

Modulation of Noxious Stimuli: Mechanisms Underlying the Human Experience of
Pain

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Bachelor of Science Honours

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Declaration

I declare that this thesis is my own account of my research and contains as its main content work that has not previously been submitted for a degree at any tertiary educational institution.

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Abstract

The aim of the current study was to explore the effects of sympathetic arousal on a healthy individual's experience of pain, and how the presence of central sensitization, experimentally induced using electrical conditioning of the forearm, affects this interaction. It was hypothesized that following electrical conditioning, sympathetic arousal would lead to higher subjective ratings of pain and heightened nociceptive reflexes. Furthermore, it was expected this effect would be more pronounced in participants classified as high in pain catastrophizing. To test these hypotheses, the study used a repeated-measures design, comparing ratings of pain and blink reflex data to a nociceptive stimulus at baseline and post-conditioning. On a number of trials, the nociceptive stimulus was presented with concurrent acoustic stimulation, intended to evoke arousal. Results did not support the hypotheses, as electrical conditioning did not lead to an increase in pain or nociceptive reflexes during heightened states of arousal. Catastrophizing was also found not to have a significant result on the outcome. Alternative explanations, and the implications of these findings are discussed, along with suggestions for future research.

Modulation of Noxious Stimuli: Factors Underlying the Human Experience of Pain

Current research suggests chronic pain conditions affect up to 20% of females, and 17.1% of males in the general Australian population (Blyth et al., 2001). In the workplace, chronic pain conditions are responsible for 36.5 million lost workdays annually in Australia alone, resulting in a cost estimate of approximately \$5.1 billion (AUD) (van Leeuwen, Blyth, March, Nicholas & Cousins, 2006). Furthermore, pain-related disability is significantly associated with increased use of health care services (Blyth, March, Brnabic & Cousins, 2004), resulting in a further \$7 billion in health system expenditure.

Chronic pain conditions also have a considerable personal cost for the afflicted individual. The pain and sensory disturbances associated with chronic pain conditions are often so severe that they result in serious disability, and interference in daily activities (Marinus et al., 2011). Diminished ability to perform daily tasks is further associated with poorer perceptions of personal health, and a marked rise in psychological distress (Blyth et al., 2001; Breivik, Collett, Ventafridda, Cohen & Gallacher, 2006). The relationship between chronic pain and poor mental health is well documented, with literature highlighting comorbidity issues such as depression, anxiety, poor self-esteem, and social isolation (Demyttenaere et al., 2007; Bair, Wu, Damush, Sutherland & Kroenke, 2008). Such statistics highlight the substantial indirect and hidden financial costs of pain on the Australian economy, and showcase the importance of future research seeking to uncover the disrupted sensory mechanisms that result in chronic conditions.

The biopsychosocial model, first put forth by Engel (1978), is now accepted as the most heuristic approach to understanding and researching chronic pain. This model views illness as a complex interaction of biological, psychological, and social factors

(Gatchel, 2005). Incoming sensory information about the external environment is subject to a process of transduction and modulation, during which the input is influenced by factors, such as current physiological state (Gatchel, Peng, Peters, Fuchs & Turk, 2007). Research suggests that sympathetic arousal can precipitate symptoms of pain, be a modulating factor in the amplification or inhibition of pain, and perpetuate chronic pain conditions (Duckro, Chibnall & Tomazic, 1995; Gaskin, Greene, Robinson & Geisser, 1992; Kinder, Curtiss & Kalichman, 1992; Robinson & Riley, 1999).

The aim of the current study was to increase general understanding of the interaction between increased physiological arousal and the perception of noxious stimuli in individuals presenting with chronic pain conditions. In order to do this, it is important to first understand how arousal affects the experience of pain in healthy participants, in order to provide a baseline by which to compare abnormal pain mechanisms. Therefore, the study aimed to examine how arousal influences the detection, moderation and maintenance of pain in the central and peripheral nervous system, and affects the subjective experience of pain in healthy human participants.

Basic Pain Pathway

Information about tactile stimuli in the external environment is carried to the central nervous system via a large network of afferent nerve fibres located in the peripheral nervous system (Landon, 1976). Only selections of these sensory neurons are designed to convey information relating to pain, and these are termed ‘nociceptors’. When a painful chemical, thermal or mechanical stimulus is detected by a nociceptor, a complicated process of transduction takes place, in which the physical sensation is transformed into a neural signal that can be conveyed to the central nervous system (Torsney & Fleetwood-Walker, 2012). Two types of nerve fibres are involved in carrying nociceptive information to the spinal cord – small, myelinated A-delta, and

unmyelinated C nerve fibres (Greenspan & Bolanowski, 1996; Levine & Taiwo, 1994). The myelin sheath surrounding the A-delta fibres allows information to reach the spinal cord at a much quicker rate relative to the C fibres; therefore, individuals often feel sharp, acute pains prior to experiencing a delayed, dull ache (Julius & Basbaum, 2001; Scholz & Woolf, 2002). The neurons terminate at the dorsal horn of the spinal cord, where incoming signals are exposed to a series of complex excitatory and inhibitory influences (Costigan & Woolf, 2000).

The complex process of transduction that takes place in the peripheral nervous system is crucial to the detection of harmful stimuli in the environment and the actioning of appropriate protective responses (Julius & Basbaum, 2001). However, pain has the potential to become debilitating when incoming nociceptive signals become distorted at both the peripheral and central nervous systems, leading to the development and maintenance of chronic pain conditions (Nelson, 2013).

Peripheral and Central Sensitization

Peripheral sensitization, also known as primary hyperalgesia, is said to have occurred when lowered pain threshold, and increased sensitivity to pain is observed at the location of the nerve injury (Kilo, Schmelz, Koltzenburg & Handwerker, 1994; LaMotte, Shain, Simone, & Tsai, 1991). Mechanisms underlying peripheral sensitization work on a rapid timescale, with injury resulting in the release of chemical messengers called inflammatory mediators. These substances alter the gene expression of nociceptors, making them much more responsive to stimulation. This process triggers a flood of sensory information, which is relayed from the periphery to the dorsal horn, and alters central signal processing (Ashmawi & Freire, 2016; Rocha et al., 2007).

The outcome of this process is central sensitization, or secondary hyperalgesia. The undamaged nerves surrounding the site of injury also become supersensitive, and

able to evoke feelings of pain to otherwise innocuous stimuli (Ali, Meyer & Campbell, 1996). Studies have indicated that the characteristics of primary and secondary hyperalgesia differ. By demonstrating that sensitization of undamaged peripheral nociceptors does not account for secondary hyperalgesia, researchers have implicated changes to the central processing of afferent nociceptive signals as the cause (Meyer, Ringkamp, Campbell & Raja, 2005; Raja, Campbell & Meyer, 1984). In particular, pain-facilitatory bulbo-spinal pathways that mediate the spread of pain and tenderness around sites of injury and inflammation are thought to contribute to central sensitization (Jaggi & Singh, 2011; Millan, 1999; Millan, 2002).

When primary and secondary hyperalgesia occur together, a vicious cycle of feedback is created, in which increased sensitivity to otherwise innocuous stimuli results in constant nociceptive input, leading to the maintenance of altered central signal processing, and prolonged sensitization of undamaged adjacent nerves (Nelson, 2013). In order to treat chronic pain conditions this cycle must be disrupted, and in order to disrupt the cycle, it is essential to first have an understanding of the abnormal pain mechanisms that maintain primary and secondary hyperalgesia.

Involvement of the Sympathetic Nervous System

The role of the sympathetic nervous system in the development and maintenance of chronic pain conditions has been an ongoing source of debate (Kurvers et al., 1994; Paice, 1995; Schott, 1995; Veldman, Reynen, Arntz & Goris, 1993). Emerging research suggests that dysfunction of the sympathetic nervous system may be the result of adrenergic supersensitivity, as opposed to sympathetic hyperactivity (Drummond, Finch & Smythe, 1991; Harden et al., 1994). Tissue injury is able to evoke adenosensitivity in the injured sensory neurons and nearby tissues (Rubin et al., 1997; Sato & Perl,

1991). As a consequence, circulating catecholamines (i.e., neurotransmitters such as adrenaline and noradrenaline) are able to trigger nociceptive firing (Perl, 1999).

Bruehl and Chung (2006) outline this hypothetical model in finer detail (see Appendix A for visual representation of model). Following nerve injury, afferent nerve endings become sensitized to otherwise innocuous stimuli (Birklein, Schmelz, Schifter & Weber, 2001). The cause for this sensitization is diminished sympathetic activity, causing peripheral catecholaminergic receptors located on injured sensory nerves to become increasingly responsive (Birklein, Riedl, Claus & Neundorfer, 1998; Kurvers, Daemen, Slaaf, Strassen & Van Den Wildenberg, 1998). This effect is then maintained as new axonal sprouts regenerating from the injured nerve develop the same heightened sensitivity to catecholamines, such as noradrenaline (Chemali, Gorodeski & Chelimsky, 2001) and adrenaline (Chabal, Jacobson, Russell & Burchiel, 1992; Scadding, 1981).

Sensitized nerves are also capable of producing spontaneous action potentials (Woolf & Mannion, 1999). Nociceptive fibres relaying sensory information can concurrently develop sensitivity to adrenergic excitation, resulting in an increased neural response to sympathetic discharge or circulating catecholamines (Drummond, Finch, Skipworth & Blockey, 2001), and feelings of spontaneous pain, independent of external stimulation. This catecholamine induced nociceptive firing floods pain receptors in the dorsal horn, and contributes to the maintenance of altered central processing (Gracely, Lynch & Bennett, 1992; Woolf, Shortland & Coggeshall, 1992).

Implications of Adrenergic Supersensitivity

Research suggests that emotional states associated with high sympathetic arousal, such as anxiety, depression, and stress, can increase levels of circulating catecholamines (Light, Kothandapani & Allen, 1998; Tsigos, Reed, Weinkove, White & Young, 1993). As chronic pain conditions are strongly associated with mental health

conditions such as anxiety disorders and depression (Bair, Robinson, Katon & Kroenke, 2003; Outcalt et al., 2015), and those suffering from chronic pain are more likely to experience stressful life events, and interpret them with a higher degree of seriousness (Geertsen, de Bruijn-Kofman, de Bruijn, van de Wiel & Dijkstra, 1998), understanding the role of sympathetic arousal, and how it influences an individual's experience of pain is critical to the development of efficacious treatment plans for chronic pain conditions.

