The Thermal Grill as a Tool to Investigate Analgesic Clinical Pharmacology

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June 2014

A thesis submitted in fulfilment of the requirements for the degree Doctor of Philosophy

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Abstract

Human experimental pain models are important aids in the study of pain mechanisms, and have been extensively used in clinical drug development to demonstrate the analgesic potential of new compounds. However, the peripheral nature of such pain models makes it difficult to separate the peripheral and central mechanisms of pain. Whilst peripheral mechanisms underlie acute pain, central mechanisms are believed to underlie chronic pain conditions; therefore using an illusion to trick the brain into believing it is experiencing pain may allow investigation of these central mechanisms. One such illusion is the thermal grill illusion, where interlaced innocuous warm and cool temperature bars (thermal grill) produce a paradoxical burning pain sensation. Considering the uniqueness of the thermal grill illusion and the thermal grills' potential ability to investigate the interaction between the nociceptive and thermoreceptive pathways, the objective of this thesis was to investigate whether the response to the thermal grill was tolerable in patients with chronic pain to determine whether the thermal grill illusion could be used to screen for novel centrally acting analgesics in the future. Previously the response to the thermal grill had not been systematically investigated in patients with chronic pain. In order to address this objective, the response to the thermal grill illusion was characterised in pain-free participants, in patients with heterogeneous chronic pain conditions and also in patients with homogenous chronic pain conditions to determine 1) whether the response to the thermal grill differs between pain-free participants and patients with chronic pain, 2) whether the response to the thermal grill differs between body location and body side and 3) whether the thermal grill can differentiate chronic pain phenotypes. In addition, the response to the thermal grill was longitudinally

investigated in patients with chronic medication overuse (MOH) and chronic tension-type headache (CTTH) whom were receiving a novel pharmacological and non-pharmacological therapy for their headaches respectively. Initial studies demonstrated a reduced response to the thermal grill illusion in patients with heterogeneous chronic pain compared to pain-free participants. Although not significant, subsequent studies revealed a similar pattern of reduced response in patients with chronic sciatica pain and CTTH, suggesting that any real differences observed in the previous study were not robust or that the true effect size was small. Amongst all populations, the average intensity of pain experienced from the thermal grill illusion was quite low, thus questioning the utility of the thermal grill as a model to assess the efficacy of analgesics, given the inability of the thermal grill test to reach the clinically relevant substantial pain threshold. Additionally, the test-retest reliability of the thermal grill response over time in patients with MOH and CTTH was poor, further questioning the thermal grills' ability to longitudinally assess the efficacy of analgesics. Although the thermal grill is unlikely to be a suitable tool to assess the efficacy of analgesics, the thermal grill may still be a useful tool to better understand the physiology of pain, given the paradoxical reduced pain observed in patients with certain types of chronic pain.

Declaration

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Acknowledgements

I would like to start by thanking my three supervisors, Prof. Paul Rolan, Dr. Femke Buisman-Pijlman and A/Prof. Mark Hutchinson for their guidance, support and encouragement throughout my PhD candidature. Your ongoing belief, faith and trust in me as an individual and as an independent researcher has helped shape me into the person I am today, and I thank you for that immensely.

The research presented in this thesis was made possible by an Australian Postgraduates Award, as well as support from the Pain and Anaesthesia Research Clinic. Throughout my candidature I was fortunate to present my research locally, nationally and internationally, which was made possible by the travel grants provided to me by the Australian Pain Society, the Faculty of Health Sciences (University of Adelaide), the School of Medical Sciences (University of Adelaide), as well as my supervisor Prof. Paul Rolan.

I would also like to acknowledge and personally thank the following people for their contribution to my research: Melanie Gentgall and all the staff at the Pain and Anaesthesia Research Clinic for their assistance during my clinical trials and all the laughs in between; Nigel Kelly from Flinders Biomedical Engineering (Flinders University) for the design and construction of the thermal grill; Dr. John Semmler from the Discipline of Physiology (University of Adelaide) for the kind use of study equipment; Prof. Lorimer Moseley and the team at the Body in Mind Research Institute (University of South Australia) for the generous use of study equipment and laboratory space, and for always making me feel welcome in their clinical laboratory;

Dale Caville from the Discipline of Anatomy and Pathology (University of Adelaide) for the production and printing of my novel thermal colour bar, as well as the professional image of the thermal grill; and my fellow PhD colleagues Yuen Kwok, Jacinta Johnson and James Swift from the Discipline of Pharmacology (University of Adelaide) for their assistance in patient recruitment for chapters 3, 5 and 7 respectively.

Undergoing a PhD is not only about arriving at a particular destination, but also about enjoying the journey, therefore I would like to take this opportunity to thank all past and present PhD candidates in the 'post grad room' (room N511C) for all the laughs, gossip sessions, YouTube videos, memes, imgurs, Facebook stalking, music, coffees, lunches and drinking sessions. These all kept me sane and made this journey much more enjoyable.

To my extended family (grandparents, aunts, uncles, cousin, as well as my dearly departed grandparents and our angel Georgia): thank you for always believing in me; for your enthusiasm and encouragement; hugs and kisses; for always thinking I'm smarter than I actually am and for all of the laughs at our 'small' family gatherings. The closeness as a family that we share is unbelievable and I could not imagine my life without each and every one of you in it.

To my girls, my besties and my sisters from another mister, Kassi, Dani and Lauren: our phone chats, texts, tea breaks, Saturday morning market catch-ups, dinners, nights out, and your continued friendship, support and understanding has kept me sane

throughout this PhD journey. I am forever grateful for our friendship and will continue to cherish it for years to come. I would also like to thank my friend and mentor Dr. Margaret Centenera for her support and encouragement to keep focussed and keep writing, whether over a coffee, wine or port!

To my mother and father in law (Jasminka and Jovanco), sister and brother-in-law (Daniela and Pejo), and my gorgeous nephew (Jovan) and nieces (Elena and Katarina): thank you all for welcoming me into your family with open arms and for your constant love, support, friendship, kisses and cuddles. I love you all.

To my sister, best friend and business partner Martha: thank you for always being there for me, through thick and thin and through the good times and the bad. We've shared lots of laughs, lots of tears, had lots of fun, our fair share of sibling arguments and have spent countless hours making delicious raw desserts for our business Nutrition Republic. Thank you for your unconditional love and friendship and thank you for giving me a precious nephew, whom I love with all my heart. To my nephew Louis, thank you for allowing me to experience an unbelievable love. Your smile literally melts my heart. To my brother-in-law and business partner Terry, thank you for your friendship and for understanding that Martha and I come together in one package and that you're stuck with me for life. I look forward to the future and our future business ventures together.

To my parents Peter and Patty: I will be forever grateful for your unconditional love, support, encouragement, guidance, friendship and financial assistance since the day I

was born. This has shaped me into the person that I am today. Without you both, I would not have been able to undertake this PhD, and for that I am forever grateful. From the bottom of my heart I thank you for all that you have done for me, it is truly above and beyond that what most parents do for their children. I love you both and could not imagine my life without you two.

Last, but not least, a massive thank you to my husband, best friend and business partner Ilija for your unconditional love, continued support, constant encouragement and reassurance, sacrifice and patience. You have been on this rollercoaster journey with me each and every step of the way, and for that you deserve a PhD too! As this enormous door now finally closes, I am looking forward to the many more that we will open together. I love you and could not have done this without you.

Abbreviations

5-HT	Serotonin
5-HTT	Serotonin transporter
ACC	Anterior cingulate cortex
AIDS	Acquired immunodeficiency syndrome
AMHs	A-δ mechano-heat nociceptive afferents
ANOVA	Analysis of variance
ASI	Anxiety severity index
BAC	Breath alcohol concentration
BDI-II®	Beck Depression Inventory®-II
BMI	Body mass index
C-warm	C-fibres responsive to warm
C2	C-fibres responsive to cold, warmth and heat
CAP	Capsaicin
CH	C-fibres responsive to noxious heat
CI	Confidence interval
CMH	C-fibres responsive to noxious mechanical and heat stimuli
CMHC	C-fibres responsive to noxious mechanical, heat and noxious cold stimuli
COLD	Lamina I thermoreceptive specific cells
CPT	Cold pain threshold
CRPSI	Chronic regional pain syndrome type I
CTTH	Chronic tension-type headache
CU	Clinical unit
CWC	Warm stimulus flanked by two cool stimuli
EEG	Electroencephalography
EPT	Electrical pain threshold
F	Female
fMRI	Functional magnetic resonance imaging
GFR	Glomerular filtration rate
HADS	Hospital anxiety and depression scale
HADS-A	Hospital anxiety and depression scale (anxiety)
HADS-D	Hospital anxiety and depression scale (depression)
Hep B	Hepatitis B
Hep C	Hepatitis C

HIV	Human immunodeficiency virus
HPA	Hypothalamo-pituitary-adrenal
HPC	Lamina I multimodal cells
HPT	Heat pain threshold
i.d.	Intradermal
IQR	Interquartile range
LFTs	Liver functions tests
M	Male
mA	Milliampere
MDD	Major depressive disorder
MDvc	Ventral caudal medial dorsal nucleus
MOH	Medication overuse headache
MS	Multiple sclerosis
NNT	Number needed to treat
NRS	Numerical rating scale
NS	Nociceptive specific cells
NSAIDs	Non-steroidal anti-inflammatory drugs
^{o}C	Degrees celcius
OIH	Opioid induced hyperalgesia
P	Pearson
PARC	Pain and anaesthesia research clinic
PET	Positron emission tomography
QST	Quantitative sensory testing
S	Spearman
S1	Primary somatosensory cortex
S2	Secondary somatosensory cortex
SCL-90-R®	Symptom checklist-90-R
SD	Standard deviation
SEM	Standard error of the mean
SMT	Spinomesencephalic
SRT	Spinoreticular tract
STAI	State trait anxiety index
STAI-T	State trait anxiety index (trait)
STT	Spinothalamic tract
tDCS	Transcranial direct current stimulation
TG	Thermal grill

TGI	Thermal grill illusion
TLR-4	Toll-like receptor 4
TLRs	Toll-like receptors
TMS	Transcranial magnetic stimulation
TRPA1	Transient receptor potential ankyrin 1
TRPM8	Transient receptor potential melastatin 8
TRPV1	Transient receptor potential vanilloid 1
TRPV2	Transient receptor potential vanilloid 2
TRPV3	Transient receptor potential vanilloid 3
TRPV4	Transient receptor potential vanilloid 4
VAS	Visual analogue scale
VMpo	Posterior aspects of ventral medial nucleus
VP	Ventral posterior nucleus
VPI	Ventro-posterior-inferior nuclei
VPL	Ventro-posterior-medial thalamic nuclei
WARM	Lamina I warm cells
WCW	Cool stimulus flanked by two warm stimuli
β-CD	Hydroxypropyl-β-cyclodextrin

Chapter 1. Introduction

1.1 Physiological Pain

Pain is defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (IASP, 1994). Pain may be classified as physiological (nociceptive) or pathological. Pathological pain can either be further divided into inflammatory (arising from tissue injury and associated inflammation), neuropathic (arising from injury to the peripheral or central nervous system), idiopathic (arising from no detectable cause) or due to cancer (Cao and Zhang, 2008; Costigan et al., 2009; Jarvis and Boyce-Rustay, 2009; Jensen and Finnerup, 2009). Unlike pathological pain, physiological pain is transitory in nature and occurs in response to noxious (painful) stimuli (Marchand, 2008; Costigan et al., 2009). Physiological pain provides an important protective mechanism for our survival, by warning us to prevent or minimise potential tissue (Latremoliere and Woolf, 2009).

1.1.1 Chronic Pain

When pain persists beyond the point of tissue healing, pain becomes chronic. Chronic pain is defined as pain experienced every day for three months or more in the previous six months (Access Economics, 2007). Unlike physiological pain, chronic pathological pain serves no useful biological function (Millan, 1999). Inflammatory and neuropathic pain form the 2 main categories of chronic pathological pain. Following tissue injury, inflammatory mediators sensitise peripheral nociceptors resulting in inflammatory pain (Linley et al., 2010).

Inflammatory pain is associated with sensory disturbances, which are characterised by spontaneous pain, increased responsiveness to noxious stimuli (hyperalgesia) and pain perceived in response to normally non-noxious stimuli (allodynia) (Eide, 2000; Latremoliere and Woolf, 2009). These features, as well as others (described below), may also occur in neuropathic pain. The International Association for the Study of Pain defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system" (IASP, 1994), however Treede and colleagues (2008) more recently proposed a more precise definition: "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system". Patients with neuropathic pain may also experience evoked or spontaneous abnormal sensations (paraesthesias), which may have unusually unpleasant qualities (dysaesthesias) (Watkins and Maier, 2002; Finnerup and Baastrup, 2012). Although not usually considered by patients as 'pain', dysaesthesias can be one of the most debilitating symptoms experienced by patients with chronic neuropathic pain (Finnerup and Baastrup, 2012).

> *"Chronic pain is a thief. It breaks into your body and robs you blind. With lightning fingers, it can take away your livelihood, your marriage, your friends, your favorite pastimes and big chunks of your personality. Left unapprehended, it will steal your days and your nights until the world has collapsed into a cramped cell of suffering." (Claudia Willis, Time Magazine, February 2005).*

Chronic pain remains a major unmet medical need, with few treatments of novel mechanism of action having been introduced into clinical practice in recent decades. It has been estimated that 1 in 5 (3.2 million) Australians suffer chronic pain (2007). Current treatments for chronic inflammatory or neuropathic pain (e.g. non-steroidal anti-inflammatory drugs, antidepressants, anticonvulsants, opioids) are either partly effective or limited by their side

effects. Antidepressants (e.g. tricyclic antidepressants) are one of the first choice of treatment for neuropathic pain due to their low number needed to treat (NNT) (approximately 1.3 for diabetic neuropathy (Saarto and Wiffen, 2007). Unfortunately, cardiovascular (e.g. postural hypotension, heart block, arrhythmias), sedative and anticholinergic effects (e.g. dry mouth, constipation, urinary retention) are all adverse effects of tricyclic antidepressants and often lead to withdrawal from this type of treatment (Saarto and Wiffen, 2007). Anticonvulsants (e.g. gabapentin, pregabalin) are another first choice treatment for neuropathic pain, especially when the pain is lancinating or burning (Moore et al., 2011). However, adverse effects (e.g. impaired mental and motor function) and relatively high NNT (5.8 for moderate (>30%) and 6.8 for substantial (>50%) pain reduction) often limit their clinical use (Moore et al., 2011). Furthermore, the use of opioids in chronic pain management has limited efficacy (Ballantyne and Shin, 2008; Trescot et al., 2008).

Currently no treatments for neuropathic pain provide more than 50% of patients with adequate pain relief (described as a reduction in mean pain scores of at least 30% for clinical significance (Farrar et al., 2001)). Consequently, many patients with chronic pain experience little or no pain relief, which greatly impacts their quality of life negatively. Furthermore, chronic pain is a major burden to the society and economy (Renn and Dorsey, 2005); costing Australia an estimated $34.4 billion annually, therefore ranking chronic pain as the third most expensive health problem in Australia today (Access Economics, 2007). Due to Australia's aging population, it is estimated that the number of people suffering from chronic pain will increase to 5 million by 2050 (Access Economics, 2007), making it an urgent priority for the discovery and development of effective treatments for chronic pain.

1.2 Human Experimental Pain Models

Sufferers of chronic pain do not necessarily experience pain consistently throughout the day, but instead sporadically and for variable periods of time. This variability makes the short-term examination of the effects of a new treatment difficult in patients with chronic pain. The use of an experimental pain model can potentially reduce the variability of chronic pain by producing a controlled response for a defined period of time. Thus, human experimental pain models are important aids in the study of pain mechanisms, and have been extensively used in clinical drug development to demonstrate the analgesic potential of new compounds (Hughes et al., 2002) in small groups of participants (Arendt-Nielsen et al., 2007). However, nearly all experimental pain studies have been performed in pain-free volunteers, with very few examined in chronic pain patients. Despite the attractiveness of healthy volunteer studies, the key mechanisms activated in chronic pain may not be engaged, increasing the likelihood of false positive results. Unlike chronic pain patients, pain-free volunteers do not experience underlying pain prior to noxious stimuli; therefore represent a more homogenous population compared to chronic pain patients. Furthermore, numerous experimental pain studies have demonstrated that chronic pain patients have abnormal central pain processing compared to pain-free volunteers (Staud et al., 2007; Fernandez-de-las-Penas et al., 2009; Bezov et al., 2010; Lee et al., 2011; Lewis et al., 2012; Suokas et al., 2012; Stabell et al., 2013). Consequently, experimental pain studies should be investigated in chronic pain patients, so that the heterogeneity of chronic pain and the central pain processing abnormalities observed in chronic pain patients can be further elucidated.

1.2.1 Limitations of Currently Used Pain Models

One major limitation of currently used pain models is that they activate peripheral nociceptive input, making it difficult to separate the peripheral and central mechanisms involved in pain

processing, Given that the vast bulk of such studies have been performed in healthy pain-free participants (see large list of studies in reviews Staahl et al., (2009a) and Staahl et al., (2009b)), it is necessary to strongly activate peripheral nociceptors in such pain models. Such models have reasonable utility for predicting the efficacy of analgesics in acute pain, as the pathways involved in acute clinical pain involve those that underlie nociceptive pain. However, the mechanisms by which chronic pain is maintained may be different from those of acute pain, with the current emphasis being on central mechanisms rather than ongoing activation of peripheral nociceptors, therefore, commonly used experimental pain models make it difficult to investigate pure central nervous system mechanisms of pain processing. Hence, in order to dissect these processes occurring in the periphery and the brain, an experimental pain model that induces pain through largely central rather than peripheral mechanisms might shed insights into the mechanisms of chronic pain and be a screening tool for new drugs for chronic pain. One potential way to investigate the central mechanisms of pain may be to use an illusion, where the brain is tricked into believing it is experiencing pain.

1.3 Illusions

Illusions are distortions of sensory perception, potentially revealing how the brain usually organises and interprets sensory stimulation. The interest in illusions has evolved over time, with illusions initially being investigated as pure curiosities; often being incorporated into carnival side shows. Sensory psychologists then discovered that illusions could be used to gain a better understanding of the way in which the brain processes sensory information (Johannsen, 1971). Most commonly, visual and auditory illusions have been used and have been successful in deciphering some of the mechanisms that underlie both vision and hearing respectively. One such illusion is the Müller-Lyer Illusion, which has helped neuroscientists' study the way the brain and visual system perceive and interpret images (Müller-Lyer, 1889). In this illusion, two lines of the same length are presented with arrowheads on either end on the lines in differing directions; which causes the illusion that the two lines are of different lengths (see Figure 1.3.1).

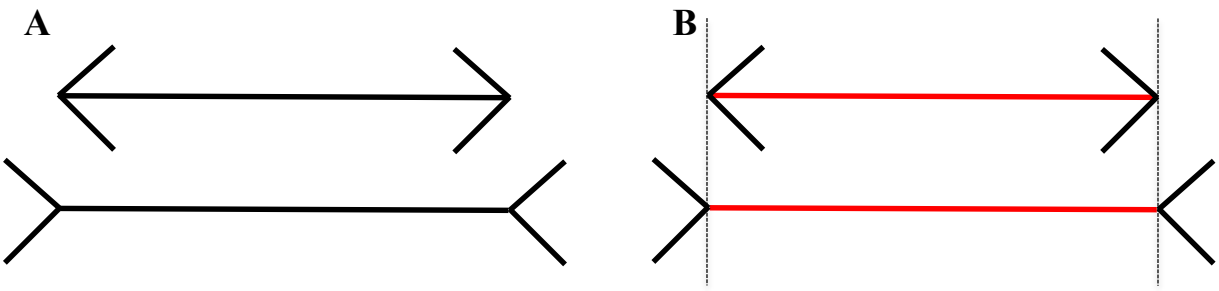

Figure 1.3.1. The famous Müller-Lyer illusion.

Participants are asked which horizontal line is longer in image A. Image B demonstrates that the horizontal line in both the top and bottom image are identical in length. Image adapted from Müller-Lyer (1889).

Another commonly used illusion is the Rubber Hand Illusion (see Figure 1.3.2), which demonstrates how sight, touch and proprioception combine to create a convincing feeling of body ownership (Ramakonar et al., 2011).

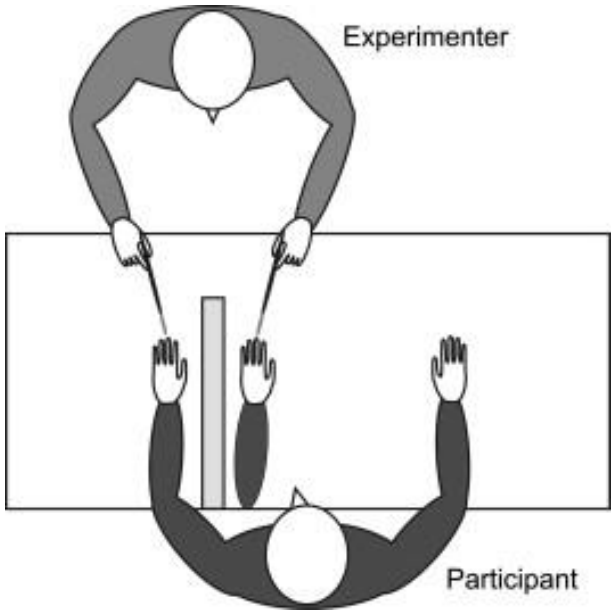

Figure 1.3.2. Experimental set up of the rubber hand illusion.

The participants real hand (far left) is shielded with a screen and the rubber hand (middle hand) is positioned in the participants direct view in such a position that it could be the participants real hand. The experimenter then simultaneously strokes the participants hand and the rubber hand (middle hand) until the illusion is induced. Reprinted from Haans and Ijsselsteijn (2012) with kind permission from Elsevier.

This then poses the question that perhaps an illusion of pain may allow further understanding of the mechanisms that underlie central pain conditions? One interesting illusion for the use of pain research is the thermal grill illusion. The thermal grill illusion is a thermal paradox, where a sensation of burning pain is experienced when innocuous warm and cool temperatures are touched simultaneously. The thermal grill illusion of pain is believed to be a purely central phenomenon (Craig and Bushnell, 1994), where a burning pain is felt without activating peripheral nociceptive fibres. This could potentially provide an experimental pain model that is analogous to central pain. Therefore, the thermal grill pain model has numerous potential applications, such as: providing a more comprehensive tool to study the mechanisms of central pain; describing pain phenotypes; and assessing the efficacy of potential analgesic compounds.

1.4 Thermal Grill

The thermal grill is a device that consists of interlaced warm and cool bars, which are innocuous when touched separately, however produce a paradoxical sensation of burning pain (known as the "thermal grill illusion") when touched simultaneously (Thunberg, 1896).

1.4.1 History of the Thermal Grill Illusion

This phenomenon of paradoxical burning pain caused by a thermal grill was first described by Torsten Thunberg more than 100 years ago (Thunberg, 1896). Thunberg was interested in investigating what kind of sensations would arise from simultaneous stimulation of the skin by cold and warm objects. He created a device of cold and warm spiral tubes, which were interlaced. When the coils were applied so that the temperature of the cold coil was 24 ^{o}C and the temperature of the warm coil was 44 ^{o}C, Thunberg (1896) described the sensation "as if the temperature was suddenly raised and a feeling of 'hot' ensued," coupled with the sensation of a burning sensation being about to arise (Alrutz, 1898a). Many other researchers at the time and in the following decades were interested in studying heat sensation, and whether heat was a fusion of warmth and cool, or a separate sensation. Initially, the thermal grill illusion was investigated as a scientific curiosity, with most of the earliest work in the field being anecdotal evidence (Cutolo, 1918; Alston, 1920; Burnett and Dallenbach, 1927; Burnett and Dallenbach, 1928; Ferrall and Dallenbach, 1930; Jenkins, 1938b; Jenkins, 1938a). It was not until 1994 that the thermal grill illusion was re-discovered as potential research tool for pain by Craig and Bushnell; and the first systematic study of the thermal grill illusion was conducted in humans accompanied by electrophysiological data from anaesthetised cats (Craig and Bushnell, 1994).

1.4.2 Possible Underlying Mechanisms of the Thermal Grill Illusion

How spatially interlaced warm and cool bars causes a sensation that is disproportionate in magnitude to each individual warm and cool stimulus has puzzled many. Some hypotheses for this phenomenon are discussed below.

Alrutz first proposed that the perception of heat was not a specific sensation, but instead a fusion of simultaneous activation of specific warm and cool spots on the skin (Alrutz, 1898b). Simultaneous activation of specific warm and cold sensory channels by the warm and cool temperature bars of the thermal grill was thought to evoke this fusion of heat (Craig and Bushnell, 1994). Modern physiological findings have contradicted Alrutz's fusion hypothesis as it has been demonstrated that heat is modulated separately from warm and cool (Craig and Bushnell, 1994). In addition, Bach and colleagues (2011) demonstrated that the perceived qualities participants experienced from the thermal grill were in surplus of the qualities participants' perceived by the thermal grill's constituent cool and warm temperatures individually, further disproving the fusion hypothesis. However, the underlying mechanisms of the thermal grill illusion remain to be fully elucidated.

The prevailing theory of the thermal grill illusion is the thermosensory disinhibition hypothesis put forth by Craig and Bushnell, based on electrophysiological recordings from lamina I spinothalamic tract (STT) neurons in anaesthetised cats (Craig and Bushnell, 1994). Craig and Bushnell demonstrated that the cool bars of the thermal grill activate lamina I thermoreceptive specific (COLD) cells, which are activated by cooling and receive input from specific cold receptors, and multimodal (HPC) cells, which are responsive to heat, pinch and cold and also receive input from cold sensitive C-polymodal nociceptors. At innocuous cool temperatures (> ~15^{o}C), COLD cell activity normally exceeds HPC cell activity (Craig et al.,

1996). However, when subjected to the grill stimulus (interlaced cool and warm bars) COLD cell activity was halved without affecting HPC activity or any other STT neurons (see Figure 1.4.2.1A) (Craig and Bushnell, 1994). This demonstrates that interlaced warm bars to a cool stimulus shifts the relative pattern of activity in favour of the HPC (C-polymodal) channel, therefore producing a pattern similar to that observed during noxious cold or heat stimulation, which explains the painful burning sensation experienced (see Figure 1.4.2.1B) (Craig and Bushnell, 1994).

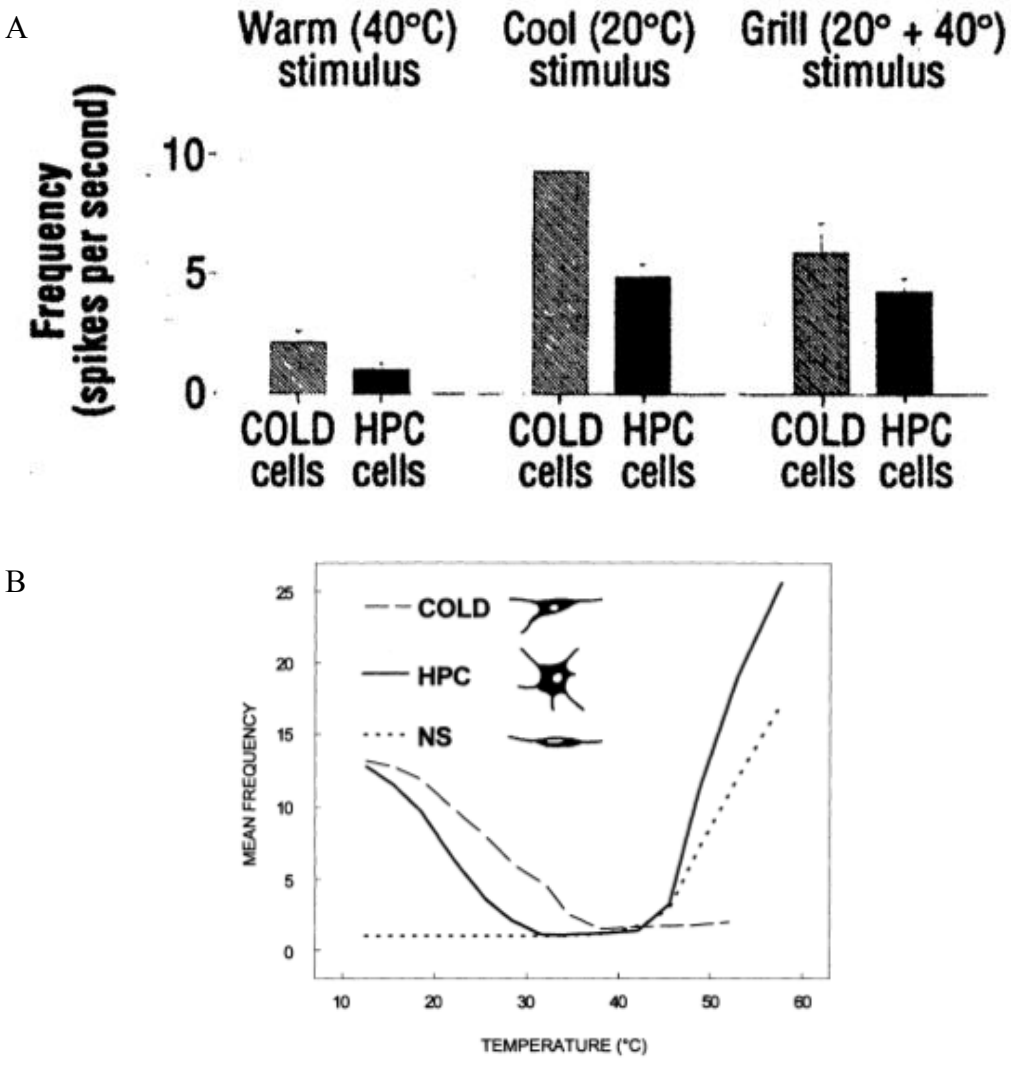

Figure 1.4.2.1. Physiological characteristics of recorded lamina I STT neurons.

A) Graph represents the average discharge rates of COLD lamina I STT cells and HPC lamina I STT cells in response to a warm (40 ^{o}C) stimulus, a cool (20 ^{o}C) stimulus and the thermal grill (combination of 40 ^{o}C and 40 ^{o}C) stimulus. These graphs demonstrate that the thermal grill significantly reduced COLD cell discharge,

whilst HPC cell activity was minimally affected ($P < 0.003$) (Craig and Bushnell, 1994). B) Graph represents the thermal stimulus-response function of COLD (dashed line), HPC (solid line) and NS (dotted line) lamina I STT cells plotted against the thermode temperature (Craig, 1996). Reprinted from (A) Craig and Bushnell (1994) and (B) Craig (1996) with kind permission from AAAS and Springer Science and Business respectively.

Craig and Bushnell (1994) explained that the reduction in COLD cell activity unmasked HPC activity by disinhibition, probably at the thalamocortical level, concluding that the TGI demonstrates a central integration of ascending pain and temperature sensory channels (see Figure 1.4.2.2). Craig and Bushnell's (1994) proposed mechanism of the thermal grill illusion is consistent with the population-coding hypothesis of somatic sensations, where specific sensory labelled lines (e.g. cold labelled line, pain labelled line etc.) crosstalk to generate and shape somatosensory perception (Ma, 2010). The population-coding hypothesis is further explained in Section 1.5.

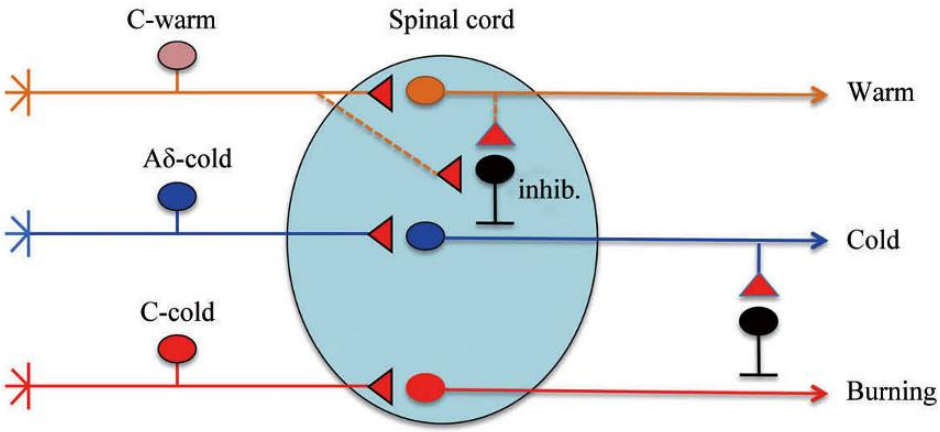

Figure 1.4.2.2. Proposed mechanism of the thermal grill illusion.

Innocuous cool temperatures activate both the Aδ-cold labelled line (COLD cells) and the C-cold pain-labelled line (HPC cells). Under innocuous cool conditions, the Aδ-cold labelled line inhibits the C-cold pain-labelled line, with this inhibition most likely occurring in the brain. Under the conditions of the thermal grill, where a warm stimulus is introduced alongside a cool stimulus, the activity of the Aδ-cold labelled line is supressed by the activation of C-warm fibres (WARM cells), with this inhibition beginning at the level of the spinal cord. Inhibition of the Aδ-cold labelled line then allows C-cold fibres to activate the normally masked burning pain-labelled line (Ma, 2012). Reprinted from Ma (2012) with kind permission from Springer.

Findings from a recent Masters Thesis by Jason Lam (2012) lend support to Craig and Bushnell's (1994) thermosensory disinhibition hypothesis. Unlike most studies investigating the thermal grill, which use interlaced warm and cool stimuli to elicit the thermal grill illusion, Lam (2012) investigated the effect of a cool stimulus (cool bar, 20 ^{o}C), flanked by two warm stimuli (warm bars, 40 ^{o}C) on either side (WCW), compared to a warm stimulus (warm bar), flanked by two cool stimuli (cool bars) on either side (CWC). Lam (2012) hypothesised that if Craig and Bushnell's (1994) thermosensory disinhibition hypothesis did indeed explain the basis of the thermal grill illusion, then increasing the relative activity of HPC to COOL channels, by alternating the number of cool and warm stimuli, should alter the perception of the thermal grill illusion. Indeed, the WCW configuration evoked significantly greater pain and unpleasantness to the thermal grill illusion compared to the CWC configuration at both the forearm and the calf (see Figure 1.4.2.3). Additionally, the WCW configuration was mainly described as "burning", whereas the CWC configuration was mainly described as "neutral". Therefore, Craig and Bushnell's (1994) thermosensory disinhibition hypothesis may explain the difference in response between the WCW and CWC configurations, where a reduced COLD inhibition in the WCW configuration allowed for the participants to experience a greater illusion of pain compared to the CWC configuration.

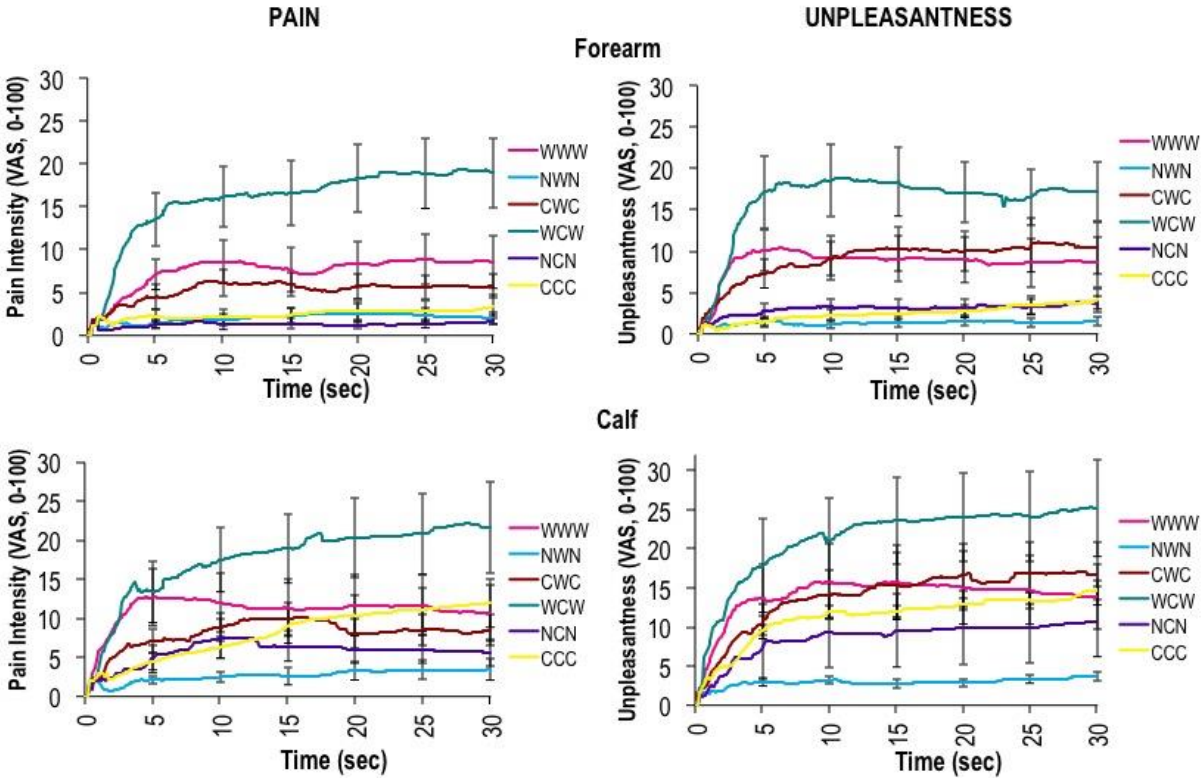

Figure 1.4.2.3 Time course of average pain (left graphs) and unpleasantness (right graphs) ratings for each thermal grill configuration during thermal grill stimulation on both the forearm (top graphs) and calf (bottom graphs).

Each colour represents a different thermal grill configuration. Abbreviations: WWW, all bars warm (40 ºC); NWN, warm (40 ºC) centre bar flanked by neutral bars (33 ºC); CWC, warm (40 ºC) centre bar flanked by cool (20 ºC) bars; NCN, cool (20 ºC) centre bar flanked by neutral (33 ºC) bars; CCC, all bars cool (20 ºC) (Lam, 2012). Reprinted with permission from Lam (2012).

Bouhassira and colleagues comprehensively examined the thermal grill at various temperature configurations, with the temperature of the cool bars being set to either +4, +6, +8 or +10 ºC above the participants individual cold pain threshold (CPT) and the temperature of the warm bars being set to either -4, -6, -8 or -10 ºC below the participants heat pain threshold (HPT), allowing for a total of 16 different thermal grill configurations to be examined (Bouhassira et al., 2005). When the temperature of the cool bars of the grill remained constant and the temperature of the warm bars of the grill increased, paradoxical pain was experienced by a

greater percentage of participants, which may be explained by a progressive reduction of COLD cell activation and consequently a growing disinhibition of HPC cells (Bouhassira et al., 2005). These results appear to be consistent with Craig and Bushnell's (1994) thermosensory disinhibition hypothesis. However, a similar increase of paradoxical pain was also observed when the temperature of warm bars of the grill remained constant and the temperature of the cool bars of the grill decreased, which Bouhassira and colleagues argue does not seem to be compatible with Craig and Bushnell's (1994) thermosensory disinhibition hypothesis, as these results suggests a similar (symmetrical) inhibitory relationship between the 'warm channel' and HPC cells (Bouhassira et al., 2005). However, unpublished data (Craig and Bushnell, 1994) obtained from additional cells using colder probes indicate that HPC activity continues to increase as the temperature of the stimulus decreases, whereas COLD cell activity does not (see reference number 15 under "references and notes" (Craig and Bushnell, 1994)). Therefore, Bouhassira and colleagues' (2005) findings of increased paradoxical pain when the temperature of the warm bars of the grill remained constant, whilst the temperature of the cool bars of the grill decreased appears to be consistent with Craig and Bushnell's (1994) unpublished findings.

Using mild temperatures ($\geq$ 27 ^{o}C and 35-40 ^{o}C), Green (2002) demonstrated that innocuous warm and cool temperatures could produce a non-painful thermal grill illusion, a finding that Green (2002) argues can not be supported by Craig and Bushnell's (1994) thermosensory disinhibition hypothesis, and thus suggested that this non-painful heat sensation may be the result of summation of afferent activity in warm and cool fibres. Recently, Harper and Hollins (2014) demonstrated that cool adaptation reduced the painfulness of the thermal grill illusion, whereas warm and neutral adaptation did not affect the thermal grill response, suggesting that the cool bars of the thermal grill are responsible for the nociceptive qualities of the thermal grill illusion as suggested by Craig and Bushnell (1994) and demonstrating that the thermal

grill illusion is more complex than the simple addition of warm and cool signals as suggested by Green (2002); although their findings cannot refute Green's (2002) additive hypothesis of non-painful heat at mild temperatures. Given that Green (2002) used mild temperatures to evoke non-painful heat and that Craig and Bushnell (1994) used greater temperatures sufficient to activate temperature sensitive nociceptors, Green (2002) suggested that two or more interactive processes that operate over different but overlapping temperature ranges might underlie the thermal grill illusion.

1.4.3 Similarities of the Thermal Grill Illusion and Central Pain

Several similarities between the thermal grill illusion and central pain perception exist. In the central nervous system, pathways specific for pain and temperature overlap both in their anatomy and function (Craig 1998). Evidence for this central interaction between pain and temperature is provided by the observation that cold stimuli can reduce the pain reported from electrical stimulation of a peripheral nerve (Bini et al., 1984); and that cool perception is lost following selective blockade of myelinated peripheral fibres responsible for cool perception, resulting in an innocuous cool stimulus now being perceived as painful (Mackenzie et al., 1975). Further evidence is provided by the thermal grill illusion, which is believed to result from the integration of ascending pain and thermal sensory channels (Craig and Bushnell, 1994; Craig et al., 1996), demonstrating that the thermal grill reveals a fundamental feature of the organisation of the nervous system, being that a fundamental interaction between the feelings of pain and temperature exist (Craig, 2008).

Many patients with central pain have dysfunctional thermal sensitivities (Craig, 2008), and often experience unremitting burning pain (Costigan et al., 2009). Often, a loss of warm and cool sensations is observed in these patients (Craig, 2008; Maier et al., 2010). The thermal

grill produces very similar characteristics, where by a burning pain is experienced, whilst reduced warm and cool sensations are reported (Craig, 2008).

The thermal grill demonstrates a disinhibition of second (burning) pain by a warm-induced reduction of its ongoing inhibition by cooling (Craig, 2008). It has been suggested that the unremitting burning pain felt by central pain patients is caused by the thermosensory loss, which consequently releases (or disinhibits) integrated polymodal nociceptor activity (defined by Craig (2008)). Consequently, the thermal grill serves as a model of central gating of pain and temperature, rather than a model of central sensitisation. Therefore the thermal grill may provide a tool to elucidate dysfunctional thermosensory integration in patients with pain (Craig, 2008).

1.4.4 Current Thermal Grill Research

1.4.4.1 Pharmacological Modulation of the Thermal Grill Illusion

At the initiation of this thesis, only two studies investigating the pharmacology of the thermal grill illusion were available. An additional study was published more recently (2013). The first two studies investigated the neuropharmacological mechanisms involved in the thermal grill illusion, whereas, the third study attempted to determine the classes of peripheral axons that may contribute to the thermal grill illusion.

Recently, Kern and colleagues demonstrated that the thermal grill illusion could be pharmacologically modified in pain-free volunteers (Kern et al., 2008b). They demonstrated that intravenous morphine (0.1mg/kg), an opioid analgesic, decreased both the intensity and the unpleasantness of the thermal grill illusion compared to placebo; increased participant's

heat pain thresholds and decreased participant's cold pain thresholds. Therefore morphine had no differential effect on the heat sensation associated with the thermal grill and the thermal sensations produced by conventional thermal threshold testing. Morphine has previously been demonstrated to enhance COLD cell activity and supress HPC cell activity (Craig and Hunsley, 1991), thus Bouhassira and colleagues (2005) findings of decreased cold pain thresholds, increased heat pain thresholds and decreased intensity and unpleasantness of the thermal grill illusion are consistent with Craig and Bushnell's (1994) thermosensory disinhibition hypothesis; although Bouhassira and colleagues (2005) suggest that their findings are due to morphine's suppression of HPC cells rather than an enhancement of COLD cells as cool detection thresholds were not altered. As morphine reduces nearly all experimentally produced painful stimuli, these findings suggest that the thermal grill is valid model of pain.

Furthermore, Kern and colleagues demonstrated that low dose ketamine (0.2 mg/kg bolus over 10 minutes followed by a continuous infusion of 6 μg/kg/min infusion until the end of the testing session), a general anaesthetic used at a lower does to modify central neuropathic pain, significantly reduced both the intensity and the unpleasantness of the thermal grill illusion compared to placebo (Kern et al., 2008a). Of particular interest was that ketamine, unlike morphine, did not increase or decrease participant's heat and cold pain thresholds respectively; decrease the intensity of pain induced by noxious thermal stimuli; or decrease the innocuous sensations evoked by stimuli at the warm and cool temperatures used to produce paradoxical pain (Kern et al., 2008a). These results demonstrate that "the central mechanism underlying the thermal grill is pharmacologically distinguishable from the neural mechanisms underlying both innocuous thermal sensations and noxious thermal sensations" (Craig, 2008, p 216). This finding is particularly important, as this distinction between central and neuronal mechanisms differentiates the thermal grill against currently used pain models.

Therefore, it appears that the anti-dysaesthetic qualities of ketamine were selectively detected by the thermal grill, suggesting that the thermal grill may be a unique experimental pain model to investigate the dysaesthetic qualities of central pain and to screen potential anti-dysaesthetic therapies for central pain.

To summarise, morphine was able to reduce both the peripheral and central effects of pain, whereas ketamine was only able to reduce the central effects of pain. Most experimental pain models activate peripheral nociceptors and measure peripheral responses to stimuli; therefore they are not particularly useful to screen for efficacy of centrally acting pain-modifying medicines, such as ketamine. However, the thermal grill was able to significantly detect ketamine's ability to reduce the central effects of pain. Most experimental pain models are unable to differentially determine the central versus peripheral action of pain-modifying medicines; therefore pharmaceuticals may not be appropriately assessed in early drug development. Consequently, the thermal grill may be a novel experimental model to measure the central effects of pain and the efficacy of centrally acting analgesics.

Using menthol, an agonist at the transient receptor potential melastatin 8 (TRPM8), and cinnamaldehyde, an agonist at the transient receptor potential ankyrin 1 (TRPA1), Averbeck and colleagues (2013) attempted to elucidate the classes of peripheral axons that may contribute to the thermal grill illusion. Transient receptor potential (TRPs) ion channels, located in the free nerve endings of afferent fibres in the skin, operate as specialised thermal receptors (Schepers and Ringkamp, 2009). In humans, TRPM8 is expressed in A-δ cold sensitive afferents and a proportion of C-fibres that are responsive to both innocuous and noxious cold (specifically C2 fibres, described in section 1.5.5), whilst TRPA1 is often co-expressed in neurons that express the transient potential vanilloid 1 (TRPV1), but not TRPM8

(Story et al., 2003; Kobayashi et al., 2005). Both menthol and cinnamaldehyde increased participants' cold pain thresholds and increased the intensity of heat evoked from the thermal grill illusion. Additionally, cinnamaldehyde decreased participants' heat pain thresholds.

As stated above (section 1.4.2), the prevailing theory of the mechanism that underlies the thermal grill illusion is the thermosensory disinhibition hypothesis proposed by Craig and Bushnell (1994), where the warm bars of the thermal grill are believed to reduce the normal inhibition exerted on HPC cells by COLD cells, resulting in disinhibition of HPC cells and the consequent experience of a paradoxical burning sensation. Averbeck and colleagues (2013) postulated that the enhancement of the intensity of heat evoked from the thermal grill following the application of topical menthol may be due to an increased disinhibition of HPC activity in the spinal cord, whilst the enhancement of the intensity of heat evoked from the thermal grill following the application of topical cinnamaldehyde may be due to an increase in C-nociceptive input, perhaps increasing the activity of HPC neurons in the spinal cord. The authors concluded that their results provide indirect evidence that COLD cells, which are sensitive to menthol, and multimodal HPC cells, which are sensitive to cinnamaldehyde, both contribute to the paradoxical burning sensation experienced from the thermal grill (Averbeck et al., 2013), which is consistent with Craig and Bushnell's (1994) thermosensory disinhibition hypothesis.

1.4.4.2 Neuroimaging studies

Both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have been used to investigate the thermal grill illusion. Using PET, Craig and colleagues (1996) demonstrated that the thermal grill (combination of 20 ^{o}C and 40 ^{o}C), similar to noxious heat (47 ^{o}C) and noxious cold stimuli (5 ^{o}C), caused significant activation

in the anterior cingulate cortex (ACC), whereas the thermal grill's constituent cool (20 ^{o}C) or warm (40 ^{o}C) stimuli did not cause activation of this cortical region, when thermal stimuli were applied to the palmar surface of right-handed participants dominant hand for 60 seconds (see Figure 1.4.4.2.1). Specifically, direct comparison of cortical activation patterns between the thermal grill and noxious cold condition showed no statistically significant difference, suggesting that the thermal grill illusion resembles the burn of cold pain (Craig et al., 1996).

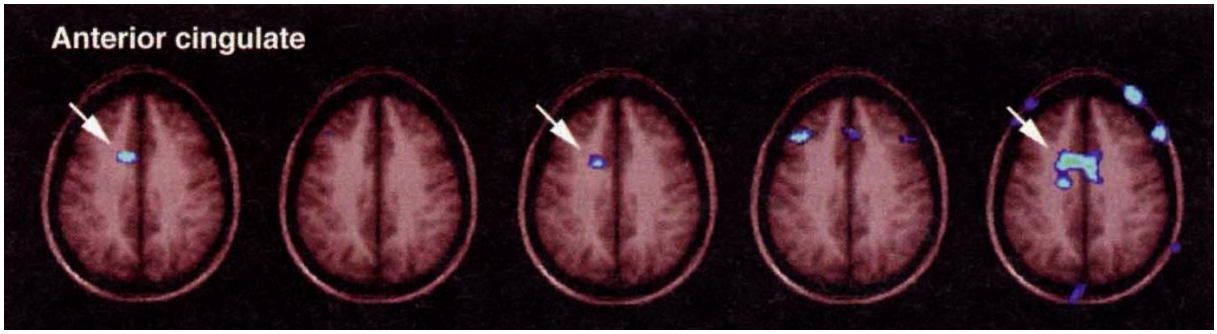

Figure 1.4.4.2.1. Positron emission tomography of the anterior cingulate cortex.

Normalised axial 31-slice PET images through the ACC showing significant regional cerebral blood flow activation for each stimulus condition compared with the neutral (34^{o}C) condition. Left is contralateral to the thermal stimulus (Craig et al., 1996). Reprinted with permission from Craig *et al.*, (1996).

Craig and colleagues (1996) went on to conclude that their results confirm a special role of the ACC in pain, and that the activation of the ACC is an integral component of the neurobiological basis of the thermal grill illusion. The ACC has been implicated in the affective component of pain (e.g. the unpleasantness), demonstrating that the thermal grill caused participants to believe that they were experiencing a noxious thermal sensation. These findings are further supported by a thermal matching study, which demonstrated that the thermal grill produced a stimulus intensity of approximately 46 ^{o}C, which is similar to the human heat pain threshold, demonstrating that the thermal grill is producing an illusion of a noxious thermal sensation (Leung et al., 2005).

More recently, an fMRI study of the thermal grill illusion demonstrated that unlike the thermal grill's constituent cool (18 ^{o}C) or warm (41 ^{o}C) stimuli, the thermal grill (combination of 18 ^{o}C and 41 ^{o}C) caused significant activation in the contralateral thalamus, when thermal stimuli were applied to the left calf of right-handed participants for 30 seconds (Lindstedt et al., 2011a). Neuroimaging studies have demonstrated that thalamic aberrations appear to play a key role in central pain syndromes (Veldhuijzen et al., 2007), potentially suggesting an important overlapping mechanism of the thermal grill illusion and such pain pathologies (Lindstedt et al., 2011a).

1.4.5 Factors that may Influence the Thermal Grill Illusion

Unfortunately, the thermal grill illusion is not a robust phenomenon, with studies demonstrating that approximately 6-52% of healthy volunteers do not experience the illusion (Bouhassira et al., 2005; Leung et al., 2005; Kern et al., 2008a; Kern et al., 2008b; Li, 2009; Li et al., 2009; Brunello, 2010; Kostka, 2011; Boettger et al., 2012; Boettger et al., 2013). Experimental factors, biological factors and psychological factors may influence the response to the thermal grill illusion. Some of these factors are discussed below.

1.4.5.1 Experimental Factors

One important experimental factor that influences the response to the thermal grill illusion is the settings of the thermal grill. Bouhassira and colleagues demonstrated that larger temperature differences between the warm and cool bars of the thermal grill results in more participants experiencing the thermal grill illusion, and at a greater intensity (Bouhassira et al., 2005). These findings have been replicated in further studies by Kern and colleagues (Kern et al., 2008a; Kern et al., 2008b), as well as by Leung and colleagues (2005) and Boettger and colleagues (Boettger et al., 2011; Boettger et al., 2012; Boettger et al., 2013). To

ensure that the painful and / or burning sensation experienced from the thermal grill is a result of participants' experiencing the thermal grill illusion, and not as a result of activation of peripheral nociceptors, the temperatures of the cool and warm bars must remain within innocuous ranges (i.e. above participants' cold pain threshold and below participants' heat pain threshold). However, a sufficient difference in temperature differences between the cool and warm bars is essential; temperature differences as small as 5 ^{o}C to 10 ^{o}C produced very low levels of paradoxical pain, whereas sufficient levels of paradoxical pain were experienced when temperature differences were 20 ^{o}C to 25 ^{o}C (ref Bouhassira et al 2005).

1.4.5.2 Biological Factors

One important biological factor that may influence the response to the thermal grill illusion is an individual's thermal pain thresholds. For instance, individuals who are either poor or non-responders to the thermal grill illusion may have greater cold pain thresholds and / or heat pain thresholds, thus may require a larger temperature difference between the warm and cool temperature bars to experience the thermal grill illusion. This is unlikely the case for studies that customised the temperature of the warm and cool temperature bars to participants' cold and heat pain thresholds, such as those by Bouhassira and colleagues (2005), Kern and colleagues (2008a; 2008b) and Boettger and colleagues (2011; 2012; 2013). However, for studies that used a fixed temperature combination for all participants, thermal pain thresholds may influence the response to the thermal grill illusion.

A recent thesis by Kostka (2011) demonstrated that participant's cold pain threshold was the only thermal threshold that reliably correlated with participants thermal grill response. Of all thermal thresholds (cold detection threshold, warm detection threshold, cold pain threshold and heat pain threshold), cold pain threshold is the most variable, which may explain the large

variability of response to the thermal grill between individuals (Rolke et al., 2006a; Kostka, 2011). Others have also demonstrated that participants' cold pain thresholds are the only thermal thresholds that consistently correlate with thermal grill response (Brunello, 2010; Lindstedt et al., 2011b; Averbeck et al., 2013), which is consistent with Craig and Bushnells' (1994) thermosensory disinhibition hypothesis. Additionally, Lindstedt and colleagues (2011) demonstrated that participants' heat pain thresholds were also correlated with thermal grill response. Cold and heat pain thresholds significantly correlate (Essick et al., 2004; Lindstedt et al., 2011b; Kim et al., 2013), such that the more sensitive a person is to cold pain (i.e. increased cold pain threshold), the more sensitive that person is also to heat pain (i.e. decreased heat pain threshold) and vice versa; thus it is not surprising that heat pain thresholds were also found to correlate with participants response to the thermal grill.

An abundance of literature exists demonstrating that gender significantly affects the response to painful experimental stimuli, with women generally being more sensitive compared to men (Fillingim et al., 2009). To date, there have been no reports of gender differences in response to the thermal grill illusion regarding pain and unpleasantness ratings (Brunello, 2010; Boettger et al., 2011; Boettger et al., 2012; Boettger et al., 2013), warm and cool ratings of the thermal grill illusion or the occurrence of the thermal grill illusion (Li et al., 2009). However, Li and colleagues (2009) demonstrated a significant difference in reaction time (time recorded from contact time to the thermal grill and initiation of the illusion) to the thermal grill, with larger reaction times reported in females compared to males.

The body location at which the thermal grill is elicited has previously been demonstrated to influence the response to the thermal grill illusion. Until recently, all studies investigating the thermal grill had been performed on either the palm or the forearm. A recent Masters thesis

by Maria Brunello (2010) investigated whether the thermal grill illusion could be elicited at body sites other than the upper extremities. Brunello compared the response to the thermal grill on the non-dominant side palm, back, calf and foot of pain-free healthy volunteers. Participants rated the sensation from the thermal grill as significantly more painful on their back compared to their calf and foot, and significantly more unpleasant on their back compared to their palm, calf and foot. Additionally, the intensity of pain experienced from the thermal grill was significantly greater for the palm and back when assessed during the last 15 seconds of thermal grill contact (45-60 s) compared to when assessed during the first 15 seconds (0-15 s), demonstrating an effect of time, however no significant effect of time was observed for the calf or foot (Brunello, 2010).

Another recent Masters thesis by Jason Lam (2012) also demonstrated significant differences in response to the thermal grill across the upper and lower extremities. Unlike the study by Brunello (2010), significantly greater ratings of pain and unpleasantness were observed on the lower extremities (calf) compared to the upper extremities (forearm). Although Brunello (2010) did not assess the response to the thermal grill on the forearm, both Averbeck and colleagues (2013) and Bach and colleagues (2011) demonstrated no significant differences in response to the thermal grill between the forearm and the palm. One reason for greater responses being observed on the calf compared to the forearm may be because the order of thermal stimuli were not randomised in the study by Lam (2012), thus participants' always received thermal stimuli on the forearm before the calf.

Hunter and colleagues investigated the response to the thermal grill illusion on the forearm, chin, cheek and forehead (Hunter et al., 2012). Their findings, presented at the 2012 International Association for the Study of Pain World Congress on Pain, demonstrated

significant differences in response to the thermal grill between the forearm and the chin and forehead, with greater responses observed on the forearm. Although not significant, it appeared that thermal grill responses were also greater at the forearm compared to the cheek. Another recent abstract, presented at the 2010 Association for Chemoreception Sciences Annual Meeting, compared the response to the thermal grill on both the palm and tongue, with responses in the tongue being perceived as cold and non-painful, whilst a hot, burning sensation was perceived on the palm (Tournier et al., 2010).

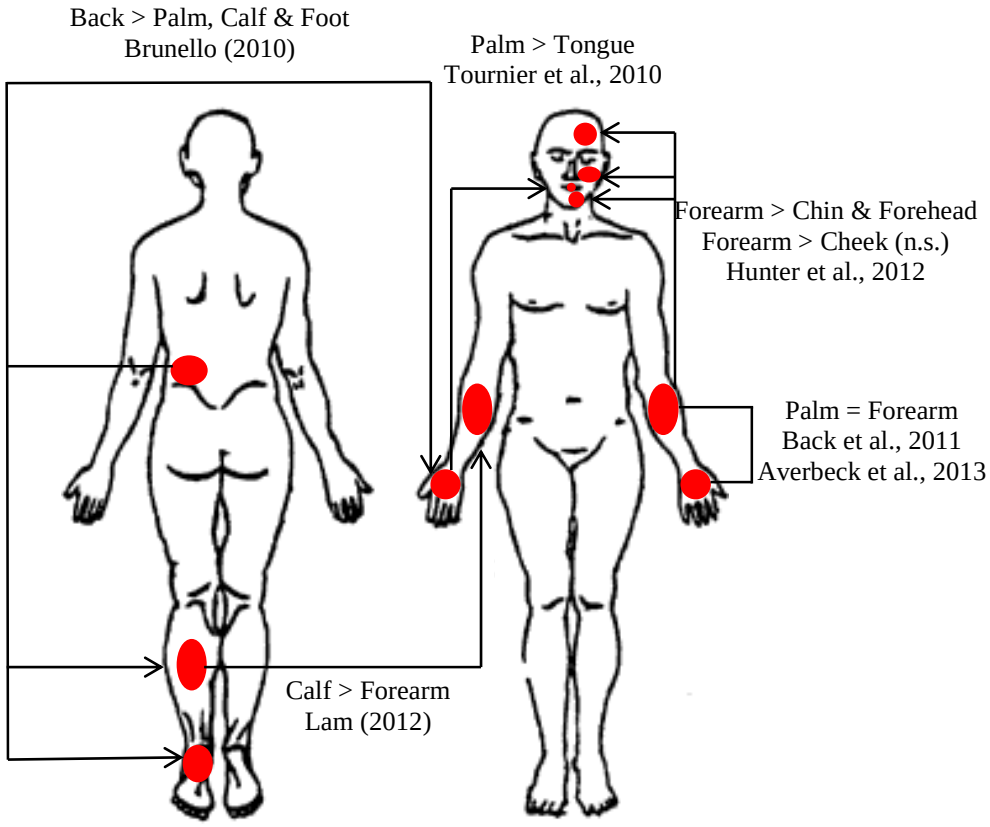

Figure 1.4.5.2.1. Body location differences in response to the thermal grill illusion.

Differences in response to the thermal grill illusion across body locations are depicted in this figure. The direction of the arrow indicates that a particular body region has a greater response to the thermal grill compared to the body region that the arrow originates from. No arrow on either end of the line connecting body location indicates that no significant difference has been demonstrated between those body regions. >: greater than; =: no difference; n.s.: not significant.

Body side has previously been shown to affect the response to experimental pain stimuli, such as intradermal capsaicin (Aykanat et al., 2012) and electrical stimulation (Neri and Agazzani, 1984), due to the affect of handedness / dominance. Similarly, body side may influence the response to the thermal grill illusion. In healthy pain-free volunteers, no significant difference in response to the thermal grill has been observed across body side (left vs. right), demonstrating no lateralisation to the thermal grill illusion (Boettger et al., 2011; Boettger et al., 2012; Averbeck et al., 2013; Boettger et al., 2013). However, a case report in a patient with complex regional pain syndrome type I demonstrated that the patient experienced a heightened response to the thermal grill on their affected arm hand compared to their unaffected arm hand (Heavner et al., 1997).

1.4.5.3 Psychological Factors

Psychological factors, such as anxiety, attention, anticipation and catastrophising, have been shown to affect the perception of pain (Geisser et al., 1993; Petrovic et al., 2000; Tang and Gibson, 2005; Babiloni et al., 2006; Seminowicz and Davis, 2006; Thompson et al., 2008; Starr et al., 2010). Using electroencephalography (EEG), Li (2009) investigated the response to both innocuous and noxious thermal sensations and the thermal grill illusion. In response to thermal stimuli (non-painful cold, non-painful warm, painful cold, painful heat and the thermal grill), participants who reported the thermal grill illusion as painful (painful thermal grill responders) demonstrated a larger decrease in EEG power of Alpha2 on the left frontal area compared to participants who did not report the thermal grill illusion as painful (non-painful thermal grill responders). In addition, painful thermal grill responders demonstrated higher baseline EEG power in Alpha2 band compared to non-painful thermal grill responders. Alpha oscillations have been linked with individuals' vigilance, anxiety, perception, attention and semantic memory (Klimesch, 1999; Knyazev et al., 2004; Knyazev et al., 2006). For

example, both higher baseline alpha power and higher reactivity of alpha rhythms have been observed in participants with higher levels of anxiety (Knyazev et al., 2005; Knyazev et al., 2006; Li, 2009). Consequently, Li (2009) suggested that the difference in power of the Alpha2 band at baseline and the differences in reactivity of Alpha2 rhythms between painful thermal grill responders and non-painful thermal grill responders may reflect differences in participants state of anxiety, attention and anticipation to the experience of pain.

Recent abstracts presented at the 2012 International Association for the Study of Pain 14th World Congress on Pain (Christoffersen et al., 2012), 2013 EFIC 8th Pain in Europe Congress (Scheuren et al., 2013) and the 2013 XXI National Congress of the Italian Society of Psychophysiology (Valzano et al., 2013) demonstrated that anxiety, catastrophising, trait rumination and pain expectancy correlated with participants response to the thermal grill. Christoffersen and colleagues (2012) demonstrated that participant's state anxiety significantly positively correlated with the intensity of pain experienced from the thermal grill during the 2nd and 3rd minute (out of 3 minutes) of exposure to the thermal grill, but only when they placed their first hand on the thermal grill and not their second. Valzano and colleagues (2013) demonstrated a significant positive correlation between participants with high levels of catastrophising and their pain intensity and unpleasantness ratings of the thermal grill illusion. In addition, pain catastrophising scores were significantly higher in thermal grill 'responders' compared to 'non-responders'. Lastly, Sheuren and colleagues (2013) demonstrated that thermal grill 'responders' were characterised by higher pain catastrophising and higher pain expectancy scores compared to 'non-responders' and that the occurrence of the thermal grill illusion mainly depended on an interaction between participants trait rumination and pain expectancy. Therefore the abovementioned psychological factors may influence the response to the thermal grill illusion.

Psychological and psychiatric disorders affecting pain perception, such as depression and schizophrenia, have also been implicated in altering the perception of the thermal grill illusion. Recently, both Boettger and colleagues (2011) and Pinerua-Shuhaubar and colleagues (2011) demonstrated that sad mood induction significantly increased the intensity of pain and the unpleasantness experienced from the thermal grill compared to baseline in pain-free healthy participants. In the study by Boettger and colleagues (2011), both cold and heat pain thresholds were not affected by sad mood induction, nor were the reported pain and unpleasantness ratings to thermal pain thresholds. Thermal pain thresholds were not investigated in the study by Pinerua-Shuhaubar and colleagues (2011). In contrast, Pinerua-Shuhaubar and colleagues (2011) demonstrated that the sum of pain intensity and unpleasantness experienced from the thermal grill was significantly greater in unmedicated patients with minor depression compared to pain-free healthy participants.

Boettger and colleagues (2012; 2013) extended their research of psychological factors and pain perception to major mental disorders, such as major depressive disorder (MDD) and schizophrenia. In these two studies, the response to the thermal grill illusion was investigated in unmedicated patients with MDD and healthy controls and unmedicated patients with acute paranoid schizophrenia on both the left and right hand for 30 s. Similar to Bouhassira and colleagues, the temperatures of the cool and warm temperature bars were customised to participants' cold and heat pain thresholds respectively. In line with previous studies (Bar et al., 2005; Bar et al., 2007; Schwier et al., 2010; Bar et al., 2011), both cold and heat pain thresholds were significantly increased in patients with MDD compared to healthy controls, although patients' pain and unpleasantness ratings at their thermal pain thresholds did not differ compared to healthy controls. Not surprisingly, thermal grill thresholds (temperature differential at which participants first indicated a painful sensation as indicated on the VAS as > 6 / 100 mm) also differed significantly between patients with MDD and healthy controls,

with patients requiring a larger temperature differential between the cool and warm bars to elicit such a painful sensation. Even when correcting the temperature of the cool and warm bars to reflect patients' altered cold and heat pain threshold, patients with MDD reported significantly less pain to the thermal grill illusion compared to healthy controls. Thus, the predominant finding of Boettger and colleagues (2013) study was that the response curve of the thermal grill illusion was shifted towards higher stimulus intensities in patients with MDD, similar to that observed for both cold and heat pain thresholds. The authors postulated the below hypothesis supporting higher thermal grill stimulus intensities: there is evidence for differential processing of A-δ and C-fibres in patients with MDD, in particular smaller A-δ laser-evoked potential amplitudes in patients with MDD compared to healthy controls (Terhaar et al., 2011). A-δ fibres responsive to innocuous cooling converge on COLD neurons in the spinal cord dorsal horn, thus a reduction in amplitude of A-δ fibres may shift the stimulus-response curve to lower temperatures in patients with MDD compared to healthy controls. As reported by Craig and Bushnell (1994), the discharge pattern of COLD neurons changes during thermal grill stimulation, resulting in disinhibition of HPC cells and the experience of pain. Thus, Boettger and colleagues (2013) suggested that a shift in noxious cold sensations, and a hypothetical shift in innocuous cold sensations, towards lower temperatures in patients with MDD may maintain COLD cell inhibition of HPC cells even at lower temperatures, thereby increasing the overall thermal grill thresholds. In support of this hypothesis analyses revealed that the increased temperature differential between the cool and warm bars required for the perception of the thermal grill illusion in patients with MDD was mainly driven by patients' significant increase in their cold pain thresholds (Boettger et al., 2013).

Similar to patients with MDD (see above, section 1.5.5.3.2), cold and heat pain thresholds as well as thermal grill thresholds were significantly increased in unmedicated patients with

schizophrenia compared to healthy controls (Boettger et al., 2012). Although cold and warm detection thresholds were not investigated in this study, Jochum and colleagues (2006) previously demonstrated that patients with schizophrenia had elevated warm detection thresholds, as well as elevated heat pain thresholds compared to controls, thereby overall supporting the abovementioned hypothesis for increased thermal grill thresholds in patients with schizophrenia. These findings in patients with MDD and schizophrenia demonstrate the importance of investigating both cold and heat pain thresholds when investigating the response to the thermal grill illusion; and suggest that customising the temperature of the cool and warm temperature bars is necessary, opposed to a standard fixed temperature combination, especially when investigating the response to the thermal grill illusion between two different populations.

Serotonin (5-HT), a neurotransmitter involved in mood and depression, also influences pain perception both peripherally and centrally. 5-HT can either inhibit or facilitate pain, depending on the 5-HT receptor subtypes it acts on (Eide and Hole, 1993). Deficiencies of the uptake transporter for serotonin (5-HTT) have been implicated in the development of thermal hyperalgesia in rodents. Following nerve injury, 5-HTT knock out mice display reduced thermal hyperalgesia compared to their wild type counterparts (Vogel et al., 2003; Palm et al., 2008). In humans, polymorphisms in the 5-HTT have shown to influence the analgesic effect of remifentanil, an opioid analgesic, with low expressing individuals demonstrating a greater analgesic effect following remifentanil compared to high expressing individuals (Kosek et al., 2009). Polymorphisms in the 5-HTT have also been implicated in the perception of the thermal grill illusion. Recently, Lindstedt and colleagues (2011) demonstrated that genetically inferred (opposed to measured directly) levels of expression of the 5-HTT influenced participants' heat and cold pain thresholds, as well as ratings of unpleasantness to the thermal grill illusion. In particular the low 5-HTT expression group were significantly less sensitive to

both heat and cold pain compared to the high 5-HTT expressing group, with a gender-by-genotype interaction demonstrating that low 5-HTT expressing women were less sensitive to cold pain compared to low 5-HTT expressing men. Of particular interest was that in the low 5-HTT expressing group, women rated the unpleasantness of the thermal grill illusion as significantly lower than women in the high 5-HTT expressing group, with no such differences being observed in men. This association between genetically inferred levels of expression of the 5-HTT and participants' response to the thermal grill illusion may account for the large inter-individual variability observed in response to the thermal grill illusion (Lindstedt et al., 2011b).

1.4.6 The Thermal Grill as a New/Unique Model for Central Pain

Advantages of the thermal grill, for investigation of the mechanisms that underlie chronic pain and as a potential tool to screen for analgesic efficacy, are that it produces pain without causing any tissue damage and therefore represents a relatively harmless and ethically acceptable pain model (Kern et al., 2008b). At the initiation of this PhD thesis, only 11 studies investigating the thermal grill illusion had been published in peer-reviewed journals, with 2 of these studies being case report studies (Craig and Bushnell, 1994; Craig et al., 1996; Heavner et al., 1997; Morin et al., 2002; Fruhstorfer et al., 2003; Bouhassira et al., 2005; Leung et al., 2005; Defrin et al., 2008; Kern et al., 2008a; Kern et al., 2008b; Li et al., 2009). These initial studies characterised the response to the thermal grill illusion in pain-free volunteers; demonstrated that the response to the thermal grill could be pharmacologically modified and provided brief insight into the differing response to the thermal grill illusion in a patient with CRPS and MS. Consequently, the study design and the proposed research outcomes that governed this thesis were based on the limited amount of literature available at the commencement of my PhD research (1st of March 2010).

Since the commencement of this thesis, the literature in this field has doubled (Kammers et al., 2010; Bach et al., 2011; Boettger et al., 2011; Lindstedt et al., 2011a; Lindstedt et al., 2011b; Pinerua-Shuhaibar et al., 2011; Boettger et al., 2012; Seckel et al., 2012; Averbeck et al., 2013; Boettger et al., 2013; Harper and Hollins, 2014). These additional studies further characterised the response to the thermal grill illusion in pain-free volunteers, under both neutral and sad mood induction; explored the response to the thermal grill illusion in patients who suffer from psychiatric disorders, such as major depression and schizophrenia; manipulated the response to the thermal grill illusion by selectively activating cool and warm sensing ion channels; demonstrated a differential effect of cool, warm and neutral adaptation to the perception of the thermal grill illusion and implicated genetic polymorphisms of 5-HTT expression with the response to the thermal grill illusion.

Considering the uniqueness of this experimental pain model, in particular at the time when this PhD was initiated in 2010, very few papers have been published, with no papers in the relevant population of chronic pain patients, albeit the abovementioned case reports. This is most likely due to there being no commercially available thermal grill; therefore at this stage a thermal grill can only be obtained on a 'construct-it-yourself' basis. Recently, an editorial in the journal PAIN® encouraged researches' to pursue the thermal grill for clinical research into the basis of central pain (Craig, 2008). This editorial suggestion was the motivation for undertaking this research into the thermal grill illusion.

Craig (2008) posited that if the fundamental dysfunction in central pain is due to the same mechanism that underlies the thermal grill illusion of pain, then any pharmacological compound that inhibits the thermal grill response may also alleviate central pain (Craig, 2008). Therefore, the thermal grill may represent a novel experimental pain model for testing

analgesics (Kern et al., 2008b). Additionally any absence or altered response to the thermal grill illusion in patients with chronic pain may be a diagnostic tool for central pain (Craig, 2008). Accordingly, the thermal grill may be a suitable investigative tool to uncover the basis for the interaction between the nociceptive and thermal sensory systems, and therefore the basis for central pain (Craig, 2008; Kern et al., 2008a). In order to expand on the understanding of the mechanisms that underlie the thermal grill illusion, the neurobiological mechanisms that underlie pain and temperature perception will now be discussed.

1.5 Neurobiological Mechanisms of Pain and Temperature Perception

Significant anatomical and functional overlap exists between ascending pain and temperature pathways in the central nervous system (Craig, 1998). Clinically, this is observed by the frequent use of temperature descriptors used by patients with chronic pain to describe their pain disorders, with temperature descriptors incorporated into widely used and validated pain questionnaires, such as the McGill Pain Questionnaire (Melzack, 1975). However, debate exists about how somatic sensations, such as pain and temperature, are encoded by the nervous system (Ma, 2010). One attractive model is the population-coding hypothesis of somatic sensations, where specific sensory labelled lines crosstalk to generate and shape somatosensory perception (Ma, 2010). Labelled lines exist for both innocuous and noxious thermal sensations; for example, innocuous cold is transmitted via a cold-labelled line, innocuous warm via a warm-labelled line, and noxious cold and heat via a pain-labelled line. The population-coding hypothesis can explain thermal paradoxes, such as the thermal grill illusion (Ma, 2010)(see section 1.5.5). Craig (2003), Brunello (2010) and Lam (2012) have recently reviewed this topic of pain and temperature perception. The following is an overview of this area.

1.5.1 The Periphery

The peripheral nervous system functions as a relay network between the extremities and organs of the human body and the central nervous system. Communication between the extremities and organs and the central nervous system occurs via primary afferent neurons. Primary afferent neurons transmit sensory information from receptors to the spinal cord. Afferent fibres originating in the periphery fall into three categories: large diameter (> 10 μm), heavily myelinated, fast conducting (30-100 m/sec) A-β fibres; medium diameter (2-6 μm), thinly myelinated, intermediate conducting (5-30 m/sec) A-δ fibres and small

diameter (0.4-1.2 μm), non-myelinated, slowly conducting (0.5-2 m/sec) C fibres (Millan, 1999; Marchand, 2008). Aβ-fibres are predominately involved in light touch and proprioception, thus will not be discussed in further detail (Marchand, 2008). A-δ and C fibres are primarily responsible for the transmission of nociceptive messages (Marchand, 2008).

A-δ fibres are responsible for the transient sharp or pricking 'first' pain felt immediately after injury; precise localisation of pain; and the rapid spinal response which triggers the nociceptive withdrawal reflex (Johnson, 1997; Renn and Dorsey, 2005; Vanderah, 2007; Marchand, 2008). Aδ fibres are activated by extreme temperatures (> 45^{o}C or < 5^{o}C) and high-intensity mechanical stimulation. C fibres are responsible for the prolonged aching, burning, and diffuse 'second' pain (Johnson, 1997; Marchand, 2008). C fibres transmit noxious information from a variety of modalities; including mechanical, thermal and chemical stimuli; and are therefore termed C-polymodal nociceptors (Johnson, 1997; Vanderah, 2007). The mechanisms that underlie experimentally induced pain also involve activation of primary afferent fibres. Thus, the periphery serves as the interface for all currently used human experimental pain models.

1.5.2 The Spinal Cord

The grey matter of the spinal cord consists of 10 laminae (I-X) (Rexed, 1952). Pain processing occurs predominately in laminae I, II and V of the dorsal horn, with A-δ fibres primarily projecting to laminae I and V, and C fibres to laminae I and II (Craig, 2003; Dubin and Patapoutian, 2010). For the purposes of this thesis, focus herein will be on lamina I neurons, due to the hypothesised involvement of these neurons in the thermal grill illusion (see section 1.4.2).

Lamina I neurons receive input from nociceptors, thermoreceptors and polymodal afferents and are the major primary afferent termination site of Aδ and C-fibres (Han et al., 1998). Lamina I consists of several distinct types of second-order neurons, including nociceptive specific cells (NS), cells responsive to noxious heat, pinch and cold (HPC), wide dynamic range cells (WDR), cooling specific cells (COLD) and cells responsive to innocuous warm (WARM).

NS cells primarily receive input from A-δ fibre nociceptors, have almost no ongoing discharge and respond to noxious mechanical and heat stimuli (Craig and Andrew, 2002; Craig, 2003). HPC cells primarily receive input from C-fibre nociceptors, have little ongoing discharge and respond to temperatures < 25 ^{o}C and > 45 ^{o}C (Craig et al., 2001; Craig, 2003). NS and HPC lamina I STT neurons have been associated with first and second pain respectively (Craig, 2003). HPC cells are believed to underlie the burning pain experienced from noxious heat and the burning sensation elicited by noxious cold and the thermal grill illusion of pain (Craig et al., 2001). The sensitivity of HPC cells to noxious cold is graded below ~24 ^{o}C; their maintained response to cold accelerates at noxious temperatures (<15 ^{o}C), emphasising that pain is not a binary (yes or no) modality (Craig, 2003).

Another class of lamina I neurons are WDR cells, however these cells are predominately located in lamina V (Johnson, 1997; Verdugo et al., 2007). As the name implies, WDR cells are sensitive to a wide range of stimuli and respond to both innocuous and noxious cutaneous stimuli, noxious cold and noxious heat (Dostrovsky and Craig, 1996; Craig, 2003)). Unlike NS and HPC cells, WDR cells are modality-ambiguous (Craig, 2003). WDR cells receive input from A-β, A-δ and C-fibres (Marchand, 2008).

Pure thermoreceptive-specific lamina I neurons also exist. COLD cells display a tonic and graded response to cooling from approximately normal skin temperature (~34 ^{o}C), which plateaus around 15 ^{o}C, is inhibited by warming and paradoxically excites above 44 ^{o}C (Craig and Bushnell, 1994; Dostrovsky and Craig, 1996; Craig et al., 2001; Craig, 2003; Zhang et al., 2006). WARM cells receive input from C-fibre thermoreceptors and display a graded response to warming from a threshold of 35-37 ^{o}C, with responses plateauing at noxious temperatures (Andrew and Craig, 2001).

1.5.3 Ascending Tracts: from the Dorsal Horn to the Brain

Primary afferent fibres enter the dorsal horn of the spinal cord via the dorsal root (Renn and Dorsey, 2005). Upon entering the spinal cord and before synapsing with second-order neurons, the axons of primary afferent fibres bifurcate into ascending and descending branches that run 2-3 spinal segments within the Lissauer's tract, sending collateral projections to the superficial layers of the dorsal horn (Renn and Dorsey, 2005; Verdugo et al., 2007). This then allows the nociceptive message to be transmitted across multiple segments of the spinal cord, rather than to a signal spinal segment (Renn and Dorsey, 2005). Primary afferent fibres then synapse with second-order projection neurons in the dorsal horn (Renn and Dorsey, 2005). Second order projection neurons then transmit the nociceptive message via ascending pathways in the spinal cord to higher centres in the central nervous system (CNS), ultimately terminating in the thalamus (Haggard et al., 2013). Within the thalamus, second order projection neurons synapse with third order neurons, which in turn further process and transmit the nociceptive message to cortical and limbic structures in the brain (Millan, 1999). Within the cortical and limbic structures, the nociceptive message is finally interpreted as pain (Millan, 1999; Dostrovsky, 2000)(see Figure 1.5.3.1). A similar process is observed for primary afferent fibres originating in the trigeminal region; however,

these fibres enter the medullary caudalis nucleus of the trigeminal system (trigeminal nucleus) via the trigeminal nerve (Millan, 1999).

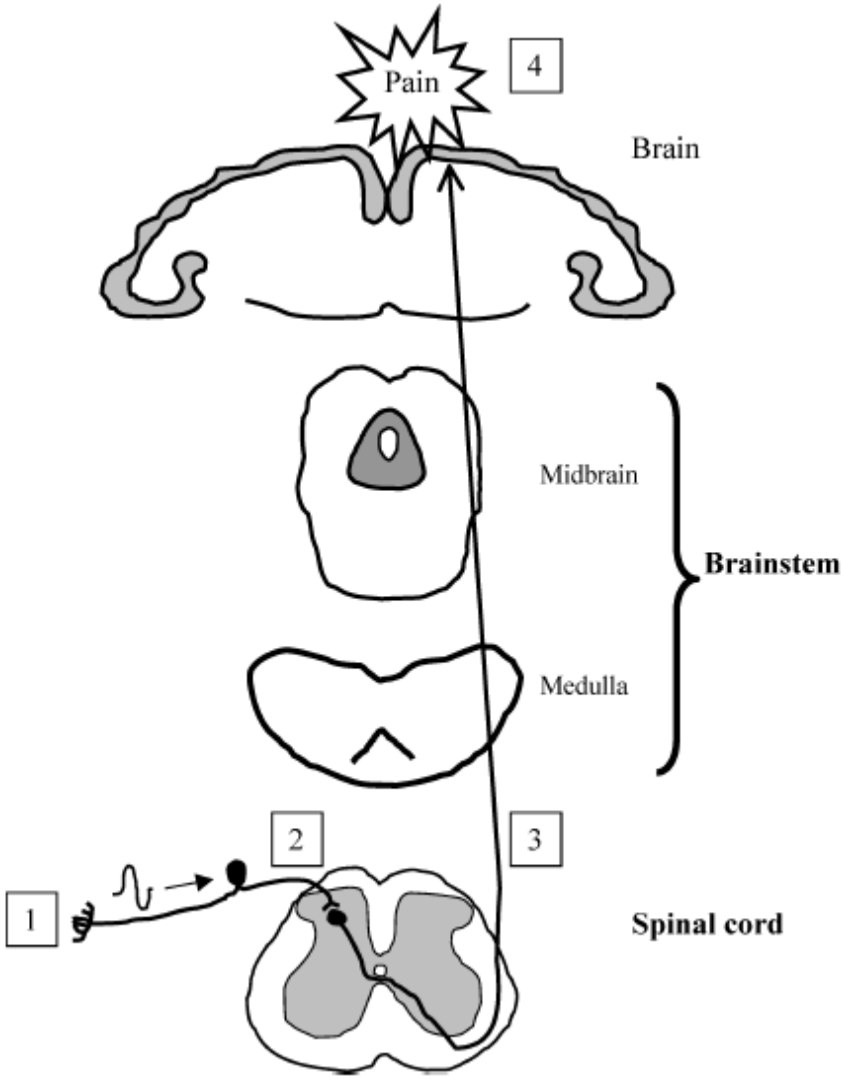

Figure 1.5.3.1. Ascending pain pathway.

Schematic of ascending pain pathway from the periphery to the brain. Primary afferent fibres transmit nociceptive information from the periphery (1) to the spinal cord dorsal horn (2). In the dorsal horn, primary afferent fibres synapse with second order neurons. Second order neurons then ascend via the spinal cord (3) and brainstem to the thalamus. In the thalamus, second order neurons synapse with third order neurons. Third order neurons then transmit the nociceptive message to the brain (4), where it is interpreted as pain (Renn and Dorsey, 2005). Reprinted from Renn and Dorsey (2005) with kind permission from Wolters Kluwer Health.

Secondary neurons travel to supraspinal centres via three main ascending pathways: the spinothalamic tract (STT - spinal cord to thalamus); the spinomesencephalic tract (SMT – spinal cord to mesencephalon) and the spinoreticular tract (SRT – spinal cord to reticular formation) (Renn and Dorsey, 2005). For the purposes of this thesis, focus herein will be on the STT, due to this pathways hypothesised involvement in the thermal grill illusion (see Section 1.4.2).

The STT is the most prominent ascending tract that transmits sensations of pain (in particular the sensory-discriminatory aspect of pain (Basbaum et al., 2009)) and temperature from the grey matter of the spinal cord to the thalamus (Willis et al., 1979; Hodge and Apkarian, 1990; Craig, 1998; Verdugo et al., 2007). STT neurons ascend to the thalamus via the anterolateral white matter of the spinal cord (Willis, 1985; Johnson, 1997). Before ascending, STT neurons cross the midline in the spinal cord, thus ascend to the thalamus via the contralateral anterolateral white matter and synapse in the thalamus on the contralateral side to the initial peripheral stimulus (Willis, 1985; Millan, 1999; Purves et al., 2001; Haggard et al., 2013)(see Figure 1.5.3.2 A).

Sensations of pain and temperature at the face follow a separate route to the thalamus (Purves et al., 2001). Facial nociceptors and thermoreceptors descend via the trigeminal tract to the spinal nucleus of the trigeminal complex in the caudal medulla and terminate in two subdivisions of the spinal trigeminal complex: the pars interpolaris and pars caudalis (Millan, 1999; Purves et al., 2001). Primary afferent axons synapse with second order neurons in these two trigeminal nuclei. Similar to the spinal cord, axons from the second order trigeminal neurons cross the midline and ascend to the contralateral thalamus in the trigeminothalamic

tract (Purves et al., 2001)(see Figure 1.5.3.2B). The trigeminothalamic tract is analogous to, and continuous with, Lissaeur's tract in the spinal cord.

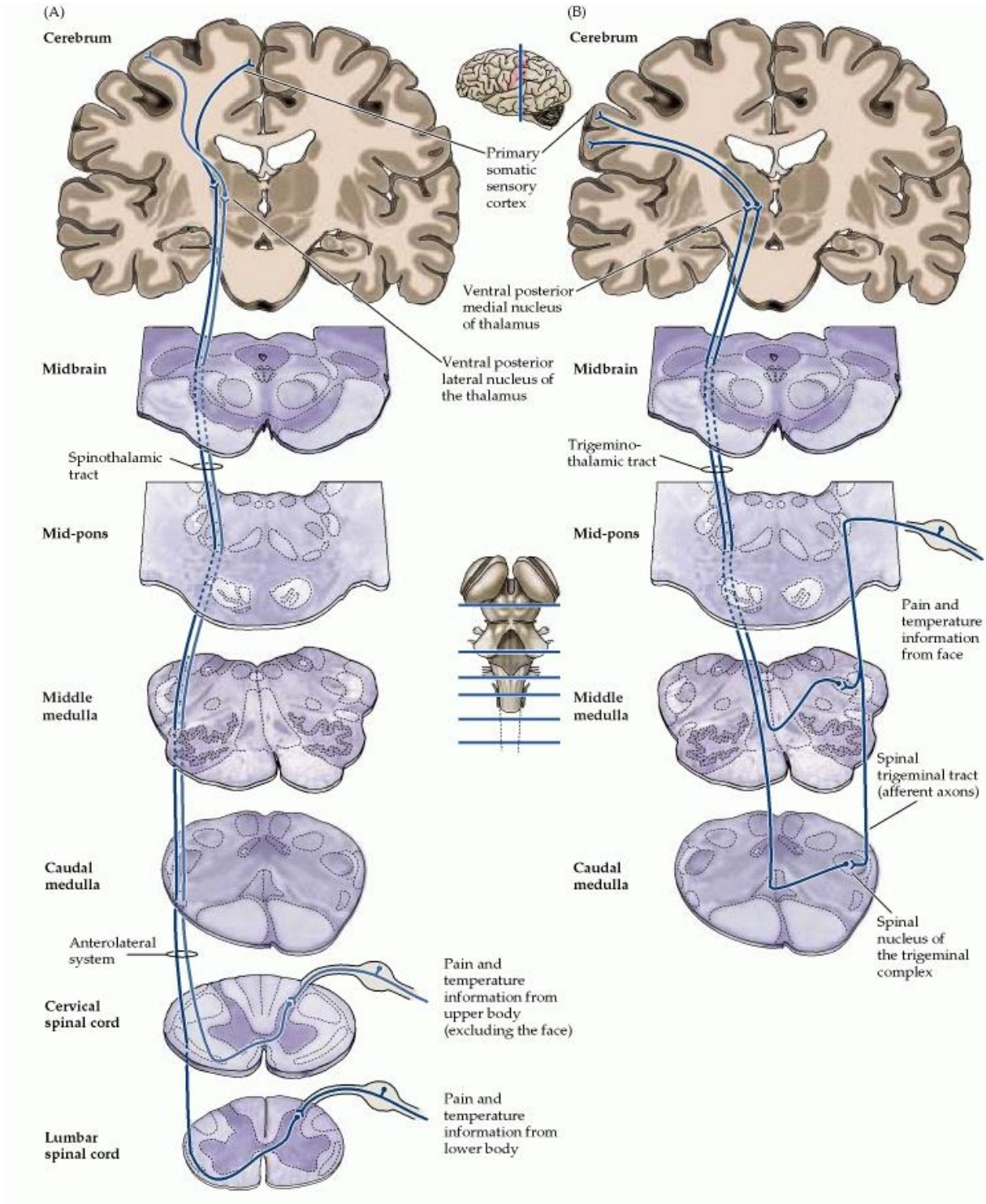

Figure 1.5.3.2. Major pathways for pain and temperature sensation.

Sensations of pain and temperature from the body (excluding the face) ascend to the thalamus via the spinothalamic tract (A), whereas sensations of pain and temperature from the face follow a separate route to the

thalamus via the trigeminothalamic tract (B) (Purves et al., 2001). Reprinted from Purves *et al.,* (2001) with kind permission from Sinauer Associates.

1.5.4 Connections to the Thalamus and Projections to the Cortex

Before reaching the cortex, all nociceptive information is received and processed in the thalamus (Dostrovsky, 2000). Coding of the sensory-discriminatory aspect of pain is thought to occur in the lateral thalamus, whereas coding of the affective-motivational aspect of pain is thought to occur in the medial thalamus (Treede et al., 1999; Perl, 2011). Due to the intimate connection between the thalamus and cortex, the activity of thalamic nuclei influences cortical functioning (Perl, 2011).

Second order neurons travelling via the STT project to the primary somatosensory cortex (S1) via ventro-posterior-lateral (VPL) thalamic nuclei if arising from the spinal cord or via ventro-posterior-medial (VPM) thalamic nuclei if arising from the trigeminal nucleus, and to the secondary somatosensory cortex (S2) via the ventro-posterior-inferior (VPI) nuclei (Verdugo et al., 2007; Haggard et al., 2013). Craig (2002; 2003), along with his colleagues (1994; 2004), as well as Blomqvist and colleagues (2000) and Dostrovsky and Craig (1996), have provided evidence for a lamina I relay in the posterior aspect of the ventral medial nucleus (VMpo) and the ventral caudal medial dorsal nucleus (MDvc), described below, although this has been subject to controversy (Treede, 2002; Willis et al., 2002).

The VMpo receives topographic, discriminative nociceptive specific and thermoreceptive specific lamina I spino- and trigemino-thalamic projections (Craig et al., 2000). In primates, lamina I STT nociceptive (NS and HPC) and thermoreceptive (WARM and COLD) neurons project to a lateral thalamic relay nucleus, VMpo, and to a medial thalamic relay nucleus,

MDvc (Craig et al., 1994; Craig, 2003). There is also weak input to the ventral posterior nucleus (VP) and some input to the ventral posterior inferior nucleus (VPI) (Craig, 2003). Nociceptive (NS and HPC) and thermoreceptive (WARM and COLD) neurons have been recorded in the VMpo of awake humans (Davis et al., 1999).

Microstimulation of the VMpo in awake humans elicits discrete, graded sensations of cool, warmth and pain (Davis et al., 1999; Ohara and Lenz, 2003). Craig (2003) has postulated that the VMpo is a dedicated lamina I spino-thalamo-cortical relay nucleus that specifically represents pain and temperature. The VMpo projects to the dorsal margin of the insula cortex and to area 3a in the primary somatosensory cortex (Craig, 1998; Craig, 2002; Craig and Blomqvist, 2002; Craig, 2003). Stimulation of the dorsal insular cortex causes well-localised pain in awake humans (Ostrowsky et al., 2002); lesions of this region reduce sensations of pain and temperature (Schmahmann and Leifer, 1992; Greenspan et al., 1999) and functional imaging studies of innocuous and noxious thermal stimuli demonstrate activation in this region (Craig et al., 1996; Craig, 2002). Similarly lesions to area 3a reduce sensations of pain (Kenshalo et al., 1989; Whitsel et al., 2009; Vierck et al., 2013) and microstimulation of area 3a facilitates pain (Yezierski et al., 1983). Additionally, antidromic activation of VMpo from area 3a has been demonstrated (Craig, 2003). There is now considerable evidence to support that the VMpo nucleus is crucial for the perception of pain and temperature (Blomqvist et al., 2000; Craig, 2003).

