback. This brief instruction is intended to increase the credibility of the control arm and make it more engaging for the participants in this group. In the control program there is also the equivalent of the 'stages' as per the training program - i.e. participants may be visually shown the probes that are being placed on their skin. Importantly however no responses will be sought from them.

Pain assessments

Pain intensity and unpleasantness will be assessed by mechanical visual analogue scale (VAS)[19]. These scales have been repeatedly demonstrated to provide reliably separate assessment of intensity and unpleasantness, to be internally consistent, and to approximate ratio scale measurement accuracy [20].

Pain location/ spread will be characterised by having the participant draw their regions of pain on a paper or electronic body map or photo of themselves.

Pain-related disability will be assessed with the Roland-Morris Disability Questionnaire (attached), and back perceptions will be assessed with the FreBAQ questionnaire (attached).

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