If the model of adrenergic supersensitivity outlined by Bruehl and Chung (2006) is correct, and affective distress does result in higher levels of circulating catecholamines, then subjective ratings of pain would be expected to increase during sympathetic arousal in individuals suffering from chronic pain conditions. There is research to support this hypothesis, demonstrating that arousal evoked through injection of the neurotransmitter adrenaline (Ali et al., 2000; Choi & Rowbotham, 1997; Torebjörk, Wahren, Wallin, Hallin & Koltzenberg, 1995), and acoustic startle (Drummond et al., 2001) was significantly associated with increased subjective ratings of pain in a sample of individuals suffering from various forms of chronic pain. However, a correlational relationship does not indicate causation, and it is unclear whether subjective pain ratings increased due to adrenergic supersensitivity to circulating catecholamines, or a general failure in inhibitory spinal or supraspinal mechanisms that act on afferent nociceptive signals during sympathetic arousal in chronic pain patients (Drummond, 2001).

To overcome this limitation, more studies are needed using samples of healthy participants. By measuring a healthy individual's subjective and physiological responses to pain whilst they are aroused, researchers are able to draw a baseline to which they can compare the responses of individuals suffering from chronic conditions. Furthermore, by experimentally inducing primary hyperalgesia in healthy subjects, any

changes to how pain is processed during sympathetic arousal can more reliably be seen as due to central sensitization.

High Frequency Electrical Stimulation

Researchers have been able to mimic the effects of hyperalgesia in healthy participants, using methods such high frequency electrical stimulation (HFS). Wall and Woolf (1984) were among the first to demonstrate that a C fibre that had been stimulated once would stay sensitized for up to three minutes, whereas a C fibre that had been stimulated once a second, for a period of twenty seconds, would remain hypersensitive for up to ninety minutes. HFS mimics this wind-up effect, by delivering a series of high frequency electrical bursts (100Hz) in a small time frame, resulting in an increase in the synaptic strength of stimulated nociceptors, and long-term potentiation of nociceptive fibres terminating at the dorsal horn (Klein, Stahn, Magerl & Treede, 2008; Lang, Klein, Magerl & Treede, 2007; Pfau et al., 2011).

HFS has been shown to reliably increase sensitivity to mechanical punctuate stimuli, at both the conditioned site (i.e. the area that received electrical stimulation), and in the areas adjacent (Klein, Magerl, Hopf, Sandkuhler & Treede, 2004; Sluka, Judge, McColley, Reveiz & Taylor, 2000; Vo & Drummond, 2013). These symptoms are consistent with the presence of primary and secondary hyperalgesia (Klein et al., 2008; Pfau et al., 2011).

Analgesia

Bilateral forehead analgesia has been found to occur following cold – (Knudsen & Drummond, 2009) and heat-induced (Knudsen & Drummond, 2011) limb pain, as well as HFS (Vo & Drummond, 2013). Vo and Drummond (2013) found that analgesia to pressure pain on the ipsilateral forehead developed following high frequency electrical stimulation of the forearm, but not ultraviolet B radiation. As high

frequency stimulation is associated with signs of secondary hyperalgesia (Klein et al., 2008; Lang et al., 2007; Pfau et al., 2011), whereas ultraviolet B radiation is thought to result in only primary hyperalgesia (Bishop, Ballard, Holmes, Young & McMahon, 2009; Harrison, Young & McMahon, 2004), it is thought central sensitization may bear some association with pain inhibitory mechanisms, such as stress-induced analgesia (Gamero et al., 1998; Janssen, Arntz & Bouts, 1998) and diffuse noxious inhibitory controls (DNIC) (Villanueva & Le Bars, 1994). DNIC occurs when painful stimulation of one area leads to a decrease in pain at another location (Butler & Finn, 2009). In healthy humans, this effect can only be triggered by nociceptive conditioning stimuli, which activates A-delta and C fibres, leading to descending inhibition on convergent neurons in the dorsal horn (Le Bars, Villanueva, Bouhassira & Willer, 1992).

Nociceptive Blink Reflex

The nociceptive blink reflex – involuntary closure of the eyelids induced via painful stimulation of facial nerves (Kaube et al., 2002; Giffin, Katsarava, Pfundstein, Ellrich & Kaube, 2004) – has been used to delineate the role of pain modulation processes induced by high frequency stimulation of the forearm. The blink reflex provides a non-invasive way of studying trigeminal transmission and its connections with the brainstem (Giffin et al., 2004), and objective physiological data that can be used to study central processing of nociceptive stimuli.

Electrical stimulation of the trigeminal supraorbital nerve is a common way of eliciting the blink reflex (Blumenthal et al., 2005; Ellrich, Bromm, & Hopf, 1997; Ellrich & Treede, 1998; Giffin et al., 2004; Vo & Drummond, 2014a). This reflex is comprised of an early ipsilateral R1 component, and a bilateral R2 and R3 component (Ellrich & Hopf, 1996; Hopf, 1994; Rossi, Risaliti, & Rossi, 1989). Of these, only the R2 component can be elicited through activation of nociceptive fibres (Ellrich et al.,

1997), as the response is mediated by wide dynamic range interneurons, which are activated by noxious mechanical stimuli (Ellrich & Treede, 1998). Therefore, pain research in general focuses on the R2 component of the nociceptive blink reflex.

Effects of Arousal on Pain Perception in Healthy Humans

Studies using samples of healthy participants are able to provide clearer insight into the possibility of adrenergic supersensitivity. In healthy humans, many cortical areas that respond to nociceptive input are also activated in response to sympathetic arousal (Critchley, Corfield, Chandler, Mathias & Dolan, 2000; Tölle et al., 1999; Vogt, Berger & Derbyshire, 2003). Sympathetic activation forms part of the descending inhibitory control pathway that suppress pain (Millan, 2002; Tracey & Mantyh, 2007). This stress-induced suppression of pain has two components. First, descending pathways originating from noradrenergic cells in the brainstem begin to exert influence on the afferent neurons in the dorsal horn of the spinal cord (Millan, 2002). Next, opioids are released, which bind to the receptors on primary afferent neurons, and cells in the brainstem, leading to the suppression of activity of these neurons, and consequently analgesia (Ossipov et al., 2004).

By experimentally inducing central sensitization, researchers are able to investigate the effects of disrupted pain mechanisms on the perception of noxious stimuli in healthy participants. For example, the application of capsaicin to areas of the ventral forearm has been used to reliably evoke primary, and secondary hyperalgesia (Drummond, 1995; Drummond, 1998). Janssen and colleagues (1998) found that healthy participants reported higher subjective pain ratings to electrical stimulation of an area of skin sensitized using capsaicin, following intravenous injection of adrenaline in three increasing doses. However, intravenous injection of adrenaline can produce false-positive results, due to complications in accessibility of target tissues (Birklein,

Riedl, Claus, Neundörfer & Handwerker, 1997) and sensitive dosage requirements (Drummond, 1995; Drummond, 1998).

In a later study, Drummond and colleagues (2001) sought to overcome these limitations by investigating the effects of normal sympathetic activation. Heat from a halogen globe was focused on an area of skin sensitized using capsaicin, and participants were asked to rate pain intensity at short intervals. During one of the heating periods a startling acoustic stimulus was presented through headphones. Contrary to the hypothesized outcome, pain ratings decreased during various forms of sympathetic arousal. The authors postulated that minimal release of noradrenaline in the capsaicin treated site, due to a greater degree of vasoconstriction in the digits than in the capsaicin-treated skin, might explain why ratings of pain did not increase. Thermal hyperalgesia in capsaicin treated skin has been shown to increase during more prolonged forms of sympathetic activation, such as body cooling (Drummond, 2001), suggesting that brief startle stimuli may not sufficiently excite nociceptors during vasoconstriction (Elam, Olausson, Skarphedinsson & Wallin, 1999).

Catastrophizing

The time span during which the sympathetic nervous system remains activated is a crucial factor in determining whether arousal results in suppression or amplification of pain (Schlereth & Birklein, 2008). For example, fear has been shown to reduce pain perception, and suppress pain behaviour, whilst anxiety, directed toward a projected threat in the future, can amplify pain (Rhudy & Meagher, 2000).

Pain catastrophizing, defined as “an exaggerated negative “mental set” brought to bear during actual or anticipated pain experience” (Sullivan et al., 2001, p. 53), plays a crucial role in shaping an individual’s experience of pain (Geisser, Robinson & Riley, 1998). For example, in a series of zero-order correlations performed by Sullivan and

colleagues (2001), catastrophizing accounted for 7 to 31% of variance in pain ratings. Furthermore, the variable is positively associated with increased perception of pain in both healthy participants (Sullivan, Rouse, Bishop & Johnston, 1997; Sullivan & Neish, 1998; Sullivan, Tripp & Santor, 2000; Sullivan et al., 2001) and individuals suffering from chronic pain (Sullivan, Lynch & Clark, 2005; Turner, Jensen, Warms & Cardenas, 2002).

Experimental pain procedures are a primary means for investigating pain processing in humans, therefore it is important to clarify the association between catastrophizing and standardized noxious stimuli (Edwards, Smith, Stonerock & Haythornthwaite, 2006). In samples of healthy participants, higher levels of catastrophizing were associated with lowered pain threshold (Edwards, Haythornthwaite, Sullivan & Fillingam, 2004), lowered pain tolerance (Edwards, Campbell & Fillingam, 2005; Thorn et al., 2004), higher pain intensity (France, France, al'Absi, Ring & McIntyre, 2002), and greater pain temporal summation following experimentally induced thermal hyperalgesia (Edwards et al., 2006).

One possible mechanism by which catastrophizing might influence the experience of pain is by promoting sensitization in the central nervous system (Edwards et al., 2004; Geisser et al., 2003; Gracely et al., 2004). Evidence supports an association between brains areas associated with catastrophizing (Gracely et al., 2004; Seminowicz & Davis, 2006) and the brain stem (Desbois, Le Bars & Villanueva, 1999; Desbois & Villanueva, 2001; Monconduit & Villanueva, 2005; Villanueva, Desbois, Le Bars & Bernard, 1998), which moderates the diffuse noxious inhibitory control effect (Le Bars, 2002). Therefore, it is plausible that catastrophizing may affect sensitivity to pain by exerting an indirect influence on inhibitory pathways.

Current Aims and Hypotheses

Hypothesis 1: Primary and Secondary Hyperalgesia. The first aim of the study was to ensure the presence of changes to central signalling processes, in line with primary and secondary hyperalgesia. Based on the results of previous research (Vo & Drummond, 2013; Vo & Drummond, 2014a; Vo & Drummond, 2014b) it was hypothesized that high frequency stimulation would evoke primary and secondary hyperalgesia to mechanical punctuate stimuli, but not other sensory modalities, in the conditioned forearm, indicated by an increase in subjective ratings of pain and sharpness to psychophysical stimuli applied to the area.