Lamina I STT neurons also project to the MDvc, a medial thalamic relay nucleus (Craig, 2003). The MDvc projects to area 24c in the fundus of the anterior cingulate cortex (ACC)(Craig, 2003). Most functional imaging studies of pain demonstrate activation of the ACC (Talbot et al., 1991; Derbyshire and Jones, 1998; Casey, 1999; Tracey, 2005; Tracey

and Mantyh, 2007; Tracey, 2011) and lesions of the ACC can affect pain clinically (Craig, 2003). The ACC is believed to play a prominent role in the affective-motivational processing of pain (Treede et al., 1999), whilst the primary somatosensory cortex, secondary somatosensory cortex (albeit controversial) and insula cortex codes for the sensory-discriminatory aspect of pain (Treede et al., 1999). The insular cortex may also contribute to the affective-motivational processing of pain due to its projections to the limbic system (Treede et al., 1999).

Craig and colleagues (1996) suggest that HPC activity is conveyed by the medial lamina I pathway via the MDvc to the ACC and that COLD activity is conveyed by the lateral lamina I pathway via the VMpo to the insula. Under normal conditions, cold-evoked COLD activity in the lateral lamina I pathway normally inhibits cold-evoked HPC activity in the medial lamina I pathway, however in the presence of a warm stimulus (thermal grill), this inhibition is unmasked, resulting in activation of the ACC and the experience of pain.

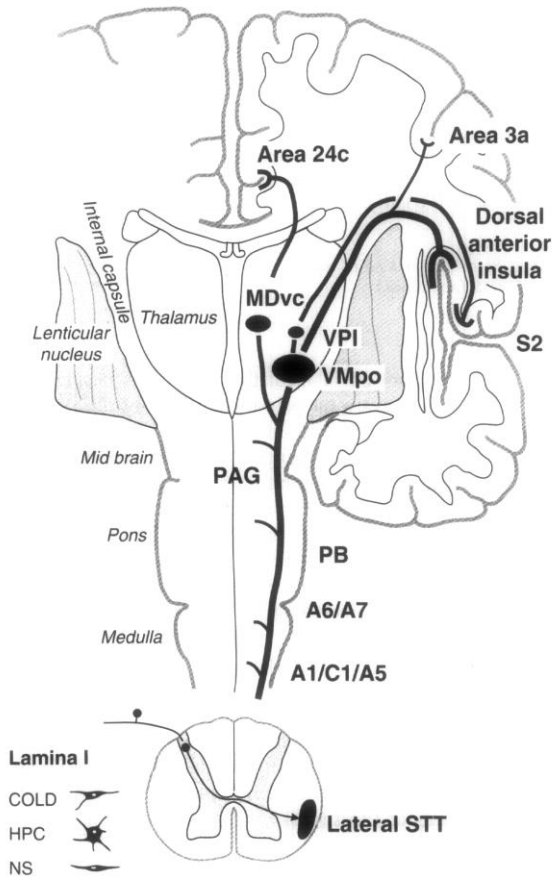

Figure 1.5.5.1. Ascending projections of the lamina I spino-thalamo-cortical system.

Schematic diagram summarising the ascending projections of three major classes of lamina I cells (COLD, HPC, NS) in the macaque monkey. COLD, HPC and NS axons decussate and ascend in the lateral STT, eventually terminating in the thalamus in the VMpo, VPI and MDvc. The VMpo then projects to the dorsal margin of the insular cortex and to area 3a in the primary somatosensory cortex, the VPI to the secondary somatosensory cortex and the MDvc to area 24c in the fundus of the anterior cingulate cortex (Dostrovsky, 2000). Reprinted from Craig and Dostrovksy (1999) with kind permission from Elselvier.

1.5.5 Innocuous Cool and Warm Detection

Experimental evidence, including human conduction blockade experiments and thermal imaging studies, have demonstrated that both cool and cold sensations are processed via different mechanisms and pathways compared to warm and hot sensations (Fruhstorfer, 1984; Craig et al., 1996; Wrigley, 2006). Within the same body region, there are significant differences in the number of cool and warm receptors that exist. For example, on the hand there are approximately 1-5 cold receptors per cm^2, whilst in the same region there are approximately 0.4 warm receptors per cm^2 (cited by Li (2009)). Although differences in receptor densities are observed between cold and warm receptors, sensitivities to cold and warm stimuli are highly correlated, demonstrating that the more sensitive a body region is to cold, the more sensitive it is to warm as well (Stevens and Choo, 1998; Li et al., 2009).

Thermoreceptive afferents terminate in the skin as unspecialised free nerve endings (Klement and Arndt, 1991). In humans, warm and cold thermal detection thresholds are approximately 34 ^oC and 31 ^oC respectively (Erpelding et al., 2012). Between individuals, little deviation in warm and cold detections thresholds is observed, with warm and cold detection thresholds only differing up to 5 ^oC (Erpelding et al., 2012).

A-δ fibres responsive to cooling, discharge at normal skin temperature and have spot-like receptive fields (0.25-5 mm in diameter) (Kenshalo and Duclaux, 1977; Long, 1977; Campero et al., 2001). Cold fibres display steady state activity at temperatures between 20 ^oC and 40 ^oC (Darian-Smith et al., 1973; Dubner et al., 1975; Kenshalo and Duclaux, 1977), which is maximal between 20 ^oC and 30 ^oC (Dostrovsky and Craig, 1996), and either lessens or ceases at skin temperatures below 17 ^oC and above 40 ^oC respectively (Schepers and Ringkamp, 2009); below 17 ^oC, different classes of afferent fibres transduce noxious cold (discussed in

section 1.5.6). Cold afferent activity is suppressed by dynamic warming (Iggo, 1969; Kenshalo and Duclaux, 1977; Craig et al., 2001) and paradoxically excited by noxious heat (> 45 ^{o}C) (Dodt and Zotterman, 1952a; Kenshalo and Duclaux, 1977; Long, 1977; Campero et al., 2001).

Two distinct groups of cold neurons have been distinguished; low threshold neurons, which have an activation temperature near 30 ^{o}C and are likely to be involved in innocuous cool signalling, and high threshold neurons, which have an activation temperature below 20 ^{o}C and are largely capsaicin sensitive, thus these neurons may be analogous to those mediating noxious cold (Thut et al., 2003). TRPM8, the cold- and menthol-gated ion channel, is believed to transduce sensations of cool and is activated at temperatures below 26 ^{o}C (McKemy et al., 2002; Peier et al., 2002). TRPM8 has been identified on both low threshold cold neurons (myelinated A-δ and non-myelinated C-fibres), as well as high threshold cold neurons (C-fibres) (Kobayashi et al., 2005). However, menthol, an agonist at the TRPM8 receptor evoked a more robust current in low threshold neurons compared to high threshold neurons, potentially supporting the above notion that low threshold neurons transduce innocuous cold (Thut et al., 2003).

Mackenzie and colleagues (1975) demonstrated that selective A-δ nerve block impaired the detection of cold temperatures delivered to human hairy skin. Furthermore, A-δ fibre blockade resulted in the activation of non-myelinated C-fibres and the experience of a heat/burning sensation in response to an innocuous cold stimulus (Mackenzie et al., 1975). Others have also replicated these findings (Fruhstorfer, 1984; Yarnitsky and Ochoa, 1990); Yarnitsky and colleagues (1990) suggested that A-δ fibre blockade unmasked the normal inhibition exerted on non-myelinated C-fibres by myelinated A-δ fibres, thus allowed

normally innocuous cool temperatures to induce a burning sensation. These findings suggest that A-δ fibres are necessary for the perception of innocuous cold (associated with a cold-labelled line) and that innocuous cold can activate C-fibres to evoke a heat or burning sensation (associated with a pain-labelled line), however this sensation is normally inhibited by the simultaneous activation of the cold-labelled line (Ma, 2010; Ma, 2012)(See Figure 1.5.5.1A and B).

Simultaneous presentation of innocuous warm and cool temperatures, using a thermal grill, can replicate the above sensations of heat/burning, which can best be described as the sensation experienced when ice-cold feet meets warm water. It is believed that the heat/burning experienced from the thermal grill is due to an antagonistic relationship between cold, heat or pain, and warm labelled lines (Ma, 2010)(see Figure 1.5.5.1C).

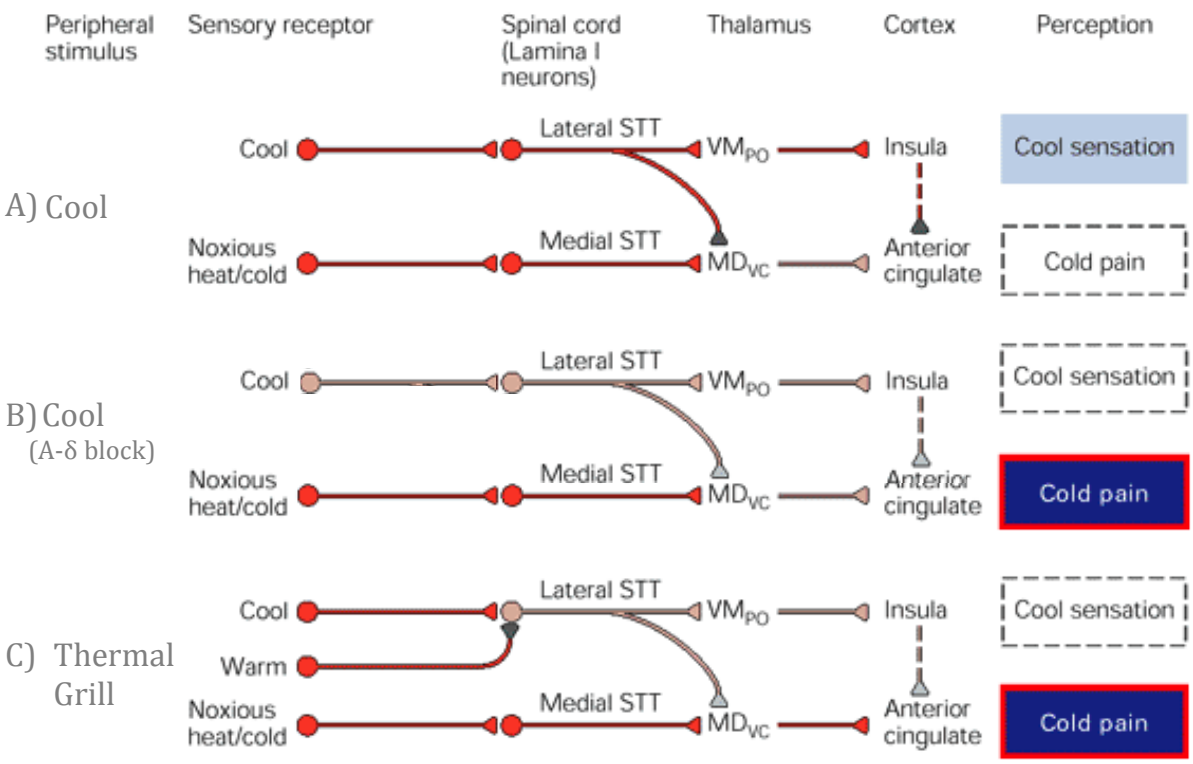

Figure 1.5.5.1 Proposed mechanism of innocuous cool and the thermal grill illusion

Proposed mechanism that underlies innocuous cool and the thermal grill illusion. A) An innocuous cool stimulus activates both A-δ fibres, which are responsible for transmitting sensations of "cool" (along a cool labelled line)

and C-fibres, which are responsible for transmitting sensations of noxious heat and cold (along a pain labelled line). Under normal conditions, the cool labelled line has an inhibitory effect on the pain labelled line, resulting in a cool sensation being experienced. B) A-δ fibre blockade results in blockade of the cool labelled line, hence the normal inhibition exerted by the cool labelled line onto the pain labelled line is disinhibited, resulting in a painful sensation, similar to the burn of cold pain, being experienced. C) When an innocuous warm stimulus is introduced alongside an innocuous cool stimulus (thermal grill), the warm stimulus activates a warm labelled line, which inhibits the cool labelled line. Similar to observed in (B), the cool labelled line is no longer able to exert its' inherent inhibition on the pain labelled line, resulting in a painful sensation, similar to the burn of cold pain, being experienced. Adapted from Basbaum and Jessell (2000) with kind permission from McGraw-Hill Medical.

Warm afferents are unmyelinated C-fibres, have single spot-like receptive fields (<1-2 mm in diameter) and are inhibited by cooling (Hensel and Iggo, 1971; Darian-Smith et al., 1979; Duclaux and Kenshalo, 1980). Warm fibres display graded, steady state activity at temperatures between 30 ^{o}C and 45-48 ^{o}C, reaching maximal activity between 40 ^{o}C and 45 ^{o}C (Duclaux and Kenshalo, 1980). Above and below these temperatures, less activity in these fibres is observed (Dodt and Zotterman, 1952b; Hensel and Iggo, 1971; Duclaux and Kenshalo, 1980). Both TRPV3 and TRPV4 are believed to transduce sensations of warmth (Guler et al., 2002; Smith et al., 2002; Chung et al., 2004).

Thermosensory C-fibres in humans can be divided into multiple subtypes based on electrophysiological recordings performed by Campero and colleagues (2009). These include the following: C-warm, C2, CH, CMH and CMHC. C-warm respond to warm temperatures and are inactivated by noxious cold and heat; C2 respond to both innocuous and noxious cold (0-30 ^{o}C) and also to warm/hot temperatures (38-48 ^{o}C); CH specifically to noxious heat; CMH to both noxious mechanical and noxious heat and CMHC polymodal nociceptors to mechanical, heat and noxious cold stimuli. Based on the features of these thermosensitive C-

fibres and A-δ (described above), Campero and colleagues (2009) proposed the population-coding hypothesis for thermoreception and perception (see Figure 1.5.5.2). The population-coding hypothesis nicely explains several thermal paradoxes, such as the thermal grill illusion (Ma, 2010)(see section 1.4.2)

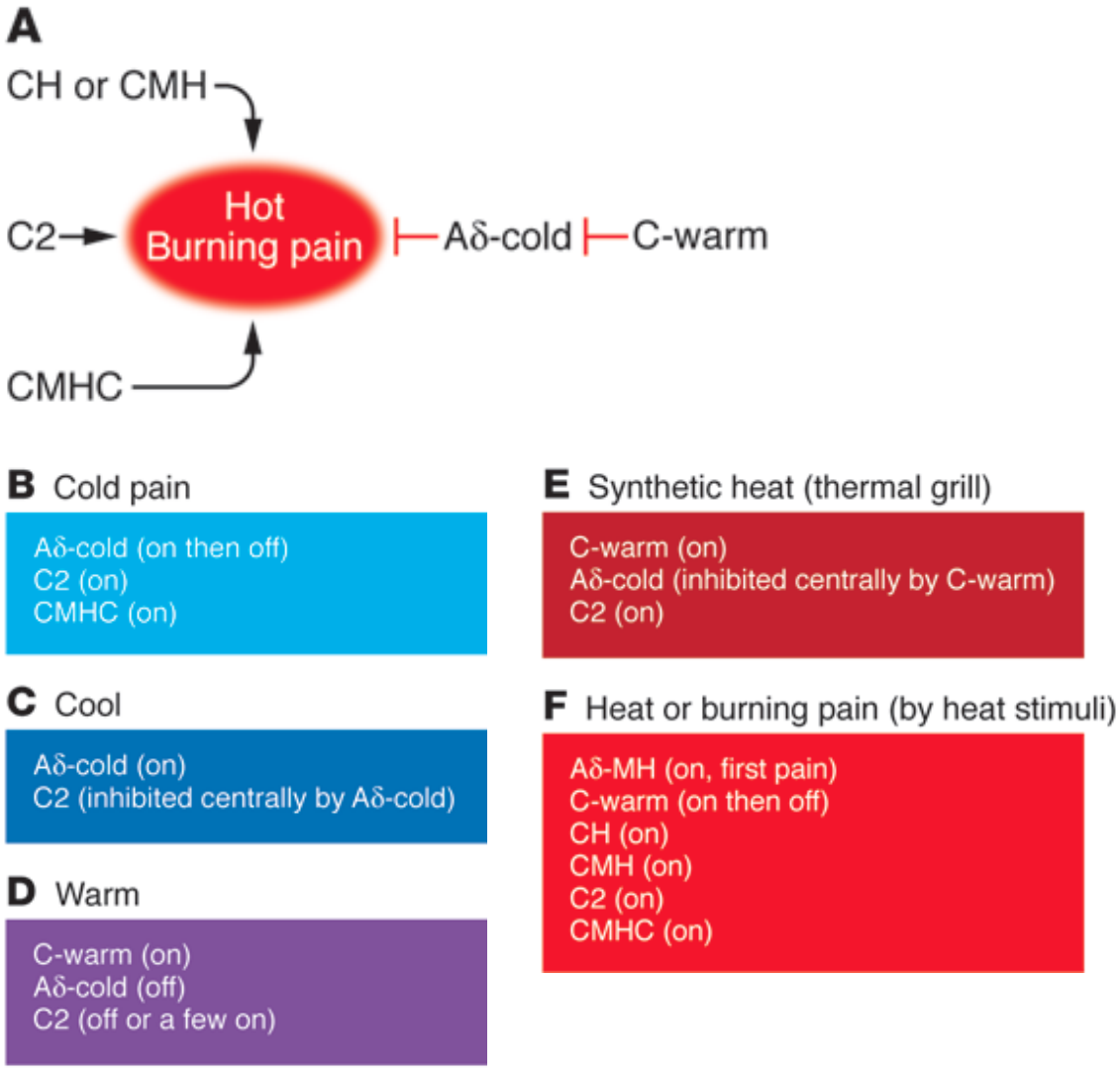

Figure 1.5.5.2. Population coding of thermal perceptions

Activation of A-δ fibres normally inhibits the hot and/ or burning pain elicited by CH, CMH, C2, and CMHC fibers. C-warm fibers inhibit A-δ fibres, resulting in disinhibition of the normal inhibition exerted by A-δ fibres on CH, CMH, C2, and CMHC fibres, resulting in the experience of heat and/ or a burning pain, such as that experienced from the thermal grill illusion (A). B-F represents which fibres are involved in specific sensations and which fibres are activated ("on") or silent or inactivated ("off"). CH, C-fibers responding only to noxious heat; CMH, C-fibers responding to noxious mechanical stimuli and heat; C2, C-fibers responding cold and warmth/heat; CMHC, C-fibers responding to noxious mechanical stimuli, heat, and noxious cold; A-δ cold, A-

fibers responding to innocuous cold; C-warm, C-fibers responding to warm temperatures; A-δ-MH, A-type fibers responding to mechanical stimuli and heat (Ma, 2010). Reprinted from Ma (2010) with kind permission from the American Society for Clinical Investigation.

1.5.6 Noxious Cold and Heat Detection

Similar to thermoreceptive afferents, nociceptive afferents terminate as unspecialised free nerve endings (Dubin and Patapoutian, 2010). Nociceptors responsible for mediating noxious heat are mainly located in the skin (Tillman et al., 1995; Morin and Bushnell, 1998). Unlike nociceptors responsible for mediating noxious heat and thermoreceptors responsible for mediating innocuous heat and cold (discussed above in section 1.5.5), nociceptors responsible for mediating noxious cold are located below the skin, primarily along vein walls (Fruhstorfer and Lindblom, 1983; Klement and Arndt, 1991; Klement and Arndt, 1992; Chen et al., 1996; Morin and Bushnell, 1998). Nociceptors responsible for mediating noxious heat have also been reported along vein walls as well (Klement and Arndt, 1991).

Unlike the high sensitivity of the visual and auditory organs, the perception of pain by nociceptors only occurs in response to stimuli (thermal, mechanical or chemical) that are potentially tissue damaging (Dubin and Patapoutian, 2010). Psychophysical studies have demonstrated that human cold and heat pain thresholds are approximately 12 ^{o}C and 45 ^{o}C respectively (Erpelding et al., 2012), however these values can vary greatly depending on experimental, biological and psychological factors (discussed below in section 1.5.7). Unlike innocuous warm and cool thermal detection thresholds, Erpelding and colleagues (2012) demonstrated that both cold and heat pain thresholds varied greatly, from 0 ^{o}C to 28 ^{o}C for cold pain and 39 ^{o}C to 50 ^{o}C for heat pain. In addition, cold pain thresholds varied more than heat pain thresholds (Erpelding et al., 2012), demonstrating noxious cold to be a less definite

percept compared to noxious heat (McKemy, 2013). In support of the above statement, participants selected a wider range of descriptors to describe the sensation experienced from a noxious cold stimulus compared to a noxious heat stimulus. (Morin and Bushnell, 1998). Additionally, participants continued to experience a sensation of cold for a significantly greater length of time following a noxious cold stimulus (latency to cessation of sensations, 13.7 s) compared to innocuous cool (5 s), innocuous warm (2.8 s) and noxious heat stimuli (5.4 s) (Morin and Bushnell, 1998). High threshold cold neurons, discussed above in section 1.5.5, may mediate cold pain via TRPA1, whereas noxious heat is transduced via TRPV1 and TRPV2 (Caterina et al., 1997; Caterina et al., 1999).

A-δ nociceptive fibres have relatively small receptive fields and are activated by noxious mechanical stimuli and both noxious cold and heat (Price and Dubner, 1977; Chery-Croze, 1983; Davis, 1998). Following a noxious cold stimulus, A-δ nociceptive fibres are thought to encode the initial pricking sensation experienced (Davis, 1998). In response to heat stimuli, 2 types of A-δ nociceptors have been classified, type I and type II A-δ mechano-heat nociceptive afferents (AMHs).

Type I AMHs have a high heat threshold for activation (> 53 ^{o}C), display a delayed onset of response to heat stimuli (~10 s) and sensitise to prolonged heat stimuli, demonstrating peak discharge towards the end of a stimulus (Treede et al., 1995), making them ideal candidates, along with C-fibres for slowly developing second pain (Raja et al., 1988; Treede et al., 1992; Dubin and Patapoutian, 2010). TRPV2 channels are activated by high temperatures (~52 ^{o}C) and are expressed in a subpopulation of A-δ fibres that respond to high threshold noxious heat (Basbaum et al., 2009; Eid and Cortright, 2009), thus may be responsible for the transduction of noxious heat on these types of AMHs.

Type II AMHs have lower heat thresholds compared to type I AMHs (~46 ^{o}C, which is similar to the human heat pain threshold), respond rapidly (< 1 s) to heat, are sensitive to capsaicin (the active ingredient in chilli peppers), and adapt to prolonged heat stimuli, demonstrating peak discharge at stimulus onset (Treede et al., 1995; Ringkamp et al., 2001). TRPV1 channels are activated by temperatures above 43 ^{o}C (Tominaga et al., 1998) and also by capsaicin, thus are likely to transduce sensations of noxious heat on these types of AMHs.

TRPA1, a polymodal receptor activated by noxious cold (< 17 ^{o}C), is often expressed on neurons that express TRPV1, thus Type II AMHs may also mediate noxious cold (Story et al., 2003). In humans, type II AMHs are proposed to mediate first pain to noxious heat (Treede et al., 1995; Basbaum et al., 2009). Using CO_2 laser heat stimuli, Treede and colleagues (1995) demonstrated that Type II AMHs are not observed in the glabrous skin of monkeys, and Campbell and LaMotte (1983) demonstrated that neither is first pain in the glabrous skin of humans. Using contact heat stimuli, Granovsky and colleagues (2005) also demonstrated that the glabrous skin on the palm in humans has few, if any, Type II AMHs. However, evidence also exists for sharp evoked pain on the glabrous skin, albeit at a lesser intensity than in hairy skin, from laser and contact heat stimuli (Iannetti et al., 2006; Hashmi and Davis, 2010).

Most C-fibre nociceptive afferents are polymodal in nature (Basbaum et al., 2009). They respond to a variety of noxious stimuli, including mechanical, thermal (cold and heat) and chemical (e.g. capsaicin, bradykinin, acid pH) stimuli (Verdugo et al., 2007). The receptive field sizes of C-fibre nociceptors are extremely variable and vary considerably between body locations (Meyer et al., 1991; Schmidt et al., 1997). In humans, Schmidt and colleagues (1997) demonstrated that the receptive field size of C-fibres were greatest on the leg (~198 mm^2), smaller on the foot (~88 mm^2) and smallest on the toe (~35 mm^2). C-fibres threshold for activation by noxious cold and heat varies from 0 ^{o}C to 20 ^{o}C and 38 ^{o}C to 48 ^{o}C

respectively (Campero et al., 1996), via TRPA1 and TRPV1 respectively. The properties of C-fibres make them well suited as high threshold cold neurons, discussed above in section 1.5.5. However, it is important to note that cold pain is not the result of activity in one type of afferent, but instead evoked by activity in more than one type of afferent (Campero et al., 1996). As discussed in section 1.5.5, multiple C-fibre subtypes coding noxious heat exist (C2, CH, CHM and CMHC).

1.5.7 Factors that may Influence Warm/Hot and Cool/Cold Detection

Experimental factors, biological factors and psychological factors may influence the response to innocuous warm and cool and noxious heat and cold temperature perception. Some of these factors are discussed below.

1.5.7.1 Experimental

Experimental factors that may influence thermal perception include environmental factors, the sex of the investigator and the sequence in which thermal stimuli is presented to participants. Environmental factors include the temperature of the room in which the testing is being performed, participants' baseline skin temperature at the time of testing, and noise and distraction to the participant whilst testing is being performed.

Strigo and colleagues (2000) demonstrated that room temperature altered participants' baseline skin temperature and consequently their perception of heat and cold stimuli. Stimulus intensity ratings were significantly lower when tested in a cool room (15 ^{o}C), compared to a neutral (25 ^{o}C) and warm (35 ^{o}C) room; no differences in intensity ratings were observed between the neutral and warm rooms. Additionally, Hirosawa and colleagues (1984)

demonstrated that as the room temperature increased or decreased, participants' skin temperature increased or decreased and both warm and cool perception thresholds increased or decreased respectively, such that a positive correlation between skin temperature and warm and cool perception thresholds was observed.

Recently, Pavlokovic and colleagues (2009) investigated the effects of intrinsic noise generated by a conventional thermal testing device (TSA-II Neurosensory Analyzer, TSA-II) and thermal detection and thermal pain thresholds. In that study cool and warm detection thresholds and cold and heat pain detection thresholds were investigated using a TSA-II, which emits a continuous noise of approximately 60 dB, and a custom-built thermo-testing device that was silent during the testing procedure; both thermodes were the same size (9 cm^2). Pavlakovic and colleagues (2009) demonstrated that intra-subject variability (the minimum to maximum temperature range when thermal detection and thermal pain detection thresholds were measured 3 times for consistency) was significantly lower when using the custom-built silent thermo-testing device compared to the TSA-II (Medoc) for heat detection thresholds, heat pain detection thresholds and cold pain detection thresholds.

The sex of the investigator administering the thermal tests has also been shown to influence participants' thermal pain perception. Tashani and colleagues (2010) demonstrated that pain intensity ratings were significantly higher in both male and females in response to the cold-pressor test in the presence of an investigator of the opposite sex. Similarly, Levine and Simone (1991) demonstrated a trend for greater pain reported in females when tested in the presence of a male compared to in the presence of a female in response to the cold-pressor test. In contrast, males reported significantly less pain in the presence of a female investigator compared to a male investigator. Unlike the study by Tashani and colleagues, both male and

female investigators were selected for their attractiveness in order to evoke gender related motives. Levine and Simone (1991) concluded that reported pain appears to be under the social influence of the gender of the person to whom the report of pain is being made. A recent systematic review by Racine and colleagues (2012) came to the conclusion that although the sex of the investigator influenced participants' response to some laboratory pain tests, investigator sex cannot clearly explain sex differences in experimentally induced pain.

Comparing the test order of thermal stimuli, differences in response have been observed depending on whether heating precedes cooling or cooling precedes heating. Most thermal quantitative sensory testing protocols involve cool detection thresholds being assessed before warm detection thresholds and cold pain thresholds being measured before heat pain thresholds. Recently, Kuhtz-Buschbeck and colleagues (2011) investigated the effect of thermal sequence in 287 (170 women, 117 men) pain-free volunteers. Thermal thresholds were investigated using two different sequences: 1) cool detection, warm detection, cold pain, heat pain (most commonly used sequence) and 2) warm detection, cool detection, heat pain and cold pain. Both cold detection thresholds and cold pain thresholds were significantly lower following sequence 2 compared to sequence 1, demonstrating the importance of keeping the stimulus sequence fixed for all participants for any given experiment.

1.5.7.2 Biological

Biological factors that may influence thermal perception include participants' anthropometry, gender, body location (including glabrous and hairy skin) and body side. Li (2009) demonstrated that both cold and warm detection thresholds were correlated to participants body mass index (BMI), such that participants with a greater BMI had increased cold and warm detection thresholds (i.e. less sensitive). More recently, Neziri and colleagues (2011)

demonstrated that participants' BMI correlated with their cold pain thresholds, such that participants' with the greatest BMI had the lowest cold pain threshold. As discussed above in section 1.5.6, receptors that mediate noxious cold are thought to be located below the skin, either within subcutaneous tissue or even along vein walls, which would support the abovementioned findings from Neziri and colleagues (2011) of a significant correlation between participants BMI and cold pain thresholds. Thus, body dimensions may be one of the factors that influence thermal thresholds.

Gender has been implicated as a covariate in numerous experimental models of pain, including thermal pain perception, with women generally being more sensitive compared to men (Fillingim et al., 2009). Comparing nine body locations, women displayed lower heat pain thresholds (i.e. more sensitive) compared to men at eight of the nine different body locations, which included the face, upper arm, forearm, thenar, abdomen, thigh, leg and dorsum of the foot (Meh and Denislic, 1994). Rolke and colleagues (2006) demonstrated that women had significantly greater cold pain threshold (i.e. more sensitive) and lower heat pain thresholds (i.e. more sensitive) compared to men when measured on the face, hand and foot. Neziri and colleagues (2011) also demonstrated this on the toe, back and scapula. Similarly, comparing gender differences amongst children and adolescence, girls displayed both increased cold detection and cold pain thresholds (i.e. more sensitive) and decreased warm detection and heat pain threshold (i.e. more sensitive) compared to boys (Blankenburg et al., 2010). Additionally, increased cold detection thresholds have been demonstrated in women on the face compared to men (Matos et al., 2011), as well as decreased warm detection thresholds and heat pain thresholds in women on the forearm compared to men (Fillingim et al., 1999a; Fillingim et al., 1999b; Bragdon et al., 2002; Wise et al., 2002; Edwards et al., 2004; Fillingim et al., 2004; Moore et al., 2013). However, others have reported no significant

differences in thermal pain perception between men and women (Fillingim and Maixner, 1996; Jones et al., 2003; Essick et al., 2004; Matos et al., 2011).

Although the sex of the investigator administering the thermal test has shown to influence participants' thermal pain perception (discussed above), a recent systematic literature review by Racine and colleagues (2012) on the biopsychosocial factors that alter pain sensitivity concluded that the literature does not clearly support that the sex of the investigator influences differences observed between men and women in response to experimentally induced pain.

Significant differences in cool detection thresholds, warm detection thresholds, cold pain thresholds and heat pain thresholds across body regions has been observed. Both thermal detection and thermal pain thresholds are usually lowest on the cheek (i.e. more sensitive) and greatest on the foot (i.e. less sensitive), with responses on the hand usually being in between (Stevens and Choo, 1998; Rolke et al., 2006b; Blankenburg et al., 2010). Differences in response across body regions may be due to differences in the cortical representation of body locations, which can be inferred by spatial acuity, and differences in the afferent fibres that innervate the glabrous and hairy skin. For example, both the palm and cheek have similar spatial acuity, measured by tactile two-point discrimination, whereas the palm has a greater spatial acuity compared to the leg (Stevens and Choo, 1996). Differences in cortical representation reflect differences in peripheral innervation density and/ or central convergence of thermoreceptive and nociceptive information across different body locations (Brunello, 2010).

Regarding differences in afferent fibres that innervate glabrous and hairy skin, Iggo (1969) demonstrated that both myelinated and unmyelinated fibres innervate the hairy skin, whilst

only thinly myelinated fibres innervate glabrous skin. Of the thinly myelinated afferent fibres, Type II AMHs are thought to be absent or scarce in the glabrous skin (discussed above in section 1.5.6). In support of this, cold pain thresholds were demonstrated to be significantly lower on the glabrous skin of the hand (thenar eminence) compared to the hairy skin (top side of hand) (Harrison and Davis, 1999), whilst heat pain was perceived at a lesser intensity on the glabrous skin of the foot (bottom of foot) compared to the hairy skin (top of foot)(Hashmi and Davis, 2010).

Generally, studies have demonstrated that body side (left versus right) does not influence thermal pain thresholds (Meh and Denislic, 1994; Rolke et al., 2006a; Boettger et al., 2012; Boettger et al., 2013). However, Neziri and colleagues (2011) demonstrated that participants had significantly lower heat pain thresholds on their left side (toe, back and scapula) compared to their right side, whereas no differences in cold pain threshold were observed across body side. In that study, Neziri and colleagues (2011) employed an increase and decrease in temperature rate of 1.5 ^{o}C per second, whereas the abovementioned studies employed a rate of 1.0 ^{o}C per second or less, which may account for the difference in findings. In addition, left versus right side were not compared in the same individuals, instead participants were randomised to either receive cold and heat stimuli on their left or right side, thus interindividual variability may account this difference (Neziri et al., 2011).

1.5.7.3 Psychological

Psychological factors, such as anxiety, have been shown to modulate the perception of pain (Fillingim, 2013). Thompson and colleagues (2008) demonstrated that participants' level of anxiety on the anxiety severity index (ASI) positively correlated with affective pain for cold and heat stimuli in both men and women, and to sensory pain (for cold and heat stimuli) and

pain intensity (for heat stimuli only) for women only. More recently, Thompson and colleagues (2011) demonstrated that anxiety sensitivity, also assessed using the ASI, was positively associated with the emotional qualities of cold pain reported by both men and women. In response to the cold-pressor test, participants' cognitive anxiety dimension score of the 20-item Pain Anxiety Symptom Scale was a significant predictor of pain tolerance in women only (Tashani et al., 2010). Additionally, Thibodeau and colleagues (2013) demonstrated that pain-anxiety constructs, not trait anxiety, were associated with cold and heat pain perception in both men and women. Trait anxiety has been found to correlate to pain sensitivity, with Jones and colleagues (2003) demonstrating that men with higher trait anxiety, as measured on the State Trait Anxiety Inventory (STAI-T), reported significantly higher levels of pain intensity, pain unpleasantness and demonstrated lower pain tolerance to the cold pressor test compared to men with low anxiety trait anxiety. Lower pain thresholds to the cold pressor test, in addition to the above measures, were also observed in these men when the combined STAI (both state and trait anxiety) score was analysed. Keogh and Cochrane (2002) also demonstrated that participants with high anxiety reported lower pain thresholds to the cold pain test and high sensory and affective pain levels compared to participants with low anxiety. However, others have demonstrated no association between anxiety and pain (Watson et al., 2005; George et al., 2006; Moore et al., 2013).

Psychiatric disorders affecting pain perception, such as depression, have also been implicated in thermal perception. Altered heat (Bar et al., 2003; Bar et al., 2005; Bar et al., 2007; Bar et al., 2011; Boettger et al., 2013) and cold pain thresholds (Schwier et al., 2010; Boettger et al., 2013) have been observed in both medicated and unmedicated patients with depression, with patients being significantly less sensitive to thermal pain (greater heat pain thresholds and lower cold pain threshold) compared to healthy controls. Although patients with depression often have lower cold and greater heat pain thresholds compared to healthy controls (as

discussed above in section 1.4.5.3), Bar and colleagues (2011) observed that pain intensity reported at patients' thermal pain threshold was greater than that of healthy controls, demonstrating pseudohyperalgesia in patients with depression. However, in apparently healthy volunteers, measures of depression, assessed using the Beck Depression Inventory-II, were not associated with thermal pain perception in either males or females (Thibodeau et al., 2013).

1.5.8 Summary of Pain and Temperature Perception

Similar to other areas of neuroscience, pain and temperature perception is an extremely vast area that encompasses various topics. The above section has provided a broad understanding of the neurobiology of pain and temperature perception; with particular focus on the pathways thought to be involved in the thermal grill illusion.

1.6 Gaps in Knowledge

To date there have been no systematic studies on the TGI in the relevant population of chronic pain patients. However, two separate case reports have been published, one in a patient with complex regional pain syndrome (type I) (CRPSI) (Heavner et al., 1997) and one in a patient with multiple sclerosis (MS) (Morin et al., 2002). An intolerable burning sensation was experienced when the patient with CRPSI placed their affected hand on the thermal grill, whereas the patient with MS rated the thermal grill as only slightly painful on their affected side hand. Both patients rated the cool elements as painful (cold allodynia) and the warm elements as warm. Unlike the patient with MS, pain-free participants rated the thermal grill as moderately painful. Thus, the thermal grill failed to produce the normal illusion of pain in the patient with MS (Morin et al., 2002). Consequently, it was suggested that the TGI of pain may be useful in the diagnosis of chronic/neuropathic pain (Craig, 2008). Given these two opposing responses to the TGI in the patient with CRPSI and the patient with MS, we wished to investigate the response to the TGI in a larger population of chronic pain patients.

1.7 Objectives and Aims

Considering that: 1) the case report by Heavner and colleagues (1997) reported an intolerable burning sensation to the TGI in a patient with CPRS1; 2) that previous work from our laboratory demonstrated that patients with chronic pain have an enhanced response to experimental stimuli compared to pain-free participants irrespective of the affected body region (Cathcart et al., 2009a; Cathcart et al., 2009b; Cathcart et al., 2010; Aykanat et al., 2012); and 3) that ketamine could selectively reduce the paradoxical pain associated with the thermal grill illusion, without altering participants' thermal pain thresholds or their responses to both non-painful and painful thermal stimuli (Kern et al., 2008a), the objective of this thesis was to investigate whether the response to the TGI was tolerable in patients with

chronic pain to determine whether the TGI could be used to screen for novel centrally acting analgesics in the future.

Previous studies investigating the thermal grill illusion had employed either a fixed thermal grill configuration, where the temperatures of the warm and cool temperature bars were the same for all participants, or a custom thermal grill configuration, where the temperatures of the cool and warm temperature bars were individually determined for each participant. Studies that used the fixed thermal grill configurations selected temperature combinations that were likely to be in the non-noxious range for all participants (i.e. 22/38 ^{o}C, 20/40 ^{o}C, 18/42 ^{o}C). The method utilised to customise the cool and warm temperature bars involved measuring participants' cold and heat pain thresholds and setting the temperatures of the bars above and below their cold and heat pain thresholds respectively (i.e. 2 ^{o}C, 4 ^{o}C, 6 ^{o}C above participants' cold pain threshold and 2 ^{o}C, 4 ^{o}C, 6 ^{o}C below participants' heat pain threshold). Although utilising a customisable thermal grill configuration appeared like an ideal methodological approach to take, findings from Bouhassira and colleagues (2005) suggested that the proximity of the temperatures of the thermal grill bars to participants' thermal pain thresholds was not related to the occurrence of paradoxical pain; rather, the magnitude of the temperature differential between the cool and warm bars was related to the occurrence of paradoxical pain (as discussed in section 1.4.5.1). Therefore, for ease of application and for standardisation of thermal grill configurations between participants, thermal grill configurations were not customised to individuals' thermal pain thresholds for this thesis throughout all my studies (outlined below).

In order to address the abovementioned objective of this thesis, the aims of this thesis were to:

1) Characterise the response to the thermal grill in pain-free volunteers on both the palm and the cheek. In particular:
    a. Can previous findings of increased response to the thermal grill by increasing the temperature differential between the warm and cool temperature bars be replicated?
    b. Does repeated exposure to the thermal grill result in temporal summation?
    c. Does gender influence the response to the thermal grill?
    d. Is the thermal grill illusion tolerable on the cheek?
    e. Does contact time to the thermal grill influence the thermal grill response?
    f. Is the thermal grill response related to baseline thermal pain sensitivity?

2) Characterise the response to the thermal grill in patients with heterogeneous chronic pain. In particular:
    a. Is the thermal grill illusion tolerable in patients with chronic pain?
    b. Are chronic pain patients' responses to the thermal grill either reduced, the same or heightened compared to pain-free volunteers?

3) Characterise the response to the thermal grill in patients with homogeneous chronic pain conditions. In particular:
    a. Does the response to the thermal grill differ between patients with homogeneous chronic pain conditions and pain-free volunteers?

b. Does the response to the thermal grill differ across body region?

c. Does the response to the thermal grill differ between patients affected and unaffected body region?

d. Compare the response to the thermal grill with thermal quantitative sensory testing for aims (a) to (c). Can the thermal grill detect differences in response for aims (a) to (c) that are not detected by thermal quantitative sensory testing?

e. Do patients with chronic pain have a blunted hypothalamo-pituitary-adrenal axis compared to pain-free volunteers?

f. Do depressive symptoms correlate with thermal quantitative sensory testing and the response to thermal grill?

g. Do early morning salivary cortisol levels correlate with depressive symptoms, thermal quantitative sensory testing and the response to thermal grill?

4) Investigate whether the thermal grill illusion can be pharmacologically modified in patients with medication overuse headache. In particular:

a. Can the thermal grill detect the efficacy of pharmaceuticals that cannot be detected by thermal quantitative sensory testing?

b. Does the response to the thermal grill differ between patients with medication overuse headache and pain-free volunteers?

c. Does the response to the thermal grill differ across body region?

d. Does the response to the thermal grill differ between medication overuse headache patients affected and unaffected body regions?

e. Compare the response to the thermal grill with thermal quantitative sensory testing for aims (b) to (d). Can the thermal grill detect differences in response for aims (b) to (d) that are not detected by thermal quantitative sensory testing?

f. Does the thermal grill have a good test-retest reliability in patients with medication overuse headache?

5) Investigate whether the thermal grill illusion can be non-pharmacologically modified in patients with chronic tension-type headache. In particular:

a. Can the thermal grill detect the efficacy of non-pharmacological therapies that cannot be detected by thermal quantitative sensory testing?

b. Can the thermal grill detect the efficacy of non-pharmacological therapies that cannot be detected by thermal quantitative sensory testing after an hour long stressful mental task?

c. Does the response to the thermal grill differ between patients with chronic tension-type headache and pain-free volunteers?

d. Does the response to the thermal grill differ across body region?

e. Does the response to the thermal grill differ between chronic tension-type headache affected and unaffected body regions?

f. Compare the response to the thermal grill with thermal quantitative sensory testing for aims (c) to (e). Can the thermal grill detect differences in response for aims (c) to (e) that are not detected by thermal quantitative sensory testing?

g. Does the thermal grill have a good test-retest reliability in patients with chronic tension-type headache?

6) Investigate whether the response to the thermal grill can differentiate chronic pain phenotypes. In particular:
    a. Does the response to the thermal grill differ between patients with chronic unilateral sciatic pain, medication overuse headache and chronic-tension type headache? If so, are any differences also observed for quantitative thermal sensory testing?
7) Investigate whether the thermal grill illusion can enhance the response to intradermal capsaicin. In particular:
    a. Can the thermal grill enhance capsaicin-induced spontaneous pain, flare, hyperalgesia and cutaneous allodynia?

Several studies were conducted as part of this PhD in an attempt to ultimately address the abovementioned objective. For an outline of the studies conducted as part of this thesis, please see Figure 1.7.1.

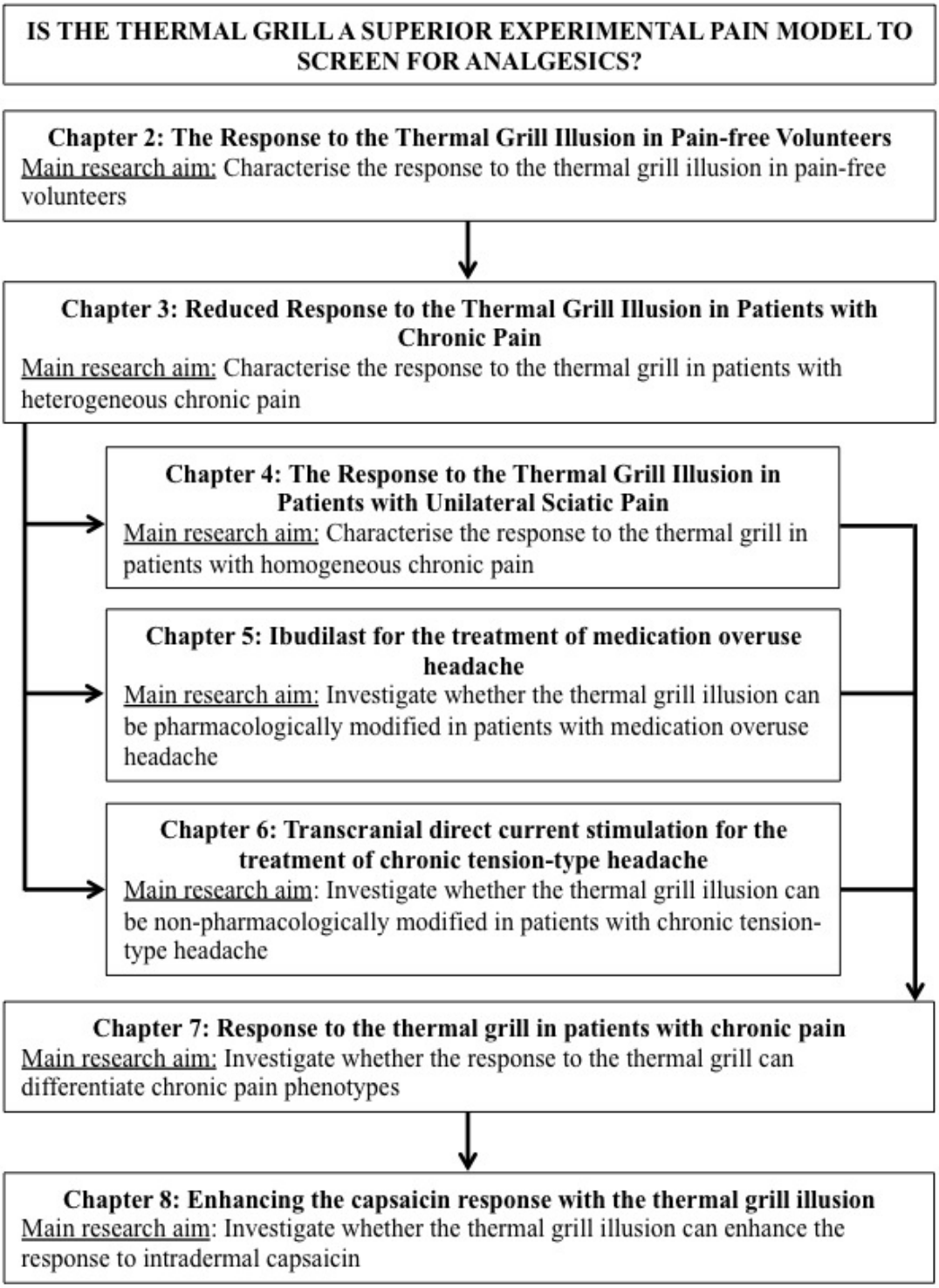

Figure 1.7.1 Outline of the studies conducted as part of this thesis.

This figure represents an outline of the studies conducted as part of this PhD in chronological order. Each box contains the chapter title, followed by the main research aim of each chapter. The more specific aims for each chapter are listed in section 1.7 (above) and in each respective chapter. The large arrow from chapter 3 to chapters 4, 5 and 6 indicates that chapters 4, 5 and 6 were run concurrently. The large arrow from chapters 4, 5 and 6 to chapter 7, indicates that chapter 7, although not a new study, brings together results from chapters 4, 5 and 6 to determine whether the thermal grill can predict chronic pain phenotypes.

Chapter 2. The Response to the Thermal Grill Illusion in Pain-Free Volunteers

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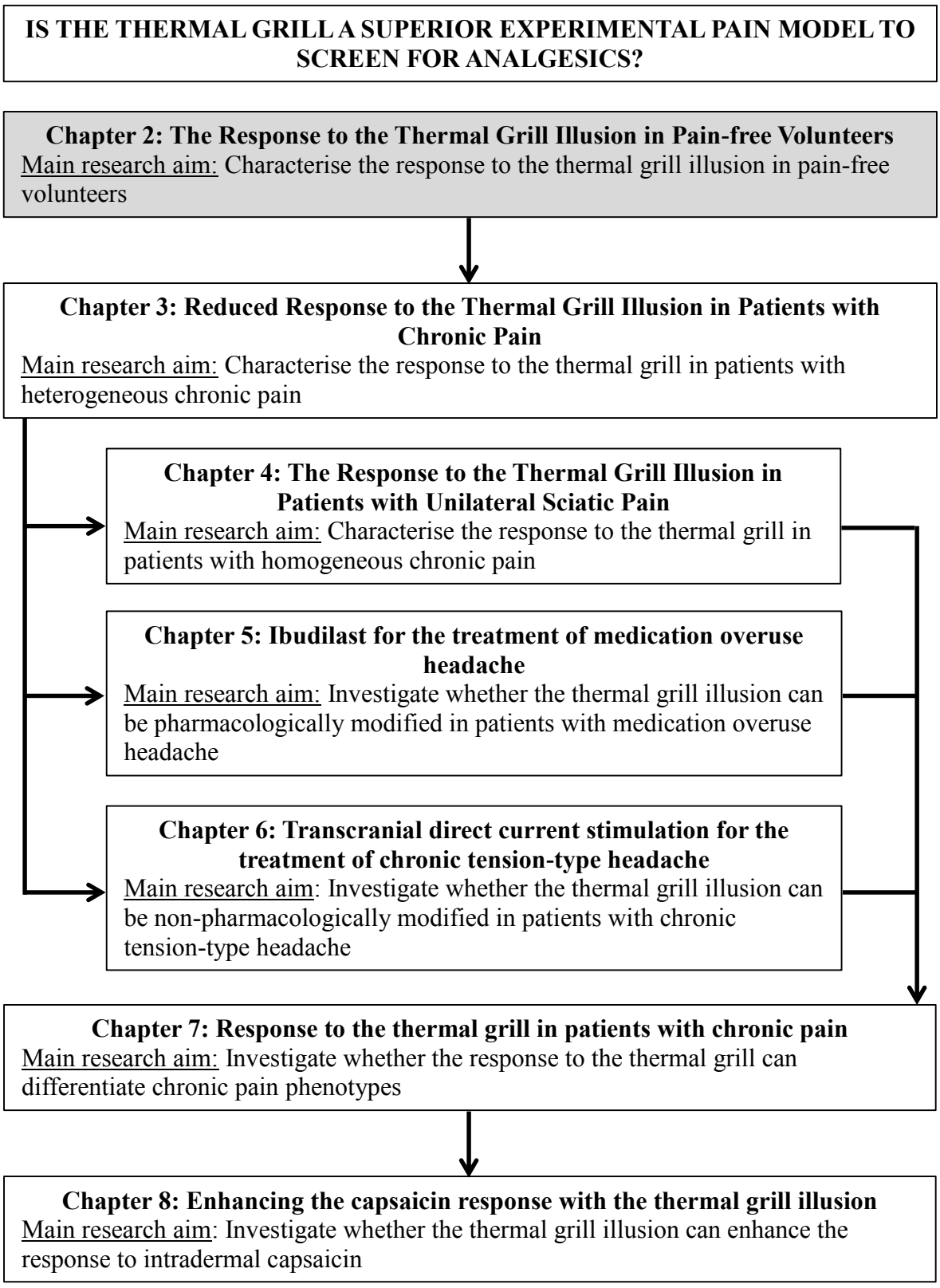
IS THE THERMAL GRILL A SUPERIOR EXPERIMENTAL PAIN MODEL TO SCREEN FOR ANALGESICS?
Chapter 2: The Response to the Thermal Grill Illusion in Pain-free Volunteers
Main research aim: Characterise the response to the thermal grill illusion in pain-free volunteers
Chapter 3: Reduced Response to the Thermal Grill Illusion in Patients with Chronic Pain
Main research aim: Characterise the response to the thermal grill in patients with heterogeneous chronic pain
Chapter 4: The Response to the Thermal Grill Illusion in Patients with Unilateral Sciatic Pain
Main research aim: Characterise the response to the thermal grill in patients with homogeneous chronic pain
Chapter 5: Ibudilast for the treatment of medication overuse headache
Main research aim: Investigate whether the thermal grill illusion can be pharmacologically modified in patients with medication overuse headache
Chapter 6: Transcranial direct current stimulation for the treatment of chronic tension-type headache
Main research aim: Investigate whether the thermal grill illusion can be non-pharmacologically modified in patients with chronic tension-type headache
Chapter 7: Response to the thermal grill in patients with chronic pain
Main research aim: Investigate whether the response to the thermal grill can differentiate chronic pain phenotypes
Chapter 8: Enhancing the capsaicin response with the thermal grill illusion
Main research aim: Investigate whether the thermal grill illusion can enhance the response to intradermal capsaicin

Introduction

Previous studies have postulated the potential applications of the thermal grill in central pain patients. I propose to use this apparatus to investigate pain patient phenotypes and to determine whether the thermal grill illusion may be a biomarker of treatment response. However, so that protocols are appropriately designed, I propose to further study healthy volunteers to determine: how to obtain consistent responses in the largest proportion of participants; the optimal temperature settings of the thermal grill; the effect of contact time to the thermal grill; the effect of repeated exposure to the thermal grill compared to repeated exposure to another commonly used human experimental pain model, being electrical stimulation; the effect of gender to the thermal grill illusion; whether the thermal grill response is related to baseline thermal pain sensitivity and whether the thermal grill can be used on other body locations, such as the face, to determine whether the thermal grill is feasible to use in patients with headache conditions. Therefore, the aim of this study was to further characterise the response to the thermal grill illusion in pain-free volunteers.

Noxious stimuli administered repeatedly over a short interval of time results in a progressive increase in pain, a phenomenon known as temporal summation. Previously, the effect of repeated exposure to the thermal grill (temporal summation) had not been investigated; therefore I chose to compare the effect of repeated exposure to the thermal grill with electrical stimulation. Electrical stimulation provides a peripherally mediated stimulus and has been extensively used to assess temporal summation in healthy volunteers (Arendt-Nielsen et al., 1994; Arendt-Nielsen et al., 2000; Farrell and Gibson, 2007; Neziri et al., 2010; Zheng et al., 2010), as well as patients with various chronic pain conditions (Banic et al., 2004; Ashina et al., 2006).

Materials and Methods

Thermal Grill

The thermal grill was designed and constructed by Flinders Biomedical Engineering (Adelaide, Australia) (see Figure 2.3). The thermal grill consists of two main parts, the Control Unit and the Bar Box. In the centre of the Bar Box (smaller box) is the stimulation surface, where participants were required to place their palm or cheek orthogonally to the long axis of the bars. The stimulation surface consists of six 12 mm wide and 120 mm long aluminium bars separated by approximately 2 mm of thermal insulation. The temperature of the individual bars is controlled by settings on the Control Unit. The temperature of the cold bars can be set in the range of ambient temperature (22 ^{o}C) down to 5 ^{o}C and the hot bars from ambient temperature up to 50 ^{o}C. Thermistors placed in each bar provide continuous temperature feedback of the thermode-skin interface.

Electrical Stimulator

The electrical stimulator consists of two main pieces of equipment, the Constant Current Stimulator (Digitimer Ltd, model DS7A) and the Digital Sweep Function Generator (Topward Electrical Instruments Co., Ltd., model 8120). The function and frequency of the stimulus is controlled by the Constant Current Stimulator and the voltage, current and output function are controlled by the Digital Sweep Function Generator. The stimulus is delivered to the participants via alligator clip connections, which are connected to the Digital Sweep Function Generator.

Subjects

16 (8 females) healthy, right-hand dominant, pain-free participants were chosen to participate in this study. Participants were recruited from the Pain and Anaesthesia Research Clinic's

(PARC) volunteer database and from the general public by advertisement. Ethics approval was obtained from the Royal Adelaide Hospital Research Ethics Committee. Signed consent was obtained from each participant before enrolment into the study. Participants were financially reimbursed for their time and inconvenience. All participants were naïve to the thermal grill effect.

Inclusion/Exclusion Criteria

Key Inclusion Criteria

Key inclusion criteria were: aged between 18 and 65 years old inclusive; being in good general health and being right-hand dominant.

Exclusion Criteria

Key exclusion criteria were as follows: pregnant or lactating women; significant scarring on the non-dominant palm; currently experiencing an active inflammatory process (e.g. acute pain or influenza etc.) or having a clinically significant infection in the previous 4 weeks; history of excessive alcohol use; known history of Hep B, Hep C or HIV; contraindication to cold pain testing (e.g. limb ischemia or Raynaud's phenomenon); having a SCL-90-R® score greater than 2 standard deviations from the mean[1]; presence of non-prescribed drugs of abuse in urine drug screen; current or past history of any chronic pain condition or recurrent condition that alters perception (such as migraine); recent use of opioids (e.g. morphine use within last week, or codeine use (> 30 mg) within last 5 days), adjuvant analgesics (e.g. tricyclics, gabapentin or pregabalin), anxiolytics, anti-depressants and anti-epileptics within last month; regular use of analgesics (excluding paracetamol – paracetamol must have been withdrawn for at least 24 hours prior to the main study day).

1 The SCL-90-R® evaluates a broad range of psychological problems and symptoms of psychopathology.

Study Overview

This single-blind, open descriptive study was conducted over 2 experimental testing days.

Main Study Day: Day 1

The main part of the study consisted of 4 experimental test blocks of approximately 60 minutes duration (see Figure 2.1). Before testing commenced, participants were required to equilibrate to the internal climate for 60 minutes; therefore the duration of the entire study visit was approximately 120 minutes. Alcohol and caffeine containing foods and beverages were not allowed for 24 hours before the experimental day. A negative breath alcohol test was required for continuance in the study.

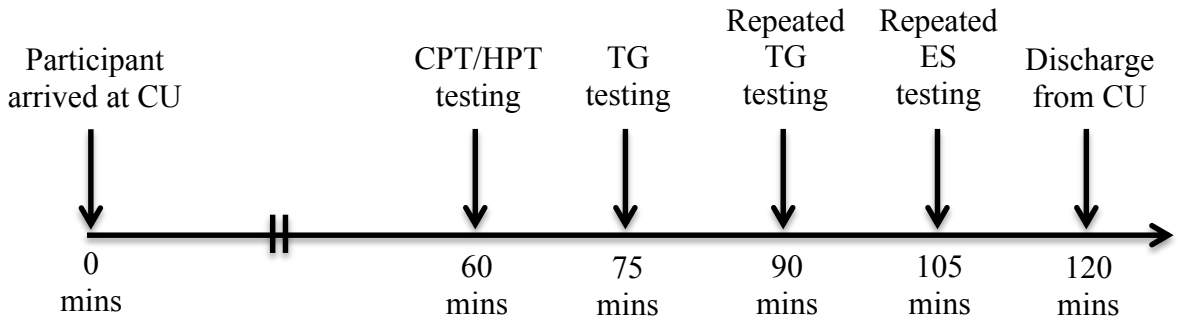

Figure 2.1. Flow Chart of Main Study Day: Day 1

Schedule on main study day 1. CU: clinical unit; CPT: cold pain threshold; HPT: heat pain threshold; TG: thermal grill; ES: electrical stimulation.

Test 1: Thermal Threshold Testing

Participants' individual cold pain and heat pain thresholds were determined using a TSA-II Neurosensory Analyzer (TSA-II) via the Method of Limits (Moloney et al., 2012). The thermode (3 cm x 3 cm) was strapped to the palmar surface of the non-dominant palm, and the participant was given a hand-held control feedback. The temperature of the thermode was

initially set at 32 ^{o}C. The temperature of the thermode either heated up (for heat pain) or cooled down (for cold pain) at a constant rate of 1 ^{o}C / s. When the temperature of the thermode was first detected as 'just becoming painful' the participant was required to press a button on the hand-held control feedback, which halted the stimulus. The thermode then automatically and quickly returned to 32 ^{o}C. The temperature at which the participant halted the stimulus was automatically recorded. This temperature was the participant's heat pain or cold pain threshold. After a 20-25 s delay, the procedure was repeated twice more to obtain an average heat pain and cold pain threshold.

Test 2: Thermal Grill Testing

Participants were exposed to three interlaced cool and warm temperature combinations (22/38 °C, 20/40 °C and 18/42 °C) in randomised order, with an interval of at least 2 minutes between each assessment. The temperature combinations chosen were based on the temperature combinations used in a previous study (Leung et al., 2005). Participants were asked to place their non-dominant palm on the thermal grill, orthogonally to the long axis of the bars for approximately 30 s. Once participants had placed their palm on the thermal grill for 5 s, they were asked to fill in an assessment form with their dominant hand whilst keeping their non-dominant palm on the thermal grill. Participants were required to rate the: intensity of pain and the unpleasantness produced from the thermal grill on an 11-point NRS (left anchor, "no pain" and "not unpleasant," [0]; right anchor "worst pain imaginable" and "very unpleasant," respectively [10]); intensity of heat experienced from the thermal grill on a novel 100 mm visual analogue scale (VAS) thermal colour bar (no anchors, see Figure 2.4), as well as their tolerability to the temperature bars on a 100 mm VAS (left anchor, "tolerable," [0 mm]; right anchor "not tolerable," [100 mm]). Once participants had answered these questions, participants were allowed to remove their palm from the thermal grill. Participants were then asked to rate 'how close the temperature bars felt to burning you' on a 100 mm

VAS (left anchor, “not close,” [0 mm]; right anchor “very close,” [100 mm]). Participants were also given an opportunity to write about the sensation(s) they experienced.

Test 3: Single vs. Repeated Contact Thermal Grill Testing

We wished to determine whether repeated exposure to the thermal grill resulted in temporal summation, therefore participants were asked to place their non-dominant palm on the thermal grill repeatedly. The temperature of cool and warm temperature bars were set to 20 °C and 40 °C respectively (20/40 °C).

Part 1: Single Contact

Participants were required to place their non-dominant palm on the thermal grill orthogonally to the long axis of the bars for 3 s. Participants were then asked to fill in the same assessment form as described above in the section titled “test 2: thermal grill testing”.

Part 2: Repeated Contact

Participants were required to place their non-dominant palm on the thermal grill as mentioned above in the subsection titled “part 1: single contact” for 3 s, then remove their palm for 1 second and place their palm on the thermal grill again for 3 s 15 consecutive times. Once all 15 tests were complete, participants were then asked to fill in the same assessment form as described above in the section titled “test 2: thermal grill testing”.

Test 4: Electrical Stimulation

Electrical stimulation was incorporated into this study as a positive control, as electrical stimulation is a currently used and validated experimental pain model that activates peripheral nerve fibres and is capable of producing reliable temporal summation. Participants' electrical pain threshold (EPT), the point at which the electrical stimulus was first deemed as painful, was first determined.

Part 1: Determining Electrical Pain Threshold

Two pre-gelled 5/16" x 4" silver/silver chloride disposable ring electrodes were placed on the non-dominant hand ring finder: one positioned between the metacarpal-phalangeal joint (base of the finger) and the proximal inter-phalangeal joint and the other positioned between the proximal inter-phalangeal joint and the distal inter-phalangeal joint. Alligator leads, which were plugged into the Digital Sweep Function Generator, were then attached to the two electrodes. The Digital Sweep Function Generator was set to 400 V. When participants were ready to begin they were asked to close their eyes to minimise distraction. The current (mA) was initially set at 0 mA. Electrical pulses (1 ms duration) were delivered at an increasing current (0.1 mA at 0.7 Hz) until participants reported the sensation as "just becoming painful", at which point the stimulus was stopped, and the current was recorded as the participant's electrical pain threshold.

Part 2: Single Contact

Participants were administered one electrical pulse (1 ms duration) at their electrical pain threshold and were asked to rate the: intensity of pain and the intensity of unpleasantness of the electrical pulse on an 11-point NRS and their tolerability of the electrical pulse on a 100 mm VAS.

Part 3: Repeated Contact

Participants were administered a train of 15 electrical pulses (1 ms duration at 5 Hz) and asked to rate the same outcomes as mentioned above in the section titled "part 2: single contact".

Main Study Day: Day 2

Participants who completed study day 1 were asked to return for a follow up visit to investigate the response to the thermal grill on the face, to determine whether the thermal grill is feasible to use in patients with headache conditions, and to investigate the effect of contact time to the thermal grill. Day 2 of the study consisted of 1 experimental test block of approximately 45 minutes duration (see Figure 2.2). Alcohol and caffeine containing foods and beverages were not allowed for 24 hours before the experimental day. A negative breath alcohol test was required for continuance in the study.

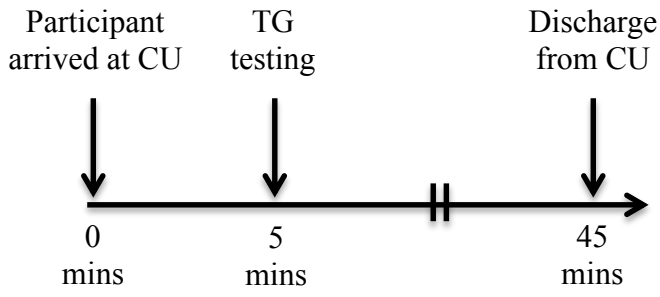

Figure 2.2. Flow Chart of Main Study Day: Day 2

Schedule on main study day 2. CU: clinical unit; TG: thermal grill.

Thermal Grill Testing

Similar to study day 1, participants were exposed to three interlaced cool and warm temperature combinations (22/38 °C, 20/40 °C and 18/42 °C) in a randomised order, with an interval of at least 2 minutes between each assessment. Participants were asked to place either their left or right cheek on the thermal grill, orthogonally to the long axis of the bars, for either 3 s or 30 s in a randomised order to avoid any period affect. Additional randomisation was performed to ensure that the same cheek was not assessed in consecutive order. Therefore each participant performed 12 assessments with the thermal grill. Once participants removed their cheek from the thermal grill they were asked to fill in an assessment form (as described for study day 1).

Statistical Analysis

The D'Agostino and Pearson omnibus normality test was performed to test for normality of the data. When assessing for normality of the data in this study and all studies within this thesis, if one of the parameters being compared was non-normally distributed, then that particular analysis was performed using non-parametric statistics. For example, when assessing whether increasing temperature differentials between the warm and cool temperature bars increased the response to the thermal grill for the outcome "intensity of pain", if the outcomes for even one of the three settings at which the thermal grill was assessed (22/38 ^{o}C, 20/40 ^{o}C, 18/42 ^{o}C) was non-normally distributed, then non-parametric statistics were used. Parametric statistics were only used when all parameters being compared were normally distributed.

Due to the non-parametric distribution of the data, male versus female age was compared using the Kolmogorov-Smirnov test. Therefore, these values are presented as median and IQR.

Single versus repeated contact to the thermal grill illusion was compared using a two-tailed paired t-test for the outcome "intensity of heat". Due to the non-parametric distribution of the data, the "intensity of pain", "unpleasantness", "tolerability to the thermal grill" and rating of "how close the bars felt to burning you" were compared using the Wilcoxon matched-pairs signed rank test.

Contact time (3 s vs. ~30 s) with the thermal grill the thermal grill illusion was compared using a paired t-test for the outcomes "intensity of heat" experienced from the thermal grill and the rating of "how close the bars felt to burning you". Due to the non-parametric distribution of the data, the "intensity of pain", "unpleasantness" and "tolerability to the thermal grill" were compared using the Wilcoxon matched-pairs signed rank. Contact time (3 s vs. 30 s) with the thermal grill was compared for both the left and right cheek using a two-way repeated measures ANOVA with Bonferroni's multiple comparisons test. These graphs on the cheek are represented as mean ± SEM.

Single versus repeated electrical stimulation was compared using a paired t-test for the outcomes "intensity of pain", "unpleasantness" and "tolerability".

On the non-dominant palm, the effect of increasing temperature differentials between the warm and cool temperature bars was compared using a one-way repeated measures ANOVA with Tukey's multiple comparison test for the "intensity of heat" and "unpleasantness"

experienced from the thermal grill. Due to the non-parametric nature of the data, "intensity of pain", "tolerability to the thermal grill" and "how close to bars felt to burning you" were compared using the Friedman test with Dunn's multiple comparisons test. On both the left and right cheek at both 3 s and 30 s, the effect of increasing temperature differentials between the warm and cool temperature bars were compared using a one-way repeated measures ANOVA with Tukey's multiple comparison test for the "intensity of heat" experienced from the thermal grill. Due to the non-parametric nature of the data, "intensity of pain", "unpleasantness", "tolerability to the thermal grill" and "how close to bars felt to burning you" were compared using the Friedman test with Dunn's multiple comparisons test.

The effect of gender (males vs. females) on the response to the thermal grill was compared using a two-way repeated measures ANOVA with Bonferroni's multiple comparisons test. These graphs are represented as mean ± SEM. The effect of gender on cold and heat pain thresholds and electrical pain thresholds was compared using an unpaired t-test. These values are represented as mean ± SEM.

Correlations between thermal pain threshold and the response to the thermal grill illusion were analysed using Pearson's correlation for the outcomes "intensity of heat" and "unpleasantness". Due to the non-parametric distribution of the data, the outcomes "intensity of pain", "tolerability to the thermal grill illusion" and "how close the bars felt to burning you" were analysed using Spearman's correlation. Correlations between cold and heat pain thresholds, thermal pain thresholds and electrical pain thresholds, as well as correlations between electrical pain thresholds and the response to single or repeated electrical stimuli were all analysed using Pearson's correlation. In order to account for multiple comparisons, a Bonferroni correction was performed, where a new significance threshold was calculated by dividing the original significance level (0.05) by the number of comparison performed.

Body side (left vs. right cheek) was compared using a two-way repeated measures ANOVA with Bonferroni's multiple comparisons test for both 3 s and 30 s contact to the thermal grill. These graphs are represented as mean ± SEM. Body location (left palm vs. left cheek) was compared using a two-way repeated measures ANOVA with Bonferroni's multiple comparisons test. These graphs are represented as mean ± SEM.

Statistical analysis for all studies presented in this thesis was performed using Prism software version 6 (GraphPad Software, San Diego, CA, USA). A *P* value of less than 0.05 was required for statistical significance, unless otherwise stated.

Results

Subjects

16 pain-free (8M, 8F) participants completed this study. The median age of the participants was 22 years (IQR: 20 to 23.8 years). Males and females did not differ in age ($p = 0.58$) (see Table 2.1 for values). 12 (6M, 6F) participants from study 1 completed study 2. The median age of the participants was 21.5 years (IQR: 19.3 to 23 years). Males and females did not differ in age ($p = 0.338$) (see Table 2.1 for values).

Cold and heat pain thresholds

The mean (± SEM) cold and heat pain thresholds were 7.4 ^{o}C ± 1.4 ^{o}C and 47.2 ^{o}C ± 0.6 ^{o}C respectively. CPT (mean difference: 3.7; 95% CI for difference: -2.1 to 9.4; $p = 0.191$) and HPT (mean difference: -2.4; 95% CI for difference: -4.8 to 0.003; $p = 0.0503$) did not differ between males and females (see Table 2.1 for values). A significant correlation was observed between cold and heat pain thresholds ($r = -0.61$, $p = 0.013$), such that for every 0.6 ^{o}C decrease in cold pain threshold, participants experience a 1 ^{o}C increase in heat pain threshold (i.e. the less sensitive participants are to cold, the less they also were to heat).

Effect of increasing temperature differentials between the warm and cool temperature bars evoked by the thermal grill

Increasing temperature differentials between the warm and cool temperature bars produced significantly greater responses for intensity of pain ($p = 0.0002$), intensity of heat ($p < 0.0001$), unpleasantness ($p = 0.0022$), tolerability ($p = 0.027$) and "how close the bars felt to burning you" ($p = 0.0017$) when tested on participants non-dominant palm. These results demonstrate that the largest thermal grill responses were generally reported when the warm

and cool temperature bars were at their maximal temperature differentials (i.e. at the 18/42 ^{o}C thermal grill configuration)(see Figure 2.5). Larger temperature differentials between the warm and cool temperature bars (e.g. 16/44 °C, 14/46 °C) were not investigated to ensure that the temperatures of the warm and cool temperature bars remained innocuous. No significant correlations were observed between participants cold and heat pain thresholds and their response to the thermal grill for all outcomes on the left palm (see Table 2.2). Similar to responses on the palm, the largest response to the thermal grill illusion was generally observed at the 18/42 ^{o}C thermal grill configuration on the cheek. Increasing temperature differentials between the warm and cool temperature bars tended to produce significantly greater responses when participants' cheek was placed on the thermal grill for 30 s rather than 3 s. Responses to the thermal grill when exposed for 3 s appeared to be more variable compared to when exposed for 30 s. Significant differences in response to the thermal grill were observed between different thermal grill configurations for the outcomes "'how close the bars felt to burning you" after 3 s stimulation ($p = 0.049$) (see Figure 10.2.3 in appendix) and "intensity of pain" ($p = 0.0072$) and "unpleasantness" ($p = 0.0002$) after 30 s stimulation on the right cheek (see Figure 2.6A-E); and for the outcomes "tolerability" ($p = 0.019$) after 3 s stimulation and "intensity of pain" ($p = 0.023$) after 30 s stimulation on the left cheek (see Figure 10.9.3 in appendix). Due to incomplete data collection for one participant, 11 (out of 12) participants were included in this analysis.

Effect of time on the thermal grill response

On the specific question "please rate your tolerability of the temperature bars, left anchor "tolerable" (0 mm), right anchor "not tolerable" (100 mm)," an increase in response (i.e. greater intolerability) was observed when participants placed their non-dominant palm on the thermal grill for ~30 s compared to 3 s ($p = 0.046$)(see Figure 2.9D). For all other outcomes, duration of time on the thermal grill did not affect the response to the thermal grill illusion on

the non-dominant palm (see Figure 2.9A-C and E). Duration of time (3 s vs. 30 s) on the thermal grill did not affect response to the thermal grill illusion for all outcomes when assessed on the left cheek (see Figure 2.10). However, on the right cheek, significant differences in response to the thermal grill illusion were observed between 3 s and 30 s stimulation for the outcomes "intensity of heat" (overall main effect, $p = 0.0325$) and "unpleasantness" (at the 22/30 ^{o}C thermal grill configuration: $p < 0.05$, no exact value provided) (see Figure 10.2.4 in appendix), where slightly greater responses were observed when the right cheek was stimulation for 3 s compared to 30 s.

Effect of single vs. repeated contact to the thermal grill

No significant differences in response to the thermal grill illusion were observed between single and repeated contact to the thermal grill for all outcomes (see Figure 2.7D-F and Figure 9.2.1A-B in appendix).

Effect of single vs. repeated electrical stimulation

Unlike responses to the thermal grill, repeated administration of an electrical stimulus at participants' electrical pain threshold (mean ± SEM: 4.2 mA ± 0.6 mA) produced significantly greater responses for all outcomes compared to a single electrical stimulus (see Figure 2.7A-C). For "intensity of pain" the mean values were 3.3 (out of 10) following single electrical stimulus, however increased to 5.4 following repeated administration of the electrical stimulus (mean, 95% CI for difference: 2.1, 1.2 to 2.9). For "unpleasantness", the mean values were 4.4 following single electrical stimulus, however increased to 6.1 following repeated administration of the electrical stimulus (1.7, 0.6 to 2.8). On the specific question "please rate your tolerability of the temperature bars, left anchor "tolerable" (0 mm), right anchor "not tolerable" (100 mm)," the mean values were 29 mm following single electrical

stimulus, however increased to 46 mm following repeated administration of the electrical stimulus (17 mm, 9 mm to 26 mm). No significant difference in response to electrical pain thresholds (see Table 2.1 for values), single electrical stimulus or repeated electrical stimuli was observed between males and females for all outcomes (see Figure 10.2.2 in appendix). Additionally, no significant correlations were observed between participants electrical pain thresholds and their response to single and repeated electrical stimulation to all outcomes on the left palm (see Table 2.3).

Correlation between thermal pain thresholds and electrical pain thresholds

No significant correlations were observed between participants' cold ($r = -0.278$, $p = 0.297$) and heat pain thresholds ($r = -0.044$, $p = 0.873$) and their electrical pain thresholds on the left hand.

Effect of gender on the thermal grill response

No significant difference in response to the thermal grill was observed between males and females for all thermal grill outcomes on the palm (see Figure 2.8). However, females generally rated the thermal grill outcomes "unpleasantness" and "how close the bars felt to burning you" greater than males (see Figure 2.8C and E). For the specific outcome "how close the bars felt to burning you", females reported significantly greater burning sensation compared to males when tested on the right cheek for 3 s (see Figure 10.2.6E in appendix). For all other outcomes, gender did not affect the response to the thermal grill illusion on the cheek, however females generally reported greater sensitivity to the thermal grill illusion compared to males for all outcomes on the both the right and left cheek for both 3 s and 30 s stimulation. Additionally, female responses to the thermal grill displayed a greater range of response compared to males (see Figure 10.2.6 in appendix). Due to incomplete data collection for one participant, 5 (out of 6) female participants were included in this analysis.

Effect of body side on the thermal grill response

Comparing body side (left vs. right cheek), an overall main effect for significantly less pain at 3 s ($p = 0.035$) and heat at 30 s (0.042) was observed at the right cheek (see Figure 10.2.5A and G in appendix respectively). For all other outcomes, no significant differences in response to the thermal grill illusion were observed between the left and right cheek at both 3 s and 30 s (see Figure 10.2.5 in appendix).

Effect of body location on the thermal grill response

Comparing body location (left palm vs. cheek), significantly less heat was reported at the left cheek at the 18/42^{o}C thermal grill configuration (mean difference: -16 mm, 95% CI for difference: -29 mm to -3 mm). Additionally, an overall main effect for significantly less pain ($p = 0.016$) and unpleasantness ($p = 0.029$) at the left cheek was also observed. No difference was observed for the outcomes "tolerability" and "how close the bars felt to burning you" (see Figure 2.11A-E).

Discussion

In this study, I characterised the response to the thermal grill illusion on the non-dominant palm of pain-free participants to determine: the optimal temperature settings of the thermal grill; the effect of contact time to the thermal grill; the effect of repeated exposure to the thermal grill compared to repeated exposure to another commonly used human experimental pain model, being electrical stimulation; the effect of gender to the thermal grill illusion and whether the thermal grill response is related to baseline thermal pain sensitivity. Additionally, I assessed the tolerability of the thermal grill on both the left and right side cheek for both 3 and 30 seconds to determine whether the thermal grill is feasible to use in patients with headache conditions and to assess the effect of time. To my knowledge at the initiation of this study, this was the first study to investigate the effect of repeated exposure to the thermal grill illusion, the effect of body side to the thermal grill response, the effect of time to the thermal grill response, as well as the response to the thermal grill illusion on the face.

One noticeable feature of this study is that the thermal grill illusion did not really produce pain, but instead, the thermal grill produced an altered sensory experience that manifested as an aversive heat stimulus (approx. 60 mm on our novel 100 mm colour bar on the palm and between 39 mm and 50 mm on the cheek). In line with previous studies investigating the TGI in pain-free participants, the results of this study demonstrate that the perceptual quality of the TGI is more unpleasant than painful (Lindstedt et al., 2011a; Lindstedt et al., 2011b; Lam, 2012). Dysaesthesias, in particular, thermal dysaethesias, are often experienced by patients with chronic pain (Baron, 2009), with dysaethesias being one of the most debilitating consequences of chronic pain conditions (Finnerup and Baastrup, 2012). Consequently, the thermal grill may be a useful tool to investigate the dysaesthetic qualities of chronic pain and potentially screen for novel anti-dysaesthetic therapies for chronic pain. Previous studies investigating the thermal grill in pain-free participants have not quantitatively investigated the

intensity of heat experienced from the thermal grill. Consequently, I developed a novel thermal colour bar in order to better capture the response to the TGI. One aim of this study was to evaluate this novel thermal colour bar. In this study I report that this novel thermal colour bar was the most suitable measure to assess the thermal grill illusion, as it produced the greatest response.

Similar to previous studies investigating the TGI in pain-free participants, I demonstrated that increasing temperature differentials between the warm and cool temperature bars increased the response to the TGI (Bouhassira et al., 2005; Leung et al., 2005; Boettger et al., 2011; Boettger et al., 2012; Boettger et al., 2013). Although the largest pain response to the TGI was reported when the thermal grill configuration was 18^{o}C / 42^{o}C, the thermal grill did not produce a very painful stimulus on the non-dominant palm (median 2 on an 11-point NRS, interquartile range 1 to 5, on the non-dominant palm), being below 4 (out of 10), which is generally accepted as the minimum for clinically relevant pain (Jensen et al., 2003). Similarly, participants' median pain response for both the left and right cheek at 3 and 30 s was between 1 and 2 on an 11-point NRS. The reported pain intensity in this study is similar to previous studies investigating the TGI in pain-free participants, where similar thermal grill configurations produced pain intensity ratings between 7 mm and 47 mm on a 100 mm VAS, on either the palm or the forearm (Bouhassira et al., 2005; Leung et al., 2005; Kern et al., 2008a; Kern et al., 2008b; Boettger et al., 2011; Lindstedt et al., 2011a; Lindstedt et al., 2011b; Pinerua-Shuhaibar et al., 2011; Boettger et al., 2012; Boettger et al., 2013). At the time of this study, this was the first known study that investigated the response to the thermal grill on the face. Since this study, another study, in abstract form only, has also investigated the response to thermal grill on the cheek, however the intensity of pain was not recorded in that study.

Gradual increases in subjective pain ratings have previously been observed in response to repetitive thermal, mechanical and electrical stimulation of nociceptive C-fibres (second pain) (Price, 1972; Price et al., 1977; Arendt-Nielsen et al., 1994; Fillingim et al., 1998; Nie et al., 2005; Granot et al., 2006; Staud et al., 2006; Fillingim et al., 2009). This temporal summation of second pain occurs when consecutive stimuli are administered at a frequency of greater than 0.33 Hz (Price, 1972). Temporal summation of first pain (Aδ-fibres) has also been observed (Arendt-Nielsen et al., 1996; Vierck et al., 1997), albeit to a lesser extent, although controversy exists in the literature (Arendt-Nielsen et al., 2000). Similar to previous studies (Arendt-Nielsen et al., 1994; Arendt-Nielsen et al., 2000), this study demonstrated that repeated electrical stimulation resulted in significantly greater ratings of pain and unpleasantness following 15 consecutive electrical stimuli, compared to pain and unpleasantness ratings following a single electrical stimulus. Unlike repeated electrical stimulation, repeated thermal grill stimulation did not result in temporal summation. Previously, the temporal summation response to repeated thermal grill stimulation had not been investigated. One limitation of this finding is that the stimulus parameters for electrical stimulation and the thermal grill stimulus differed. The stimulus parameters for electrical stimuli were set to known parameters that would induce temporal summation, whereas as temporal summation had not previously been investigated using the thermal grill, it was unknown whether the stimulus parameters of the thermal grill illusion would result in temporal summation. Due to the nature of the thermal grill illusion, the thermal grill could not be administered at the same frequency as electrical stimuli. However, unlike the electrical stimulus (1 ms), the thermal grill stimulus was applied for 3 s, therefore the difference in frequency administration may not have influenced the response too much. Others have demonstrated that noxious thermal stimuli (49^{o}C and above) administered to the palm at inter-stimulus intervals of up to 3 s have resulted in temporal summation (Vierck et al., 1997; Staud et al., 2006). Although, the warm bars of the thermal grill were set at an innocuous

temperature of 40°C, Leung and colleagues (2005) previously demonstrated that thermal grill stimulation for 3 s resulted in a stimulus intensity of approximately 46°C (Leung et al., 2005).

For most outcomes, contact time to the thermal grill (3 s vs. 30 s) did not influence participants' response to the thermal grill illusion on the palm and both the left and right cheeks, demonstrating that contact time to the thermal grill was not a significant covariate for response in this study. It is important to note that limited conclusions can be made when comparing the effect of contact time to the thermal grill on the palm due to different methods used for subjective participant reporting. When assessed for 3 s, participants were asked to fill in the assessment form once they had removed their palm from the thermal grill, whereas when assessed for ~30 s, participants were instructed to start filling in the assessment form once 5 s had elapsed. Consequently, the different outcome measures (i.e. pain, heat, unpleasantness etc.) were investigated at different time points throughout participants contact to the thermal grill, such that the intensity of pain was assessed closer to ~10 s, whereas tolerability was assessed closer to ~30 s and burning sensation after exposure to the thermal grill. At the time that this study was conducted, no known peer-reviewed studies had investigated the effect of time on the response to the thermal grill. However, shortly after this study was conducted, two recent theses (Li, 2009; Brunello, 2010) came to light, which investigated the time course of the thermal grill illusion. In the study by Li (2009), ratings of pain and distress from the thermal grill illusion significantly increased over a period of 3 minutes for painful thermal grill responders (n = 10); defined as participants who reported the thermal grill illusion as painful compared to the thermal grill's constituent cool and warm temperatures when tested separately. Interestingly, ratings of pain and distress from the thermal grill illusion did not increase for non-painful thermal grill responders (n = 11), thus the time course of the thermal grill differed between painful and non-painful thermal grill responders. Additionally, ratings of pain and distress increased over time for non-painful cold,

painful cold and painful heat, suggesting temporal summation, however decreased for non-painful warm, suggesting habituation. Unfortunately, painful and non-painful thermal grill responders could not be analysed in this study, as the response to the individual cool and warm temperatures of the thermal grill were not analysed separately. In the study by Brunello (2010), the intensity of pain experienced from the thermal grill was significantly greater at the 45 – 60 s time point compared to the 0 – 15 s time point when tested at the palm and back. More recently, Pinerua-Shuhaibar and colleagues (2011) demonstrated a significant increase in 'pain intensity', 'unpleasantness' and 'overall pain' to the thermal grill illusion over a period of 8 minutes when assessed on the dominant palm in both pain-free volunteers (n = 28) and patients with minor depression (n = 26) (Pinerua-Shuhaibar et al., 2011). Both greater participant numbers and contact time to the thermal grill in the aforementioned studies may account for the significant increase in pain intensity, distress and unpleasantness to the thermal grill illusion observed in these studies over time. Similarly, Bach and colleagues (2011) reported a trend for perceptual change to the thermal grill illusion over time ($p = 0.058$); where reports of "cold" became less frequent, whilst the reports of "hot" and "scalding" increased with increasing stimulus duration (1 s to 7 s) (Bach et al., 2011). However, unlike the aforementioned studies, Bach and colleagues (2011) did not measure pain intensity and unpleasantness.

In accordance with the literature, participants' cold and heat pain thresholds were significantly correlated (Essick et al., 2004; Lindstedt et al., 2011b; Kim et al., 2013), however, no significant correlation was observed between participants' thermal pain thresholds and their response to the thermal grill illusion. Previous studies have demonstrated that participants' cold pain thresholds consistently correlated with thermal grill outcomes, in particular, pain, unpleasantness and thermal intensity (Brunello, 2010; Kostka, 2011; Lindstedt et al., 2011b; Averbeck et al., 2013). In addition, Lindstedt and colleagues (2011b)

demonstrated participants' heat pain thresholds were also correlated to the thermal grill outcomes pain and unpleasantness. Similarly, no correlation was observed between participants cold and heat pain thresholds and their electrical pain threshold, or between their electrical pain thresholds and their response to electrical stimulation on their left palm.

Numerous studies have demonstrated that gender is a significant covariate of response across many experimental pain models, including studies investigating thermal pain perception; the vast majority of studies reporting that women are more sensitive compared to men (Fillingim et al., 2009). No significant difference in response to the thermal grill was observed between men and women in this study. Women appeared to report greater sensitivity to most thermal grill outcomes on both the left palm and the left and right cheek (see Figure 2.8 and Figure 11.2.6 in appendix), however this difference was not significant. Similarly, cold and heat pain thresholds did not differ between men and women, although significance was approached for heat pain thresholds ($p = 0.0503$). Perhaps significance may have been achieved if participant numbers were larger. Either way, this demonstrates the importance of gender selection and gender balancing when recruiting participants for experimental pain studies. Brunello (2010), Li and colleagues (2009), as well as Boettger and colleagues (2011, 2012) demonstrated that gender did not affect the response to the thermal grill. However, Li and colleagues (2009) demonstrated that reaction times to detect thermal stimuli, including the thermal grill stimulus, were greater in women compared to men.

Body side (right vs. left cheek) generally did not affect the response to the thermal grill illusion, demonstrating no to minimal lateralisation to the thermal grill illusion. Previously, this had not been investigated. More recently, others have also reported no lateralisation to the thermal grill illusion, in particular between the right and left palm and forearm (Boettger et al., 2011; Boettger et al., 2012; Averbeck et al., 2013; Boettger et al., 2013).

Comparing body location (left palm vs. cheek), significantly less "pain", "heat" and "unpleasantness" was experienced on the cheek compared to the palm in this study. Others have also reported body location differences in response to thermal grill (see section 1.4.5.2 in chapter 1). These differences in response to the thermal grill illusion across body regions may be due to differences in the cortical representation of body locations, which reflects differences in peripheral innervation density and/ or central convergence of thermoreceptive and nociceptive information across different body locations (Brunello, 2010). Previously, differences in cool and warm thermoreception have been observed across body locations, with the lower extremities displaying reduced sensitivity to cool and warm thermal stimuli compared to the upper extremities (Stevens and Choo, 1998). Assuming that Craig and Bushnell's (1994) thermosensory disinhibition hypothesis is the basis for the thermal grill illusion (discussed in section 1.4.2), and considering that thermoreception differs across body location, it is not surprising that the perception of the thermal grill illusion has been demonstrated to differ across body location. Although thermal detection thresholds were not investigated in this study, Brunello (2010) suggested that body site differences to the thermal grill were likely related to differences observed in cold detection threshold, rather than warm detection threshold, as warm afferents are not believed to play a role in the TGI. Both the forearm and the hand have similar thermal sensitivities (Stevens and Choo, 1998), which is consistent with a similar response to the thermal grill illusion (Bach et al., 2011; Averbeck et al., 2013). Both the hand and the back have larger thermal sensitivities than the calf (Stevens and Choo, 1998), which is consistent with a reduced response to the thermal grill illusion on the calf (Brunello, 2010). The palm has similar thermal sensitivities to the cheek (Stevens and Choo, 1998), however a reduced response to the thermal grill was observed on the cheek in this study, which may reflect differences in spinal and trigeminal processing of thermal stimuli. In fact, expression of TRPM8, the cool sensing receptor (discussed in section 1.5.5), was found to differ between the trigeminal and dorsal root ganglion, with greater TRPM8 expression observed in the trigeminal ganglia (~35% vs. ~23%) (Kobayashi et al., 2005),

which may explain the difference in thermal grill response between the cheek and palm. A recent thesis by Jason Lam (2012) also demonstrated significant differences in response to the thermal grill across the upper and lower body regions. Unlike the study by Brunello (2010), significantly greater ratings of pain and unpleasantness were observed on the calf compared to the forearm. One reason for greater responses being observed on the calf compared to the forearm may be because the order of thermal stimuli were not randomised in the study by Lam (2012), thus participants' always received thermal stimuli on the forearm before the calf, potentially allowing for an order effect. The effect of stimulus order to the thermal grill illusion has previously not been investigated; however order effects have been demonstrated in other thermal experimental pain models. Additionally, although the foot has a large cortical representation, the study by Brunello (2010) demonstrated reduced thermal grill illusion in the foot compared to upper body regions. In that study the thermal grill was tested on the heel. Skin thickness is greater at the heel and may be a factor that influences thermal sensitivity. Although the tongue has a larger cortical representation than the palm, responses at the tongue were perceived as cold and non-painful compared to hot and burning sensation perceived on the palm (Tournier et al., 2010). This may be due to differences in receptors on the skin and on the tongue.

To my knowledge, this was the first study to investigate the effect of repeated exposure to the thermal grill illusion, the effect of body side to the thermal grill response, as well as the response to the thermal grill illusion on the face. This study demonstrated that neither repeated exposure, gender, time or body side influenced the response to the thermal grill. Similar to previous studies, increasing temperature differentials between the warm and cool temperature bars evoked larger responses to the thermal grill illusion. Furthermore, the response to the thermal grill was both tolerable and reproducible on the cheek, albeit at a lesser intensity than on the palm, thus may be feasible to use in patients' with headache

conditions. I propose to use this apparatus to investigate pain patient phenotypes and to determine whether the thermal grill illusion may be a biomarker of treatment response. These methodological findings have been an important first step to ensure the validity of my subsequent studies.

Tables

Table 2.1. Participant Demographics

	Males	Females	P value	Combined
Participant numbers				
Study day 1	8	8	-	16
Study day 2	6	6	-	12
Age (years, median and IQR)				
Study day 1	23 (20.5, 23.8)	21.5 (18.3, 24.3)	0.58	22 (20, 23.8)
Study day 2	22.5 (20, 23)	20 (18, 31.5)	0.34	21.5 (19.3, 23)
CPT (^{o}C, mean ± SEM)	5.6 ±1.8	9.3 ± 2.0	0.19	7.4 ± 5.5
HPT (^{o}C, mean ± SEM)	48.4 ± 0.5	46.0 ± 1.0	0.05	47.2 ± 2.5
EPT (mA, mean ± SEM)	4.6 ± 0.9	3.8 ± 0.8	0.51	4.2 ± 2.3

IQR: interquartile range; SEM: standard error of the mean; CPT: cold pain threshold; HPT: heat pain threshold; EPT: electrical pain threshold; ^{o}C: degrees Celsius; mA: milliampere.

Table 2.2. Correlation of Thermal Pain Thresholds and Thermal Grill Response

R and *P* values from the correlation analysis performed between thermal pain thresholds and the response to the thermal grill are presented for each thermal grill outcome (listed vertically) at each thermal grill configuration (listed horizontally).

	Cold Pain Threshold			Heat Pain Threshold		
Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Intensity of Pain						
R value	-0.32	-0.28	-0.17	0.3	0.2	0.22
P value	0.17	0.24	0.49	0.25	0.46	0.41
Intensity of Heat (c)						
R value	0.2[P]	-0.042[P]	0.047[P]	-0.21[P]	-0.11[P]	-0.19[P]
P value	0.45[P]	0.88[P]	0.86[P]	0.44[P]	0.68[P]	0.49[P]
Unpleasantness						
R value	-0.1[P]	-0.38[P]	-0.1[P]	-0.1[P]	-0.38[P]	-0.1[P]
P value	0.71[P]	0.15[P]	0.71[P]	0.71[P]	0.15[P]	0.71[P]
Tolerability						
R value	0.12	-0.15	0.31	0.04	0.0059	-0.17
P value	0.65	0.56	0.25	0.88	0.98	0.51
Burning Sensation						
R value	0.006	-0.061	-0.18	-0.024	-0.08	0.23
P value	0.96	0.8	0.51	0.88	0.74	0.4

°C: degrees Celsius; C: colour bar. [P]: Analysed with Pearson's correlation. Significance level < 0.00333.

Table 2.3. Correlation of Electrical Pain Threshold and Electrical Pain Response

R and *P* values from the correlation analysis performed between electrical pain thresholds and the response to electrical pain are presented for each outcome (listed vertically) following a single electrical stimulus or repeated electrical stimuli.

	Single Stimulus	Repeated Stimuli
Intensity of Pain		
R value	-0.11	0.16
P value	0.69	0.56
Unpleasantness		
R value	-0.3	0.075
P value	0.025	0.78
Tolerability		
R value	-0.076	0.13
P value	0.78	0.63

All analysed with Pearson's correlation. Significance level < 0.00625.

Figures

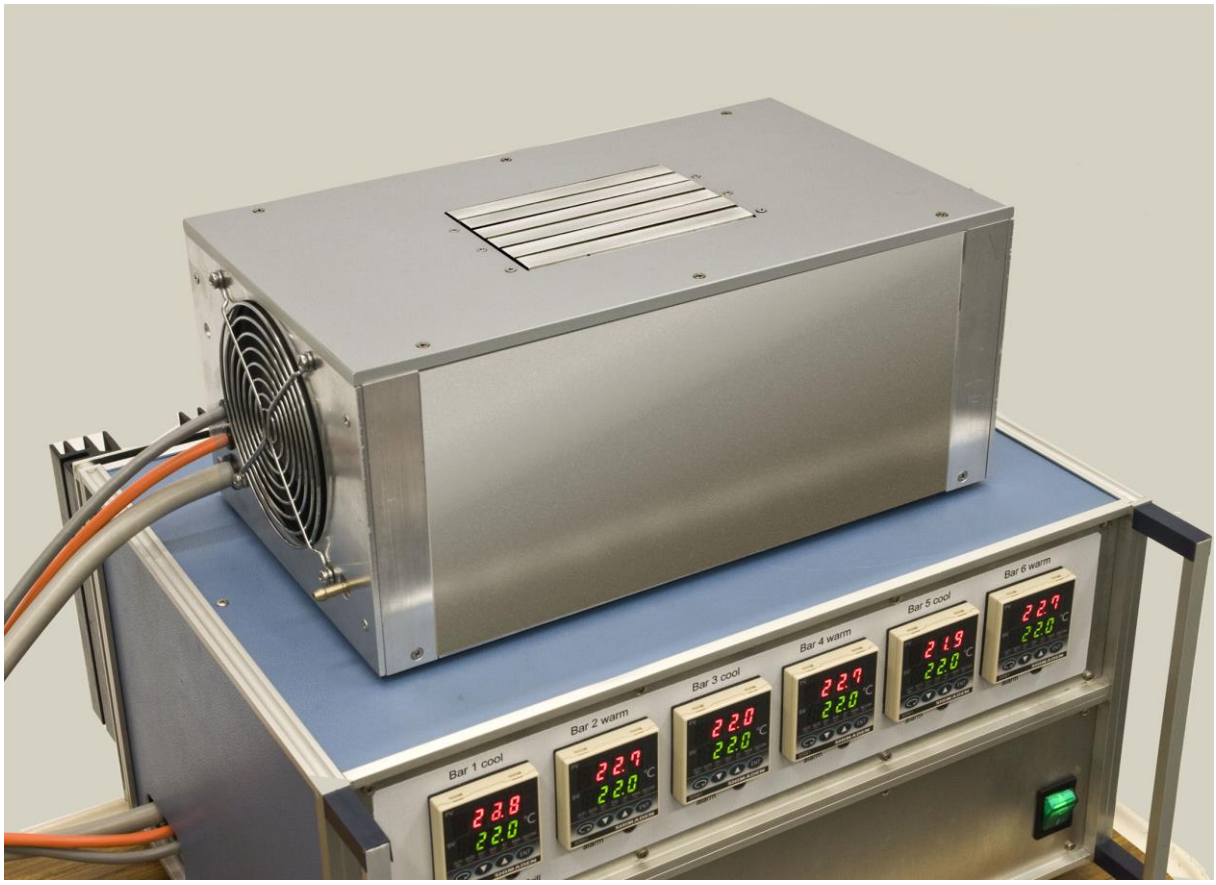

Figure 2.3. Image of thermal grill

In the centre of the Bar Box (smaller box) is the stimulation surface, where participants were required to place their non-dominant palm orthogonally to the long axis of the bars. The stimulation surface consists of six 12 mm wide and 120 mm long aluminium bars separated by approximately 2 mm of thermal insulation. The Control Unit (larger box) set the temperature of the individual bars to alternating cool and warm temperatures.

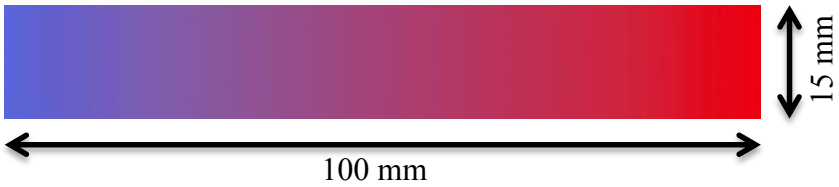

Figure 2.4. Image of novel thermal colour bar

This thermal colour bar was used for all studies from chapters 2 to 7. The thermal colour bar was printed on photo gloss paper and stuck into participants' source documents.

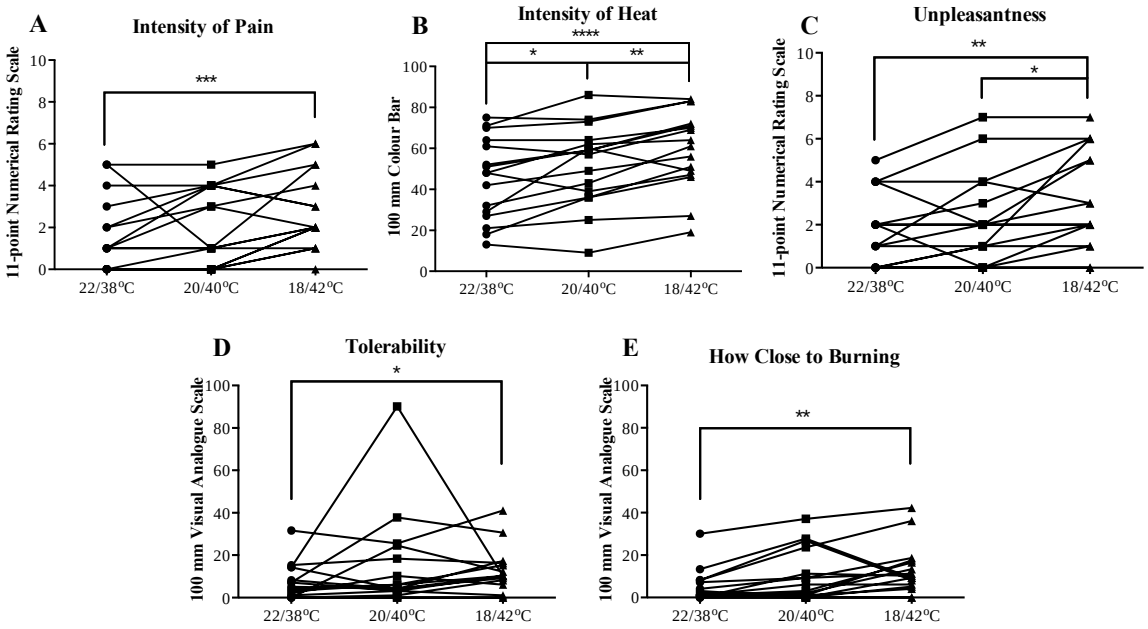

Figure 2.5. Increasing temperature differentials between the warm and cool temperature bars on the non-dominant (left) palm.

Effect of increasing temperature differentials between the warm and cool temperature bars on the responses to the thermal grill illusion at participants non-dominant palm. As the temperature differentials between the warm and cool bars increased, the response to the thermal grill significantly increased for all thermal grill outcomes (A-E). * $P < 0.05$, ** $P < 0.01$, **** $P < 0.0001$.

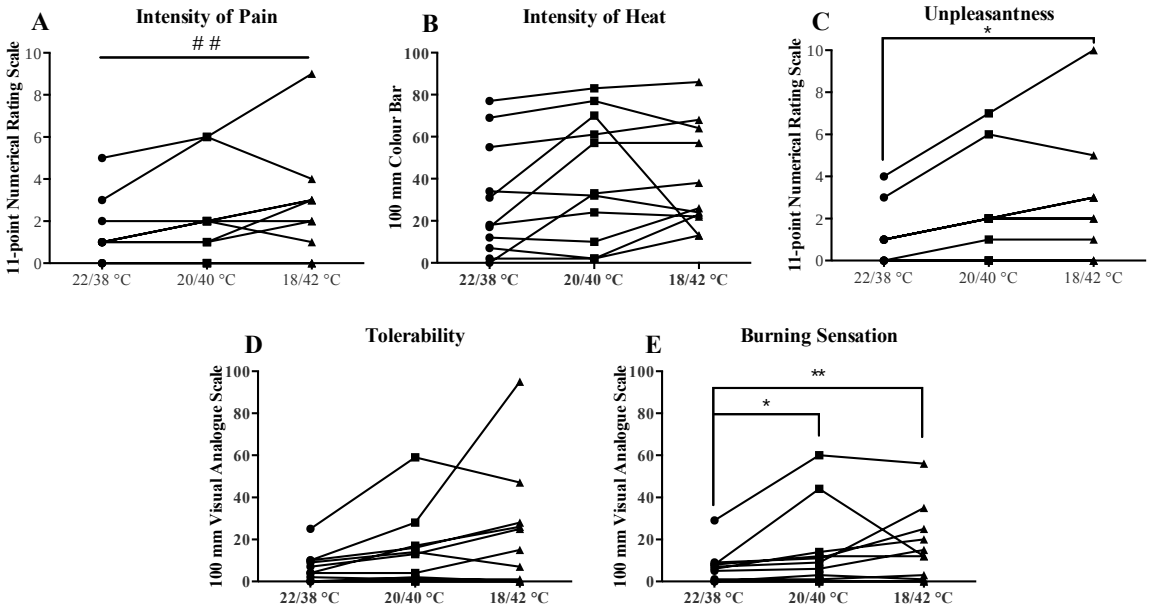

Figure 2.6. Increasing temperature differentials between the warm and cool temperature bars on the right cheek.

Effect of increasing temperature differentials between the warm and cool temperature bars on the responses to the thermal grill illusion at participants right cheek when tested for 30 s. As the temperature differentials between the warm and cool bars increased, the response to the thermal grill significantly increased for the outcomes intensity of pain (A), unpleasantness (C) and perceived burning quality (E). * $P < 0.05$, ** $P < 0.01$, ## $P < 0.01$ for an overall main effect.

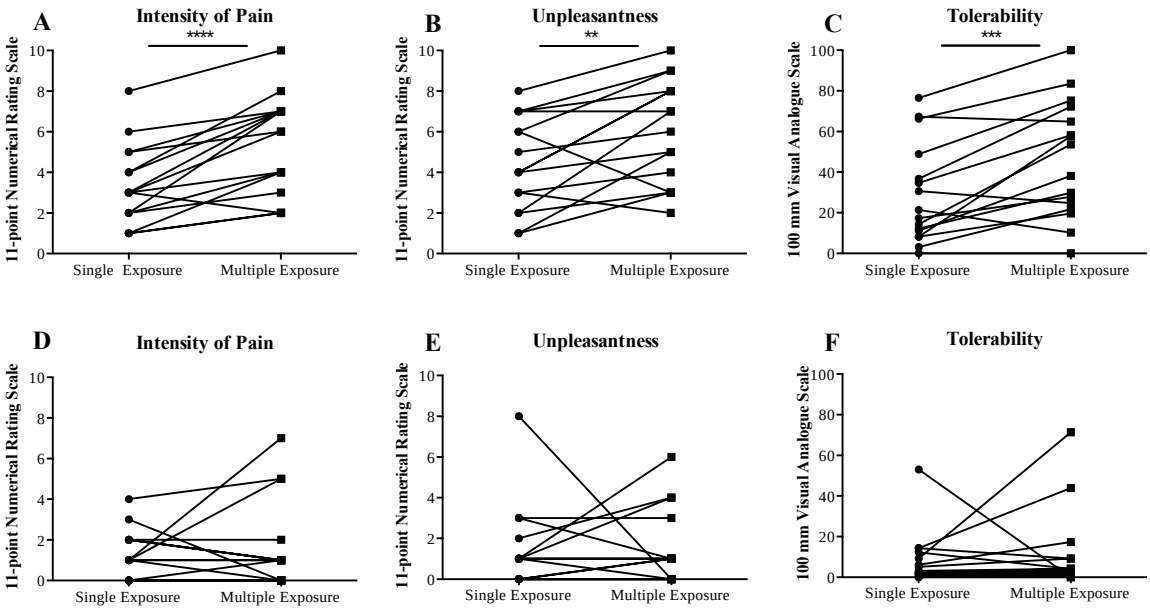

Figure 2.7. Single vs. repeated exposure to electrical stimulation and the thermal grill illusion.

Effect of single vs. repeated exposure to electrical stimulation (A-C) and the thermal grill illusion (D-F). Following repeated exposure to electrical stimuli, significantly more pain (A), unpleasantness (B) and less tolerability (C) was observed compared to a single electrical stimulus, whereas the response to the thermal grill did not differ between single and repeated exposure to the thermal grill for all outcomes (D-F). ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$.

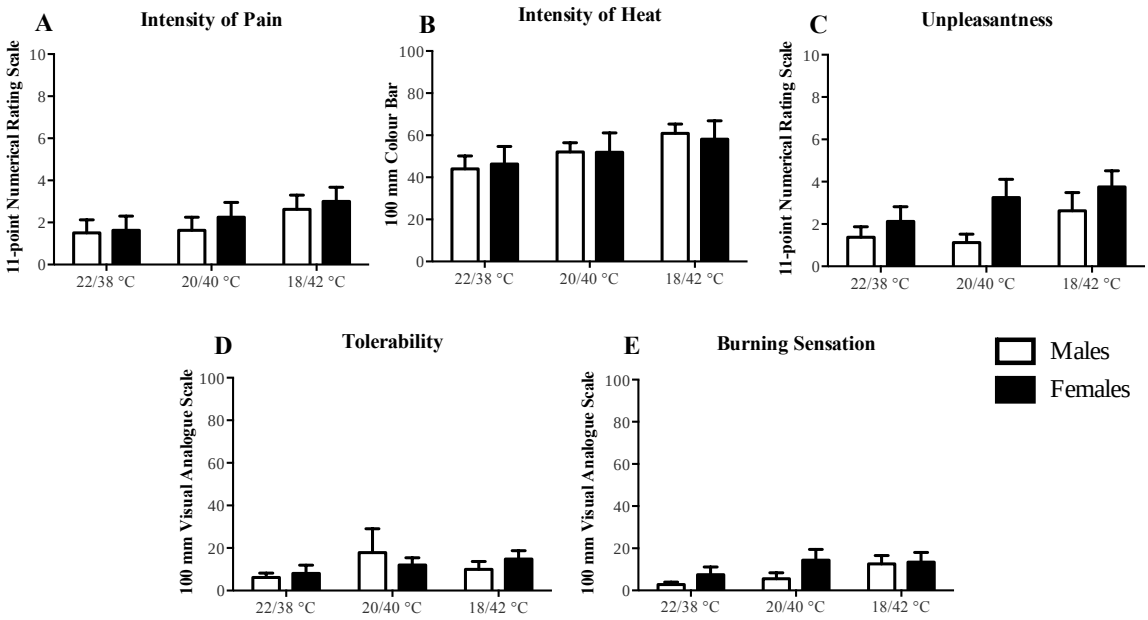

Figure 2.8. Effect of gender to the thermal grill illusion.

The response to the thermal grill illusion at the non-dominant side palm in males (white bars) and females (black bars). No significant differences in response to the thermal grill were observed between males and females for all thermal grill outcomes. All graphs are represented as mean ± SEM.

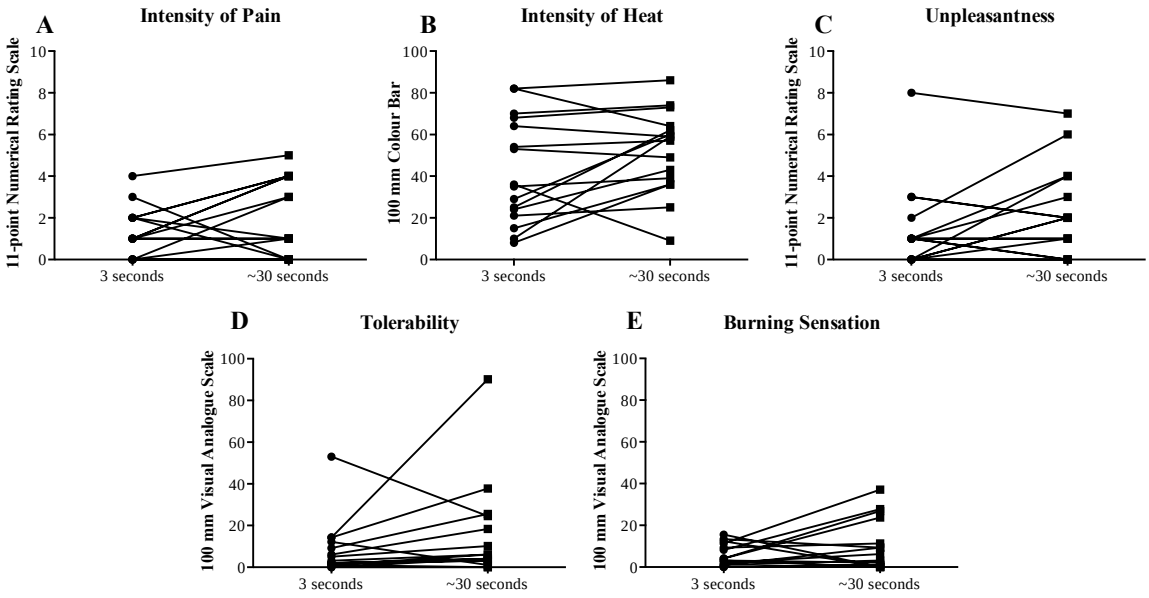

Figure 2.9. Effect of contact time to the thermal grill illusion.

The response to the thermal grill illusion at the non-dominant palm when tested after 3 s and ~30 s contact at the 20/40 ºC thermal grill configuration. The effect of contact time did not affect the response to the thermal grill illusion for all thermal grill outcomes.

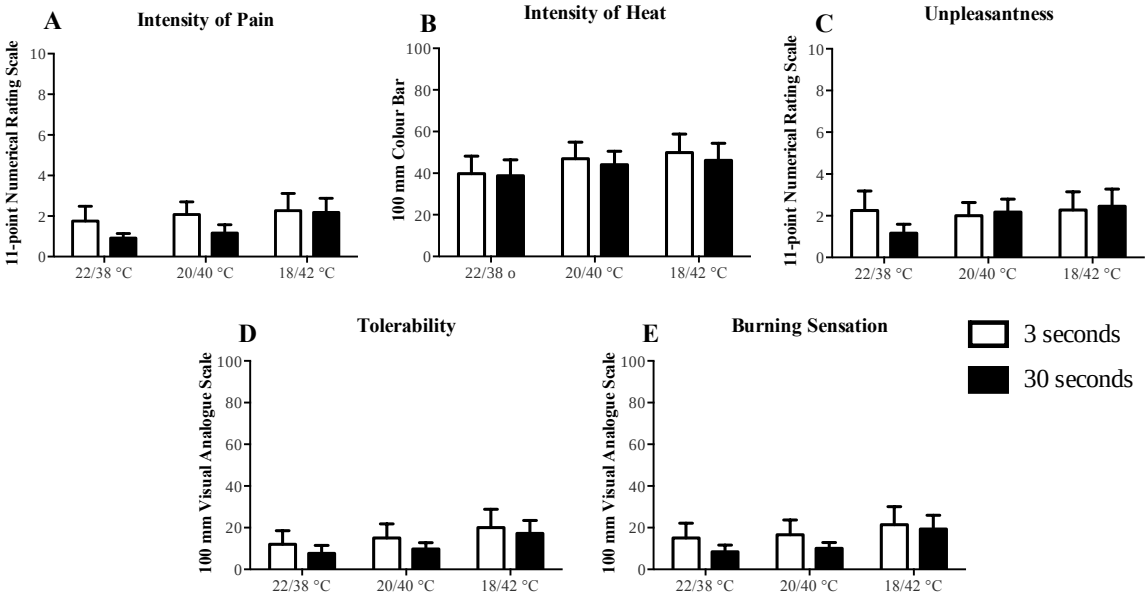

Figure 2.10. Effect of contact time to the thermal grill illusion.

The response to the thermal grill illusion at the left cheek when tested after 3 s and 30 s contact. The effect of contact time did not affect the response to the thermal grill illusion for all thermal grill outcomes. All graphs are represented as mean ± SEM.

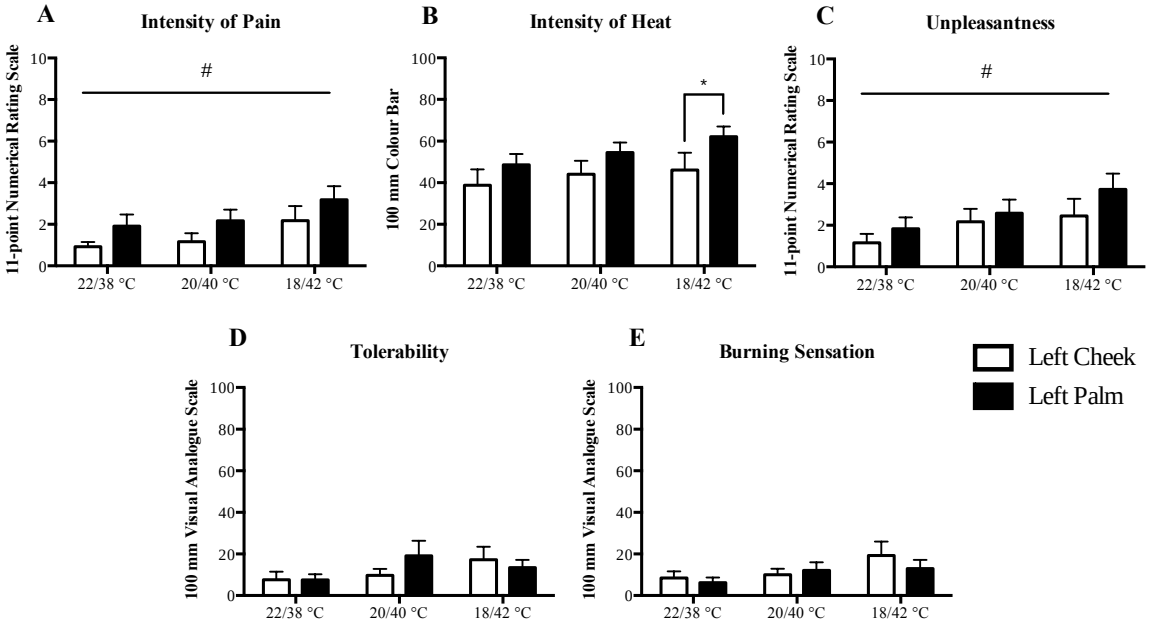

Figure 2.11. Effect of body location to the thermal grill illusion.

The response to the thermal grill illusion at the left cheek (white bars) and palm (black bars). Significantly less pain (A), heat (B) and unpleasantness (C) to the thermal grill illusion was observed on the cheek compared to the palm. All graphs are represented as mean ± SEM. * $P < 0.05$; # $P < 0.05$ for an overall main effect.

Chapter 3. Reduced Response to the Thermal Grill Illusion in Chronic Pain Patients

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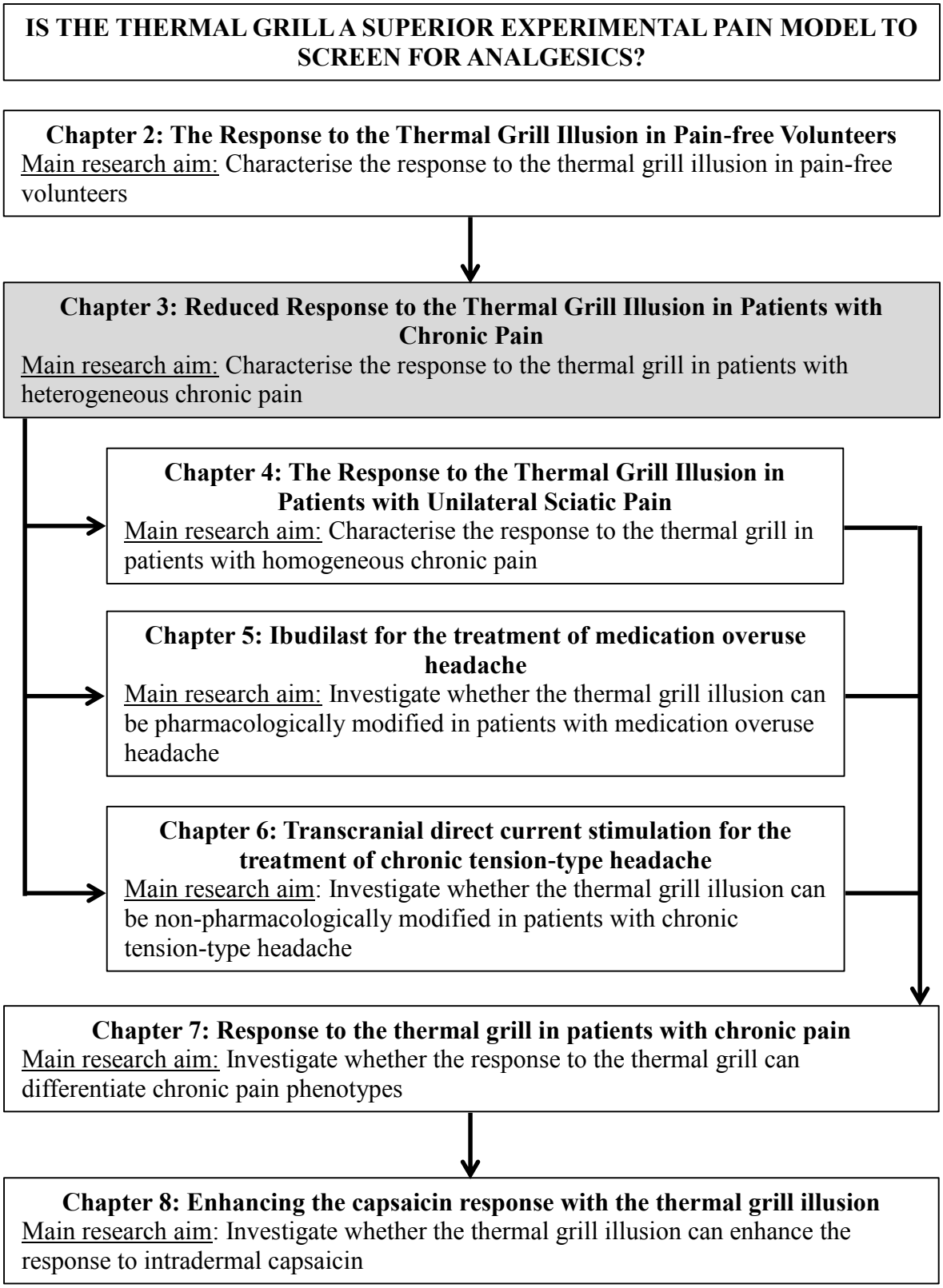
IS THE THERMAL GRILL A SUPERIOR EXPERIMENTAL PAIN MODEL TO SCREEN FOR ANALGESICS?
Chapter 2: The Response to the Thermal Grill Illusion in Pain-free Volunteers
Main research aim: Characterise the response to the thermal grill illusion in pain-free volunteers
Chapter 3: Reduced Response to the Thermal Grill Illusion in Patients with Chronic Pain
Main research aim: Characterise the response to the thermal grill in patients with heterogeneous chronic pain
Chapter 4: The Response to the Thermal Grill Illusion in Patients with Unilateral Sciatic Pain
Main research aim: Characterise the response to the thermal grill in patients with homogeneous chronic pain
Chapter 5: Ibudilast for the treatment of medication overuse headache
Main research aim: Investigate whether the thermal grill illusion can be pharmacologically modified in patients with medication overuse headache
Chapter 6: Transcranial direct current stimulation for the treatment of chronic tension-type headache
Main research aim: Investigate whether the thermal grill illusion can be non-pharmacologically modified in patients with chronic tension-type headache
Chapter 7: Response to the thermal grill in patients with chronic pain
Main research aim: Investigate whether the response to the thermal grill can differentiate chronic pain phenotypes
Chapter 8: Enhancing the capsaicin response with the thermal grill illusion
Main research aim: Investigate whether the thermal grill illusion can enhance the response to intradermal capsaicin

Statement of Authorship

Title of Paper	Reduced Response to the Thermal Grill Illusion in Chronic Pain Patients
Publication Status	Published
Publication Details	Sumracki NM, Buisman-Pijlman TA, Hutchinson M, Gentgall M and Rolan P (2014). Reduced response to the thermal grill illusion in chronic pain patients. Pain Medicine 15: 647-660.

Author Contributions

By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

Name of Principal Author (Candidate)	Nicole Sumracki
Contribution to the Paper	Had a major input in the experimental design, recruited participants, conducted all experimental procedures, performed all statistical analyses, produced all graphical representation of the data collected, and prepared the manuscript for submission.

Signature Date 16 June 2014

Name of Co-Author	Femke Buisman-Pijlman
Contribution to the Paper	Involved in the experimental design, contributed to the data interpretation and preparation of the manuscript.

Signature Date 16 June 2014

Name of Co-Author	Mark Hutchinson
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Signature Date 16 June 2014

Name of Co-Author	Melanie Gentgall
Contribution to the Paper	Responsible for the clinical trial logistics and provided editorial assistance.

Signature Date 28 May 2014

Name of Co-Author	Paul Rolan
Contribution to the Paper	Involved in the experimental design, contributed to the data interpretation and preparation of the manuscript and was responsible for the medical welfare of trial participants.

Signature Date 16 June 2014

Pre-intro to paper

To date there have been no systematic studies on the TGI in the relevant population of chronic pain patients (Craig and Bushnell, 1994; Craig et al., 1996; Fruhstorfer et al., 2003; Bouhassira et al., 2005; Leung et al., 2005; Defrin et al., 2008; Kern et al., 2008a; Kern et al., 2008b; Li et al., 2009; Kammers et al., 2010; Bach et al., 2011; Boettger et al., 2011; Lindstedt et al., 2011a; Lindstedt et al., 2011b; Pinerua-Shuhaibar et al., 2011; Boettger et al., 2012; Seckel et al., 2012; Averbeck et al., 2013; Boettger et al., 2013; Harper and Hollins, 2014). However, two separate case reports have been published, one in a patient with complex regional pain syndrome (type I) (CPRS1) (Heavner et al., 1997) and one in a patient with multiple sclerosis (MS) (Morin et al., 2002). An intolerable burning sensation was experienced when the patient with CPRS1 placed their affected hand on the thermal grill, whereas the patient with MS rated the thermal grill as only slightly painful on their affected side hand. Both patients rated the cool elements as painful (cold allodynia) and the warm elements as warm. Unlike the patient with MS, pain-free participants rated the thermal grill as moderately painful (Craig et al., 1996; Morin et al., 2002). Therefore, the thermal grill failed to produce the normal illusion of pain in the patient with MS (Morin et al., 2002). Consequently, it was suggested that the TGI of pain may be useful in the diagnosis of chronic/neuropathic pain (Craig, 2008). Given these two opposing responses to the TGI in the patient with CPRS1 and the patient with MS, I wished to investigate the response to the TGI in a larger population of chronic pain patients.

Additionally, in chapter 2, the thermal grill did not produce a very painful stimulus in pain-free participants (median 2 on an 11-point numerical rating scale, interquartile range 1 to 5), being below 4 (out of 10), which is generally accepted as the minimum for clinically relevant pain (Jensen et al., 2003). Instead, the thermal grill produced an altered sensory experience that manifested as an aversive heat stimulus (approx. 60 mm on our 100 mm novel colour

bar). Therefore another aim of this study was to evaluate my novel thermal colour bar in patients with chronic pain.

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Reduced Response to the Thermal Grill Illusion in Chronic Pain Patients

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Acknowledgements and Disclosures: We would like to thank the staff at the Pain and Anaesthesia Research Clinic for assistance with the conduct of this study and Jonathan Tuke for statistical assistance. N.M.S. is grateful for an Australian Postgraduates Award. M.R.H. is grateful for an Australian National Health and Medical Research Council C.J. Martin Fellowship (465423; 2007–2010) and an Australian Research Council Research Fellowship (DP110100297; 2011–current). The authors report no conflict of interest.

Abstract

Objective. Sensory illusions may reveal fundamental features of the nervous system. The thermal grill illusion is such a pain illusion, where interlaced warm and cool temperature bars (thermal grill) produce a paradoxical burning sensation. Previous studies have only systematically investigated the thermal grill illusion in pain-free volunteers. The objective of this study was to investigate whether the response to the thermal grill illusion was tolerable in patients with chronic pain and whether the response differed between patients with chronic pain and pain-free volunteers.

Subjects. Sixteen pain-free participants and 18 chronic pain patients (seven not receiving opioids and 11 receiving opioids).

Methods. The thermal grill response was investigated using a custom-built thermal grill. Heat and cold pain thresholds were also determined.

Results. Chronic pain patients reported less intense pain, heat, and unpleasantness to the thermal grill compared with pain-free participants; in particular, there was an overall main effect for significantly less heat from the thermal grill compared with pain-free participants ($P = 0.016$). At the 22/38°C combination, although the majority of pain-free participants experienced the illusion to some degree, the majority of pain patients in both groups did not (median pain score 0). Although perceived heat from the thermal grill was significantly lower in chronic pain patients, both heat and cold pain thresholds did not differ among the three populations.

Conclusions. This preliminary data suggest that the thermal grill response may provide insights into pain sensitivity that are not detected by conventional thermal quantitative sensory testing.

Key Words. Thermal Grill Illusion; Chronic Pain; Pain Model; Cold Pain Thresholds; Heat Pain Thresholds

Introduction

Chronic pain remains a major unmet medical need, with few treatments of novel mechanism of action having been introduced into clinical practice in recent decades. Experimental pain models have been proposed to be useful tools to accelerate the development of analgesic drugs by screening for potential efficacy in small groups of participants [1]. Given that the vast bulk of such studies have been performed in healthy pain-free participants (see large list of reviewed studies [2,3]), it is necessary to strongly activate peripheral nociceptors in such pain models. Due to the similarity of this pathway with the pathways of acute

clinical pain, such models have reasonable utility for predicting the efficacy of analgesics in acute pain. However, the mechanisms by which chronic pain is maintained may be different from those of acute pain, with the current emphasis being on central mechanisms rather than ongoing activation of peripheral nociceptors. Hence, an experimental pain model that induces pain through largely central rather than peripheral mechanisms might shed light on the mechanisms of chronic pain and be a screening tool for new drugs for chronic pain.

One experimental pain model that may be suitable for this purpose is the thermal grill illusion (TGI); where interlaced innocuous warm (e.g., 40°C) and cool (e.g., 20°C) temperature bars (thermal grill) produce a sensation of burning pain (known as the TGI) when presented simultaneously [4,5]. Given the innocuous temperatures of the constituent warm and cool bars, it is unlikely that there is as extensive activation of nociceptors when using this model compared with conventional thermal pain testing. Consequently, the TGI of pain is believed to be a purely central phenomenon [6]. To date there have been no systematic studies on the TGI in the relevant population of chronic pain patients [5–21]. However, two separate case reports have been published, one in a patient with complex regional pain syndrome (type I) (CPRS1) [22] and one in a patient with multiple sclerosis (MS) [23]. An intolerable burning sensation was experienced when the patient with CPRS1 placed their affected hand on the thermal grill, whereas the patient with MS rated the thermal grill as only slightly painful on their affected side hand. Both patients rated the cool elements as painful (cold allodynia) and the warm elements as warm. Unlike the patient with MS, pain-free participants rated the thermal grill as moderately painful [7,23]. Therefore, the thermal grill failed to produce the normal illusion of pain in the patient with MS [23]. Consequently, it was suggested that the TGI of pain may be useful in the diagnosis of chronic/neuropathic pain [24]. Given these two opposing responses to the TGI in the patient with CPRS1 and the patient with MS, we wished to investigate the response to the TGI in a larger population of chronic pain patients. Considering that the case report by Heavner et al. [22] reported an intolerable burning sensation to the TGI in a patient with CPRS1, and that previous work from our laboratory demonstrated that patients with chronic pain have an enhanced response to experimental stimuli compared with pain-free participants irrespective of the affected body region [25–28], the objective of this study was to investigate whether the response to the TGI was tolerable in patients with chronic pain to determine whether the TGI could be used to screen for novel analgesics in the future. A heterogeneous chronic pain patient population was selected for this study to extrapolate tolerability to the TGI to a broad range of painful conditions. We hypothesized that patients with chronic pain would have an altered response to the TGI compared with pain-free participants.

Given that one potential use of the TGI will be to screen for the action of novel analgesics, it is also important to assess whether the response is altered by medication, especially in a manner that may not be detected by conventional thermal pain testing. In a recent study by Kern and colleagues [6], low-dose ketamine selectively reduced the intensity of pain and unpleasantness of the TGI, without altering participants' thermal pain thresholds. Our laboratory has previously demonstrated that opioid-dependent subjects without a clinically significant pain problem receiving opioid substitution therapy were hyperalgesic to the cold pain test [29], showing that the confounding effects of medication need to be considered when studying a patient population. Hence, we additionally hypothesized that there might be further alteration in pain patients to the TGI if they were taking chronic opioid medication. Therefore, a group of patients with chronic pain who were taking chronic opioids for their pain were included in this study.

Previous studies investigating the thermal grill in pain-free participants have not quantitatively investigated the intensity of heat experienced from the thermal grill. Consequently, we developed a novel thermal color bar in order to better capture the response to the TGI. One aim of this study was to evaluate our novel thermal color bar.

To summarize, we have compared the responses to the TGI in patients with chronic pain and in patients with chronic pain who were receiving chronic opioid therapy to those in a pain-free population, to determine whether the response to the TGI is either reduced, the same, or heightened in patients with chronic pain compared with pain-free participants. Additionally, we compared conventional thermal quantitative sensory testing among the three populations.

Materials and Methods

Thermal Grill

The thermal grill was designed and constructed by Flinders Biomedical Engineering (Adelaide, South Australia, Australia) (see Figure 1). The thermal grill consists of two main parts, the Control Unit and the Bar Box. In the center of the Bar Box is the stimulation surface, which consists of six 12-mm wide and 120-mm long aluminum bars separated by approximately 2 mm of thermal insulation. The temperature of the individual bars is generated by Peltier elements and is controlled by settings on the Control Unit. The temperature of the cold bars can be set in the range of ambient temperature (22°C) down to 5°C and the hot bars from ambient temperature up to 50°C. Thermistors placed in each bar provide continuous temperature feedback of the thermode-skin interface.

Ethics

Ethics approval was obtained from the Royal Adelaide Hospital Research Ethics Committee. Signed consent was obtained from each participant prior to enrolment into the study. Participants were financially compensated for their time and inconvenience.

Figure 1 Image of the thermal grill. In the center of the Bar Box (smaller box) is the stimulation surface, where participants were required to place their nondominant palm orthogonally to the long axis of the bars. The stimulation surface consists of six 12-mm wide and 120-mm long aluminum bars separated by approximately 2 mm of thermal insulation. The Control Unit (larger box) set the temperature of the individual bars to alternating cool and warm temperatures.

Subjects

Sixteen healthy pain-free participants (*pain-free*), seven chronic pain patients not on opioid therapy (*pain*) and 11 chronic pain patients on chronic opioid therapy (*pain + opioids*) were chosen to participate in this study. Both *pain* and *pain + opioids* groups also used additional pain-modifying medications, which are outlined in (Table 1). Participants were recruited from the Pain and Anaesthesia Research Clinic's (PARC) volunteer database and from the general public by advertisement. All participants were naïve to the thermal grill effect.

Inclusion/Exclusion Criteria

Key Inclusion Criteria

Key inclusion criteria were: 1) aged between 18 and 65 years old inclusive; 2) being in good general health; 3) experiencing pain at least 5 days per week for at least the last 3 months (*pain* and *pain + opioids* groups only); 4) ongoing opioid therapy with a dose equivalent to 20 mg morphine per day (*pain + opioids* group only); and 5) not on opioid therapy. Pain was not constrained by diagnosis or location (*pain* and *pain + opioids* participants).

Exclusion Criteria

Key exclusion criteria were as follows. All groups: pregnant or lactating women; significant scarring on the nondominant palm (to prevent interference with temperature perception); currently experiencing an active inflammatory process (e.g., acute pain or influenza, etc.) or having a clinically significant infection in the previous 4 weeks; history of excessive alcohol use; known history of hepatitis B, hepatitis C, or HIV; contraindication to cold pain testing (e.g., limb ischemia or Raynaud's phenomenon); positive breath alcohol concentration test on the main study day; or presence of nonprescribed drugs of abuse in urine drug screen. *Pain-free* group only: current or past history of any chronic pain condition or recurrent condition that alters perception (such as migraine); recent use of opioids (e.g., morphine use within last week, or codeine use (>30 mg) within last 5 days), adjuvant analgesics (e.g., tricyclics, gabapentin, or pregabalin), anxiolytics, antidepressants and anti-epileptics within last month; regular use of analgesics (excluding paracetamol; paracetamol must have been withdrawn for at least 24 hours prior to the main study day).

Experimental Procedure

The main part of the study consisted of two experimental sessions of approximately 30 minutes' duration. During the first experimental session, thermal grill testing was performed. During the second experimental session, heat and cold pain thresholds (HPTs and CPTs) were determined. Alcohol- and caffeine-containing foods and beverages were not allowed for 24 hours before the experimental day. *Pain* and *pain + opioids* participants took their pain-modifying/analgesic medications as per usual on the main study day to avoid participants experiencing both pharmacological and psychological withdrawal symptoms.

Session 1: Thermal Grill Testing

Pain and *pain + opioids* participants were asked to rate the pain felt on average from their chronic pain condition on an 11-point numerical rating scale (NRS)(left anchor, "no pain," [0]; right anchor, "worst pain imaginable," [10]) and on a 100-mm visual analog scale (VAS) (left anchor, "no pain," [0 mm]; right anchor "worst pain imaginable," [100 mm]). Then all participants were exposed to three interlaced cool and warm temperature combinations (22/38°C, 20/40°C, and 18/42°C) in randomized order. The temperature combinations chosen were based on the temperature combinations used in a previous study [7]. Participants were required to place their nondominant palm on the thermal grill, orthogonally to the long axis of the bars for approximately 30 seconds. Once participants had placed their palm on the thermal grill for 5 seconds, they were asked to fill out an assessment form with their dominant hand while keeping their nondominant palm on the thermal grill. This method was chosen, instead of the usually used method of rating stimulus qualities after completion of the test, so that participants relied less on their recall ability, thus potentially resulting in more accurate stimulus ratings. Participants were required to rate: 1) the intensity of pain and the unpleasantness produced from the thermal grill on

Table 1 Demographic data of *pain* and *pain + opioids* participants

Participant number	Gender	Age	Pain score (numerical rating scale, 0–10)	Pain score (visual analog scale, 0–100)	Painful condition	Duration of pain (years)	Opioid type	Morphine equivalent dose	Concomitant analgesics/ adjuvants
Pain group									
1	F	36	5	53	Osteoarthritis of knee	3	—	—	Ibuprofen
2	M	66	3	29	Sciatic pain	1	—	—	None
3	M	60	7	68	Sciatic pain	5	—	—	Citalopram, paracetamol
4	F	64	4	36	Chronic back pain	11	—	—	None
5	F	45	6	50	Peripheral nerve injury	4	—	—	Gabapentin, amitriptyline
6	F	57	7	59	Non-cardiac chest pain	4	—	—	Paracetamol
7	F	46	6	65	Fibromyalgia and back pain	5	—	—	None
—	5F, 2 M	53 ± 11	5.4 ± 0.6	51 ± 5	—	5 ± 3	—	—	—
Pain ± opioids group									
1	F	63	7	69	Sciatic pain	11	Morphine	200	Amitriptyline, pregabalin, paracetamol
2	M	43	7	68	Chronic low back and leg pain	29	Oxycodone	80	None
3	F	65	5.5	53	Osteoarthritis	4	Oxycodone	120	None
4	F	49	5	48	Chronic low back pain	17	Oxycodone	36	Diclofenac
5	M	54	8	88	Osteoarthritis of hip	3	Oxycodone	80	None
6	F	59	4	42	Chronic low back and shoulder pain	20	Methadone	30	None
7	M	45	6	58	Osteoarthritis of shoulder	3	Morphine	70	Venlafaxine, diazepam
8	M	42	8	75	Fibromyalgia	4	Paracetamol/ codeine	30	Duloxetine
9	F	64	5	46	Osteoarthritis	14	Tramadol	107	Celecoxib, paracetamol/ codeine
10	F	62	8	89	Chronic low back pain	7	Morphine	40	Oxycodone hydrochloride, paracetamol/codeine
11	F	33	7	69	Complex regional pain syndrome	7	Oxycodone	120	Pregabalin, oxycodone hydrochloride, paracetamol/codeine
—	7F, 4 M	52 ± 11	6.4 ± 0.4	64 ± 5	—	11 ± 8	—	83 ± 16	—

F = female; M = male.

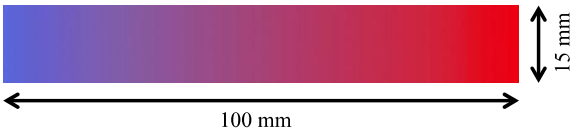

Figure 2 Image of novel thermal color bar. The thermal color bar measured 100 mm in width and 15 mm in length. Participants were asked to "please place a vertical line through the color bar that corresponds to the intensity of heat experienced from the temperature bars." No anchors were provided.

an 11-point NRS (left anchor, "no pain" and "not unpleasant," [0]; right anchor, "worst pain imaginable" and "very unpleasant," respectively [10]); 2) intensity of heat experienced from the thermal grill on a novel 100-mm VAS thermal color bar (no anchors, see Figure 2); as well as 3) their tolerability to the temperature bars on a 100-mm VAS (left anchor, "tolerable," [0 mm]; right anchor "not tolerable," [100 mm]). Once participants had answered these questions, participants were allowed to remove their palm from the thermal grill. Participants were then asked to rate "how close the temperature bars felt to burning you," (left anchor, "not close," [0 mm]; right anchor, "very close," [100 mm]), "how similar was the intensity of pain experienced from the temperature bars to the intensity of pain you experience from your chronic pain condition," (*pain* and *pain + opioids* groups only), and "how similar was the sensation experienced from the temperature bars to the sensation you experience from your chronic pain condition," (*pain* and *pain + opioids* groups only) on an 100-mm VAS (left anchor, "not similar," [0 mm]; right anchor, "very similar," [100 mm]). Participants were also given an opportunity to write about the sensation(s) they experienced.

Session 2: Thermal Threshold Testing

Participants' individual CPTs and HPTs were determined using a TSA-II Neurosensory Analyzer (TSA-II) via the Method of Limits. The thermode (3 cm × 3 cm) was strapped to the palmar surface of the nondominant palm, and the participant was given a hand-held feedback control. The temperature of the thermode was initially set at 32°C. The temperature of the thermode either heated up (for heat pain) or cooled down (for cold pain) at a constant rate of 1°C/second. When the temperature of the thermode was first detected as "just becoming painful," the participant was required to press a button on the hand-held feedback control, which halted the stimulus. The thermode then automatically and quickly returned to 32°C. The temperature at which the participant halted the stimulus was automatically recorded. This temperature was the participant's HPT or CPT. After a 20–25-second delay, the procedure was repeated twice more to obtain an average HPT and CPT.

Statistical Analysis

The D'Agostino and Pearson omnibus normality test was performed to test for normality of the data. The CPTs, HPTs, intensity of heat experienced from the TGI, and intensity of unpleasantness experienced from the TGI were compared among the *pain-free*, *pain*, and *pain + opioids* participants' mean using a one-way ANOVA with Tukey's multiple comparison test. Therefore, these graphs are presented as mean ± SEM.

Pain-free, pain, and *pain + opioids* participants' median intensity of pain experienced from the thermal grill, tolerability to the thermal grill, and "how close the bars felt to burning you," were compared using the Kruskal–Wallis test with Dunn's multiple comparison test due to the nonparametric distributions of the data. Therefore, these graphs are presented as median with interquartile range. Median similarity of the pain experienced from the thermal grill to the pain experienced from participants' chronic pain condition and similarity of the sensation experienced from the thermal grill to the sensation experienced from participants' chronic pain condition were compared using the Mann–Whitney test due to the nonparametric distributions of the data. Therefore, these graphs are presented as median with interquartile range.

Pain-free, pain, and *pain + opioids* participants' "intensity of pain," and the "intensity of unpleasantness" to the TGI were also pooled across each thermal grill configuration, and the medians were compared using the Kruskal–Wallis test with Dunn's multiple comparison test. *Pain* and *pain + opioids* participants' duration of chronic pain was compared using an unpaired *t*-test with Welch's correction. *Pain* and *pain + opioids* participants' average pain experienced from their chronic pain condition was compared using an unpaired Mann–Whitney test for the 11-point NRS and an unpaired *t*-test for the 100-mm VAS.

Results

Subjects

Sixteen *pain-free* (eight females), seven *pain* (five females) and 11 *pain + opioids* (seven females) participants completed this study. The average age (mean years ± SD) of *pain-free*, *pain*, and *pain + opioids* participants was 24.1 ± 9.8, 53.4 ± 11.2, and 52.6 ± 10.9 years, respectively. The average duration (mean years ± SD) of pain for *pain* and *pain + opioids* participants was 4.7 ± 3.1 and 10.8 ± 8.4 years, respectively, (mean difference: 6.1 years, 95% CI for difference 0.1 to 12.1 years). There were no significant differences between mean average pain experienced by *pain* and *pain + opioids* participants from their chronic pain condition, as assessed by an 11-point NRS (median pain: *pain* = 7; *pain + opioids* participants = 6) and a 100-mm VAS (–13 mm difference, 95% CI for difference –29 mm to 3 mm) (see Table 1 for full patient demographics).

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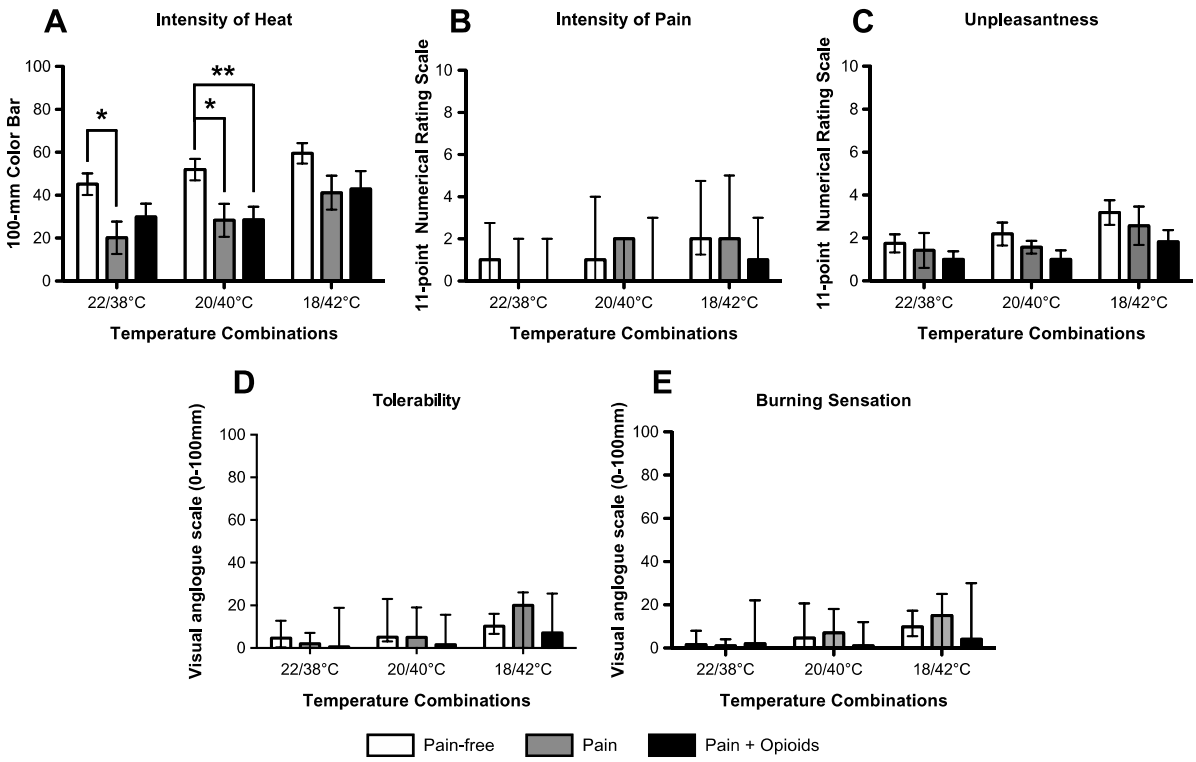

Figure 3 Response to the thermal grill illusion in *pain-free*, *pain*, and *pain + opioids* participants. Intensity of heat (A), intensity of pain (B), intensity of unpleasantness (C), tolerability (D), and perceived burning quality (E) to the thermal grill illusion at the thermal grill configurations: 22/38°C; 20/40°C and 18/42°C. Intensity of pain (B), tolerability (D), and perceived burning (E) are represented as median and interquartile range. Intensity of heat (A) and intensity of unpleasantness (C) are represented as mean ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$.

Response to the Thermal Grill Illusion:
Pain-Free *Participants vs Chronic Pain Patients*

Intensity of Heat (100 mm Visual Analog Scale Thermal Color Bar)

Pooling the data across each thermal grill configuration, both pain populations reported significantly lower scores for heat than the *pain-free* group, mean, 95%CI for difference: *pain* participants (–22 mm, –35 mm to –9 mm), *pain + opioids* participants (–20 mm, –31 mm to –8 mm). When analyzed separately for each thermal grill temperature combination, *pain* participants reported significantly less heat (mean, 95% CI for difference) to the TGI compared with *pain-free* participants at the 22/38°C configuration (–25 mm, –47 mm to –3 mm) and both *pain* and *pain + opioids* participants reported significantly less heat to the TGI at the 20/40°C configuration (*pain* participants: –24 mm, –46 mm to –1 mm; *pain + opioids* participants: –26 mm, –45 mm to –7 mm). Although a similar pattern of response was observed at the 18/42°C configuration, these differences compared with *pain-free* failed to reach statistical significance (*pain* participants: –18 mm, –43 mm to 6 mm; *pain + opioids* participants: –19 mm, –40 mm to 3 mm) (see Figure 3A).

Intensity of Pain and Unpleasantness (11-Point Numerical Rating Scale)

A general pattern of response was observed that *pain* and *pain + opioids* participants reported less pain and less unpleasantness to the TGI compared with *pain-free* participants.

For "intensity of pain," the values were low in all three groups, but particularly lowest in the *pain + opioids* group. In that group, median values were 0 at the 22/38°C and 20/40°C configuration and 1 at 18/42°C. Given the low median values, no significant differences among groups were demonstrated. Differences in reported pain to the TGI approached significance between *pain-free* and *pain + opioids* participants when data was pooled across

each thermal grill configuration (difference in rank sum: 15.36; $P > 0.05$). There were no differences at specific configurations (22/38°C: $P = 0.54$; 20/40°C: $P = 0.33$; 18/42°C: $P = 0.20$) (see Figure 3B).

For "unpleasantness," the mean values for the *pain* group were lower than the *pain-free* group and the *pain + opioids* group were lower still. However, none of the differences were statistically significant and again may reflect the low mean scores. Pooling the data across each thermal grill configuration demonstrated a significant group difference between *pain-free* and *pain + opioids* participants for unpleasantness to the TGI (difference in rank sum: 15.85; $P < 0.05$). There were no differences at specific configurations (22/38°C: $P = 0.53$; 20/40°C: $P = 0.23$; 18/42°C: $P = 0.29$) (see Figure 3C).

Tolerability and Perceived Burning (100 mm Visual Analog Scale)

On the specific question "please rate your tolerability of the temperature bars," median VAS scores were generally low ranging between 1 mm and 20 mm, although individual participants gave high scores (see Figure 3D). Tolerability of the TGI did not differ significantly among the groups at the 22/38°C ($P = 0.81$), 20/40°C ($P = 0.26$), or 18/42°C ($P = 0.49$) configuration. Similarly, median VAS scores for "how close were the bars to burning you" were very low, ranging between 1 mm and 15 mm, although again individual participants did report high values (see Figure 3E). Perceived burning quality to the TGI did not differ significantly among the groups at the 22/38°C ($P = 0.86$), 20/40°C ($P = 0.82$), or 18/42°C ($P = 0.78$) configuration.

Similarity of Pain and Sensation to Chronic Pain Condition (100 mm Visual Analog Scale)

On the specific question "how similar is the intensity of pain experienced from the temperature bars to the intensity of pain you experience from your chronic pain condition," median VAS scores were generally low ranging between 1 mm and 19 mm, although individual participants gave high scores (see Figure 4A). No statistical differences in responses between *pain* and *pain + opioids* participants were observed at the 22/38°C ($P = 0.65$), 20/40°C ($P = 0.27$), or 18/42°C ($P = 0.08$) configuration.

Similarly, median VAS scores for "how similar is the sensation you experienced from the temperature bars to the sensation you experience from your chronic pain condition" were generally low, ranging between 1 mm and 15 mm, although individual participants gave high scores (see Figure 4B). No statistical differences in responses between *pain* and *pain + opioids* participants were observed at the 22/38°C ($P = 0.96$), 20/40°C ($P = 0.18$), or 18/42°C ($P = 0.32$) configuration.

Effect of Increasing Temperature Differentials Between the Warm and Cool Temperature Bars Evoked by the Thermal Grill: Pain-Free *Participants*

Increasing temperature differentials between the warm and cool temperature bars produced significantly greater responses for intensity of pain, intensity of heat, unpleasantness, tolerability, and "how close the bars felt to burning you" for *pain-free* participants. These results demonstrate that the largest thermal grill responses were generally reported when the warm and cool temperature bars were at their maximal temperature differentials (i.e., at the

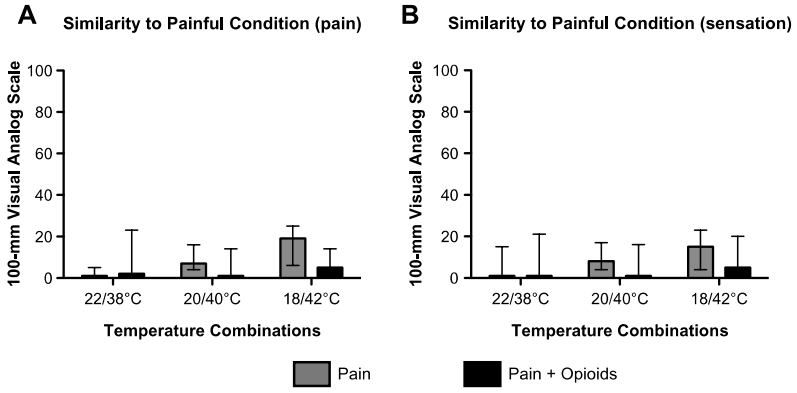

Figure 4 Response to the thermal grill illusion in *pain* and *pain + opioids* participants. Similarity of intensity of pain experienced from thermal grill illusion to the intensity of pain experienced from participants chronic pain condition (A) and similarity of sensation experienced form the thermal grill to the sensation experienced from participants chronic pain (B) at the thermal grill configurations: 22/38°C, 20/40°C, and 18/42°C. Data represented as median and interquartile range.

18/42°C thermal grill configuration)(see Table 2 and Figure 5). Similar findings were observed in *pain* and *pain + opioids* participants.

Cold and Heat Pain Thresholds: Pain-Free *Participants vs Chronic Pain Patients*

Neither CPTs nor HPTs differed significantly among *pain-free*, *pain*, and *pain + opioids* participants ($P = 0.206$ and $P = 0.579$, respectively) (see Figure 6). There appears to be an outlier in the *pain + opioids* group, as the highest CPT and lowest HPT was reported by the same participant (see Figure 6).

Discussion

We report the first study investigating the paradoxical burning sensation produced by a thermal grill in patients with chronic pain. The main aim of this study was to investigate whether the response to the TGI was tolerable in patients with chronic pain to determine whether the TGI could be used to screen for novel analgesics in the future; and to compare the response to the TGI in *pain-free*, *pain*, and *pain + opioids* participants. The thermal grill was well tolerated by all patients with chronic pain, with no patients removing their palm before all assessments were completed. Our expectation was that patients with chronic pain would report greater pain and unpleasantness to the TGI compared with pain-free participants, based on previous studies, which demonstrated that patients with chronic pain usually report the same or greater pain and unpleasantness to painful experimental stimuli compared with pain-free participants [25–28,30–33], as well as a previous case report of a patient with CPRS1 who demonstrated an intolerable burning sensation to the TGI [22]. Unexpectedly, patients with chronic pain had reduced responses to the TGI compared with pain-free participants. In particular the intensity of heat experienced from the thermal grill was significantly lower for the *pain* and *pain + opioids* participants compared with *pain-free* participants. Additionally, *pain* and *pain + opioids* participants displayed a general pattern of reduced response to the TGI for the intensity of pain and unpleasantness experienced from the thermal grill compared with the *pain-free* participants. This reduced response to the thermal grill is unlikely to be a reflection of altered thermal thresholds, as no significant difference in thermal thresholds was observed among the three groups, indicating that the finding of reduced response to the thermal grill is likely to be specific to the illusion. Therefore, the key finding of this study is that even with this relatively small sample size, the thermal grill was able to detect a significant difference among the three populations, whereas no significant difference was observed for conventional thermal thresholds. Whatever minor differences there may or may not have been in conventional thermal thresholds among the three populations, which may have been revealed in a larger-sized study, this study suggests that conventional thermal thresholds are less sensitive than the thermal grill, as significant differences among the three populations were observed using the thermal grill. A recent study by

Table 2 Effect of increasing temperature differential °C between the warm and cool temperature bars in *pain-free* participants

	Thermal grill temperature combinations tested			Difference between thermal grill temperature combinations		
Response measure	22/38	20/40	18/42	22/38 and 20/40	20/40 and 18/42	22/38 and 18/42
Intensity of pain (0–10) (median, interquartile range)	1 (0 to 3)	1 (0 to 4)	2 (1 to 5)	$P > 0.05$, difference in rank sum –8	$P > 0.05$, difference in rank sum –12.5	**$P < 0.05$, difference in rank sum = –20.5**
Intensify of heat (100 mm) (mean, 95% CI)	45 (35 to 56)	52 (41 to 63)	60 (49 to 70)	**–7 mm (–12 mm to –1 mm)**	**–8 mm (–13 mm to –2 mm)**	**–14 mm (–20 mm to –9 mm)**
Unpleasantness (0–10) (mean, 95% CI)	2 (1 to 3)	2 (1 to 3)	3 (2 to 4)	0, –1 to 0	**–1, –2 to 0**	**–1, –2 to –1**
Tolerability (0–100 mm) (median, interquartile range)	5 (0 to 13)	5 (3 to 22)	10 (7 to 16)	$P > 0.05$, difference in rank sum –8.5P	$P > 0.05$, difference in rank sum –5.5	**$P < 0.05$, difference in rank sum –14.0**
Closeness to burning (0–100 mm) (median, interquartile range)	2 (1 to 8)	5 (0 to 21)	10 (5 to 17)	$P > 0.05$, difference in rank sum –9.0	$P > 0.05$, difference in rank sum –9.0	**$P < 0.05$, difference in rank sum = –18.0**

CI = confidence interval.
Significant differences between thermal grill temperature combinations are highlighted in bold text.

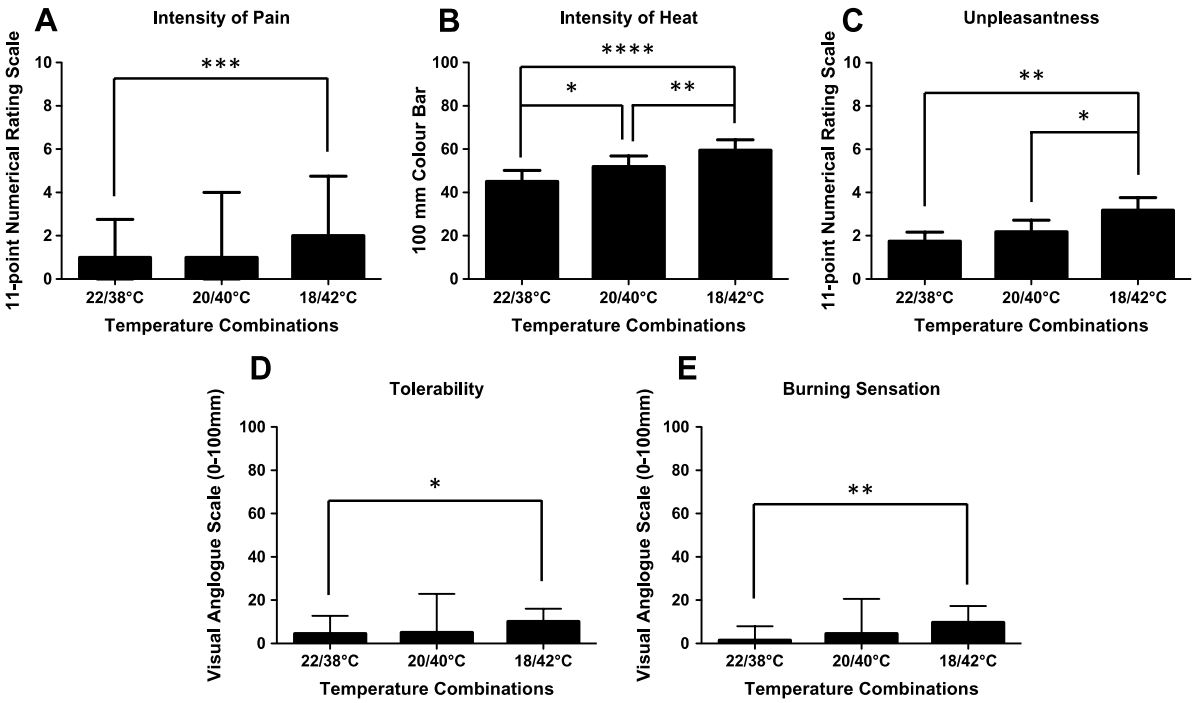

Figure 5 Increasing temperature differentials between the warm and cool temperature bars in *pain-free* participants. Effect of increasing temperature differentials between the warm and cool temperature bars on the responses to the thermal grill illusion for: Intensity of pain (A); intensity of heat (B); intensity of unpleasantness (C); tolerability (D); and perceived burning quality (E) in *pain-free* participants. Intensity of pain (A), tolerability (D), and perceived burning (E) are represented as median and interquartile range. Intensity of heat (B) and intensity of unpleasantness (C) are represented as mean ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$.

Chen and colleagues [34] also investigated HPTs among *pain-free*, *pain,* and *pain + opioids* participants. In that study, significant differences were observed among *pain-free*, *pain*, and *pain + opioids* participants, with *pain + opioids* participants displaying reduced HPTs (i.e., more sensitive) compared with *pain-free* and *pain* participants. No significant differences were observed for CPTs. In that study, Chen and colleagues [34] demonstrated that in order to detect a 1.2°C difference in mean HPT among the three groups with a standard deviation of less than 3°C and a power of 80%, 31 participants per group were required, demonstrating a very low effect size and requiring almost three times the participants that were in this study. Greater sensitivity allows for a larger range of response to be captured, thereby increasing the likelihood that a significant difference between two or more groups can be observed, if indeed a difference does exist. Furthermore, not only does greater sensitivity allow for the recruitment of less participants, thereby making the thermal grill a more ethically acceptable pain model, but it

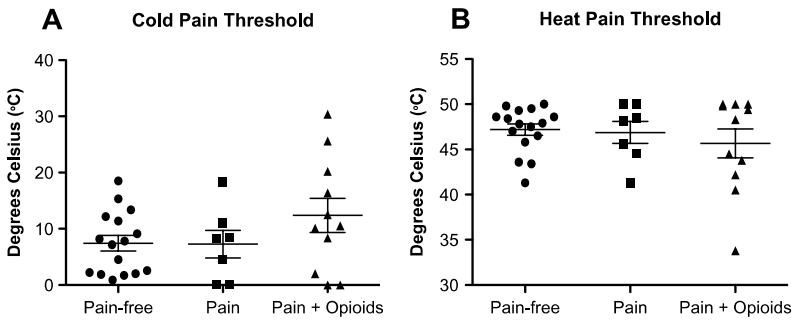

Figure 6 Cold and heat pain thresholds in *pain-free*, *pain*, and *pain + opioids* participants. Cold (A) and heat (B) pain thresholds in *pain-free*, *pain*, and *pain + opioids* participants. Data represented as mean ± SEM.

also reduces the time and costs associated with recruiting larger sample sizes, such as the increased participant numbers required to detect a significant difference using conventional thermal threshold testing. Hence, rather than concluding that there is no significant difference among our three populations using conventional thermal thresholds, this study's results suggest that the thermal grill has a greater sensitivity compared with conventional thermal thresholds to detect a difference among these three populations, thus warrants further investigation.

The prevailing theory of the TGI is the thermo-sensory disinhibition hypothesis put forth by Craig and Bushnell [5] based on electrophysiological recordings from anesthetized cats lamina I spinothalamic tract neurons. Craig and Bushnell [5] demonstrated that the cool bars of the thermal grill activate lamina I thermoreceptive specific (COLD) cells, which are activated by cooling and receive input from specific cold receptors and multimodal (HPC) cells, which are responsive to heat, pinch, and cold and also receive input from cold-sensitive C-polymodal nociceptors. At innocuous cool temperatures (>~15°C), COLD cell activity normally exceeds HPC cell activity [7]. However, when subjected to the grill stimulus (interlaced cool and warm bars), COLD cell activity was halved, while HPC activity was not affected [5]. This demonstrates that the thermal grill stimulus shifts the pattern of activity in favor of the HPC channel, similar to the pattern of activity produced by a noxious cold or heat stimulus, which explains the painful burning sensation experienced [5]. Craig and Bushnell [5] explained that the reduction in COLD cell activity unmasked HPC activity by disinhibition, probably at the thalamocortical level, concluding that the TGI demonstrates a central integration of ascending pain and temperature sensory channels. The results of the present study would suggest a central involvement of the TGI as reduced responses were observed in both *pain* and *pain + opioids* participants compared with *pain-free* participants when tested on their palm, a region that was not affected by their primary pain pathology. Our finding of reduced response to the TGI in patients with chronic pain suggest that these patients have altered central integration of ascending pain and temperature signals, consistent with the current view that chronic pain is associated with long-term structural and functional changes in the spinal cord and brain [35,36].

There are some factors that may have influenced the response to the TGI, such as age, medication use, as well as psychological factors affecting perception (e.g., depression). Age has previously been implicated in the response to conventional thermal threshold testing, with increasing age in pain-free participants being associated with decreased CPTs and increased HPTs [37]. Although age differed significantly among the *pain-free*, *pain*, and *pain + opioids* participants, conventional HPTs and CPTs did not differ significantly among the three groups, suggesting that the response differences observed among *pain-free*, *pain*, and *pain + opioids* participants to the TGI were unlikely to be influenced by age. To date, none of the studies investigating the TGI have reported or specifically investigated whether age is a significant covariate of response. Therefore, future studies investigating the response to the TGI need to control for age and/or investigate the effect of age on the response to the TGI.

Another potential confounder is concomitant analgesic medication. Acute opioid administration reduced both the intensity of pain and the unpleasantness to the TGI in pain-free participants [11], similar to the effects of acute morphine administration in other acute pain models [38–42]. However, in patients chronically exposed to opioids, thermal pain sensitivity either remains the same or is heightened, as a result of tolerance and/or opioid-induced hyperalgesia, compared with pain-free individuals [29,43]. Given that we saw reduced responses in pain patients both on and off opioids compared with the *pain-free* participants, it is unlikely that opioids were responsible for the reduced response. However, both *pain* and *pain + opioids* participants were allowed to consume their additional pain-modifying medications (see Table 1) on the study day, to avoid both pharmacological and psychological withdrawal responses.

Asking patients to withhold classes of medications for which known tolerance develops (i.e., opioids) would have resulted in pharmacological withdrawal in the *pain + opioids* participants. Even for those drug classes not known to have significant pharmacological tolerance (i.e., antidepressants, anti-epileptics), both *pain* and *pain + opioids* participants may have experienced psychological withdrawal due to patients' faith in the medications that they consumed daily for their pain. Therefore, asking patients to avoid consuming their pain-modifying medications (i.e., opioids, antidepressants, etc.) prior to the study day may have confounded the interpretation of our findings. Previously, the analgesic effect of these drugs (see Table 1) has not been investigated using the thermal grill experimental pain model, thus their effect on the thermal grill outcomes is unknown. Importantly, both HPTs and CPTs did not differ significantly among *pain-free*, *pain* and *pain + opioids* participants, thus any effect of these medications would be specific to the illusion and not to thermal pain sensitivity in general. Although pain-modifying medications were not withdrawn in this study for previously mentioned reasons, future studies should exclude patients who consume certain classes of pain-modifying medications (antidepressants, anti-epileptics) to avoid any potential effects of these medications, as well as ask patients to withdraw their non-opioid medications (paracetamol, ibuprofen) for at least 24 hours prior to experimental testing day to exclude any potential effects of non-opioid analgesics, although this may introduce symptoms of psychological withdrawal. Previous experimental pain studies comparing patients with chronic pain and pain-free controls, especially patients receiving chronic opioids for their pain, have demonstrated that patients with chronic pain are usually hyperalgesic to thermal pain stimuli [34,44–47]. These studies' findings are in the opposite direction, in which thermal hypoalgesia was experienced to the thermal grill in patients with chronic pain compared with pain-free controls. Therefore,

another key finding of this study was that the thermal grill produced a paradoxical and unusual response in patients with *pain* and *pain + opioids*, despite no significant change in patients' thermal pain thresholds.

Psychological factors affecting perception, such as depression, have also been implicated in pain perception. Recently, both Boettger et al. [15] and Pinerua-Shuhaubar et al. [18] demonstrated that sad mood induction significantly increased the intensity of pain and the unpleasantness experienced from the TGI compared with baseline in pain-free healthy participants. Pinerua-Shuhaubar et al. [18] further demonstrated that the sum of pain intensity and unpleasantness experienced from the TGI was significantly higher in patients with minor depression compared with pain-free healthy participants. Considering that depressive disorders are highly prevalent in patients with chronic pain [48], subclinical depression is a potential confounder in this study. However, this is not consistent with our findings of a reduced, rather than increased response to the TGI in patients with chronic pain, as well as no differences in standard thermal thresholds among the three study populations.

More recently, Boettger and colleagues extended their research of psychological factors and pain perception to major mental disorders, such as major depressive disorder (MDD) [21] and schizophrenia [20]. In these two studies, the response to the TGI was investigated in unmedicated patients with MDD, in healthy controls, and in unmedicated patients with acute paranoid schizophrenia on both the left and right hand for 30 seconds. Similar to Bouhassira and colleagues [10], the temperatures of the cool and warm temperature bars were customized to participants' CPTs and HPTs, respectively. In line with previous studies [49–52], CPTs were significantly decreased and HPTs were significantly increased in patients with MDD compared with healthy controls [21]. Similarly, thermal grill thresholds (temperature differential at which participants first indicated a painful sensation as indicated on the VAS as > 6/100 mm) also differed significantly between patients with MDD and healthy controls, with patients requiring a larger temperature differential between the cool and warm bars to elicit such a painful sensation. Even when correcting the temperature of the cool and warm bars to reflect patients' altered CPTs and HPTs, patients with MDD reported significantly less pain to the TGI compared with healthy controls. Thus, the predominant finding of Boettger and colleagues' [21] study was that the response curve of the TGI was shifted toward higher stimulus intensities in patients with MDD, similar to that observed for both CPTs and HPTs. The authors [21] postulated the following hypothesis supporting higher thermal grill stimulus intensities: There is evidence for differential processing of A-δ and C-fibers in patients with MDD, in particular smaller A-δ laser-evoked potential amplitudes in patients with MDD compared with healthy controls [53]. A-δ fibers responsive to innocuous cooling converge on COLD neurons in the spinal cord dorsal horn, thus a reduction in amplitude of A-δ fibers may shift the stimulus-response curve to lower temperatures in patients with MDD compared with healthy controls [21]. As reported by Craig and Bushnell [5], COLD cell activity is halved during thermal grill stimulation, resulting in disinhibition of HPC cells and the experience of pain. Thus, Boettger and colleagues [21] suggested that a shift in noxious cold sensations and a hypothetical shift in innocuous cold sensations toward lower temperatures in patients with MDD may maintain COLD cell inhibition of HPC cells even at lower temperatures, thereby increasing the overall thermal grill thresholds. In support of this hypothesis, analyses revealed that the increased temperature differential between the cool and warm bars required for the perception of the TGI in patients with MDD was mainly driven by patients' significant decrease in their CPTs [21]. Similar to patients with MDD, CPTs were significantly decreased, while HPTs as well as thermal grill thresholds were significantly increased in patients with schizophrenia compared with healthy controls [20]. Although cold and warm detection thresholds were not investigated in Boettger and colleagues' [20] study, Jochum and colleagues [54] previously demonstrated that patients with schizophrenia had elevated warm detection thresholds compared with controls, thereby overall supporting the above hypothesis for increased thermal grill thresholds in patients with schizophrenia. Reduced response to the TGI in these pathological conditions is consistent with our results of a reduced response to the TGI in patients with chronic pain. These findings in patients with MDD and schizophrenia demonstrate the importance of investigating both CPTs and HPTs when investigating the response to the TGI, and suggests that customizing the temperature of the cool and warm temperature bars is necessary, as opposed to a standard fixed temperature combination, especially when investigating the response to the TGI between two different populations. However, unlike the two studies by Boettger and colleagues [20,21], significant differences between patients and controls were not observed for CPTs and HPTs in our study. The aforementioned studies had more participants than our study, which may explain why significant differences in thermal pain thresholds were observed in those studies and not in our study.

Similar to previous studies investigating the TGI in pain-free participants, we demonstrated that increasing temperature differentials between the warm and cool temperature bars increased the intensity of pain, unpleasantness, and heat to the TGI [8,10]. Although the largest pain response to the TGI was reported when the thermal grill configuration was 18°C/42°C, the thermal grill did not produce a very painful stimulus in *pain-free* participants (median 2 on an 11-point NRS, interquartile range 1 to 5), being below 4 (out of 10), which is generally accepted as the minimum for clinically relevant pain [55]. The reported pain intensity in our study is similar to previous studies investigating the TGI in pain-free participants, where similar thermal grill configurations produced pain intensity ratings between 7 mm and 47 mm on a 100-mm VAS [6,8–11,15,16,18,20,21]. Instead, the thermal grill produced an altered sensory experience in our study that manifested as an aversive heat stimulus (approx. 60 mm on a 100-mm VAS color bar). In line with previous studies

investigating the TGI in pain-free participants, our results demonstrate that the perceptual quality of the TGI is more unpleasant than painful [9,16]. Dysesthesias, in particular thermal dysethesias, are often experienced by patients with chronic pain [56], with dysethesias being one of the most debilitating consequences of chronic pain conditions [57]. Consequently, the thermal grill may be a useful tool to investigate the dysesthetic qualities of chronic pain and potentially screen for novel antidysesthetic therapies for chronic pain. Previous studies investigating the thermal grill in pain-free participants have not quantitatively investigated the intensity of heat experienced from the thermal grill. Consequently, we developed a novel thermal color bar in order to better capture the response to the TGI. One aim of this study was to evaluate our novel thermal color bar. In this study we report that our novel thermal color bar was the most sensitive measure to detect a significant difference among *pain-free*, *pain*, and *pain + opioids* participants. As stated above, the thermal grill produced more of an aversive heat stimulus, rather than a painful stimulus, therefore the color bar enabled a wider dynamic range of response to be captured. This wider dynamic range of response allowed any differences among the three populations to be observed more easily. Our findings highlight the importance of using a well-suited rating scale for any given stimulus, potentially minimizing false negative findings in experimental pain studies.

One limitation of this study is that the individual warm and cool temperatures used to elicit the TGI were not tested individually (e.g., 18°C, 20°C, 22°C, 38°C, 40°C, and 42°C) in order to determine whether participants reported pure cool and warm sensations at these temperatures and not other types of sensations or pain. Ideally, this should have been measured; however, the design of our thermal grill did not allow all six bars to be set to either cool or warm temperatures. Another limitation of this study was the relatively low patient numbers in both the *pain* and *pain + opioids* group. However, given that the objective of our research program is to evaluate whether the thermal grill is a useful tool to screen for novel analgesic drugs, the thermal grill's superior sensitivity to detect differences among these three populations, even with a relatively small sample size, is the important conclusion of this study, thus warrants further investigation.

In our study, we deliberately selected patients to be heterogeneous with respect to the type of pain they experienced and the location of their pain in order to detect an overall effect to the TGI and to extrapolate tolerability to the TGI to a broad range of painful conditions. Consequently, the response to the TGI was not investigated in the *pain* and *pain + opioids* participants' region of primary pain pathology. Future studies need to investigate the response to the TGI in more homogenous chronic pain patient populations, specifically in the region of their primary pain pathology. However, it is apparent that the ability of the thermal grill to differentiate between *pain-free* and extremely heterogeneous *pain* and *pain + opioids* participants warrants further investigation as a tool to detect sensory differences between pain-free participants and patients with chronic pain that are not normally detected by standard quantitative sensory testing, in particular in studies with such low participant numbers. Furthermore, responses to the TGI may also be able to differentiate etiological differences in chronic pain.

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Chapter 4. Thermal Grill Response in Patients with Unilateral Sciatica

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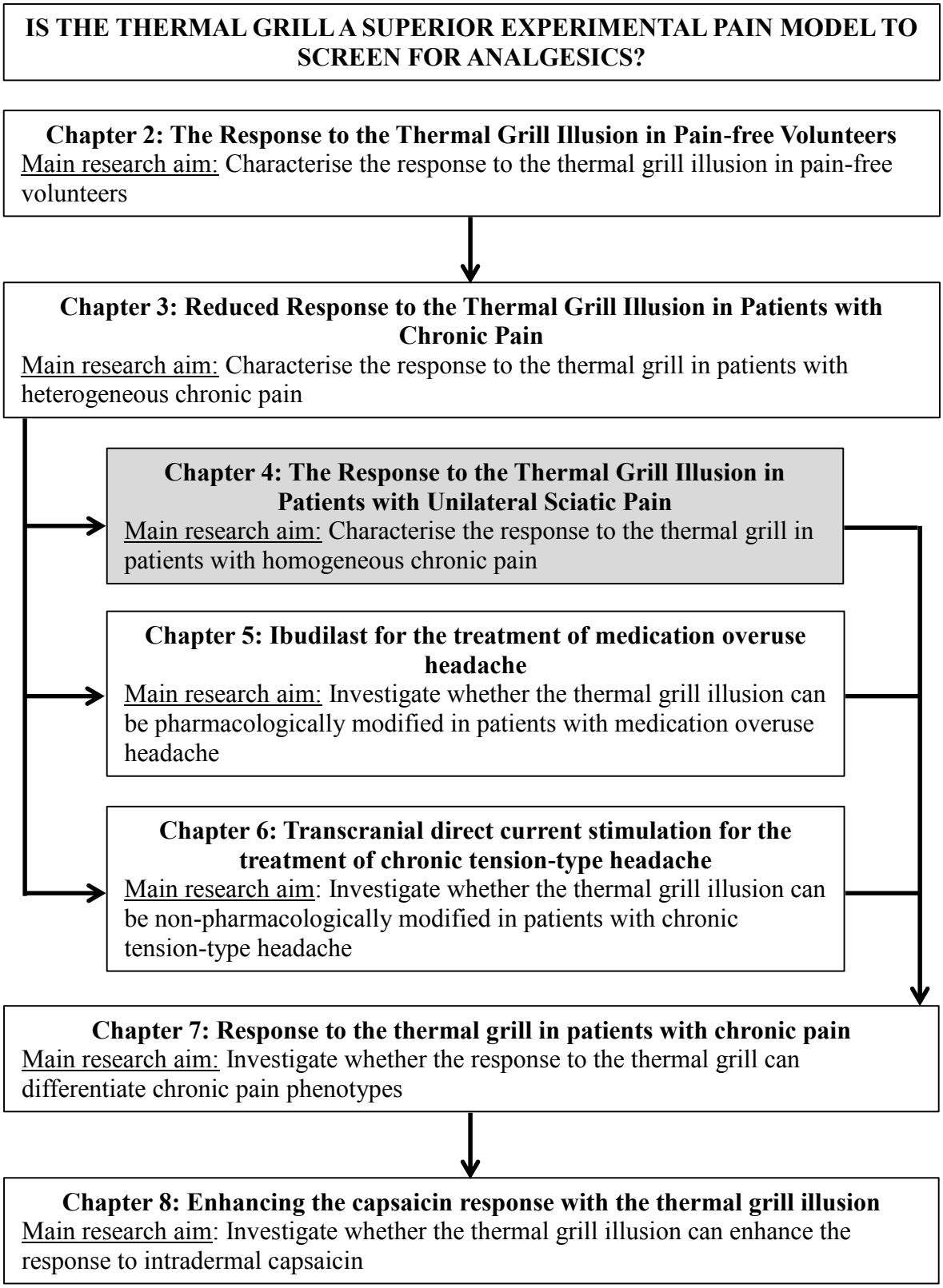

IS THE THERMAL GRILL A SUPERIOR EXPERIMENTAL PAIN MODEL TO SCREEN FOR ANALGESICS?
Chapter 2: The Response to the Thermal Grill Illusion in Pain-free Volunteers
Main research aim: Characterise the response to the thermal grill illusion in pain-free volunteers
Chapter 3: Reduced Response to the Thermal Grill Illusion in Patients with Chronic Pain
Main research aim: Characterise the response to the thermal grill in patients with heterogeneous chronic pain
Chapter 4: The Response to the Thermal Grill Illusion in Patients with Unilateral Sciatic Pain
Main research aim: Characterise the response to the thermal grill in patients with homogeneous chronic pain
Chapter 5: Ibudilast for the treatment of medication overuse headache
Main research aim: Investigate whether the thermal grill illusion can be pharmacologically modified in patients with medication overuse headache
Chapter 6: Transcranial direct current stimulation for the treatment of chronic tension-type headache
Main research aim: Investigate whether the thermal grill illusion can be non-pharmacologically modified in patients with chronic tension-type headache
Chapter 7: Response to the thermal grill in patients with chronic pain
Main research aim: Investigate whether the response to the thermal grill can differentiate chronic pain phenotypes
Chapter 8: Enhancing the capsaicin response with the thermal grill illusion
Main research aim: Investigate whether the thermal grill illusion can enhance the response to intradermal capsaicin

Introduction

One major limitation of the previous study (chapter 3) was the heterogeneity of the chronic pain population investigated. This population consisted of patients with various primary pain pathologies, who experienced pain at different body locations, and were taking a variety of pain and disease modifying medications. Consequently, the response to the thermal grill and thermal pain thresholds were not necessarily tested in the region of patients' primary pain pathology. Therefore, I chose to investigate the response to the thermal grill and thermal pain threshold in a more homogenous chronic pain population, including in the region of their primary pathology, in order to determine whether the reduced response to the thermal grill illusion observed in patients with heterogeneous chronic pain compared to pain-free participants (chapter 3) could be replicated in patients with homogeneous chronic pain.

The homogeneous chronic pain population that I chose was unilateral sciatica. Sciatic pain is generally defined as pain radiating to the leg, normally below the knee and into the foot and toes, and tends to approximate the dermatomal distribution of the nerve root affected (usually L5, S1)(Konstantinou and Dunn, 2008). Sciatic pain is often associated with numbness and pins and needles, which are both key symptoms of neuropathic pain, as well as muscle weakness and reflex changes (Konstantinou and Dunn, 2008). The unilateral nature of this pain condition makes these patients a suitable patient population to investigate, as they allow the response to the thermal grill and thermal pain thresholds to be investigated on both the patients' affected and unaffected leg, therefore allowing comparison between the patient's affected and unaffected body regions. Additionally, a component of neuropathic pain is present in this highly prevalent and poorly treated pain condition. Most importantly, unilateral sciatica is a chronic pain condition that originates in the periphery, allowing investigation of thermal pain sensitivity from the periphery to the brain.

In chapter 3, I demonstrated that my novel thermal colour bar was the most sensitive measure to detect a significant difference in response to the thermal grill illusion between patients with chronic pain and pain-free participants. As this was the main significant difference observed between patients with chronic pain and pain-free participants to the thermal grill illusion, it is important to investigate whether factors specific to patients with chronic pain (e.g. psychological or biological), other than their chronic pain, may have influenced these results.

It has been suggested that individuals who suffer from mood disorders, such as depression, have altered colour perception (Barrick et al., 2002; Carruthers et al., 2010). Numerous studies have demonstrated that depressive disorders are more common in patients with chronic pain compared people who do not suffer from chronic pain conditions (Ohayon and Schatzberg, 2003; Ohayon and Schatzberg, 2010), with approximately 50% of patients suffering from chronic pain also displaying clinically diagnosable symptoms of depression (Dworkin and Gitlin, 1991). Furthermore, a positive correlation between pain severity and depressive symptoms has been observed in patients with chronic pain and depression (Ohayon and Schatzberg, 2010). Therefore, I chose to also investigate the depressive state of patients with chronic unilateral sciatica pain and pain-free participants in this study, using the widely accepted and validated Beck Depression Inventory®-II (BDI®-II) (1996)(Beck et al., 1996). Beck et al 1996, demonstrated that the BDI®-II had a high one week test-retest reliability (Pearson r = 0.93)(Beck et al., 1996). Therefore, an advantage of the BDI®-II is that it is not oversensitive to daily variations in mood (Beck et al., 1996), which provides confidence that any variability observed between participants is not likely to be due to their affective mood state on the day of testing.

The hypothalamo-pituitary-adrenal (HPA) axis is a major part of the neuroendocrine system that controls stress and regulates body processes such as energy storage and expenditure, immune function, mood and emotion, and digestion (Fries et al., 2009). The HPA axis is responsible for providing the energy substrates that support the sympathetic 'fight or flight' response, providing cognitive appraisal of the stressful situation and the behavioural and endocrine adaptation to stress (Sapolsky et al., 2000; Blackburn-Munro and Blackburn-Munro, 2001). Continued or prolonged stress may disturb the HPA axis to such an extent that the negative feedback mechanisms are disrupted, potentially resulting in the adaptive responses of the HPA axis becoming maladaptive (Blackburn-Munro and Blackburn-Munro, 2001). Cortisol is a steroid hormone produced by the adrenal gland. Cortisol levels follow a diurnal cycle, where cortisol levels peak at approximately 30 minutes after awakening and reaches its lowest levels in the middle of the night (Fries et al., 2009). Cortisol is released in response to stressors (a stimulus that threatens normal homeostatic mechanisms e.g. physical threat, illness, infection, pain, fear, worry etc.) to restore homeostasis by activating the sympathetic 'fight or flight' response (Blackburn-Munro and Blackburn-Munro, 2001).

Many chronic pain syndromes are associated with ongoing stress and consequent hypocortisolism, therefore various chronic pain syndromes have been investigated for relative hypocortisolism as a marker of HPA axis deregulation (Kuehl et al., 2010). An association between HPA axis dysfunction and fibromyalgia (Griep et al., 1993; Crofford et al., 1994; Lentjes et al., 1997; Griep et al., 1998), low back pain (Geiss et al., 1997; Lentjes et al., 1997; Griep et al., 1998; Muhtz et al., 2013) and rheumatoid arthritis (Straub et al., 2002), as well as other chronic pain syndromes, has been demonstrated (Kuehl et al., 2010). Furthermore, HPA axis dysfunction has been observed in patients with depression, in particular hyperactivity of the HPA axis resulting in cortisol level increase (Bhagwagar et al., 2005; Jabben et al., 2011; Manthey et al., 2011). It has been well established that free cortisol response on awakening

can serve as an accurate index of the HPA axis (Lovell et al., 2011). Numerous studies have demonstrated that free cortisol levels rise by 50-60% within the first 30 minutes after awakening in healthy volunteers (Pruessner et al., 1997; Schmidt-Reinwald et al., 1999; Wust et al., 2000). Therefore, two early morning salivary samples were collected, one on awakening and one 30 minutes after awakening.

The main aim of this study was to determine whether the reduced response to the thermal grill illusion observed in patients with heterogeneous chronic pain compared to pain-free participants (chapter 3) could be replicated in patients with homogeneous chronic pain. Considering that the chronic pain patient population selected for this study was more homogeneous than the heterogeneous chronic pain population in chapter 3, it was hypothesised that patients with chronic unilateral sciatic pain would also demonstrate reduced responses to the thermal grill illusion, to a larger amount of thermal grill outcomes and even to a greater extent than the patients with chronic pain in chapter 3.

Another aim was to determine whether the response to the thermal grill differs across body regions and whether the response to the thermal grill differs between patients with unilateral sciatica affected and unaffected body regions. Similar to my findings in chapter 2, as well as findings from other studies (see section 1.4.5.2 in introduction), it was hypothesised that responses to the thermal grill would differ across body locations, with responses at the palm being the greatest and responses at the cheek and calf being lower. Considering that responses to the thermal grill illusion were significantly lower in patients with chronic pain compared to pain-free volunteers on their palm, a region that was not affected by their primary pain pathology, it was hypothesised that responses to the thermal grill on the affected leg calf of patients with chronic unilateral sciatica pain would be lower than responses on the unaffected

leg calf. Thermal quantitative sensory testing was also performed for the abovementioned aims so that the response to the thermal grill and thermal quantitative sensory could be compared in order to determine whether the thermal grill can detect differences that are not detected using thermal quantitative sensory testing.