Hypothesis 2: Forehead Analgesia to Pressure-Pain. It was further hypothesized that the presence of central sensitization would decrease sensitivity to pressure pain, but not other sensory modalities, in the forehead (Vo & Drummond, 2014a), with analgesia being more pronounced on the side of the forehead ipsilateral to the experimental forearm.

Hypothesis 3: Effects of Arousal on Pain Perception Prior to HFS. The main aim of the current study was to explore the effects of sympathetic arousal on a healthy individual's experience of pain, and how the presence of central sensitization, experimentally induced using electrical conditioning of the forearm, affects this interaction. Based on previous research (Millan, 2002; Tracey & Mantyh, 2007) it was hypothesized that, prior to HFS, startle stimuli would evoke an analgesic effect to supraorbital stimulation of the forehead, indicated by lower subjective ratings of pain relative to supraorbital stimulation presented alone.

Hypothesis 4: Effects of Arousal on Pain Perception Following HFS. In line with previous research (Vo & Drummond, 2014a), it was hypothesized that electrical conditioning of the forearm would result in a reduction in R2 AUC of blink reflexes contralateral to HFS, and an increase in R2 AUC ipsilateral to HFS. Furthermore, in the

presence of primary hyperalgesia, arousal evoked through acoustic startle was expected to increase sensitivity to supraorbital stimulation of the forehead, indicated by higher subjective ratings of pain and sharpness and amplification of the nociceptive blink reflex.

Hypothesis 5: Catastrophizing. It was hypothesized that participants who scored highly on the Pain Catastrophizing Scale (Sullivan, Bishop & Pivik, 1995) would report higher subjective ratings of pain and sharpness to supraorbital stimulation, both at baseline and following conditioning, relative to participants who scored lowly. It was further hypothesized that catastrophizing would exacerbate pain intensity during states of heightened arousal, with this effect being more pronounced following HFS.

Methods

Participants

The sample consisted of nine males and 12 females, aged between 18 and 49 ($M= 25.24$, $SD=10.17$). Participants were undergraduate psychology students who enrolled in the Research Participant Portal, and volunteers from the general population recruited through convenience sampling. In compensation for their time, psychology students received two hours of research credit, and external volunteers were awarded a coffee voucher. Exclusion criteria included pregnancy, breastfeeding, and any existing physical or psychiatric disorder, use of any medication, or reliance on a pacemaker or any other implanted device. Participants gave their written informed consent for the procedures, which were approved by the Murdoch University human research ethics committee (see Appendix B).

Design

The study used a repeated measures design, consisting of a baseline and post-conditioning phase (see Appendix C for timeline depiction of each phase). During the

baseline phase participants underwent a series of psychophysical tests to measure initial sensitivity to blunt-pressure, and mechanical stimuli, followed by supraorbital and acoustic stimulation. After introducing the experimental manipulation (i.e. HFS) these procedures were repeated, and the results compared to assess the impact of the electrical conditioning. The same sample was used during both phases, thus eliminating between subject confounds that may have contributed towards type I or type II errors, and reducing the amount of participants required to provide valid data (Girden, 1992).

Procedure

All experiments were conducted by the same researcher (JW), in a laboratory maintained at $21 \pm 1^\circ\text{C}$. Upon arrival, each participant was presented with a copy of the information letter, detailing the purpose and nature of the experiment, and a consent form (see Appendix D). Once the participant had given their informed consent, they were asked to complete the Pain Catastrophizing Scale (Sullivan et al., 1995) (see Appendix E).

The Pain Catastrophizing Scale is a thirteen-item measure, which asks the individual to reflect on a previous painful experience, and rate to what degree they experience a number of thoughts and feelings whilst experiencing pain, on a scale from 0 (not at all) to 4 (all the time). The thirteen items are divided into three subscales – magnification, rumination, and helplessness. A total score is computed by summing the individual's responses to all thirteen items, with possible scores ranging from 0-52. The three-factor model of pain catastrophizing has been successfully replicated in a number of factor analyses (Osman et al., 1997; Van Damme, Crombez & Eccleston, 2002), and the scale demonstrates adequate to excellent internal consistency ($\alpha = .87$), and high test-retest reliability ($r = .75$) (Sullivan et al., 1995).

Human skin has a natural resistance to electricity, which can be exacerbated by a higher level of dead cells. Therefore, in order to minimize skin electrical resistance and reduce its role as a confounding variable, the test sites – namely, the ventral forearms, the supraorbital region, orbicularis oculi muscles, and a site behind the ear – were cleansed and exfoliated using a combination of pumice stone and alcohol wipes. The participant was then directed to a comfortable armchair, where they remained seated for the remainder of the procedure.

Psychophysical tests. Measurements of sensitivity to blunt pressure, and mild sharpness were taken from both ventral forearms, and each side of the forehead. One forearm was assigned as the test arm. Sensitivity to blunt pressure, and mild sharpness were collected from two areas on this forearm – a primary area, and an area approximately 1 cm distal termed the secondary area. In the control arm, an area equivalent to the primary site also underwent psychophysical testing. The laterality of the test and control sites was counter-balanced across participants, in order to minimize order effects. Measurements were taken from an equivalent area on each side of the forehead.

Sharpness. A 10g von Frey monofilament (Neuro-pen, Owen Mumford, USA) was used to assess sensitivity to mild sharpness. The instrument was applied perpendicular to the surface of the skin, with sufficient pressure to bend the monofilament for 1 second. To induce a slightly more intense sharpness, a sharp tip with a calibrated spring mechanism exerting a force of 40g (Neuro-pen, Owen Mumford, USA) was applied for two seconds. Participants reported feelings of pain and sharpness after each presentation of a stimulus, using a verbal rating scale, ranging from 0 (indicating no pain/no sharpness) to 10 (indicating extreme pain/extreme sharpness).

Prior to commencing testing, participants were trained to give consistent ratings to the psychophysical stimuli.

Pressure-pain. To assess sensitivity to pressure-pain, an algometer with a 8mm diameter rubber tip (FDX, Wagner Instruments, USA) was applied perpendicular to the surface of the skin, by exerting a force of 100g/s until the participant reported pain. Digital readings from an algometer have been found to provide valid measurements of pressure-pain thresholds in previous studies (Kinser, Sands & Stone, 2009).

The order of presentation for each stimulus was standardized across all experiments, with each test performed only once each round, except when the measures taken from the same test site differed by more than 2 points during baseline. In this instance, the final measurement was the average of the two readings. Psychophysical testing was conducted at baseline (prior to the participant undergoing HFS), and repeated ten minutes following electrical conditioning, with the exception of pressure-pain threshold, which was also measured after one minute.

Blink reflex and acoustic stimulation. In order to evoke a blink reflex, two electrodes were attached to the supraorbital region on each side of the forehead with adhesive tape. Stimulation was delivered using two custom-built concentric electrodes, composed of a copper wire cathode centred within a ring-shaped stainless steel anode with an inner diameter of 10mm and an outer diameter of 20mm.

Modified disposable Cleartrode electrodes (ConMed Corporation, NY, USA) were used to record electromyographic (EMG) data. Relative to other methods, EMG provides a more advanced method of detecting action potentials produced by the blink reflex, and is unobtrusive (Davis & Heninger, 1972; Blumenthal et al., 2005). Four of the electrodes were attached to the orbicularis oculi muscles of the lower eyelid, and the outer corner of each eye. One ground electrode was attached behind the right ear (see

Appendix E). Electrical signals produced by the muscles were amplified using an electromyographic bio-potential amplifier (Biopac Systems, Inc., USA). An MP 100 Biopac Systems Analogue/Digital Channel receptor interpreted the data at 2,000 Hz (Biopac Systems, Inc., USA), and this information was then displayed on a computer monitor via AcqKnowledge software (Biopac Systems, Inc., USA).

Electrical stimuli consisted of a triple-pulse train with 0.5ms pulse duration, and an inter-pulse interval of 5ms, delivered at 2mA. Triple-pulse stimulation is more suited to examining nociceptive pathways relative to single pulse, as it increases the sensation of pain and consistently elicits a blink reflex waveform (Giffin et al., 2004).

Tone bursts were generated using a Biopac STM 100 module (Biopac Systems, Inc., USA), and data was recorded using the Biopac MP150 system (Biopac Systems, Inc., USA). Tones were delivered to both ears concurrently, at 95dBA for a duration of 3ms through 3M Eartone insert earphones (Etymotic Research, Inc., USA). At this intensity, acoustic stimuli are able to reliably elicit a startle response (Davis, 1984), and provide a direct and clinically relevant method of evoking sympathetic arousal (Drummond et al., 2001).

Stimulus presentation. Each participant received a total of 100 bursts of stimulation, distributed evenly across the baseline and experimental phase. Stimulation consisted of a mixture of supraorbital stimulation presented alone (ipsilateral or contralateral to HFS), acoustic stimulation presented alone, or supraorbital and acoustic stimulation presented concurrently (ipsilateral or contralateral to HFS). On trials in which both stimuli were presented, the tone burst was delivered 9ms before the electrical stimulation. The sequence order was randomized prior to conducting testing, and was standardized across all participants (see Appendix G). Participants were unaware of the order of presentation.

Rating scale to supraorbital stimulation (without audio). Following the presentation of the electrical stimulus, participants were required to report which side of the forehead the stimulus was presented (i.e. left or right), and rate pain and sharpness along a scale of 0 (no pain/sharpness) to 10 (extreme pain/sharpness).

Rating scale to acoustic stimulation (without electrical). Following presentation of the acoustic stimulus, participants were required to report loudness and discomfort along a scale of 0 (no loudness/discomfort) to 10 (extreme loudness/discomfort). By asking participants to rate loudness and discomfort, the role of attention as a confound was reduced, as they were required to keep their full attention on the presentation of the stimulus.

Rating scale to concurrent stimulation. When electrical and acoustic stimuli were presented concurrently, participants were asked to report which side of the forehead the supraorbital stimulation was presented, and rate pain, sharpness, loudness, and discomfort along a scale of 0 (no pain/sharpness/loudness/discomfort) to 10 (extreme pain/sharpness/loudness/discomfort), in that order.