Additional aims of this study were to determine whether patients with chronic unilateral sciatic pain have a blunted hypothalamo-pituitary-adrenal (HPA) axis compared to pain-free volunteers; whether early morning salivary cortisol correlated with BDI®-II scores, thermal pain thresholds and the response to the thermal grill; whether BDI®-II scores correlated with thermal pain thresholds and the response to the thermal grill; and whether body mass index (BMI) correlated with thermal pain thresholds and the response to the thermal grill. Based on the abovementioned literature, it was hypothesised that patients with unilateral sciatic pain would display heightened depressive symptoms compared to pain-free volunteers, as well as a blunted HPA axis. Previously, sad mood induction (Boettger et al., 2011; Pinerua-Shuhaibar et al., 2011), minor depression (Pinerua-Shuhaibar et al., 2011) and major depression (Boettger et al., 2013) have been demonstrated to influenced the response to the thermal grill illusion, therefore it was hypothesised that BDI®-II scores would correlate with thermal pain thresholds and the response to the thermal grill. Considering that HPA axis dysfunction has been observed in patients with chronic pain and depression, it was hypothesised that early morning salivary cortisol levels would correlate with BDI®-II scores, thermal pain thresholds and the response to the thermal grill in patients with chronic unilateral sciatic pain. As discussed above in chapter 1 (section 1.5.7.2), body mass index (BMI) can influence an individuals cold detection and cold pain threshold as well as warm detection threshold, such that individuals with a greater BMI are less sensitive to these types of thermal stimuli (Li, 2009; Neziri et al., 2011); thus it was hypothesised that participants BMI would correlate with thermal pain thresholds and consequently the response to the thermal grill illusion.

Materials and Methods

Thermal grill

As previously described in chapter 2.

Ethics

Ethics approval was obtained from the Royal Adelaide Hospital (RAH) Research Ethics Committee. Signed consent was obtained from each participant prior to enrolment into the study. Participants were financially compensated for their time and inconvenience.

Participants

20 healthy pain free participants (*pain-free*), 10 patients with chronic sciatic pain not on opioid therapy (*sciatic*) and 10 patients with sciatic pain on chronic opioid therapy (*sciatic + opioids*) were chosen to participate in this study. Sciatica was diagnosed on clinical grounds by the presence of pain in the L5/S1 dermatomal distribution accompanied by dysaethesia of a shocking or burning quality of pain. Participants were to have negligible symptoms in their contralateral leg. Participants were recruited from the Pain and Anaesthesia Research Clinic's (PARC) volunteer database and the general public by advertisement. All participants were naïve to the thermal grill effect. Key inclusion criteria were as follows. All groups: aged between 18 and 65 years old inclusive; presence of all four limbs and being in good general health. *Pain* and *pain + opioids* groups only: average pain score ≥ 40 mm on 100 mm visual analogue scale over previous week and experiencing pain at least 5 days per week for more than 3 months (*pain* and *pain + opioids* groups only). *Pain + opioids* group only: ongoing opioid therapy with a dose equivalent to 20 mg morphine per day for at least 3

months without recent (1 month) dose change. Key exclusion criteria were as follows. All groups: pregnant or lactating women; significant scarring or tattoos on participants cheeks, palms and calves; sensory deficits on participants cheeks, palms and calves resulting from medical conditions, such as diabetes, alcoholic neuropathy, severe thyroid, liver or kidney diseases; currently experiencing an active inflammatory process (e.g. acute pain, influenza, active infection, rheumatoid arthritis) or having a clinically significant infection in the previous 4 weeks; history of excessive alcohol use; impaired immune response, e.g. HIV/AIDS sufferers, Hep B or C sufferers; presence of non-prescribed drugs of abuse in urine drug screen; recent use of opioids (e.g. morphine use within last week, or codeine use (> 30 mg) within last 5 days)(excludes *pain + opioids* participants), adjuvant analgesics (e.g. tricyclics, gabapentin or pregabalin), anxiolytics, anti-depressants and anti-epileptics within last month; recent (within 8 weeks) interventional pain management procedures that may have altered QST response, including neuraxial or local anaesthetic block to the affected area; oral or inhaled corticosteroid medications; clinically diagnosed major psychiatric disorder, such as major depression; bipolar disorder; schizophrenia; anxiety disorder and psychosis; immunosuppressant drugs (e.g. azathioprine, methotrexate, cyclosporine) and a known disorder of thermal pain sensitivity (e.g. Raynaud's Phenomenon). *Pain-free* group only: current or past history of any chronic pain condition or recurrent condition that alters perception (such as migraine). *Pain* and *pain + opioids* groups only: change in pain medication dose/type/frequency within 4 weeks of participants scheduled study visit.

Main study day

Participants were asked to refrain from taking paracetamol, aspirin (except low dose prophylaxis), non-steroidal anti-inflammatory drugs (NSAIDs), sedatives or other pain modifying medications or treatments including topically applied pain treatments for 24 hours (or 5 half lives – whichever was longest) before the experimental day. *Pain + opioids*

participants continued taking their opioid medication as per usual. *Pain + opioids* participants taking paracetamol / codeine or ibuprofen / codeine formulations were provided with a codeine only prescription for the 24 hour period prior to the experimental day, so that paracetamol and ibuprofen could be withdrawn. Opioids were not withdrawn to avoid withdrawal reactions. Alcohol and caffeine containing foods and beverages were not allowed for 24 hours before the experimental day. At the screening session, participants were provided with 2 saliva tubes and instructed to collect 2 early morning salivary cortisol samples on the morning on their scheduled main study day; one on awakening and one 30 minutes post awakening.

Schedule on main study day

Participants were interviewed about any changes in their health since the screening visit and any changes to medication use during this period. Participants were required to provide a urine sample and a breath alcohol test was performed. A negative breath alcohol test and urine drug test for non-prescribed drugs of abuse was required for continuance in the study. Additionally, a negative urine pregnancy test was required for women of childbearing potential for continuance in the study. *Pain* and *pain + opioids* participants were asked to rate the intensity of pain experienced on average from their sciatic pain over the previous 7 days on a 100mm VAS (left anchor: "no pain", right anchor: "worst pain imaginable"). A score of greater than 40 mm was required for continuance in the study. Participants were required to complete the BDI®-II[1]. Participants were then familiarised to the experimental procedures to ensure that they can tolerate and adequately perform the tests. Before any assessments

1 The BDI®-II is a 21-item self-report instrument that assesses the severity of depressive symptoms in adolescents and adults over the last 2 weeks. Each item is rated on a 4-point scale (0-3) with total scores ranging from 0 to 63. A score of: 0-13 indicates minimal depression, often observed in a normal healthy population; 14-19 indicates mild depression; 20-28 indicates moderate depression and 29-63 indicates severe depression (Beck et al., 1996).

commenced, participants were required to equilibrate to the internal environment for 60 minutes (Figure 4.1). Participants were seated upright throughout all assessments.

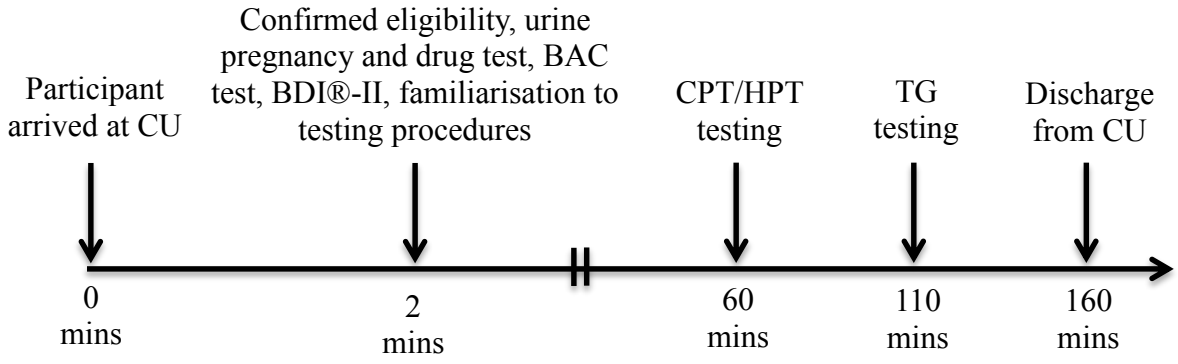


Figure 4.1. Schedule on Main Study Day

CU: clinical unit; BAC: breath alcohol concentration; BDI®-II: Beck Depression Index®-II; CPT: cold pain threshold; HPT: heat pain threshold; TG: thermal grill.

Thermal threshold testing

Patients' individual cold pain (CPT) and heat pain thresholds (HPT) were determined using a PATHWAY[2] device (model ATS, Medoc, Israel) via the Method of Limits on *pain* and *pain + opioids* participants affected and unaffected side calf, palm and cheek (dominant and non-dominant side for *pain-free* participants). The thermode (3 cm x 3 cm) was strapped to the fleshiest part of the calf, the palmar surface of the palm and positioned on the flesh of the cheek, and the patient was given a hand-held feedback control. Participants' cold pain and heat pain thresholds were determined using the same methods as described in chapter 2.

[2]PATHWAY is a newer model of the TSA-II NeuroSensory Analyzer previously used in chapters 2 and 3.

Thermal grill testing

Patients were exposed to three interlaced cool and warm temperature combinations (22/38 °C, 20/40 °C and 18/42 °C) in randomised order on *pain* and *pain + opioids* participants affected and unaffected side calf, palm and cheek (dominant and non-dominant side for *pain-free* participants), thus a total of 18 tests were performed. Patients were required to place their calf, cheek or palm on the thermal grill, orthogonally to the long axis of the bars for 30 s. Prior to thermal grill testing, *pain* and *pain + opioids* participants were required to rate the pain they experience on average from their sciatic pain on a 100 mm VAS (left anchor: "no pain", right anchor: "worst pain imaginable"). Immediately following contact to the thermal grill patients were required to rate the: intensity of pain, intensity of heat, unpleasantness and their tolerability to the thermal grill on a 100 mm VAS (left anchor, "no pain", "not hot", "not unpleasant" and "tolerable," [0 mm]; right anchor "worst pain imaginable", "unbearably hot", "very unpleasant" and "not tolerable," respectively [100 mm]). Participants were also required to rate the intensity of heat on a novel 100 mm VAS thermal colour bar (no anchors, described previously in chapter 2). Participants were also given an opportunity to write about the sensation(s) they experienced from the thermal grill.

Statistical analysis

The D'Agostino and Pearson omnibus normality test was performed to test for normality of the data.

Due to the non-parametric nature of the data, age, Beck depression inventory scores, salivary cortisol on awakening and salivary cortisol 30 minutes post awakening between *pain-free* and *sciatica* participants were compared using the Kolmogorov-Smirnov test, therefore these data

are represented as median and IQR. Whereas, body mass index was compared using an unpaired t-test, therefore this data is represented as mean and 95% confidence interval.

Due to the non-parametric nature of the data *pain-free* participants salivary cortisol on awakening and salivary cortisol 30 minutes post awakening was compared using Wilcoxon matched-pairs signed rank test, therefore these data are represented as median and IQR. For *sciatica* participants a paired t-test was used, therefore these data are represented as mean and 95% confidence interval.

Two-way repeated measures ANOVA with Bonferroni's multiple comparison test was used to compare the response to the thermal grill illusion between *pain-free* and *sciatica* participants. An unpaired t-test was used to compare *pain-free* and *sciatica* participants' cold pain thresholds on the affected/dominant and unaffected/non-dominant side palm and heat pain thresholds on the affected/dominant side palm and unaffected side cheek, palm and calf, therefore these data are represented as mean ± SEM. Due to the non-parametric nature of the data the Kolmogorov-Smirnov test was used to compare cold pain thresholds on the affected/dominant and unaffected/non-dominant side cheek and calf and heat pain thresholds on the affected/dominant side cheek and calf, therefore these data are represented as median and IQR. Consequently, the appearance of the graphs displayed within this chapter and the appendix differ between the dominant/affected and non-dominant/unaffected side cheek and calf for heat pain thresholds.

Comparing body side (affected/dominant vs. unaffected/non-dominant) the response to the thermal grill illusion was compared using a two-way repeated measures ANOVA with Bonferroni's multiple comparison test for both *pain-free* and *sciatica* participants, therefore

these data are represented as mean ± SEM. For *pain-free* participants, cold pain threshold at the palm and heat pain thresholds at the cheek and palm were compared using a paired t-test,. Due to the non-parametric nature of the data, cold pain thresholds at the cheek and calf and heat pain thresholds at the calf were compared using a Wilcoxon matched-pairs signed rank test. For *sciatica* participants, cold pain threshold at the cheek and palm and heat pain thresholds at the palm and calf were compared using a paired t-test. Due to the non-parametric nature of the data, cold pain thresholds at the calf and heat pain thresholds at the cheek were compared using a Wilcoxon matched-pairs signed rank test.

Comparing body location (cheek vs. palm vs. calf) the response to the thermal grill illusion was compared using a two-way repeated measures ANOVA with Tukey's multiple comparisons test for both *pain-free* and *sciatica* participants, therefore these data are represented as mean ± SEM. Due to the non-parametric nature of the data, *pain-free* participants cold pain thresholds on both the affected/dominant and unaffected/non-dominant side and heat pain thresholds on the affected side were compared using Freidman's test with Dunn's multiple comparisons test. Heat pain thresholds on the unaffected/non-dominant side were compared with a one-way repeated measures ANOVA with Tukey's multiple comparisons test. For *sciatica* participants cold and heat pain thresholds on their unaffected side were compared using a one-way repeated measures ANOVA with Tukey's multiple comparisons test, whilst cold and heat pain thresholds on their affected side were compared using Friedman's test with Dunn's multiple comparisons test.

Depending on the normality of the data, correlations between cold pain thresholds, heat pain thresholds, the response to the thermal grill illusion, Beck depression inventory scores, salivary cortisol on awakening, salivary cortisol 30 minutes post awakening, body mass

index, average pain intensity and duration of pain were performed using Pearson's or Spearman's correlation. In order to account for multiple comparisons, a Bonferroni correction was performed as described in chapter 2. Unlike in chapter 2, correlations across multiple body locations were assessed in this study. Each body location was treated as a separate analysis; therefore Bonferroni's correction was only performed within one body location.

A *P* value of less than 0.05 was required for statistical significance, unless otherwise stated.

Results

Subjects

20 (10M, 10F) *pain-free*, 9 (5M, 4F) *sciatica* and 2 (1M, 1F) *sciatica + opioids* participants completed this study. Due to difficulties and major delays in *sciatica* and *sciatica + opioids* patient recruitment, the target population of 10 *sciatica* and 10 *sciatica + opioids* patients per group was not reached. Consequently, *sciatica + opioids* participants were not included in any of the below analyses due to the extremely low patient number (N = 2) in that group. Pain-*free* participants affected side was defined as their dominant hand side, thus all *pain-free* participants were examined on their dominant side (18/20 right handed). Whereas, *sciatica* participants affected side leg and dominant hand side differed for 3 (out of 9) participants. Comparing *pain-free* and *sciatica* participants, no significant differences were observed between age (median and IQR, *pain-free*: 42 (25.5 to 61) years; *sciatica*: 53 (40 to 60) years, p = 0.34), Beck depression inventory score (median and IQR, *pain-free*: 2.5 (0 to 4.8); *sciatica*: 3 (1 to 9), p = 0.89), awakening cortisol levels (median and IQR, *pain-free*: 16 (13 to 22) nmol/L; *sciatica*: 17 (10.8 to 20.8) nmol/L, p = 0.98) and 30 minutes post-awakening cortisol levels (median and IQR, *pain-free*: 23 (18.3 to 26.8) nmol/L; *sciatica*: 19 (14.5 to 24.5) nmol/L, p = 0.49). Body mass index was significantly greater in patients with *sciatica* compared to *pain-free* participants (mean difference: 5.0 kg/m^2, 95% CI for difference: 1.6 to 8.4 kg/m^2) (see Table 4.1 for participant demographics). Comparing cortisol levels on awakening and 30 minutes post awakening, *pain-free* participants cortisol levels significantly increased 30 minutes post awakening (median and IQR, awakening: 16 (13 to 22) nmol/L; 30 minutes post awakening: 23 (18 to 27) nmol/L, p = 0.013), whereas no difference was observed for patients with *sciatica* (mean difference: 3.4 nmol/L, 95% CI for difference: -1.9 to 8.7 nmol/L).

Pain-free participants versus patients with unilateral sciatica

Cold and heat pain thresholds

Both cold and heat pain thresholds did not differ between *pain-free* and *sciatica* participants' affected/dominant (see Figure 4.2) and unaffected/non-dominant (see Figure 11.4.1 in appendix) side cheek, palm and calf.

Thermal grill response

Patients with *sciatica* reported significantly less "unpleasantness" (mean difference: -23 mm, 95% CI for difference: -40 mm to -5 mm) and "intolerability" (mean difference: -17 mm, 95% CI for difference: -33 mm to -2 mm) to the thermal grill illusion compared to *pain-free* participants at the 18/42 ^{o}C thermal grill configuration on their affected side cheek (see Figure 4.3D, E). However, generally, the response to the thermal grill did not differ between *pain-free* and *sciatica* participants on both their affected/dominant and unaffected/non-dominant cheek, palm and calf (see Figures 4.3 and 11.4.2 in appendix and Table 4.2 for *P* values). Due to a missing data value in the *sciatica* group, only 8 *sciatica* participants were included for the following analysis: intensity of heat (colour bar) experienced from the thermal grill on the affected side calf.

Effect of body location (cheek, palm or calf)

Cold and heat pain thresholds

Significant differences were observed across *pain-free* participants body locations for both cold and heat pain thresholds. Cold pain thresholds were significantly lower (i.e. less sensitive) at *pain-free* participants calf compared to their palm on both their affected/dominant (difference in rank sum: 18, $p < 0.05$) and unaffected/non-dominant side

(difference in rank sum: 17.5, $p < 0.05$)(see Figure 4.4A, C). Heat pain thresholds were significantly greater (i.e. less sensitive) at *pain-free* participants calf compared to their cheek on their unaffected/non-dominant side (mean difference: 2.1 ^{o}C, 95% CI for difference: 0.5 ^{o}C to 3.6 ^{o}C)(see Figure 4.4D). Heat pain thresholds did not differ at *pain-free* participants affected side ($p = 0.21$)(see Figure 4.4B). Cold pain thresholds were significantly lower (i.e. less sensitive) at *sciatica* patients' affected calf compared to their affected side palm (difference in rank sum: 11, $p < 0.05$)(see Figure 4.5A), whereas no significant differences were observed between patients' body location on their unaffected side ($p = 0.23$)(see Figure 4.5C). Heat pain thresholds did not differ across *sciatica* participants' body location at both their affected ($p = 0.069$) and unaffected side ($p = 0.35$)(see Figure 4.5B, D).

Thermal grill response

Significant differences were observed across *pain-free* participants body locations for their responses to the thermal grill illusion. *Pain-free* participants consistently reported lower responses to the thermal grill on their calf compared to the palm on both their affected/dominant and unaffected/non-dominant side (see Figure 4.6 and Tables 4.3 and 4.4 for mean differences and 95% CI for the differences). Significant differences between the palm and cheek were also observed in some instances. The response to the thermal grill also differed across *sciatica* participants body locations, with responses at the calf generally being the lowest (see Figure 4.7 and Tables 4.5 and 4.6 for mean differences and 95% CI for the differences).

Effect of body side (affected/dominant versus unaffected/non-dominant)

Cold and heat pain thresholds

Heat pain thresholds were significantly reduced (i.e. less sensitive) at *pain-free* participants' unaffected/non-dominant cheek compared to their affected/dominant cheek (mean difference: -0.7 ºC, 95% CI for difference: 0.0 ºC to -1.4 ºC, p = 0.038)(see Figure 4.8B). Cold pain thresholds did not differ between *pain-free* participants' affected/dominant and unaffected/non-dominant cheek (difference in rank sum: -0.0, p = 0.29)(see Figure 4.8A). Cold and heat pain thresholds did not differ between *pain-free* participants' affected/dominant and unaffected/non-dominant palm (mean difference CPT: -1.7 ºC, 95% CI for difference: -4.2 ºC to 0.7 ºC; mean difference HPT: 0.3 ºC, 95% CI for difference: -0.3 ºC to 1.0 ºC) and calf (difference in rank sum CPT: 0.0, p = 0.56; difference in rank sum HPT: 0.1, p = 0.57)(see Figure 4.8C-F). Cold pain thresholds were significantly increased (i.e. less sensitive) and heat pain thresholds were significantly reduced (i.e. less sensitive) at *sciatica* participants unaffected side palm and calf compared to their affected side palm (mean difference CPT: 3.2 ºC, 95% CI for difference: 0.3 ºC to 6.2 ºC; mean difference HPT: -1.9 ºC, 95% CI for difference: -0.6 ºC to 3.2 ºC) and calf (median difference CPT: 6.5 ºC, p = 0.039; mean difference HPT: -1.9 ºC, 95% CI for difference: -3.0 ºC to -0.9 ºC) respectively (see Figure 4.9C-F). Cold and heat pain thresholds did not differ between *sciatica* participants' affected and unaffected cheek (mean difference CPT: 0.4 ºC, 95% CI for difference: -2.1 ºC to 2.9 ºC; median difference HPT: -0.4 ºC, p = 1.0)(see Figure 4.9A, B).

Thermal grill response

On the cheek, significantly less "unpleasantness" and "intolerability" to the thermal grill illusion was observed on *pain-free* participants' affected/dominant side compared to their unaffected/non-dominant side at the 20/40 ºC thermal grill configuration (see Figure 4.10D, E

and Table 4.7 for mean differences and 95% CI for differences). On the palm, significantly less "pain" and "intolerability" to the thermal grill illusion was observed on the affected/dominant side compared to their unaffected/non-dominant side at the 22/38 ^{o}C and 18/42 ^{o}C thermal grill configuration respectively (see Figure 4.10F, J and Table 4.8 for mean differences and 95% CI for differences). Whereas, on the calf, significantly more "intensity of heat", "intensity of heat" (colour bar) and "unpleasantness" was observed on the affected/dominant side compared to their unaffected/non-dominant side at the 20/40 ^{o}C thermal grill configuration (see Figure 4.10L, M, N and Table 4.7 for mean differences and 95% CI for differences). On the palm, significantly more "pain" to the thermal grill illusion was observed on *sciatica* participants' affected side compared to their unaffected side at the 18/42 ^{o}C thermal grill configuration (see Figure 4.11F and Table 4.8 for mean differences and 95% CI for difference). No other significant differences between the *sciatica* participants' affected and unaffected side were observed (see Figure 4.11 and Table 4.8).

Correlations

Cold and heat pain thresholds

Significant correlations were observed between *pain-free* participants cold and heat pain thresholds on their affected/dominant and unaffected/non-dominant side cheek[3] (affected/dominant: r = -0.59, p = 0.007; unaffected/non-dominant: r = -0.78, p = 4.8^{e-005}) and palm[4] (affected/dominant: r = -0.91, p = 2.0^{e-008}; unaffected/non-dominant: r = -0.77, p = 6.1^{e-005}), such that the less sensitive participants were to cold pain (i.e. lower cold pain threshold), the less sensitive they also were to heat pain (i.e. higher heat pain threshold). No such correlation was observed on their affected/dominant or unaffected/non-dominant side calf[3] (affected/dominant: r = -0.31, p 0.19; unaffected/non-dominant: r = -0.40, p = 0.084).

3 Analysed using Spearman's correlation

4 Analysed using Pearson's correlation

Significant correlations were also observed between *sciatica* participants cold and heat pain thresholds on their affected side cheek[5] (r = -0.82, p 0.011) and unaffected side palm[6] (r = -0.76, p = 0.017), whereas no significant correlations were observed at all other body locations (affected side palm[6]: r = -0.49, p 0.18; affected side calf[5]: r = -0.56, p = 0.12; unaffected side cheek[6]: r = -0.23, p = 0.55; unaffected side calf[6]: r = -0.083, p 0.83).

Thermal pain thresholds and thermal grill illusion

Once adjusting the significance level to account for multiple comparisons (< 0.00333), only some significant, but inconsistent correlations were observed between *pain-free* participants cold and heat pain thresholds and their response to the thermal grill illusion, in particular on their cheek and palm, such that participants' with increased cold pain thresholds (i.e. more sensitive) and decreased heat pain (i.e. more sensitive) thresholds had the greatest response to the thermal grill illusion (see Table 4.9). Therefore, the more sensitive a participant was to cold and heat, the more sensitive they were to the thermal grill illusion as well. Consequently, the correlation coefficients (*R*) of cold pain thresholds and the response to the thermal grill are positive values, whereas, the correlation coefficients of heat pain thresholds and the response to the thermal grill are negative values. However, *pain-free* participants thermal pain thresholds and their response to the thermal grill illusion on their affected/dominant and unaffected/non-dominant calf did not correlate. As these correlations were not consistent across body location, these findings should be interpreted with caution. Cold and heat pain thresholds did not correlate with *sciatica* participants' response to the thermal grill illusion on patients affected and unaffected side cheek, palm and calf, albeit for one thermal grill outcome on the affected side palm (see Table 4.10).

5 Analysed using Spearman's correlation

6 Analysed using Pearson's correlation

Beck depression inventory and thermal pain thresholds

Pain-free participants Beck depression inventory scores inconsistently correlated with cold and heat pain thresholds. For example, Beck depression inventory scores were found to correlate with cold pain thresholds at the affected/dominant side palm and unaffected/non-dominant side cheek, and with heat pain thresholds at the affected and unaffected side palm (see Table 11.4.1 in appendix), such that participants' with increased beck depression inventory scores had increased cold pain thresholds and decreased heat pain. Therefore, participants' with larger beck depression inventory scores were more sensitive to both cold and heat pain. However, as these correlations were not consistent across body location, these findings should be interpreted with caution. Whereas, *sciatica* participants' beck depression inventory scores did not to correlate with cold or heat pain thresholds, albeit one correlation between patients' Beck depression inventory score and their cold pain threshold at their affected calf (see Table 11.4.2 in appendix).

Beck depression inventory and thermal grill illusion

Pain-free participants Beck depression inventory scores correlated with the thermal grill outcome "intensity of heat" at the 22/38 ^{o}C, 20/40 ^{o}C and 18/42 ^{o}C thermal grill configuration on their affected/dominant side cheek. Beck depression inventory scores did not correlate with participants' response to the thermal grill illusion for any other thermal grill outcomes at all other body locations (see Table 11.4.3 in appendix). *Sciatica* participants' beck depression inventory scores correlated with the thermal grill outcome "intensity of heat" (colour bar) at the 20/40 ^{o}C and 18/42 ^{o}C thermal grill configuration on their affected calf. Beck depression inventory scores did not correlate with patients' response to the thermal grill illusion for any other thermal grill outcomes at all other body locations (see Table 11.4.4 in appendix).

Beck depression inventory and salivary cortisol

Pain-free participants Beck depression inventory scores did not correlate with early morning salivary cortisol on awakening (r = 0.096, p = 0.7) or 30 mins post-awakening (r = -0.21, p = 0.38). Awakening salivary cortisol could not be quantified for one *pain-free* participant; therefore only 19 *pain-free* participants were included for all awakening salivary cortisol analyses. Similarly, *sciatica* participants' Beck depression inventory scores did not correlate with early morning salivary cortisol on awakening (r = -0.072, p = 0.83) or 30 mins post-awakening (r = -0.52, p = 0.2). Neither awakening nor 30 minutes post-awakening salivary cortisol could be quantified for one *sciatica* participant; therefore only 8 *sciatica* participants were included for all awakening and 30 mins post-awakening salivary cortisol analyses. In order to account for multiple comparisons, the significance level was reduced to < 0.025.

Salivary cortisol and thermal pain thresholds

Pain-free participants salivary cortisol collected on awakening and 30 mins post-awakening did not correlate with participants' cold or heat pain thresholds at all body locations (see Table 11.4.5 in appendix). *Sciatica* participants' awakening and 30 mins post-awakening salivary cortisol levels did not correlate with cold pain thresholds at all body locations. On awakening, salivary cortisol levels correlated with patients heat pain thresholds on their affected calf only, however awakening salivary cortisol levels did not correlate with patients heat pain thresholds on their unaffected calf or any other body locations. 30 mins post-awakening, salivary cortisol levels correlated with patients heat pain thresholds on their affected and unaffected side palm, however did not correlate at any other body locations (see Table 11.4.6 in appendix).

Salivary cortisol and thermal grill illusion

Pain-free participants salivary cortisol collected on awakening correlated with the thermal grill outcome "unpleasantness" at the 18/42 ^{o}C thermal grill configuration on their affected/dominant side cheek. Awakening salivary cortisol did not correlate with participants' response to the thermal grill illusion for any other thermal grill outcomes at all other body locations. Salivary cortisol collected 30 mins post-awakening did not correlate with participants' response to the thermal grill illusion for any thermal grill outcomes at all other body locations (see Table 11.4.7 in appendix). On awakening, *sciatica* participants salivary cortisol correlated with the thermal grill outcome "unpleasantness" at the 22/38 ^{o}C and 18/42 ^{o}C thermal grill configuration on their affected calf. Awakening salivary cortisol did not correlate with patients' response to the thermal grill illusion for any other thermal grill outcomes at all other body locations. 30 mins post-awakening, salivary cortisol did not correlate with patients' response to the thermal grill illusion for any thermal grill outcomes at all other body locations (see Table 11.4.8 in appendix).

Body mass index and thermal pain thresholds

Pain-free participants body mass index did not correlate with participants' cold or heat pain thresholds at all body locations (see Table 11.4.9 in appendix). *Sciatica* participants' body mass index did not tend to correlate with cold or heat pain thresholds, albeit one correlation between patients' body mass index and their heat pain threshold at their affected side cheek (see Table 11.4.10 in appendix).

Body mass index and thermal grill illusion

Pain-free participants body mass index correlated with a the following thermal grill outcomes: "intensity of pain" on the affected/dominant side palm at the 20/40 ^{o}C thermal grill

configuration; "intensity of pain" on the unaffected/non-dominant side cheek and palm at the 18/42 ^{o}C thermal grill configuration; and "tolerability" on the unaffected/non-dominant side palm at the 18/42 ^{o}C thermal grill configuration. Body mass index did not correlate with participants' response to the thermal grill illusion for any other thermal grill outcomes at all other body locations (see Table 11.4.11 in appendix). *Sciatica* participants' body mass index did not correlate with patients' response to the thermal grill illusion for any thermal grill outcomes at any body locations (see Table 11.4.12 in appendix).

Intensity of pain and cold and heat pain threshold

The "intensity of pain" experienced on average from patients sciatic pain did not correlate with patients' cold or heat pain thresholds at all body locations (see Table 11.4.13 in appendix).

Intensity of pain and thermal grill illusion

The "intensity of pain" experienced on average from patients sciatic pain did not correlate with patients' response to the thermal grill illusion for all outcomes at all body locations (see Table 11.4.14 in appendix).

Duration of pain and cold and heat pain threshold

Duration of pain did not correlate with patients' cold or heat pain thresholds at all body locations (see Table 11.4.15 in appendix).

Duration of pain and thermal grill illusion

Duration of pain did not correlate with patients' response to the thermal grill illusion for all outcomes at all body locations (see Table 11.4.16 in appendix).

Discussion

The main aim of this study was to determine whether the reduced response to the thermal grill illusion observed in patients with heterogeneous chronic pain compared to pain-free participants (see chapter 3) could be replicated in patients with homogeneous chronic pain. Consequently, the response to the thermal grill illusion was investigated in pain-free participants (*pain-free*) and patients with unilateral sciatica (*sciatica*). Unlike hypothesised, the response to the thermal grill illusion generally did not significantly differ between *pain-free* and *sciatica* participants affected/dominant and unaffected/non-dominant side cheek, palm and calf, albeit for the outcomes "tolerability" and "unpleasantness" at the affected side cheek at the 18/42 ^{o}C thermal grill configuration, where patients with *sciatica* displayed significantly reduced responses (i.e. greater tolerability and less unpleasantness) (see Figure 4.3D and E and Table 4.2). Although not significant, *sciatica* participants' response to the thermal grill was generally in the same direction to that observed in patients with chronic pain in chapter 3; with responses to the thermal grill being lower compared to *pain-free* participants (see Figures 4.3 and 11.4.2). These findings suggest that any real differences observed in chapter 3 are not robust or that the true effect size is small. Comparing this study with my previous study in chapter 3, the response to the thermal grill was assessed using slightly adapted methodology in this study, therefore it cannot be ruled out that methodological differences may have influenced participants response to the thermal grill. Thus, whilst I was unable to replicate my previous findings of a significantly reduced response to the thermal grill illusion in patients with chronic pain (see chapter 3), a similar pattern of response to the thermal grill was observed in patients with *sciatica*.

Additionally, cold and heat pain thresholds did not differ between *pain-free* and *sciatica* participants' affected/dominant and unaffected/non-dominant side cheek, palm and calf, in accordance with my previous findings (see chapter 3); although cold pain thresholds appeared

to be increased (i.e. more sensitive) at *sciatica* patients unaffected leg and affected and unaffected side cheek compared to *pain-free* participants unaffected/non-dominant side leg (see Figure 11.4.1E). Previously, Nygaard and Mellgren (1998) demonstrated no significant differences in heat pain thresholds between patients with unilateral sciatica and pain-free volunteers on both patients affected and unaffected side dermatome. Similarly, Strian and colleagues (1991) demonstrated no significant differences in heat pain thresholds between patients with unilateral sciatica and pain-free volunteers on their affected side dermatome, however significantly reduced heat pain thresholds (i.e. more sensitive) were observed on patients unaffected side dermatome compared to pain-free volunteers. Although not investigated in this study, warm detection thresholds have been shown to be elevated (i.e. less sensitive) in patients with unilateral sciatica compared to pain-free volunteers in the dermatome of their affected leg (Strian et al., 1991; Nygaard and Mellgren, 1998; Quraishi et al., 2004), whilst cold detection thresholds have been shown to be decreased (i.e less sensitive) in both the affected (Nygaard and Mellgren, 1998; Quraishi et al., 2004) and unaffected leg dermatomes (Nygaard and Mellgren, 1998).

Another aim of this study was to investigate the characteristics of the response to the thermal grill illusion in *pain-free* participants and patients with *sciatica* at the cheek, palm and calf. Comparing body side (affected/dominant vs. unaffected/non-dominant side), both *pain-free* and *sciatica* participants response to the thermal grill generally did not differ across participants affected/dominant and unaffected/non-dominant side (see Figures 4.10 and 4.11), demonstrating no to minimal, as well as inconsistent lateralisation to the thermal grill illusion; consistent with my previous findings in chapter 2, as well as others (Boettger et al., 2011; Boettger et al., 2012; Averbeck et al., 2013; Boettger et al., 2013). Although these findings are not surprising for *pain-free* participants, it was initially hypothesised that the response to the thermal grill illusion would be lowest at the affected side calf compared to the unaffected

side calf, based on my previous findings in chapter 3, where a reduced response to the thermal grill illusion was observed in patients with chronic pain on their non-dominant palm, a region that was not affected by their primary pain pathology. Although the response to the thermal grill illusion did not differ between *sciatica* patients affected and unaffected side calf, in accordance with my hypothesis, cold and heat pain thresholds differed between patients affected and unaffected side calf, with patients displaying reduced sensitivities on their affected side (or conversely, increased sensitivities on their unaffected side). Reduced cool detection thresholds and increased warm detection and heat pain thresholds have previously been reported for patients with unilateral sciatica on their affected leg dermatome compared to their unaffected leg (Strian et al., 1991; Zwart et al., 1998; Zwart and Sand, 2002; Schiff and Eisenberg, 2003). These differences were also observed between sciatica patients affected and unaffected side palm, suggesting that these differences between patients affected and unaffected side calf and palm are not only due to local neuropathy from patients affected leg, as one would presume based on the abovementioned literature, but perhaps also due to differential attention or gating of sensory input in the presence of chronic pain (Moseley et al., 2012). These differences are unlikely to reflect patients' dominance, as cold and heat pain thresholds did not significantly differ between *pain-free* participants affected/dominant and unaffected/non-dominant side, albeit a slightly lower heat pain threshold on *pain-free* participants unaffected cheek, which cannot be explained. Differences in spinal and trigeminal processing of thermal pain stimuli may account for why no difference was observed between *sciatica* patients affected and unaffected side cheek.

Comparing cold pain thresholds between *pain-free* and *sciatica* participants affected/dominant and unaffected/non-dominant leg, increased cold pain thresholds (i.e. increased sensitivity) were observed at sciatica participants unaffected leg calf (mean cold pain threshold = 6.4 ^{o}C, Figure 4.5C) compared to sciatica participants affected leg calf and

pain-free participants dominant and non-dominant side calf, where median cold pain thresholds were approximately 0 ^{o}C (see Figures 4.4A, C and 4.5A), although this difference was not significant between sciatica and pain-free participants. A similar finding was observed comparing pain-free volunteers and patients with unilateral sciatica heat pain thresholds. Strian and colleagues (1991) demonstrated that patients with sciatica pain displayed reduced heat pain thresholds (i.e. increased sensitivity) on their unaffected side dermatome compared to their affected side dermatome and also pain-free controls. Strian and colleagues (1991) suggested that nerve root compression decreases nociceptive activity on the affected side dermatome and weakens the spinal pain inhibiting system on both the affected and unaffected side dermatome, resulting in a minimal change in heat pain threshold on the affected side dermatome due to the combination of decreased nociceptive activity and inhibitory control, and a decrease in heat pain threshold (i.e. increased sensitivity) on the unaffected side dermatome where nociceptive activity is still normal, but there is a decrease in inhibitory control. Cold pain thresholds were not investigated in the study by Strian and colleagues (1991), however these findings may explain why cold pain thresholds were higher on the unaffected leg in *sciatica* participants in the current study. Although heat pain thresholds differed between *sciatica* participants affected and unaffected leg in this study, heat pain thresholds did not appear to differ compared to *pain-free* participants, therefore it cannot be determined whether heat pain thresholds were increased in *sciatica* participants' unaffected leg or decreased in their affected leg.

Unlike thermal pain threshold testing, the thermal grill does not activate peripheral nociceptors, nor is the thermal grill a reaction time test. As discussed previously in section 1.3, the burning pain associated with the thermal grill illusion is believed to be a purely central phenomenon (Craig and Bushnell, 1994), where the central unmasking of a cold-labelled line by a warm-labelled line, disinhibits a pain-labelled line (discussed in section

1.5.5) (Ma, 2010; Ma, 2012). Thus, while cold and heat pain threshold testing depends on the functioning and conduction velocity of peripheral nerve fibres, the response to the thermal grill illusion is dependent on the brain's interpretation of simultaneous warm and cool stimuli. In patients with chronic pain, cold and heat pain threshold testing is likely to depend on the functioning and conduction velocity of peripheral nerve fibres, with damaged nerve fibres conducting at slower velocities or even less effectively, as well as loss of inhibitory control at the level of the spinal cord. Decreased sensitivity to both cold and heat pain on sciatica participants affected side calf and palm compared to their unaffected side may reflect peripheral and spinal cord dysfunction associated with their chronic sciatic pain. The inability of the thermal grill response to differentiate between sciatica participants affected and unaffected side, whilst thermal pain threshold testing was able to, may suggest a lack of higher-level central dysfunction in this pain condition (i.e. third order neurons and above). These findings may also support the notion that peripheral nociceptors are not involved in the burning pain associated with the thermal grill illusion, thus that the thermal grill is a purely central phenomenon, as initially proposed by Craig and Bushnell (1994).

Comparing body location (cheek vs. palm vs. calf), the predominant finding in both *pain-free* and *sciatica* participants was that the response to the thermal grill illusion was lowest at the calf compared to the palm and in some instances the cheek as well, with responses at the cheek generally being intermediate, consistent with my hypothesis, and consistent with differences in cortical representation across body regions (discussed in section 1.4.5.2 and chapter 2). Differences in response to the thermal grill illusion across body region were also observed in chapter 2 and have previously been reported by others (see section 1.4.5.1 in chapter 1). Recently, two Master's theses examined the response to the thermal grill illusion on the calf, with both studies reporting opposing findings (Brunello, 2010; Lam, 2012). The study by Brunello (2010) reported the greatest pain and unpleasantness from the thermal grill

on the upper body (back) compared to the lower extremities (calf), whereas Lam (2012) reported the greatest pain and unpleasantness from the thermal grill on the lower extremities (calf) compared to the upper extremities (forearm). The order of thermal stimuli were not randomised in the study by Lam (2012), a design flaw in itself, thus participants' always received thermal stimuli on the forearm before the calf, which may explain why participants reported increased pain and unpleasantness to the thermal grill illusion on the calf compared to the forearm. Previously, an order effect to the thermal grill illusion has not been investigated.

Differences in cold and heat pain thresholds were also observed between the cheek, palm and calf. *Pain-free* participants displayed reduced cold pain thresholds at their calf compared to their palm (i.e. less sensitive) on both their dominant and non-dominant side and increased heat pain thresholds on their calf compared to their cheek (i.e. less sensitive) on their non-dominant side only. These findings are consistent with previous findings in pain-free volunteers, where thermal pain thresholds are usually lowest on the cheek (i.e. more sensitive), greatest on the foot (i.e. less sensitive) and intermediate on the hand (Stevens and Choo, 1998; Rolke et al., 2006a); thus the leg is thought to have sparser peripheral innervation and wider central convergence onto thermoreceptive and nociceptive neurons compared to the upper body (Brunello, 2010). Consequently, the warm bars of the thermal grill may inhibit COLD neurons to a lesser extent at the calf, resulting in less disinhibition of the pain pathway, thus a lower response to the thermal grill; whereas the warm bars of the thermal grill may more effectively inhibit COLD neurons with smaller receptive fields that receive less convergent information (i.e. the palm), resulting in a greater response to the thermal grill (Brunello, 2010). This was in fact observed in this study (discussed above) and is consistent with Craig and Bushnell's (1994) thermosensory disinhibition hypothesis. Additionally, decreased cold pain thresholds and increased heat pain thresholds at *pain-free*

participants calf are consistent with a reduced response to the thermal grill illusion on the calf. Similarly, patients with *sciatica* displayed reduced cold pain thresholds on their affected side calf compared to their palm (i.e. less sensitive), consistent with their responses to the thermal grill illusion, whereas cold pain thresholds did not differ across body location on their unaffected side and neither did heat pain threshold on their affected and unaffected side.

Similar to my previous findings in chapter 2, as well as the literature (Essick et al., 2004; Lindstedt et al., 2011b; Kim et al., 2013), *pain-free* participants cold and heat pain thresholds were found to significantly correlate at participants affected/dominant and unaffected/non-dominant side cheek and palm, such that the less sensitive participants were to cold pain, the less sensitive participants were also to heat pain. Whereas, cold and heat pain threshold did not consistently correlate for *sciatica* participants. Once adjusting the significance level to account for multiple comparisons (< 0.00333), only some significant, but inconsistent correlations were observed between *pain-free* participants cold and heat pain thresholds and their response to the thermal grill illusion mainly on their cheek and palm, such that the more sensitive a participant was to cold and heat pain, the more sensitive they also were to the thermal grill illusion (see Table 4.9). It is important to note that in many instances significant correlations were observed at one or two thermal grill configurations and not at all three thermal grill configurations or for some thermal grill outcomes and not others, which is likely to reflect the robust correlation analysis and Bonferroni correction for multiple comparisons used. An alternative approach to use in the future would be to use a linear mixed effects model so that the power of repeated measures (i.e. 22/38, ^{o}C 20/40 ^{o}C and 18/42 ^{o}C) can be accounted for. Unlike *pain-free* participants, no significant correlations were observed between *sciatica* participants cold and heat pain thresholds and their response to the thermal grill illusion, which is likely due the low participant numbers in the *sciatica* group (n = 9). Others have also reported correlations between cold (Brunello, 2010; Kostka, 2011; Lindstedt

et al., 2011b; Averbeck et al., 2013) and heat (Lindstedt et al., 2011b) pain thresholds and the response to the thermal grill illusion in pain-free participants. The *r* values obtained in those studies were similar to those obtained in this study.

Unlike hypothesised, Beck depression inventory scores did not correlate with *pain-free* or *sciatica* participants' response to the thermal grill illusion nor did Beck depression inventory scores consistently correlate with cold and heat pain thresholds. Previously, Beck depression inventory scores were found to correlate with the sum of pain intensity, unpleasantness and overall pain over 8 minutes of exposure with the thermal grill. Differences in contact time to the thermal grill in my study (30 s) and the study by Pinerua-Shuhaibar and colleagues (2011) (8 min) may account for why no correlation between Beck depression inventory scores and the response to the thermal grill was observed in the present study, as the response to the thermal grill has previously been shown to summate over time (as discussed in chapter 2). Additionally, differences in participant numbers in this study (*pain-free* n = 20, *sciatica* n = 9) and the study by Pinerua-Shuhaibar and colleagues (2011) (n = 54) may also account for why no correlation between Beck depression inventory scores and the response to the thermal grill was observed in the present study. Similarly, early morning salivary cortisol levels and body mass index did not correlate with *pain-free* and *sciatica* participants cold pain thresholds, heat pain thresholds or their responses to the thermal grill illusion, nor did Beck depression inventory scores correlate with early morning salivary cortisol levels. Consistent with the literature, *pain-free* participants salivary cortisol significantly increased 30 min post-awakening (Pruessner et al., 1997; Schmidt-Reinwald et al., 1999; Wust et al., 2000), whereas this was not observed for *sciatica* participants, demonstrating a blunted HPA axis in these patients, as previously described in patients with sciatic pain (Geiss et al., 1997). In addition, neither the intensity of pain experienced on average from patients sciatic pain nor the duration

of pain *sciatica* patients had experienced their pain for significantly correlated with their cold pain thresholds, heat pain thresholds or their responses to the thermal grill illusion.

In conclusion, unlike hypothesised the response to the thermal grill illusion did not significantly differ between *pain-free* and *sciatica* participants. However, although not significant, *sciatica* participants' response to the thermal grill was generally lower compared to *pain-free* participants, consistent with my previous findings in patients with chronic pain (chapter 3). These findings suggest that any real differences observed in chapter 3 are not robust or that the true effect size is small. Furthermore, unlike thermal pain thresholds, the response to the thermal grill illusion did not differ between patients affected and unaffected leg calf. Thus, these results question the utility of the thermal grill illusion as a tool to investigate pain and temperature dysfunction in patients with chronic unilateral sciatica.

Tables

Table 4.1. Participant Demographics

	Pain-free	Sciatica	*P*
N (M, F)	20 (10M, 10F)	9 (5M, 4F)	-
Age (years)	42 (25.6 to 61)[a]	49.8 ± 11.7[b]	0.4
BMI (kg/m^2)	24.2 ± 3.9[b]	29.2 ± 4.8[b]	**0.006**
BDI	2.5 (0 to 4.8)[a]	3 (1 to 9)[a]	0.89
Cortisol: awakening (nmol/L)	16 (13 to 22)[a]	16.1 ± 5.0[b]	0.61
Cortisol: 30 mins post awakening (nmol/L)	23 (18.3 to 26.8)[a]	19.5 ± 6.5[b]	0.26
Duration of pain (years)	-	15.6 ± 12.1[b]	-

a: median and IQR; b: mean ± SD. Significant values represented by bold text.

Table 4.2. Pain-Free Participants versus Patients with Sciatica: Thermal Grill Illusion

The response to the thermal grill illusion was compared between pain-free participants and patients with sciatica at participants' affected/dominant and unaffected/non-dominant side cheek, palm and calf for all five thermal grill outcomes. *P* values are presented.

	Affected/Dominant Side			Unaffected/Non-dominant side		
	Cheek	Palm	Calf	Cheek	Palm	Calf
Intensity of Pain	0.53	0.42	0.46	0.58	0.4	0.3
Intensity of Heat	0.28	0.4	0.22	0.1	0.22	0.54
Intensity of Heat (c)	0.35	0.6	0.23	0.1	0.39	0.25
Unpleasantness	0.14	0.62	0.87	0.17	0.54	0.72
Tolerability	0.15	0.35	0.18	0.19	0.18	0.96

C: colour bar.

Table 4.3. Effect of Body Location on the Response to the Thermal Grill Illusion on Pain-free Participants Affected/Dominant Side

The response to the thermal grill illusion was compared between pain-free participants affected (dominant) side cheek, palm and calf for each thermal grill outcome (listed vertically) at each thermal grill configuration (listed horizontally). Mean differences and 95% CI for differences presented. Significant values represented by bold text.

	Affected Calf vs. Cheek		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	2 mm (-8 to 13)	-1 mm (-12 to 9)	**-11 mm (-21 to 0)**
Intensity of Heat	-4 mm (-15 to 6)	-2 mm (-12 to 8)	-10 mm (-20 to 1)
Intensity of Heat (c)	-6 mm (-16 to 4)	-4 mm (-14 to 6)	-5 mm (-15 to 5)
Unpleasantness	5 mm (-6 to 16)	4 mm (-7 to 15)	-11 mm (-22 to 1)
Tolerability	-1 mm (-12 to 10)	1 mm (-10 to 12)	-10 mm (-21 to 1)
	Affected Calf vs. Palm		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	2 mm (-9 to 12)	**-11 mm (-21 to 0)**	-8 mm (-18 to 3)
Intensity of Heat	**-11 mm (-21 to -1)**	-10 mm (-20 to 0)	**-15 mm (-25 to -4)**
Intensity of Heat (c)	**-12 mm (-21 to -2)**	-8 mm (-18 to 2)	**-11 mm (-21 to -1)**
Unpleasantness	2 mm (-9 to 13)	-8 mm (-19 to 3)	-9 mm (-20 to 3)
Tolerability	-1 mm (-12 to 9)	-10 mm (-21 to 1)	-7 mm (-18 to 4)
	Affected Palm vs. Cheek		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	1 mm (-10 to 11)	-3 mm (-13 to 7)	3 mm (-13 to 7)
Intensity of Heat	7 mm (-4 to 17)	8 mm (-2 to 18)	5 mm (-5 to 15)
Intensity of Heat (c)	6 mm (-4 to 16)	3 mm (-7 to 13)	-6 mm (-4 to 16)
Unpleasantness	3 mm (-8 to 14)	**12 mm (1 to 23)**	-2 mm (-13 to 9)
Tolerability	0 mm (-11 to 11)	11 mm (0 to 22)	-3 mm (-14 to 8)

ºC: degrees Celsius; C: colour bar.

Table 4.4. Effect of Body Location on the Response to the Thermal Grill Illusion on Pain-free Participants Unaffected/Non-dominant Side

The response to the thermal grill illusion was compared between pain-free participants unaffected (non-dominant) side cheek, palm and calf for each thermal grill outcome (listed vertically) at each thermal grill configuration (listed horizontally). Mean differences and 95% CI for differences presented. Significant values represented by bold text.

	Unaffected Calf vs. Cheek		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	-4 mm (-12 to 4)	**-12 mm (-20 to 4)**	-6 mm (-14 to 2)
Intensity of Heat	-10 mm (-20 to 1)	**-17 mm (-28 to -7)**	**-13 mm (-24 to -3)**
Intensity of Heat (c)	-10 mm (-20 to 0)	**-18 mm (-28 to -8)**	-7 mm (-17 to 3)
Unpleasantness	-4 mm (-15 to 8)	**-13 mm (-24 to -1)**	-9 mm (-20 to 3)
Tolerability	-4 mm (-15 to 6)	**-17 mm (-27 to -6)**	-9 mm (-19 to 2)
	Unaffected Calf vs. Palm		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	**-10 mm (-17 to 2)**	**-17 mm (-24 to -9)**	**-13 mm (-20 to -5)**
Intensity of Heat	**-15 mm (-26 to -5)**	**-23 mm (-34 to -13)**	**-17 mm (-28 to -7)**
Intensity of Heat (c)	**-13 mm (-23 to -3)**	**-18 mm (-28 to -8)**	**-12 mm (-22 to -2)**
Unpleasantness	-8 mm (-20 to 3)	**-14 mm (-25 to -2)**	**-12 mm (-24 to -1)**
Tolerability	-10 mm (-20 to 1)	**-14 mm (-24 to -4)**	**-15 mm (-25 to -4)**
	Unaffected Palm vs. Cheek		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	6 mm (-2 to 13)	5 mm (-3 to 12)	6 mm (-1 to 14)
Intensity of Heat	5 mm (-5 to 16)	6 mm (-4 to 17)	4 mm (-6 to 15)
Intensity of Heat (c)	3 mm (-7 to 13)	0 mm (-10 to 10)	5 mm (-5 to 15)
Unpleasantness	5 mm (-7 to 16)	1 mm (-10 to 13)	4 mm (-8 to 15)
Tolerability	5 mm (-5 to 16)	-3 mm (-13 to 7)	6 mm (-4 to 16)

ºC: degrees Celsius; C: colour bar.

Table 4.5. Effect of Body Location on the Response to the Thermal Grill Illusion on Patients with Sciatica Affected/Dominant Side

The response to the thermal grill illusion was compared between sciatica patients affected side cheek, palm and calf for each thermal grill outcome (listed vertically) at each thermal grill configuration (listed horizontally). Mean differences and 95% CI for differences presented. Significant values represented by bold text.

	Affected Calf vs. Cheek		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	-6 mm (-16 to 5)	-5 mm (-15 to 6)	-2 mm (-12 to 8)
Intensity of Heat	-10 mm (-26 to 6)	-5 mm (-21 to 10)	-5 mm (-21 to 11)
Intensity of Heat (c)	-11 mm (-28 to 6)	-10 mm (-28 to 8)	-11 (-28 to 6)
Unpleasantness	4 mm (-6 to 14)	5 mm (-5 to 15)	7 mm (-3 to 17)
Tolerability	-5 mm (-15 to 5)	0 mm (-10 to 10)	-2 mm (-12 to 7)
	Affected Calf vs. Palm		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	-4 mm (-14 to 6)	-6 mm (-16 to 5)	**-16 mm (-26 to -5)**
Intensity of Heat	-13 mm (-29 to 3)	-7 mm (23 to 9)	**-22 mm (-37 to -6)**
Intensity of Heat (c)	-17 mm (-34 to 0)	-16 mm (-34 to 2)	**-26 mm (-43 to -9)**
Unpleasantness	4 mm (-6 to 14)	4 mm (-6 to 14)	-2 mm (-12 to 8)
Tolerability	-6 mm (-15 to 4)	-4 mm (-13 to 6)	**-11 mm (-20 to -1)**
	Affected Palm vs. Cheek		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	-1 mm (-12 to 9)	1 mm (-9 to 11)	**14 mm (3 to 24)**
Intensity of Heat	3 mm (-13 to 19)	1 mm (-15 to 17)	**17 mm (1 to 33)**
Intensity of Heat (c)	6 mm (-11 to 23)	6 mm (-12 to 24)	15 mm (-2 to 32)
Unpleasantness	0 mm (-10 to 10)	1 mm (-9 to 11)	9 mm (-1 to 19)
Tolerability	1 mm (-9 to 10)	4 mm (-6 to 14)	8 mm (-2 to 18)

ºC: degrees Celsius; C: colour bar.

Table 4.6. Effect of Body Location on the Response to the Thermal Grill Illusion on Patients with Sciatica Unaffected/Non-dominant Side

The response to the thermal grill illusion was compared between sciatica patients unaffected side cheek, palm and calf for each thermal grill outcome (listed vertically) at each thermal grill configuration (listed horizontally). Mean differences and 95% CI for differences presented.

	Unaffected Calf vs. Cheek		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	0 mm (-10 to 10)	-10 mm (-20 to 0)	0 mm (-10 to 9)
Intensity of Heat	-2 mm (-14 to 11)	-7 mm (-19 to 5)	-3 mm (-15 to 9)
Intensity of Heat (c)	-5 mm (-21 to 11)	-11 mm (-28 to 5)	-8 mm (-24 to 8)
Unpleasantness	11 mm (-9 to 31)	3 mm (-16 to 23)	-6 mm (-26 to 14)
Tolerability	-1 mm (-10 to 7)	-3 mm (-11 to 6)	-5 mm (-13 to 4)
	Unaffected Calf vs. Palm		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	-8 mm (-18 to 2)	-6 mm (-16 to 4)	-2 mm (-12 to 8)
Intensity of Heat	-17 mm (-29 to 4)	-8 mm (-20 to 5)	-7 mm (-21 to 4)
Intensity of Heat (c)	-21 mm (-37 to 5)	-15 mm (-31 to 1)	-11 mm (-27 to 5)
Unpleasantness	1 mm (-19 to 21)	4 mm (-15 to 24)	-7 mm (-37 to 13)
Tolerability	-4 mm (-13 to 4)	-2 mm (-11 to 6)	-4 mm (-12 to 5)
	Unaffected Palm vs. Cheek		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	7 mm (-2 to 17)	-4 mm (-14 to 6)	2 mm (-8 to 12)
Intensity of Heat	15 mm (3 to 27)	1 mm (-11 to 13)	6 mm (-7 to 18)
Intensity of Heat (c)	16 mm (0 to 32)	4 mm (-12 to 20)	3 mm (-13 to 20)
Unpleasantness	10 mm (-10.0 to 30)	-1.0 mm (-21 to 19)	2 mm (-18 to 22)
Tolerability	3 mm (-5 to 11)	0 mm (-9 to 8)	-1 mm (-9 to 8)

ºC: degrees Celsius; C: colour bar.

Table 4.7. Effect of Body Side on the Response to the Thermal Grill Illusion: Pain-free Participants

The response to the thermal grill illusion was compared between pain-free participants affected (dominant) and unaffected (non-dominant) side cheek, palm and calf for each thermal grill outcome (listed vertically) at each thermal grill configuration (listed horizontally). Mean differences and 95% CI for differences presented. Significant values represented by bold text.

	Affected vs. Unaffected Cheek		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	3 mm (-5 to 12)	6 mm (-3 to 14)	-5 mm (-14 to 3)
Intensity of Heat	7 mm (-3 to 17)	3 mm (-7 to 13)	1 mm (-9 to 11)
Intensity of Heat (c)	5 mm (-4 to 15)	4 mm (-6 to 13)	1 mm (-9 to 10)
Unpleasantness	6 mm (-2 to 13)	**9 mm (2 to 17)**	-2 mm (-10 to 5)
Tolerability	2 mm (-8 to 11)	**11 mm (2 to 20)**	-4 mm (-13 to 5)
	Affected vs. Unaffected Palm		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	**8 mm (1 to 16)**	1 mm (-7 to 8)	4 mm (-3 to 12)
Intensity of Heat	5 mm (-3 to 14)	1 mm (-7 to 9)	0 mm (-8 to 8)
Intensity of Heat (c)	2 mm (-3 to 7)	0 mm (-5 to 5)	0 mm (-5 to 5)
Unpleasantness	7 mm (-1 to 16)	-2 mm (-10 to 7)	3 mm (-5 to 12)
Tolerability	7 mm (0 to 14)	-3 mm (-10 to 5)	5 mm (-2 to 12)
	Affected vs. Unaffected Calf		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	-3 mm (-9 to 3)	-5 mm (-12 to 1)	-1 mm (-7 to 6)
Intensity of Heat	1 mm (-7 to 9)	**-12 mm (-20 to -4)**	-2 mm (-10 to 6)
Intensity of Heat (c)	1 mm (-6 to 9)	**-10 mm (-18 to -3)**	-1 mm (-8 to 7)
Unpleasantness	-3 mm (-10 to 4)	**-8 mm (-15 to -0)**	-1 mm (-8 to 7)
Tolerability	-1 mm (-8 to 6)	-7 mm (-14 to 0)	-2 mm (-9 to 5)

ºC: degrees Celsius; C: colour bar.

Table 4.8. Effect of Body Side on the Response to the Thermal Grill Illusion: Patients with Sciatica

The response to the thermal grill illusion was compared between sciatica patients affected and unaffected side cheek, palm and calf for each thermal grill outcome (listed vertically) at each thermal grill configuration (listed horizontally). Mean differences and 95% CI for differences presented.

	Affected vs. Unaffected Cheek		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	-5 mm (-13 to 3)	6 mm (-2 to 15)	3 mm (-5 to 11)
Intensity of Heat	-8 mm (-19 to 2)	0 mm (-10 to 10)	4 mm (-7 to 14)
Intensity of Heat (c)	-12 mm (-26 to 2)	0 mm (-14.0 to 14.0)	5 mm (-9 to 19)
Unpleasantness	-4 mm (-16 to 7)	3 mm (-8 to 14)	8 mm (-3 to 20)
Tolerability	-3 mm (-14 to 8)	3 mm (-8 to 14)	6 mm (-6 to 17)
	Affected vs. Unaffected Palm		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	4 mm (-5 to 13)	1 mm (-8 to 10)	-9 mm (-18 to -0)
Intensity of Heat	3 mm (-11 to 18)	-1 mm (-15 to 14)	-7 mm (-22 to 7)
Intensity of Heat (c)	-1 mm (-11 to 8)	0 mm (-10 to 10)	-7 mm (-16 to 3)
Unpleasantness	6 mm (-5 to 17)	1 mm (-10 to 12)	1 mm (-10 to 11)
Tolerability	-1 mm (-8 to 6)	-1 mm (-8 to 6)	-3 mm (-11 to 4)
	Affected vs. Unaffected Calf		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	1 mm (-5 to 6)	1 mm (-4 to 6)	4 mm (-1 to 10)
Intensity of Heat	0 mm (-9 to 8)	-1 mm (-10 to 7)	6 mm (-3 to 14)
Intensity of Heat (c)	-5 mm (-13 to 3)	1 mm (-8 to 9)	8 mm (-0 to 16)
Unpleasantness	3 mm (-13 to 18)	1 mm (-14 to 17)	-5 mm (-21 to 11)
Tolerability	1 mm (-3 to 4)	1 mm (-3 to 4)	3 mm (0 to 7)

ºC: degrees Celsius; C: colour bar.

Table 4.9. Correlations Between Thermal Pain Thresholds and the Thermal Grill Response: Pain-free Participants

R and *P* values from the correlation analyses performed at participants affected and unaffected side cheek, palm and calf are presented (described previously on page 94). Significant values represented by bold text.

		Cold Pain Threshold			Heat Pain Threshold		
	Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Affected Cheek	Intensity of Pain						
	R value	0.46	0.35	0.42	-0.43	-0.32	-0.62
	P value	0.042	0.13	0.063	0.058	0.18	0.0038
	Intensity of Heat						
	R value	0.45	0.53	0.35	**-0.59[P]**	**-0.68[P]**	-0.49[P]
	P value	0.0456	0.016	0.13	**0.0057[P]**	**0.001[P]**	0.027[P]
	Intensity of Heat (c)						
	R value	0.34	0.42	0.25	-0.54	**-0.77**	**-0.6**
	P value	0.14	0.065	0.29	0.015	< **0.0001**	**0.0054**
	Unpleasantness						
	R value	0.36	0.35	0.35	-0.54	-0.4	**-0.67**
	P value	0.12	0.13	0.13	0.014	0.078	**0.0012**
	Tolerability						
	R value	0.18	0.3	0.31	-0.15	-0.18	-0.55
	P value	0.44	0.2	0.18	0.52	0.44	0.012
Unaffected Cheek	Intensity of Pain						
	R value	0.45	0.45	0.38	-0.28[P]	-0.42[P]	-0.35[P]
	P value	0.045	0.048	0.1	0.24[P]	0.065[P]	0.13[P]
	Intensity of Heat						
	R value	**0.59**	**0.8**	0.53	**-0.59[P]**	-0.51[P]	**-0.61[P]**
	P value	**0.0061**	**0.0005**	0.016	**0.0065[P]**	0.021[P]	**0.0041[P]**
	Intensity of Heat (c)						
	R value	0.53	**0.63**	0.35	-0.55[P]	-0.54[P]	-0.38[P]
	P value	0.016	**0.0027**	0.13	0.012[P]	0.015[P]	0.094[P]
	Unpleasantness						
	R value	0.46	0.49	0.37	-0.4	-0.42	-0.4
	P value	0.04	0.029	0.113	0.081	0.066	0.081
	Tolerability						
	R value	0.22	0.43	0.37	-0.2	-0.37	-0.4
	P value	0.35	0.057	0.11	0.41	0.11	0.078

		Cold Pain Threshold			Heat Pain Threshold		
	Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Affected Palm	Intensity of Pain						
	R value	0.38	0.36	0.42	-0.29	-0.31	0.37
	P value	0.1	0.12	0.064	0.22	0.18	0.11
	Intensity of Heat						
	R value	0.57	**0.65**	**0.64**	-0.51	-0.54	-0.54
	P value	0.0083	**0.0021**	**0.0022**	0.02	0.015	0.014
	Intensity of Heat (c)						
	R value	0.47[P]	0.54[P]	0.49[P]	-0.38[P]	-0.48[P]	-0.41[P]
	P value	0.036[P]	0.013[P]	0.029[P]	0.1[P]	0.031[P]	0.072[P]
	Unpleasantness						
	R value	0.41	0.5	0.44	-0.38[P]	-0.45[P]	-0.39[P]
	P value	0.071	0.024	0.053	0.1[P]	0.044[P]	0.087[P]
	Tolerability						
	R value	0.048	0.4	0.5	0.026	-0.38	-0.44
	P value	0.84	0.084	0.026	0.91	0.096	0.055
Unaffected Palm	Intensity of Pain						
	R value	0.56	**0.64**	**0.64**	-0.422	-0.55	-0.53
	P value	0.01	**0.0023**	**0.0024**	0.0640	0.012	0.016
	Intensity of Heat						
	R value	0.5	**0.64**	**0.64**	-0.49	**-0.64**	-0.56
	P value	0.025	**0.0024**	**0.0026**	0.029	**0.0026**	0.0096
	Intensity of Heat (c)						
	R value	0.36	0.43	0.42	-0.43[P]	-0.47[P]	-0.41[P]
	P value	0.12	0.06	0.062	0.058[P]	0.038[P]	0.071[P]
	Unpleasantness						
	R value	0.5	**0.63**	**0.61**	-0.39	**-0.62**	-0.54
	P value	0.026	**0.0031**	**0.0045**	0.093	**0.0037**	0.013
	Tolerability						
	R value	0.35	0.51	**0.58**	-0.256	-0.43	-0.47
	P value	0.13	0.021	**0.0069**	0.277	0.057	0.037

		Cold Pain Threshold			Heat Pain Threshold		
	Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Affected Calf	Intensity of Pain						
	R value	0.0099	0.17	0.12	0.012	0.034	-0.12
	P value	0.68	0.47	0.61	0.96	0.89	0.61
	Intensity of Heat						
	R value	0.083	0.25	0.33	-0.41	-0.37	-0.35
	P value	0.73	0.29	0.15	0.072	0.11	0.13
	Intensity of Heat						
	R value	-0.013	0.055	0.095	-0.43	-0.22	-0.33
	P value	0.96	0.82	0.69	0.057	0.35	0.16
	Unpleasantness						
	R value	0.095	0.16	0.23	-0.097	-0.1	-0.24
	P value	0.69	0.5	0.32	0.68	0.67	0.3
	Tolerability						
	R value	0.064	0.2	0.084	0.0057	-0.13	-0.17
	P value	0.79	0.4	0.73	0.98	0.57	0.47
Unaffected Calf	Intensity of Pain						
	R value	0.28	0.15	0.34	-0.21	-0.37	-0.33
	P value	0.23	0.52	0.14	0.38	0.11	0.16
	Intensity of Heat						
	R value	0.35	0.37	0.54	-0.43	**-0.62**	**-0.57**
	P value	0.13	0.1	0.015	0.057	**0.0038**	**0.0093**
	Intensity of Heat						
	R value	-0.0091	0.28	0.29	-0.34[P]	-0.41[P]	-0.43[P]
	P value	0.97	0.23	0.22	0.14[P]	0.07[P]	0.058[P]
	Unpleasantness						
	R value	0.28	0.29	0.35	-0.19	-0.42	-0.5
	P value	0.23	0.22	0.13	0.42	0.064	0.026
	Tolerability						
	R value	0.27	0.53	0.34	-0.1	-0.21	-0.27
	P value	0.26	0.017	0.14	0.67	0.37	0.25

ºC: degrees Celcius; C: colour bar. [P]: analysed with Pearson's correlation. Significance level < 0.00333.

Table 4.10. Correlations Between Thermal Pain Thresholds and the Thermal Grill Response: Patients with Sciatica

R and *P* values from the correlation analyses performed at patients affected and unaffected side cheek, palm and calf are presented (described previously on page 94).

		Cold Pain Threshold			Heat Pain Threshold		
	Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Affected Cheek	Intensity of Pain						
	R value	-0.034	-0.059	0.05	-0.025	0017	-0.059
	P value	0.92	0.87	0.9	0.94	0.97	0.87
	Intensity of Heat						
	R value	-0.053[P]	0.093[P]	0.052[P]	-0.28	-0.15	-0.17
	P value	0.89[P]	0.81[P]	0.89[P]	0.44	0.68	0.65
	Intensity of Heat (c)						
	R value	-0.34[P]	-0.3[P]	-0.5[P]	0.0	0.067	0.23
	P value	0.37[P]	0.43[P]	0.17[P]	0.99	0.88	0.56
	Unpleasantness						
	R value	-0.039[P]	0.16[P]	0.051[P]	-0.1	-0.05	0.16
	P value	0.92[P]	0.68[P]	0.9[P]	0.78	0.89	0.68
	Tolerability						
	R value	0.16	0.29	0.0	-0.017	0.035	0.29
	P value	0.67	0.45	0.99	0.88	0.94	0.44
Unaffected Cheek	Intensity of Pain						
	R value	-0.36[P]	-0.088[P]	-0.43[P]	-0.51[P]	-0.33[P]	-0.41[P]
	P value	0.34[P]	0.82[P]	0.25[P]	0.16[P]	0.38[P]	0.28[P]
	Intensity of Heat						
	R value	-0.21[P]	-0.031[P]	-0.059[P]	-0.48[P]	-0.3[P]	-0.28[P]
	P value	0.58[P]	0.94[P]	0.88[P]	0.19[P]	0.43[P]	0.46[P]
	Intensity of Heat (c)						
	R value	-0.3[P]	-0.25[P]	-0.24[P]	-0.069[P]	0.14[P]	0.41[P]
	P value	0.44[P]	0.51[P]	0.54[P]	0.86[P]	0.73[P]	0.27[P]
	Unpleasantness						
	R value	-0.097	0.017	-0.059	-0.43	-0.46	-0.35
	P value	0.77	0.97	0.87	0.23	0.2	0.36
	Tolerability						
	R value	0.03	0.16	0.19	-0.24	-0.3	-0.11
	P value	0.94	0.67	0.62	0.51	0.41	0.77

		Cold Pain Threshold			Heat Pain Threshold		
	Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Affected Palm	Intensity of Pain						
	R value	0.33	0.61	0.71	0.2	0.034	-0.13
	P value	0.38	0.084	0.038	0.6	0.94	0.74
	Intensity of Heat						
	R value	0.45[P]	0.56[P]	0.75[P]	-0.14[P]	-0.1[P]	-0.23[P]
	P value	0.23[P]	0.12[P]	0.02[P]	0.72[P]	0.79[P]	0.55[P]
	Intensity of Heat (c)						
	R value	0.44[P]	0.58[P]	0.42[P]	0.077[P]	0.017[P]	0.18[P]
	P value	0.23[P]	0.1[P]	0.26[P]	0.84[P]	0.97[P]	0.65[P]
	Unpleasantness						
	R value	0.078[P]	0.86[P]	0.36[P]	0.24[P]	0.049[P]	0.21[P]
	P value	0.84[P]	0.83[P]	0.34[P]	0.53[P]	0.9[P]	0.59[P]
	Tolerability						
	R value	0.17	0.19	0.61	0.33	0.22	-0.1
	P value	0.65	0.63	0.09	0.37	0.57	0.78
Unaffected Palm	Intensity of Pain						
	R value	0.66	0.17	0.2	-0.31	0.11	0.1
	P value	0.06	0.67	0.61	0.4	0.78	0.81
	Intensity of Heat						
	R value	0.76[P]	0.52[P]	0.59[P]	-0.32[P]	-0.12[P]	-0.18[P]
	P value	0.017[P]	0.15[P]	0.092[P]	0.4[P]	0.77[P]	0.64[P]
	Intensity of Heat (c)						
	R value	0.33[P]	0.22[P]	0.38[P]	-0.27[P]	-0.15[P]	-0.24[P]
	P value	0.39[P]	0.57[P]	0.31[P]	0.48[P]	0.69[P]	0.53[P]
	Unpleasantness						
	R value	0.6[P]	0.41[P]	0.4[P]	-0.21[P]	-0.05[P]	-0.076[P]
	P value	0.085[P]	0.28[P]	0.29[P]	0.59[P]	0.9[P]	0.85[P]
	Tolerability						
	R value	0.15	-0.017	0.17	0.017	0.18	0.025
	P value	0.71	0.95	0.67	0.98	0.65	0.96

		Cold Pain Threshold			Heat Pain Threshold		
	Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Affected Calf	Intensity of Pain						
	R value	0.49	0.49	0.57	-0.13	-0.12	-0.13
	P value	0.18	0.18	0.11	0.73	0.65	0.71
	Intensity of Heat						
	R value	0.47	0.37	0.61	-0.49	-0.36	-0.54
	P value	0.2	0.33	0.088	0.16	0.33	0.13
	Intensity of Heat (c)						
	R value	0.55	0.78	0.55	-0.49[P]	-0.57[P]	-0.42[P]
	P value	0.13	0.027	0.13	0.18[P]	0.14[P]	0.26[P]
	Unpleasantness						
	R value	-0.16	-0.013	-0.013	0.55	0.29	0.45
	P value	0.64	0.94	0.95	0.13	0.44	0.22
	Tolerability						
	R value	0.15	0.23	0.27	-0.087	0.096	0.13
	P value	0.68	0.55	0.49	0.72	0.81	0.73
Unaffected Calf	Intensity of Pain						
	R value	0.17	0.03	0.5	0.06	0.068	0.54
	P value	0.66	0.94	0.18	0.89	0.87	0.14
	Intensity of Heat						
	R value	0.021	-0.14	0.18	0.092	0.025	0.23
	P value	0.96	0.7	0.64	0.82	0.96	0.56
	Intensity of Heat (c)						
	R value	-0.35[P]	-0.42[P]	-0.29[P]	0.17[P]	0.066[P]	0.16[P]
	P value	0.36[P]	0.26[P]	0.45[P]	0.66[P]	0.87[P]	0.68[P]
	Unpleasantness						
	R value	0.61	0.52	0.36	0.46	0.46	0.28
	P value	0.088	0.15	0.34	0.22	0.21	0.47
	Tolerability						
	R value	0.3	0.3	0.2	0.15	0.15	-0.051
	P value	0.43	0.43	0.6	0.69	0.69	0.87

°C: degrees Celcius; C: colour bar. [P]: analysed with Pearson's correlation. Significance level P < 0.0333.

Figures.

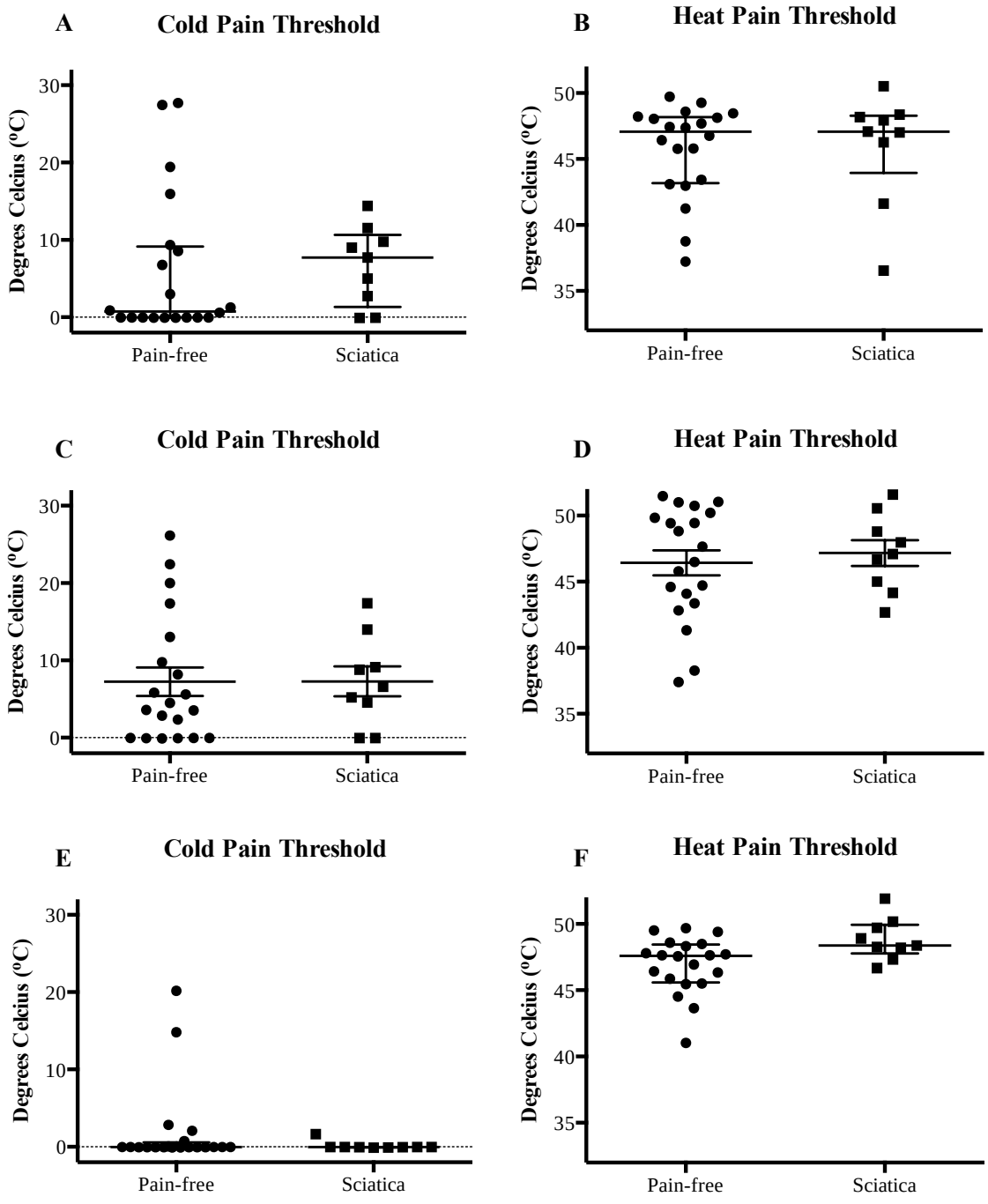
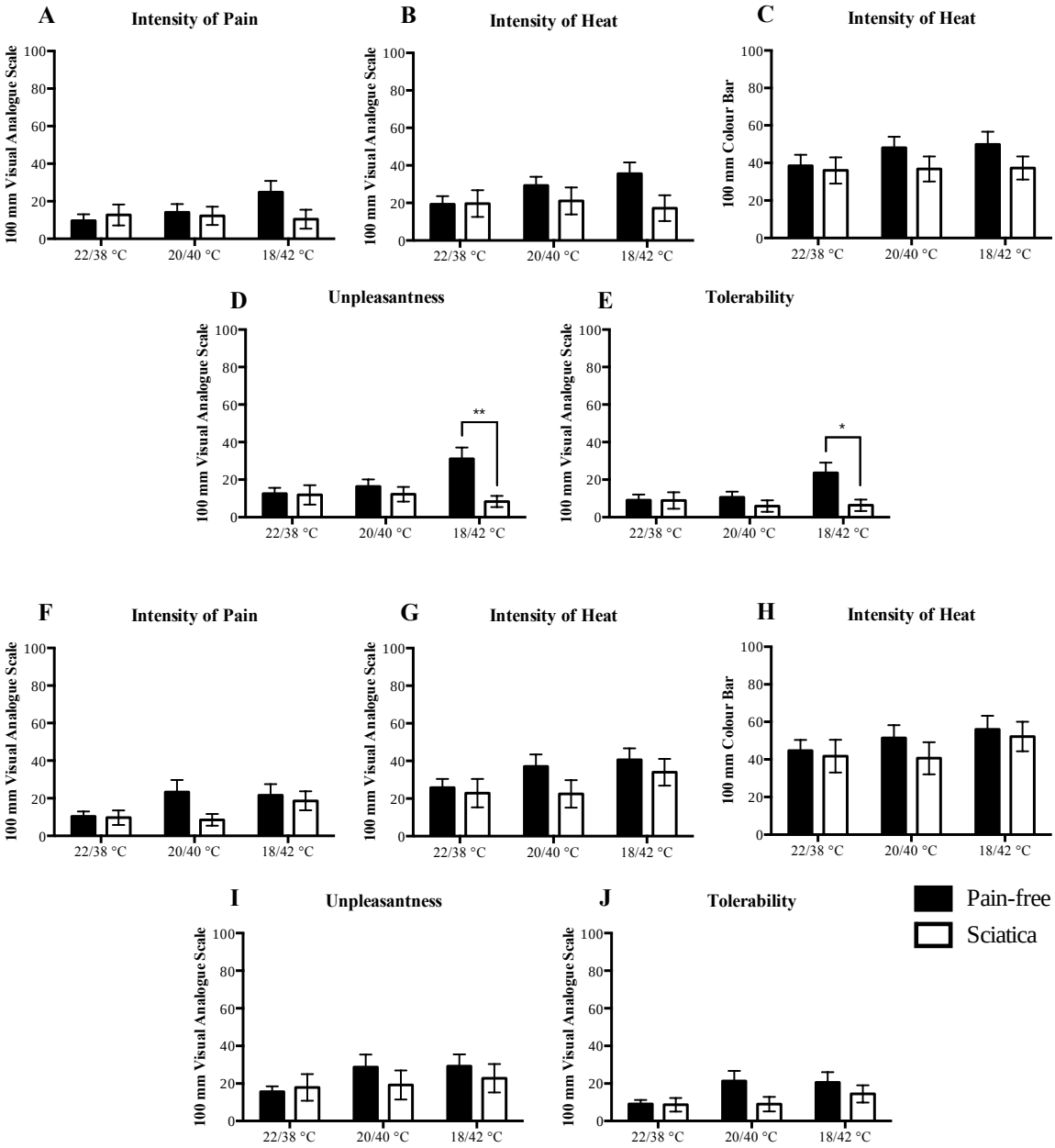


Figure 4.2. Pain-free participants versus patients with sciatica: cold and heat pain thresholds.

Cold and heat pain thresholds at the affected/dominant side cheek (A, B), palm (C, D) and calf (E, F) in pain-free participants and patients with sciatica. No significant differences were observed between pain-free participants and patients with sciatica for cold or heat pain threshold at the affected/dominant side cheek ($p = 0.34$, A and $p = 0.99$, B), palm ($p = 0.99$, C and $p = 0.64$, D) or calf ($p = 0.87$, E and $p = 0.12$, F). Graphs A, B, E and F are represented as median and interquartile range. Graphs C and D are represented as mean ± SEM.


A
Intensity of Pain
B
Intensity of Heat
C
Intensity of Heat
100 mm Visual Analogue Scale
100 mm Colour Bar
22/38 °C
20/40 °C
18/42 °C
D
Unpleasantness
E
Tolerability
**
*
F
Intensity of Pain
G
Intensity of Heat
H
Intensity of Heat
I
Unpleasantness
J
Tolerability
Pain-free
Sciatica

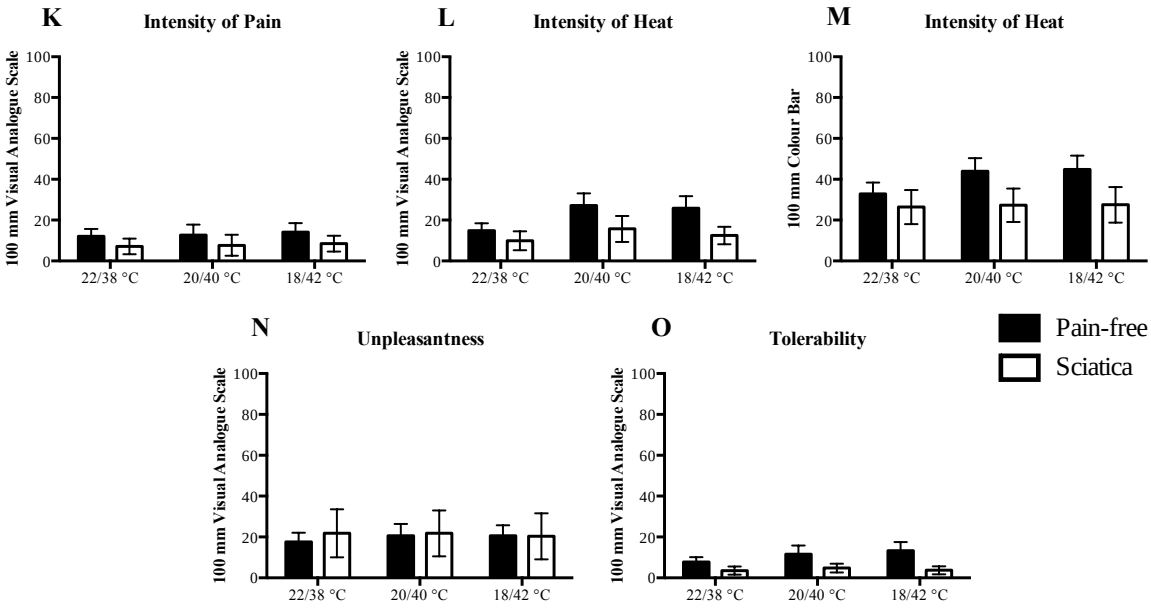


Figure 4.3. Pain-free participants versus patients with sciatica: thermal grill illusion.

The response to the thermal grill illusion at the affected/dominant side cheek (A-E), palm (F-J) and calf (K-O) in pain-free participants (black bars) and patients with sciatica (white bars). Generally, the response to the thermal grill did not significantly differ between pain-free participants and patients with sciatica at the affected/dominant side cheek (A-E), palm (F-J) or calf (K-O) for all thermal grill outcomes. All graphs are represented as mean ± SEM. * $P < 0.05$, ** $P < 0.01$.

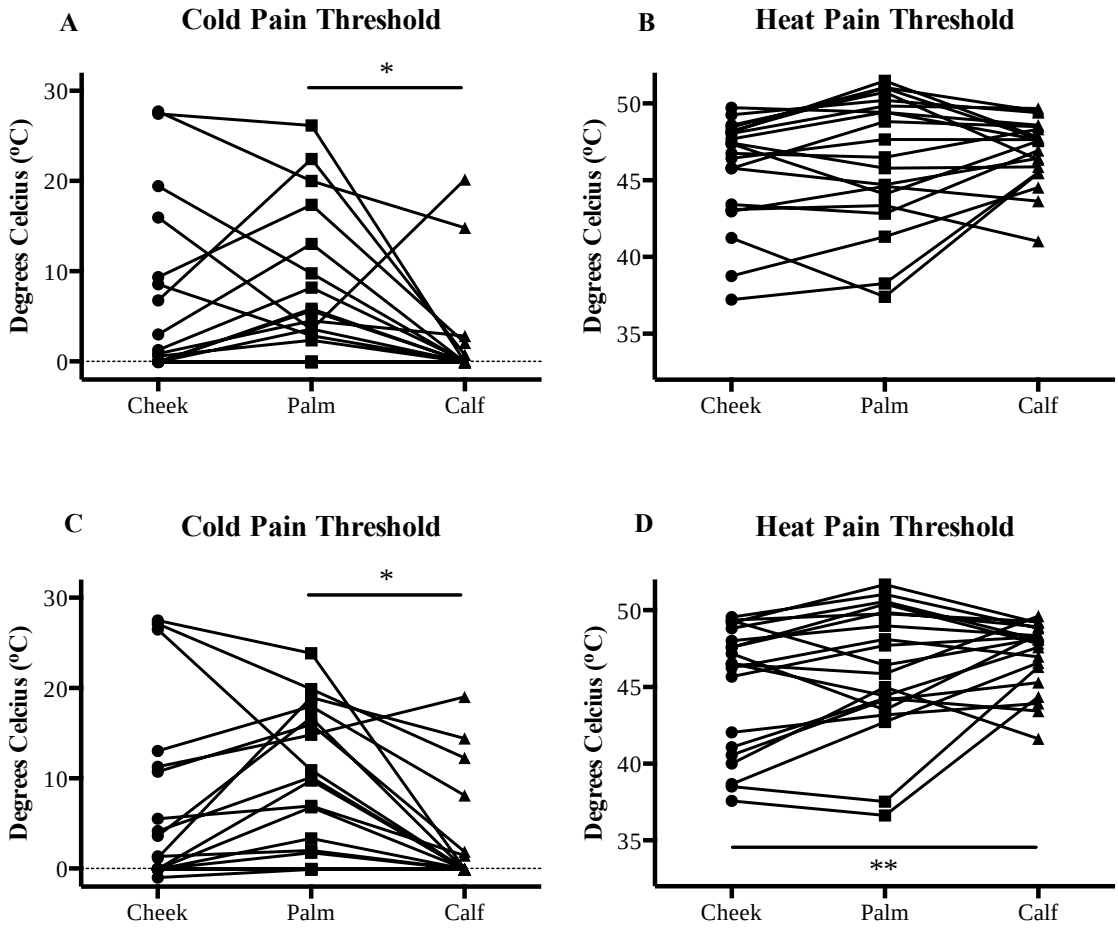


Figure 4.4. Effect of body location in pain-free participants: cold and heat pain thresholds.

Cold and heat pain thresholds at the cheek, palm and calf in pain-free volunteers on their affected/dominant (A, B) and unaffected/non-dominant side (C, D). Cold pain threshold were significantly reduced at the calf compared to the palm on both the affected/dominant ($p = 0.0099$)(A) and unaffected/non-dominant ($p = 0.02$)(C) side. Heat pain thresholds were significantly increased at the calf compared to the cheek on the unaffected/non-dominant side ($p = 0.011$)(D), whereas no significant difference between body locations was observed on the affected/dominant side ($p = 0.21$)(B). * $P < 0.05$, ** $P < 0.01$.

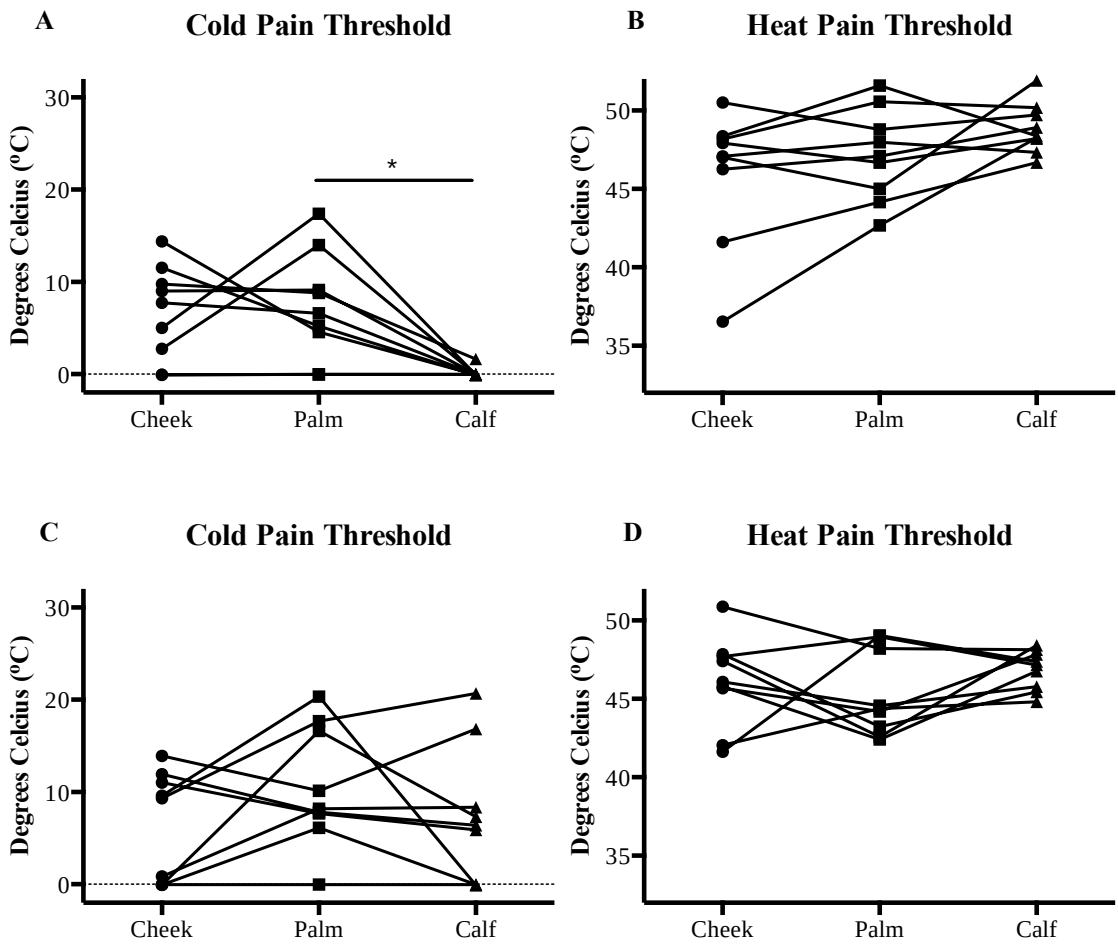


Figure 4.5. Effect of body location in patients with sciatica: cold and heat pain thresholds.

Cold and heat pain thresholds at the cheek, palm and calf in patients with sciatica on their affected/dominant (A, B) and unaffected/non-dominant side (C, D). Cold pain thresholds were significantly reduced at the calf compared to the palm on patients affected side ($p = 0.02$)(A), whereas no significant difference between body locations was observed on patients' unaffected side ($p = 0.23$)(C). Heat pain thresholds did not differ between patients' cheek, palm or calf on their affected ($p = 0.069$)(B) or unaffected side ($p = 0.35$)(D). * $P < 0.05$.

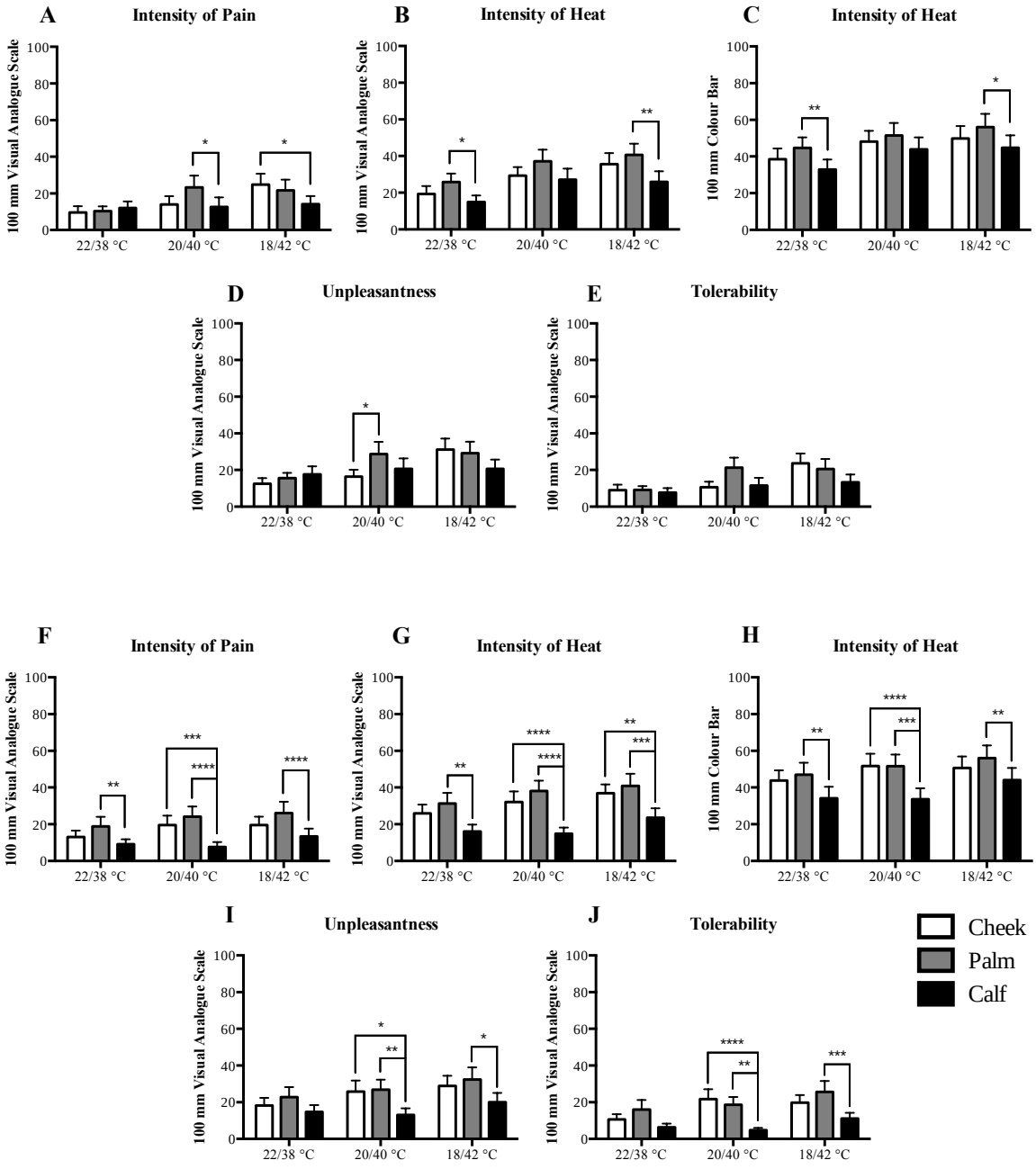


Figure 4.6. Effect of body location in pain-free participants: thermal grill illusion.

The response to the thermal grill illusion in pain-free participants on their affected/dominant (A-E) and unaffected/non-dominant (F-J) side cheek (white bars), palm (grey bars) and calf (black bars). Significant differences were observed across body locations, with responses to the thermal grill generally being the lowest on the calf compared to the palm and cheek (see Tables 4.3 and 4.4 for mean differences and 95% CI for differences on the affected/dominant and unaffected/non-dominant side respectively). Data represented as mean ± SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.

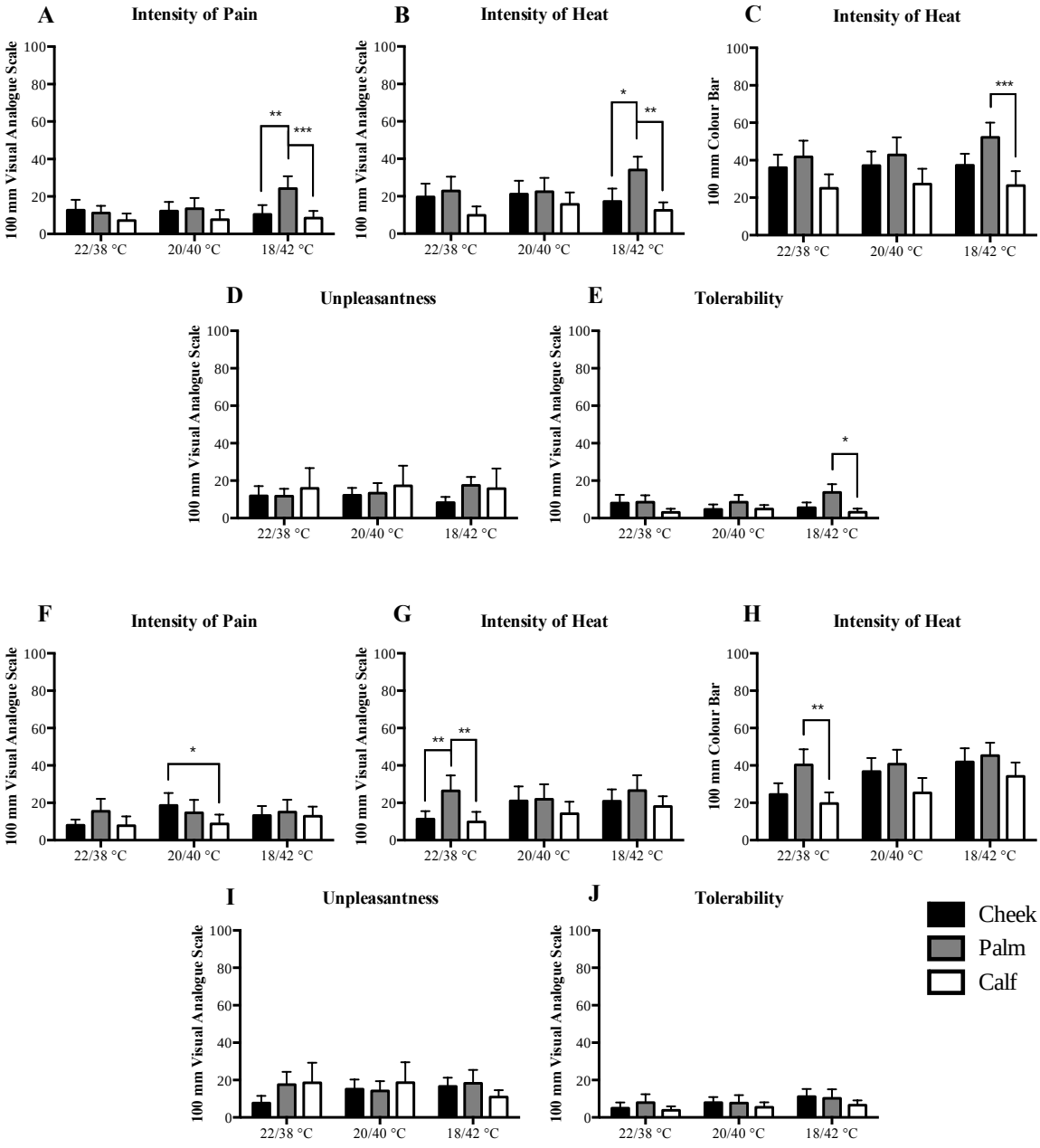


Figure 4.7. Effect of body location in patients with sciatica: thermal grill illusion.

The response to the thermal grill illusion in patients with scaitca on their affected/dominant (A-E) and unaffected/non-dominant (F-J) side cheek (white bars), palm (grey bars) and calf (black bars). Significant differences were observed across body locations, with responses to the thermal grill generally being the lowest on the calf compared to the palm and cheek (see Tables 4.5 and 4.6 for mean differences and 95% CI for differences on the affected/dominant and unaffected/non-dominant side respectively). Data represented as mean ± SEM. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

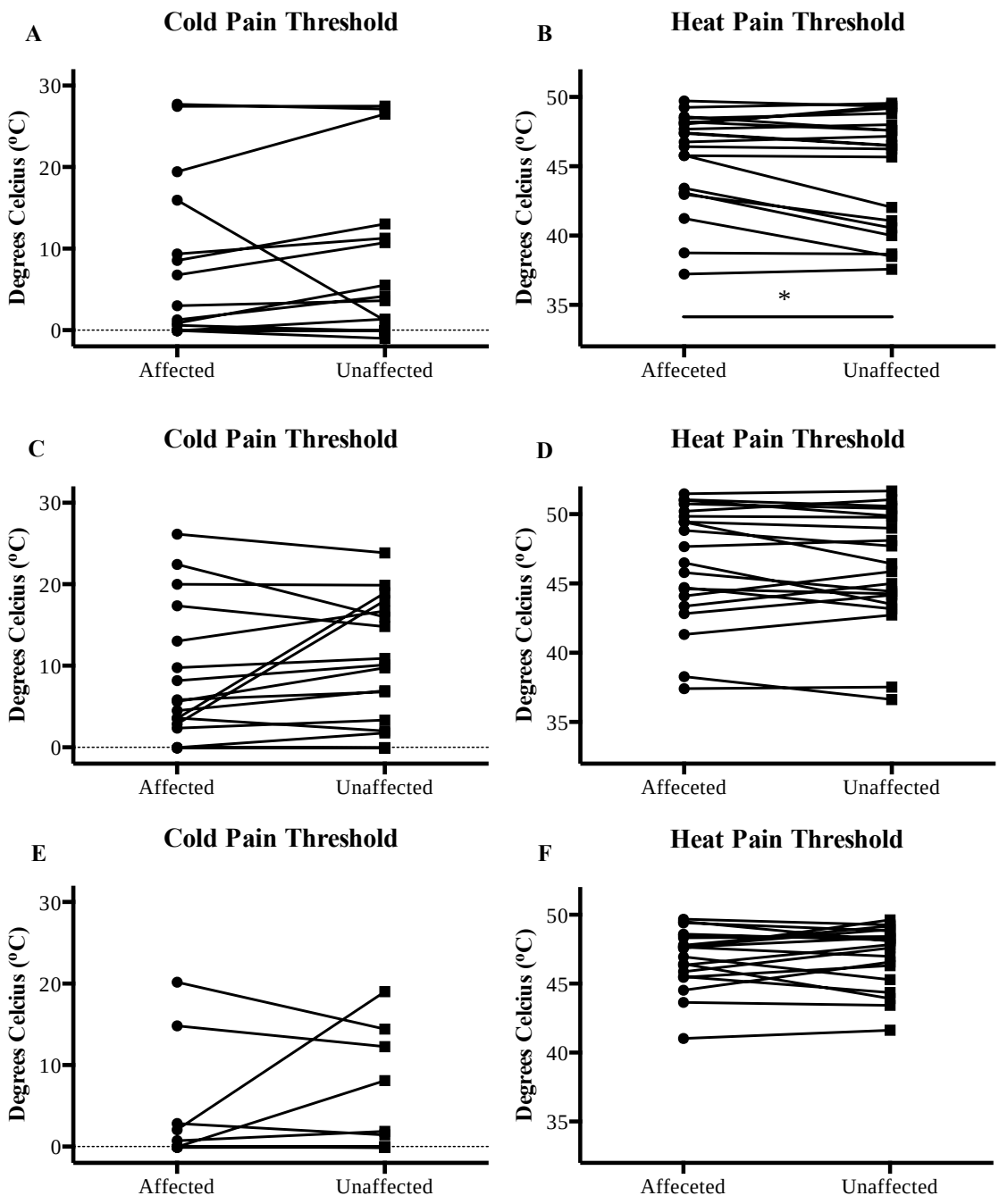


Figure 4.8. Effect of body side in pain-free participants: cold and heat pain thresholds.

Cold and heat pain thresholds at pain-free participants affected/dominant and unaffected/non-dominant side cheek (A, B), palm (C, D) and calf (E, F). Heat pain thresholds were significantly reduced at participants' unaffected/non-dominant cheek compared to their affected/dominant cheek ($p = 0.038$)(B). Cold pain thresholds did not differ between participants' affected/dominant and unaffected/non-dominant cheek (A). Additionally, cold and heat pain thresholds did not differ between participants' affected/dominant and unaffected/non-dominant palm and calf (C-F). * $P < 0.05$.

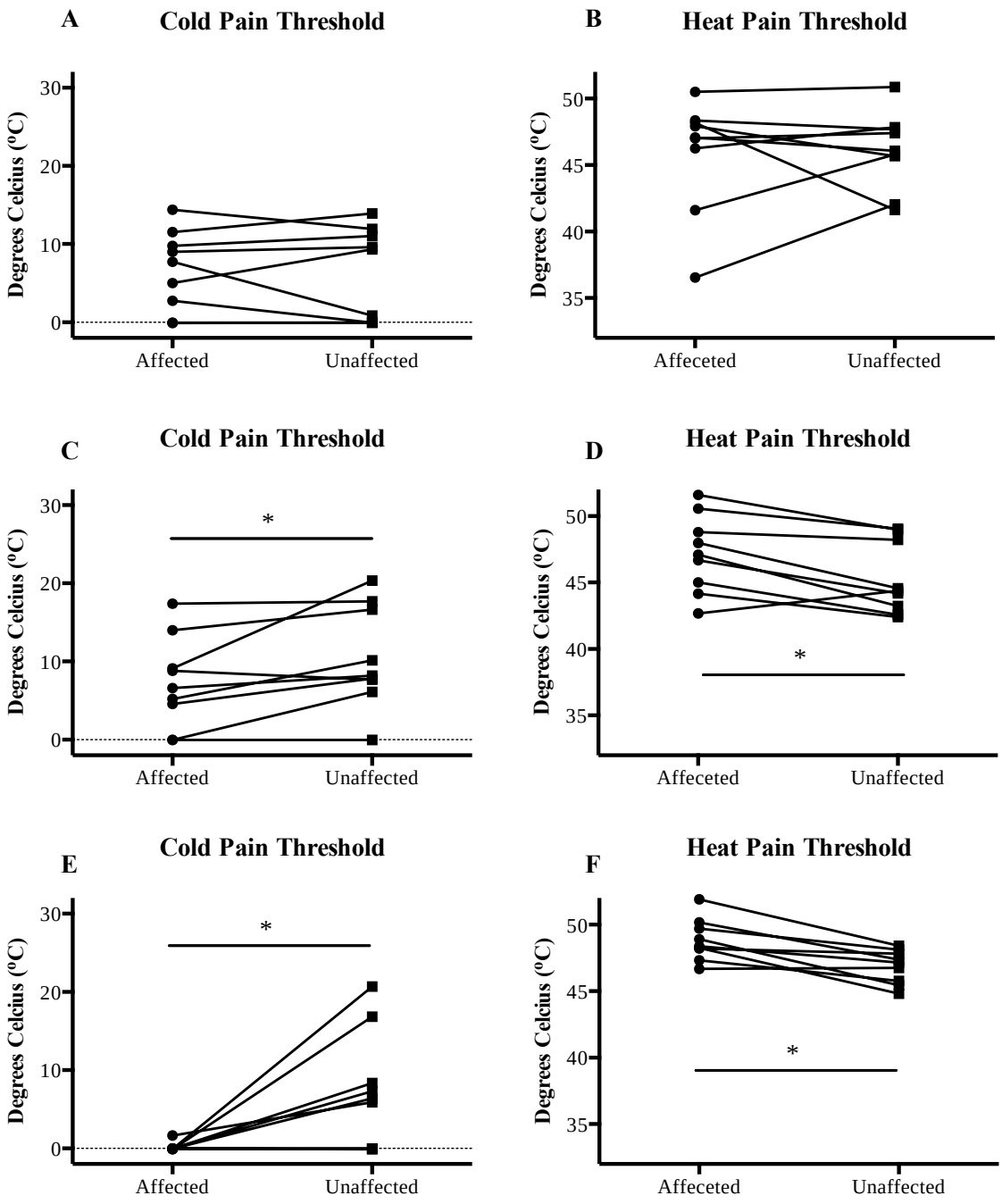
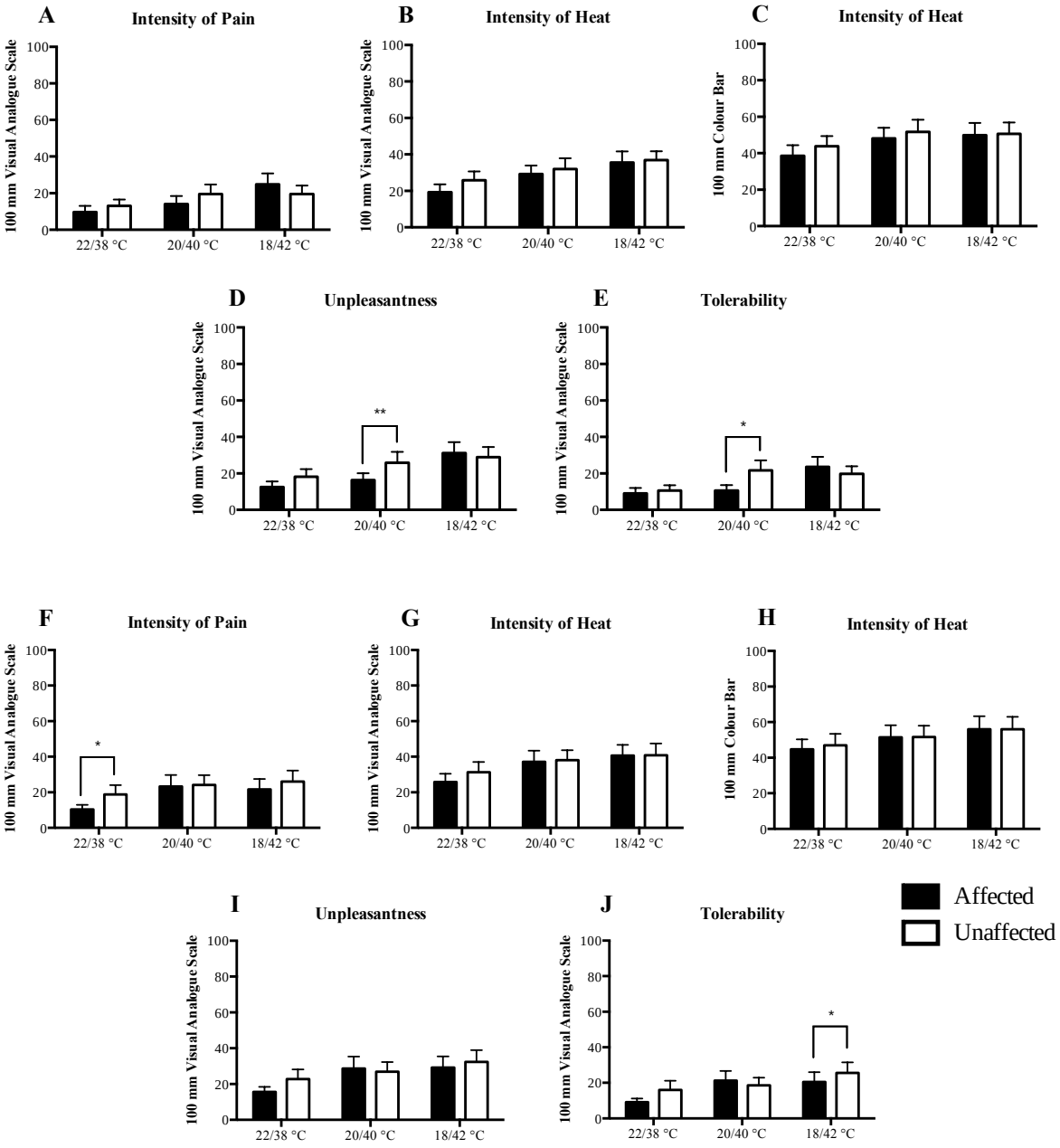


Figure 4.9. Effect of body side in patients with sciatica: cold and heat pain thresholds.

Cold and heat pain thresholds at patients with sciatica affected/dominant and unaffected/non-dominant side cheek (A, B), palm (C, D) and calf (E, F). Cold pain thresholds were significantly reduced and heat pain thresholds were significantly increased at patients' affected side palm and calf compared to their unaffected side palm ($p = 0.035$, C and $p = 0.0092$, D) and calf ($p = 0.039$, E and $p = 0.0025$, F) respectively. Cold and heat pain thresholds did not differ between patients' affected and unaffected side cheek (A, B). * $P < 0.05$.


A
Intensity of Pain
100 mm Visual Analogue Scale
B
Intensity of Heat
100 mm Visual Analogue Scale
C
Intensity of Heat
100 mm Colour Bar
D
Unpleasantness
100 mm Visual Analogue Scale
**
E
Tolerability
100 mm Visual Analogue Scale
*
F
Intensity of Pain
100 mm Visual Analogue Scale
*
G
Intensity of Heat
100 mm Visual Analogue Scale
H
Intensity of Heat
100 mm Colour Bar
I
Unpleasantness
100 mm Visual Analogue Scale
J
Tolerability
100 mm Visual Analogue Scale
*
22/38 °C
20/40 °C
18/42 °C
Affected
Unaffected

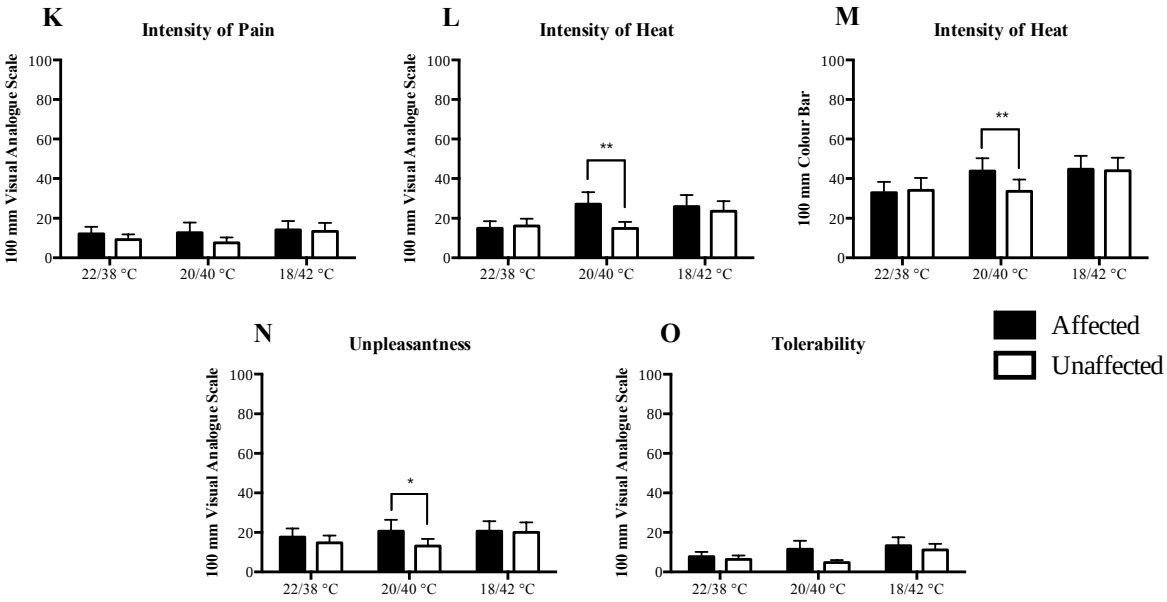
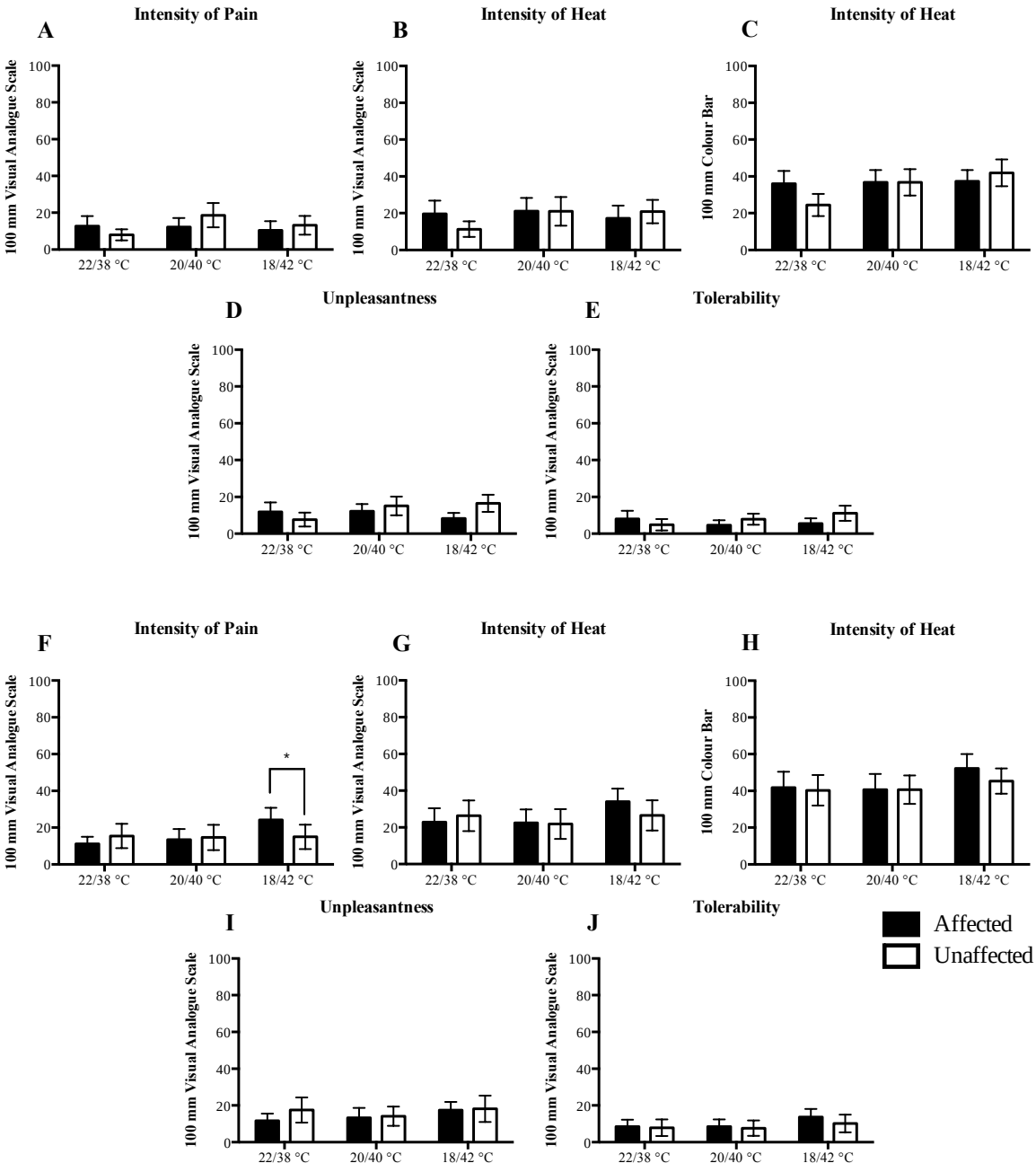


Figure 4.10. Effect of body side in pain-free participants: thermal grill illusion.

The response to the thermal grill illusion at the cheek (A-E), palm (F-J) and calf (K-O) on pain-free participants affected/dominant (black bars) and unaffected/non-dominant (white bars) side. On the cheek, significantly less unpleasantness (D) and tolerability (E) to the thermal grill illusion was observed on the affected/dominant side compared to the unaffected/non-dominant side. On the palm, significantly less pain (F) to the thermal grill illusion was observed on the affected/dominant side compared to the unaffected/non-dominant side. Whereas, on the calf, significantly more heat, heat (colour bar) and unpleasantness was observed on the affected/ dominant side compared to the unaffected/non-dominant side (see Table 4.7 for mean differences and 95% CI for differences). Data represented as mean ± SEM. * $P < 0.05$, ** $P < 0.01$.


A
Intensity of Pain
100 mm Visual Analogue Scale
22/38 °C
20/40 °C
18/42 °C
B
Intensity of Heat
100 mm Visual Analogue Scale
C
Intensity of Heat
100 mm Colour Bar
D
Unpleasantness
E
Tolerability
F
Intensity of Pain
*
G
Intensity of Heat
H
Intensity of Heat
I
Unpleasantness
J
Tolerability
Affected
Unaffected

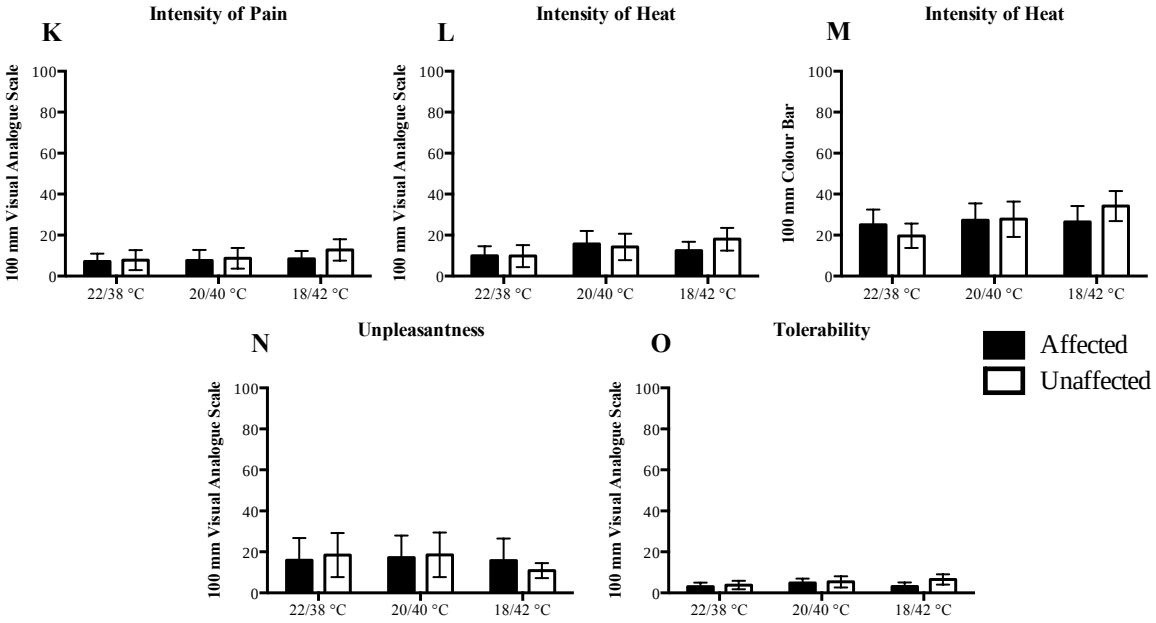


Figure 4.11. Effect of body side in patients with sciatica: thermal grill illusion.

The response to the thermal grill illusion at the cheek (A-E), palm (F-J) and calf (K-O) on patients affected/dominant (black bars) and unaffected/non-dominant (white bars) side. On the palm, significantly less pain (F) to the thermal grill illusion was observed on the unaffected/non-dominant side compared to the affected/dominant side at the 18/42 ºC thermal grill configuration (see Table 4.8 for mean differences and 95% CI for differences). No other differences between the affected/dominant and unaffected/non-dominant side were observed. Data represented as mean ± SEM. * $P < 0.05$.

Chapter 5. Thermal Grill Response and Ibudilast in Patients with Medication Overuse Headache

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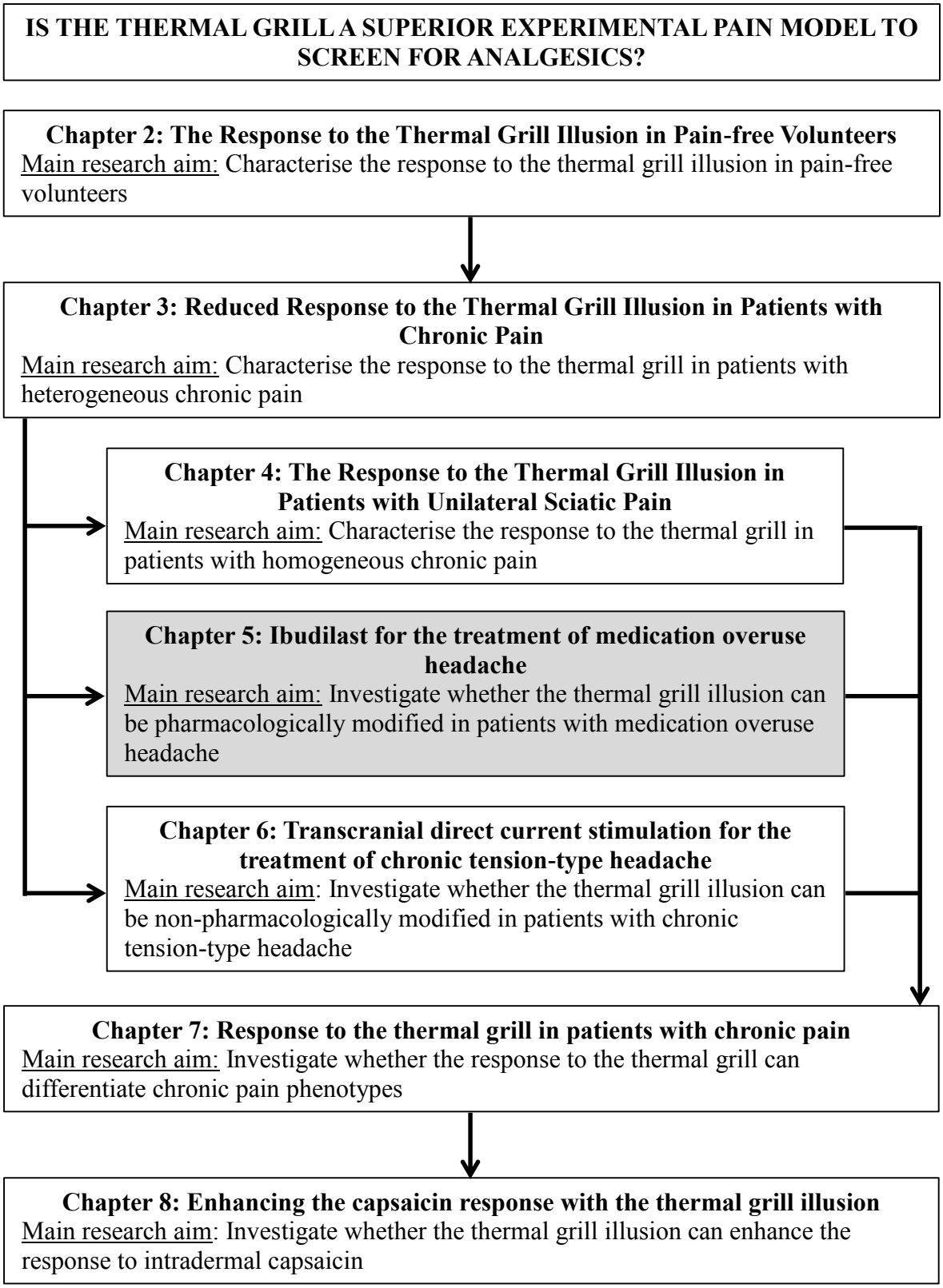
IS THE THERMAL GRILL A SUPERIOR EXPERIMENTAL PAIN MODEL TO SCREEN FOR ANALGESICS?
Chapter 2: The Response to the Thermal Grill Illusion in Pain-free Volunteers
Main research aim: Characterise the response to the thermal grill illusion in pain-free volunteers
Chapter 3: Reduced Response to the Thermal Grill Illusion in Patients with Chronic Pain
Main research aim: Characterise the response to the thermal grill in patients with heterogeneous chronic pain
Chapter 4: The Response to the Thermal Grill Illusion in Patients with Unilateral Sciatic Pain
Main research aim: Characterise the response to the thermal grill in patients with homogeneous chronic pain
Chapter 5: Ibudilast for the treatment of medication overuse headache
Main research aim: Investigate whether the thermal grill illusion can be pharmacologically modified in patients with medication overuse headache
Chapter 6: Transcranial direct current stimulation for the treatment of chronic tension-type headache
Main research aim: Investigate whether the thermal grill illusion can be non-pharmacologically modified in patients with chronic tension-type headache
Chapter 7: Response to the thermal grill in patients with chronic pain
Main research aim: Investigate whether the response to the thermal grill can differentiate chronic pain phenotypes
Chapter 8: Enhancing the capsaicin response with the thermal grill illusion
Main research aim: Investigate whether the thermal grill illusion can enhance the response to intradermal capsaicin

Introduction

Prior to this study commencement, I had demonstrated that increasing temperature differentials between the warm and cool temperature bars increased the response to the thermal grill illusion in both pain-free volunteers (chapter 2) and patients with heterogeneous chronic pain (chapter 3), that the response to the thermal grill illusion was tolerable on the cheek of pain-free participants (chapter 2), thus potentially feasible to investigate in patients with headache disorders, and that patients with heterogeneous chronic pain could tolerate the response to the thermal grill illusion when tested on the palm (chapter 3). I then had the opportunity to longitudinally (opposed to cross-sectionally as in chapter 4) investigate whether the response to the thermal grill could differentiate the response to a novel pharmacological treatment, as well as compare the test-retest reliability of both the response to the thermal grill illusion and thermal pain thresholds. Therefore, unlike my previous studies, as this was a placebo-controlled study, it allowed the opportunity to examine the stability of the thermal grill response over time.

In addition to investigating the response to the thermal grill illusion in patients with a chronic pain pathology that originated in the periphery (chapter 4), I was also interested in investigating the response to the thermal grill illusion in patients with a chronic pain condition that originated centrally and had no peripheral pathology, therefore I chose to investigate chronic headache. I chose to investigate the response to the thermal grill illusion in both patients whom suffered from medication over use headache (MOH) and chronic tension-type headache (CTTH) (see chapter 6), two conditions that are prevalent in society and that are both poorly treated. These two populations allowed me to compare patients who take chronic opioids for their pain, being the medication overuse headache patients, and patients who take simple analgesics for their pain, such as paracetamol and ibuprofen, being chronic tension-type headache patients (chapter 7).

To maximise patient recruitment and minimise resources, the MOH patients recruited for this study were part of an ongoing clinical trial conducted by Jacinta Johnson, a PhD candidate who is also within the Discipline of Pharmacology, School of Medical Sciences at the University of Adelaide. Although we both used the same patient population, our study objectives differed significantly. The primary objective of my component of this study, in line with the primary objective of this thesis, was to determine whether the thermal grill is a useful tool to screen for the efficacy of novel treatments for painful conditions, whereas the primary objective of the main study was to determine the efficacy of ibudilast in the treatment of MOH. For a complete overview of MOH, please see the recent review by Johnson and colleagues (2013).

MOH is a chronic disorder that arises from both migraine and tension-type headache, both of which are of central origin. The overuse of opioid analgesics appears to be strongly associated with the development of MOH (Bigal and Lipton, 2009; Johnson et al., 2013). MOH in patients consuming opioids is likely to share pathological features with opioid induced hyperalgesia (OIH), a phenomenon where opioids paradoxically increase pain sensitivity (Johnson et al., 2013).

Central sensitisation has been implicated in numerous chronic pain conditions and is thought to play a significant role in the pathogenesis of MOH (Johnson et al., 2013). In patients with MOH, increased pain related reflexes at both cephalic and extra-cephalic sites has been demonstrated, as well as decreased sensitisation after detoxification of overused medications, further implicating central sensitisation in the pathogenesis of MOH (Ayzenberg et al., 2006; Munksgaard et al., 2013).

Activation of spinal and trigeminal glial cells, the immunocompetent cells of the central nervous system, has been demonstrated in almost every clinically relevant animal model of enhanced pain state (Watkins et al., 2007; Wei et al., 2008; Johnson et al., 2013). Glial activation via toll-like receptor 4 (TLR-4), an innate pattern recognition receptor, plays a causal role in the initiation and maintenance of pathological pain (as cited by Johnson and colleagues (2013)). For a complete overview of the role of TLRs in chronic pain, please see the recent review by Nicotra and colleagues (2012). Johnson and colleagues (2013) discussed that the over consumption of codeine-containing analgesics on a background of repeated glial activation as a result of patients recurrent headaches, results in the development of MOH. Recent developments indicate chronic opioid administration may exacerbate pain in the long-term by non-specifically activating TLR-4 on glial cells (Johnson et al., 2013). For a detailed discussion regarding the role of TLR-4 in opioid-induced glial activation, see the review by Watkins and colleagues (2009). Activation of glial cells results in a pro-inflammatory state that facilitates pain, manifesting clinically as hyperalgesia, and has been implicated in the pathophysiology of OIH (Johnson et al., 2013). MOH as a result of opioid overuse is believed to be a manifestation of OIH and is likely to similarly be mediated by glial activation (Johnson et al., 2013). Johnson and colleagues (2013) hypothesise that MOH derives from a cumulative interaction between central sensitisation, due to repeated activation of nociceptive pathways by frequent headaches, and activation of glial cells by opioid analgesics, which further facilitates pain. Consequently, treatment strategies directed at attenuating glial activation, in particular TLR-4 activation, may be of benefit to patients with MOH.

To date the possible involvement of glial activation in the pathophysiology of MOH has not been investigated (Johnson et al., 2013); therefore no treatments targeting this mechanism have been trialled in this headache population. In animal studies, ibudilast, a non-selective glial cell inhibitor, has been demonstrated to decrease the glial production of inflammatory

cytokines and to increase the release of interleukin-10, an anti-inflammatory cytokine (Suzumura et al., 1999; Kawanokuchi et al., 2004; Mizuno et al., 2004). Hence, ibudilast was a suitable candidate drug to investigate.

One aim of this study was to determine if the presence of central hypersensitivity, as measured by the response to the thermal grill illusion and to thermal pain thresholds, could differentiate response to treatment with ibudilast in patients with MOH. It was hypothesised that treatment with ibudilast would reduce central sensitivity in patients with MOH, thus alter their response to the thermal grill illusion.

Another aim of this study was to investigate the baseline characteristics of the response to both the thermal grill illusion and thermal pain thresholds in patients with MOH and compare the response to both the thermal grill illusion and thermal pain thresholds between patients with MOH and pain-free volunteers (from chapter 4). It was hypothesised that responses to both the thermal grill illusion and thermal pain thresholds would differ between patients' cheek and palm, similar to previous finings in chapter 2 and 4. Additionally, it was hypothesised that responses to both the thermal grill illusion and thermal pain thresholds would differ compared to pain-free participants (from chapter 4), based on my findings in chapter 3. Although, differences in thermal pain thresholds were not observed between patients with chronic pain and pain-free participants in chapter 3 or 4, previous studies have demonstrated differences in thermal pain thresholds between patients with various types of headache (chronic migraine, episodic migraine, tension-type headache, cerviocogenic headache and unclassifiable headache) and pain-free participants (Langemark et al., 1989; Uthaikhup et al., 2009; Schwedt et al., 2011).

The final aim of this study was to longitudinally compare the test-retest reliability of both the response to the thermal grill illusion and thermal pain thresholds in the patients with MOH that were allocated to the placebo group. Previously, good test-retest reliability of thermal pain thresholds has been demonstrated when tested over 2 to 10 days (Sand et al., 2010; Geber et al., 2011; Wylde et al., 2011), therefore it was hypothesised that the response to both the thermal grill illusion and thermal pain thresholds in the placebo group would remain stable over time.

Materials and Methods

Thermal grill

As previously describes in chapter 2.

Ethics

Ethics approval was obtained from the Royal Adelaide Hospital (RAH) Investigational Drugs Subcommittee and Research Ethics Committee. Signed consent was obtained from each participant prior to enrolment into the study. Participants were financially compensated for their time and inconvenience.

Subjects

It was planned that 40 patients with medication overuse headache would participate in this study. Participants were recruited from the general public by advertisement. All participants were naïve to the thermal grill effect. 20 pain-free participants from chapter 4 were used as controls.

Inclusion / exclusion criteria

Key inclusion criteria

Medication overuse headache, defined by: regular use, for at least 3 months, of opioid-containing analgesics on ≥ 10 days per month; headache present on at least 15 days per month, for at least 2 months; headache developed or markedly worsened during medication overuse; and primary indication for analgesics is headache disorder.

Exclusion criteria

Key exclusion criteria were as follows: less than 18 years of age; receiving tramadol as their main opioid medication; taking triptans > 4 days per month; taking codeine for reasons other than headache (e.g. other pain conditions, cough, bowel motility); facial conditions that were likely to affect facial pain testing (e.g. excessive facial hair, facial skin disorders); severe psychiatric disorders; other chronic pain conditions that were likely to affect pain sensitivity testing (e.g. trigeminal neuralgia, arthritis); diabetic neuropathy; recent or current clinically significant active infection; known active inflammatory diseases, such as rheumatoid arthritis; history of cerebrovascular disorder; recent history of significant trauma (e.g. major surgery); recent history of drug or alcohol abuse; spinal cord injury; clinically significant findings on screening blood sample results; current malignancy; known hypersensitivity to ibudilast in Pinatos® formulation and renal or hepatic impairment, defined as baseline GFR (as calculated by the Cockcroft-Gault equation) of < 60 mL / min, LFTs (excluding bilirubin) > 3 times the upper limit of normal or bilirubin > 2 times the upper limit of normal. For females of childbearing potential the following exclusion criteria also applied: pregnancy; lack of adequate contraception (abstinence, double barrier method, intrauterine device, surgical sterilization (self or partner), hormonal contraceptive methods (oral, injected, or implanted) and breastfeeding.

Study overview

For the purposes of this PhD thesis, this double-blind, randomised, placebo-controlled, parallel-group design pilot study of ibudilast in the treatment of medication overuse headache was conducted over an 8 week period, with pharmacodynamic assessments (thermal grill and thermal pain threshold testing) being performed at baseline (week 0), week 2, week 4 and week 8 of ibudilast treatment.

Study day schedule

At baseline, week 2, week 4 and week 8, identical pharmacodynamic assessments were performed (see below). Additionally, at baseline only, patients were asked to rate the pain felt on average from their headache condition on a 100 mm visual analogue scale (VAS). On each study day, a breath alcohol test was performed and a negative result was required for continuance in the study.

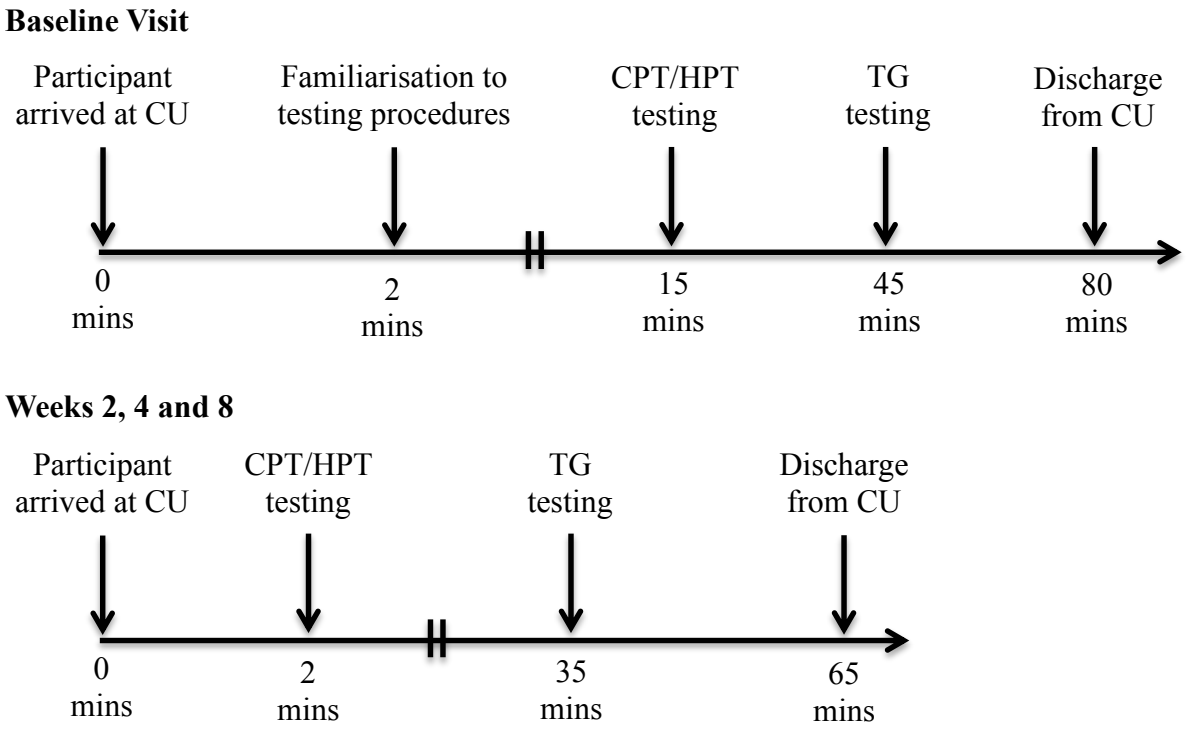

Figure 5.1. Schedule on Study Day at Baseline Visit and Weeks 2, 4 and 8.

Schedule on study day at baseline (top image) and weeks 2, 4 and 8 (bottom image). CU: clinical unit; CPT: cold pain threshold; HPT: heat pain threshold; TG: thermal grill.

Thermal threshold testing

Patients' individual cold pain and heat pain thresholds were determined using a PATHWAY device (model ATS, Medoc, Israel) via the Method of Limits on both their left and right palm and their left and right cheek as described in chapter 4.

Thermal grill testing

Patients were exposed to three interlaced cool and warm temperature combinations (22/38 °C, 20/40 °C and 18/42 °C) in randomised order on both their left and right palm and their left and right cheek, using the same testing method and assessment questions as previously described in chapter 4, thus a total of 12 tests were performed on each study day.

Statistical analysis

The D'Agostino and Pearson omnibus normality test was performed to test for normality of the data.

Age, duration of headache pain, hospital anxiety (HADS-A) and depression (HADS-D) scale and average pain from headache between the ibudilast and placebo group were compared using an unpaired t-test, therefore this data is represented as mean ± SEM. Due to the non-parametric nature of the data, morphine equivalent dose between the ibudilast and placebo group and age between pain-free participants (chapter 4) and patients with MOH was compared using the Kolmogorov-Smirnov test, whilst headache frequency between the ibudilast and placebo group was compared using the Mann-Whitney test, therefore this data is represented as median and IQR.

Cold pain thresholds, heat pain thresholds and the response to the thermal grill illusion between patients assigned to the ibudilast treatment group and patients assigned to the placebo group were compared using a second order polynomial (quadratic) equation. B0, B1 and B2 were all constrained. If significance was observed, the analysis was re-run without B0 constrained.

Comparing body side (right vs. left), the response to the thermal grill illusion across the right and left cheek and right and left palm was analysed using a 2-way repeated measures ANOVA with Bonferonni's post hoc to adjust for multiple comparisons. Therefore these data are represented as mean ± SEM. Due to the non-parametric nature of the data, cold pain thresholds between the right and left palm and both cold and heat pain thresholds between the right and left cheek were analysed using Wilcoxon matched pairs signed rank test. Heat pain thresholds between the right and left palm were analysed using a paired t-test.

Comparing body location (cheek vs. palm), the response to the thermal grill illusion across the right cheek and palm and left cheek and palm was analysed using a 2-way repeated measures ANOVA and Bonferroni's post hoc to adjust for multiple comparisons. Therefore, these data are represented as mean ± SEM. Due to the non-parametric nature of the data, cold pain thresholds between the right cheek and palm and left cheek and palm and heat pain thresholds between the left cheek and palm were analysed using Wilcoxon matched pairs signed rank test. Heat pain thresholds between the right cheek and palm were analysed using a paired t-test.

Correlations between cold and heat pain thresholds and the response to the thermal grill illusion, morphine equivalent dose, duration of pain, intensity of pain, anxiety (HADS-S) and depression (HADS-D) scores were analysed. Correlations between the response to the thermal grill illusion and morphine equivalent dose, duration of pain, intensity of pain, anxiety (HADS-A) and depression (HADS-D) scores were also analysed. Due to the non-parametric nature of the data, Spearman's correlation was used to analyse the data, unless otherwise specified. In order to account for multiple comparisons, a Bonferroni correction was performed as described in chapter 2. Similar to chapter 4, correlations across multiple body

locations were assessed in this study. Each body location was treated as a separate analysis; therefore Bonferroni's correction was only performed within one body location.

Comparing pain-free participants from chapter 4 and patients with medication overuse headache, cold pain thresholds on the left palm and heat pain thresholds on the left and right palm and left cheek were analysed using an unpaired t-test. Therefore these graphs are represented as mean ± SEM. Due to the non-parametric nature of the data, cold pain threshold on the right and left cheek and right palm and heat pain thresholds on the right cheek were analysed using the Kolmogorov-Smirnov test. Therefore these graphs are represented as median and IQR. Consequently, the appearance of the graphs displayed within this chapter and the appendix differ between the right and left side cheek for heat pain thresholds and right and left side palm for cold pain thresholds. Comparing pain-free participants and patients with medication overuse headache the response to the thermal grill illusion was analysed using a 2-way repeated measures ANOVA and Bonferroni's post hoc to adjust for multiple comparisons.

The repeatability of cold and heat pain thresholds was analysed using a 1-way repeated measures ANOVA and Tukey's post hoc to adjust for multiple comparisons for cold pain threshold on the right and left cheek and heat pain thresholds on the left cheek. Due to the non-parametric nature of the data, Freidman's test with Dunns post hoc to adjust for multiple comparisons was used for cold pain thresholds on the right and left palm and heat pain thresholds on the right cheek and right and left palm. The repeatability of the response to the thermal grill illusion was analysed using a 2-way repeated measures ANOVA and Tukey's post hoc to adjust for multiple comparisons.

A *P* value of less than 0.05 was required for statistical significance, unless otherwise stated.

Results

Subjects

33 (8M, 25F) patients with medication overuse headache completed the baseline testing session, of which 30 were right hand dominant (see Table 5.1 for patient demographics). Of these patients, 4 patients were randomised to treatment but withdrew from the study prior to completion. 1 patient was not randomised, hence did not begin treatment, due to a concurrent medical condition that developed since her screening visit. Therefore, 28 patients with medication overuse headache completed all 4 study visits and received 8 weeks of ibudilast or placebo treatment. Due to difficulties and delays in patient recruitment, the target population of 40 patients with medication overuse headache was not reached. Of the 28 patients, 16 (5M, 11F) received placebo and 12 (3M, 9F) received ibudilast. Comparing placebo and ibudilast treatment groups, no significant group differences were observed for age (mean difference: 0.1 years, 95% CI for difference: -8.2 to 8.3 years), daily oral morphine equivalent dose (median and IQR, placebo: 7.2 (3.7 to 17.2) mg/day; ibudilast: 10 (4.6 to 36) mg/day, $p = 0.7$), duration of headache pain (mean difference: 8.0 years, 95% CI for difference: -3.1 to 19.2 years), average pain from headache (mean difference: -1 mm, 95% CI for difference: -14 to 12 mm on a 100 mm visual analogue scale), headache frequency (median and IQR, placebo: 22.5 (20 to 30) days per month; ibudilast: 28 (20 to 30) days per month, $p = 0.57$); Hospital Anxiety and Depression Scale anxiety score (HADS-A) (mean difference: 3.0, 95% CI for difference: -0.6 to 6.5) and HADS depression score (HADS-D) (mean difference: 3.0, 95% CI for difference: -0.1 to 6.1) at baseline. Comparing *pain-free* and *MOH* participants, no significant differences were observed in age (median and IQR, *pain-free*: 42 (25.5 to 61) years; *MOH*: 46 (36 to 53) years, $p = 0.67$).

Baseline Characteristics of Cold and Heat Pain Thresholds and the Response to the Thermal Grill of all Patients

Body side

Comparing body side (right vs. left), no significant differences in response to the thermal grill were observed for all thermal grill outcomes (see Table 5.2 for *P* values and Figure 5.3A-E). In response to cold and heat pain thresholds, patients' cold pain thresholds were significantly lower on their right palm compared to their left palm (median difference: -1.1 ^{o}C, p = 0.0075) (see Figure 5.2C). However, no significant differences were observed between patients' right and left palm for heat pain thresholds, or between patients' right and left cheek for both cold and heat pain thresholds (see Figure 5.2A-B, D). 32 participants were included when comparing the response to the thermal grill between the right and left cheek and palm and when comparing thermal pain thresholds at the right and left palm.

Body location

Comparing body location (cheek vs. palm), significant differences in response to the thermal grill were observed for all thermal grill outcomes when comparing the left cheek and left palm (see Figure 5.5F-J), and for the outcomes "intensity of pain", "intensity of heat", "intensity of heat colour" and "unpleasantness" when comparing the right cheek and right palm (see Figure 5.5A-E) (see Table 5.3 for *P* values). On both the right and left side, the response to the thermal grill was lowest on the cheek compared to the palm. Patients' demonstrated significantly lower heat pain threshold on their right cheek compared to palm (see Figure 5.4B). However, no significant differences between patients' right cheek and palm were observed for cold pain threshold or between patients' left cheek and palm for cold and heat pain thresholds (see Figure 5.4A, C-D). 31 participants were included when comparing the response to the thermal grill illusion on the right side, whereas 32 participants were included for all other analyses.

Correlations

Cold and heat pain thresholds

Significant correlations were observed between patients' cold and heat pain thresholds at all body locations (right cheek[1]: r = -0.73, p = 0.000001; left cheek[1]: r = -0.66, p = 0.0003; right palm[1]: r = -0.65, p = 0.00005; left palm[2]: r = -0.64, p = 0.0008), such that the less sensitive patients were to cold pain, the less sensitive they also were to heat pain. 32 participants were included for these analyses on the palm.

Thermal pain thresholds and thermal grill illusion

Even once adjusting for multiple comparisons, cold and heat pain thresholds correlated with patients' response to the thermal grill illusion for most thermal grill outcomes at at least one thermal grill configuration, such that patients' with increased cold pain thresholds and decreased heat pain thresholds had the greatest response to the thermal grill illusion (see Table 5.4). Therefore, the more sensitive a patient was to cold and heat, the more sensitive they were to the thermal grill illusion as well. Consequently, the correlation coefficients (*R*) of cold pain thresholds and the response to the thermal grill are positive values, whereas, the correlation coefficients of heat pain thresholds and the response to the thermal grill are negative values. 32 participants were included in these analyses.

1 Analysed with Spearman's correlation

2 Analysed with Pearson's correlation

Morphine equivalent dose and thermal pain thresholds

Morphine equivalent dose did not correlate with patients' cold and heat pain thresholds at any body locations (see Table 11.5.1 in appendix). 32 participants were included in these analyses on the palm.

Morphine equivalence dose and thermal grill illusion

Morphine equivalent dose did not correlate with patients' response to the thermal grill illusion for all outcomes at any body locations (see Table 11.5.2 in appendix). 32 participants were included in these analyses on the right and left cheek and right palm.

Intensity of pain and thermal pain thresholds

Intensity of pain experienced from patients' headache on study day 1 (baseline visit) did not correlate with patients' cold and heat pain thresholds at any body locations (see Table 11.5.3 in appendix). 32 participants were included in these analyses on the palm.

Intensity of pain and thermal grill illusion

Intensity of pain did not correlate with patients' response to the thermal grill illusion for all outcomes at any body locations (see Table 11.5.4 in appendix). 32 participants were included in these analyses on the right and left cheek and right palm.

Duration of pain and thermal pain thresholds

Duration of headache pain did not correlate with patients' cold and heat pain thresholds at any body locations (see Table 11.5.5 in appendix). 32 participants were included in these analyses on the palm.

Duration of pain and thermal grill illusion

Duration of headache pain correlated did not correlate with patients' response to the thermal grill illusion for all thermal grill outcomes at any body locations (see Table 11.5.6 in appendix). 32 participants were included in these analyses on the right and left cheek and right palm.

Anxiety (HADS-A) and thermal pain thresholds

Anxiety scores generally did not correlate with patients' cold and heat pain thresholds at any body locations (see Table 11.5.7 in appendix). 32 participants were included in these analyses on the palm.

Anxiety (HADS-A) and thermal grill illusion

Anxiety scores generally did not correlate with patients' response to the thermal grill illusion for all thermal grill outcomes at any body locations (see Table 11.5.8 in appendix). 32 participants were included in these analyses on the right and left cheek and right palm.

Depression (HADS-D) and thermal pain thresholds

Depressive scores did not correlate with patients' cold and heat pain thresholds at any body locations (see Table 11.5.9 in appendix). 32 participants were included in these analyses on the palm.

Depression (HADS-D) and thermal grill illusion

Depressive scores generally did not correlate with patients' response to the thermal grill illusion for all thermal grill outcomes at any body locations (see Table 11.5.10 in appendix). 32 participants were included in these analyses on the right and left cheek and right palm.

Baseline Characteristics of Cold and Heat Pain Thresholds and the Response to the Thermal Grill: pain-free participants vs. patients with medication overuse headache

Cold and heat pain thresholds

Cold pain thresholds differed significantly between patients with medication overuse headache and pain-free participants at the right cheek (see Figure 5.6A), with patients displaying increased sensitivity. Although not significant, cold pain thresholds also appeared to differ between patients with medication overuse headache and pain-free participants at the left cheek (see Figure 11.5.1A in appendix), whereas no difference was observed at both the right and left palm (see figures 5.8C and 11.5.1C in appendix respectively). Heat pain threshold did not differ between patients with medication overuse headache and pain-free participants at all body locations (see Figures 5.6B, D and 11.5.1B, D in appendix respectively). 32 patients with MOH were included in these analyses on the palm.

Thermal grill illusion

No significant differences were observed for all thermal grill outcomes, at all body locations between patients with medication overuse headache and pain-free participants (see Figures 5.7 and 11.5.2 in appendix). 32 patients with MOH were included in these analyses on the right and left cheek and right palm

Repeatability of Cold and Heat Pain Thresholds and the Response to the Thermal Grill over 8 Weeks in Patients Assigned to the Placebo Group

Cold and heat pain thresholds

Patients' cold pain thresholds were significantly increased at week 4 compared to baseline on patients' right palm (mean difference: 5 ^{o}C, 95% CI for difference: 0.6 ^{o}C to 9.3 ^{o}C)(see Figure 5.8C). At all other body locations, patients' cold pain thresholds did not differ across 8 weeks of placebo treatment, nor did patients' heat pain thresholds differ across 8 weeks of placebo treatment (see Figures 5.8A-B, D and 11.5.3 in appendix). 14 participants were included in these analyses on the right and left cheek and 13 participants on the right and left palm.

Thermal grill illusion

The response to the thermal grill illusion differed significantly across the 8 weeks of placebo treatment on both the right cheek and palm (see Figure 5.9C-E, G-H, J) and left cheek and palm (see Figure 11.5.4A-C, E, J in appendix). The response to the thermal grill generally decreased over time, suggesting habituation to the illusion; however, in some instances, the response to the thermal grill increased over time (see Figures 5.9D-E and 11.5.4J). 15 participants were included in these analyses on the right and left cheek and left palm and 14 participants on the right palm. On the right palm, 13 participants were included for the outcome "intensity of heat", whilst 14 participants were included for the outcome "intensity of heat (colour bar)" on the left palm.

Effect of Ibudilast

Cold and heat pain thresholds

A non-linear regression comparing both cold and heat pain thresholds over 8 weeks of active (ibudilast) or placebo treatment revealed no significant differences between the effect time curves at all tested body locations (see Figure 5.10 for right cheek and palm and Figure 11.5.5 in appendix for left cheek and palm). 15 participants assigned to the placebo group were included in these analyses on the palm.

Thermal grill illusion

A non-linear regression comparing responses to the thermal grill over 8 weeks of active (ibudilast) or placebo treatment revealed significant differences between the effect time curves for some thermal grill outcomes. In particular the "intensity of heat", as assessed on our novel colour bar, was significantly different for all thermal grill configurations at all body locations (see Figure 5.11 for right cheek and palm at the 20/40 ^{o}C thermal grill configuration and Figures 11.5.6 to 10.5.9 in appendix for all other body locations at all thermal grill configurations). However, there appeared to be a fundamental difference in response to the thermal grill between the ibudilast and placebo group at baseline, thus the analysis was re-run for all significant values with the B0 constraint removed from the equation. Once B0 was no longer constrained, no significant difference between patients' in the ibudilast and placebo group was observed, demonstrating that B1 and B2 were the same for each data set; thus treatment with ibudilast did not alter the response to the thermal grill illusion (see Table 5.6 for all *P* values). 11 participants assigned to the ibudilast group were included in these analyses on the right cheek and 15 participants assigned to the placebo group were included in these analyses on the right palm.

Discussion

I report the first study investigating the response to the thermal grill illusion longitudinally in patients with MOH. These patients were part of an ongoing clinical trial conducted by Jacinta Johnson, titled "Ibudilast in the Treatment of Medication Overuse Headache: a double-blind, randomised, placebo-controlled pilot study" (Royal Adelaide Hospital Research Ethics Committed Protocol Number: 110324C).

One aim of this study was to determine whether central hypersensitivity, as measured by the response to the thermal grill illusion and to thermal pain thresholds, could differentiate response to pharmacological treatment in patients with chronic pain. Patients with MOH received ibudilast, a non-selective glial inhibitor, or placebo over an 8 week period. It was hypothesised that treatment with ibudilast would reduce central sensitivity in patients with MOH, thus alter their response to the thermal grill illusion. Compared to placebo, treatment with ibudilast did not alter patients' response to the thermal grill illusion. Similarly, patients' cold and heat pain thresholds were not altered either, therefore a conclusion as to whether the thermal grill can detect the efficacy of analgesics that cannot be detected by thermal quantitative sensory testing cannot be made. No significant differences between the ibudilast and placebo groups were observed at baseline for age, morphine equivalence dose, duration of pain, headache frequency, average pain, HADS-A or HADS-D scores. An explanation of why ibudilast was unsuccessful in altering patients' response to the thermal grill illusion or whether ibudilast was effective in reducing the symptoms of MOH is beyond the scope of this PhD thesis, thereby a conclusion as to whether the thermal grill can differentiate response to pharmacological treatment in patients with chronic pain cannot be made and consequently is a limitation of this thesis. From herein, I will discuss the baseline characteristic responses of MOH patients to the thermal grill illusion and thermal pain thresholds compare these to

previous findings in pain-free volunteers (chapter 4), as well as discuss the repeatability of the thermal grill illusion and thermal pain thresholds in patients assigned to the placebo group.

Another aim of this study was to investigate the baseline characteristics of the response to the thermal grill illusion in patients with MOH. Consistent with my previous findings in pain-free volunteers (chapters 2 and 4) and patients' with unilateral sciatica (chapter 4), body side (right vs. left) did not affect the response to the thermal grill illusion, demonstrating no lateralisation to the thermal grill illusion. Others have also reported no lateralisation to the thermal grill illusion, in particular between the right and left palm and forearm (Boettger et al., 2011; Boettger et al., 2012; Averbeck et al., 2013; Boettger et al., 2013). Unlike responses to the thermal grill illusion, patients' cold pain thresholds were significantly reduced on patients' right palm compared to their left palm, which is likely to reflect hand dominance, as nearly all patients (30 out of 33) were right hand dominant. However, no significant differences between patients' right and left palm were observed for heat pain thresholds or between patients' right and left cheek for cold and heat pain thresholds.

Comparing body location (palm vs. cheek), the response to the thermal grill was lowest on the cheek compared to the palm on both the right and left side. Similarly, in chapter 2 pain-free participants reported significantly less "pain", "heat" and "unpleasantness" to the thermal grill illusion on the cheek compared to the palm, whilst in chapter 4, both pain-free and sciatica participants response to the thermal grill was generally intermediate compared to the palm and calf. Others have also reported body location differences in response to thermal grill (see section 1.5.5.6 in chapter 1). Differences in heat pain thresholds were also observed between the right cheek and the palm. Unlike responses to the thermal grill, patients' displayed reduced heat pain thresholds on their right cheek compared to their palm, demonstrating a

heightened sensitivity on patients' cheek. However, no significant differences between patients' right cheek and palm were observed for cold pain threshold or between patients' left cheek and palm for cold and heat pain thresholds.

In this study, even once adjusting for multiple comparisons, significant correlations were demonstrated between patients' cold and heat pain thresholds and their response to the thermal grill illusion for most thermal grill outcomes at at least one thermal grill configuration; such that the more sensitive a patient was to cold and heat pain, the more sensitive they also were to the thermal grill illusion. As discussed in chapter 4, the correlation analysis and Bonferroni correction for multiple comparisons used were robust, thus more sophisticated statistical analyses should be performed in future studies, in particular when multiple comparisons and repeated measures are being assessed. Others have also reported correlations between cold (Brunello, 2010; Kostka, 2011; Lindstedt et al., 2011b; Averbeck et al., 2013) and heat (Lindstedt et al., 2011b) pain thresholds and the response to the thermal grill illusion. The *r* values obtained in this study were similar to those obtained in chapter 4 as well as the abovementioned studies. The observed reduced heat pain thresholds on patients' right cheek, compared to their right palm, are in disagreement with both this study and the study by Lindstedt and colleagues (2011b), as patients' reduced thermal grill response on the cheek should also be reflected by increased heat pain thresholds. This finding probably reflects the different mechanistic processing of heat pain thresholds and the thermal grill illusion. However, comparing thermal thresholds alone, others have demonstrated heightened thermal pain sensitivity on the cheek compared to the palm (and hand) in both pain-free volunteers (Ladda et al., 2006; Rolke et al., 2006a; Sand et al., 2010) and patients with various types of headache (chronic tension-type headache, cluster headache) (Langemark et al., 1989; Ladda et al., 2006), which is consistent with the data in this study.

Previously, Kern and colleagues (2008b) demonstrated that morphine reduced the pain and unpleasantness associated with the thermal grill illusion in pain-free volunteers, with morphine's effect on pain intensity being directly correlated to its effects on cold pain thresholds and cold pain intensity. It may then be expected that morphine equivalent dose should correlate with both thermal pain thresholds and thermal grill outcomes, however no significant correlations were observed in this study, which may be due to opioid tolerance and / or possible opioid-induced hyperalgesia. Additionally, neither intensity of pain, duration of pain, or patients' anxiety and depressive scores correlated with patients' cold and heat pain thresholds or thermal grill outcomes.

Additionally, I wished to compare the response to the thermal grill illusion and thermal pain thresholds between patients with MOH and pain-free volunteers (from chapter 4). Similar to my findings in patients with unilateral sciatica, no significant difference was observed in response to the thermal grill between patients with medication overuse headache and pain-free participants at all body locations. Cold pain thresholds differed significantly between patients with medication overuse headache and pain-free participants at the right cheek, and although not significant appeared to also differ on the left cheek, with patients with medication overuse headache displaying increased cold pain thresholds, thus an increased sensitivity. Whereas, heat pain thresholds at the right and left cheek and both cold and heat pain threshold at the right and left and palm did not differ between patients with medication overuse headache and pain-free participants. These differences in cold pain thresholds between pain-free participants and patients with medication overuse headache at the cheek and not the palm may be due to heightened sensitivity in patients painfully afflicted region, being the trigeminal region.

The final aim of this study was to longitudinally compare the test-retest reliability of both the response to the thermal grill illusion and thermal pain thresholds in the MOH patients that were allocated to the placebo group. Previously the repeatability of the thermal grill illusion had not been investigated. In this study, the response to the thermal grill tended to vary from week to week, indicating poor reliability of the thermal grill illusion over time, thus questioning the utility of the thermal grill illusion in longitudinal studies. Unlike hypothesised, the response to the thermal grill generally decreased over time, suggesting habituation to the illusion; however, in some instances the response to the thermal grill increased over time. Increased responses to the thermal grill illusion over time were usually observed between week 4 and week 8 testing sessions, suggesting that patients' may have 'forgotten' what the illusion felt like, thus an element of 'surprise' may have been experienced. Recently, Boettger and colleagues (2011) measured the response to the thermal grill illusion twice in one day and claimed a significant correlation between the first and second measurement without providing evidence to support this claim; significant re-test correlations were also observed for cold and heat pain thresholds. In support of this studies findings, pilot experiments reported by Li (2009, unpublished) demonstrated that participants could report both painful and non-painful sensations to the same thermal grill stimulus, demonstrating poor repeatability of the thermal grill illusion. Psychological factors such as attention and anticipation to pain were suggested as factors that may have influenced the response to the thermal grill illusion (Li, 2009), thus attention and anticipation to pain may explain the general decline in response to the thermal grill illusion observed over time. For example, perhaps patients with medication overuse headache were less attentive during subsequent study day visits and/ or had a reduced anticipation to the experience of pain. However, these factors were not investigated in this study, nor were these objectives of this study, therefore the abovementioned hypotheses are only speculative, however may warrant further investigation. Unlike the response to the thermal grill illusion, both cold and heat pain

thresholds generally did not differ across the 8 weeks of testing at all body locations, demonstrating good reliability of thermal pain threshold detection using the method of limits over time. Good test-rest reliability of thermal pain thresholds has previously been demonstrated in pain-free volunteers (Yarnitsky et al., 1996; Wasner and Brock, 2008; Agostinho et al., 2009; Heldestad et al., 2010; Pigg et al., 2010; Sand et al., 2010) and patients with chronic pain (Agostinho et al., 2009; Geber et al., 2011; Wylde et al., 2011). Unlike thermal pain threshold testing, the perception of the thermal grill illusion is a top-down process that may be more amenable to variability in a persons state compared to thermal pain threshold testing, which is more dependent on spinal reflex mechanisms.

Differences in collection methods may also account for this difference between responses to the thermal grill illusion and thermal pain thresholds over time. Assessment of the thermal grill illusion involves patients' filling in subjective rating scales, including ratings of pain and unpleasantness. Such rating scales may cause patients' to expect a painful experience following the stimulus and perhaps a less painful experience to the stimulus following treatment (i.e. perceived treatment group allocation). These types of expectations are less likely to influence patients' response to thermal pain thresholds, as patients' are asked to halt the stimulus when the warm or cool temperature starts to 'just become painful'; additionally, patients' can neither see the temperature of the device, nor assess how long the device has been in use for. Therefore, perhaps patient's perceived treatment group allocation influenced their response to the thermal grill illusion. However, similar to the psychological factors discussed above, the influence of perceived treatment group was not investigated in this study, nor was this an objective of this study, therefore the abovementioned hypothesis is only speculative, although may warrant further investigation. Consequently, additional testing is required to determine the repeatability of the thermal grill illusion in pain-free volunteers and patients with chronic pain to exclude any potential confounding effects MOH patients'

assigned to the placebo group may have had and to take into consideration participants attention and anticipation to pain.

In conclusion, both the response to the thermal grill illusion and cold and heat pain thresholds were unaltered following 8 weeks of ibudilast treatment compared to the placebo treatment group, therefore a conclusion as to whether the thermal grill can detect the efficacy of analgesics that cannot be detected by thermal quantitative sensory testing cannot be made. Furthermore, the test-retest reliability of the thermal grill appeared to be poor compared to thermal pain threshold testing, thus questioning the utility of the thermal grill illusion in longitudinal studies. Additionally, the response to the thermal grill illusion did not differ between patients with medication overuse headache and pain-free participants, therefore the thermal grill is unlikely to be a suitable tool to investigate pain and temperature dysfunction in patients with MOH.

Tables

Table 5.1. Patient Demographics

Participant Number	Gender	Age	Avg. Pain Score (Visual Analogue Scale, 0-100)	Duration of Pain (years)	Opioid Type	Morphine Equivalent Dose (mg/day)	Concomitant analgesics / adjuncts
1	M	64	73	19	Codeine	16	Amitriptyline, rizatriptan, paracetamol
2*	F	29	70	11	Codeine	6	Paracetamol, ibuprofen, sertraline (depression)
3	F	49	42	37	Codeine	6	Paracetamol, ibuprofen, doxylamine
4	F	46	80	32	Codeine	4	Sumitriptan, rizatriptan, aspirin, paracetamol, doxylamine, fluoxetine (depression)
5	M	53	53	10	Oxycodone	199	Topiramate, duloxetine, amitriptyline
6*	F	53	29	34	Codeine	5	Paracetamol, doxylamine, escitalopram (depression),
7	F	40	49	20	Codeine	7	Paracetamol, doxylamine, diazepam, sertraline (depression)
8	F	29	55	5	Codeine	1	Paracetamol, ibuprofen
9	F	51	58	38	Codeine	6	Paracetamol, ibuprofen, aspirin

Participant Number	Gender	Age	Avg. Pain Score (Visual Analogue Scale, 0-100)	Duration of Pain (years)	Opioid Type	Morphine Equivalent Dose (mg/day)	Concomitant analgesics / adjuncts
10*	F	27	68	7	Codeine	7	Ibuprofen, aspirin, sumitriptan, paracetamol
11	M	54	52	4	Codeine	9	Paracetamol, ibuprofen, diazepam
12	F	23	57	10	Codeine	2	Paracetamol, ibuprofen, amitriptyline
13	F	36	63	23	Codeine	14	Paracetamol, ibuprofen, amitriptyline, alprazolam (calm nerves/ panic attacks)
14	F	59	78	10	Codeine	23	Sumitriptan, paracetamol, fluoxetine (depression), alprazolam (anxiety), Temazepam (insomnia)
15*	F	57	54	28	Codeine	5	Topiramate, paracetamol, doxylamine, pregabalin, diazepam (muscle spasms, tinnitus/vertigo)
16	F	47	44	29	Codeine	3	Sumitriptan, paracetamol, aspirin
17	F	28	32	23	Codeine	2	Paracetamol, ibuprofen, doxylamine
18	M	52	55	18	Morphine	20	Paracetamol, rizatriptan, ibuprofen, carbamazepine, pizotifen, doxepine, temazepam (insomnia)

Participant Number	Gender	Age	Avg. Pain Score (Visual Analogue Scale, 0-100)	Duration of Pain (years)	Opioid Type	Morphine Equivalent Dose (mg/day)	Concomitant analgesics / adjuncts
19	M	37	28	20	Oxycodone	15	Propranolol, escitalopram (depression)
20	F	58	71	55	Codeine, oxycodone	6	Gabapentin, paracetamol, doxylamine, venlafaxine (depression)
21*	F	28	39	4	Codeine	8	Paracetamol, ibuprofen, zolmitriptan, fluoxetine (depression)
22	F	39	37	31	Codeine	18	Topiramate, paracetamol. zolmitriptan, topiramate (depression)
23	F	44	79	3	Codeine	6	Rizatriptan, paracetamol, ibuprofen, amitriptyline, temazepam (aids sleep), st johns wort (anxiety)
24	F	62	17	52	Codeine	1	Paracetamol, doxylamine
25	F	45	59	43	Hydromorphone, tramadol, pethidine	44	Pregabalin, diazepam
26	F	37	76	15	Oxycodone, dextropropoxyphene	8	Diazepam, paracetamol, carbamazepine, mirtazapine (depression)
27	F	49	76	22	Morphine, codeine	39	Paracetamol, venlafaxine (depression), topiramate, gabapentin (seizure prophylaxis), diazepam,

Participant Number	Gender	Age	Avg. Pain Score (Visual Analogue Scale, 0-100)	Duration of Pain (years)	Opioid Type	Morphine Equivalent Dose (mg/day)	Concomitant analgesics / adjuncts
							temazepam
28	F	36	50	8	Codeine	3	Paracetamol
29	M	50	63	34	Codeine, tramadol	16	Zolmitriptan, paracetamol, ibuprofen, aspirin
30	F	52	63	40	Codeine	5	Ibuprofen
31	M	35	64	8	Codeine	26	Aspirin, paracetamol
32	F	53	64	10	Codeine	6	Paracetamol, ibuprofen, doxylamine, sumatriptan, aspirin
33	M	45	74	23	Oxycodone, dextropropoxyphene, codeine	54	Paracetamol, ibuprofen
-	25F, 8M	44.5 ± 11.1[a]	57 ± 16[a]	22 ± 14.2[a]	-	7 (5-17)[b]	-

[a]: mean ± standard deviation; [b]: median and interquartile range; *: patient did not complete study

The response to the thermal grill illusion was compared between patients' body side (Table 5.2) and body location (Table 5.3) for each thermal grill outcome (listed vertically) at each thermal grill configuration (listed horizontally). Mean differences and 95% CI for differences presented. Significant values represented by bold text.

Table 5.2. Effect of Body Side to the Thermal Grill Response

	Left Cheek vs. Right Cheek			Left Palm vs. Right Palm		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	2 mm (-3 to 7)	-1 mm (-6 to 4)	-2 mm (-7 to 3)	-4 mm (-9 to 2)	-1 mm (-6 to 5)	4 mm (-1 to 9)
Intensity of Heat	2 mm (-5 to 9)	1 mm (-6 to 8)	-1 mm (-8 to 6)	-5 mm (-10 to 1)	-1 mm (-7 to 4)	3 mm (-3 to 9)
Intensity of Heat (c)	-1 mm (-7 to 5)	1 mm (-5 to 6)	-4 mm (-9 to 2)	-2 mm (-8 to 3)	1 mm (-4 to 6)	4 mm (-2 to 9)
Unpleasantness	3 mm (-4 to 11)	6 mm (-1 to 14)	0 mm (-8 to 5)	-6 mm (-13 to 1)	-3 mm (-10 to 4)	1 mm (-6 to 8)
Tolerability	2 mm (-4 to 8)	0 mm (-6 to 5)	0 mm (-6 to 6)	-7 mm (-14 to 0)	2 mm (-5 to 9)	3 mm (-4 to 10)

ºC: degrees Celsius; C: colour bar.

Table 5.3. Effect of Body Location to the Thermal Grill Response

	Right Palm vs. Right Cheek			Left Palm vs. Left Cheek		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	**6 mm (1 to 11)**	3 mm (-2 to 8)	4 mm (-1 to 9)	1 mm (-5 to 7)	4 mm (-2 to 9)	**9 mm (3 to 15)**
Intensity of Heat	**10 mm (2 to 18)**	6 mm (-2 to 13)	7 mm (0 to 15)	3 mm (-3 to 9)	3 mm (-3 to 9)	**11 mm (5 to 17)**
Intensity of Heat (c)	**8 mm (1 to 14)**	**7 mm (1 to 14)**	5 mm (-1 to 12)	**7 mm (1 to 13)**	**8 mm (2 to 14)**	**13 mm (7 to 18)**
Unpleasantness	6 mm (-2 to 13)	**8 mm (0 to 15)**	6 mm (-1 to 13)	-4 mm (-10 to 3)	-2 mm (-8 to 5)	**7 mm (0 to 13)**
Tolerability	7 mm (-1 to 14)	2 mm (-6 to 9)	3 mm (-5 to 10)	-2 mm (-7 to 3)	4 mm (-1 to 9)	**6 mm (1 to 11)**

ºC: degrees Celsius; C: colour bar.

Table 5.4. Correlations Between Thermal Pain Thresholds and the Thermal Grill Response at Baseline

R and *P* values from the correlation analyses performed at patients right and left cheek and palm are presented (described previously on page 94). Significant values represented by bold text.

		Cold Pain Threshold			Heat Pain Threshold		
	Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Right Cheek	Intensity of Pain						
	R value	0.45	0.35	0.44	**-0.51**	**-0.48**	**-0.55**
	P value	0.01	0.046	0.12	**0.0029**	**0.0055**	**0.0012**
	Intensity of Heat						
	R value	0.44	0.39	**0.62**	**-0.55**	**-0.48**	**-0.69**
	P value	0.012	0.028	**0.0001**	**0.0012**	**0.0053**	**<0.0001**
	Intensity of Heat (c)						
	R value	0.28	0.17	0.36	-0.42	-0.36	**-0.51**
	P value	0.12	0.34	0.046	0.017	0.043	**0.0028**
	Unpleasantness						
	R value	**0.52**	**0.49**	**0.51**	**-0.57**	0.45	**-0.57**
	P value	**0.0025**	**0.0044**	**0.0027**	**0.0007**	0.01	**0.0007**
	Tolerability						
	R value	**0.53**	**0.52**	**0.55**	**-0.56**	-0.49	**-0.59**
	P value	**0.002**	**0.0025**	**0.0012**	**0.0009**	0.043	**0.0004**
Left Cheek	Intensity of Pain						
	R value	0.26	0.28	0.23	**-0.53**	**-0.57**	-0.4
	P value	0.15	0.13	0.2	**0.002**	**0.0006**	0.025
	Intensity of Heat						
	R value	0.24	0.41	0.18	0.5	**-0.54**	-0.4
	P value	0.18	0.019	0.32	0.0033	**0.0014**	0.022
	Intensity of Heat (c)						
	R value	0.15	0.27	0.0945	-0.38[p]	-0.42[p]	-0.36[p]
	P value	0.41	0.13	0.61	0.032[p]	0.017[p]	0.043[p]
	Unpleasantness						
	R value	0.35	0.3	0.34	**-0.54**	**-0.53**	**-0.51**
	P value	0.047	0.091	0.056	**0.0015**	**0.0016**	**0.0027**
	Tolerability						
	R value	0.35	**0.43**	0.35	**-0.53**	**-0.51**	**-0.49**
	P value	0.046	**0.013**	0.51	**0.0017**	**0.0026**	**0.0049**

		Cold Pain Threshold			Heat Pain Threshold		
	Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Right Palm	Intensity of Pain						
	R value	0.29	0.33	0.2	-0.34	-0.28	-0.34
	P value	0.11	0.069	0.27	0.055	0.12	0.056
	Intensity of Heat						
	R value	**0.5**	**0.48**	0.41	-0.42	-0.31	-0.37
	P value	**0.003**	**0.0057**	0.02	0.018	0.087	0.036
	Intensity of Heat (c)						
	R value	**0.48**	0.37	0.38	**-0.46[P]**	-0.31[P]	-0.42[P]
	P value	**0.0057**	0.036	0.032	**0.0079[P]**	0.086[P]	0.016[P]
	Unpleasantness						
	R value	**0.53**	0.41	0.35	**-0.47[P]**	-0.31[P]	-0.43[P]
	P value	**0.006**	0.019	0.047	**0.0066[P]**	0.089[P]	0.014[P]
	Tolerability						
	R value	0.37	0.33	0.2	-0.36	-0.34	-0.39
	P value	0.036	0.065	0.27	0.041	0.057	0.026
Left Palm	Intensity of Pain						
	R value	0.29	0.24	0.22	**-0.54**	-0.41	**-0.51**
	P value	0.11	0.19	0.22	**0.0016**	0.018	**0.0032**
	Intensity of Heat						
	R value	**0.49**	**0.47**	0.39	**-0.69**	**-0.63**	**-0.52**
	P value	**0.0049**	**0.0068**	0.027	**<0.0001**	**<0.0001**	**0.0022**
	Intensity of Heat (c)						
	R value	0.39[P]	0.4[P]	0.33[P]	**-0.61[P]**	**-0.62[P]**	**-0.48[P]**
	P value	0.26[P]	0.025[P]	0.064[P]	**0.0002[P]**	**0.0002[P]**	**0.0051[P]**
	Unpleasantness						
	R value	**0.49**	0.38	0.15	**-0.53**	**-0.61**	**-0.64**
	P value	**0.0044**	0.031	0.42	**0.0017**	**0.0002**	**<0.0001**
	Tolerability						
	R value	0.15	0.33	0.34	-0.38	**-0.49**	**-0.56**
	P value	0.42	0.067	0.06	0.031	**0.0042**	**0.0008**

°C: degrees Celcius; C: colour bar; [P]: analysed with Pearson's correlation.

Table 5.5. Baseline Characteristics of the Thermal Grill Response: Pain-free Participants versus Patients with Medication Overuse Headache

The response to the thermal grill illusion was compared between pain-free participants and patients with medication overuse headache at participants' right and left cheek and palm for all five thermal grill outcomes. *P* values are presented.

	Right Cheek	Left Cheek	Right Palm	Left Palm
Intensity of Pain	0.65	0.94	0.99	0.96
Intensity of Heat	0.54	0.94	0.65	0.7
Intensity of Heat (c)	0.91	0.49	0.9	0.85
Unpleasantness	0.48	0.71	0.55	0.87
Tolerability	0.48	0.88	0.65	0.75

C: colour bar.

Table 5.7. Comparison of the Thermal Grill Response Over 8 Weeks for Patients Assigned to the Ibudilast and Placebo Treatment Groups

The response to the thermal grill illusion was compared between patients assigned to the ibudilast and patients assigned to the placebo treatment groups over 8 weeks at patients right and left cheek and palm for all five thermal grill outcomes (listed vertically) at each thermal grill configuration (listed horizontally). *P* values are presented.

	Right Cheek			Left Cheek			Right Palm			Left Palm		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	0.12	0.089	0.12	0.23	0.063	0.42	0.77	0.99	0.8	0.31	0.76	0.15
Intensity of Heat	0.44*	0.7*	0.056	0.91*	0.88*	0.92*	0.1	0.23	0.1	0.11	0.055	0.69*
Intensity of Heat (c)	0.44*	0.88*	0.99*	0.51*	0.72*	0.67*	0.77*	0.63*	0.9*	0.62*	0.98*	0.99*
Unpleasantness	0.13	0.22	0.094	0.091	0.083*	0.13	0.5	0.57	0.12	0.33	0.47	0.21
Tolerability	0.13	0.99	0.21	0.22	0.59*	0.15	0.3	0.96	0.41	0.46	0.48	0.088

ºC: degrees Celcius; C: colour bar; *: B0 was not constrained in these analyses.

Figures

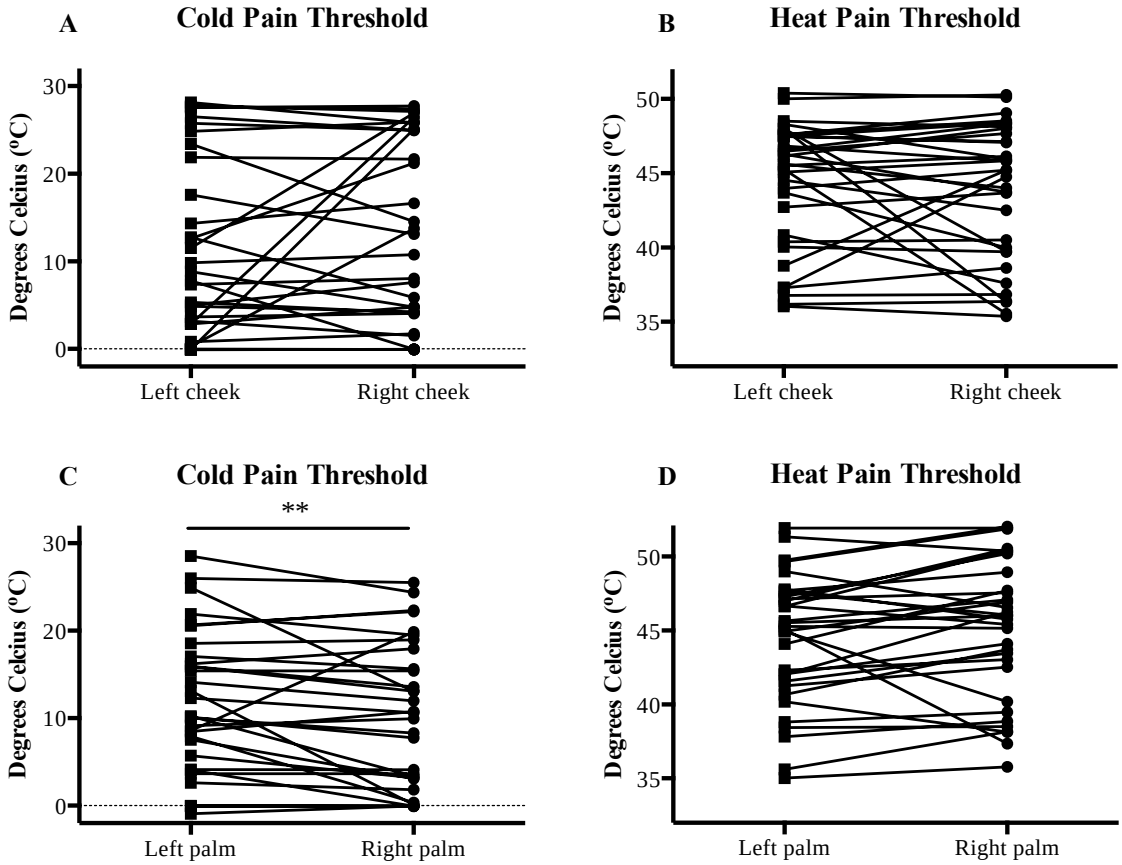

Figure 5.2. Effect of body side: cold and heat pain thresholds.

Cold and heat pain thresholds at the cheek (A, B) and palm (C, D) on patients left and right side. Patients' cold pain thresholds were significantly lower on their right palm compared to their left palm (C) ($p = 0.0075$). No significant differences were observed between patients' right and left palm for heat pain thresholds (D) ($p = 0.19$), or between patients' right and left cheek for both cold (A) ($p = 0.79$) and heat pain thresholds (B) ($p = 0.63$). ** $P < 0.01$.