Electrical detection threshold (EDT) and high frequency electrical stimulation. An individual's EDT represents the lowest intensity in which he/she is able to detect an electrical stimulus. A constant current stimulator (DS7A, Digimeter, Welwyn Garden City, UK) was used to generate the electrical stimuli, which were delivered via a custom built electrode, consisting of 24 copper pins with 0.2mm diameter tips mounted on a 2cm x 3cm Perspex block, such that the tips projected 0.5mm from the surface of the block. Research suggests that these characteristics are able to preferentially activate superficial A-delta and C fibres (Inui, Tran, Hoshiyama & Kakigi, 2000; Nilsson, Levinsson & Schouenborg, 1997).

To determine the EDT, the method of limits was employed. Beginning at 1.0mA, the researcher decreased the intensity of the stimulus by 0.1mA, until the participant was no longer able to perceive the stimulus. The researcher then increased the intensity by 0.1mA, and decreased in steps of 0.05mA, until the participant was again no longer able to perceive the stimulus. This procedure was then repeated, and the EDT was defined as the mean of the two stimulus intensities.

The current intensity of the HFS would be the EDT multiplied by 20 (up to a maximum of 8mA). This procedure consisted of five 1-sec bursts of electrical stimulation (100Hz, 2ms pulse width) with a 9-sec rest between each burst (Klein et al., 2008; Lang et al., 2007). Following each burst, the participant reported pain, sharpness and unpleasantness along a scale of 0 (no pain/sharpness/unpleasantness) to 10 (extreme pain/sharpness/unpleasantness).

Data Filtering and Reduction

Using the Acqknowledge software (Biopac Systems, Inc., USA), the EMG waveforms were filtered through a high pass filter with a cut-off frequency of 20 Hz, in order to remove electrical noise. A band-stop filter with a range of 49.5 to 50.5 Hz was then also applied to these wavelengths. The audio wavelengths were filtered using a low pass filter with a cut-off frequency of 250 Hz.

The computer program “Blinky Bill” was used to extract the amplitude (i.e. area under the curve (AUC) V/s) of the R2 component of each blink reflex. This was measured between 27 and 87ms after the stimulus onset (Ellrich & Treede, 1998). In addition, the R2 AUC of all blink reflexes administered after HFS conditioning, were expressed as a percentage of the AUC of the blink reflexes administered at baseline (before HFS conditioning) to compare the changes.

Statistical Analyses

Primary and secondary hyperalgesia. Changes in sensitivity to mild sharpness, and pressure-pain at the primary, secondary and control areas were examined in a repeated measures analysis of variance (ANOVA), to determine whether HFS was able to evoke central sensitization. Between-subjects variables were Time (before vs after HFS) and Site (primary, secondary, or control).

Forehead sensitivity. Changes in sensitivity to mild sharpness, and pressure-pain between the ipsilateral and contralateral (to HFS) side of the forehead were examined using repeated measures ANOVA. Between-subjects variables were Time (before vs after HFS) and Side (ipsilateral vs contralateral).

Supraorbital and acoustic stimulation. Based on the laterality to the experimental forearm and to the supraorbital stimulus, blink reflexes were classified as: 'ii' (ipsilateral to both electrical conditioning, and supraorbital stimulation), 'cc' (contralateral to both electrical conditioning, and supraorbital stimulation), 'ic' (ipsilateral to electrical conditioning, and contralateral to supraorbital stimulation), or 'ci' (contralateral to electrical conditioning, and ipsilateral to supraorbital stimulation).

Effects of arousal prior to HFS. A repeated measures ANOVA, with the between subject variables of Side (ipsilateral vs contralateral) and Audio (no audio vs audio), was conducted to assess the effects of sympathetic arousal on subjective ratings of pain and sharpness to supraorbital stimulation. To test for significant differences in R2 onset latency and AUC, a repeated-measures ANOVA was employed with between subject variables of Side (ipsilateral vs contralateral), Response (ipsilateral vs contralateral), and Audio (no audio vs audio).

Effects of arousal following HFS. A repeated measures ANOVA, with the between subject variables of Time (baseline vs after HFS), Side (ipsilateral vs

contralateral), and Audio (no audio vs audio), was conducted to assess the effects of sympathetic arousal on subjective ratings of pain and sharpness to supraorbital stimulation, in the presence of central sensitization. To test for significant differences in R2 onset latency and AUC at baseline and following HFS, a repeated-measures ANOVA was employed with between subject variables of Time (baseline vs after HFS), Side (ipsilateral vs contralateral), Response (ipsilateral vs contralateral), and Audio (no audio vs audio).

Catastrophizing. To assess whether an individual's level of pain catastrophizing influenced sensitivity to supraorbital stimuli during sympathetic arousal, each participant was coded as either 'low' or 'high' in catastrophizing based on the average PCS score for the sample. This variable was then included as a between-subjects factor, as opposed to a covariate, as the assumption that the variable was constant across all participants was not met.

Results

Assumption Testing for ANOVA

The following statistical analyses were completed in order to ensure the data complied with the assumptions underlying repeated-measures ANOVA. Due to the small sample size ($N = 21$), normality of scores was assessed using Shapiro-Wilk and visual inspection of boxplots. On several variables this assumption was not satisfied. As ANOVA is robust against moderate violations of normality, those encroachments were not considered to be a threat to the interpretation of analyses (Tabachnick & Fidell, 2007) (see Appendix H for a full list of violations).

Homogeneity of variance was assessed using the Fmax test ($F_{max} = \text{largest sample variance/smallest sample variance}$). According to Tabachnick and Fidell (2007), an Fmax statistic equalling less than ten indicates that the variability in each set of

scores is approximately equal, meaning the assumption has been met (Tabachnick & Fidell, 2007). Appendix I indicates that the assumption was not violated for any test.

In the instance that a factor had more than two levels, Mauchly's Test of Sphericity was used to test the sphericity assumption. When the assumption was violated, the degrees of freedom were adjusted using the Huynh-Feldt Epsilon, as recommended by Tabachnick and Fidell (2007) (see Appendix J for list of adjusted outputs).

Electrical Detection Threshold (EDT)

EDT ranged from .08 to .99 mA ($M = .46$, $SD = .31$), with calculated high frequency stimulation frequencies ranging from 1.6 to 8 mA ($M = 6.01$, $SD = 2.53$). The average pain, sharpness and unpleasantness ratings to high frequency electrical stimulation were $M = 6.13$ ($SD = 2.36$), $M = 6.32$ ($SD = 2.33$), and $M = 6.6$ ($SD = 2.69$) respectively.

Forearm Sensitivity following High Frequency Electrical Stimulation

Sensitivity to von Frey's monofilament. Subjective ratings of pain (main effect for Time: $F(1, 20) = 14.057$, $p = .001$; main effect for Site: $F(1.563, 31.258) = 11.194$, $p = .001$; Time x Site interaction: $F(1.293, 25.851) = 11.011$, $p = .001$) and sharpness (main effect for Time: $F(1, 20) = 9.933$, $p = .005$; main effect for Site: $F(2, 40) = 7.659$, $p = .002$; Time x Site interaction: $F(2, 40) = 7.042$, $p = .002$) to von Frey's monofilament increased significantly at the primary and secondary areas, following high frequency electrical stimulation (see Figure 1).

Post hoc tests revealed pain and sharpness ratings at the control site (Pain: $M = .33$, $SD = .66$; Sharpness: $M = .76$, $SD = .77$) differed significantly from the primary (Pain: $M = 1.14$, $SD = 1.28$; Sharpness: $M = 2.05$, $SD = 1.91$) and secondary areas

(Pain: $M = 1.1$, $SD = 1.38$; Sharpness: $M = 1.86$, $SD = 1.71$). There were no significant differences between the primary and secondary sites for pain or sharpness.

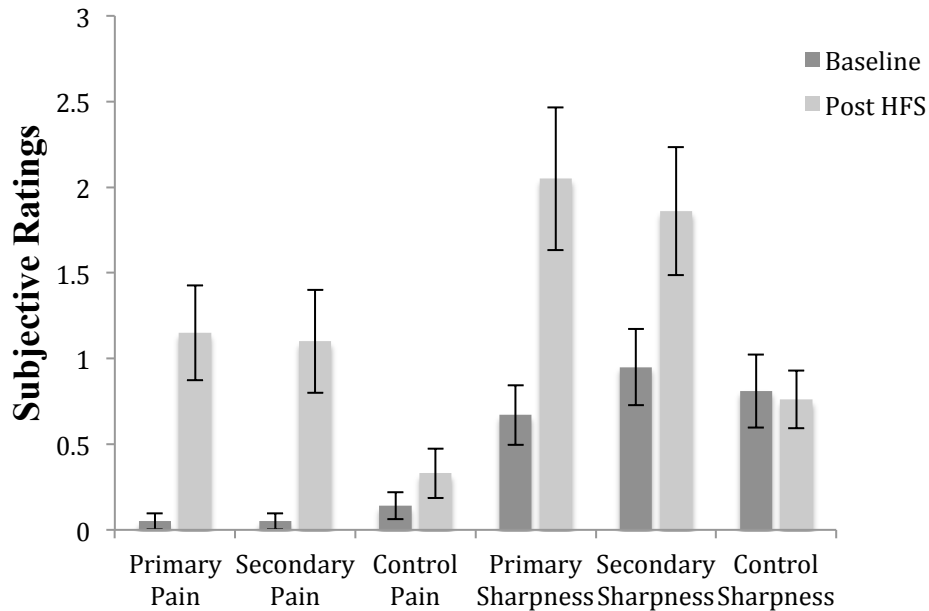


Figure 1. Mean pain and sharpness ratings to von Frey's monofilament at the primary, secondary and control areas of the forearm, before and after conditioning. Error bars denote standard error.

Sensitivity to pinprick. Subjective ratings of pain (main effect for Time: $F(1, 20) = 9.069$, $p = .007$; main effect for Site: $F(2, 40) = 6.362$, $p = .004$; Time x Site interaction: $F(1.439, 28.789) = 5.989$, $p = .012$) and sharpness (main effect for Time: $F(1, 20) = 6.558$, $p = .019$; main effect for Site: $F(2, 40) = 10.677$, $p < .001$; Time x Site interaction: $F(2, 40) = 7.202$, $p = .002$) to pinprick increased significantly at the primary and secondary areas, following high frequency electrical stimulation (see Figure 2).

Post hoc tests revealed pain ratings at the control site ($M = 1$, $SD = .95$) differed significantly from the primary ($M = 2.24$, $SD = 1.87$), but not the secondary areas ($M = 2.05$, $SD = 1.94$). However, sharpness ratings at the control site ($M = 1.62$, $SD = 1.43$)

differed significantly from both the primary ($M = 3$, $SD = 2.19$) and secondary areas ($M = 2.62$, $SD = 2.31$). There were no differences between the primary or secondary areas for pain or sharpness.