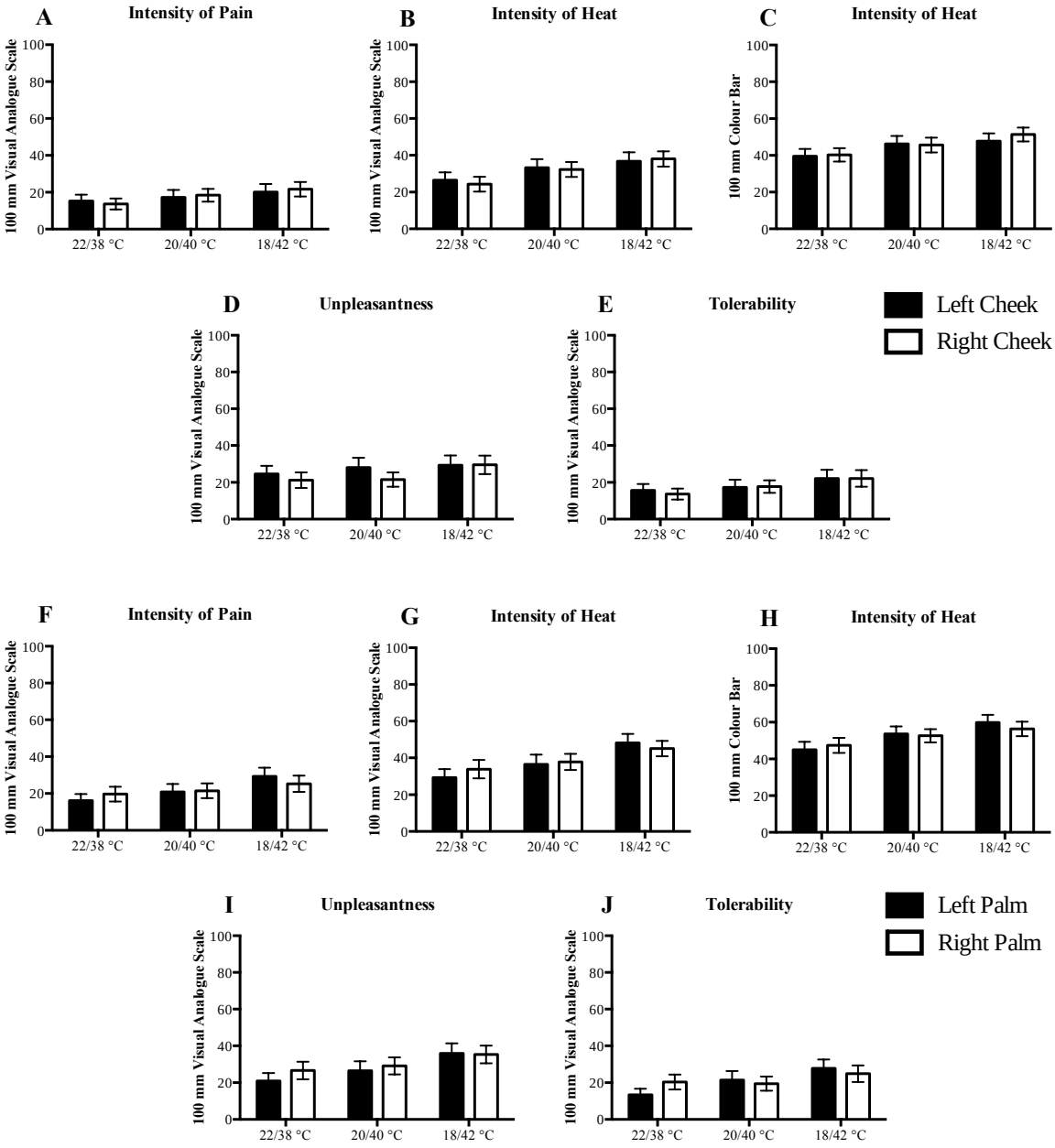

Figure 5.3. Effect of body side: thermal grill response.

The response to the thermal grill illusion at the cheek (A-E) and palm (F-J) on patients left (black bars) and right (white bars) side. The response to the thermal grill did not differ between the right and left cheek (A-E) and palm (F-J) for all thermal grill outcomes. Graphs are represented as mean ± SEM.

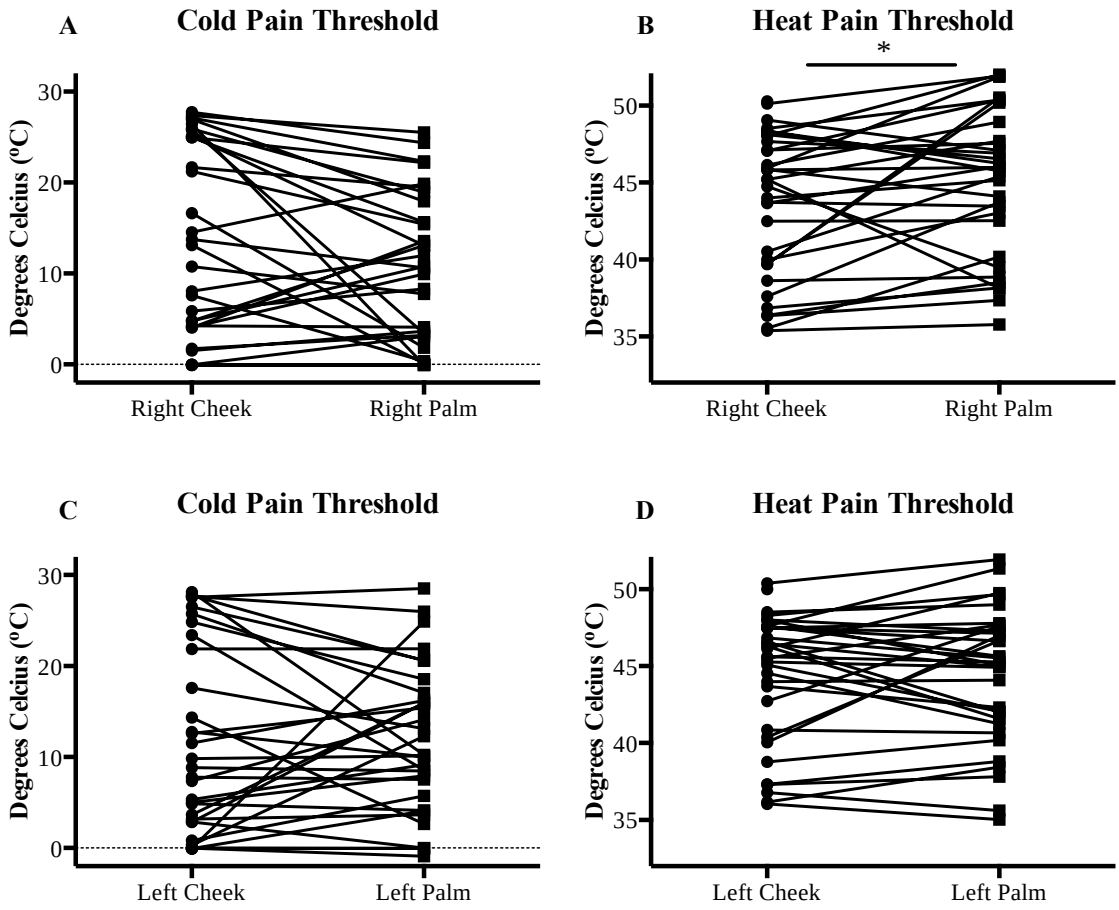

Figure 5.4. Effect of body location: cold and heat pain threshold.

Cold and heat pain thresholds at the cheek and palm on patients right (A, B) and left (C, D) side. Heat pain thresholds were significantly reduced (i.e. more sensitive) on patients right cheek compared to their palm (B) ($p = 0.022$). No significant differences were observed between patients' right cheek and palm for cold (A) ($p = 0.079$) pain thresholds, or between patients' left cheek and palm for cold (C) ($p = 1.0$) and heat pain thresholds (D) ($p = 0.64$). * $P < 0.05$.

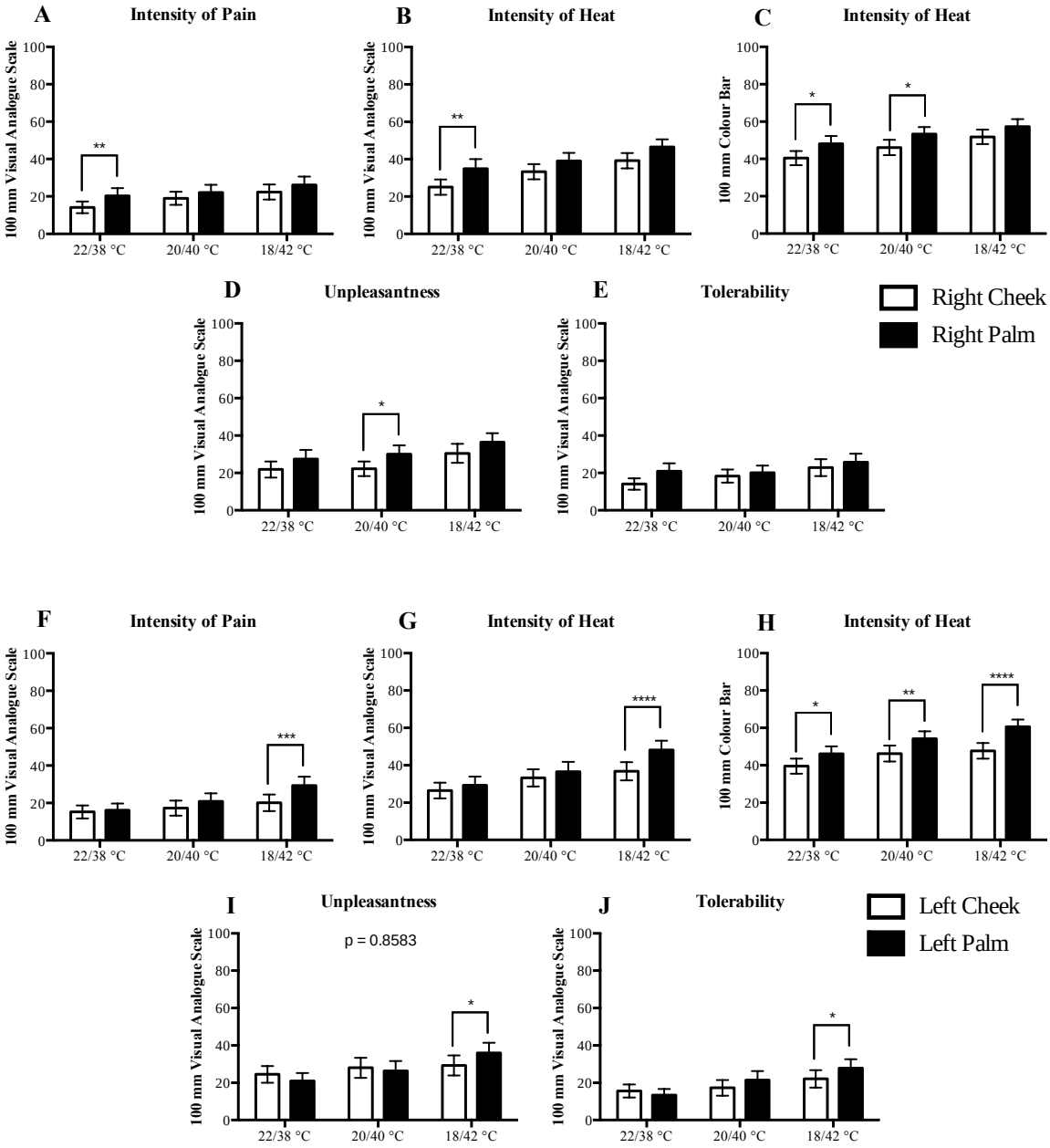

Figure 5.5. Effect of body location: thermal grill response.

The response to the thermal grill illusion at the cheek and palm on patients right (A-E) (white bars) and left (F-J) (black bars) and side. Significantly less pain, heat and unpleasantness to the thermal grill illusion was observed on the cheek compared to the palm on both the right (A, B, C, D) and left (F, G, H, I) side. Patients also reported more tolerability to the thermal grill illusion on the left cheek compared to the left palm (J) (see Table 5.3 for mean differences and 95% CI for differences). Data are represented as mean ± SEM. * $P < 0.05$; ** $P < 0.01$, *** $P < 0.001$, $P < 0.0001$.

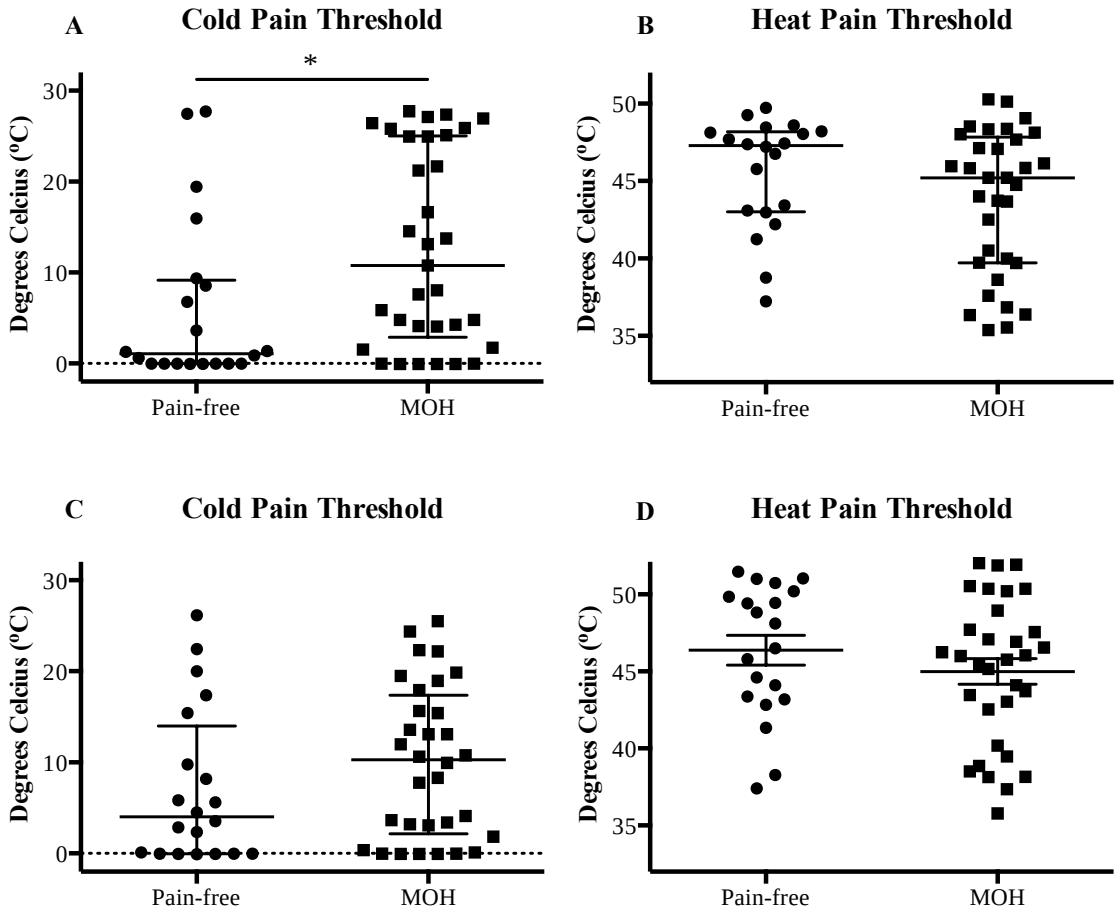

Figure 5.6. Pain-free participants versus patients with medication overuse headache: cold and heat pain thresholds.

Cold and heat pain thresholds at the right cheek (A, B) and palm (C, D) in pain-free participants and patients with medication overuse headache. Cold pain thresholds differed significantly between pain-free participants and patients with medication overuse headache on the right cheek ($p = 0.026$, A). No significant differences were observed between pain-free participants and patients with medication overuse headache for heat pain threshold on the right cheek ($p = 0.29$, B) or for both cold and heat pain thresholds on the right palm ($p = 0.28$, C and $p = 0.3$, D). Cold pain thresholds on the right cheek (A) and palm (C) and heat pain threshold on the right cheek (B) are represented as median and interquartile range. Heat pain thresholds on the right palm (D) are represented as mean ± SEM. * $P < 0.05$. MOH: medication overuse headache.

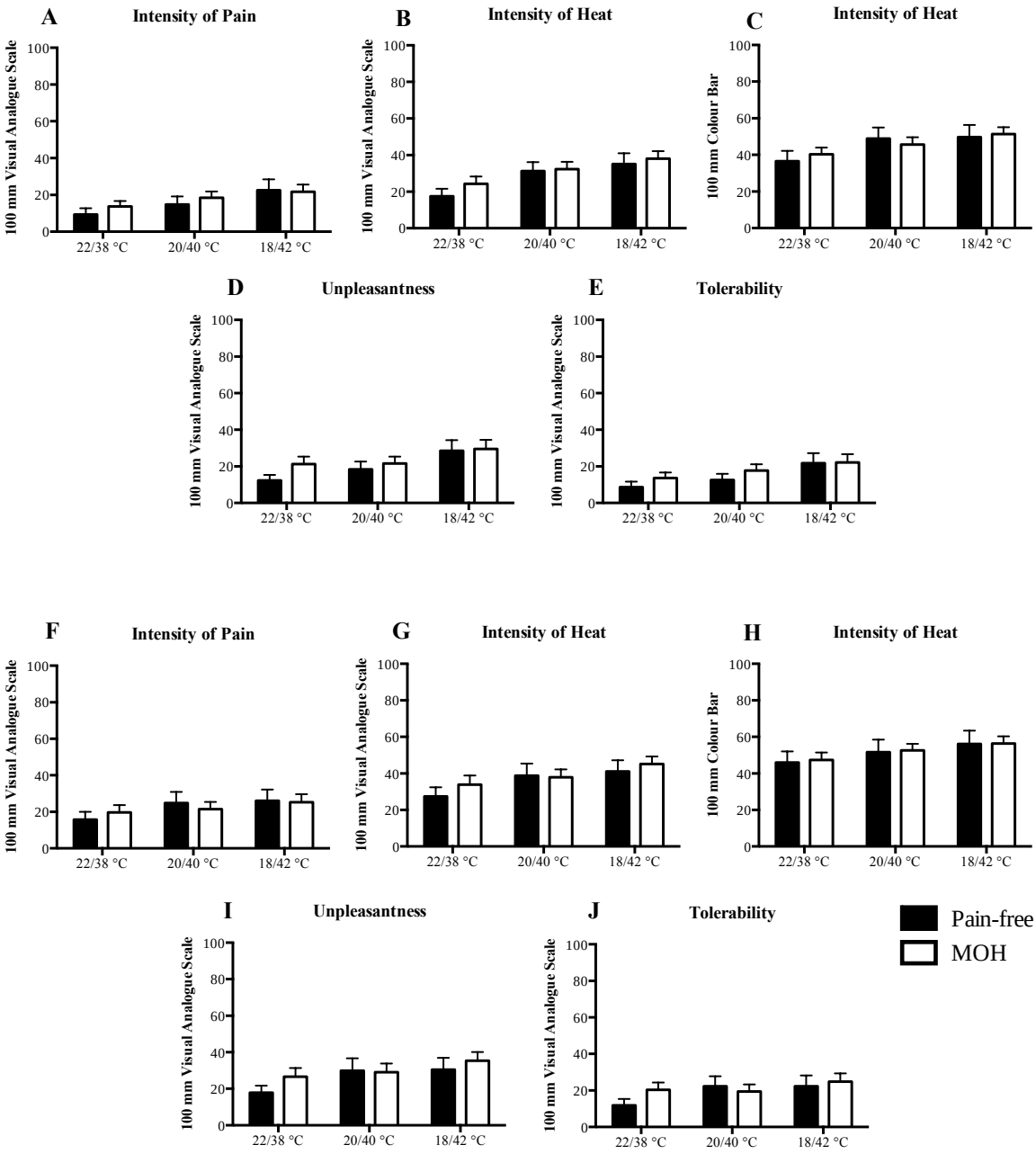

Figure 5.7. Pain-free participants versus patients with medication overuse headache: thermal grill response.

The response to the thermal grill illusion at the right cheek (A-E) and palm (F-J) in pain-free participants (black bars) and patients with medication overuse headache (white bars). The response to the thermal grill did not differ between pain-free participants and patients with medication overused headache on either the right cheek (A-E) or right palm (F-J) for all thermal grill outcomes. Graphs are represented as mean ± SEM. MOH: medication overuse headache.

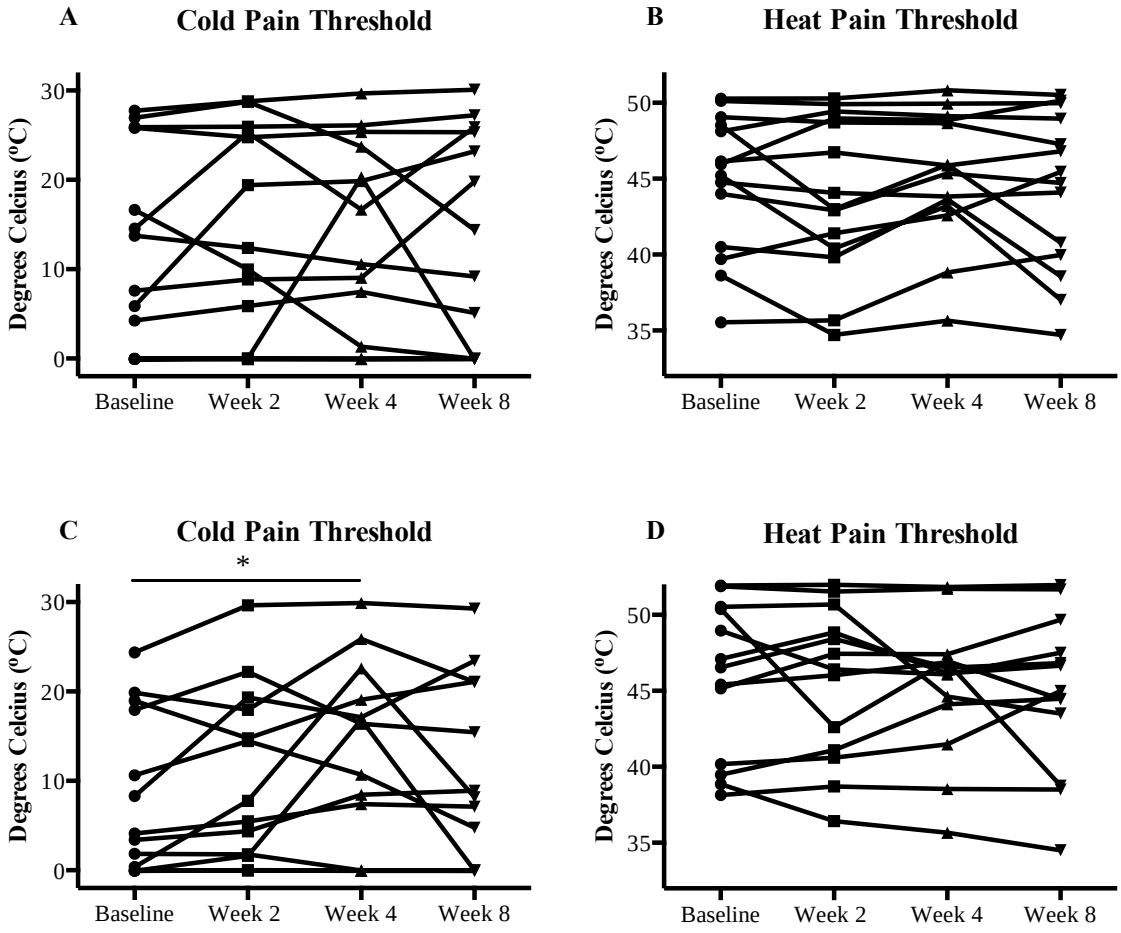

Figure 5.8. Repeatability of cold and heat pain thresholds over 8 weeks of placebo treatment.

Cold and heat pain thresholds at the right cheek (A, B) and palm (C, D) across four testing sessions conducted over 8 weeks in patients assigned to the placebo group. Patients' cold pain thresholds were significantly increased at week 4 compared to baseline on patients' right palm (C). No significant differences across the 8 weeks of placebo treatment were observed for cold pain thresholds on the right cheek (A) or heat pain threshold on the right cheek (B) or right palm (D). * $P < 0.05$.

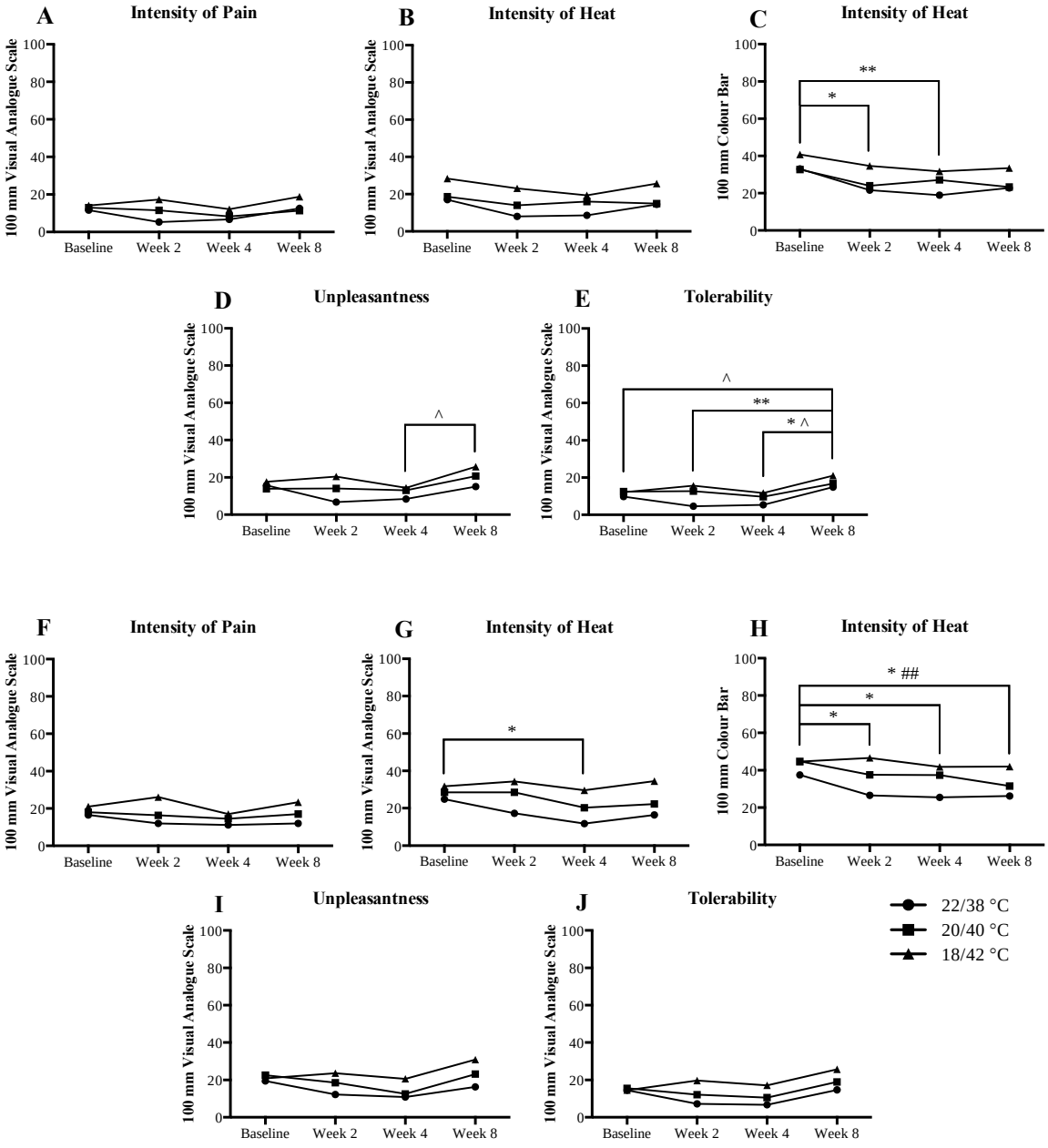

Figure 5.9. Repeatability of thermal grill illusion over 8 weeks of placebo treatment.

The response to the thermal grill at the right cheek (A-E) and palm (F-J) across four testing sessions conducted over 8 weeks in patients assigned to the placebo group. The response to the thermal grill illusion differed significantly across the 8 weeks of placebo treatment on both the right cheek (A-E) and right palm (F-J) for the outcomes "intensity of heat" (G), "intensity of heat (colour bar)" (C, H), "unpleasantness" (D) and tolerability (E) to the thermal grill illusion. Graphs are represented as mean. * $P < 0.05$ (22/38 ºC); ** $P < 0.01$ (22/38 ºC); ## $P < 0.01$ (20/40 ºC); ^ $P < 0.05$ (18/42 ºC).

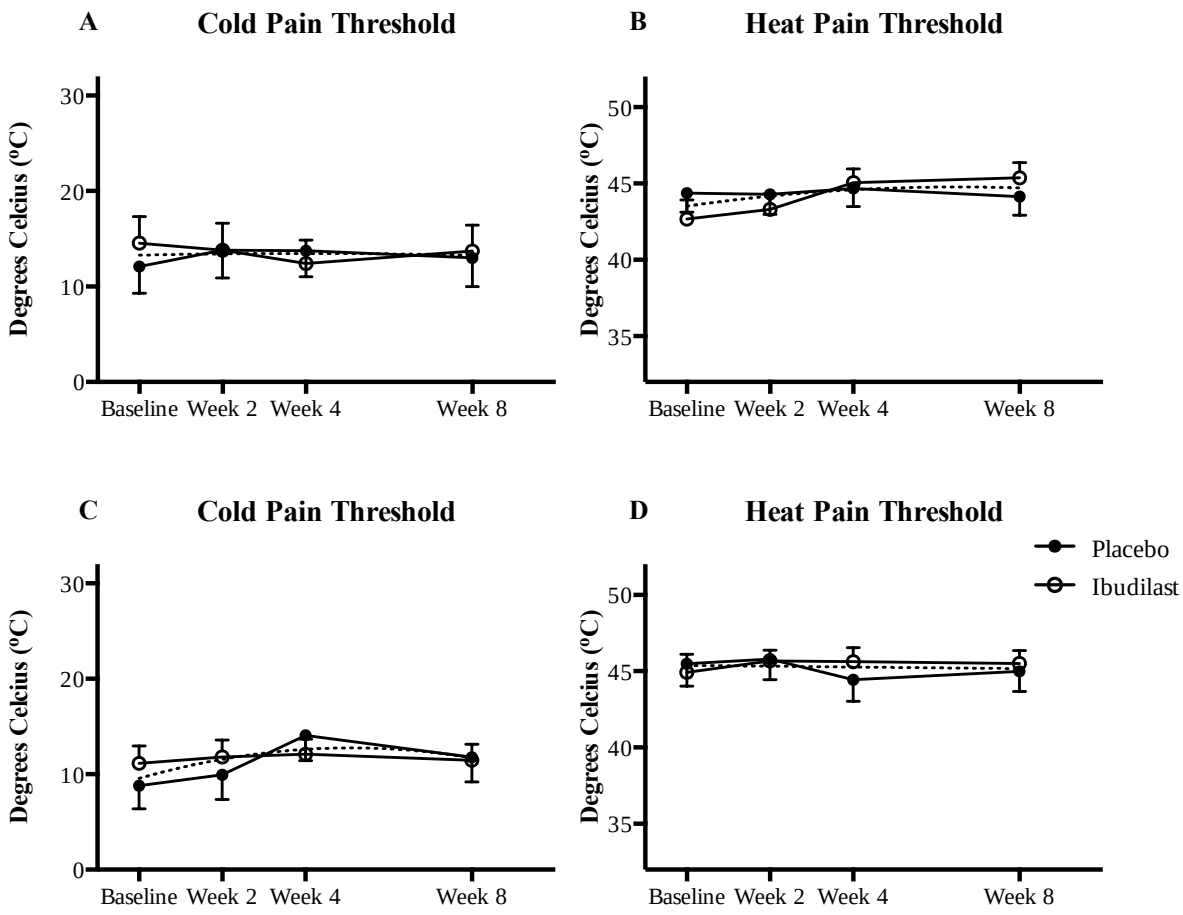

Figure 5.10. Response to ibudilast: cold and heat pain thresholds.

Cold and heat pain thresholds at the right cheek (A, B) and palm (C, D) across four testing sessions conducted over 8 weeks in patients assigned to the placebo and ibudilast groups. Comparing ibudilast and placebo, no significant differences were observed between the effect time curves for cold pain thresholds on the right cheek (A)($p = 0.92$) or palm (C)($p = 0.82$) or heat pain thresholds on the right cheek (B)($p = 0.59$) or palm (D)($p = 0.91$). Graphs are represented as mean ± SEM.

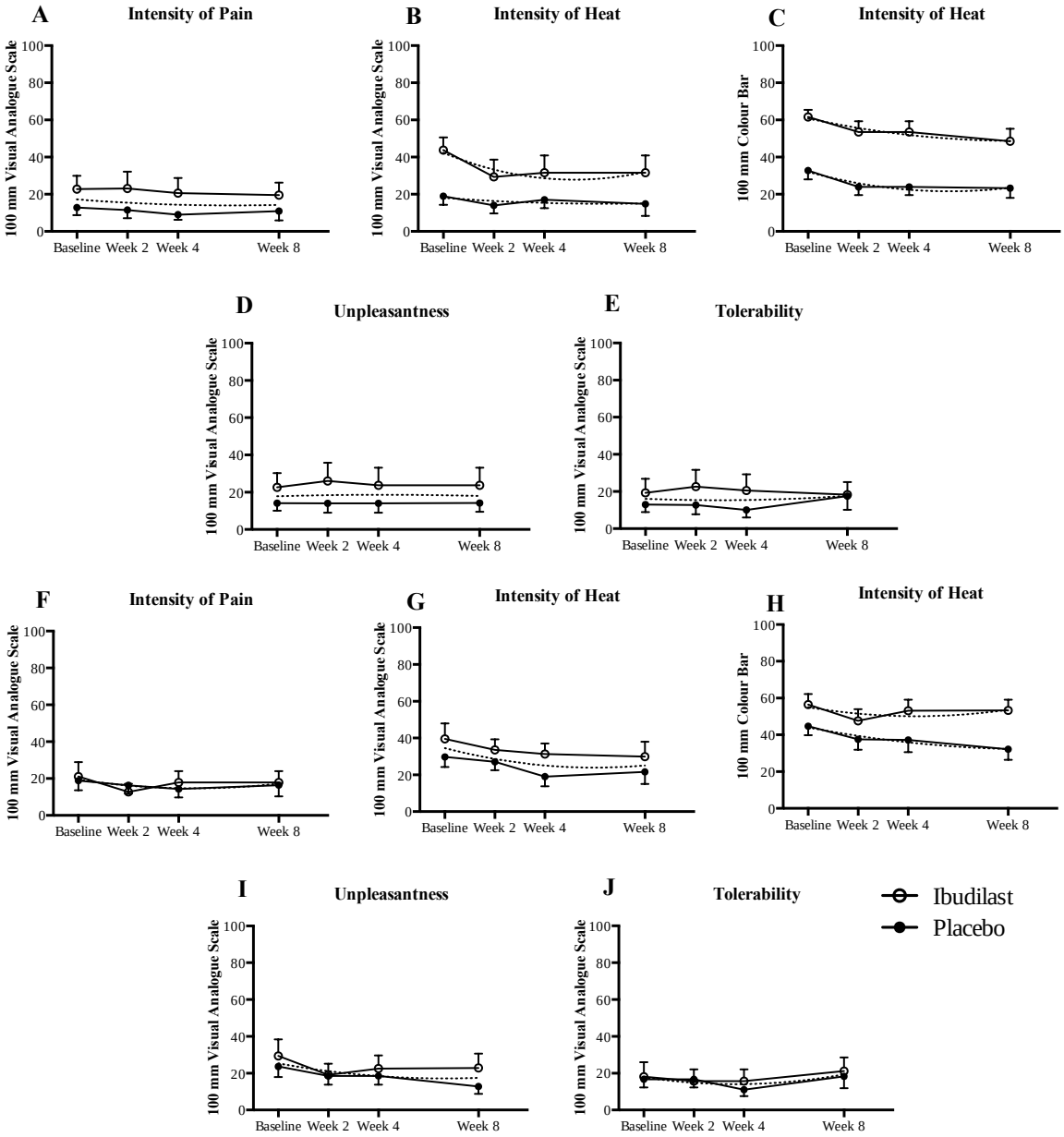

Figure 5.11. Response to ibudilast: thermal grill response.

The response to the thermal grill illusion at the right cheek (A-E) and palm (F-J) across four testing sessions conducted over 8 weeks in patients assigned to the placebo and ibudilast groups. Comparing ibudilast and placebo, no significant differences were observed between the effect time curves for all thermal grill outcomes on both the right cheek (A-E) and palm (F-J) when tested at the 20/40 ºC thermal grill configuration. Graphs are represented as mean ± SEM.

Chapter 6. Thermal Grill Response and Transcranial Direct Current Stimulation in Patients with Chronic Tension-Type Headache

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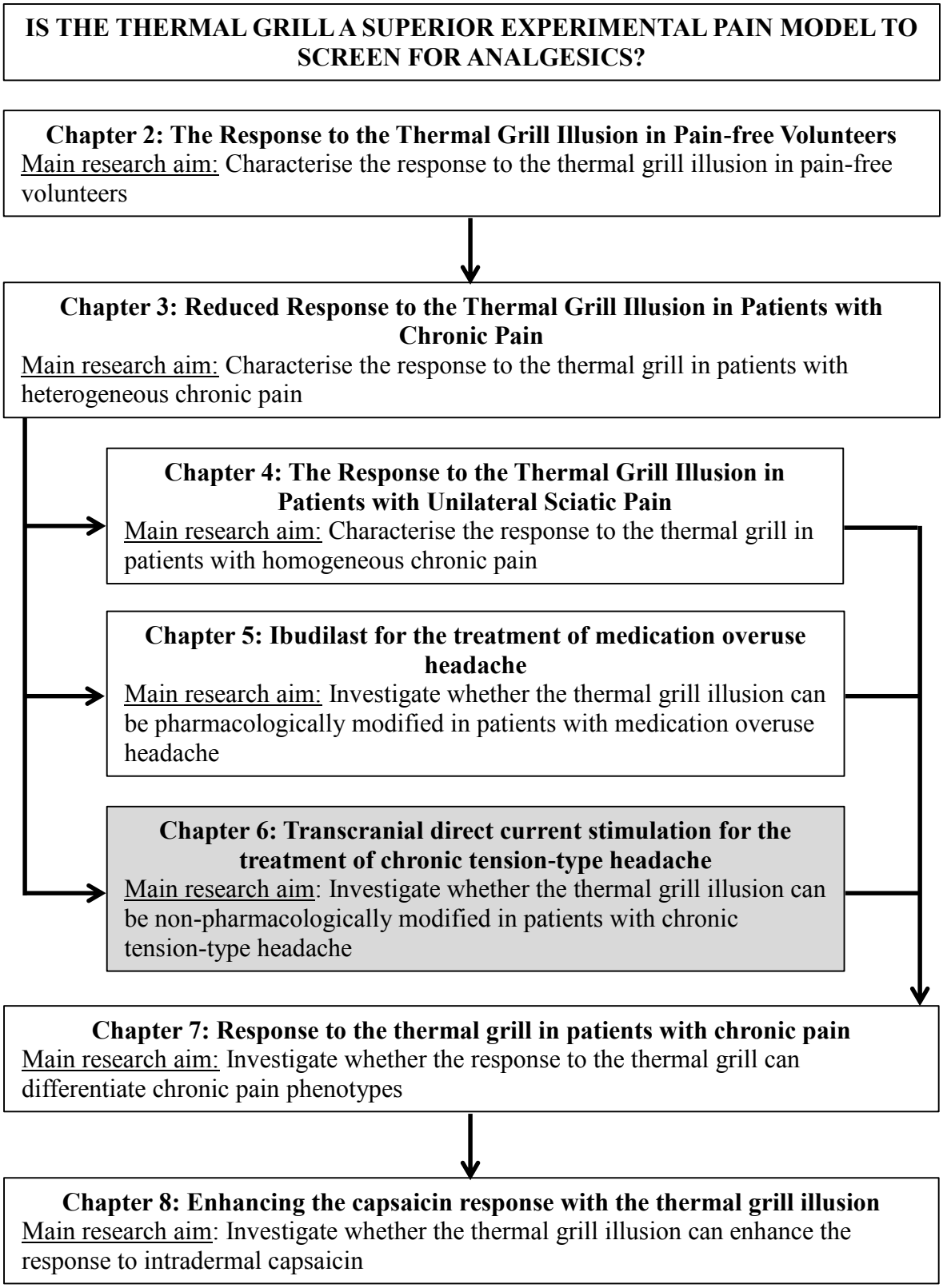

IS THE THERMAL GRILL A SUPERIOR EXPERIMENTAL PAIN MODEL TO SCREEN FOR ANALGESICS?
Chapter 2: The Response to the Thermal Grill Illusion in Pain-free Volunteers
Main research aim: Characterise the response to the thermal grill illusion in pain-free volunteers
Chapter 3: Reduced Response to the Thermal Grill Illusion in Patients with Chronic Pain
Main research aim: Characterise the response to the thermal grill in patients with heterogeneous chronic pain
Chapter 4: The Response to the Thermal Grill Illusion in Patients with Unilateral Sciatic Pain
Main research aim: Characterise the response to the thermal grill in patients with homogeneous chronic pain
Chapter 5: Ibudilast for the treatment of medication overuse headache
Main research aim: Investigate whether the thermal grill illusion can be pharmacologically modified in patients with medication overuse headache
Chapter 6: Transcranial direct current stimulation for the treatment of chronic tension-type headache
Main research aim: Investigate whether the thermal grill illusion can be non-pharmacologically modified in patients with chronic tension-type headache
Chapter 7: Response to the thermal grill in patients with chronic pain
Main research aim: Investigate whether the response to the thermal grill can differentiate chronic pain phenotypes
Chapter 8: Enhancing the capsaicin response with the thermal grill illusion
Main research aim: Investigate whether the thermal grill illusion can enhance the response to intradermal capsaicin

Introduction

Similar to my previous chapter (chapter 5), I also had the opportunity to longitudinally investigate the response to the thermal grill illusion and thermal pain thresholds in patients with chronic tension-type headache (CTTH), in particular to investigate whether the response to the thermal grill could differentiate the response to a novel non-pharmacological therapy. To maximise patient recruitment and minimise resources, the CTTH patients recruited for this study were part of an ongoing clinical trial conducted by James Swift, a PhD candidate who is also within the Discipline of Pharmacology, School of Medical Sciences at the University of Adelaide. Although we both used the same patient population, our study objectives differed significantly. The primary objective of my component of this study, in line with the primary objective of this thesis, was to determine whether the thermal grill is a useful tool to screen for the efficacy of novel treatments for painful conditions, whereas the primary objective of the main study was to determine the efficacy of transcranial direct current stimulation (tDCS) in the treatment of CTTH. For a complete overview of CTTH, please see the recent review by Bendtsen and Jensen (2009).

Tension-type headache has the greatest socioeconomic impact of any primary headache disorder due to its high prevalence (Crystal and Robbins). Tension-type headache can be divided into three subtypes: infrequent episodic tension-type headaches; frequent episodic tension-type headaches; and chronic tension-type headaches (cited by Steefel and Novak 2012). CTTH is defined as headache that occurs 15 or more days per month and affects approximately 3% of the population (Rasmussen et al., 1991). Pharmacological interventions for CTTH are often ineffective and are limited by their side effects. Consequently, non-pharmacological interventions for CTTH are often sought.

The pathophysiology of CTTH is not clearly understood, however like many other chronic pain conditions, central sensitisation is believed to play a major role in the pathogenesis of CTTH. Similar to patients with MOH, CTTH patients demonstrate increased responsiveness to innocuous and noxious stimuli at both cephalic and extra-cephalic sites compared to pain-free individuals (Bezov et al., 2010). The discovery that central sensitisation not only affects areas of the spinal column, but also regions of the brain, opens up new treatment opportunities for chronic pain conditions like CTTH.

Transcranial direct current stimulation (tDCS) is a simple, painless, non-invasive method of stimulating cortical regions of the brain using low amplitude direct current, resulting in the modulation of neuronal excitability in cortical regions (Fregni et al., 2007; Zaghi et al., 2009). Significant improvements in pain have been reported following tDCS in patients with a variety of chronic pain conditions, such as central pain in traumatic spinal cord injury, fibromyalgia, refractory chronic pelvic pain, neuropathic pain secondary to multiple sclerosis and a mixed-group of therapy-resistant chronic pain syndromes (Fregni et al., 2006a; Fregni et al., 2006b; Fenton et al., 2009; Valle et al., 2009; Antal et al., 2010; Mori et al., 2010), as well as modulation of nociception in pain-free volunteers (Boggio et al., 2008; Bachmann et al., 2010; Hansen et al., 2011). However, to date, the efficacy of tDCS has not been investigated in patients with CTTH.

Cathcart and colleagues (2010) developed a stressful mental task that was capable of inducing an acute headache episode in 91% of patients with CTTH. As stress is the most widely reported trigger of acute headache episodes in CTTH (Cathcart et al., 2010), a novel method for investigating the efficacy of CTTH interventions, such as tDCS, is to apply this model (stressful mental task) following the cessation of tDCS treatment sessions.

One aim of this study was to determine if the presence of central hypersensitivity, as measured by the response to the thermal grill illusion and to thermal pain thresholds, could differentiate response to treatment with tDCS in patients with CTTH. It was hypothesised that treatment with tDCS would reduce central sensitivity in patients with CTTH, thus alter their response to the thermal grill illusion. Another aim was to compare the response to the thermal grill illusion and to thermal pain thresholds before and after headache as induced by an hour-long stressful mental task between those patients receiving active tDCS or sham treatment. It was hypothesised that headache induced by the stressful mental task would alter patients response to the thermal grill illusion to a lesser extent in patients who received active tDCS treatment compared to sham treatment.

An additional aim of this study was to investigate the baseline characteristics of the response to both the thermal grill illusion and thermal pain thresholds in patients with chronic tension-type headache and compare the response to both the thermal grill illusion and thermal pain thresholds between patients with CTTH and pain-free volunteers (from chapter 4). It was hypothesised that responses to both the thermal grill illusion and thermal pain thresholds would differ between patients' cheek and palm, similar to previous finings in chapter 2 and 4. Additionally, it was hypothesised that responses to both the thermal grill illusion and thermal pain thresholds would differ compared to pain-free participants (from chapter 4), based on my findings in chapter 3. Although, differences in thermal pain thresholds were not observed between patients with chronic pain and pain-free participants in chapter 3, previous studies have demonstrated differences in thermal pain thresholds between patients with various types of headache (migraine, episodic chronic migraine, tension-type headache, cerviocogenic headache and unclassifiable headache) and pain-free participants (Langemark et al., 1989; Uthaikhup et al., 2009; Schwedt et al., 2011).

The final aim of this study was to longitudinally compare the test-retest reliability of both the response to the thermal grill illusion and thermal pain thresholds in the patients with chronic tension-type headache that were allocated to the placebo group. As discussed in chapter 5, good test-retest reliability of thermal pain thresholds has been demonstrated, therefore it was hypothesised that the response to both the thermal grill illusion and thermal pain thresholds would remain stable over time.

Materials and Methods

Thermal grill

As previously described in chapter 2.

Ethics

Ethics approval was obtained from the Royal Adelaide Hospital (RAH) Investigational Drugs Subcommittee and Research Ethics Committee. Signed consent was obtained from each participant prior to enrolment into the study. With the exception of all study related travel costs, participants were not financially reimbursed for their participation in this study.

Subjects

It was planned that 106 patients with chronic tension-type headache would participate in this study. Participants were recruited from the general public by advertisement. All participants were naïve to the thermal grill effect. 20 pain-free participants from chapter 4 were used as controls.

Inclusion / exclusion criteria

Key inclusion criteria

Key inclusion criteria were: male and females between 18 and 65 years; must meet the following criteria for CTTH: A) headache occurring on ≥ 15 days per month on average for > 3 months (≥ 180 days per year) and fulfilling criteria B-D; B) headache lasts hours or may be continuous; C) headache has at least two of the following characteristics (bilateral location, pressing/tightening (non-pulsating) quality, mild or moderate intensity, not aggravated by routine physical activity such as walking or climbing stairs); D) not attributed to any other

disorder and both of the following: no more than one of photophobia, phonophobia or mild nausea and neither moderate or severe nausea nor vomiting. Patients must have been suffering from CTTH for more than one year prior to commencing the trial; should have headache episodes (if untreated) of greater than 4 hours; onset of CTTH should be before the age of 50. Patients with migraine were permitted provided that migraine episodes are easily distinguished by the patients and migraine episodes no not exceed more than one per month for the preceding year.

Exclusion criteria

Key exclusion criteria were as follows: history of abuse of alcohol or drugs; known hypersensitivity to tDCS; use of antipsychotics, antiepileptics, anxiolytics or antidepressants within one month of starting the study; significant affective psychotic, cognitive and other chronic pain conditions; an anxiety, psychological or any other disorder that, in the opinion of the Principal Investigator, may be exacerbated by exposure to the stressful mental task; pregnancy; significant scarring at the planned site of investigation; known disorder of thermal pain sensitivity; headache diagnosis falls within a classification other than chronic tension type headache and any response to the TMS screening questionnaire as outlined by Rossi and colleagues (2011) that the investigators deem to be exclusionary (i.e. “do you have epilepsy or have you ever had a convulsion or a seizure?”, “have you ever had a fainting spell or syncope? If yes, please describe on which occasion(s)?”, have you ever had a head trauma that was diagnosed as a concussion or was associated with loss of consciousness?”, “do you have any hearing problems or ringing in your ears?”, “do you have cochlear implants?”, “are you pregnant or is there any chance that you might be?’, ‘do you have metal in the brain, skull or elsewhere in your body (e.g., splinters, fragments, clips, etc.)? If so, specify the type of metal”, “do you have an implanted neurostimulator (e.g., DBS, epidural/subdural, VNS)?”, “do you have a cardiac pacemaker or intracardiac lines?”, “do you have a medication infusion

device?", "are you taking any medications?", "have you ever undergone TMS in the past? If so, were there any problems?", and "have you ever undergone MRI in the past? If so, were there any problems?"

Study overview

For the purposes of this PhD thesis, this double-blind, randomised, sham-controlled, parallel-group design study of transcranial direct current stimulation (tDCS) for the treatment of chronic tension-type headache was conducted over a 15 day period, with pharmacodynamic assessments (thermal grill and thermal pain threshold testing) being performed at baseline (day 1) and day 10 of tDCS treatment and on study visit 11 (day 15) before and after the induction of a stressful mental task. For the tDCS schedule, participants underwent a series of ten identical treatment sessions conducted over a two week period. The sessions were conducted at the same time each day from Monday to Friday of week one, (Saturday and Sunday were treatment free days) and the participant returned for an identical treatment regimen on Monday to Friday of week two. On the Monday following the final treatment session (study visit 11 and day 15), the participants returned to undertake a stressful mental task as described in Cathcart *et al.,* (2010). Patient's individual cold pain and heat pain thresholds and response to the thermal grill illusion were investigated before the first tDCS treatment session, immediately following the 10th tDCS treatment session and both before and immediately after the stressful mental task.

Study day schedule

At baseline, treatment day 10 and study visit 11, identical pharmacodynamic assessments were performed (see below). Additionally, at baseline only, patients were asked to rate the pain felt on average from their headache condition on a 100 mm visual analogue scale (VAS).

On each study day, a breath alcohol test was performed and a negative result was required for continuance in the study.

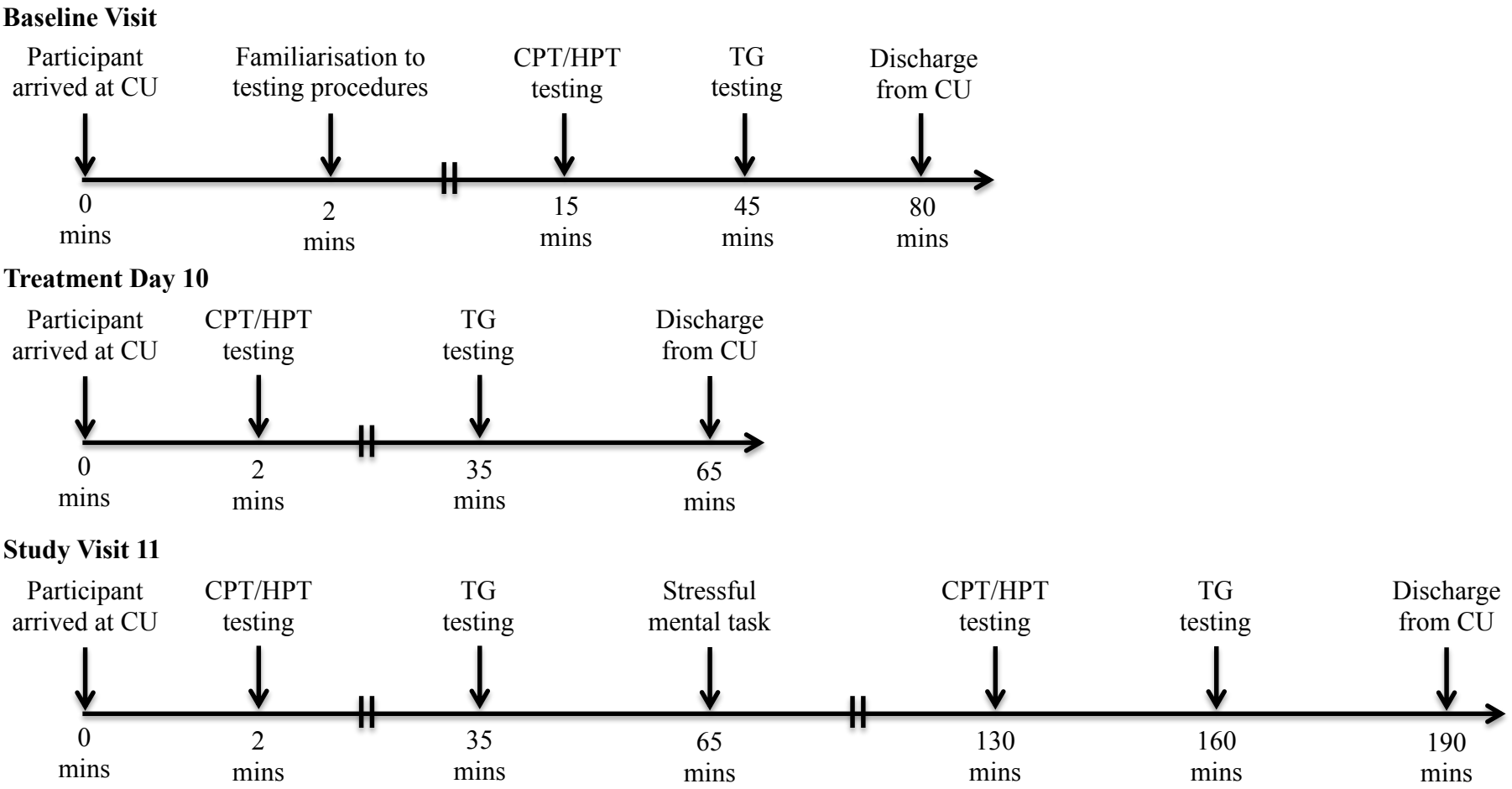


Figure 6.1. Schedule on Study Day at Baseline Visit, Treatment Day 10 and Study Visit 11.

Schedule on study day at baseline (top image), treatment day 10 (middle image) and study visit 11 (bottom image). CU: clinical unit; CPT: cold pain threshold; HPT: heat pain threshold; TG: thermal grill.

Thermal threshold testing

Patients' individual cold pain and heat pain thresholds were determined using a PATHWAY device (model ATS, Medoc, Israel) via the Method of Limits on both their left and right palm and their left and right cheek as described in chapter 4.

Thermal grill testing

Patients were exposed to three interlaced cool and warm temperature combinations (22/38 °C, 20/40 °C and 18/42 °C) in randomised order on both their left and right palm and their left and right cheek, using the same testing method and assessment questions as previously described in chapter 4, thus a total of 12 tests were performed on each study day.

Statistical analysis

The D'Agostino and Pearson omnibus normality test was performed to test for normality of the data.

Due to the non-parametric nature of the data, age, duration of headache pain and average pain from headache between the tDCS and sham group and age between pain-free participants (chapter 4) and patients with CTTH were compared using the Kolmogorov-Smirnov test, whilst headache frequency between the tDCS and sham group was compared using the Mann-Whitney test, therefore this data is represented as median and IQR.

Cold pain thresholds, heat pain thresholds and the response to the thermal grill illusion at baseline, day 10 of treatment and study visit 11 between patients assigned to the tDCS treatment group and patients assigned to the sham treatment group were compared using a

second order polynomial (quadratic) equation. B0, B1 and B2 were all constrained. If significance was observed, the analysis was re-run without B0 constrained. This data is represented as mean.

Cold pain thresholds, heat pain thresholds and the response to the thermal grill illusion pre- and post-stressful mental task between patients assigned to the tDCS treatment group and patients assigned to the sham treatment group were compared using a 2-way repeated measures ANOVA with Bonferroni's post hoc to adjust for multiple comparisons. Therefore, this data is represented as mean ± SEM.

The effect of the stressful mental task on the response to the thermal grill illusion was analysed using a 2-way repeated measures ANOVA with Bonferroni's post hoc to adjust for multiple comparisons, therefore this data is represented as mean ± SEM. The effect of the stressful mental task on cold and heat pain thresholds was analysed using a paired t-test at all body locations for cold pain threshold and at the palm for heat pain thresholds. Due to the non-parametric nature of the data, the effect of the stressful mental task on heat pain thresholds on the cheek was analysed using Wilcoxon's matched pairs signed rank test.

Comparing body side (right vs. left), the response to the thermal grill illusion across the right and left cheek and right and left palm was analysed using a 2-way repeated measures ANOVA with Bonferroni's post hoc to adjust for multiple comparisons, therefore this data is represented as mean ± SEM. Due to the non-parametric nature of the data, cold pain thresholds between the right and left palm and heat pain thresholds between the right and left cheek were analysed using Wilcoxon matched pairs signed rank test. Cold pain thresholds

between the right and left cheek and heat pain thresholds between the right and left palm were analysed using a paired t-test.

Comparing body location (cheek vs. palm), the response to the thermal grill illusion across the right cheek and palm and left cheek and palm was analysed using a 2-way repeated measures ANOVA and Bonferroni's post hoc to adjust for multiple comparisons, therefore this data is represented as mean ± SEM. Due to the non-parametric nature of the data, cold and heat pain thresholds between the right cheek and palm were analysed using Wilcoxon matched pairs signed rank test. Cold and heat pain thresholds between the left cheek and palm were analysed using a paired t-test.

Correlations between cold and heat pain thresholds and the response to the thermal grill illusion, duration of pain and intensity of pain were analysed. Correlations between the response to the thermal grill illusion and duration of pain and intensity of pain were also analysed. If the data was normally distributed, Pearson's correlation was used to analyse the data. Conversely, if the data was non-parametrically distributed, Spearman's correlation was used to analyse the data. In order to account for multiple comparisons, a Bonferroni correction was performed as described in chapter 2. Similar to chapters 4 and 5, correlations across multiple body locations were assessed in this study. Each body location was treated as a separate analysis; therefore Bonferroni's correction was only performed within one body location.

Comparing pain-free participants and patients with chronic tension-type headache, cold pain thresholds on the left palm and heat pain thresholds on the left and right palm and left cheek were analysed using an unpaired t-test. Therefore these graphs are represented as

mean ± SEM. Due to the non-parametric nature of the data, cold pain threshold on the right and left cheek and right palm and heat pain thresholds on the right cheek were analysed using the Kolmogorov-Smirnov t-test. Therefore these graphs are represented as median and IQR. Consequently, the appearance of the graphs displayed within this chapter and the appendix differ between the right and left side cheek for heat pain thresholds and right and left side palm for cold pain thresholds. Comparing pain-free participants and patients with medication overuse headache the response to the thermal grill illusion was analysed using a 2-way repeated measures ANOVA and Bonferroni's post hoc to adjust for multiple comparisons, therefore this data is represented as mean ± SEM.

The repeatability of the response to the thermal grill illusion was analysed using a 2-way repeated measures ANOVA and Tukey's post hoc to adjust for multiple comparisons, therefore this data is represented as mean ± SEM. The repeatability of cold and heat pain thresholds was analysed using Friedman's test with Dunn's multiple comparisons test to adjust for multiple comparisons at all body locations.

A *P* value of less than 0.05 was required for statistical significance, unless otherwise stated.

Results

Subjects

At the time of writing of this thesis, 12 (6M, 6F) patients with chronic tension-type headache completed this study, of which 10 were right hand dominant (see Table 6.1 for patient demographics). This study is ongoing, but recruiting slowly. Of these patients, 6 (3M, 3F) received sham tDCS treatment (sham) and 6 (3M, 3F) received active tDCS treatment (tDCS). Comparing sham and tDCS treatment groups, no significant group differences were observed for age (median and IQR, sham: 35 (25.8 to 49.5) years; tDCS: 44 (34.8 to 58.5) years, $p = 0.9$), duration of headache pain (median and IQR, sham: 12 (6.5 to 26.3) years; tDCS: 17.5 (8.8 to 25.5) years, $p = 1.0$, average pain from headache (median and IQR, sham: 49 (37 to 71) mm; tDCS: 44 (35 to 59) mm on a 100 mm visual analogue scale, $p = 0.9$) and headache frequency (median and IQR, sham: 28 (26 to 28) days per month; tDCS: 28 (21 to 28) days per month, $p = 0.73$). Comparing *pain-free* and *CTTH* participants, no significant differences were observed in age (median and IQR, *pain-free*: 42 (25.5 to 61) years; *CTTH*: 38 (28.3 to 49) years, $p = 0.32$).

Baseline Characteristics of Cold and Heat Pain Thresholds and the Response to the Thermal Grill of all Patients

Body side

Comparing body side (right vs. left), a significant difference in response to the thermal grill illusion was observed between patients' right and left cheek for the outcome "intensity of pain" at the 22/38 ^{o}C thermal grill configuration (see Figure 6.3A and Table 6.2 for mean difference and 95% CI for difference). For all other thermal grill outcomes, no significant differences were observed between patient's right and left cheek or right and left palm (see

Figure 6.3B-J) (see Table 6.2 for mean differences and 95% CI for differences). In response to cold and heat pain thresholds, no significant differences were observed between patients' right and left palm or between patients' right and left cheek (see Figure 6.2).

Body location

Comparing body location (cheek vs. palm), significant differences in response to the thermal grill were observed for the thermal grill outcomes "intensity of heat" and "intensity of heat colour" between patients' cheek and palm on both the right and left side (see Figure 6.5B-C, G-H). On both the right and left side, the response to the thermal grill was lowest on the cheek compared to the palm (see Table 6.3 for mean differences and 95% CI for differences). No significant differences between patients' cold and heat pain thresholds were observed between the cheek and palm on both the right and left side, although heat pain thresholds' on patients left cheek and left palm almost differed significantly ($p = 0.05$) (see Figure 6.4).

Correlations

Cold and heat pain thresholds

Significant correlations were observed between patients' cold and heat pain thresholds at all body locations (right cheek[1]: $r = -0.7$, $p = 0.014$; left cheek[1]: $r = -0.92$, $p = 3.01^{e-005}$; right palm[1]: $r = -0.77$, $p = 0.005$; left palm[2]: $r = -0.83$, $p = 0.001$), such that the less sensitive patients were to cold pain, the less sensitive they also were to heat pain.

1 Analysed with Spearman's correlation

2 Analysed with Pearson's correlation

Thermal pain thresholds and thermal grill illusion

Cold and heat pain threshold generally did not correlate with patients' response to the thermal grill illusion for all thermal grill outcomes at all body locations (see Table 6.4).

Intensity of pain and cold and heat pain threshold

The "intensity of pain" experienced on average from patients chronic headache did not correlate with patients' cold or heat pain thresholds at all body locations (see Table 11.6.1 in appendix).

Intensity of pain and thermal grill illusion

The "intensity of pain" experienced on average from patients chronic headache did not correlate with patients' response to the thermal grill at all body locations (see Table 11.6.2 in appendix).

Duration of pain and cold and heat pain threshold

Duration of headache pain significantly correlated with patients' cold and heat pain thresholds at their left cheek, as well as their left and right palm, such that the longer patients had experienced their pain for, the less sensitive they were to cold and heat pain. Significant correlations were not observed for the right cheek (see Table 11.6.3 in appendix).

Duration of pain and thermal grill illusion

Duration of headache pain generally did not correlate with patients' response to the thermal grill illusion for all thermal grill outcomes at all body locations (see Table 11.6.4 in appendix).

Baseline Characteristics of Cold and Heat Pain Thresholds and the Response to the Thermal Grill: Pain-free Participants versus Patients with Chronic Tension-Type Headache

Cold and heat pain thresholds

Cold and heat pain threshold did not differ between patients with chronic tension-type headache and pain-free participants at all body locations (see Figures 6.6 and 11.6.11 in appendix).

Thermal grill illusion

No significant differences were observed for all thermal grill outcomes, at all body locations between patients with chronic tension-type headache and pain-free participants (see Table 6.5 for all *P* values and Figures 6.7 and 11.6.2 in appendix).

Repeatability of Cold and Heat Pain Thresholds and the Response to the Thermal Grill across 15 days in Patients Assigned to the Sham Group

Cold and heat pain thresholds

Patients' cold and heat pain thresholds did not differ across the 3 testing sessions conducted over 15 days in patients in the sham treatment group (see Figures 6.8 and 11.6.3 in appendix).

Thermal grill illusion

The response to the thermal grill illusion differed significantly across the 3 testing sessions conducted over 15 days in patients' in the sham treatment group on both the right cheek and palm (see Figure 6.9C-J) and left palm (see Figure 11.6.4F-G, I-J in appendix). The response to the thermal grill generally decreased over time, suggesting habituation to the illusion.

Effect of tDCS

Cold and heat pain thresholds

A non-linear regression comparing both cold and heat pain thresholds over 10 days of tDCS or sham treatment revealed no significant differences between the effect time curves at all tested body locations (see Figure 6.10 for right cheek and palm and Figure 11.6.5 in appendix for left cheek and palm).

Thermal grill illusion

A non-linear regression comparing responses to the thermal grill over 10 days of tDCS or sham treatment revealed significant differences between the effect time curves for two thermal grill outcomes (see Figure 6.12 for right cheek and palm at the 20/40 ^{o}C thermal grill configuration and Figures 11.6.7 to 11.6.10 in appendix for all other body locations at all thermal grill configurations). However, there appeared to be a fundamental difference in response to the thermal grill between the tDCS and sham group at baseline, thus the analysis was re-run for all significant values with the B0 constraint removed from the equation. Once B0 was no longer constrained, no significant difference between patients' in the active and sham treatment groups was observed, demonstrating that B1 and B2 were the same for each

data set; thus treatment with tDCS did not alter the response to the thermal grill illusion (see Table 6.6 for all *P* values).

Effect of tDCS following stressful mental task

Cold and heat pain thresholds

Patients' response to both cold and heat pain thresholds did not differ between the tDCS and sham treatment groups both pre- and post-stressful mental task at all body locations tested (see Figure 6.11 for right cheek and palm and Figure 11.6.6 in appendix for left cheek and palm).

Thermal grill illusion

Patients' response to the thermal grill illusion did not differ between the tDCS and sham treatment groups both pre- and post-stressful mental task at all body locations tested, except for at the right cheek at one thermal grill configuration. Patients assigned to the tDCS group displayed significantly greater "intensity of heat" to the thermal grill on the colour bar at the 22 ^{o}/38 ^{o}C thermal grill configuration compared to patients assigned to the sham group; however no significant differences were observed following post hoc analysis. Looking at the graph (Figure 11.6.11C), patients assigned to the tDCS treatment group displayed greater ratings of "intensity of heat" both pre-stress and post-stress, thus this difference is likely to represent a fundamental difference between the tDCS and sham group, rather than a treatment difference (see Figure 6.13 for right cheek and palm at the 20/40 ^{o}C thermal grill configuration and Figures 11.6.11 to 11.6.14 in appendix for right cheek and palm at the 22/38 ^{o}C and 18/42 ^{o}C thermal grill configuration and left cheek and palm at the 22/38 ^{o}C, 20/40 ^{o}C and 18/42 ^{o}C thermal grill configuration and Table 6.7 for all *P* values).

Effect of stressful mental task

As no significant differences were observed between patients' in the tDCS and sham treatment groups for cold and heat pain thresholds and responses to the thermal grill illusion both pre- and post-stressful mental task, the two groups were combined for greater statistical power to determine whether the stressful mental task influenced patients' thermal sensitivity.

Cold and heat pain thresholds

Following the stressful mental task, patients' cold pain thresholds were significantly increased (i.e. more sensitive) on the left cheek compared to before the stressful mental task (mean difference: 1.7 ^{o}C, 95% CI for difference: 0.2 ^{o}C to 3.3 ^{o}C, p = 0.0345)(see Figure 11.6.15A in appendix). At all other body locations patients' cold pain thresholds did not differ following the stressful mental task. Similarly, patients' heat pain thresholds did not differ following the stressful mental task at all body locations (see Figure 6.14 for right cheek and palm and Figure 11.6.15 in appendix for left cheek and palm).

Thermal grill illusion

Generally, the stressful mental task did not affect patients' response to the thermal grill illusion (see Figure 6.7 for right cheek and palm and Figure 11.6.16 for left cheek and palm and Table 6.8 for all *P* values). Post hoc analysis revealed significant differences (mean difference, 95% CI for difference) between pre- and post-stressful mental task for the thermal grill outcomes "tolerability" on the right cheek at the 18/42 ^{o}C thermal grill configuration (2 mm, 0 mm to 4 mm) and on the right palm at the 20/40 ^{o}C thermal grill configuration (3 mm, 1 mm to 6 mm)(see Figure 6.15E and I). Due to incomplete data, 11 patients were included in the analysis "tolerability" on the left cheek.

Discussion

I report the first study investigating the response to the thermal grill longitudinally in patients with chronic tension-type headache (CTTH). These patients were part of an ongoing clinical trial conducted by James Swift, titled "The Efficacy of Transcranial Direct Current Stimulation in Chronic Tension-Type Headache" (Royal Adelaide Hospital Research Ethics Committee Protocol Number: 110631b).

One aim of this study was to determine if the presence of central hypersensitivity, as measured by the response to the thermal grill illusion and to thermal pain thresholds, could differentiate response to non-pharmacological treatment in patients with chronic pain. Patients with CTTH received active transcranial direct current stimulation (tDCS) or sham tDCS (sham) over a 10-day period. It was hypothesised that tDCS treatment would reduce central sensitivity in patients with CTTH, thus alter their response to the thermal grill illusion. Compared to sham treatment, tDCS treatment did not alter patients' response to the thermal grill illusion. Similarly, patients' cold and heat pain thresholds were not altered either, therefore a conclusion as to whether the thermal grill can detect the efficacy of pain modifying therapies that cannot be detected by thermal quantitative sensory testing cannot be made. Others have also demonstrated that tDCS did not alter both cold and heat pain thresholds in pain-free volunteers (Bachmann et al., 2010; Grundmann et al., 2011; Borckardt et al., 2012; Jurgens et al., 2012) and patients with chronic pain (Luedtke et al., 2012). No significant differences between the tDCS and sham treatment groups were observed at baseline for age, duration of pain, headache frequency or average pain. It is important to note that due to the extremely low patient numbers per group (n = 6) in this study, only major effects could be detected. An explanation of why tDCS was unsuccessful in altering patients' response to the thermal grill illusion or whether tDCS was effective in reducing the symptoms of CTTH is beyond the scope of this PhD thesis, therefore similar to chapter 5, a conclusion

as to whether the thermal grill can differentiate response to non-pharmacological treatment in patients with chronic pain cannot be made and consequently is a limitation of this thesis. From herein, I will discuss the effects of the stressful mental task, the baseline characteristic responses of patients with CTTH to the thermal grill illusion and thermal pain thresholds, compare these to pervious findings in pain-free volunteers (from chapter 4), as well as discuss the repeatability of the thermal grill illusion and thermal pain thresholds in patients assigned to the placebo group.

Another aim of this study was to compare the response to the thermal grill illusion and to thermal pain thresholds before and after headache as induced by an hour-long stressful mental task between those patients who received tDCS or sham treatment. It was hypothesised that headache induced by the stressful mental task would alter patients response to the thermal grill illusion to a lesser extent in patients who received active tDCS treatment compared to sham treatment. Compared to sham treatment, tDCS treatment did not alter patients' response to the thermal grill illusion or cold and heat pain thresholds following an hour-long stressful mental task. As no significant differences were observed between patients' in the tDCS and sham treatment groups for cold and heat pain thresholds and responses to the thermal grill illusion both pre- and post-stressful mental task, the two groups were combined. The stressful mental task generally did not affect patients' cold and heat pain thresholds or their response to the thermal grill illusion, although cold pain thresholds were slightly significantly elevated on the left cheek following the stressful mental task (i.e. patients were more sensitive) (see Figure 11.6.15A in appendix). Cathcart and colleagues (2009a) demonstrated that the stressful mental task reduced cold pressor test pain thresholds and increased supra-threshold cold pain ratings in both healthy volunteers (n = 25) and patients with CTTH (n = 23), however to a greater extent in patients with CTTH, following the cold-pressor test. Previously, the response to the thermal grill illusion was modulated in healthy volunteers (Boettger et al., 2011) and

depressive non-patients (Pinerua-Shuhaibar et al., 2011) using a negative mood induction procedure. In those studies the intensity of pain, unpleasantness and overall pain experienced from the thermal grill illusion were increased following negative mood induction. Unlike negative mood induction, these findings suggest that the response to the thermal grill illusion and thermal pain threshold testing are most likely not sensitive to stress. Again, it is important to note that the patient numbers in this study were quite low (n = 12).

An additional aim of this study was to investigate the baseline characteristics of the response to the thermal grill illusion in patients with CTTH. Consistent with my previous findings in pain-free volunteers (chapters 2 and 4), patients with unilateral sciatica (chapter 4) and patients with MOH (chapter 5), body side (right vs. left) generally did not affect the response to the thermal grill illusion, demonstrating no lateralisation to the thermal grill illusion. Others have also reported no lateralisation to the thermal grill illusion, in particular between the right and left palm and forearm (Boettger et al., 2011; Boettger et al., 2012; Averbeck et al., 2013; Boettger et al., 2013).

Comparing body location (palm vs. cheek), the response to the thermal grill was lowest on the cheek compared to the palm for the thermal grill outcomes "intensity of heat" and "intensity of heat colour bar" on both the right and left side, consistent with my findings in previous chapters (2, 4, 5). Others have also reported body location differences in response to thermal grill (see section 1.5.5.6 in chapter 1). Whereas, no significant difference in both cold and heat pain thresholds was observed between the palm and the cheek; although heat pain threshold appeared to be slightly lower (i.e. more sensitive) at patients cheek compared to their palm, almost reaching significance (p = 0.05) on the left side (see Figure 6.3D). Previously, Langemark and colleagues (1989) demonstrated that patients with CTTH had

reduced cold pain thresholds (i.e. were less sensitive) on their hand compared to their palm. Studies in pain-free participants have replicated these findings of reduced cold and heat pain thresholds at the cheek compared to the palm (Langemark et al., 1989; Rolke et al., 2006a; Sand et al., 2010). Subtle differences in thermal pain thresholds across body locations usually requires moderate to large participants numbers, which may be why the low patient number in this study (n = 12) was unable to detect these subtle differences in sensitivity.

Unlike my findings in pain-free participants (chapter 4) and patients with medication overuse headache (chapter 5), significant correlations were not observed between patients' cold and heat pain thresholds and their response to the thermal grill illusion. Similarly, neither intensity of pain nor duration of pain correlated with patients' response to the thermal grill illusion, consistent with my previous findings in chapter 4 and 5. Of particular interest was that duration of pain significantly correlated with patients cold and heat pain thresholds on the left cheek as well as left and right palm, such that patients who had experienced chronic tension-type headache for the longest duration of time were less sensitive to both cold and heat pain. However, no significant correlations were observed on the right cheek. Differences in correlations between the left and right cheek are surprising as no significant differences in thermal pain thresholds were observed between body sides. Correlations between duration of pain and patients thermal pain thresholds were previously not observed in patients with sciatica (chapter 4) or patients with medication overuse headache (chapter 5), and may initially appear paradoxical. Previously, duration of pain was demonstrated to negatively correlate with grey matter volume in pain processing areas of the brain in patients with chronic tension-type headache, such that patients whom had suffered with their headache for the longest duration of time had the least grey matter volume in those regions (Schmidt-Wilcke et al., 2005). Of interest was that decreases in grey matter volume were not observed in patients with medication overuse headache, indicating that the pathophysiology of these

two chronic headache conditions differs (Schmidt-Wilcke et al., 2005). Greater decreases in grey matter volume in pain processing areas of the brain in patients whom had experienced pain for the longest duration of time may underlie the abovementioned negative correlation between duration of pain and thermal pain thresholds observed in this study.

Additionally, I wished to compare the response to the thermal grill illusion and thermal pain thresholds between patients with CTTH and pain-free volunteers (from chapter 4). Similar to my findings in patients with unilateral sciatica (chapter 4) and patients with medication overuse headache (chapter 5), no significant differences were observed in response to the thermal grill between patients with CTTH and pain-free participants at all body locations. However, similar to patients with unilateral sciatica (chapter 4) there was a general pattern of reduced response to the thermal grill in patients with CTTH compared to pain-free participants, albeit to a lesser magnitude than for sciatica patients, again suggesting that any real differences observed between pain-free participants and patients with chronic pain in chapter 3 are not robust or that the true effect size is small. Unlike my patients with unilateral sciatica in chapter 4, patients in this study were not required to withdrawal their analgesic use prior to each testing session. Therefore, the use of analgesics, and not only the presence of chronic pain, may have had an effect on patients' response to the thermal grill illusion, thus confounding the interpretation of these findings. Unlike my previous findings in patients with MOH, no significant differences were observed in response to cold and heat pain threshold between patients with CTTH and pain-free participants at all body locations. In chapter 5, patients with MOH demonstrated cold hyperalgesia on the right cheek compared to pain-free participants, and although not significant appeared to display cold hyperalgesia on the left cheek as well. Differences in response to thermal stimuli between patients with CTTH and MOH may be due to the low patient number in this study (n = 12) and the high patient number in chapter 5 (n = 33), as Langemark and colleagues (1989) previously demonstrated

that patients with CTTH were hyperalgesic to both cold and heat pain compared to pain-free participants at both cephalic (face) and extracephalic (hand) sites in a larger cohort of patients (n = 32).

The final aim of this study was to longitudinally compare the test-retest reliability of both the response to the thermal grill illusion and thermal pain thresholds in CTTH patients that were allocated to the sham group. In this study, the response to the thermal grill varied from baseline to treatment day 10 (study day 12) to study visit 11 (study day 15), indicating poor test-retest reliability of the thermal grill illusion over time. Generally the response to the thermal grill decreased over time, suggesting habituation to the illusion. Similar to patients with MOH (chapter 5), perhaps patient's perceived treatment group allocation or their attention and anticipation to pain may have influenced their response to the thermal grill illusion, thus warrants further investigation (as discussed in chapter 5). Consequently, additional testing is required to determine the repeatability of the thermal grill illusion in pain-free volunteers and patients with chronic pain to exclude any confounding effects CTTH patients' assigned to the sham group may have had and to take into consideration participants attention and anticipation to pain. Unlike the response to the thermal grill illusion, both cold and heat pain thresholds did not differ across the 15 day testing period at all body locations, demonstrating good test-retest reliability of thermal pain threshold detection using the method of limits over time, replicating previous studies (as discussed in chapter 5).

In conclusion, both the response to the thermal grill illusion and cold and heat pain thresholds were unaltered following 10 days of active tDCS treatment compared to the sham treatment group, therefore similar to chapter 5, a conclusion as to whether the thermal grill can detect the efficacy of pain modifying therapies that cannot be detected by thermal quantitative

sensory testing cannot be made. In addition, following an hour-long stressful mental task, patients' response to the thermal grill illusion and their cold and heat pain thresholds did not differ between patients receiving active tDCS or sham treatment, nor did patients response to the thermal grill and their cold and heat pain thresholds differ post-stressful mental task compared to pre-stressful mental task, demonstrating that the thermal grill illusion and thermal pain threshold testing are most likely not sensitive to stress. Therefore, both the thermal grill and thermal quantitative sensory testing are unlikely to be suitable tools to investigate the effect of Cathcart and colleagues (2010) stressful mental task. Similar to my findings in chapter 5, the test-retest reliability of the thermal grill appeared to be poor compared to thermal pain threshold testing, thus questioning the utility of the thermal grill illusion in longitudinal studies. Lastly, the response to the thermal grill illusion did not significantly differ between patients with CTTH and pain-free participants, although a pattern of reduced response to the thermal grill illusion was observed in patients with CTTH, similar to that observed in patients with unilateral sciatica (chapter 4), albeit to a lesser magnitude. These findings suggest that any real differences observed between pain-free participants and patients with chronic pain in chapter 3 are not robust or that the true effect size is small. Consequently, these findings question the utility of the thermal grill as a tool to investigate pain and temperature dysfunction in patients with CTTH.

Tables

Table 6.1. Patient Demographics

Participant Number	Gender	Age	Avg. Pain Score (Visual Analogue Scale, 0-100)	Duration of Pain (years)	Concomitant analgesics / adjuncts
1	M	49	37	30	Paracetamol, codeine, doxylamine,
2	F	35	38	24	Paracetamol, codeine
3	M	49	50	30	Aspirin
4	F	41	60	10	-
5	F	28	36	22	Paracetamol, ibuprofen
6	M	55	58	5	Paracetamol, codeine, doxylamine
7	F	41	36	8	Aspirin, ibuprofen, codeine
8	M	51	72	25	Paracetamol
9	M	29	56	14	Paracetamol, ibuprofen
10	F	19	41	2	Paracetamol, ibuprofen, codeine
11	F	28	71	10	-
12	M	33	31	13	Ibuprofen
-	6F, 6M	38.2 ± 11.3[a]	48 ± 14[a]	15.3 ± 9.4[a]	-

[a]: mean ± standard deviation

The response to the thermal grill illusion was compared between patients' body side (Table 6.2) and body location (Table 6.3) for each thermal grill outcome (listed vertically) at each thermal grill configuration (listed horizontally). Mean differences and 95% CI for differences presented. Significant values represented by bold text.

Table 6.2. Effect of Body Side to the Thermal Grill Response

	Left Cheek vs. Right Cheek			Left Palm vs. Right Palm		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	**4 mm (0 to 7)**	3 mm (-1 to 6)	3 mm (-1 to 6)	5 mm (-5 to 15)	-1 mm (-11 to 9)	4 mm (-6 to 14)
Intensity of Heat	3 mm (-5 to 10)	4 mm (-4 to 12)	4 mm (-4 to 12)	1 mm (-5 to 7)	-2 mm (-8 to 3)	3.6 mm (-2 to 9)
Intensity of Heat (c)	3 mm (-9 to 15)	-1 mm (-13 to 11)	-1 mm (-13 to 11)	5 mm (0 to 11)	-1 mm (-7 to 5)	1 mm (-4 to 7)
Unpleasantness	5 mm (-4 to 13)	4 mm (-5 to 12)	-4 mm (-12 to 5)	4 mm (-5 to 14)	0 mm (-10 to 9)	5 mm (-4 to 14)
Tolerability	0 mm (-4 to 4)	1 mm (-3 to 5)	0 mm (-4 to 4)	3 mm (-4 to 10)	2 mm (-5 to 9)	0 mm (-7 to 7)

ºC: degrees Celsius; C: colour bar.

Table 6.3. Effect of Body Location to the Thermal Grill Response

	Right Palm vs. Right Cheek			Left Palm vs. Left Cheek		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	4 mm (-2 to 11)	6 mm (0 to 12)	6 mm (0 to 12)	6 mm (-3 to 14)	2 mm (-6 to 11)	7 mm (-1 to 16)
Intensity of Heat	**10 mm (2 to 18)**	**13 mm (5 to 21)**	7 mm (-1 to 15)	**8 mm (1 to 14)**	**7 mm (0 to 14**)	6 mm (0 to 13**)**
Intensity of Heat (c)	**10 mm (1 to 19)**	6 mm (-4 to 15)	4 mm (-6 to 13)	**12 mm (5 to 20)**	3 mm (-5 to 11)	6 mm (-2 to 13)
Unpleasantness	3 mm (-5 to 11)	3 mm (-5 to 11)	-2 mm (-10 to 6)	2.5 (-6.9 to 11.9)	-1 mm (-10 to 9)	6 mm (-3 to 16)
Tolerability	0 mm (-7 to 7)	2 mm (-5 to 10)	4 mm (-3 to 11)	1 mm (-5 to 7)	3 mm (-2 to 9)	4 mm (-2 to 10)

ºC: degrees Celsius; C: colour bar.

Table 6.4. Correlations Between Cold and Heat Thresholds and the Response to the Thermal Grill Illusion

R and *P* values from the correlation analyses performed at patients right and left cheek and palm are presented (described previously on page 94). Significant values represented by bold text.

		Cold Pain Threshold			Heat Pain Threshold		
	Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Right Cheek	Intensity of Pain						
	R value	0.45	0.26	0.41	-0.22[p]	-0.1[p]	-0.38[p]
	P value	0.14	0.41	0.19	0.44[p]	0.7[p]	0.22[p]
	Intensity of Heat						
	R value	0.36	0.56	0.27	-0.53[p]	-0.52[p]	-0.37[p]
	P value	0.25	0.059	0.39	0.078[p]	0.084[p]	0.23[p]
	Intensity of Heat (c)						
	R value	0.58[p]	**0.77[p]**	0.48[p]	-0.51[p]	-0.53[p]	-0.44[p]
	P value	0.048[p]	**0.0031[p]**	0.11[p]	0.094[p]	0.078[p]	0.15[p]
	Unpleasantness						
	R value	0.23	0.35	0.032	-0.19[p]	-0.23[p]	-0.27[p]
	P value	0.47	0.26	0.93	0.52[p]	0.44[p]	0.37[p]
	Tolerability						
	R value	0.18[p]	0.28[p]	0.11[p]	-0.23[p]	-0.19[p]	-0.32[p]
	P value	0.57[p]	0.39[p]	0.73[p]	0.45[p]	0.48[p]	0.3[p]
Left Cheek	Intensity of Pain						
	R value	0.6	0.41	0.46	-0.58	-0.45	-0.43
	P value	0.042	0.18	0.13	0.049	0.13	0.15
	Intensity of Heat						
	R value	0.61[p]	0.48[p]	**0.71[p]**	-0.37[p]	-0.23[p]	-0.64[p]
	P value	0.034[p]	0.11[p]	**0.0093[p]**	0.24[p]	0.35[p]	0.024[p]
	Intensity of Heat (c)						
	R value	0.48[p]	0.26[p]	0.48[p]	-0.27[p]	-0.099[p]	-0.4[p]
	P value	0.11[p]	0.41[p]	0.11[p]	0.4[p]	0.76[p]	0.19[p]
	Unpleasantness						
	R value	0.51	0.43	0.53	-0.53	-0.43	-0.54
	P value	0.092	0.16	0.077	0.075	0.14	0.069
	Tolerability						
	R value	0.4	0.39	0.65	-0.45	-0.38	-0.65
	P value	0.19	0.21	0.027	0.14	0.2	0.02

		Cold Pain Threshold			Heat Pain Threshold		
	Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Right Palm	Intensity of Pain						
	R value	0.53	0.46	0.44	-0.6[p]	-0.61[p]	-0.54[p]
	P value	0.082	0.14	0.15	0.038[p]	0.034[p]	0.071[p]
	Intensity of Heat						
	R value	0.46	0.44	0.24	-0.63[p]	-0.55[p]	-0.46[p]
	P value	0.13	0.15	0.45	0.029[p]	0.063[p]	0.13[p]
	Intensity of Heat (c)						
	R value	0.5	0.65	0.72	-0.52[p]	-0.62[p]	-0.64[p]
	P value	0.099	0.025	0.011	0.083[p]	0.032[p]	0.026[p]
	Unpleasantness						
	R value	0.47	0.52	0.35	-0.42	-0.38	-0.27
	P value	0.13	0.088	0.26	0.17	0.2	0.39
	Tolerability						
	R value	0.46	0.57	0.49	-0.42	-0.45	-0.44
	P value	0.13	0.055	0.11	0.15	0.13	0.14
Left Palm	Intensity of Pain						
	R value	0.32[p]	0.26[p]	0.23[p]	-0.41[p]	-0.15[p]	-0.39[p]
	P value	0.31[p]	0.42[p]	0.48[p]	0.19[p]	0.63[p]	0.21[p]
	Intensity of Heat						
	R value	0.48[p]	0.55[p]	0.45[p]	-0.64[p]	-0.63[p]	-0.67[p]
	P value	0.11[p]	0.063[p]	0.14[p]	0.026[p]	0.027[p]	0.016[p]
	Intensity of Heat (c)						
	R value	0.47[p]	0.51[p]	0.62[p]	-0.39[p]	-0.40[p]	-0.69[p]
	P value	0.12[p]	0.092[p]	0.032[p]	0.21[p]	0.2[p]	0.014[p]
	Unpleasantness						
	R value	0.44[p]	0.28[p]	0.23[p]	-0.46[p]	-0.35[p]	-0.4[p]
	P value	0.15[p]	0.37[p]	0.47[p]	0.14[p]	0.27[p]	0.2[p]
	Tolerability						
	R value	0.58	0.43	0.36	-0.26	-0.23	-0.19
	P value	0.05	0.16	0.25	0.4	0.46	0.55

ºC: degrees Celcius; C: colour bar; [p]: analysed with Pearson's correlation. Significance level < 0.00333.

Table 6.5. Baseline Characteristics of the Thermal Grill Response: Pain-free Participants vs. Patients with Chronic Tension-Type Headache

The response to the thermal grill illusion was compared between pain-free participants and patients with chronic tension-type headache at participants' right and left cheek and palm for all five thermal grill outcomes. *P* values are presented.

	Right Cheek	Left Cheek	Right Palm	Left Palm
Intensity of Pain	0.51	0.6	0.48	0.76
Intensity of Heat	0.38	0.45	0.66	0.85
Intensity of Heat (c)	0.71	0.46	0.78	0.86
Unpleasantness	0.67	0.43	0.35	0.55
Tolerability	0.2	0.087	0.19	0.3

C: colour bar.

The response to the thermal grill illusion was compared between patients assigned to the tDCS and patients assigned to the sham treatment groups from baseline to study visit 11 (Table 6.6) and pre- vs. post-stressful mental task (Table 6.7) for each thermal grill outcome (listed vertically) at each thermal grill configuration (listed horizontally). *P* values are presented. Significant values represented by bold text.

Table 6.6. Comparison of the Thermal Grill Response Between Patients Assigned to the tDCS and Sham Treatments Groups: Baseline to Study Visit 11

	Right Cheek			Left Cheek			Right Palm			Left Palm		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	0.99	0.75	0.67	0.99	0.89	0.94	0.23	0.53	0.41	0.1	0.77	0.47
Intensity of Heat	0.95	0.55	0.83	0.95	0.82	0.74	0.27	0.53	0.53	0.26	0.39	0.44
Intensity of Heat (c)	0.79*	0.82	0.92	0.92	0.92	0.94	0.82	0.91	1.0	0.98	0.99	0.94
Unpleasantness	0.88	0.61	0.51	0.92	0.77	0.51	0.16	0.75	0.34	0.36	0.48	0.26
Tolerability	0.75	0.43	0.37	0.45	0.39	0.25	0.03	0.13	0.093	0.08	0.28	0.92*

ºC: degrees Celsius; C: colour bar *: B0 was not constrained in these analyses.

Table 6.7. Comparison of the Thermal Grill Response Between Patients Assigned to the tDCS and Sham Treatments Groups: Pre- vs. Post-stressful Mental Task

	Right Cheek			Left Cheek			Right Palm			Left Palm		
Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Intensity of Pain	0.91	0.61	0.41	0.88	0.49	0.57	0.6	0.64	0.65	0.48	0.42	0.36
Intensity of Heat	0.61	0.41	0.33	0.7	0.63	0.33	0.66	0.21	0.38	0.41	0.35	0.35
Intensity of Heat (c)	**0.047**	0.41	0.85	0.41	0.24	0.81	0.46	0.8	0.72	0.78	0.9	0.91
Unpleasantness	0.45	0.34	0.25	0.75	0.21	0.13	0.58	0.47	0.47	0.56	0.42	0.27
Tolerability	0.35	0.31	0.24	0.55	0.17	0.14	0.27	0.18	0.19	0.19	0.18	0.066

ºC: degrees Celsius; C: colour bar.

Table 6.8. Comparison of the Thermal Grill Response in all Patients Pre- vs. Post-stressful Mental Task

The response to the thermal grill illusion was compared pre- vs. post-stressful mental task in all patients combined (n = 12) at patients right and left cheek and palm for all five thermal grill outcomes (listed vertically) at each thermal grill configuration (listed horizontally). *P* values are presented.

	Right Cheek	Left Cheek	Right Palm	Left Palm
Intensity of Pain	0.36	0.66	0.9	0.46
Intensity of Heat	0.16	0.57	0.26	0.6
Intensity of Heat (c)	0.07	0.89	0.28	0.6
Unpleasantness	0.41	0.26	0.32	0.62
Tolerability	0.29	0.1	0.13	0.51

C: colour bar.

Figures

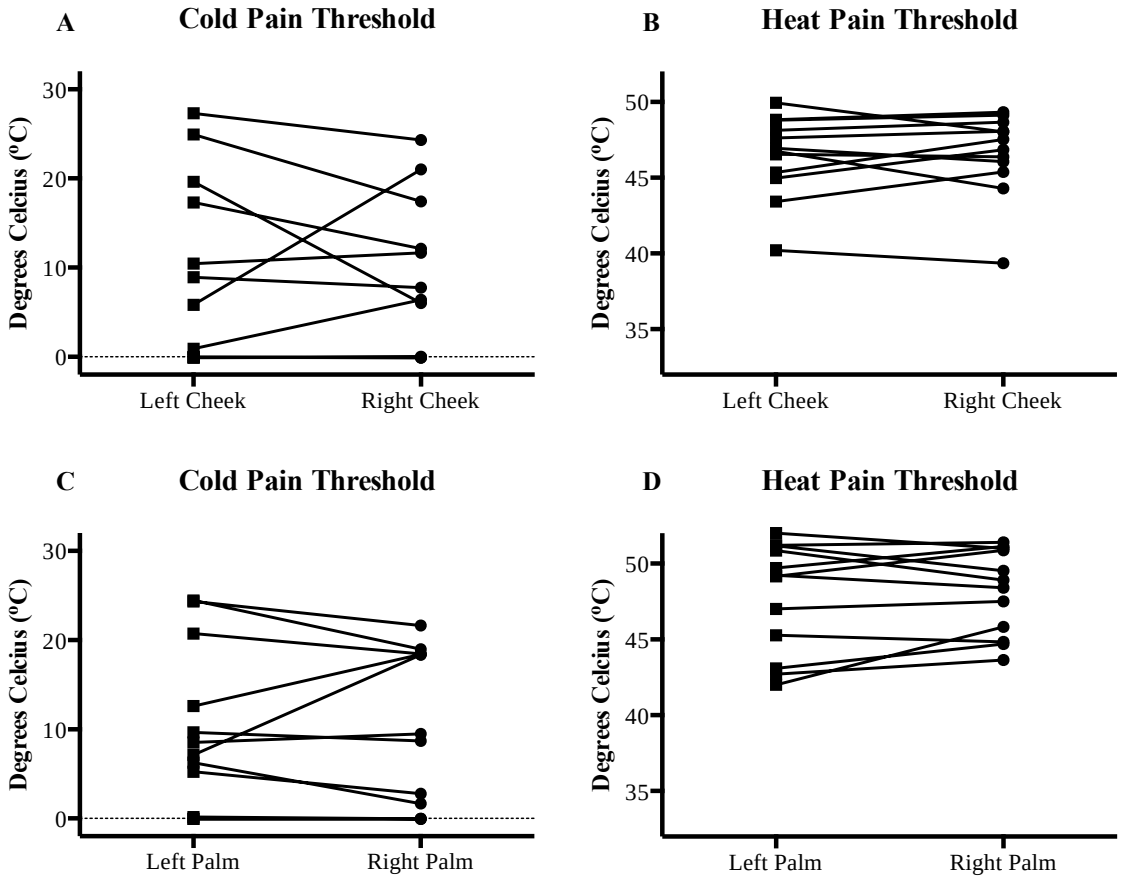


Figure 6.2. Effect of body side: cold and heat pain thresholds.

Cold and heat pain thresholds at the cheek (A, B) and palm (C, D) on patients left and right side. No significant differences were observed between patients' right and left cheek for cold (A)($p = 0.73$) and heat pain thresholds (B)($p = 0.79$), or between patients' right and left palm for cold (C)($p = 0.44$) and heat pain thresholds (D)($p = 0.47$).

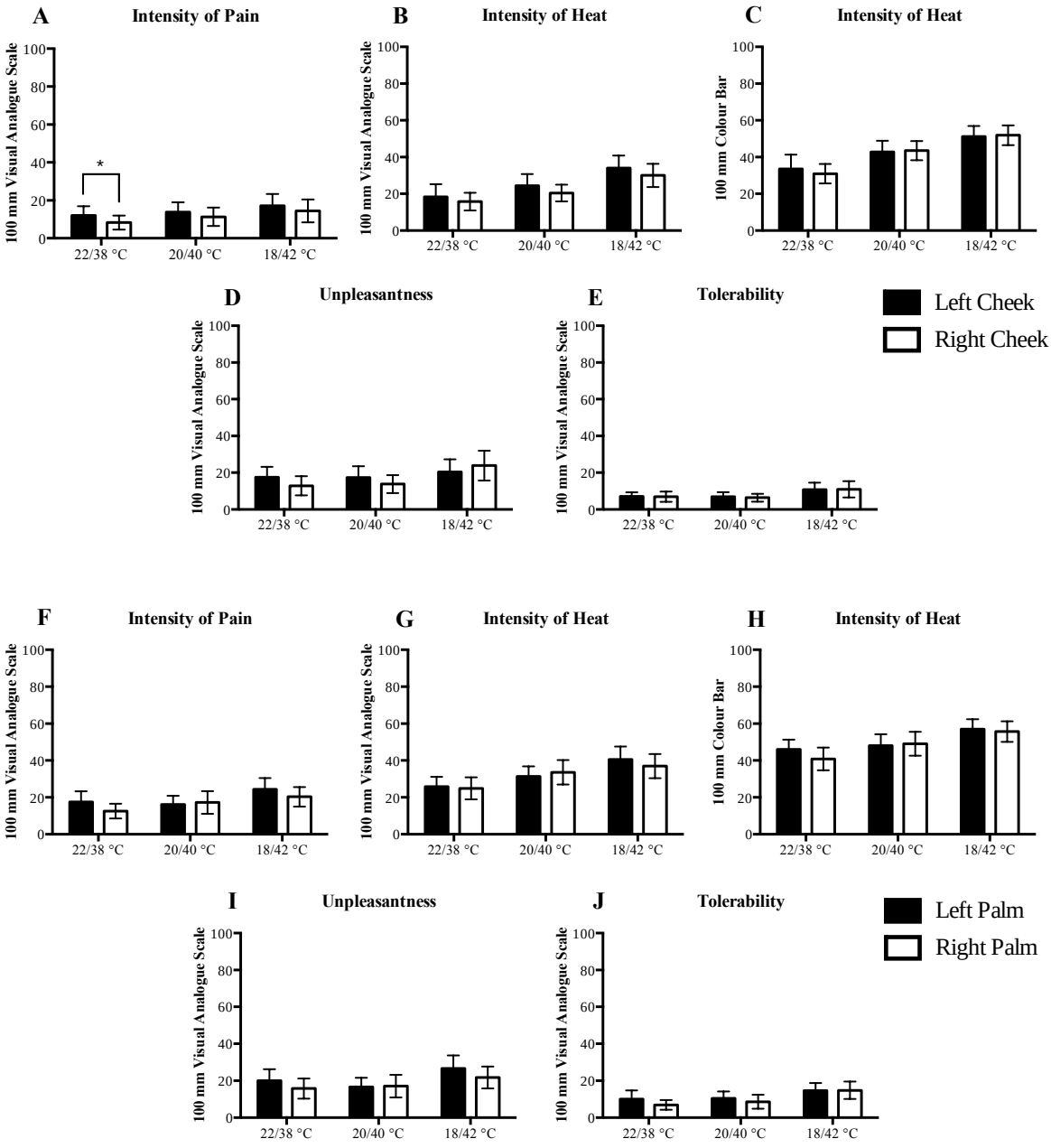


Figure 6.3. Effect of body side: thermal grill response.

The response to the thermal grill illusion at the cheek (A-E) and palm (F-J) on patients left (black bars) and right (white bars) side. On the cheek, significantly less pain (A) to the thermal grill illusion was observed on the left side compared to the right side at the 22/38 ºC thermal grill configuration only (see Table 6.2 for mean difference and 95% CI for difference). The response to the thermal grill did not differ between the left and right cheek for all other outcomes (B-E) or between the left and right palm for all thermal grill outcomes (F-J). Data are represented as mean ± SEM. * $P < 0.05$.

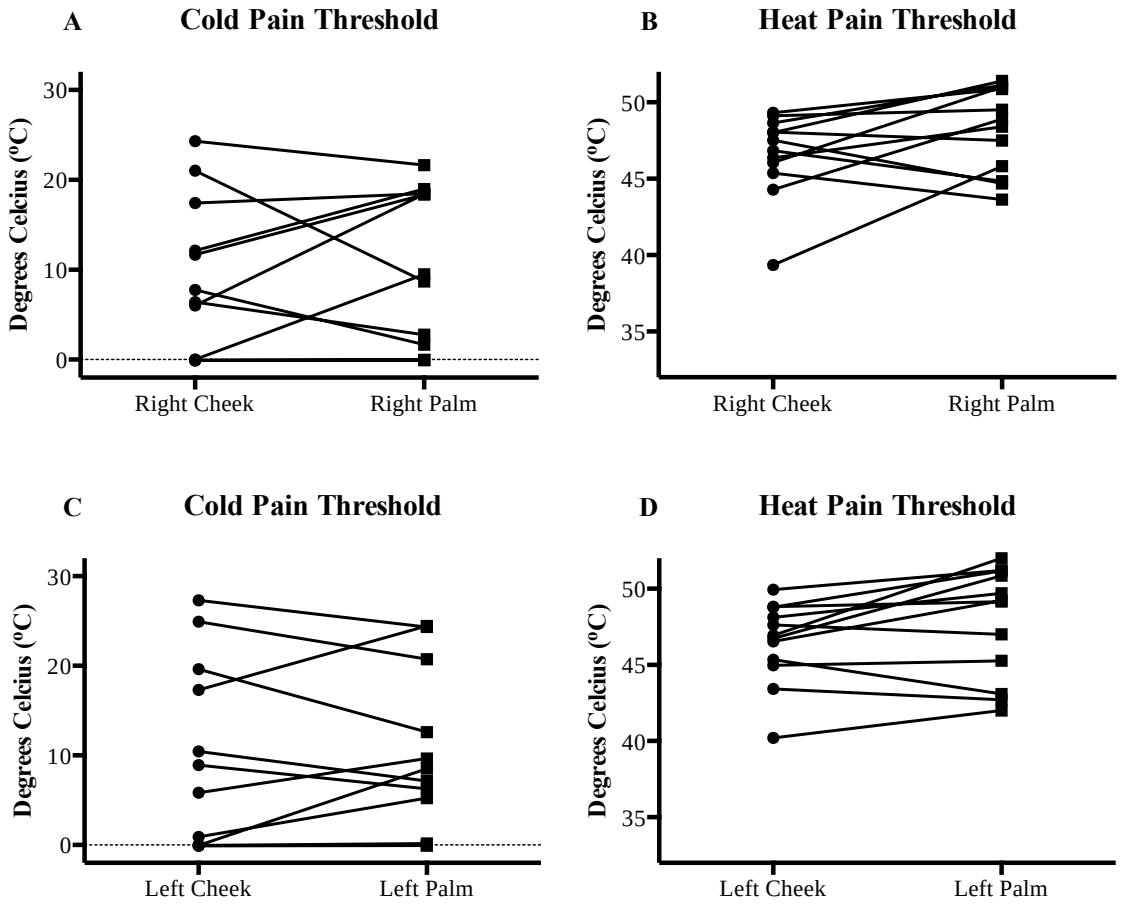


Figure 6.4. Effect of body location: cold and heat pain threshold.

Cold and heat pain thresholds at the cheek and palm on patients right (A, B) and left (C, D) side. No significant differences were observed between patients' right cheek and palm for cold ($p = 0.52$, A) and heat pain thresholds ($p = 0.13$, B), or between patients' left cheek and palm for cold ($p = 0.82$, C) and heat pain thresholds ($p = 0.05$, D), although patients' heat pain thresholds almost differed significantly between patients' left and right cheek.

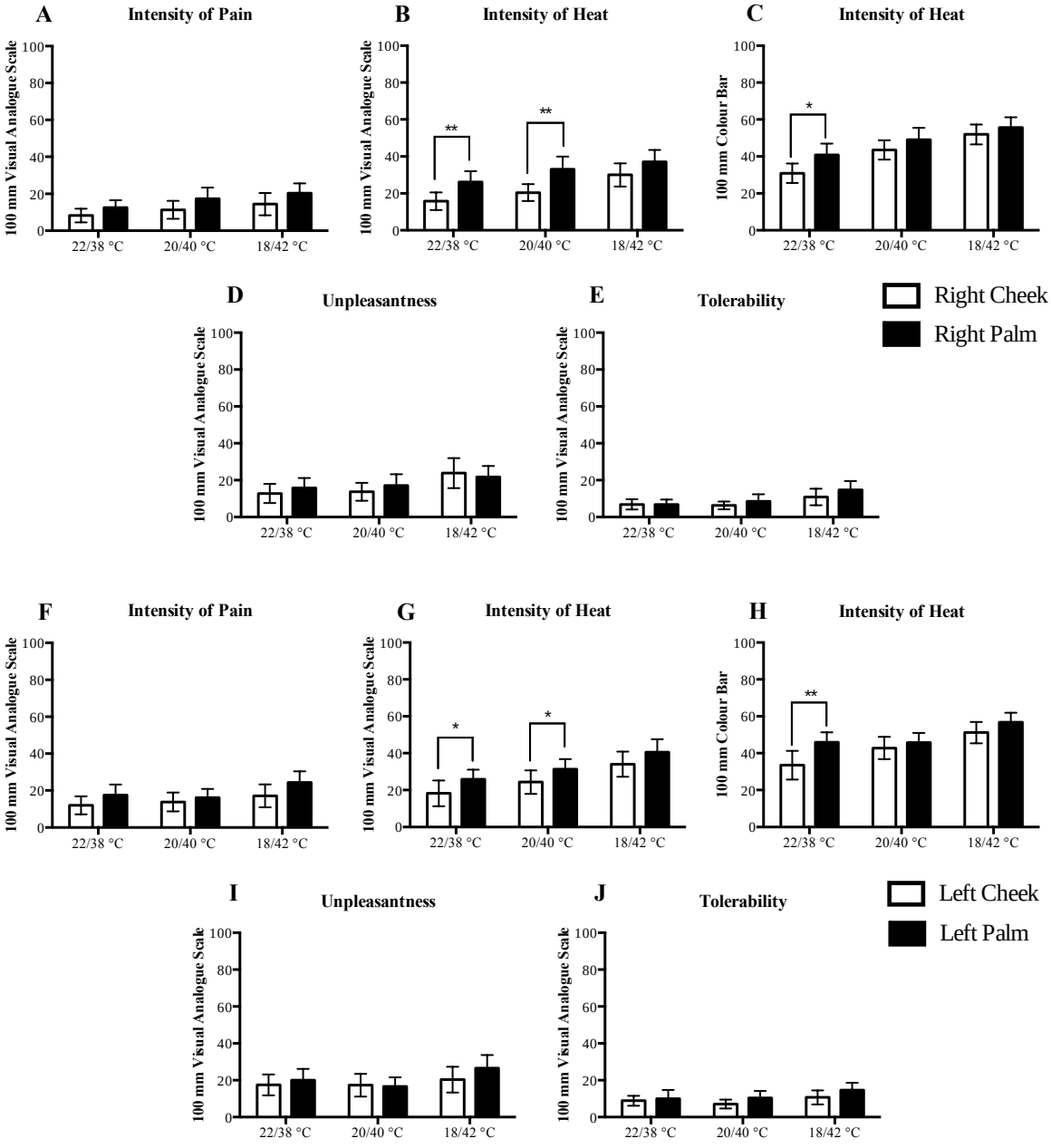


Figure 6.5. Effect of body location: thermal grill response.

The response to the thermal grill illusion at the cheek and palm on patients right (A-E) (white bars) and left (F-J) (black bars) and side. Significantly less heat to the thermal grill illusion was observed on the cheek compared to the palm on both the right (B, C) and left (G, H) side (see Table 6.3 for mean differences and 95% CI for differences). The response to the thermal grill did not differ between the cheek and palm for all other thermal grill outcomes on both the right (A, D, E) and left (F, I, J) side. Data are represented as mean ± SEM. * $P < 0.05$; ** $P < 0.01$.

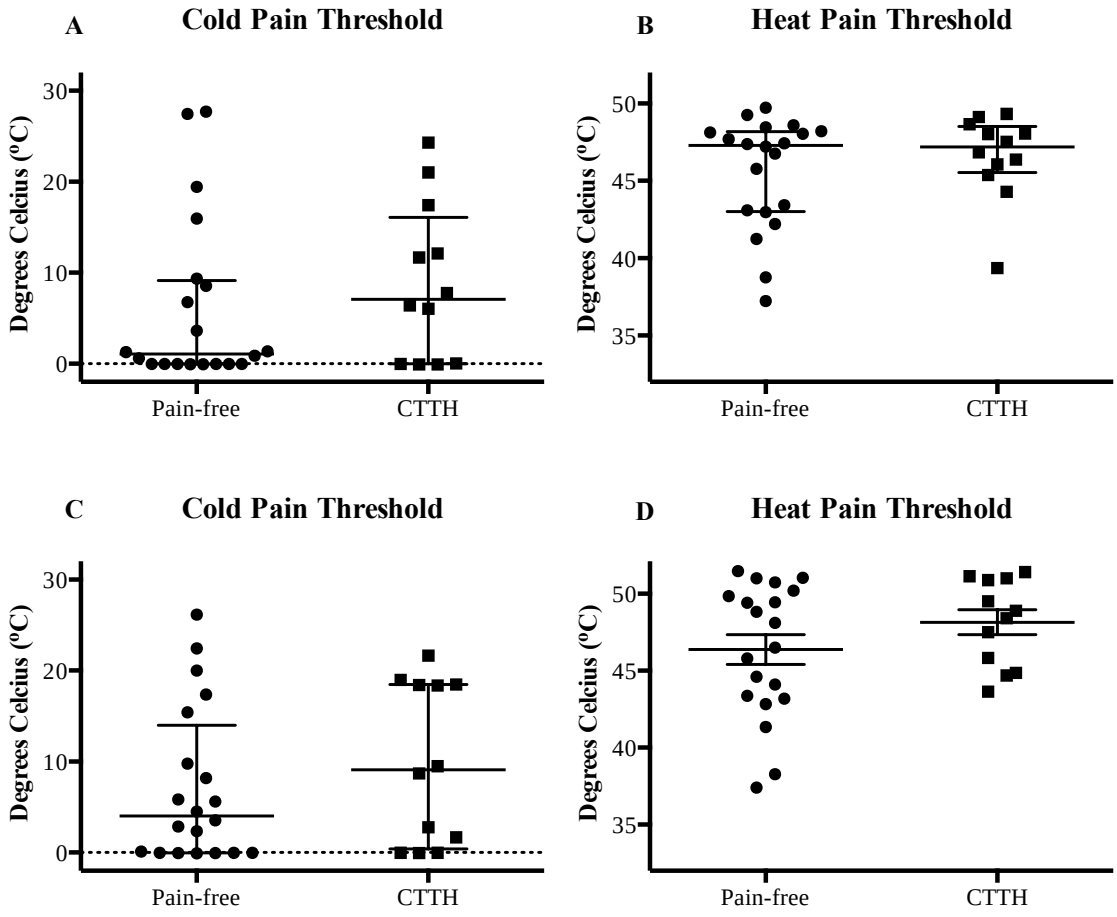


Figure 6.6. Pain-free participants versus patients with chronic tension-type headache: cold and heat pain thresholds.

Cold and heat pain thresholds at the right cheek (A, B) and palm (C, D) in pain-free participants and patients with CTTH. Cold and heat pain thresholds did not differ between pain-free participants and patients with CTTH at both the right cheek ($p = 0.44$, A and $p = 0.66$, B) and right palm ($p = 0.58$, C and $p = 0.22$, D). Graphs A, B and C are represented as median and IQR. Graph D is represented as mean ± SEM. CTTH: chronic tension-type headache.

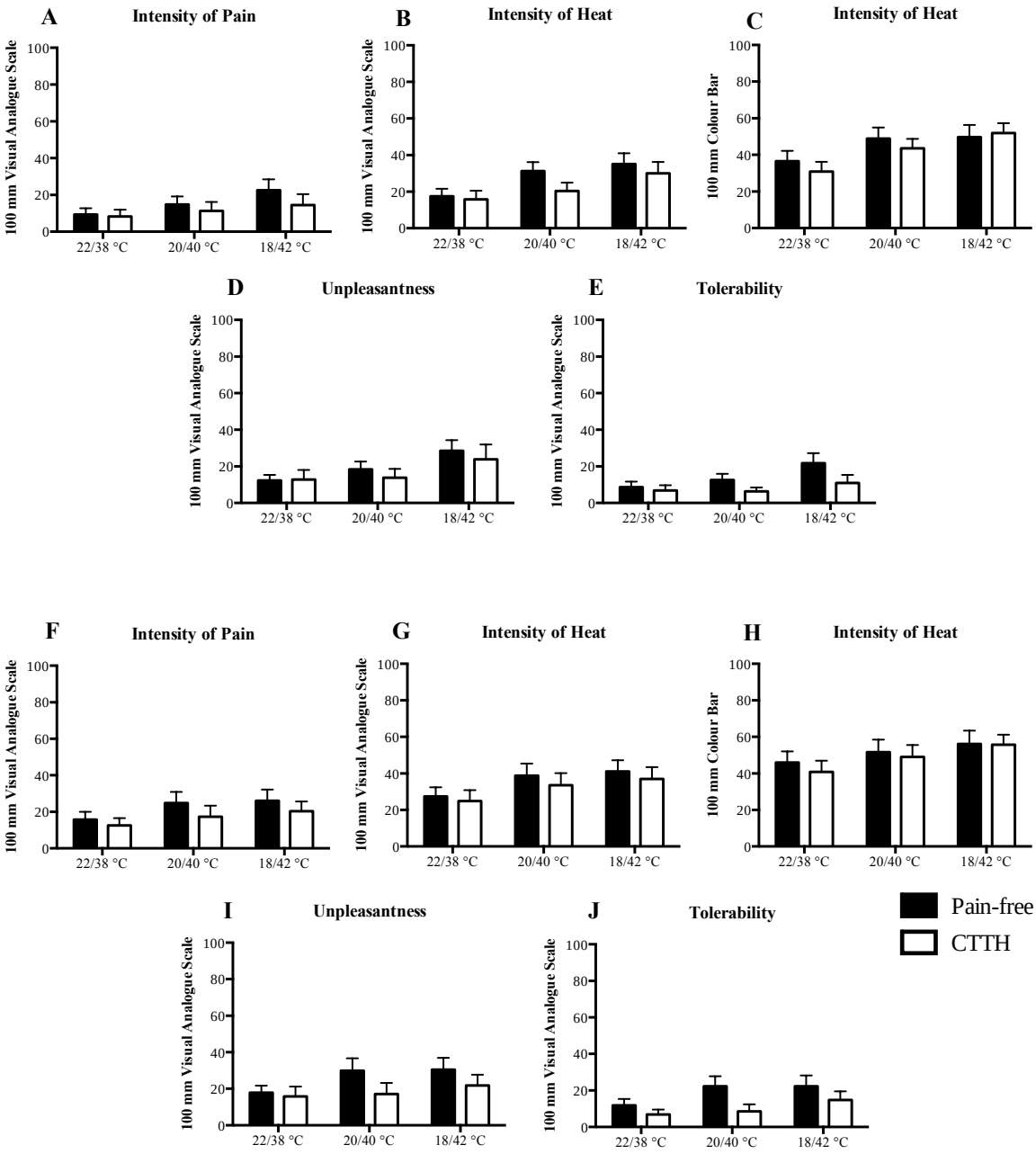


Figure 6.7. Pain-free participants versus patients with chronic tension-type headache: thermal grill response.

The response to the thermal grill illusion at the right cheek (A-E) and palm (F-J) in pain-free participants (black bars) and patients with CTTH (white bars). The response to the thermal grill did not differ between pain-free participants and patients with medication overused headache on either the right cheek (A-E) or palm (F-J) for all thermal grill outcomes. All graphs are represented as mean ± SEM. CTTH: chronic tension-type headache.

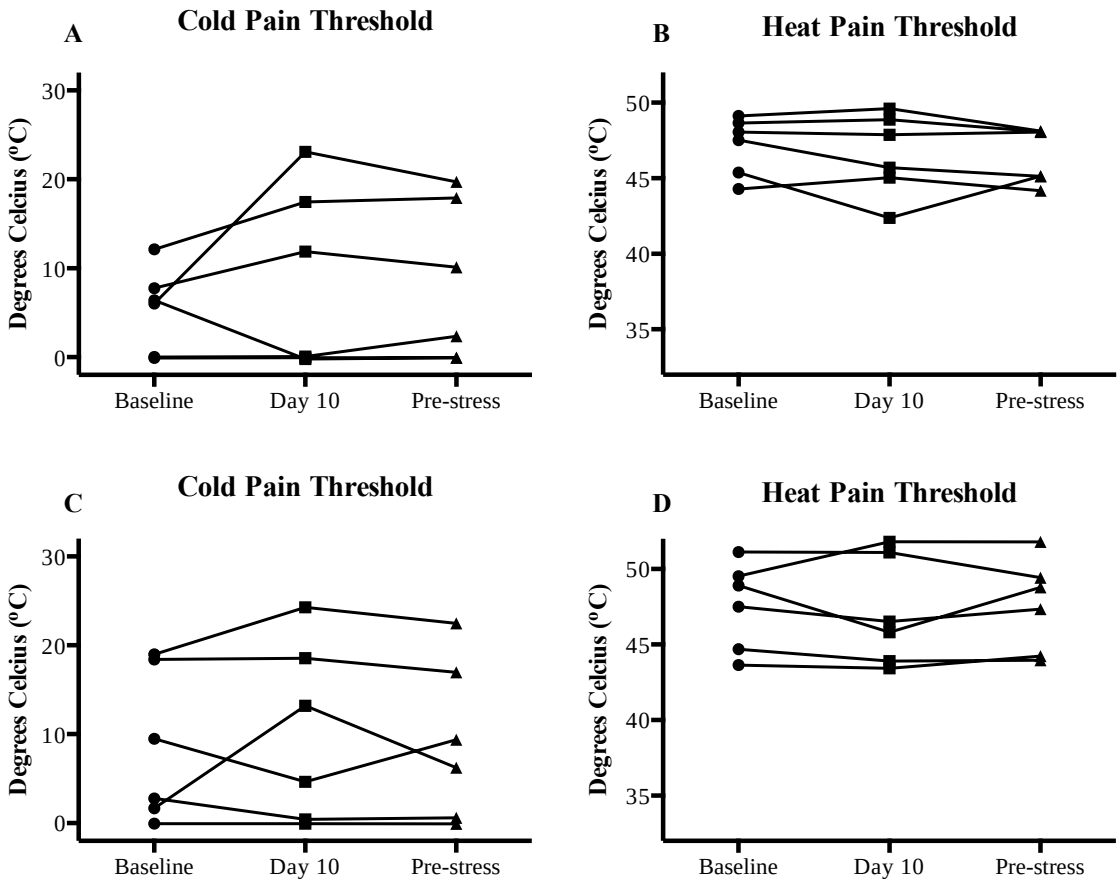


Figure 6.8. Repeatability of cold and heat pain thresholds across 15 days in patients assigned to the sham group.

Cold and heat pain thresholds at the right cheek (A, B) and palm (C, D) across three testing sessions conducted over 15 days in patients assigned to the sham treatment group. Both cold and heat pain thresholds did not significantly differ between testing sessions at both the right cheek ($p = 0.18$, A and $p = 0.2$ B) and palm ($p = 0.57$, C and $p = 0.25$, D).

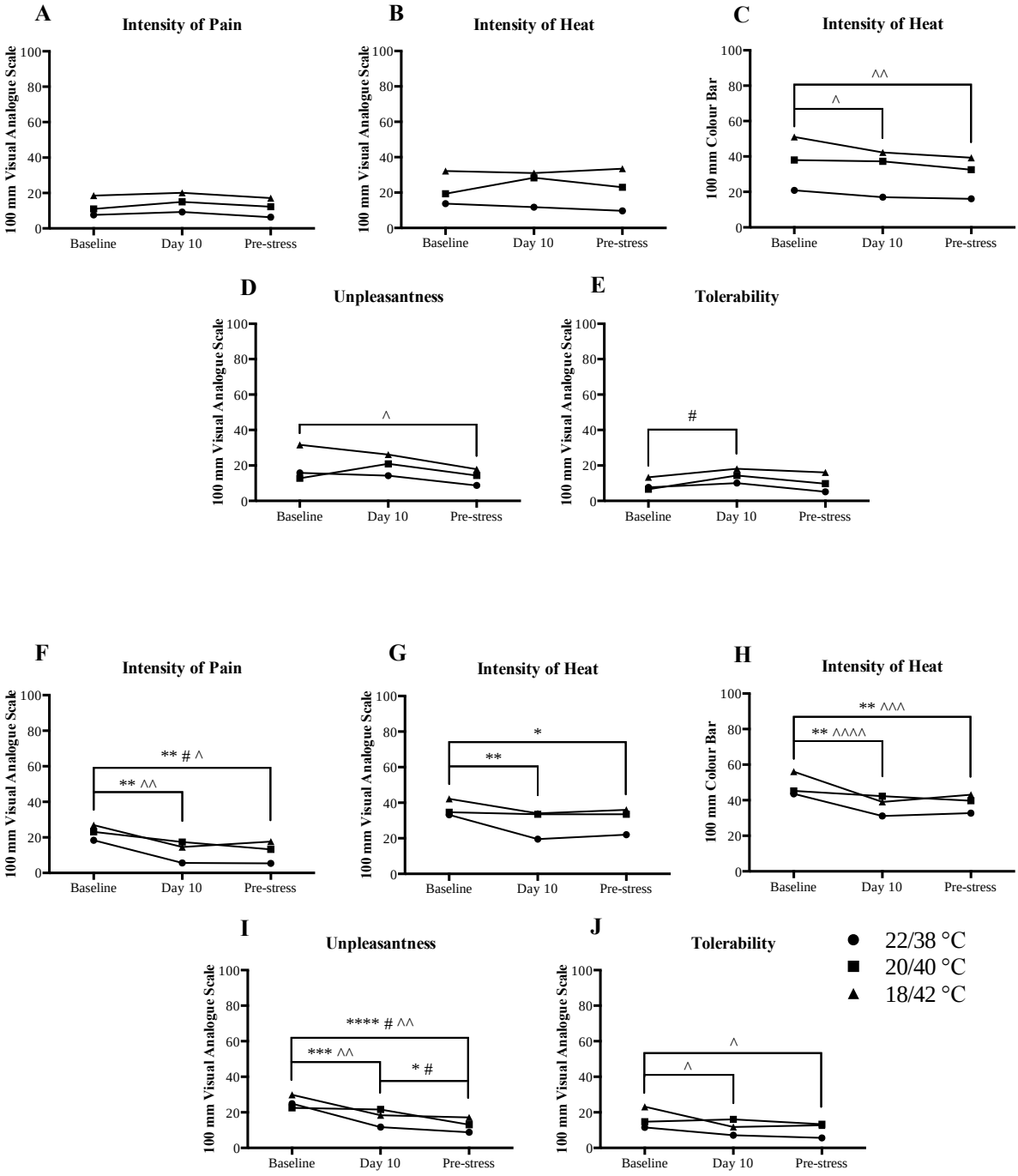


Figure 6.9. Repeatability of thermal grill illusion across 15 days in patients assigned to the sham group.

The response to the thermal grill at the right cheek (A-E) and palm (F-J) across three testing sessions conducted over 15 days in patients assigned to the sham treatment group. Generally, a decline in response to the thermal grill illusion was observed over time. Graphs are represented as mean. * $P < 0.05$ (22/38 ºC); ** $P < 0.01$ (22/38 ºC); *** $P < 0.001$ (22/38 ºC); **** $P < 0.0001$ (22/38 ºC); # $P < 0.05$ (20/40 ºC); ^ $P < 0.05$ (18/42 ºC); ^^ $P < 0.01$ (18/42 ºC); ^^^ $P < 0.001$ (18/42 ºC); ^^^^ $P < 0.0001$ (18/42 ºC).

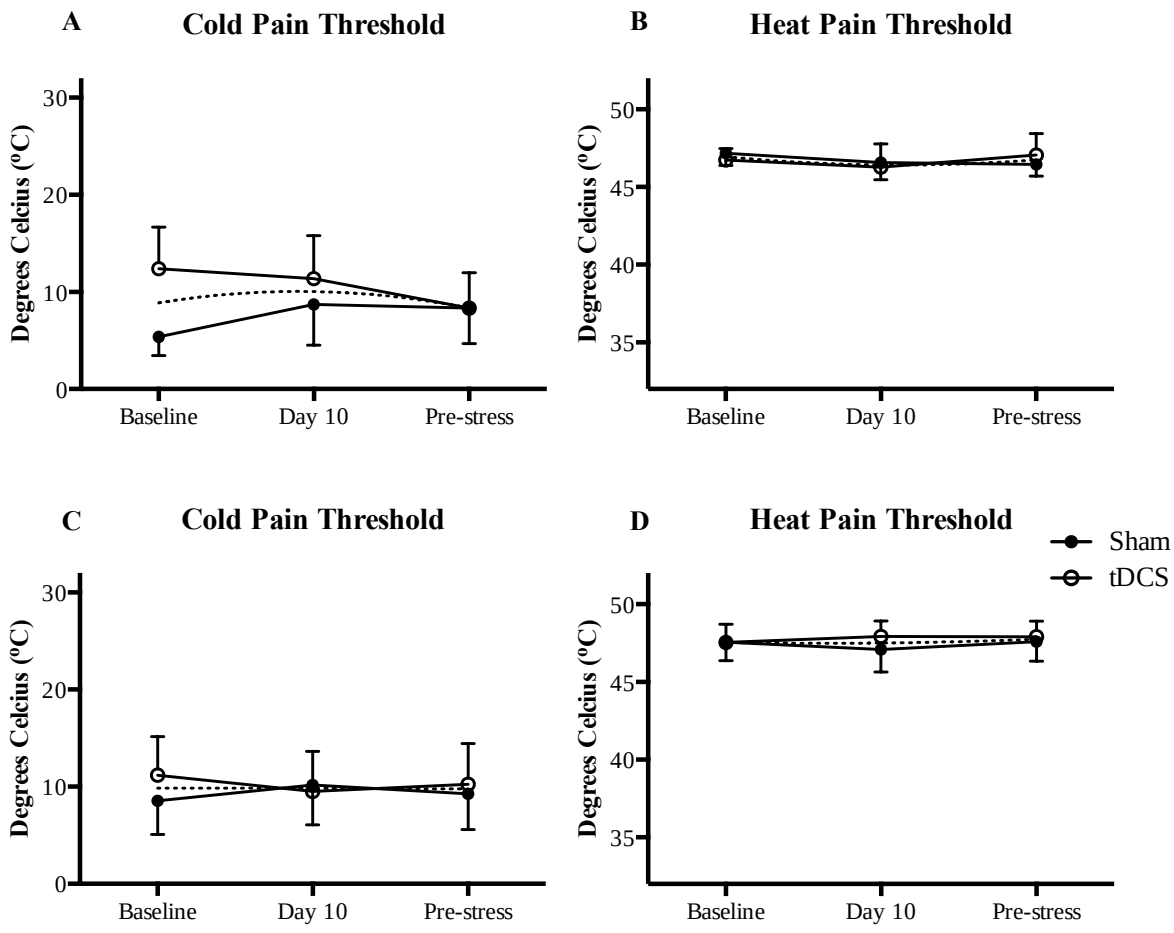


Figure 6.10. Response to tDCS (baseline to pre-stressful mental task): cold and heat pain thresholds.

Cold and heat pain thresholds at the right cheek (A, B) and palm (C, D) across three testing sessions conducted over 15 days in patients assigned to the sham and tDCS treatment groups. Comparing the tDCS and sham groups, no significant differences were observed between the effect time curves for cold pain thresholds on the right cheek (A)($p = 0.59$) or palm (C)($p = 0.96$) or heat pain thresholds on the right cheek (B)($p = 0.96$) or palm (D)($p = 0.96$). Graphs are represented as mean ± SEM.

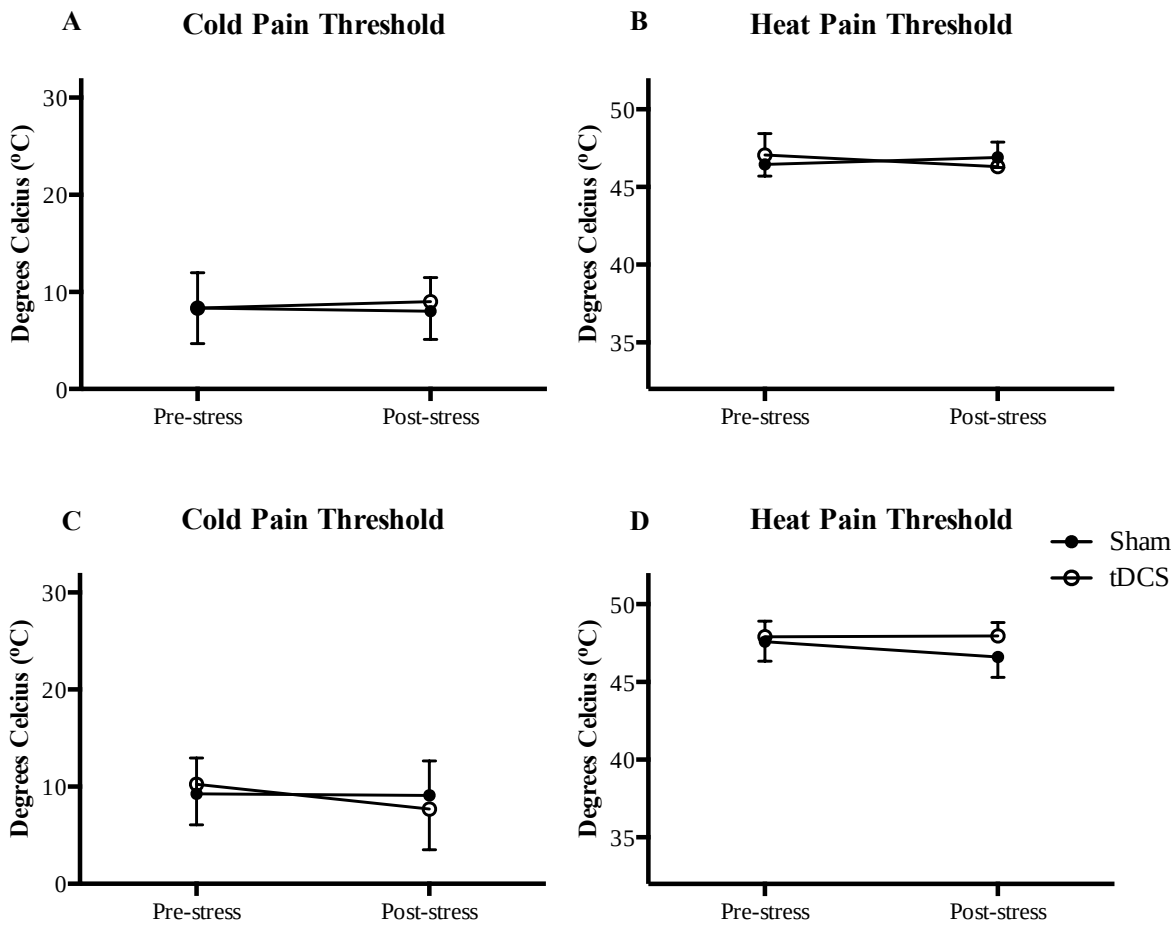


Figure 6.11. Response to tDCS (pre- to post-stressful mental task): cold and heat pain thresholds.

Cold and heat pain thresholds at the right cheek (A, B) and palm (C, D) pre- and post-stressful mental task in patients assigned to the sham and tDCS treatment groups. Comparing the tDCS and sham groups, no significant differences were observed between the effect time curves for cold pain thresholds on the right cheek (A)($p = 0.92$) or palm (C)($p = 0.97$) or heat pain thresholds on the right cheek (B)($p = 1.0$) or palm (D)($p = 0.6$). Graphs are represented as mean ± SEM.

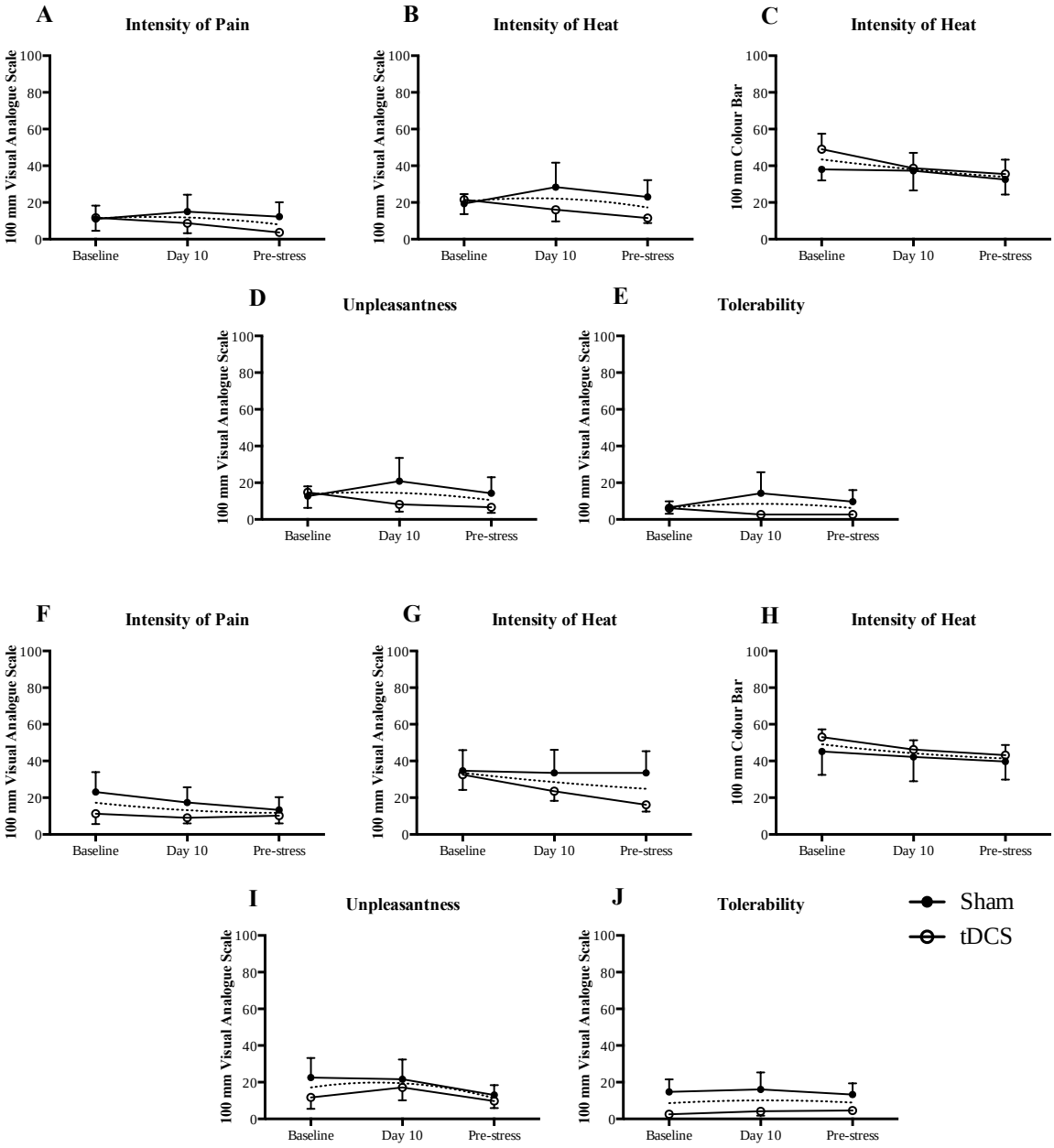


Figure 6.12. Response to tDCS (baseline to pre-stressful mental task): thermal grill response.

Response to the thermal grill illusion at the right cheek (A-E) and palm (F-J) across three testing sessions conducted over 15 days in patients assigned to the sham and tDCS treatment groups at the 20/40 ºC thermal grill configuration. Comparing the tDCS and sham groups, no significant differences were observed between the effect time curves for all thermal grill outcomes on both the right cheek (A-E) and palm (F-J). Graphs are represented as mean ± SEM.

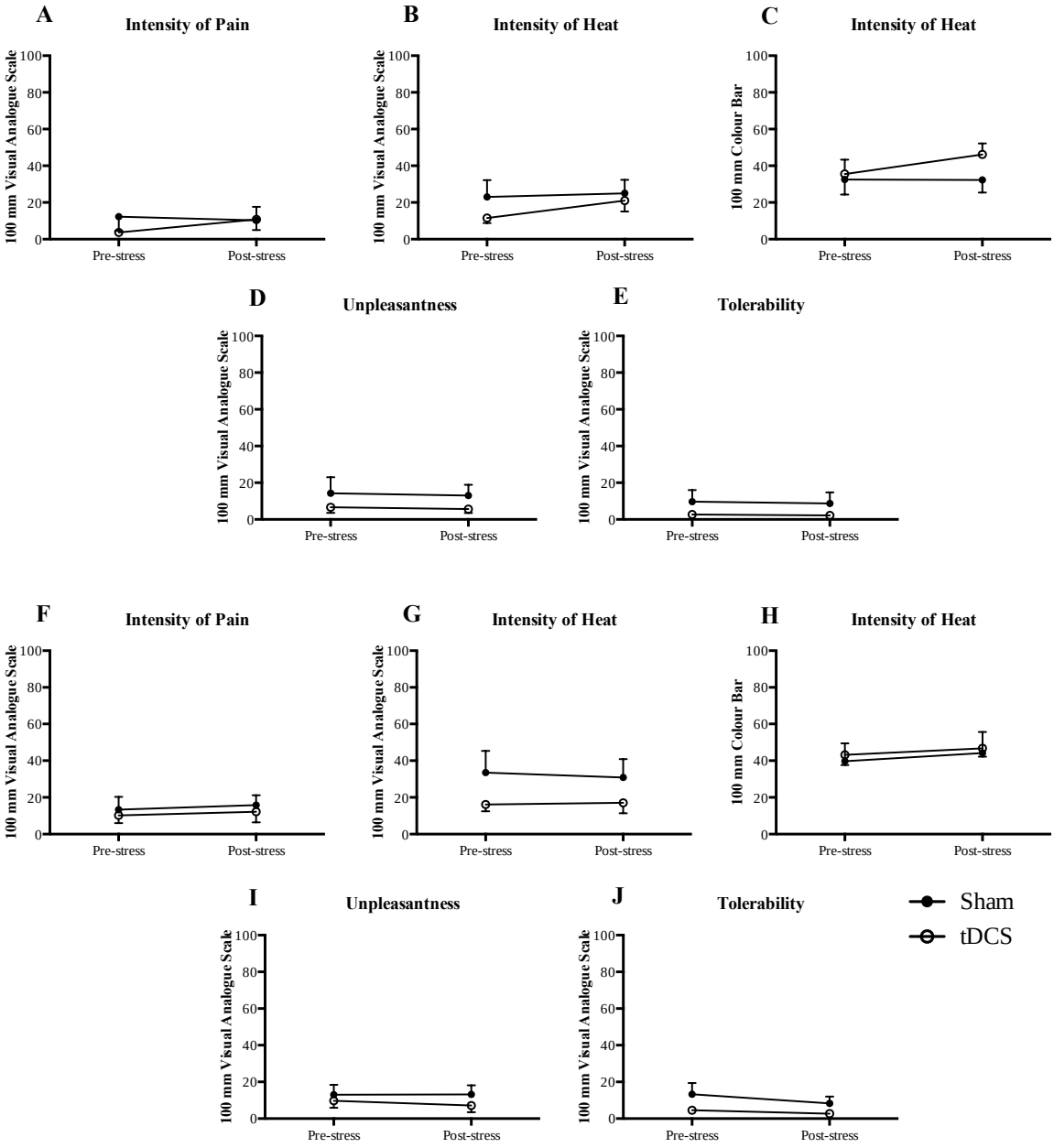


Figure 6.13. Response to tDCS (pre- to post-stressful mental task): thermal grill response.

Response to the thermal grill illusion at the right cheek (A-E) and palm (F-J) pre- and post-stressful mental task in patients assigned to the sham and tDCS treatment groups at the 20/40 ºC thermal grill configuration. Comparing the tDCS and sham groups, no significant differences were observed for all thermal grill outcomes on both the right cheek (A-E) and palm (F-J). Graphs are represented as mean ± SEM.

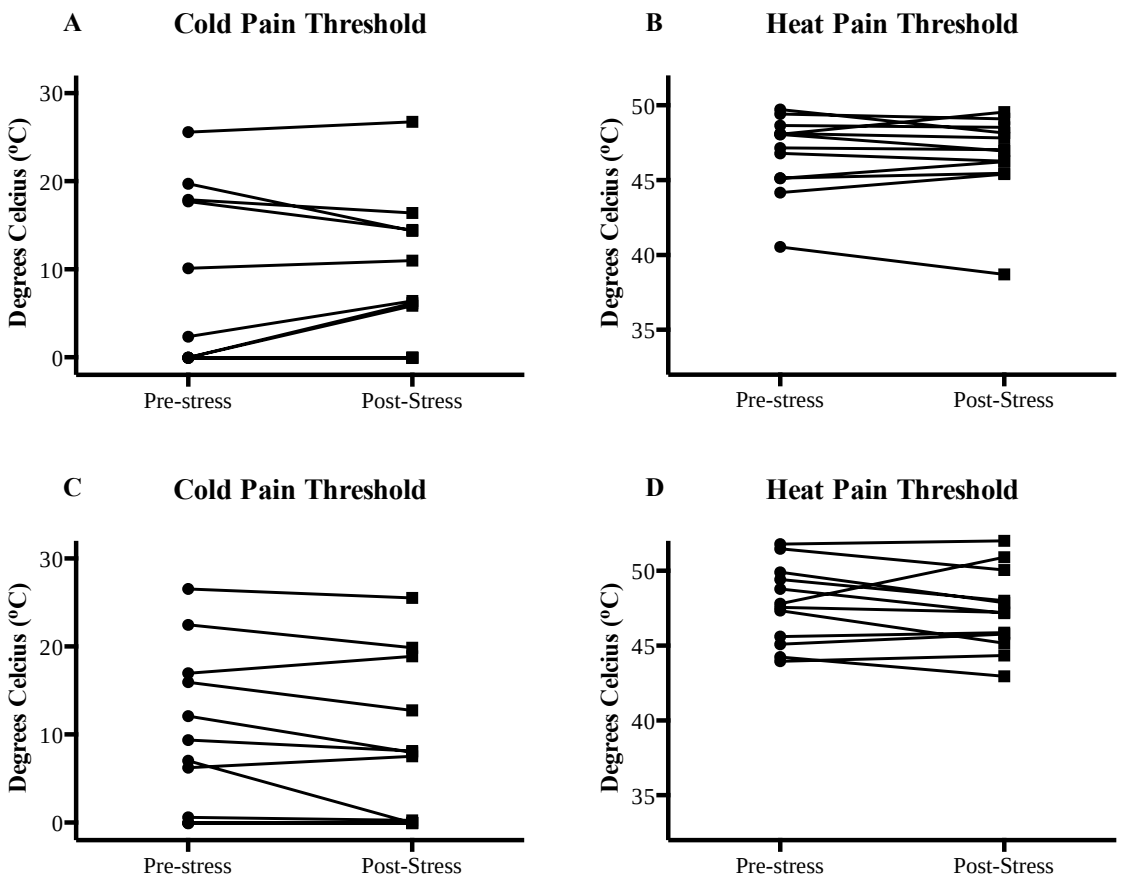


Figure 6.14. Effect of stressful mental task: cold and heat pain thresholds.

Cold and heat pain thresholds at the right cheek (A, B) and palm (C, D) pre- and post-stressful mental task in all patients (tDCS and sham groups combined). Cold and heat pain thresholds did not differ pre- to post-stressful mental task on the right cheek ($p = 0.51$, A; $p = 0.58$, B) or palm ($p = 0.089$, C; $p = 0.3$, D).

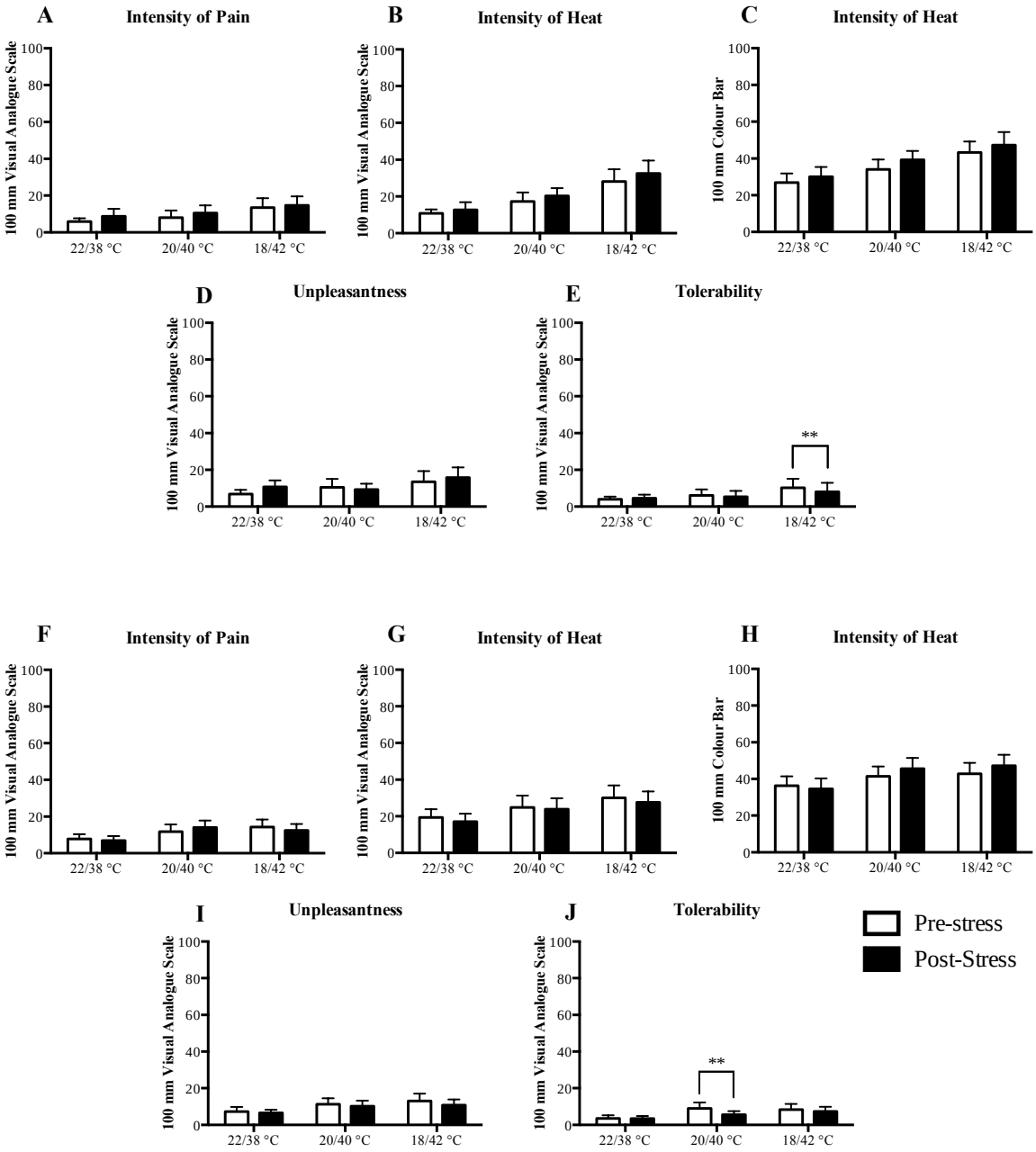
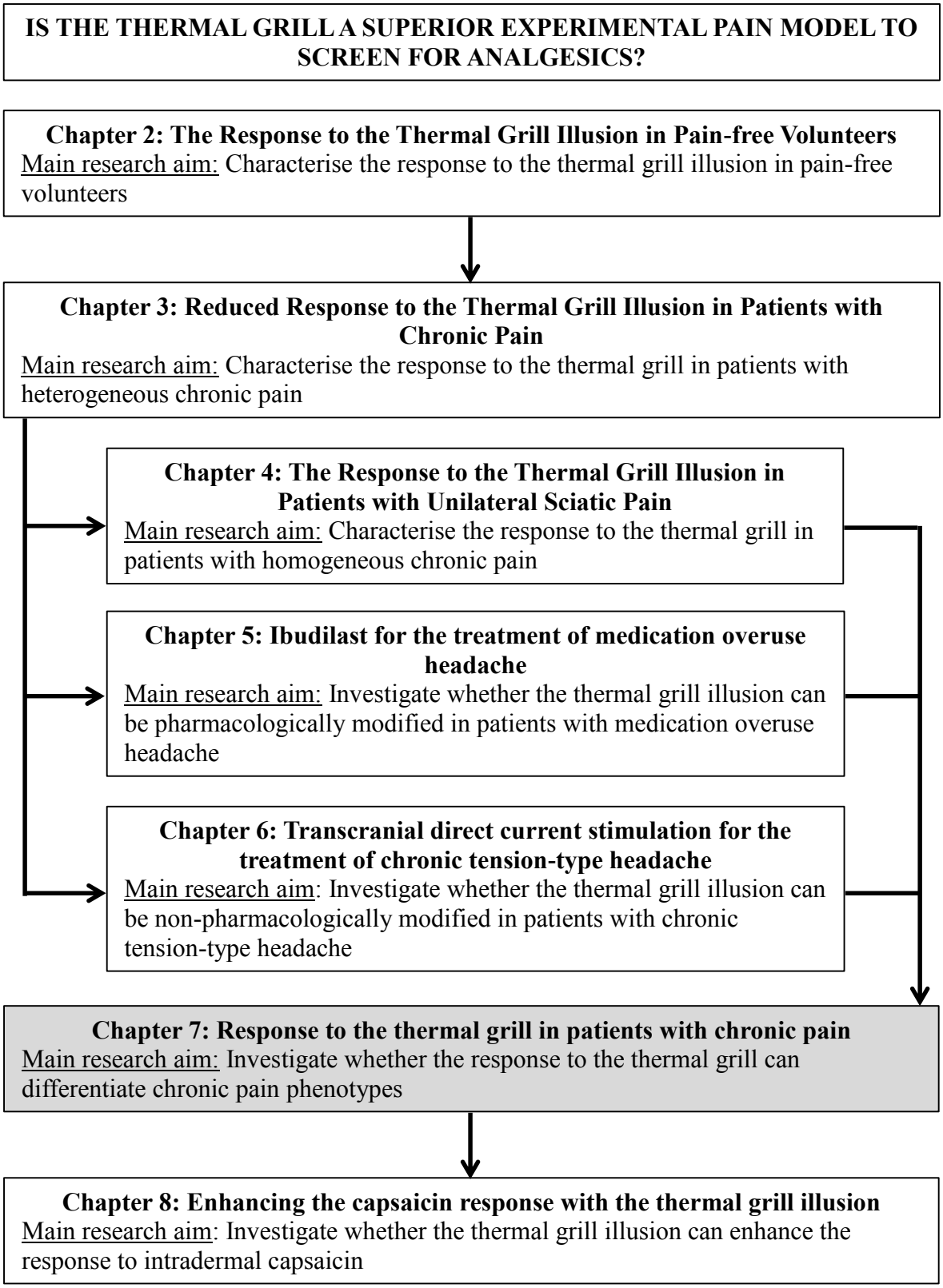


Figure 6.15. Effect of stressful mental task: thermal grill response.

The response to the thermal grill illusion pre- and post-stressful mental task on the right cheek (A-E) and palm (F-J) in all patients (tDCS and sham groups combined). On the cheek (E) and palm (J), significantly less tolerability to the thermal grill was observed post-stressful mental task at the 18/42 ºC and 20/40 ºC thermal grill configurations respectively. For all other outcomes, no significant differences pre- and post-stressful mental task were observed. Graphs are represented as mean ± SEM. ** $P < 0.01$.

Chapter 7. Thermal Grill Response in Patients with Unilateral Sciatica, Medication Overuse Headache and Chronic Tension-Type Headache


IS THE THERMAL GRILL A SUPERIOR EXPERIMENTAL PAIN MODEL TO SCREEN FOR ANALGESICS?
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Main research aim: Characterise the response to the thermal grill illusion in pain-free volunteers
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Main research aim: Investigate whether the thermal grill illusion can be non-pharmacologically modified in patients with chronic tension-type headache
Chapter 7: Response to the thermal grill in patients with chronic pain
Main research aim: Investigate whether the response to the thermal grill can differentiate chronic pain phenotypes
Chapter 8: Enhancing the capsaicin response with the thermal grill illusion
Main research aim: Investigate whether the thermal grill illusion can enhance the response to intradermal capsaicin

Introduction

Across chapters 4, 5 and 6, I investigated the response to the thermal grill illusion in patients with three separate homogeneous chronic pain conditions. These studies allowed me to investigate the response to the thermal grill in patients whose chronic pain condition originated in the periphery (unilateral sciatica, chapter 4), and those that originated centrally and had no peripheral pathology (medication overuse headache and chronic tension-type headache, chapters 5 and 6 respectively). Additionally, of the patients whose chronic pain originated centrally, I was able to investigate patients who took chronic opioid-based medicines for their pain (chapter 5) and patients who took simple analgesics, such as paracetamol and ibuprofen, for their pain (chapter 6). Compared to pain-free volunteers, the response to the thermal grill illusion did not differ significantly between patients with unilateral sciatica (chapter 4); patients with medication overuse headache (chapter 5) or patients with chronic tension-type headache (chapter 6). However, whether differences in response to the thermal grill differed between these three patient populations was unknown, therefore I was interesting in comparing the response to the thermal grill across these differing chronic pain aetiologies to investigate whether the response to the thermal grill could differentiate chronic pain phenotypes. Thermal pain thresholds were also compared across the three populations. Responses to both the thermal grill illusion and thermal pain thresholds in pain-free volunteers (chapter 4) are also provided for reference, however were not included in the analyses.

Materials and Methods

As previously stated in chapters 4, 5 and 6.

Statistical analysis

The D'Agostino and Pearson omnibus normality test was performed to test for normality of the data.

Age and duration of pain between patients sciatic pain, medication overuse headache and chronic tension-type headache were compared using a one-way repeated measures ANOVA with Tukey's multiple comparisons test, therefore this data is represented as mean ± SD. Due to the non-parametric nature of the data, average pain from patients sciatic pain, medication overuse headache and chronic tension-type headache was compared using the Friedman's test with Dunn's multiple comparisons test, therefore this data is represented as median and IQR.

Cold pain thresholds on patients non-dominant side palm and heat pain thresholds on patients non-dominant side cheek, palm and dominant side palm were compared using a one-way ANOVA with Sidak's multiple comparisons test, therefore these graphs are represented as mean ± SEM. Due to the non-parametric nature of the data, heat pain thresholds on patients dominant side cheek and cold pain thresholds on patients dominant side cheek and palm and non-dominant side cheek were compared using the Kruskal-Wallis test with Dunn's multiple comparisons test, therefore these graphs are represented as median and IQR.

The response to the thermal grill illusion was compared using a two-way repeated measures ANOVA with Bonferroni's multiple comparison test, therefore these graphs are represented as mean ± SEM.

A *P* value of less than 0.05 was required for statistical significance.

Results

Subjects

33 (8M, 25F) patients with medication overuse headache (*MOH*), 9 (5M, 4F) patients with unilateral sciatica (*sciatica*) and 12 (5M, 7F) patients with chronic tension-type headache (*CTTH*) were compared. Age (mean ± SD, MOH: 44.4 ± 11.1 years; sciatica: 49.8 ± 11.7 years; CTTH: 38.2 ± 11.3 years, $p = 0.069$), duration of pain (mean ± SD, MOH: 22.0 ± 14.2 years; sciatica: 15.6 ± 12.1 years; CTTH: 16.1 ± 9.7 years, $p = 0.25$) and the average pain experienced from patients chronic pain condition (median and IQR, MOH: 58, 47 to 71 mm; sciatica: 65, 49 to 76 mm; CTTH: 46, 36 to 60 mm on a 100 mm visual analogue scale, $p = 0.11$) did not differ between the 3 patient groups. When comparing the average pain experienced from patients chronic pain condition, this information was not obtained from 2 *sciatica* patients, therefore only 7 *sciatica* patients average pain scores were included in this analysis. Further patient demographics can be found in tables 4.1 (chapter 4), 5.1 (chapter 5) and 6.1 (chapter 6).

Cold and heat pain thresholds

An overall main effect of group was observed for heat pain thresholds on the dominant side cheek ($p = 0.0499$), with patients with *MOH* displaying lower thresholds (i.e. more sensitive) compared to *sciatica* and *CTTH* patients (see Figure 7.1B). However, heat pain thresholds did not differ between the non-dominant side cheek, dominant palm and non-dominant palm. Similarly, cold pain thresholds did not differ between the 3 patient groups at all body locations (see Figures 7.1 and 11.7.1 in appendix). Due to missing data values, 32 patients with *MOH* were included in the above analyses on the palm.

Thermal grill response

The response to the thermal grill illusion did not differ between the 3 patient groups for all thermal grill outcomes at all body locations (see Table 7.1 for *P* values and Figures 7.2 and 11.7.1 in appendix). Due to missing data values, 32 patients with *MOH* were included in the above analyses on the dominant and non-dominant side cheek and non-dominant side palm.

Discussion

The aim of this chapter was to compare the response to the thermal grill between patients with medication overuse headache (MOH), patients with unilateral sciatica (*sciatica*), and patients with chronic tension-type headache (*CTTH*), to investigate whether the response to the thermal grill could differentiate chronic pain phenotypes. The response to the thermal grill illusion did not significantly differ between *MOH, sciatica* or *CTTH* patients, although patients with *sciatica* consistently displayed reduced responses to the thermal grill compared to *MOH* patients, whilst *CTTH* patients response were generally in between those of *MOH* and *sciatica* patients. Similarly, patients' cold and heat pain thresholds did not significantly differ on the dominant and non-dominant side cheek and palm, albeit an overall main effect of group for heat pain thresholds; where patients with *MOH* displayed lower thresholds (i.e. more sensitive) compared to patients with *sciatica* or *CTTH* on their dominant side cheek, although post hoc analysis did not reveal a significant difference. Considering that thermal pain thresholds did not differ between the 3 patient populations, it is difficult to conclude whether or not the thermal grill illusion has the ability to differentiate chronic pain phenotypes. To my knowledge, thermal pain thresholds have not previously been compared between patients with *MOH, sciatica* or *CTTH,* thus my findings cannot be compared amongst others. One limitation of this comparison between these 3 patient populations is the relatively low patient numbers in both the *sciatica* and *CTTH* groups, which may have masked any potential differences between the 3 groups. Therefore, future studies need to investigate the response to the thermal grill illusion in larger groups of patients to verify whether differences in response to the thermal grill exist between patients with different types of chronic pain conditions; thus whether the thermal grill can differentiate chronic pain phenotypes.

In conclusion, these findings cannot conclusively answer whether or not the thermal grill illusion has the ability to differentiate chronic pain phenotypes, thus warrants further investigation in larger groups of patients.

Tables

Table 7.1. Response to the Thermal Grill Illusion Between Different Pain Patient Populations

The response to the thermal grill illusion was compared between patients with unilateral sciatica, medication overuse headache and chronic tension-type headache at patients' dominant and non-dominant side cheek and palm for all five thermal grill outcomes. *P* values are presented.

	Dominant Cheek	Non-Dominant Cheek	Dominant Palm	Non-Dominant Palm
Intensity of Pain	0.52	0.73	0.51	0.84
Intensity of Heat	0.11	0.32	0.29	0.48
Intensity of Heat (c)	0.44	0.44	0.51	0.58
Unpleasantness	0.23	0.22	0.16	0.31
Tolerability	0.079	0.13	0.099	0.21

C: colour bar.

Figures

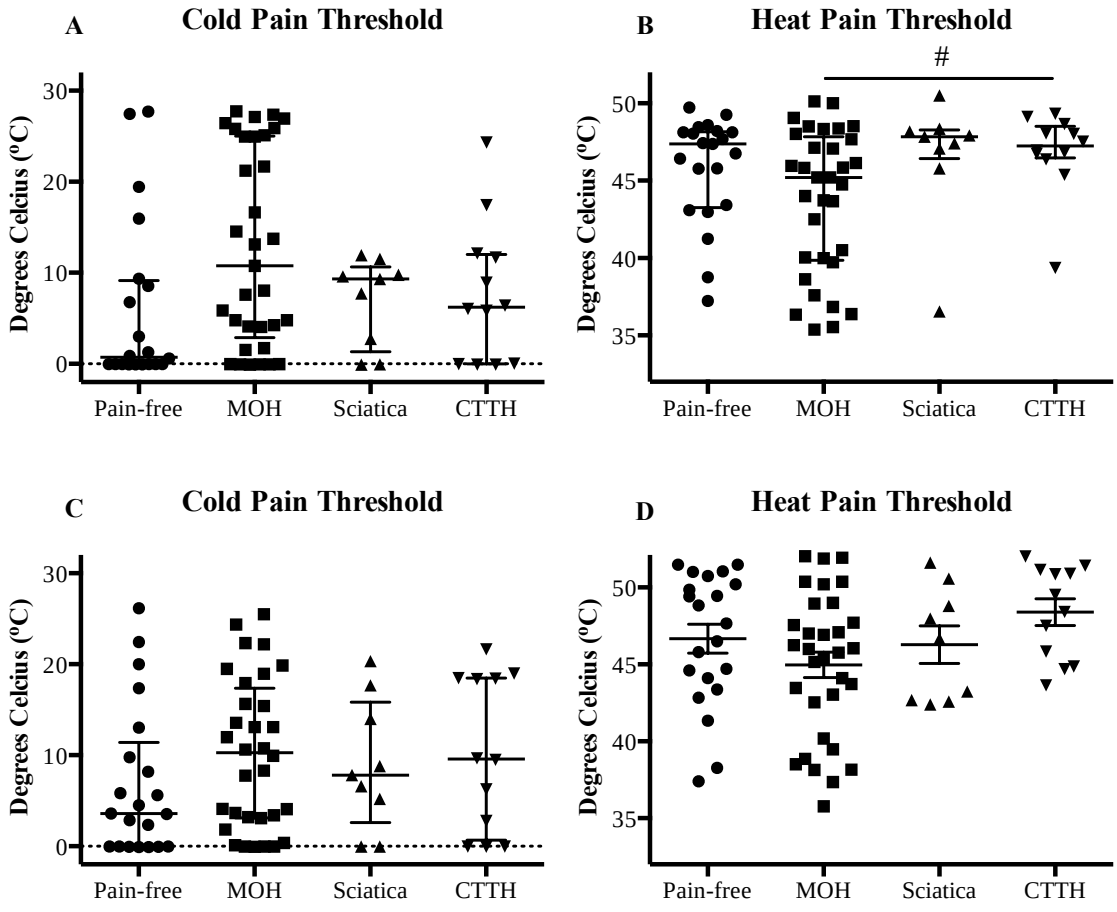

Figure 7.1. Cold and heat pain thresholds on the dominant side cheek and palm

Cold and heat pain thresholds on the dominant side cheek (A, B) and palm (C, D) in pain-free participants, patients with medication overuse headache, patients with sciatic pain and patients with chronic tension-type headache. Cold pain thresholds did not differ on the dominant side cheek (A, $p = 0.14$) and palm (C, $p = 0.36$), nor did heat pain thresholds on the dominant side palm (D, $p = 0.11$). An overall main effect of group was observed for heat pain thresholds on patients' dominant side cheek (B, $p = 0.05$). Graphs A, B and C are presented as median and interquartile range. Graph D is presented as mean ± SEM. MOH: medication overuse headache; CTTH: chronic tension-type headache. # $P < 0.05$ for an overall main effect.

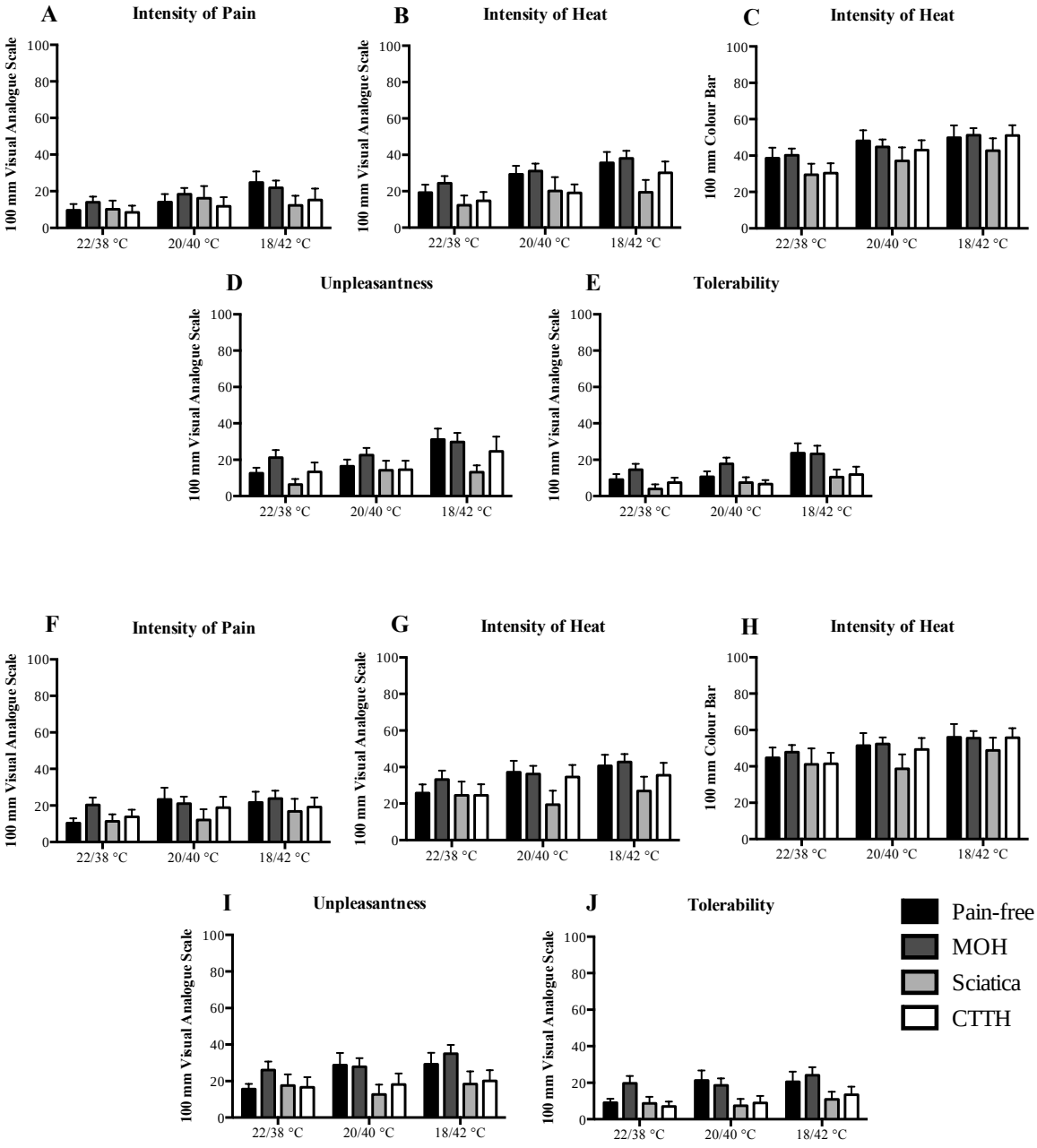

Figure 7.2 Response to the thermal grill illusion on the dominant side cheek and palm

The response to the thermal grill illusion on the dominant side cheek (A-E) and palm (F-J) in pain-free participants (black bars), patients with medication overuse headache (darker grey bars), patients with sciatic pain (lighter grey bars) and patients with chronic tension-type headache (white bars). The response to the thermal grill illusion did not differ on the dominant side cheek (A-E) or palm (F-J). All graphs are represented as mean ± SEM. MOH: medication overuse headache; CTTH: chronic tension-type headache.

Chapter 8. The Effect of the Thermal Grill Illusion on the Response to Intradermal Capsaicin in Healthy Male Volunteers

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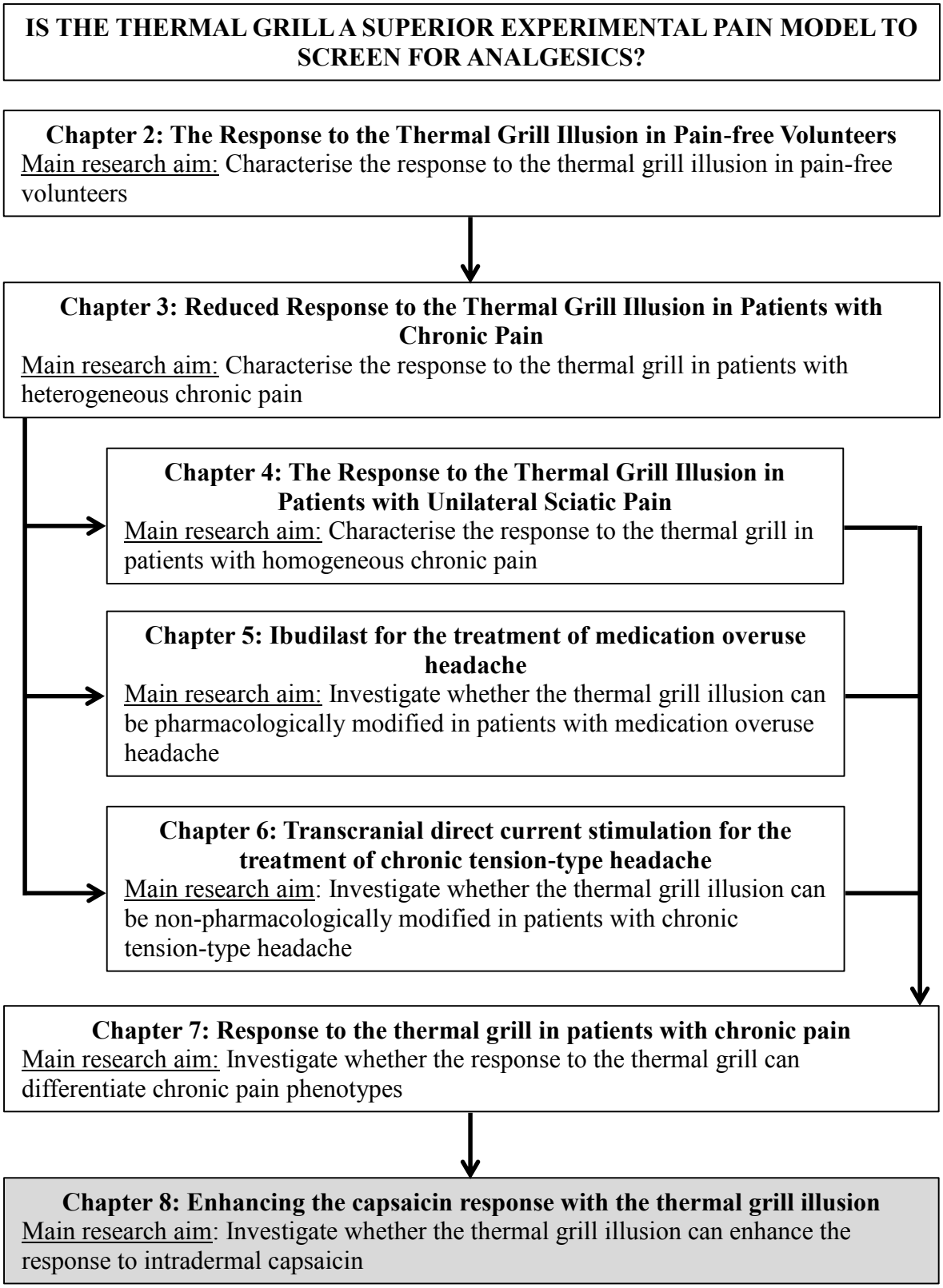
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Introduction

To date, I have investigated the thermal grill illusion in pain-free volunteers, heterogeneous chronic pain patients (mixture of chronic pains) and more homogenous chronic pain patients (patients with unilateral sciatica, medication overuse headache and chronic tension-type headache). Amongst all of these populations the intensity of pain experienced from the thermal grill illusion on the dominant palm has been quite low, with mean pain responses being as low as 8 mm (out of 100 mm) in patients with chronic tension-type headache when tested at the lowest thermal grill setting and as high as 24 mm (out of 100 mm) in patients with medication overuse headache when tested at the highest thermal grill setting. These responses are below the level of 40 mm (out of 100 mm), which is generally regarded as the minimum for clinically relevant pain (Jensen et al., 2003). Consequently, the thermal grill is unlikely to be a suitable model to assess the efficacy of analgesics when used on its own given the inability of the thermal grill test to reach the clinically relevant substantial pain threshold (see chapters 2-6).

Capsaicin, the active ingredient in chilli peppers, is an agonist at the transient receptor potential vanilloid 1 (TRPV1) (Caterina et al., 1997), a ligand gated ion channel, expressed predominately by nociceptive afferent neurons (Baron, 2006). Binding to TRPV1 causes an influx of cations resulting in depolarisation of the cell and firing of action potentials (Levine and Alessandri-Haber, 2007). TRPV1 is a polymodal receptor which is activated by elevated temperatures (~43^{o}C), acidic conditions (pH < 5.9) and chemical stimuli (e.g. capsaicin, bradykinin, etc.)(Caterina et al., 1997; Tominaga et al., 1998; Caterina et al., 2000; Chuang et al., 2001; Vlachova et al., 2003; Schumacher, 2010; Chung et al., 2011). When injected intradermally, capsaicin causes an area of cutaneous flare, localised spontaneous pain, hyperalgesia and allodynia (Simone et al., 1989; LaMotte et al., 1991; Koltzenburg et al., 1992). These symptoms are generally mild, transient in nature and occur in a dose-dependent

manner (Simone et al., 1989; Gustafsson et al., 2009); lasting approximately 90 min for flare, 10-50 min for pain and up to 6 and 24 hours for allodynia and hyperalgesia in some individuals respectively, although peak response for allodynia and hyperalgesia is generally observed between 5-15 and 15-30 min respectively followed by a gradual decline over time (Simone et al., 1989; LaMotte et al., 1991; Torebjork et al., 1992; Liu et al., 1998; Hughes et al., 2002; Gustafsson et al., 2009; Aykanat et al., 2012; Hutchinson et al., 2013). These symptoms are similar to those experienced in neuropathic pain, and hence this model has been investigated as a possible model of neuropathic pain in humans.

The dose range of capsaicin used for testing has varied widely. Our laboratory has previously shown good dose response data over the range 1 to 100 μg (Gustafsson et al., 2009), however other investigators have used doses up to 1000 μg in pain-free volunteers (Sang et al., 1996). In our previous studies with sciatica patients (Aykanat et al., 2012; Sumracki et al., 2012), a lower dose of 10 μg was used. However, our most recent study (Sumracki et al., 2012) failed to produce an adequate hyperalgesia profile following this capsaicin dose, thus was insufficient to meet the study objectives. Therefore, a dose of 100 μg in 10 μL into the dominant forearm was selected for this study. Unlike my previous studies, the forearm was selected in this study, due to the potential difficulties and uncertainty of investigating the response to intradermal capsaicin on the palm. Previously, the response to the thermal grill was not found to differ between the forearm and the palm (Bach et al., 2011; Averbeck et al., 2013).

On its own, the intradermal capsaicin model has shown to be a poor predictor for detecting the efficacy of centrally acting drugs, with some studies demonstrating efficacy (Park et al., 1995; Wallace et al., 1997; Eisenach et al., 1998; Sang et al., 1998; Gottrup et al., 2000;

Eisenach et al., 2002; Wallace et al., 2002c; Eisenach et al., 2003; Gottrup et al., 2004a; Gottrup et al., 2004b; Wallace et al., 2007; Klein et al., 2008; Michaux et al., 2012; Wallace et al., 2012) and others not (Wallace et al., 2002a; Wallace et al., 2002b; Wallace et al., 2004; Kraft et al., 2008; Wallace and Schulteis, 2008; Wang et al., 2008; Andresen et al., 2011; Lam et al., 2011; Sumracki et al., 2012; Vuilleumier et al., 2013). Due to the novel non-nociceptive nature of the thermal grill, perhaps combining the thermal grill stimulus with a nociceptive stimulus, such as intradermal capsaicin, may provide a unique model to investigate the efficacy of centrally acting analgesics. In order to investigate whether combining the thermal grill illusion of pain with the intradermal capsaicin pain model produces a greater capsaicin response, this test condition was compared with a standard model of warmth/heat, using the same temperature setting used for the warm bars of the thermal grill.

The objective of this study was to compare the effect of the thermal grill illusion with standard warmth/heat on capsaicin-induced spontaneous pain, flare, hyperalgesia and cutaneous allodynia responses.

Materials and Methods

Thermal grill

As previously described in chapter 2.

Ethics

Ethics approval was obtained from the Royal Adelaide Hospital (RAH) Investigational Drugs Subcommittee and Research Ethics Committee. Signed consent was obtained from each participant prior to enrolment into the study. Participants were financially compensated for their time and inconvenience.

Participants

12 healthy right-hand dominant, pain-free participants were chosen to participate in this study. Participants were recruited from the general public by advertisement. All participants were naïve to the thermal grill effect. Key inclusion criteria were: male aged between 18 and 65 years old inclusive; being in good general health and being right-hand dominant. Key exclusion criteria included: significant scarring or tattoos on the dominant (right) volar forearm; sensory deficits on the dominant (right) volar forearm resulting from medical conditions, such as diabetes, alcohol neuropathy, sever thyroid, liver or kidney diseases; dark skin colouration that precludes flare assessment; currently experiencing an active inflammatory process (e.g. acute pain, influenza, active infection, rheumatoid arthritis) or having a clinically significant infection in the previous 4 weeks; history of excessive alcohol use; impaired immune response, e.g. HIV/AIDS sufferers, Hep B or C sufferers, organ transplant recipients or known current history of malignancy; having a SCL-90-R Symptom

Checklist score greater than 2 standard deviations from the mean; presence of non-prescribed drugs of abuse in urine drug screen; current or past history of any chronic pain condition or recurrent condition that alters perception (such as migraine); recent use of opioids (e.g. morphine use within last week, or codeine use (> 30 mg) within last 5 days), adjuvant analgesics (e.g. tricyclics, gabapentin or pregabalin), anxiolytics, anti-depressants and anti-epileptics within last month; clinically diagnosed major psychiatric disorder, such as major depression; bipolar disorder; schizophrenia; anxiety disorder and psychosis; immunosuppressant drugs (e.g. azathioprine, methotrexate, cyclosporine) and a known disorder of thermal pain sensitivity (e.g. Raynaud's Phenomenon).

Capsaicin Preparation

Capsaicin in 38% hydroxypropyl-β-Cyclodextrin (β -CD) was prepared and dispensed as described previously (Gustafsson et al., 2009). A 100 μg dose was selected based on previous work from our laboratory. For each injection, 10 μL of solution was drawn into a 0.3 mL sterile insulin syringe (BD Ultra-Fine II) by the Royal Adelaide Hospital Department of Pharmacy.

Familiarisation

As part of the screening session, participants were familiarised to the key study assessments, describe below, in response to a single intradermal capsaicin injection of 100 μg in 10 μL 38% β –CD. All outcome measures were tested 5 minutes post-injection.

Study overview

This randomised, 2-way cross over study was conducted over 2 x 160 minute testing sessions, with a minimum one week washout period in between each session. Prior to enrolment into the study, participants underwent a screening session. The two study conditions were thermal grill testing (interlaced cool and warm bars set to 20 and 40 ^{o}C respectively, described previously in chapter 2) and warm heat testing (3 x 3 cm^2 thermode set to 40 ^{o}C using a PATHWAY device, described previously in chapter 4), with the order of testing allocation being randomised.

Schedule day schedule

Participants were interviewed about any changes in their health since the screening visit and any changes to medication use during this period. Participants were asked to refrain from analgesics (e.g. paracetamol, ibuprofen, aspirin), alcohol and caffeine containing foods and beverages for 24 hours before each experimental day. A negative breath alcohol test and urine drug test for non-prescribed drugs of abuse was required for continuance in the study. Participants were re-familiarised to the testing procedures. Before any assessments commenced, participants were required to equilibrate to the internal environment for 60 minutes (see Figure 8.1).

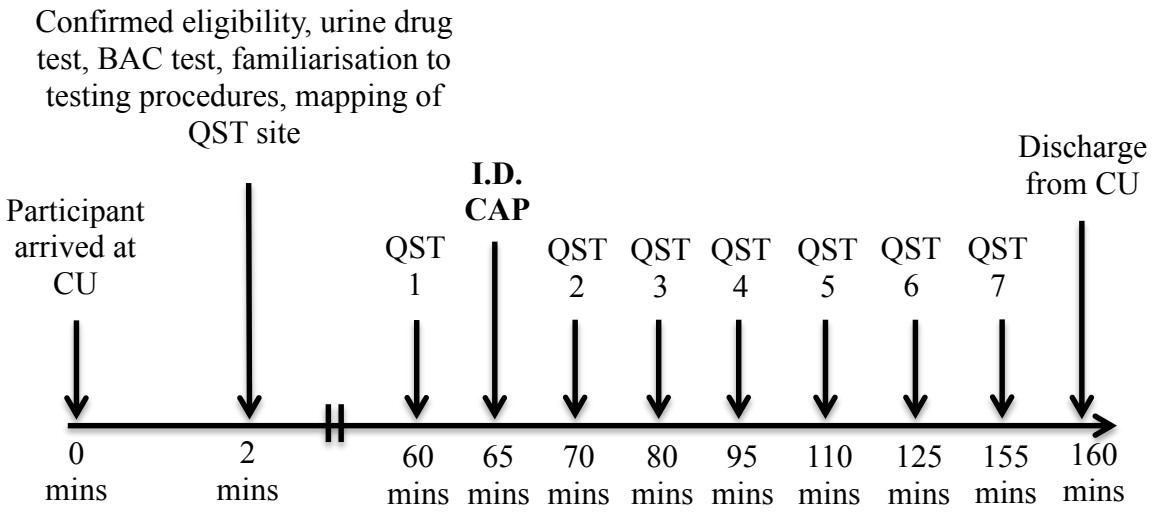

Figure 8.1. Schedule on Main Study Days.

Schedule on study days 1 and 2. Thermal grill or warm stimulus (depending on randomisation) followed by spontaneous pain, area of flare, cutaneous allodynia, cutaneous allodynia VAS, hyperalgesia and hyperalgesia VAS were performed pre-capsaicin (QST 1) and post-capsaicin (QST 2 – 7). CU: clinical unit; BAC: breath alcohol concentration; QST: quantitative sensory testing; I.D.: intradermal; CAP: capsaicin.

Assessment methods

Participants sat upright during assessments and were requested not to talk to minimize distractions during assessment procedures. The assessment area was mapped using a black soft tipped marker. The injection site was determined as the midpoint between the elbow crease and the base of the palm. Eight radial lines were then mapped, with small black dots marked at 1 cm intervals. The length of each radial line depended on the size of the participants' volar forearm. The length of each radial line was recorded, and the same measurements were used for study day 2. Spontaneous pain, flare, cutaneous allodynia, cutaneous allodynia VAS, hyperalgesia and hyperalgesia VAS were assessed (in that order) pre-capsaicin injection and at 5, 15, 30, 45, 60 and 90 min post capsaicin injection. The same assessor (N.M.S.) performed all assessments to maintain consistency between assessments.

Spontaneous pain

Spontaneous pain was assessed using a 100 mm visual analogue scale (VAS). Participants were instructed to draw a vertical line upon a 100 mm horizontal line, with ends labelled 'no pain' and the 'worst pain imaginable'. The length was recorded with a ruler.

Flare

The area of flare (cm^2) was assessed by tracing the visually identified area of reddened skin directly onto an overlaying transparent acetate sheet, using a soft-tipped marker. The area was then calculated using digital planimetry.

Cutaneous Allodynia

The average radius (mm) of cutaneous allodynia was assessed using a

foam paint brush (foam brush 25 mm *ROYMAC, Australia), gently stroked across the skin along 8 compass directions at a rate of 1 cm/sec. Participants were instructed to say 'yes' when they experienced an 'increase in pain' and the point along the radial line was recorded with a blue soft-tipped marker. The average sum of each radii between the marked dot and the injection site was later determined. This has been found to be more appropriate than measuring an area of allodynia or hyperalgesia, as not all assessments result in eight points of response (Aykanat et al., 2012). Participants were also required to rate the intensity of pain experienced from the foam paintbrush on a 100 mm VAS (as described for spontaneous pain).

Hyperalgesia

The average radius (mm) of capsaicin-induced hyperalgesia was assessed using a calibrated von Frey hair (number 5.46), a plastic rod that bends at a defined pressure of 26 g (TouchTest

800-821-9319, Semmes Weinstein, Stoelting, IL, USA). The von Frey hair was applied along 8 compass directions at 1 cm increments, starting peripherally from the injection site. Participants were instructed to say 'yes' if they noticed an 'increase in pain', and the average of these points was then recorded and measured as described for allodynia. Participants were also required to rate the intensity of pain experienced from the von Frey hair on a 100 mm VAS (as described for spontaneous pain).

Statistical analysis

Spontaneous pain, flare, cutaneous allodynia, cutaneous allodynia VAS, hyperalgesia and hyperalgesia VAS were analysed using a two-way repeated measures ANOVA. Bonferroni's multiple comparisons test was performed to adjust for multiple comparisons.

A *P* value of less than 0.05 was required for statistical significance.

Results

Subjects

12 healthy, right-hand dominant, male pain-free volunteers completed this study (mean age ± SD, 27.3 ± 9.9 years). All participants were naïve to the thermal grill effect and had previously never received intradermal capsaicin.

Spontaneous pain

Pre-injection values of pain were 4 mm (95% CI 0 mm to 8 mm) and 6 mm (95% CI -4 mm to 15 mm) in response to the warm and thermal grill stimulus respectively, indicating a low level of pain in response to both the warm and thermal grill stimulus before receiving capsaicin injection. The effect time profiles for both the warm and thermal grill stimulus differed slightly, with the maximal response following the warm stimulus occurring at t = 15 min and the maximal response following the thermal grill stimulus occurring at t = 5 min, followed by a gradual decrease over time. In response to the warm stimulus, the maximal VAS response was 51 mm (95% CI 37 mm to 66 mm), whereas the maximal VAS response in response to the thermal grill stimulus was 34 mm (95% CI 19 mm to 50 mm). The AUC (see Table 8.1 for all AUC values) of VAS scores was 35% (95% CI 16.2% to 53.7%) lower following the thermal grill stimulus compared to the warm stimulus (see Figure 8.3A).

Flare

As expected, pre-injection values of flare were zero in response to the warm and thermal grill stimulus. The effect time profiles for both the warm and thermal grill stimulus were similar, with the peak response occurring at t = 15 min, followed by a gradual decrease over time. In response to the warm and thermal grill stimulus, the maximal flare response was 17.4 cm^2

(95% CI 14.2 cm^2 to 20.6 cm^2) and 19.9 cm^2 (95% CI 14.6 cm^2 to 25.1 cm^2) respectively. No significant difference in flare response was observed between the warm and thermal grill stimulus (see Figure 8.3B).

Cutaneous allodynia

As expected, pre-injection values of cutaneous allodynia were zero in response to the warm and thermal grill stimulus. The effect time profiles for both the warm and thermal grill stimulus were similar, with the peak response occurring at t = 5 min, followed by a gradual decrease over time. In response to the warm and thermal grill stimulus, the maximal average radius was 12 mm (95% CI 3 mm to 22 mm) and 15 mm (95% CI 5 mm to 24 mm) respectively. As expected, pre-injection values of pain intensity experienced from cutaneous allodynia testing was extremely low, with responses following the warm and thermal grill stimulus being 1 mm (95% CI 0 mm to 1 mm) and 1 mm (95% CI 0 mm to 1 mm) respectively. The effect time profiles for both the warm and thermal grill stimulus differed slightly, with the maximal response following the warm stimulus occurring at t = 5 min (mean: 22 mm, 95% CI 8 mm to 36 mm) and the maximal response following the thermal grill stimulus occurring at t = 15 min (mean: 20 mm, 95% CI 7 mm to 19 mm). No significant difference in the average radius of cutaneous allodynia or pain intensity experienced from cutaneous allodynia testing was observed between the warm and thermal grill stimulus (see Figure 8.3C and D).