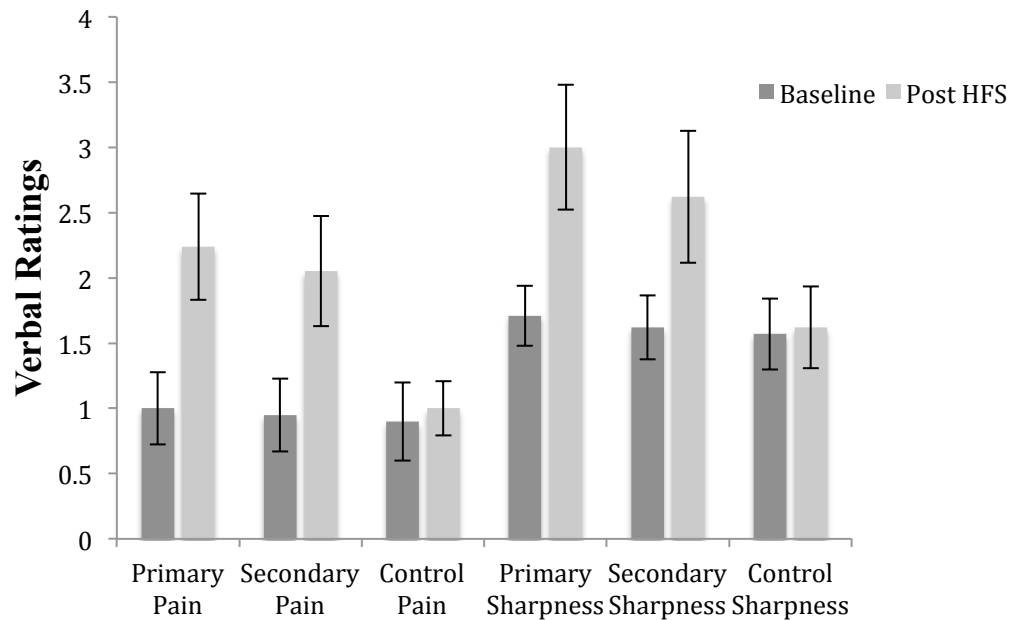


Figure 2. Mean pain and sharpness ratings to pinprick at the primary, secondary, and control areas of the forearm, before and after HFS. Error bars denote standard error.

Pressure-pain threshold. Pressure-pain sensitivity decreased marginally at the primary and secondary areas of the forearm, and increased slightly at the control site following conditioning. None of the effects that involved Time or Side were statistically significant (see Figure 3).

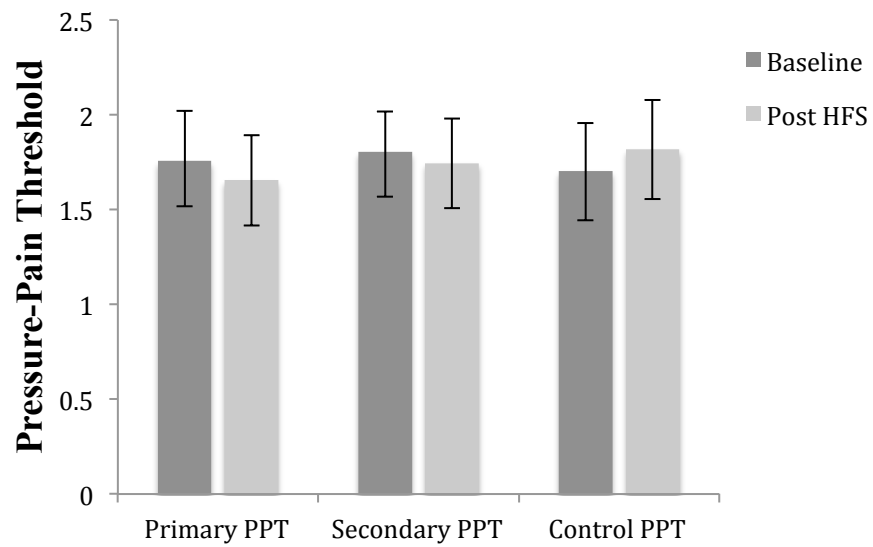


Figure 3. Mean PPT for the primary, secondary, and control areas of the forearm, following HFS. Error bars denote standard error.

Forehead Sensitivity following High Frequency Electrical Stimulation

Sensitivity to von Frey’s monofilament. Subjective ratings of pain and sharpness to von Frey’s monofilament increased on both sides of the forehead, following conditioning, but none of the effects that involved Time or Side were statistically significant (see Figure 4).

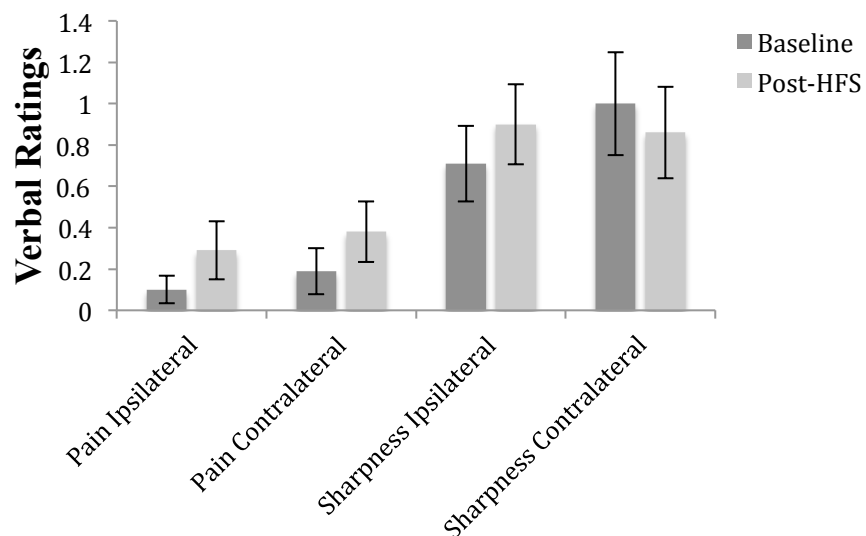


Figure 4. Mean ratings of pain and sharpness to von Frey's monofilament on the ipsilateral and contralateral (to HFS) sides of the forehead, before and after conditioning. Error bars denote standard error.

Sensitivity to pinprick. Subjective ratings of pain to pinprick increased bilaterally following conditioning. However, ratings of sharpness decreased on the ipsilateral, and increased on the contralateral sides of the forehead. None of the effects that involved Time or Side were statistically significant (see Figure 5).

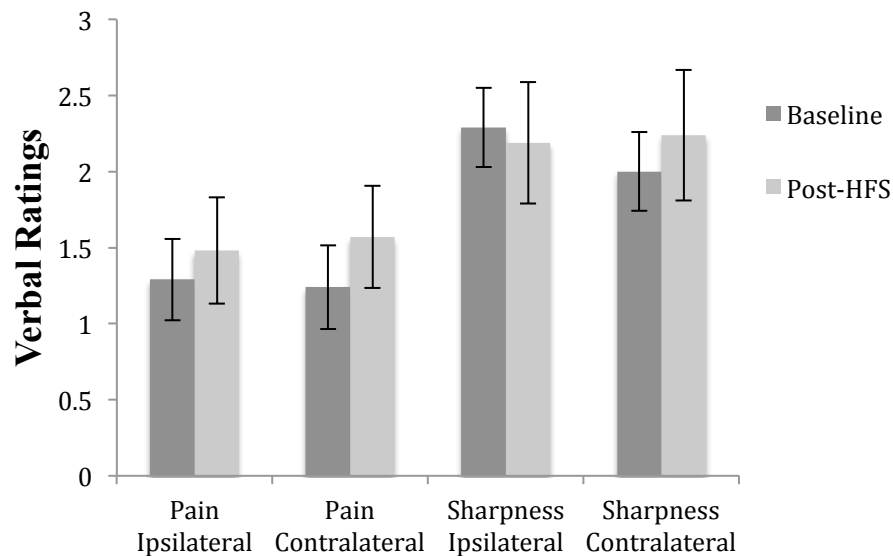


Figure 5. Mean ratings of pain and sharpness to pinprick on the ipsilateral and contralateral sides of the forehead, before and after conditioning. Error bars denote standard error.

Pressure pain threshold. There was a significant interaction between Time and Side, indicating that HFS beared some effect on pressure-pain sensitivity in the forehead (Time x Side interaction: $F(2, 40) = 3.282, p = .048$). Pressure-pain threshold decreased on the ipsilateral ($M = .991, SD = .464$), and increased on the contralateral side of the

forehead ($M = 1.074$, $SD = .438$), one minute following high frequency electrical stimulation. However, this effect was reversed after ten minutes, as pressure-pain threshold increased on the ipsilateral ($M = 1.111$, $SD = .556$) and decreased marginally on the contralateral sides of the forehead ($M = 1.045$, $SD = .428$). Overall, there was a bilateral increase in pressure-pain (indicating decreased sensitivity to blunt pressure) relative to baseline, which was more pronounced on the ipsilateral side of the forehead. (see Figure 6).

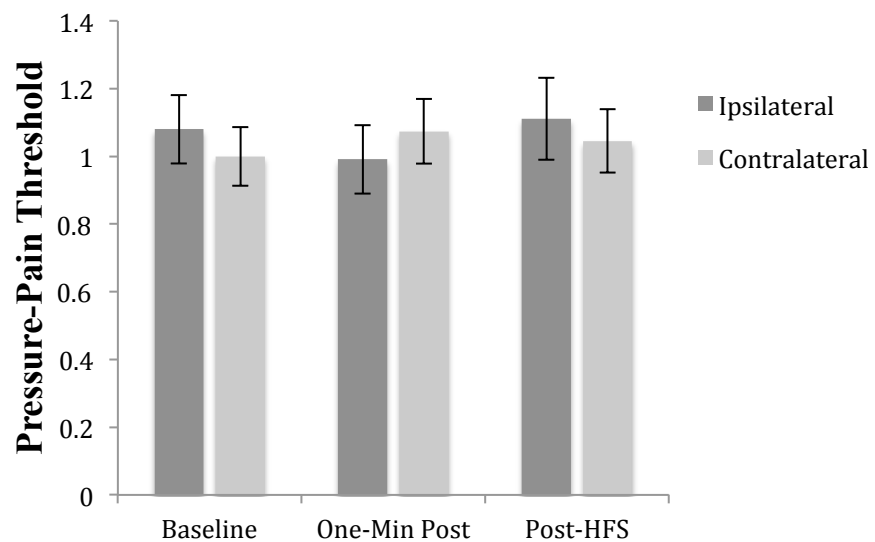


Figure 6. Mean PPT on the ipsilateral and contralateral sides of the forehead, recorded at baseline, one minute following conditioning, and ten minutes following conditioning. Error bars denote standard error.

Effects of Arousal Prior to Conditioning

Subjective Ratings. Participants reported significantly higher ratings of pain and sharpness, when a supraorbital stimulus was presented with audio (Pain: $M = 3.138$, $SD = 1.54$; Sharpness: $M = 4.145$, $SD = 1.6$), relative to when supraorbital stimulation was presented alone (Pain: $M = 2.898$, $SD = 1.45$; Sharpness: $M = 3.781$, $SD = 1.46$),

irrespective of the laterality (Pain: $F(1, 20) = 4.504, p = .047$; Sharpness: $F(1,20) = 7.023, p = .015$) (see Figure 7).

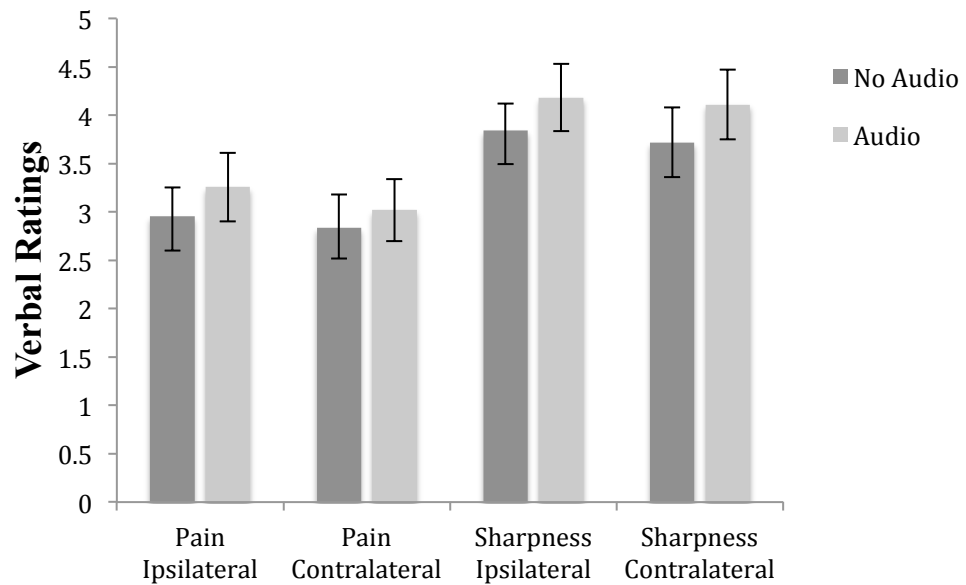


Figure 7. Mean ratings of pain and sharpness to supraorbital stimuli presented to the ipsilateral or contralateral side of the forehead, with or without audio, prior to HFS. Error bars denote standard error.

R2 Onset Latency. There was a significant main effect for Audio ($F(1, 20) = 35.280, p < .001$). R2 onset latency was significantly shorter when supraorbital and audio stimuli were presented concurrently ($M = 38.067, SD = 5.36$), relative to supraorbital stimulation presented alone ($M = 44.551, SD = 7.83$). Main effect for side was insignificant (see Figure 8).

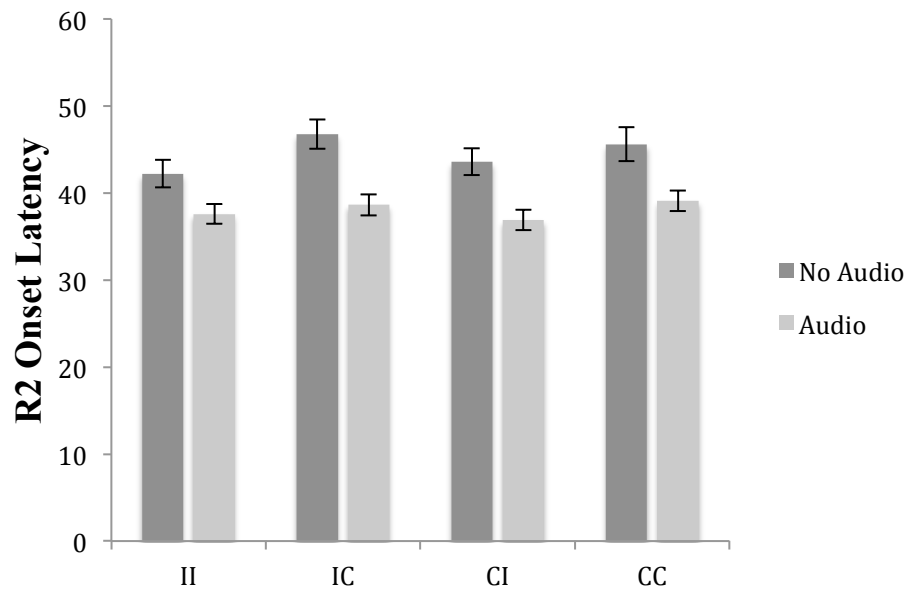


Figure 8. Mean R2 onset latency for blink reflexes measured: II (ipsilateral to HFS, ipsilateral to supraorbital stimulation), IC (ipsilateral to HFS, contralateral to supraorbital stimulation), CI (contralateral to HFS, ipsilateral to supraorbital stimulation) and CC (contralateral to HFS, contralateral to supraorbital stimulation), with or without audio. Error bars denote standard error.

R2 AUC. There was a significant main effect for Audio ($F(1, 20) = 94.417, p < .001$), with concurrent supraorbital and audio stimulation eliciting greater R2 AUC amplitude ($M = .002034, SD = .001074$) relative to supraorbital stimulation presented alone ($M = .001324, SD = .000863$). The main effect for Side was insignificant (see Figure 9).

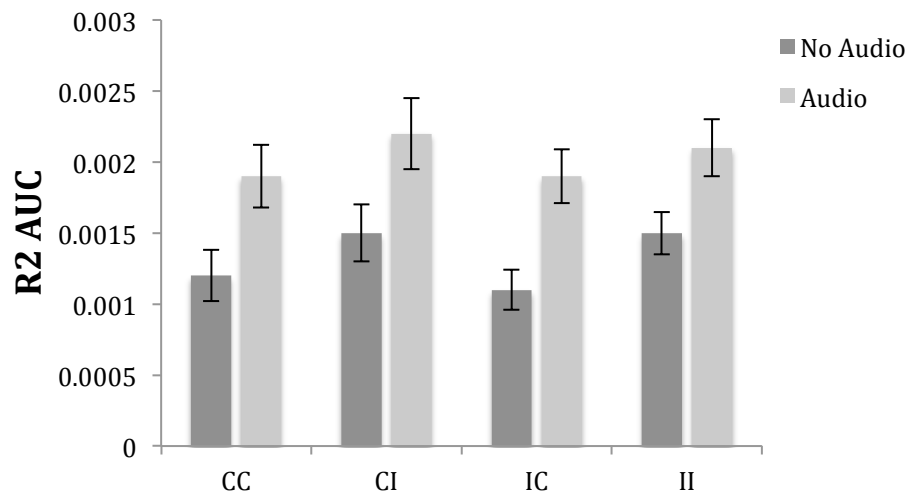


Figure 9. R2 AUC for blink reflexes measured: II, IC, CI, and CC, with or without audio. Error bars denote standard error.

Effects of Arousal Following Electrical Conditioning

Ratings of pain and sharpness to supraorbital stimuli. There was a significant main effect for Audio for both pain and sharpness ratings to supraorbital stimulation of the forehead (pain: $F(1, 20) = 8.534, p = .008$; sharpness: $F(1, 20) = 9.567, p = .006$). Post-hoc tests revealed ratings of pain and sharpness were significantly higher when supraorbital and acoustic stimulation were presented concurrently (pain: $M = 3.067, SD = 1.74$; sharpness: $M = 4.102, SD = 1.95$) relative to when the electrical stimulus was presented alone (pain: $M = 2.824, SD = 1.63$; sharpness: $M = 3.795, SD = 1.86$), irrespective of forearm conditioning.

For pain, no effects involving Time or Side were found to be significant, indicating that subjective ratings of pain to supraorbital stimuli presented to the forehead remained constant irrespective of conditioning, or laterality. There was a significant Time x Side interaction ($F(1, 20) = 4.523, p = .046$) for sharpness, with

ratings of sharpness decreasing on the contralateral (Baseline: $M = 3.914$, $SD = 1.64$; Post-HFS: $M = 3.726$, $SD = 2.24$) and increasing on the ipsilateral side of the forehead (Baseline: $M = 4.01$, $SD = 1.43$; Post-HFS: $M = 4.143$, $SD = 2.32$) following conditioning, irrespective of acoustic stimulation (see Appendix K).

R2 Onset Latency. R2 onset latency was significantly shorter when measured ipsilateral ($M = 42.98$, $SD = 6.82$) relative to contralateral to supraorbital stimulation presented alone ($M = 46.09$, $SD = 7.55$). Audio led to a significant decrease in onset for both variables, with this interaction being more pronounced for ipsilateral ($M = 37.58$, $SD = 5.19$) in comparison to contralateral responses ($M = 39.3$, $SD = 5.71$), irrespective of conditioning (main effect for Audio: $F(1, 20) = 43.51$, $p < .001$; main effect for Response: $F(1, 20) = 73.4$, $p < .001$; Response x Audio interaction: $F(1, 20) = 23.65$, $p < .001$) (see Figure 10).

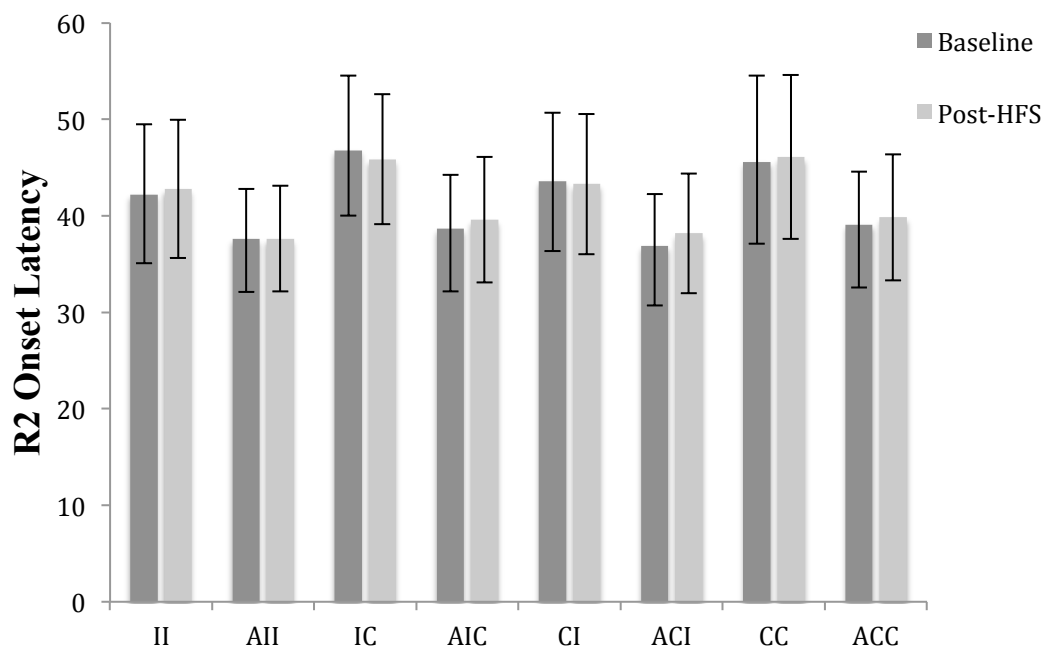


Figure 10. Mean R2 onset latency measured: II, IC, CI, and CC, with or without audio, before and after HFS. Error bars denote standard error.

R2 AUC. Prior to HFS, concurrent electrical and acoustic stimulation was associated with significantly higher R2 AUC amplitude ($M = .002$, $SD = .00019$) relative to supraorbital stimulation alone ($M = .0013$, $SD = .00015$). Following conditioning, R2 AUC decreased for both the no audio ($M = .0012$, $SD = .00015$) and audio conditions ($M = .0018$, $SD = .00016$), though acoustic stimulation was still significantly associated with higher R2 AUC amplitude (main effect for Time: $F(1, 20) = 8.44$, $p = .009$; main effect for Audio: $F(1, 20) = 96.7$, $p < .001$; Time x Audio interaction: $F(1, 20) = 6.91$, $p = .016$). No further effects involving Time or Side were statistically significant (see Appendix L).

Catastrophizing

Analysis of the means revealed subjective ratings of pain to supraorbital stimulation decreased following electrical conditioning for participants high in catastrophizing (Baseline: $M = 3.23$, $SD = 1.73$; Post-HFS: $M = 2.93$, $SD = 1.91$), whilst remaining stable for those low in catastrophizing (Baseline: $M = 2.83$, $SD = 1.22$; Post-HFS: $M = 2.82$, $SD = 1.85$). High catastrophizers reported higher levels of pain to concurrent stimulation ($M = 3.19$, $SD = 1.84$) relative to low catastrophizers ($M = 2.96$, $SD = 1.66$). However, no effects involving Catastrophizing were found to be statistically significant (see Appendix M).

Discussion

The main aim of the current study was to explore the effects of sympathetic arousal on a healthy individual's experience of pain, and how the presence of central sensitization, experimentally induced using electrical conditioning of the forearm, affects this interaction. In order to test this relationship, pain evoked by supraorbital stimulation with or without concurrent acoustic stimulation was assessed before and after electrical conditioning of the forearm (intended to induce central sensitization) in

order to compare changes in processing of noxious stimuli caused by disrupted pain processing. By gaining a better understanding of this interaction, researchers are better able to understand mechanisms that produce signs of persistent central sensitization in chronic pain conditions.

Hypothesis One: Primary and Secondary Hyperalgesia

In order to draw valid conclusions about the effects of central sensitization on the perception of pain during sympathetic arousal, it was first necessary to ensure HFS was able to evoke the expected changes to central signaling processes, in line with primary and secondary hyperalgesia. It was hypothesized that following electrical conditioning, subjective ratings of pain and sharpness in response to mechanical punctuate stimuli would increase at the primary and secondary areas in the forearm, whilst remaining stable at the control site.

This hypothesis was supported, as both ratings of pain and sharpness to von Frey's monofilament and pinprick increased significantly at the primary and secondary sites from baseline. In particular, post-hoc tests revealed that pain and sharpness ratings at the primary and secondary sites were significantly higher than at the control area following HFS conditioning. These findings support previous studies, in which hyperalgesia to sharp stimuli was found to develop at the site of electrical stimulation as well as the adjacent areas (Klein et al., 2008; Lang et al., 2007; Pfau et al., 2011; Vo & Drummond, 2013). Furthermore, the lack of a significant effect of HFS on sensitivity to blunt pressure in this research study is also in line with previous studies (Vo & Drummond, 2014a).

Hypothesis Two: Forehead Analgesia to Pressure-Pain

It was further hypothesized that HFS would evoke bilateral analgesia to blunt pressure-pain, with the decrease in sensitivity being more pronounced on the side of the

forehead ipsilateral to electrical conditioning. As pain originating from deep tissues is associated with activity in different brain structures than stimulation of superficial tissues (Henderson, Bandler, Gandevia & Macefield, 2006; Takahashi et al., 2011; Uematsu, Shibata, Miyauchi & Mashimo, 2011), it was hypothesized that pain ratings would remain unchanged across other sensory modalities.

Results supported these hypotheses, as pressure-pain threshold increased bilaterally, ten minutes following HFS, indicating a decreased sensitivity to blunt pressure but not other sensory modalities. Furthermore, results suggested a trend toward pronounced ipsilateral forehead analgesia, though this effect did not reach significance, possibly due to small sample size. Changes to subjective ratings of pain and sharpness ratings to von Frey's monofilament and pinprick were non-significant, reinforcing the dissociation between superficial and deep nociceptive pathways.

These findings are in line with previous research, in which various forms of limb pain have been found to evoke analgesia to pressure-pain on the forehead, with the effect being more pronounced on the ipsilateral than contralateral side of the forehead (Knudsen & Drummond, 2009; Knudsen & Drummond, 2011; Vo & Drummond, 2013) and dissociated from pain in other sensory modalities (Vo & Drummond, 2014a).

It is believed that the bilateral analgesic response is in part mediated by central pain inhibitory mechanisms, such as stress-induced analgesia (Chesher & Chan, 1977; Gamaro et al., 1998; Janssen et al., 1998; Willer, Dehen & Cambier, 1981) or diffuse noxious inhibitory controls (Villanueva & Le Bars, 1994). The mechanism underlying exacerbated ipsilateral forehead analgesia is less certain, though it has been suggested that stimulation of A-delta and C fibres can trigger a pain inhibitory pathway descending from the locus coeruleus (Hitoto, Tsuruoka, Hiruma & Matsui, 1998; Men & Matsui, 1994). This pathway acts on dynamic range neurons in the dorsal horn of the

spinal cord, suppressing nociceptive activity by acting on adrenoreceptors (Bouhassira, Le Bars, Villanueva, 1987; Jones & Gebhart, 1986; Rahman, D'Mello & Dickenson, 2008; Sluka & Westlund, 1992). Support for this mechanism comes from animal studies, in which noradrenaline increased in the dorsal horn ipsilateral to a hindpaw inflamed by carrageenan but not contralaterally (Tsuruoka, Hitoto, Hiruma & Matsui, 1999), suggesting that the adrenergic pathway was active only in the ipsilateral dorsal horn (Tsuruoka, Matsutani & Inoue, 2003).

Hypothesis Three: Effects of Arousal on Pain Perception Prior to HFS

As sympathetic activation forms parts of the descending inhibitory control pathway that suppresses pain (Millan, 2002; Tracey & Mantyh, 2007), it was hypothesized that arousal, evoked through presentation of an audio stimulus, would decrease sensitivity to electrical supraorbital stimulation, prior to HFS. Contrary to the hypothesized outcome, subjective ratings of pain and sharpness were significantly higher when supraorbital stimulation was paired with acoustic startle stimulus.

These findings are contrary to literature suggesting arousal inhibits nociceptive and pain-like responses (Bobey & Davidson, 1970; Malow, 1981; Rhudy, France, Bartley, McCabe & Williams, 2009; Rhudy & Meagher, 2000). Rhudy and Meagher (2001) provide one possible explanation, proposing a differentiation between high-intensity imminent threats, which activate acute defensive systems leading to pain inhibition, and unpredictable anxiety-provoking threats, which may result in pain facilitation. According to this theory, an environment containing unpredictable, moderately aversive threats would be expected to enhance an individual's experience of pain.

Hubbard et al. (2011) provide support for this differentiation, showing that aversive, unpredictable threats enhanced the nociceptive reflex. They suggested this

anxiety-enhanced nociceptive response might be due to withdrawal of descending inhibitory influences, or an increase in descending facilitation by supraspinal centers involved in arousal, threat detection, and affect-driven responses. To investigate the possibility that anticipation of acoustic startle may have augmented pain responses in the current study, blink latencies and R2 AUC at baseline were analysed using a two-way ANOVA. When supraorbital stimulation was paired with acoustic startle, R2 onset latency was significantly shorter than when electrical stimulation was presented alone. Similarly, R2 AUC increased during trials involving concurrent presentation of electrical and audio stimuli.

In order to confirm this possible association, future research should include measures of the R3 component of the nociceptive blink reflex. Ellrich, Katsarava Przywara and Kaube (2001) suggest that R3 may form part of the startle reaction, due to findings that awareness of the upcoming presentation of a noxious stimulus can result in total suppression of the reflex. Studies have found an association between heightened startle reactivity, and anticipatory threat of an aversive stimulus (Grillon & Davis, 1995). Grillon, Ameli, Woods, Merikangas & Davis (1991) found acoustic startle responses were facilitated during periods in which there was a possibility of a mild, but aversive electric shock relative to periods in which there was no possibility of shock. Bradley, Silakowski & Lang (2008) also found enhanced startle reflex and heightened autonomic arousal, during times of perceived threat.

During the current study participants were unaware of the order of presentation of the aversive stimuli, meaning that they were unsure whether they would receive an audio stimulus or supraorbital stimulation alone, or both concurrently. Therefore, the unpredictability of the moderately aversive stimuli could have resulted in pain facilitation. Future research examining startle reactivity, measured through the R3

component of the nociceptive blink reflex, is needed in order to appropriately test this possibility.

Hypothesis Four: Effects of Arousal on Pain Perception Following HFS

In line with previous research (Vo & Drummond, 2014a), it was hypothesized that electrical conditioning of the forearm would result in a reduction in R2 AUC of blink reflexes contralateral to HFS, and an increase in R2 AUC ipsilateral to HFS. This hypothesis was not supported as electrical conditioning of the forearm had no significant impact on R2 AUC amplitude for blink reflexes measured ipsilateral or contralateral to HFS.

These findings are at odds with previous studies. Due to mechanisms such as DNIC, application of noxious stimuli (such as HFS) applied to one area of the body is able to reduce pain perception at a different, remote site of the body (Quartana, Campbell & Edwards, 2009). Under certain conditions, facilitatory adrenergic influences mediated by cortical areas such as the midbrain, pons, and rostral ventromedial medulla (Urban and Gebhart, 1999; Vera-Portocarrero et al., 2006; Torsney, 2011; Millan, 2002; Drummond, 2012), are able to overcome descending supraspinal inhibitory influences (Brightwell & Taylor, 2009; Jeong & Holden, 2009; Makino, Kohase, Sanada & Umino, 2010; Martins et al., 2010; Taylor, Roderick & Basbaum, 2000), thus accounting for the ipsilateral increase in R2 AUC. It is possible that conditions needed to evoke facilitatory adrenergic influences were not met in the current study. As the previous study did not include audio as a variable, it is possible acoustic stimulation may account for this discrepancy. To test this theory a repeated-measures ANOVA was conducted, excluding conditions including audio for R2 AUC data. However, even when audio was removed as a variable, electrical conditioning still failed to elicit significant changes in R2 AUC amplitude for blink reflexes ipsilateral or

contralateral to HFS. Further research is needed to investigate factors that may mediate facilitatory adrenergic influences in the presence of central sensitization.

It was further hypothesized that, following electrical conditioning, arousal would result in shorter R2 onset latency and greater R2 AUC amplitude relative to baseline. This hypothesis was not supported. HFS was significantly associated with a decrease in R2 AUC for both the no audio (i.e. II, IC, CI and CC) and audio (i.e. A_II, A_IC, A_CI and A_CC) conditions, although concurrent stimulation still evoked greater AUC amplitude relative to supraorbital stimulation alone following this decrease. Arousal was significantly associated with shorter R2 onset latency and increased sensitivity to pain and sharpness relative to supraorbital stimulation alone. However, HFS had no significant impact on this interaction, suggesting central sensitization did not increase sensitivity to nociceptive stimuli during sympathetic arousal, as hypothesized.

These findings have several implications. According to the model of adrenergic supersensitivity (Bruehl & Chung, 2006) following electrical conditioning of the forearm, sensitized nerves should develop hypersensitivity to adrenergic excitation (Drummond et al., 1991; Harden et al., 1994), resulting in increased nociceptive firing in response to catecholamines, such as adrenaline and noradrenaline, and the maintenance of central sensitization (Gracely et al., 1992; Woolf et al., 1992). As acoustic stimulation is able to evoke a state of sympathetic arousal (Light et al., 1998; Tsigos et al., 1993), therefore increasing the levels of circulating catecholamines, participants would be expected to report higher levels of pain and heightened nociceptive reflexes to concurrent supraorbital and acoustic stimulation. Whilst arousal was able to evoke greater R2 AUC amplitude, shorter R2 onset latency and heightened

sensitivity to pain, these effects were independent of HFS meaning central sensitization did not increase sensitivity to circulating catecholamines as predicted.

It is speculated that increased synaptic concentrations of noradrenaline in central nociceptive pathways may contribute to facilitation of nociceptive blink reflexes (Makino et al., 2010; Vo & Drummond, 2015). Noradrenaline is able to excite α_1 -adrenoceptors, an excitatory subclass of adrenergic receptors, located on nociceptive afferent fibres (Millan, 1999). Under certain conditions, noradrenergic facilitation may replace inhibitory pain controls (Ali et al., 1999; Dogrul, Coskun & Uzbay, 2006; Donello et al., 2011) leading to increased pain and hyperalgesia (Ren, Zou, Fang & Lin, 2005). This pain mechanism provides a more plausible explanation for the findings of the current study.

Hypothesis Five: Catastrophizing

In previous studies, pain catastrophizing was associated with lowered pain threshold (Edwards et al., 2004), lowered pain tolerance (Edwards et al., 2005; Thorn et al., 2004), and higher pain intensity (France et al., 2002). Therefore, it was hypothesized that participants deemed 'high' in catastrophizing, determined by scores on the PCS (Sullivan et al., 1995), would report higher subjective ratings of pain and sharpness to supraorbital stimulation, both at baseline and following conditioning, relative to participants deemed 'low' in catastrophizing. It was further hypothesized that catastrophizing would exacerbate pain intensity during states of heightened arousal, with this effect being more pronounced following HFS.

These hypotheses were not supported. Catastrophizing exerted no significant effects on subjective ratings of pain and sharpness to supraorbital stimulation during baseline tests, or following electrical conditioning of the forearm. These results are at odds with previous findings, in which catastrophizing accounted for a considerable

proportion of variance in pain ratings (Sullivan et al., 2001), and was associated with increased pain perception in samples of healthy participants (Sullivan et al., 1997; Sullivan & Neish, 1998; Sullivan et al., 2000; Sullivan et al., 2001).

In a study conducted by France and colleagues (2002), it was found that pain catastrophizing was not associated with the nociceptive flexion reflex (a spinal reflex subserving withdrawal from noxious stimuli). As the nociceptive reflex is mediated by wide dynamic range interneurons in the dorsal horn, these results suggest that pain catastrophizing is associated with alterations in supraspinal pain-inhibitory and – facilitatory processes, as opposed to spinal gating mechanisms (Sullivan et al., 2001). Results from the current study support this conclusion, as pain catastrophizing failed to evoke significant changes in R2 onset latency or AUC, suggesting that nociceptive reflexes do not provide an accurate measure of the effects of pain catastrophizing. In contrast, diffuse noxious inhibitory controls (DNIC) are commonly used to assess descending supraspinal pain-inhibitory pathways, by comparing pain ratings to noxious stimuli before and after application of a conditioning stimulus (Quartana et al., 2009). Weissman-Fogel, Sprecher and Pud (2008) identified a negative relationship between pain catastrophizing and DNIC following presentation of a conditioning stimulus, suggesting an association between catastrophizing and diminished inhibition of pain, mediated by the presence of central sensitization.

Pain intensity has been found to bear an effect on this relationship. Functional neuroimaging shows that during mild pain, catastrophizing is associated with exaggerated activity in areas of the brain implicated in the processing of the affective dimensions of pain, such as the prefrontal cortex, insular cortex, and caudal anterior cingulate cortex. During states of intense pain, catastrophizing was associated with decreased activity in the caudal anterior cingulate cortex and insular cortex, suggesting

that severe pain may result in the failure of supraspinal inhibitory control mechanisms (Seminowicz & Davis, 2006). However, it is unlikely that noxious stimuli presented in the study breached this threshold of pain severity, as supraorbital and acoustic intensities were determined with the intention to evoke only mild pain or discomfort.

A better explanation for the discrepancy between previous research and the results of the current study, would relate to the conceptualization and measurement of pain catastrophizing. The PCS is based on the conceptualization of catastrophizing as a trait or dispositional variable, according to which maladaptive cognitions lie dormant, and need a cue in order to become manifest (Beck, Rush, Shaw & Emery, 1979). Trait measures of pain catastrophizing may fail to provide valid and reliable measures of variance in pain report, as they rely on recall of a referent event that may be distal to the moment of measurement (Quartana et al., 2009). In contrast, measures of state or situational pain catastrophizing (i.e. participants are asked to rate levels of catastrophizing immediately following introduction of a noxious stimulus) report a stronger correlational relationship with verbal ratings of pain (Dixon, Thorn & Ward, 2004; Edwards et al., 2005; Edwards et al., 2006). Therefore it is plausible that pain catastrophizing did not bear any significant effects on subjective ratings of pain to supraorbital stimulation in the present study, due to an inadequacy in the measures employed to accurately assess pain catastrophizing.

Limitations

The first major limitation of the current study was a strong reliance on self-report measures of pain. To overcome this limitation, participants were blind to the hypotheses (therefore minimising potential biases), and objective physiological measures of nociceptive activity were also collected.

A second limitation relates to generalizability of the findings. Young and well-educated students comprised a large proportion of the sample; therefore it is unclear whether these outcomes are applicable to a wider population. Furthermore, the assumption of normality was not met for a large majority of variables assessed in the repeated measures ANOVA. As previously mentioned, ANOVA is robust against moderate violations of normality, with type I error rates approximating nominal rates (Boneau, 1960; Glass, Peckham & Sanders, 1972). However, some variables were bordering on severe, and this may have resulted in a reduction in statistical power.

Finally, there is a possibility that the testing sequence resulted in order effects. Baseline supraorbital stimulation, and HFS could have affected sensitivity to psychophysical stimuli during second-phase data collection, through processes such as DNIC. As the procedure could not be altered to counterbalance the testing sequences, researchers waited for ten minutes after electrical conditioning of the forearm before proceeding with second-round psychophysical testing in an attempt to minimise any possible order effects.

Conclusions

The main aim of the current study was to explore the effects of sympathetic arousal on a healthy individual's experience of pain, and how the presence of central sensitization, experimentally induced using electrical conditioning of the forearm, affects this interaction. As in previous studies (Klein et al., 2008; Lang et al., 2007; Pfau et al., 2011; Vo & Drummond, 2013; Vo & Drummond, 2014a; Vo & Drummond, 2014b) HFS was able to reliably evoke central sensitization. This allowed for the comparison between healthy pain processes and disrupted pain mechanisms, following electrical conditioning of the forearm. Arousal, evoked through acoustic stimulation, was associated with increased sensitivity to supraorbital stimulation of the forehead,

increased R2 AUC amplitude, and shorter R2 onset latency. However, central sensitization (evoked through electrical conditioning of the forearm) had no significant effect on these interactions, suggesting primary hyperalgesia is not characterized by increased sensitivity to circulating catecholamines, as put forth by Bruehl and Chung (2006). Furthermore, high levels of pain catastrophizing were not associated with decreased pain tolerance or heightened pain sensitivity as hypothesized. Further research is needed to investigate the interaction between heightened sympathetic arousal and the role of excitatory α_1 -adrenoceptors, in order to better understand the relationship between increased arousal and the human experience of pain.

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