Hyperalgesia

As expected, pre-injection values of hyperalgesia were extremely low, with responses following the warm and thermal grill stimulus being 2 mm (95% CI -1 mm to 6 mm) and 0 mm (95% CI -0.1 mm to 1 mm) respectively. The effect time profiles for both the warm and

thermal grill stimulus were similar, with the peak response occurring at t = 60 min. Responses appeared to decline from t = 60 min to t = 90 min, however the rate of decline can not be commented on as t = 90 min was the final measurement. In response to the warm and thermal grill stimulus, the maximal average radius was 31 mm (95% CI 21 mm to 40 mm) and 28 mm (95% CI 21 mm to 34 mm) respectively. As expected, pre-injection values of pain intensity experienced from hyperalgesia testing were extremely low, with responses following the warm and thermal grill stimulus being 3 mm (95% CI 0 mm to 5 mm) and 1 mm (95% CI 0 mm to 2 mm) respectively. The effect time profiles for both the warm and thermal grill stimulus differed, with the maximal response following the warm stimulus occurring at t = 30 min (mean: 25 mm, 95% CI 14 mm to 35 mm) and the maximal response following the thermal grill stimulus occurring at t = 5 min (mean: 26 mm, 95% CI 10 mm to 42 mm). No significant difference in the average radius of hyperalgesia or pain intensity experienced from hyperalgesia testing was observed between the warm and thermal grill stimulus (see Figure 8.3E and F).

Discussion

In this study, two experimental pain stimuli, one purely non-nociceptive in nature (thermal grill, combination of 20 ^{o}C and 40 ^{o}C), and one purely nociceptive in nature (i.d. capsaicin, 100μg), were combined to investigate whether the combination of these two painful stimuli provides a unique model to investigate the efficacy of centrally acting analgesics. Rekindling the i.d. capsaicin pain model with a 40 ^{o}C stimulus has previously shown to increase the response to intradermal capsaicin (Dirks et al., 2003), therefore a warm stimulus (40 ^{o}C stimulus) was also incorporated to investigate whether combining the thermal grill illusion of pain with the i.d. capsaicin pain model also produces a greater capsaicin response. Compared to the warm stimulus, 35% less spontaneous pain was observed following the thermal grill stimulus. No significant difference in response between the thermal grill and warm stimulus was observed for all other outcomes. Therefore, combining the thermal grill illusion with the i.d. capsaicin did not produce a greater capsaicin response compared to the warm stimulus for all outcomes measured. Comparing the time profile of spontaneous pain, no significant difference in response was observed between the warm and thermal grill stimulus at the 5 min post-capsaicin time point, however a significant difference emerged following 5 min post-capsaicin. Therefore, the addition of the warm stimulus caused capsaicin-induced spontaneous pain to summate.

This heightened capsaicin induced spontaneous pain observed following the warm stimulus has previously been demonstrated by others using the heat/capsaicin sensitisation model (Petersen and Rowbotham, 1999; Dirks et al., 2003). The heat/capsaicin model, developed by Petersen and colleagues (1999), involves pre-heating the skin with a heat stimulus (45 ^{o}C) for 5 min prior to the application of topical capsaicin. Topical capsaicin is then applied to the test site for 30 min and then wiped off. Heat rekindling, using a 40 ^{o}C stimulus, is then performed for 5 min at 40 min intervals following the cessation of topical capsaicin treatment (starting

75 min post initial skin pre-heating), usually at 5 separate time points (last rekindling at 235 min post skin pre-heating). Participants are asked to rate their level of pain during skin pre-heating and during each heat rekindling. Secondary hyperalgesia to brush and von Frey stimuli is also measured prior to initial skin pre-heating (45 ^{o}C), following topical capsaicin and both prior to and following the heat rekindling procedure. Using this model, heat rekindling following i.d. capsaicin also produced greater areas of secondary hyperalgesia to both brush and von Frey stimuli compared to capsaicin only (Petersen and Rowbotham, 1999; Dirks et al., 2003). Although skin pre-heating was used in the study by Petersen and colleagues (1999), Dirks and colleagues (2003) investigated whether the heighted secondary hyperalgesia observed following heat/capsaicin sensitisation was due to the initial skin pre-heating procedure, the heat rekindling procedure, or both procedures, and demonstrated that the long-lasting secondary hyperalgesia was due to the repeated rekindling procedure rather than a synergistic or additive effect between skin pre-heating and capsaicin. Thus, the fact that skin pre-heating was not performed in this study is irrelevant.

Although the warm stimulus caused increased spontaneous pain compared to the thermal grill following i.d. capsaicin, no differences in allodynia (brush) or hyperalgesia (von Frey) were observed in this study. Unlike the aforementioned studies, which rekindled the skin for 5 min, the warm and thermal grill stimuli were only applied for 30 s in this study. This may explain why the warm stimulus did not increase the area of allodynia or hyperalgesia in this study. Both capsaicin induced allodynia and hyperalgesia are believed to be centrally occurring phenomena, thus perhaps 30 s of peripheral stimulation provided by the warm stimulus is not enough to influence these outcomes. Whereas, capsaicin induced spontaneous pain is mediated peripherally, thus the 30 s peripheral stimulus is sufficient to increase spontaneous pain.

The burning pain associated with the thermal grill illusion is thought to occur via unmasking of the medial spinothalamic tract following warm induced inhibition of the normal inhibition exerted by the lateral spinothalamic tract on the medial spinothalamic tract (Craig et al., 1996) (see Figure 8.2). As previously discussed, i.d. capsaicin exerts its effects via activation of TRPV1, which is primarily located on nociceptive C-fibres. Consequently, it was hypothesised that the thermal grill would enhance the response to intradermal capsaicin due to additional activation of the medial spinothalamic tract via C-fibre nociceptor activation. Contrary to my hypothesis, no summation of capsaicin-induced pain was observed following the thermal grill test. This is both an interesting and paradoxical finding that does not support Craig and Bushnell's (1994) thermosensory disinhibition hypothesis, thus warrants further investigation. It is uncertain however whether the thermal grill attenuated capsaicin-induced spontaneous pain or failed to enhance capsaicin-induced pain due to the design of this study. Some reasons for this difference in spontaneous pain between the warm and thermal grill stimulus post-capsaicin may be: 1) that the cool bars (20 ^{o}C) of the thermal grill may be dampening down the response to i.d. capsaicin (i.e. attenuated capsaicin-induced pain), 2) that the thermal grill may have no effect on capsaicin-induced spontaneous pain (i.e. failed to enhance capsaicin-induced pain) or 3) that only half of the area provided by the thermal grill provided heat to the forearm (as the other half provided cool). The latter (3) is less likely, as although only half the area provided by the thermal grill provided heat to the forearm, the stimulation surface provided by the warm bars of the thermal grill was greater than the surface area provided by the warm stimulus.

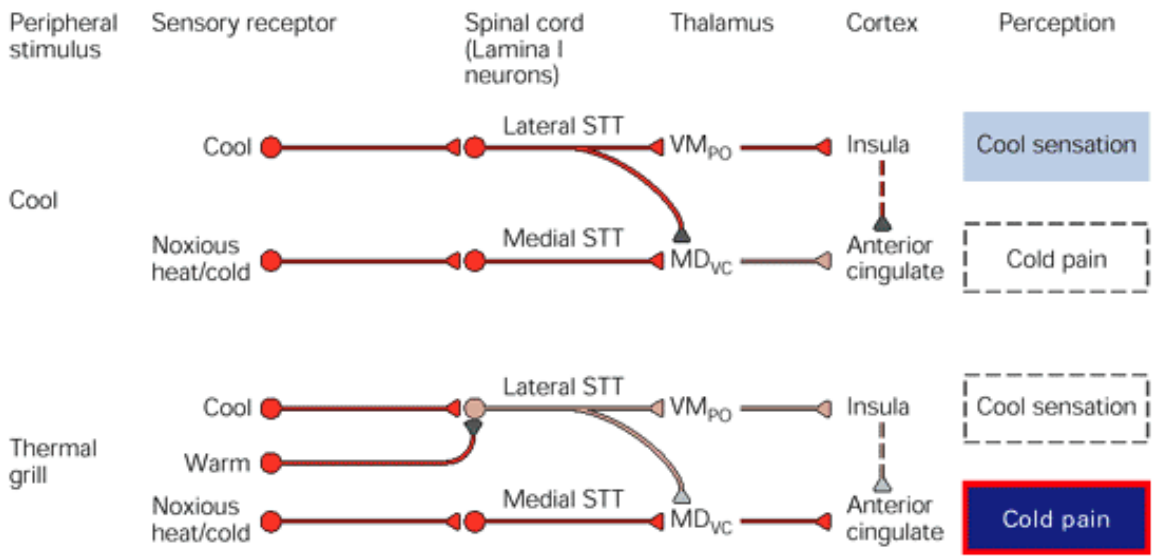

Figure 8.2. Proposed mechanism of the thermal grill illusion

Proposed mechanism that underlies the thermal grill illusion. An innocuous cool stimulus activates both A-δ fibres, which are responsible for transmitting sensations of "cool" (along a cool labelled line) and C-fibres, which are responsible for transmitting sensations of noxious heat and cold (along a pain labelled line). Under normal conditions, the cool labelled line has an inhibitory effect on the pain labelled line, resulting in a cool sensation being experienced. When an innocuous warm stimulus is introduced alongside an innocuous cool stimulus (thermal grill), the warm stimulus activates a warm labelled line, which inhibits the cool labelled line. Therefore, the cool labelled line is no longer able to exert its' inherent inhibition on the pain labelled line, resulting in a painful sensation, similar to the burn of cold pain, being experienced. Reprinted from Basbaum and Jessell (2000) with kind permission from McGraw-Hill Medical.

Cool/cold packs are often used to reduce inflammatory types of pains (Babes et al., 2002). Innocuous cold is mediated by sensory neurons expressing transient receptor potential melastatin 8 (TRPM8), also known as the menthol receptor, which is activated by temperatures below 26 ^{o}C (McKemy et al., 2002; Peier et al., 2002) and by menthol, the cooling component in peppermint. In humans, cooling of capsaicin treated skin area has been demonstrated to reduce or attenuate capsaicin-induced spontaneous pain (LaMotte et al., 1991; Koltzenburg et al., 1992; Kilo et al., 1995; Mohr et al., 2008; Knolle et al., 2013). Using rat trigeminal neurons, Chung and Wang (2011) demonstrated that this reduction in

pain is likely due to cold temperatures inhibiting agonist activation of TRPV1. Menthol has also been demonstrated to reduce the intensity of sensory irritation following capsaicin (Green and McAuliffe, 2000), as well as warmth (Green, 1986), moderate heat (Green, 1992) and heat induced pain (Albin et al., 2008) in humans as well as heat induced pain in rats (Klein et al., 2010; Klein et al., 2012).

Co-localisation of TRPM8 and TRPV1 may explain why the thermal grill elicited 35% less spontaneous pain compared to the warm stimulus in the presence of i.d. capsaicin. Although controversial, co-localisation of TRPM8 and TRPV1 has been demonstrated pre-clinically in up to 50% of dorsal root ganglia and trigeminal neurons (Okazawa et al., 2004; Pud et al., 2006; Takashima et al., 2007; Dhaka et al., 2008); whilst some studies have failed to demonstrate co-localisation of TRPM8 and TRPV1 in dorsal root ganglion neurons (Peier et al., 2002; Story et al., 2003; Kobayashi et al., 2005). One possibility is that inflammation increases the co-expression of TRPM8 and TRPV1 (Dhaka et al., 2006; Dhaka et al., 2008). Dhaka and colleagues (2008) injected Complete Freund's Adjuvant (CFA), an inflammatory agent, into the hind paw of rats and compared the dorsal root ganglions of L4-L6. Following CFA the number of TRPV1 expressing neurons significantly increased, whilst TRPM8 expression remained the same, with increased TRPV1 expression observed in TRPM8 neurons. If TRPM8 does in fact co-localise with TRPV1 in some neurons, in particular following inflammation, this may explain why participants experienced significantly less pain in response to the thermal grill stimulus post-capsaicin compared to the warm stimulus. Co-localisation of TRPM8 and TRPV1 and increased recruitment of TRPV1 following inflammation, for example from intradermal capsaicin, may explain why the level of spontaneous pain experienced from the thermal grill and warm stimulus differed from 15 min post-capsaicin and not immediately at 5 min post-capsaicin (see Figure 8.3A). Additionally, increased recruitment of TRPV1 following inflammation may explain why spontaneous pain

following the warm stimulus continued to increase until 15 min post-capsaicin, rather than an initial peak in pain and gradual decline over time, which was observed following the thermal grill stimulus and is normally observed following i.d. capsaicin (Simone et al., 1989; LaMotte et al., 1991; Hughes et al., 2002; Gustafsson et al., 2009; Aykanat et al., 2012; Hutchinson et al., 2013).

Although cooling has previously been shown to reduce capsaicin-induced pain (discussed previously), this was generally observed when noxious cold temperatures (0 ^{o}C) were applied to the skin (LaMotte et al., 1991; Mohr et al., 2008) or when the skin was constantly cooled below 25 ^{o}C (Knolle et al., 2013). In the study by Knolle and colleagues (2013), capsaicin-induced pain was completely attenuated at all time points when a cold pack was applied over skin treated with an 8% capsaicin patch; however, the cold pack was applied throughout the entire duration of the study resulting in a constant mean skin temperature of 20.5 ^{o}C. In my study the cool bars of the thermal grill (20 ^{o}C) were only applied for 30 sec at a time, which would have most likely been insufficient to cool participants skin temperature to below 25 ^{o}C.

Alternatively, the thermal grill may have had no effect on capsaicin-induced pain (i.e. failed to enhance capsaicin-induced pain). It was initially hypothesised that the thermal grill would enhance the response to intradermal capsaicin synergistically in the brain; however, the results of this study do not appear to support a synergistic relationship between the ascending pathways involved in the thermal grill illusion and capsaicin-induced pain. Instead, these results suggest that the thermal grill illusion and capsaicin-induced pain occur via parallel but non-overlapping pathways, a finding that does not appear to be congruent with Craig and Bushnell's (1994) thermosensory disinhibition hypothesis. However, as discussed above, the current study design does not allow me to conclude whether the thermal grill attenuated

capsaicin-induced pain or failed to enhance capsaicin-induced pain; consequently, additional testing is required.

One way to investigate whether the thermal grill attenuated capsaicin-induced pain or failed to enhance capsaicin-induced pain would be to assess capsaicin-induced spontaneous pain, flare, allodynia and hyperalgesia in the same group of individuals both prior to and following the warm and thermal grill stimulus under the following 6 conditions: 1) warm stimulus alone, 2) cool stimulus alone, 3) thermal grill stimulus alone, 4) i.d. capsaicin and warm stimulus, 5) i.d. capsaicin and cool stimulus and 6) i.d. capsaicin and thermal grill stimulus. Additionally, to avoid any additional potential differences in stimulus type (i.e. thermode vs. thermal grill) due to contact size surface area, future studies should elicit all thermal stimuli (warm, cool or thermal grill) using the same device (i.e. the thermal grill). As discussed previously in chapter 3, the design of my thermal grill did not allow for all 6 bars to be set to either warm or cool temperatures or did not allow all the warm bars to be switched on, whilst the cool bars were switched off and vice versa. Therefore, this should be taken into consideration when constructing a thermal grill for future studies.

Of particular interest was that participants rated the intensity of pain experienced from the thermal grill illusion abnormally low at baseline (pre-capsaicin), with mean responses being close to 0 mm on a 100 mm visual analogue scale (0, “no pain” to 100, “worst pain imaginable”), which was virtually identical to participants response to the individual warm (40 ^{o}C) stimulus (see Figure 8.3A). In my previous study (see chapter 4), pain-free participants rated the intensity of pain experienced from the thermal grill as approximately 23 mm (out of 100 mm) when investigated on the dominant palm at the same thermal grill configuration (20/40 ^{o}C). Although the body location tested in this study (dominant forearm)

and in chapter 4 (dominant palm) differed, Averbeck and colleagues (2013) previously demonstrated that the response to the thermal grill did not differ between the forearm and the palm. Previously, it has been demonstrated that up to 52% of healthy pain-free volunteers do not experience the thermal grill illusion (Bouhassira et al., 2005; Leung et al., 2005; Kern et al., 2008a; Kern et al., 2008b; Li, 2009; Li et al., 2009; Brunello, 2010; Kostka, 2011; Boettger et al., 2012; Boettger et al., 2013). Therefore, one explanation for this abnormally low response to the thermal grill illusion at baseline may be due to a high proportion of participants being non- or weak-responders to the thermal grill illusion. Another explanation may be due to participants' prior experience to capsaicin-induced pain at the familiarisation session on the screening day. People often rate pain comparatively; consequently, compared to capsaicin-induced pain, any pain induced by the thermal grill prior to i.d. capsaicin may not have been perceived as painful due to participants' prior experience with capsaicin-induced pain at the screening session. Although, these above reasons cannot explain the reduced pain experienced to the thermal grill post-capsaicin compared to the warm stimulus, this appears to be an abnormally low baseline response to the thermal grill pre-capsaicin, especially considering that the intensity of pain experienced form the thermal grill has previously been demonstrated to be greater than the intensity of pain experienced from the individual temperatures of the cool (20 ^{o}C) and warm (40 ^{o}C) bars (Leung et al., 2005; Brunello, 2010; Lam, 2012). Consequently, future studies may wish to selectively screen for participants who perceive the thermal grill illusion as painful.

The aim of this study was to investigate whether combining two experimental pain stimuli, one purely non-nociceptive in nature (thermal grill), and one purely nociceptive in nature (i.d. capsaicin), was a unique model to investigate the efficacy of centrally acting analgesics. Following i.d. capsaicin, no summation of pain was observed to the thermal grill stimulus compared to the warm stimulus. Rather, significantly less pain was observed in response to

the thermal grill stimulus post-capsaicin compared to the warm stimulus; however, whether the thermal grill attenuated capsaicin-induced pain or failed to enhance capsaicin-induced pain cannot be explained, thus warrants further investigation. Consequently, the neurobiological mechanisms underlying this finding cannot be explained, however may be due to the cool bars of the thermal grill dampening down the response to i.d. capsaicin. Therefore, in conclusion, combining these two experimental pain stimuli (thermal grill and i.d. capsaicin) is unlikely to be a useful model to investigate the efficacy of centrally acting analgesics, given the inability of the thermal grill test to reach the clinically relevant substantial pain threshold (> 40 mm) following i.d. capsaicin, however may still help to further understand the neurobiological mechanisms of the thermal grill illusion.

Tables

Table 8.1 Area Under the Effect Time Curves of Capsaicin-Induced Outcomes Following the Thermal Grill and Warm Stimulus

Mean area under the effect time curves and 95% CI are presented for each capsaicin-induced outcome following the thermal grill and warm stimulus. Mean differences in area under the effect times curves and 95% CI for differences between the thermal grill and warm stimulus are also presented.

Outcome measured	Test	Mean AUC (95% CI)	Mean difference (95% CI)
Spontaneous Pain (mm * min)	Thermal grill Warm	1728 (962, 2493) 2656 (1844, 3469)	-929 (-1427, -431)
Flare (cm^2 * min)	Thermal grill Warm	1151 (804, 1497) 961 (803, 1119)	190 (-308, 688)
Allodynia (mm * min)	Thermal grill Warm	658 (294, 1022) 582 (103, 1061)	76 (-422, 674)
Allodynia Pain (mm * min)	Thermal grill Warm	973 (388, 1558) 972 (293, 1651)	1 (-498, 499)
Hyperalgesia (mm * min)	Thermal grill Warm	2208 (103, 1061) 2274 (1509, 3038)	-66 (-565, 432)
Hyperalgesia Pain (mm * min)	Thermal grill Warm	1540 (782, 2297) 1727 (1030, 2424)	-187 (-686, 311)

AUC: Area under the curve; CI: confidence interval.

Figures

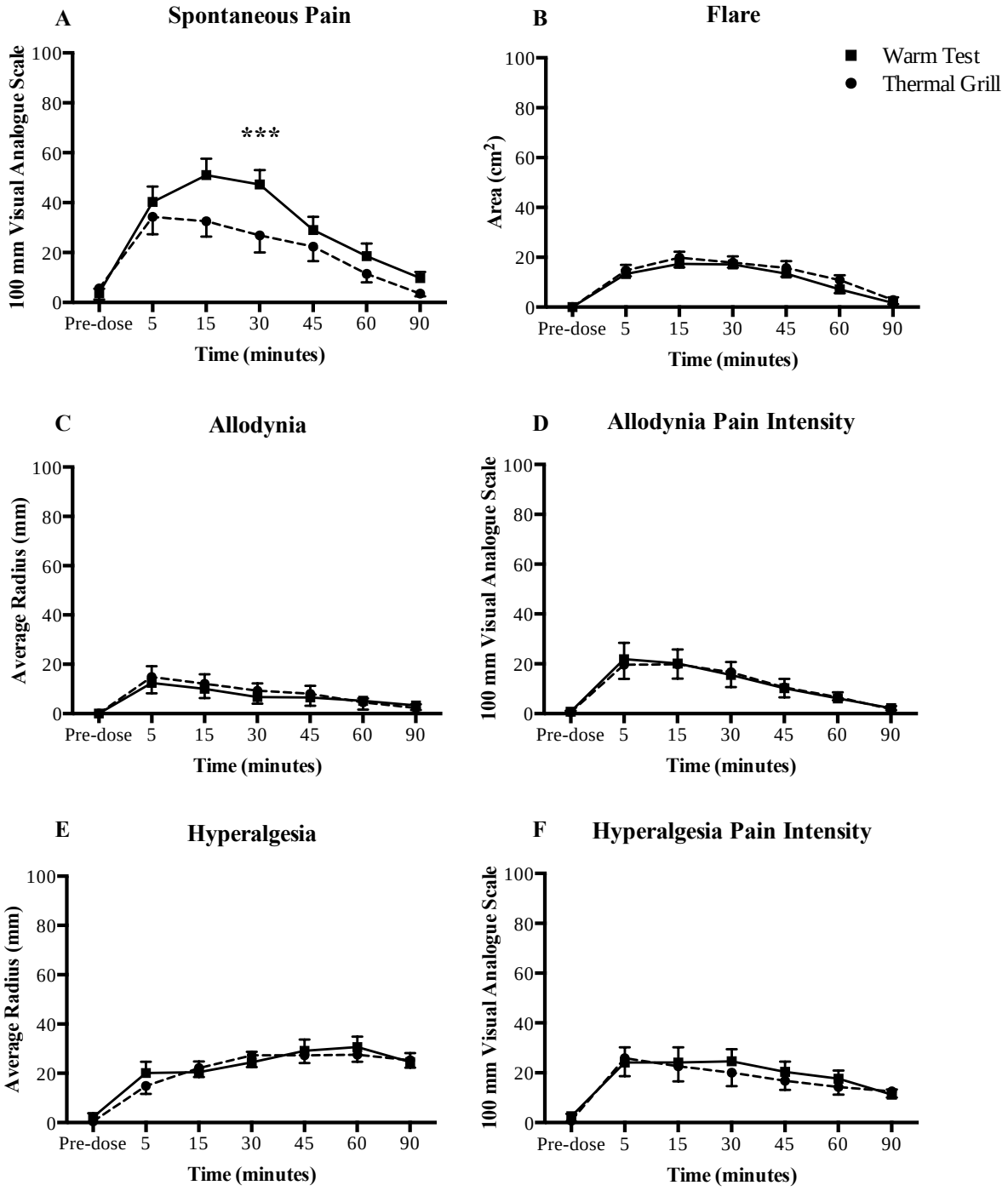

Figure 8.3. Response to intradermal capsaicin.

The response to intradermal capsaicin on participants dominant (right) forearm both pre- and post-capsaicin following 30 s exposure to either the thermal grill (•) or warm stimulus (■). Participants experienced 35% less spontaneous pain from the thermal grill compared to the warm stimulus following i.d. capsaicin (95%

confidence interval: 16% to 54%)(A). No significant differences were observed for all other outcomes (B, C, D, E, F). All graphs are represented as mean ± SEM. *** $P < 0.001$.

Chapter 9. Discussion

At the initiation of this PhD thesis, only 11 studies investigating the thermal grill illusion had been published in peer-reviewed journals, with 2 of these studies being case report studies (Craig and Bushnell, 1994; Craig et al., 1996; Heavner et al., 1997; Morin et al., 2002; Fruhstorfer et al., 2003; Bouhassira et al., 2005; Leung et al., 2005; Defrin et al., 2008; Kern et al., 2008a; Kern et al., 2008b; Li et al., 2009). These initial studies characterised the response to the thermal grill illusion in pain-free volunteers; demonstrated that the response to the thermal grill could be pharmacologically modified and provided brief insight into the differing response to the thermal grill illusion in a patient with CRPS and MS. Consequently, the study design and the proposed research outcomes that governed this thesis were based on the limited amount of literature available at the commencement of my PhD research (1st of March 2010). Since the initiation of my PhD, the literature has doubled (Kammers et al., 2010; Bach et al., 2011; Boettger et al., 2011; Lindstedt et al., 2011a; Lindstedt et al., 2011b; Pinerua-Shuhaibar et al., 2011; Boettger et al., 2012; Seckel et al., 2012; Averbeck et al., 2013; Boettger et al., 2013; Harper and Hollins, 2014). These additional studies further characterised the response to the thermal grill illusion in pain-free volunteers, under both neutral and sad mood induction; explored the response to the thermal grill illusion in patients who suffer from psychiatric disorders, such as major depression and schizophrenia; manipulated the response to the thermal grill illusion by selectively activating cool and warm sensing ion channels; demonstrated a differential effect of cool, warm and neutral adaptation to the perception of the thermal grill illusion and implicated genetic polymorphisms of 5-HTT expression with the response to the thermal grill illusion. Additionally, a handful of research theses investigating the response to the thermal grill were also submitted in recent years (Li, 2009; Brunello, 2010; Kostka, 2011; Lam, 2012). Considering the uniqueness of the thermal grill illusion and the thermal grills' potential ability to investigate the interaction between the

nociceptive and thermoreceptive pathways, no studies in the relevant population of chronic pain patients had previously been published, albeit the abovementioned case reports. Consequently, this thesis sought to investigate the response to the thermal grill in patients with chronic pain.

The objective of this thesis was to investigate whether the response to the thermal grill was tolerable in patients with chronic pain to determine whether the thermal grill illusion could be used to screen for novel centrally acting analgesics in the future. In order to address this objective, I characterised the response to the thermal grill illusion in pain-free participants (chapters 2 and 4), in patients with heterogeneous chronic pain conditions (chapter 3) and also in patients with homogenous chronic pain conditions (chapters 4, 5 and 6) in order to determine 1) whether the response to the thermal grill differs between pain-free participants and patients with chronic pain, 2) whether the response to the thermal grill differs between body location and body side and 3) whether the thermal grill can differentiate chronic pain phenotypes (as well as others listed in section 1.7). In addition, the response to the thermal grill was longitudinally, opposed to cross-sectionally in chapters 3 and 4, investigated in patients with medication overuse headache (*MOH*) whom were receiving a novel pharmacological therapy for their headaches (chapter 5) and also in patients with chronic tension-type headache (*CTTH*) whom were receiving a novel non-pharmacological therapy for their headaches (chapter 6)(see section 1.7 for an overview of each study chapters' aims) in order to 1) determine whether the response to the thermal grill could differentiate treatment group allocation that cannot be detected by thermal quantitative sensory testing and 2) compare the test-retest reliability of the response to the thermal grill illusion over time (as well as others listed in section 1.7). Amongst all of these populations, the intensity of pain experienced from the thermal grill illusion on the dominant palm was quite low, being below the level of 40 mm (out of 100 mm), which is generally regarded as the minimum for

clinically relevant pain (Jensen et al., 2003). Due to the novel non-nociceptive nature of the thermal grill, the thermal grill stimulus was combined with a nociceptive stimulus (intradermal capsaicin) to investigate whether combining these two experimental pain models provided a unique model to investigate the efficacy of centrally acting analgesics. Following intradermal capsaicin, no summation of pain was observed to the thermal grill stimulus (20/40 ^{o}C) compared to a standard warm stimulus (40 ^{o}C), demonstrating that combining these two experimental pain stimuli is unlikely to be a useful model to investigate the efficacy of centrally acting analgesics. Consequently, the results of this thesis demonstrate that the thermal grill is unlikely to be a suitable model to assess the efficacy of analgesics either when used on its own or when combined with a nociceptive stimulus, such as intradermal capsaicin, given the inability of the thermal grill test to reach the clinically relevant substantial pain threshold (see chapters 2-6 and 8).

One noticeable feature of these studies is that the thermal grill produced an altered sensory experience that manifested as an aversive heat stimulus, rather than a painful experience. In line with previous studies investigating the thermal grill illusion, the results of this thesis demonstrate that the perceptual quality of the thermal grill illusion was generally more unpleasant than painful (Lindstedt et al., 2011a; Lindstedt et al., 2011b; Lam, 2012). Dysaesthesias, in particular thermal dysaethesias, are often experienced by patients with chronic pain (Baron, 2009), with dysaethesias being one of the most debilitating consequences of chronic pain conditions (Finnerup and Baastrup, 2012). Consequently, in chapter 3 it was suggested that the thermal grill may be a useful tool to investigate the dysaesthetic qualities of chronic pain and potentially screen for novel anti-dysaesthetic therapies for chronic pain.

At the initiation of this PhD, previous studies investigating the thermal grill response in pain-free participants had not quantitatively investigated the intensity of heat experienced from the thermal grill. Consequently, I developed a novel thermal colour bar in order to better capture the response to the thermal grill illusion. As the thermal grill produced more of an aversive heat stimulus, rather than a painful stimulus, the colour bar enabled a wider dynamic range of response to be captured. This wider dynamic range of response allowed differences between pain-free participants and patients with heterogeneous chronic pain to be observed more easily (chapter 3), highlighting the importance of using a well-suited rating scale for any given stimulus; potentially minimising false negative findings in experimental pain studies.

Unlike hypothesised and unlike my previous findings of a reduced response to the thermal grill illusion in patients with heterogeneous chronic pain compared to pain-free participants (chapter 3), the response to the thermal grill did not differ significantly between pain-free participants and patients with homogeneous chronic pain conditions (chapters 4, 5 and 6). However, although not significant, both *sciatica* and *CTTH* participants' response to the thermal grill was generally lower compared to *pain-free* participants, consistent with my previous findings in patients with heterogeneous chronic pain (chapter 3). These findings suggest that any real differences observed between pain-free participants and patients with heterogeneous chronic pain (chapter 3) are not robust or that the true effect size is small. However, these paradoxical findings of a reduced response to the thermal grill in patients with chronic pain, rather than a similar or increased response, which is usually observed in patients with chronic pain in response to experimental painful stimuli (Bezov et al., 2010; Lee et al., 2011; Aykanat et al., 2012; Soee et al., 2013; Stabell et al., 2013), suggests that the thermal grill may remain an interesting tool to understand the physiology of pain. Additionally, the response to the thermal grill did not significantly differ between the 3 different populations of patients with homogeneous chronic pain conditions (chapter 7); therefore the response to the

thermal grill was unable to differentiate chronic pain phenotypes. However, although not significant, patients with *sciatica* consistently displayed reduced responses to the thermal grill compared to *MOH* patients. Lack of significance may reflect the relatively low number of patients in the *sciatica* group, thus future studies need to investigate the response to the thermal grill illusion in larger groups of patients to verify whether the thermal grill can differentiate chronic pain phenotypes. Nevertheless, the inability of the thermal grill to significantly differentiate pain-free participants and patients with homogeneous chronic pain (chapters 4, 5 and 6), as well as patients with different types of homogeneous chronic pain conditions (chapter 7), questions the clinical utility of the thermal grill illusion, in particular in small to moderately sized studies. Consequently, the thermal grill is unlikely to be a useful tool to investigate the dysaesthetic qualities of chronic pain; whereas, whether the thermal grill has the ability to screen for novel anti-dysaesthetic therapies is still unknown.

In a comprehensive quantitative sensory testing study using the DFNS protocol (German Research Network on Neuropathic Pain), Maier and colleagues (2010) demonstrated that patients with neuropathic pain (n = 1236) were often hypoesthetic to non-nociceptive stimuli, including cool and warm detection thresholds. Previously, Brunello (2010) suggested that body site differences to the thermal grill illusion were likely related to differences in cool detection thresholds, rather than warm detection thresholds, as warm afferents are not believed to play a role in the thermal grill illusion; body regions displaying reduced cool detection thresholds were also found to have a reduced response to the thermal grill illusion. Differences in cool detection threshold may also underlie the difference in response to the thermal grill illusion between pain-free participants and patients with heterogeneous chronic pain in chapter 3 and a similar pattern of reduced response to the thermal grill in patients with *sciatica* (chapter 4) and *CTTH* (chapter 6). However, cool detection thresholds were not

investigated in this thesis, therefore this is only speculation and should ideally be investigated as this may help to better understand the neurobiology of the thermal grill illusion.

Further evidence to support that differences in response to the thermal grill relate to cool perception can be found in recent studies by Boettger and colleagues (2012, 2013). Previously, Boettger and colleagues (2012, 2013) demonstrated that patients with major depressive disorder (MDD) and schizophrenia reported significantly less pain to the thermal grill illusion and significantly greater thermal grill thresholds compared to healthy pain-free controls volunteers, and that this difference in response was mainly driven by a significant decrease in patients cold pain thresholds (see section 1.4.5.3 and chapter 3 for further discussion). Compared to pain-free volunteers, smaller A-δ fibre laser-evoked potential amplitudes have been demonstrated in patients with MDD, whilst C-fibre responses were not found to differ (Terhaar et al., 2011). A-δ fibres responsive to innocuous cooling converge on COLD neurons in the spinal cord dorsal horn, thus a reduction in amplitude of A-δ fibres may shift the stimulus-response curve to lower temperatures in patients with MDD compared to healthy controls. As reported by Craig and Bushnell (1994), the discharge pattern of COLD neurons changes during thermal grill stimulation, resulting in disinhibition of HPC cells and the experience of pain. Therefore, Boettger and colleagues (2012, 2013) suggested that a shift in noxious cold sensations and a hypothetical shift of innocuous cool sensations towards lower temperatures in patients with MDD and schizophrenia may maintain COLD cell inhibition of HPC cells even at lower temperatures, thereby increasing the overall thermal grill thresholds. Supporting their hypothesis, Boettger and colleagues (2013) demonstrated that the differences in perception of the thermal grill illusion between patients with MDD and controls was influenced by the temperature of the cold bars and not the warm bars. Consequently, these findings of a reduced response to the thermal grill in patients with reduced noxious cold perception and potentially reduced innocuous cool perception are

consistent with Craig and Bushnell's (1994) thermosensory disinhibition hypothesis. However, similar to this thesis, one limitation of the studies by Boettger and colleagues (2012, 2013) is that cool detection thresholds were not investigated, thus the influence of innocuous cool perception on the response to the thermal grill is still speculative.

Similar to previous studies, both cold (Brunello, 2010; Kostka, 2011; Lindstedt et al., 2011b; Averbeck et al., 2013) and heat pain (Lindstedt et al., 2011b) thresholds correlated with pain-free participants (chapter 4) and patients with *MOH* (chapter 5) response to the thermal grill illusion at the cheek and palm, such that participants' with increased cold pain thresholds and decreased heat pain thresholds had the greatest response to the thermal grill illusion. As discussed in chapters 4 and 5, in many instances significant correlations were observed at one or two thermal grill configurations and not at all three thermal grill configurations or for some thermal grill outcomes and not others. This is likely to reflect the robust correlation analysis and Bonferroni correction for multiple comparisons used, thus, more sophisticated statistical analyses (i.e. linear mixed effects model) should be performed in future studies so that the power of repeated measures can be accounted for (i.e. 22/38, ^{o}C 20/40 ^{o}C and 18/42 ^{o}C). Correlations between a person's cold pain threshold and their response to the thermal grill illusion are consistent with Craig and Bushnell's (1994) thermosensory disinhibition hypothesis. In line with previous studies (Essick et al., 2004; Lindstedt et al., 2011b; Kim et al., 2013), my findings in chapter 2, 4, 5 and 6 demonstrated significant correlations between a person's cold and heat pain thresholds, such that the more sensitive a person was to cold pain (i.e. increased cold pain threshold), the more sensitive that person was also to heat pain (i.e. decreased heat pain threshold) and vice versa; thus it is not surprising that heat pain thresholds were also found to correlate with participants response to the thermal grill.

In addition to investigating the intensity of the thermal grill illusion in pain-free participants and patients with chronic pain and comparing the response to the thermal grill between pain-free participants and patients with chronic pain, this thesis comprehensively investigated the response to the thermal grill by: investigating the effect of increasing temperature differentials between the cool and warm temperature bars; investigating whether the response to the thermal grill illusion differed across participants body location and body side; investigating whether the presence of central hypersensitivity, as measured by the response to the thermal grill illusion and to thermal pain thresholds, could differentiate the response to pharmacological treatment in patients with *MOH* and non-pharmacological treatment in patients with *CTTH* and comparing the test-retest reliability of the thermal grill illusion and thermal pain thresholds in patients with medication overuse headache and chronic tension-type headache. Other minor objectives were also investigated and are discussed in each respective chapter. Therefore, the results of this thesis are based upon findings across multiple, comprehensive studies.

Similar to previous studies investigating the TGI in pain-free participants, I demonstrated that increasing temperature differentials between the warm and cool temperature bars increased the response to the TGI (Bouhassira et al., 2005; Leung et al., 2005; Boettger et al., 2011; Boettger et al., 2012; Boettger et al., 2013). As discussed in section 1.4.2, these results appear to be consistent with Craig and Bushnell's (1994) thermosensory disinhibition hypothesis.

At the initiation of this PhD, the response to the thermal grill had previously not been investigated on the cheek. One objective of this thesis was to investigate whether the thermal grill was feasible to use in patients with headache disorders. Consistent with previous studies (see section 1.4.5.1 for in-depth discussion), the findings of this thesis demonstrate that the

response to the thermal grill illusion differed across body location, with responses at the calf generally being the lowest, responses at the palm the highest and responses at the cheek somewhere in between (see Figure 9.1). These differences in response across body location may be due to differences in the cortical representation of the body, which reflects differences in peripheral innervation density and/ or central convergence of thermoreceptive and nociceptive information across different body locations (discussed in chapter 2)(Brunello, 2010). As discussed in chapter 4, these findings are consistent with Craig and Bushnell's (1994) thermosensory disinhibition hypothesis, in which reduced peripheral innervation density at the calf and larger central convergence of cold thermoreceptive input onto central thermoreceptive neurons from the calf may reduce the amount of inhibition exerted by the warm bars of the thermal grill on COLD neurons, thus reducing the response to the thermal grill (Brunello, 2010). These differences in response to the thermal grill across body location may have clinical implications for further research using the thermal grill, such that it may be most beneficial to investigate the body region where the thermal grill elicits the greatest response.

Not surprisingly, and also consistent with Craig and Bushnell's (1994) thermosensory disinhibition hypothesis, generally no difference in response to the thermal grill was observed between body sides (i.e. left vs. right), demonstrating no to minimal lateralization to the thermal grill illusion. These findings have also been replicated by others (Boettger et al., 2011; Boettger et al., 2012; Averbeck et al., 2013; Boettger et al., 2013). Consequently, it is unlikely that future studies need to investigate the response to the thermal grill on both the left and right body side. However, the effect of handedness was not investigated in this PhD and to my knowledge has not been investigated by others; thus is may be beneficial to investigate whether the response to the thermal grill differs between right- and left-handed individuals, or

alternatively only investigate the response to the thermal grill in, for example, right-handed individuals.

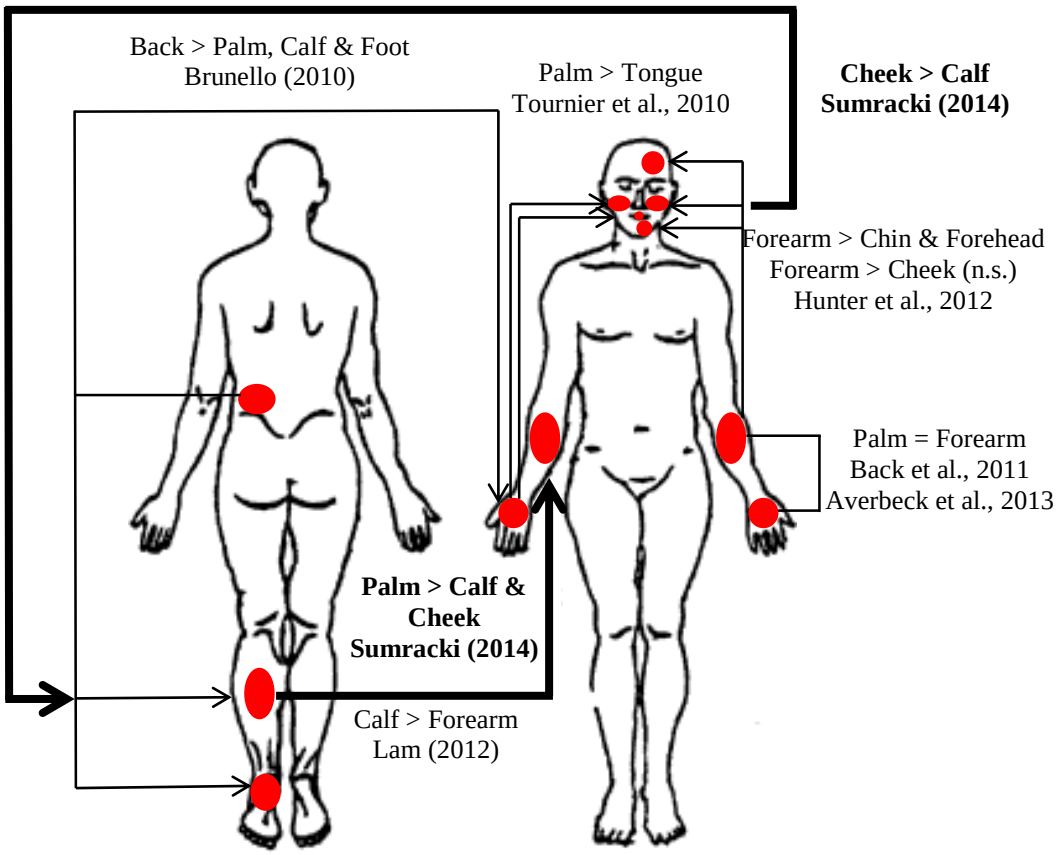

Figure 9.1. Body location differences in response to the thermal grill illusion.

Differences in response to the thermal grill illusion across body locations are depicted in this figure. Similar to Figure 1.4.5.2.1, the direction of the arrow indicates that a particular body region has a greater response to the thermal grill compared to the body region that the arrow originates from. No arrow on either end of the line connecting body location indicates that no significant difference has been demonstrated between those body regions. Differences in response to the thermal grill illusion across body locations demonstrated in this thesis are highlighted in bold.

Neither pharmacological nor non-pharmacological treatment influenced the response to the thermal grill illusion or altered patients with *MOH* (chapter 5) or *CTTH* (chapter 6) thermal pain thresholds respectively. An explanation of why these treatments did not alter *MOH* and *CTTH* patients' response to the thermal grill illusion or their thermal pain thresholds is

beyond the scope of this PhD thesis, however is briefly discussed in chapters 5 and 6 respectively.

As stated previously, the *MOH* and *CTTH* patients recruited for this study were part of two separate ongoing clinical trials conducted by Jacinta Johnson and James Smith, respectively, both of whom are PhD candidates within the same laboratory. Although the final outcomes of these two studies are unknown, preliminary data suggests that ibudilast did not reduce headache outcomes in patients with *MOH*, whereas preliminary analyses of headache outcomes in patients with *CTTH* receiving tDCS have not yet been performed*;* therefore a conclusion as to whether the thermal grill can differentiate response to pharmacological or non-pharmacological treatment in patients with chronic pain cannot be made based on these findings.

Although I cannot draw conclusive answers regarding the ability of the thermal grill to differentiate the response to pharmacological or non-pharmacological treatment for chronic pain, in chapters 5 and 6 I demonstrated that the response to the thermal grill generally decreased over time in patients with *MOH* and *CTTH*, suggesting habituation to the illusion, as well as indicating poor test-rest reliability of the thermal grill illusion; thereby questioning the utility of the thermal grill in longitudinal studies and supporting my abovementioned findings that thermal grill is unlikely to be a suitable model to assess the efficacy of analgesics.

Previously, the response to the thermal grill illusion has been pharmacologically manipulated in pain-free participants using a single IV dose of morphine, an opioid analgesic, and ketamine, a dissociative anaesthetic (discussed previously in section 1.4.4.1)(Kern et al.,

2008a; Kern et al., 2008b). Both morphine and ketamine significantly reduced the intensity of pain and unpleasantness experienced from the thermal grill illusion. Whilst single dose studies are useful to explore the potential efficacy of a pharmacological treatment and validate the utility of an experimental pain model, studies that incorporate long-term dosing regimes are required to determine whether any given analgesic is efficacious for any given chronic pain condition. Consequently, although the reduction in pain intensity and unpleasantness observed in the studies by Kern and colleagues (2008a, 2008b) appears promising for the thermal grill as a tool to investigate analgesic clinical pharmacology, the instability of the thermal grill response over time questions the thermal grills' ability to longitudinally assess the efficacy of analgesics.

These findings of a reduced response to the thermal grill illusion over time in the placebo/sham patient groups cannot be explained by Craig and Bushnell's (1994) thermosensory disinhibition hypothesis. Perhaps psychological factors may have influenced the response to the thermal grill, such as patients perceived treatment group allocation, or their attention and anticipation to pain (discussed in chapters 5 and 6). However, these factors were not investigated, nor were these objectives of this thesis, therefore the abovementioned hypotheses are only speculative, although may warrant further investigation. Consequently, additional testing is required to determine the repeatability of the thermal grill illusion in pain-free volunteers and patients with chronic pain to exclude any confounding effects *MOH* or *CTTH* patients' assigned to the placebo group may have had and to take into consideration participants attention and anticipation to pain.

Lastly, unlike hypothesised, no synergistic relationship between the ascending pathways involved in the thermal grill illusion and capsaicin-induced pain were observed in chapter 8,

suggesting that the thermal grill illusion and capsaicin-induced pain occur via parallel but non-overlapping pathways, a finding that does not appear to be congruent with Craig and Bushnell's (1994) thermosensory disinhibition hypothesis.

Limitations of this Thesis and Recommendations for Future Work

One major limitation of this thesis is that this thesis cannot conclusively determine whether the thermal grill illusion can be pharmacologically or non-pharmacologically modified in patients with chronic pain (as discussed above and in chapters 5 and 6). This is due to a variety of factors, including the ongoing nature of these clinical trials at the time of this thesis submission, as well as the inability to analyse and report other students unpublished PhD findings. However, this limitation does not detract from the overall objective of this thesis, which was to investigate whether the response to the thermal grill was tolerable in patients with chronic pain to determine whether the thermal grill illusion could be used to screen for novel centrally acting analgesics in the future. Consequently, further investigation into the pharmacological and non-pharmacological manipulation of the thermal grill illusion in patients with chronic pain is warranted.

Another limitation of this thesis was the relatively low number of patients recruited, in particular in chapters 3, 4 and 6. This was due to difficulties in recruiting patients who met the strict inclusion and exclusion criteria, as well as difficulties in patients being able to commit to the time demanding treatment protocol in chapter 6. Unfortunately, patient recruitment is often an ongoing problem with clinical research. One way to increase the number of patients recruited for such studies may be to broaden the inclusion and exclusion criteria so that more patients are eligible to participate. Broadening the inclusion and exclusion criteria may be more representative of the average person suffering from a particular painful condition.

However, broadening inclusion and exclusion criteria also comes with its caveats, making interpretation of results or the understanding of any differences or dysfunctions in patients with chronic pain more difficult. Therefore, this should be approached with caution. On the discussion of participant recruitment, one further limitation of this thesis is that the pain-free participants recruited in chapter 4 were also used as controls for chapters 5 and 6 as it was not feasible to recruit additional participants due to the nature of the study design of chapters 5 and 6. Additionally, one may argue that another limitation of this thesis is that the patient data from chapters 4, 5 and 6 (patients with *sciatica, CTTH* and *MOH*) was collated and re-analysed in chapter 7. Although re-analysis of these patient groups may not have been statistically ideal, chapter 7 allowed me to investigate whether the response to the thermal grill could differentiate chronic pain phenotypes, which had previously not been investigated. Although not significant, slight differences in response to the thermal grill illusion were observed between the 3 patient populations (as discussed above and in chapter 7). Consequently, the response to the thermal grill illusion should be further investigated in larger groups of patients to determine whether the thermal grill can differentiate chronic pain phenotypes.

Although findings in chapter 3 (Sumracki et al., 2014) demonstrated that the novel thermal colour bar developed was the most sensitive measure to detect a significant difference in response to the thermal grill between pain-free participants and patients with heterogeneous chronic pain, one limitation of this novel rating scale is that no formal psychometric analyses were performed to asses the reliability and validity of this scale. Therefore it would be encouraged to investigate the reliability and validity of this scale prior to further use by other laboratories.

As discussed previously (chapter 3), one limitation of this thesis is that the individual warm and cool temperatures used to elicit the thermal grill illusion were not tested individually (e.g., 18°C, 20°C, 22°C, 38°C, 40°C, and 42°C) in order to determine whether participants only reported pure cool and warm sensations at these temperatures and not any other types of sensations or pain. Ideally, this should have been measured; however, the design of our thermal grill did not allow all six bars to be set to either cool or warm temperatures. Instead, the cool and warm bars of the thermal grill could be set from ambient temperature (22 ^{o}C) down to 5 ^{o}C and ambient temperature up to 50 ^{o}C respectively. Therefore, future thermal grills' should be designed so that all temperature bars can be set to either cool or warm temperatures.

Another potential limitation of this thesis is that the temperature combinations used to elicit the thermal grill illusion were not customised for each participant, rather they were fixed and the same for all participants (22/38 ^{o}C, 20/40 ^{o}C and 18/42 ^{o}C) irrespective of each individuals' cold and heat pain thresholds. Recently, Boettger and colleagues (2012, 2013) demonstrated that the stimulus response curve of the thermal grill illusion was shifted towards higher stimulus intensities (i.e. larger difference between the warm and cool temperature bars) for patients with schizophrenia and MDD compared to pain-free volunteers and that this shift in stimulus intensity was in accordance with a shift in patients cold and heat pain thresholds to lower and higher temperatures respectively (i.e. less sensitive), in particular patients cold pain thresholds. Consequently, customising the temperatures of the warm and cool temperature bars to participants cold and heat pain thresholds allowed the rightward shift in stimulus response to be observed, whereas this would have been masked if a fixed thermal grill stimulus was used for both pain-free participants and patients with schizophrenia and MDD (Boettger et al., 2013). These findings in patients with schizophrenia and MDD demonstrate the importance of customising the temperature of the warm and cool temperature

bars to participants cold and heat pain thresholds, in particular when investigating the response to the thermal grill in patients with pathological conditions, such as chronic pain or other conditions that may affect thermal pain perception (i.e. MDD), especially when comparing the response to the thermal grill between two different populations. At the initiation of this PhD I decided to utilise fixed thermal grill configurations for ease of application and for standardisation of thermal grill configurations between participants based on Bouhassira and colleagues (2005) findings that the proximity of the temperatures of the thermal grill bars to participants' thermal pain thresholds was not related to the occurrence of paradoxical pain; rather, the magnitude of the temperature differential between the cool and warm bars was related to the occurrence of paradoxical pain. Although my initial study investigating the response to the thermal grill illusion in patients with heterogeneous chronic pain demonstrated a reduced response to the thermal grill illusion in patients with chronic pain, no significant differences between cold and heat pain thresholds were observed, which suggested to me that the response to the thermal grill was independent of participants cold and heat pain thresholds. Consequently, for consistency across studies, the temperature settings of the thermal grill remained fixed for all additional studies investigating the response to the thermal grill in patients with chronic pain (chapters 4, 5 and 6), which were all initiated before the studies by Boettger and colleagues (2012, 2013) were published. Additionally, using a fixed temperature approach for all participants across all body locations meant that at times the temperatures of the warm and cool bars exceeded participants heat and cold pain thresholds, thus would have been perceived as painful. Perhaps future studies should customise the temperature of the warm and cool temperature bars in order to investigate whether a customised approach is better able to differentiate pain-free volunteers and patient groups and to ensure that the temperatures of the warm and cool temperature bars remain innocuous for all participants. Additionally, similar to the studies by Boettger and colleagues (2012, 2013), it may be beneficial for future studies to investigate thermal grill thresholds (the

point at which the thermal grill first elicits a painful response) to determine whether this measurement is better able to differentiate the response to the thermal grill between pain-free participants and chronic pain patient groups. Thermal grill thresholds could be investigated by initially setting all the temperature bars of the thermal grill to a neutral temperature (32 ^{o}C) and gradually increasing and decreasing the temperatures of the warm and cool bars respectively until participants first report a paradoxical painful sensation.

As previously discussed above, an additional limitation of this thesis is that cool detection thresholds were not investigated. Consequently, whether differences in response to the thermal grill between pain-free participants and patients with heterogeneous chronic pain in chapter 3 and a similar pattern of reduced response to the thermal grill in patients with chronic *sciatica* (chapter 4) and *CTTH* (chapter 6) depends on participants cool detection threshold is still unknown and should ideally be investigated as this may help to better understand the neurobiology of the thermal grill illusion.

Previously, Morin and colleagues (2002) demonstrated that the thermal grill failed to produce the normal illusion of pain in a patient with multiple sclerosis (MS) who experienced central pain as a result of a lesion that involved the spinothalamic tract, consistent with Craig and Bushnell's (1994) thermosensory disinhibition hypothesis. Morin and colleagues (2002) explained that this altered response to the thermal grill in the patient with MS was not surprising given that their reduced thermosensory transmission would have resulted in a pre-existing disinhibition of pain, consequently preventing additional disinhibition by the thermal grill. Consequently, Craig (2008) suggested that the absence of the thermal grill effect may be a diagnostic for central pain. Perhaps the thermal grill may even be a useful diagnostic tool for patients with loss of nerve function, such as diabetic polyneuropathy (DPN). Not only

may the thermal grill be a useful diagnostic tool for conditions such as DPN, the thermal grill may even be a useful tool to track disease progression and potentially disease reversal.

As discussed in section 1.4.5, the thermal grill illusion is not a robust phenomenon, with studies demonstrating that approximately 6-52% of healthy volunteers do not experience the illusion (Bouhassira et al., 2005; Leung et al., 2005; Kern et al., 2008a; Kern et al., 2008b; Li, 2009; Li et al., 2009; Brunello, 2010; Kostka, 2011; Boettger et al., 2012; Boettger et al., 2013). Perhaps this lack of response to the thermal grill in a proportion of healthy volunteers may predict which individuals may be more likely to develop chronic pain conditions following injury. One potential way to investigate this may be to investigate the response to the thermal grill illusion both pre- and post-surgical procedures which are known to have a high incidence of chronic neuropathic pain developing post-surgery.

Summary and Conclusion

As discussed earlier, various aspects of this thesis support or are in accordance with Craig and Bushnell's (1994) thermosensory disinhibition hypothesis, such as my observations that the response to the thermal grill increases when the temperature differential between the cool and warm temperature bars increases, that the response to the thermal grill differs between body locations, that there is generally no difference in response to the thermal grill between body sides and that cold pain thresholds tend to correlate with thermal grill outcomes. However, some findings of this thesis do not support or cannot be explained by Craig and Bushnell's (1994) thermosensory disinhibition hypothesis, such as my findings of a variable, in particular reduced, response to the thermal grill when investigated longitudinally in patients with *MOH* and *CTTH*; although external factors such as patients perceived treatment group allocation, attention or anticipation may have influenced patients response to the thermal grill (discussed

above and in chapters 5 and 6), or that the thermal grill did not enhance capsaicin-induced pain (discussed above and in chapter 8). Thus, further work is required to determine whether Craig and Bushnell's (1994) thermosensory disinhibition hypothesis underlies the thermal grill illusion.

This thesis demonstrates for the first time that the response to the thermal grill illusion is tolerable in patients with various types of chronic pain; that the response to the thermal grill is either the same or slightly reduced in patients with chronic pain compared to pain-free participants, a unique and paradoxical findings in itself; that the response to the thermal grill, although not significant, is consistently reduced in patients with *sciatica* compared to patients with *MOH*; that the thermal grill is tolerable on the cheek in pain-free participants, patients with *sciatica* and also patients whom suffer from chronic headache conditions (*MOH*, *CTTH*); and that unlike a warm/heat (40 ^{o}C) stimulus, the thermal grill (20/40 ^{o}C) does not cause capsaicin-induced spontaneous pain to summate. Amongst all of the populations investigated, the intensity of pain experienced from the thermal grill illusion on the dominant palm was quite low, being below the level of 40 mm (out of 100 mm), which is generally regarded as the minimum for clinically relevant pain (Jensen et al., 2003). Consequently, the results of this thesis demonstrate that the thermal grill is unlikely to be a suitable model to assess the efficacy of analgesics either when used on its own or when combined with a nociceptive stimulus, such as intradermal capsaicin, given the inability of the thermal grill test to reach the clinically relevant substantial pain threshold (see chapters 2-6 and 8). Additionally, the inability of the thermal grill to significantly differentiate pain-free participants and patients with homogeneous chronic pain (chapters 4, 5 and 6), as well as patients with different types of homogeneous chronic pain conditions (chapter 7), questions the clinical utility of the thermal grill illusion, in particular in small to moderately sized studies. Consequently, the

thermal grill is unlikely to be a useful tool to investigate the dysaesthetic qualities of chronic pain.

Although the thermal grill is unlikely to be a suitable tool to assess the efficacy of analgesics, the thermal grill may still be a useful tool to 1) screen for anti-dysaesthetic therapies, given the predominant heat sensation produced by the thermal grill; 2) better understand the physiology of pain, given the paradoxical reduced pain observed in some types of patients with chronic pain; 3) diagnose central pain, given the lack of response to the thermal grill in a patient with multiple sclerosis and 4) predict the occurrence of chronic neuropathic pain following injury, given that a proportion of healthy participants are non-responders to the thermal grill. Future studies comparing the response to the thermal grill between two or more different populations should customise the temperature of the cool and warm bars to participants cold and heat pain thresholds, as well as investigate thermal grill thresholds. Additionally, future studies should investigate cool detection thresholds as this may help to better understand the neurobiology of the thermal grill illusion (as discussed above) and whether or not Craig and Bushnell's (1994) thermosensory disinhibition hypothesis underlies the thermal grill illusion. Although not significant in this study, future studies need to investigate the response to the thermal grill illusion in larger groups of patients to verify whether the thermal grill can differentiate patients with different types of chronic pain conditions. In particular, if the thermal grill proves to be a useful diagnostic tool for chronic neuropathic pain, the thermal grill may be able to differentiate patients with differing pain aetiologies.

Chapter 10. References

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Chapter 11. Appendices

Supplementary Tables and Figures

Chapter 2

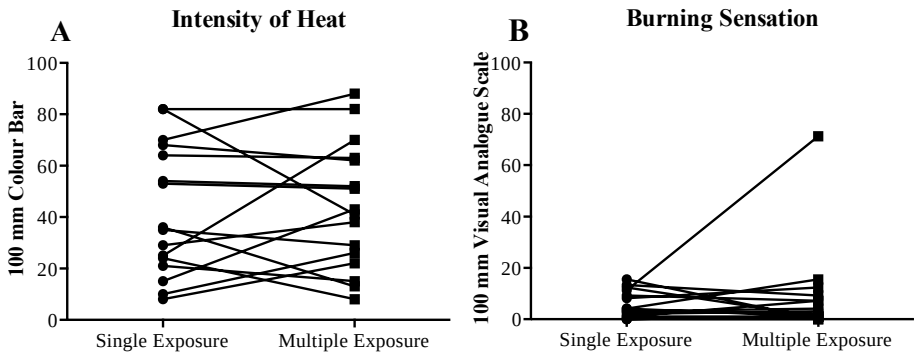


Figure 11.2.1. Single vs. repeated exposure to the thermal grill illusion.

Effect of single vs. repeated exposure to the thermal grill illusion for the outcomes. The response to the thermal grill did not differ between single and repeated exposure to the thermal grill.

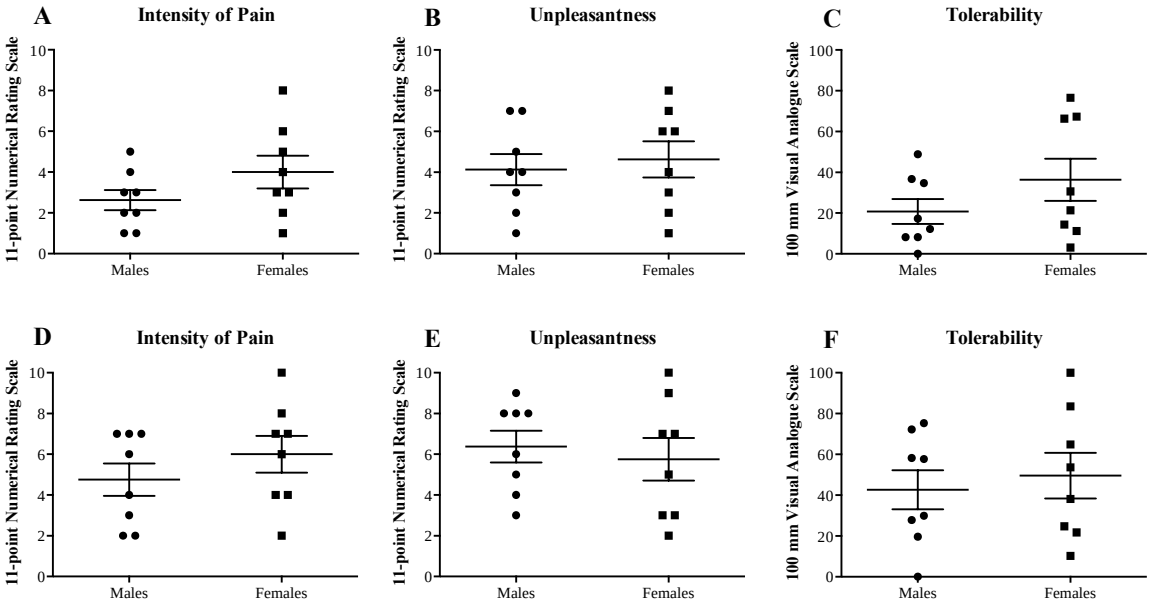
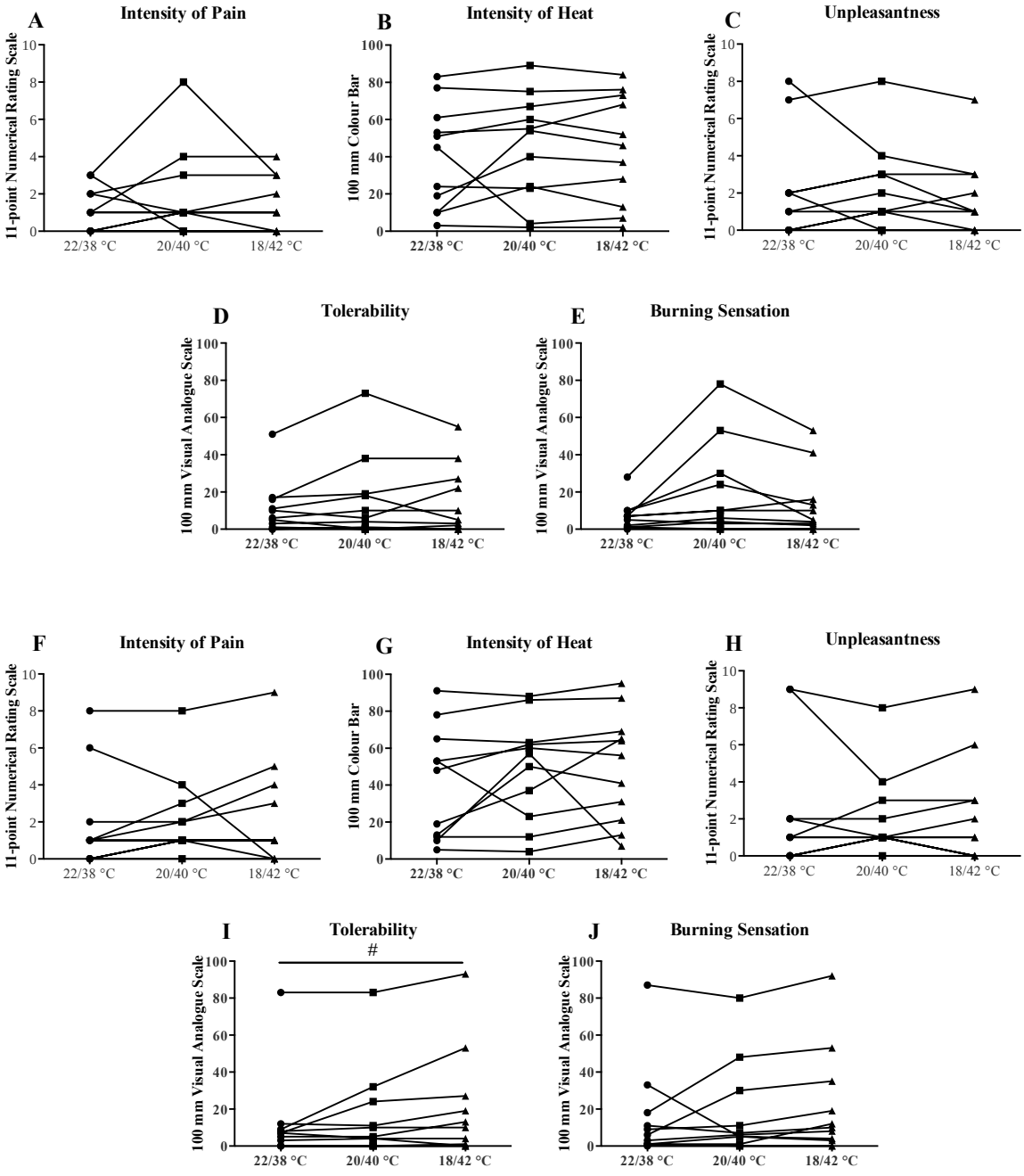


Figure 11.2.2. Effect of gender to electrical stimulation.

Effect of gender on the responses to a single electrical stimulus (A-C) and multiple electrical stimuli (D-F). The response to single or multiple electrical stimuli did not differ between males and females. All graphs are represented as mean ± SEM.


A
Intensity of Pain
11-point Numerical Rating Scale
B
Intensity of Heat
100 mm Colour Bar
C
Unpleasantness
11-point Numerical Rating Scale
D
Tolerability
100 mm Visual Analogue Scale
E
Burning Sensation
100 mm Visual Analogue Scale
F
Intensity of Pain
11-point Numerical Rating Scale
G
Intensity of Heat
100 mm Colour Bar
H
Unpleasantness
11-point Numerical Rating Scale
I
Tolerability
#
100 mm Visual Analogue Scale
J
Burning Sensation
100 mm Visual Analogue Scale
22/38 °C
20/40 °C
18/42 °C

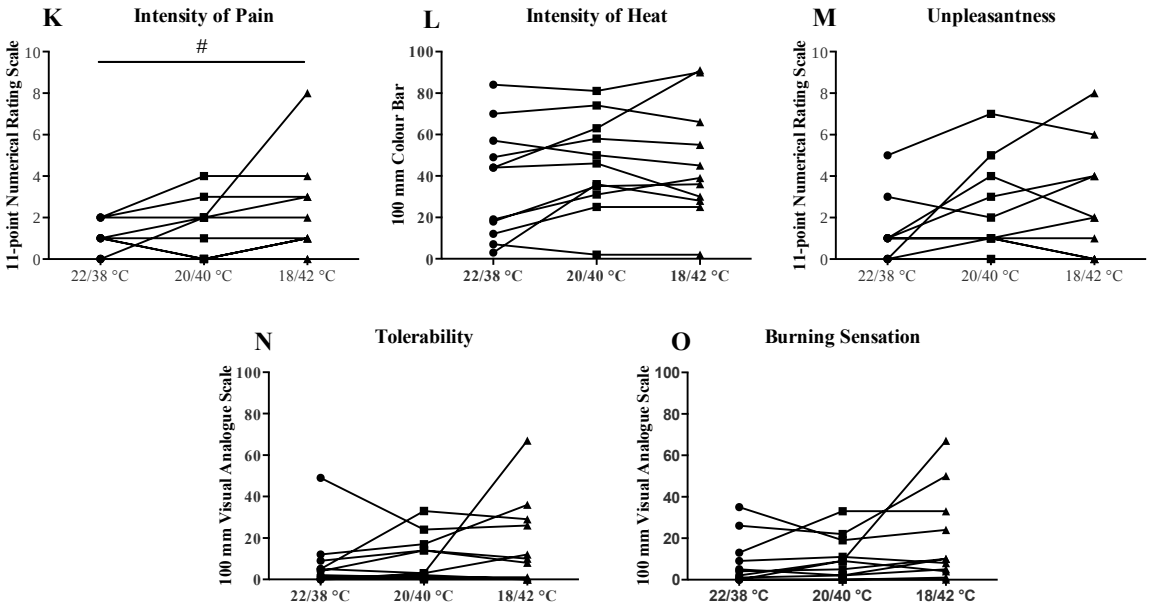


Figure 11.2.3. Increasing temperature differentials between the warm and cool temperature bars on the cheek.

Effect of increasing temperature differentials between the warm and cool temperature bars on the responses to the thermal grill illusion at participants right (A-E) and left (F-J) cheek when tested for 3 s and at participants left cheek (K-O) when tested for 30 s. As the temperature differentials between the warm and cool bars increased, an overall main effect for significantly less tolerability (I) at the left cheek (3 s) and more pain (K) at the left cheek (30 s) was observed. # $P < 0.05$ for an overall main effect.

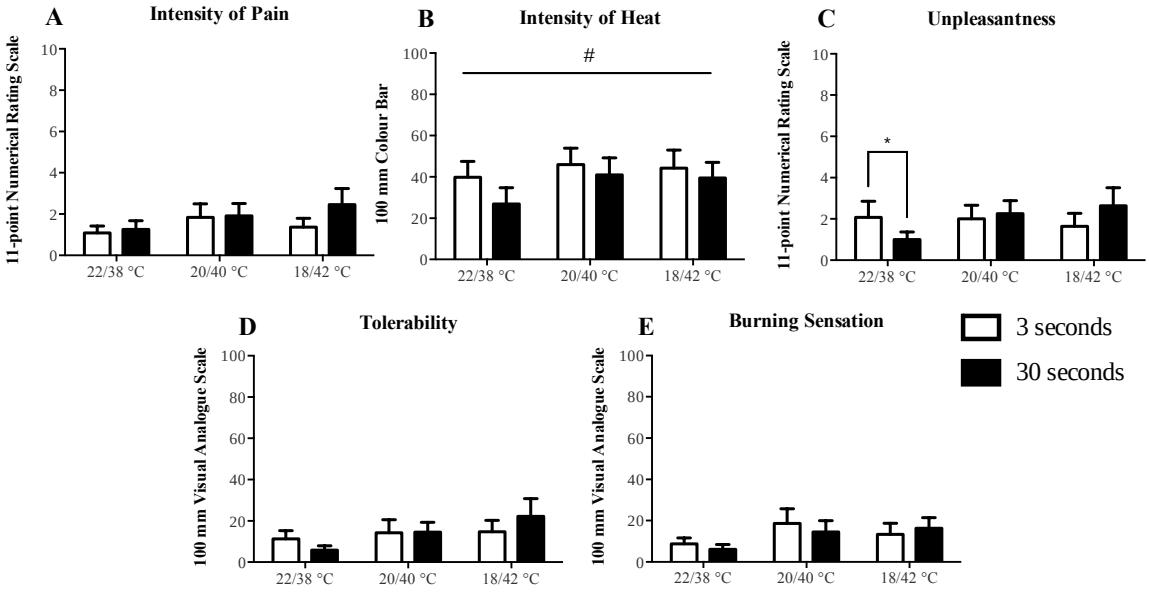


Figure 11.2.4. Effect of contact time to the thermal grill illusion.

The response to the thermal grill illusion at the right cheek when tested after 3 s and 30 s contact. The effect of contact time did not affect the response to the thermal grill illusion for all thermal grill outcomes. Significantly less heat (B) and unpleasantness (C) to the thermal grill illusion was observed after 30 s contact to the thermal grill compared to 3 s contact. All graphs are represented as mean ± SEM. * $P < 0.05$, # $P < 0.05$ for an overall main effect.

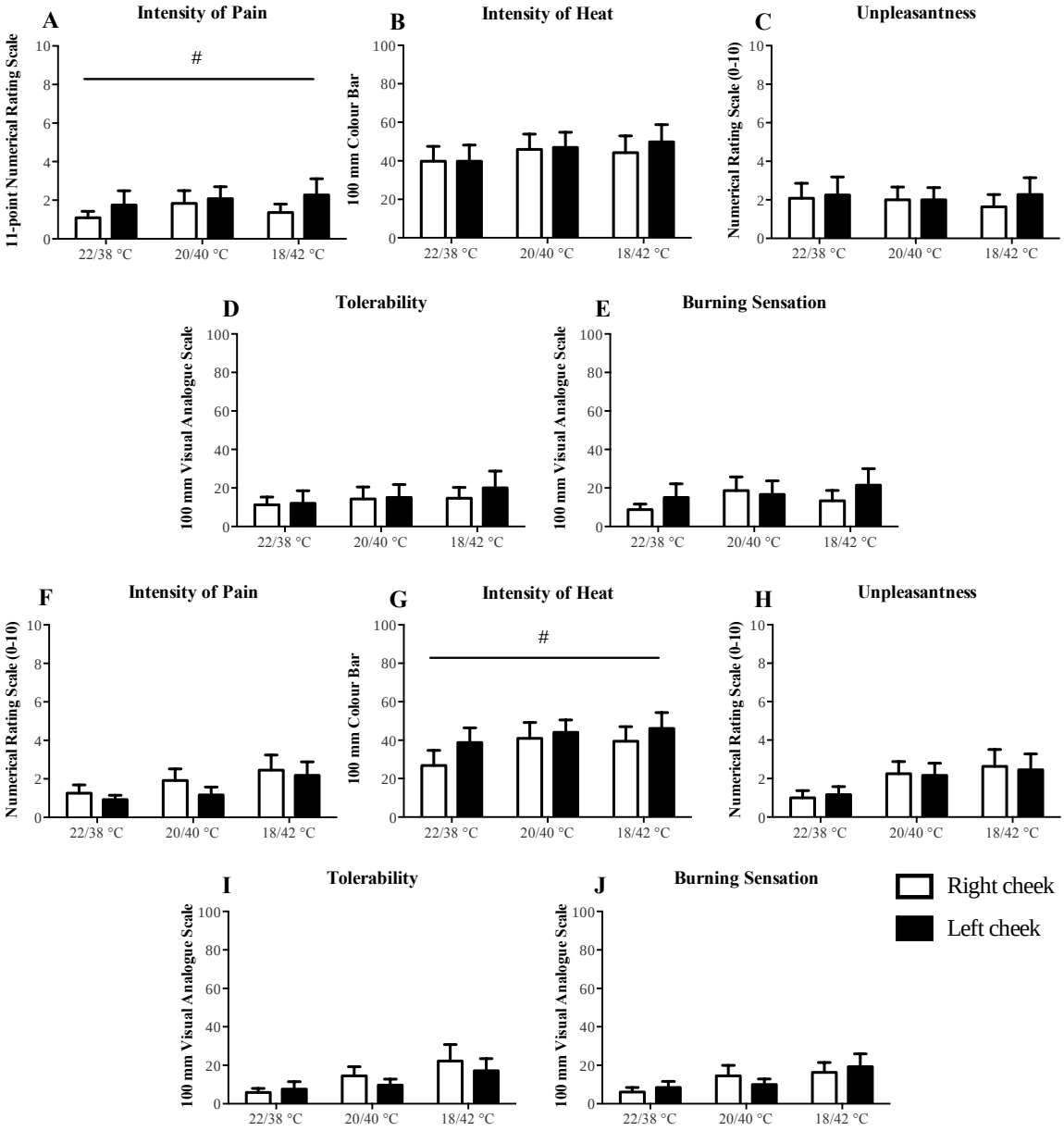
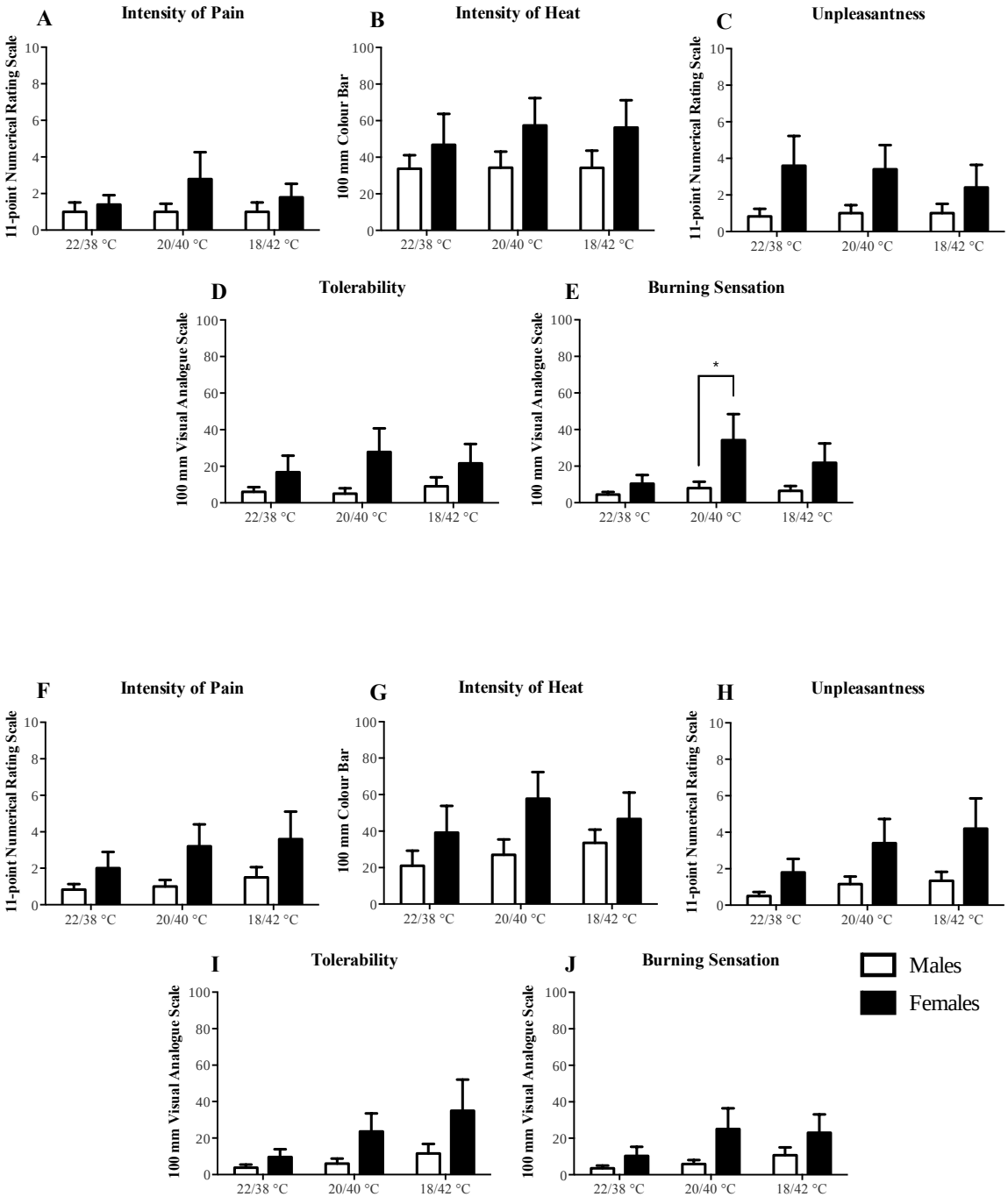


Figure 11.2.5. Effect of body side to the thermal grill illusion.

The response to the thermal grill illusion at the left (black bars) and right (white bars) cheek following 3 s (A-E) and 30 s (F-J) contact to the thermal grill. An overall effect for significantly less pain (A) and heat (G) to the thermal grill was observed at the right cheek compared to the left cheek following 3 s and 30 s contact to the thermal grill respectively. All graphs are represented as mean ± SEM. # $P < 0.05$ for an overall main effect.


A
Intensity of Pain
11-point Numerical Rating Scale
B
Intensity of Heat
100 mm Colour Bar
C
Unpleasantness
11-point Numerical Rating Scale
D
Tolerability
100 mm Visual Analogue Scale
E
Burning Sensation
100 mm Visual Analogue Scale
*
F
Intensity of Pain
11-point Numerical Rating Scale
G
Intensity of Heat
100 mm Colour Bar
H
Unpleasantness
11-point Numerical Rating Scale
I
Tolerability
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100 mm Visual Analogue Scale
22/38 °C
20/40 °C
18/42 °C
Males
Females

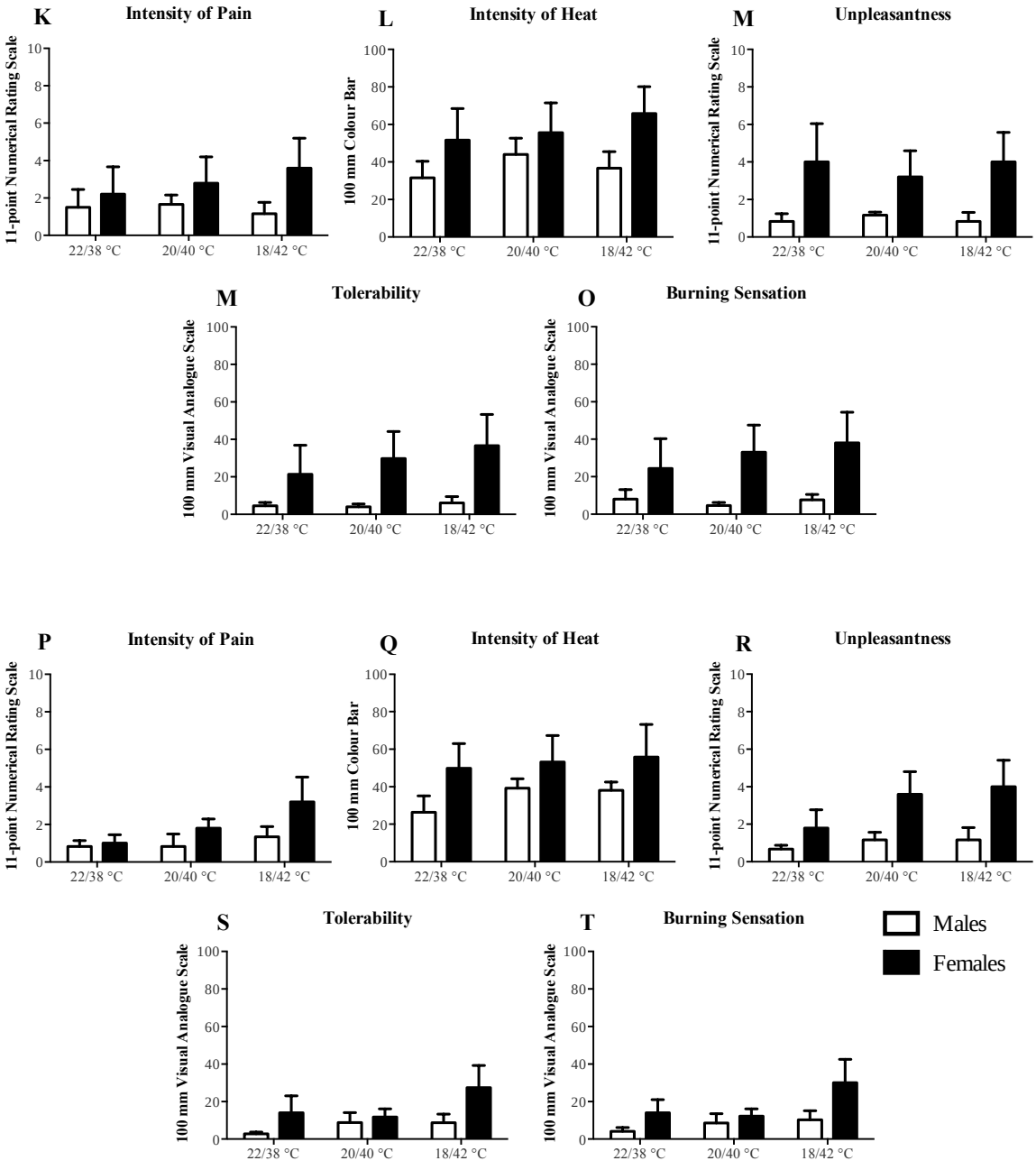


Figure 11.2.6. Effect of gender to the thermal grill illusion

The response to the thermal grill illusion in males (white bars) and females (black bars) on the right cheek at 3 s (A-E) and 30 s (F-J) and left cheek at 3 s (K-O) and 30 s (P-T). The response to the thermal grill did not significantly differ between males and females, albeit for one outcome at the right cheek (E), although females tended to display increased responses to the thermal grill. All graphs are represented as mean ± SEM. * $P < 0.05$.

Chapter 3

No additional tables or figures to present.

Chapter 4

Tables

Table 11.4.1. Correlations Between Beck Depression Inventory Scores and Cold and Heat Pain Thresholds: Pain-free Participants

R and *P* values from the correlation analysis performed between participants Beck depression inventory scores and their cold and heat pain thresholds (listed horizontally) at participants affected and unaffected side cheek, palm and calf (listed vertically). Significant values represented by bold text.

	Cold Pain Threshold	Heat Pain Threshold
Affected Cheek		
R value	0.51	-0.52
P value	0.021	0.019
Unaffected Cheek		
R value	**0.6**	-0.52
P value	**0.0051**	0.02
Affected Palm		
R value	**0.64**	**-0.6**
P value	**0.0024**	**0.005**
Unaffected Palm		
R value	0.52	**-0.6**
P value	0.019	**0.005**
Affected Palm		
R value	0.46	-0.5
P value	0.042	0.023
Unaffected Palm		
R value	0.34	-0.31
P value	0.14	0.19

All analysed with Spearman's correlation. Significance level < 0.0125.

Table 11.4.2. Correlations Between Beck Depression Inventory Scores and Cold and Heat Pain Thresholds: Patients with Sciatica

R and *P* values from the correlation analysis performed between patients Beck depression inventory scores and their cold and heat pain thresholds (listed horizontally) at patients affected and unaffected side cheek, palm and calf (listed vertically).

	Cold Pain Threshold	Heat Pain Threshold
Affected Cheek		
R value	-0.12	-0.19
P value	0.75	0.6
Unaffected Cheek		
R value	-0.013	-0.21
P value	0.95	0.57
Affected Palm		
R value	0.27	-0.48
P value	0.47	0.19
Unaffected Palm		
R value	0.49	-0.19
P value	0.19	0.6
Affected Calf		
R value	-0.8	0.53
P value	0.01	0.15
Unaffected Calf		
R value	0.6	0.4
P value	0.091	0.29

All analysed with Spearman's correlation. Significance level < 0.00833.

Table 11.4.3. Correlations Between Beck Depression Inventory Scores and the Thermal Grill Response: Pain-free Participants

R and *P* values from the correlation analyses performed at participants affected and unaffected side cheek, palm and calf are presented (described previously on page 94).

		Affected Side			Unaffected Side		
	Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Cheek	Intensity of Pain						
	R value	0.44	0.33	0.31	0.18	0.17	0.063
	P value	0.052	0.15	0.18	0.45	0.48	0.79
	Intensity of Heat						
	R value	0.53	0.54	0.48	0.44	0.37	0.38
	P value	0.015	0.015	0.033	0.051	0.11	0.1
	Intensity of Heat						
	R value	0.19	0.44	0.29	0.34	0.26	0.28
	P value	0.42	0.051	0.21	0.14	0.27	0.23
	Unpleasantness						
	R value	0.24	0.096	0.29	0.23	0.26	0.07
	P value	0.31	0.69	0.21	0.34	0.28	0.72
	Tolerability						
	R value	0.18	0.31	0.25	0.21	0.21	0.16
	P value	0.45	0.18	0.3	0.37	0.38	0.51
Palm	Intensity of Pain						
	R value	0.036	0.08	0.067	0.097	0.24	0.3
	P value	0.88	0.74	0.78	0.68	0.31	0.21
	Intensity of Heat						
	R value	0.24	0.28	0.3	0.32	0.43	0.33
	P value	0.32	0.23	0.19	0.16	0.06	0.15
	Intensity of Heat						
	R value	0.19	0.11	0.14	0.14	0.095	0.094
	P value	0.42	0.65	0.57	0.6	0.69	0.69
	Unpleasantness						
	R value	0.2	0.22	0.22	-0.0069	0.35	0.31
	P value	0.4	0.35	0.36	0.98	0.13	0.19
	Tolerability						
	R value	-0.056	0.17	0.24	0.093	0.21	0.24
	P value	0.81	0.48	0.31	0.7	0.38	0.3

		Affected Side			Unaffected Side		
	Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Calf	Intensity of Pain						
	R value	-0.062	-0.14	-0.032	-0.027	0.16	0.0027
	P value	0.8	0.55	0.89	0.91	0.5	0.99
	Intensity of Heat						
	R value	0.18	0.013	0.15	0.0069	0.16	0.047
	P value	0.44	0.96	0.54	0.98	0.51	0.84
	Intensity of Heat						
	R value	0.19	-0.013	0.12	0.19	0.21	0.071
	P value	0.43	0.96	0.61	0.43	0.37	0.77
	Unpleasantness						
	R value	0.091	-0.064	0.011	-0.12	-0.023	-0.039
	P value	0.7	0.79	0.96	0.61	0.92	0.87
	Tolerability						
	R value	0.0023	-0.14	-0.082	0.0023	-0.14	-0.082
	P value	0.92	0.55	0.73	0.99	0.55	0.73

ºC: degrees Celcius. All analysed with Spearman's correlation. Significance level < 0.000833.

Table 11.4.4. Correlations Between Beck Depression Inventory Scores and the Thermal Grill Response: Patients with Sciatica

R and *P* values from the correlation analyses performed at patients affected and unaffected side cheek, palm and calf are presented (described previously on page 94). Significant values represented by bold text.

		Affected Side			Unaffected Side		
	Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Cheek	Intensity of Pain						
	R value	0.051	0.0	-0.1	-0.41	-0.33	-0.41
	P value	0.9	0.98	0.78	0.26	0.361	0.26
	Intensity of Heat						
	R value	0.051	-0.23	-0.33	-0.41	-0.36	0.1
	P value	0.9	0.53	0.36	0.26	0.31	0.77
	Intensity of Heat						
	R value	0.084	-0.29	-0.36	-0.034	-0.54	-0.29
	P value	0.83	0.44	0.32	0.92	0.13	0.44
	Unpleasantness						
	R value	0.18	-0.18	-0.38	-0.41	-0.33	-0.0084
	P value	0.64	0.62	0.28	0.24	0.35	0.97
	Tolerability						
	R value	0.21	-0.33	-0.52	-0.56	-0.5	-0.051
	P value	0.58	0.3	0.14	0.1	0.16	0.87
Palm	Intensity of Pain						
	R value	-0.35	-0.077	0.067	0.089	-0.51	-0.41
	P value	0.32	0.78	0.87	0.82	0.15	0.26
	Intensity of Heat						
	R value	-0.33	-0.092	-0.0084	0.017	-0.31	-0.17
	P value	0.36	0.8	0.97	0.97	0.4	0.65
	Intensity of Heat						
	R value	-0.38	-0.0084	-0.16	-0.093	-0.33	-0.072
	P value	0.29	0.95	0.67	0.78	0.37	0.85
	Unpleasantness						
	R value	-0.48	-0.46	-0.34	0.0	-0.48	-0.51
	P value	0.18	0.2	0.35	0.98	0.18	0.15
	Tolerability						
	R value	-0.43	-0.51	0.17	-0.49	-0.53	-0.48
	P value	0.13	0.14	0.66	0.16	0.13	0.17

		Affected Side			Unaffected Side		
	Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Calf	Intensity of Pain						
	R value	-0.56	-0.53	-0.6	-0.41	-0.48	0.13
	P value	0.11	0.11	0.084	0.22	0.17	0.98
	Intensity of Heat						
	R value	-0.48	-0.51	-0.53	-0.28	-0.37	-0.13
	P value	0.16	0.15	0.13	0.44	0.3	0.72
	Intensity of Heat						
	R value	-0.61	**-0.95**	-0.76	-0.52	-0.62	-0.56
	P value	0.074	**0.0002**	0.018	0.15	0.068	0.11
	Unpleasantness						
	R value	0.09	0.025	0.064	0.077	0.025	-0.2
	P value	0.82	0.95	0.87	0.85	0.96	0.57
	Tolerability						
	R value	-0.38	-0.49	-0.52	-0.32	-0.32	-0.46
	P value	0.23	0.13	0.082	0.34	0.34	0.19

ºC: degrees Celcius. All analysed with Spearman's correlation. Significance level < 0.000555.

Table 11.4.5 Correlations Between Salivary Cortisol and Cold and Heat Pain Thresholds: Pain-free Participants

R and *P* values from the correlation analysis performed between participants early morning salivary cortisol levels, both awakening and 30 mins post awakening, and their cold and heat pain thresholds (listed horizontally) at participants affected and unaffected side cheek, palm and calf (listed vertically).

	Awakening		30 mins Post-Awakening	
	Cold Pain Threshold	Heat Pain Threshold	Cold Pain Threshold	Heat Pain Threshold
Affected Cheek				
R value	0.23	0.25	-0.11	-0.17
P value	0.34	0.31	0.65	0.47
Unaffected Cheek				
R value	-0.089	0.29	-0.048	-0.15
P value	0.72	0.22	0.84	0.52
Affected Palm				
R value	-0.19	0.16	-0.068	-0.039
P value	0.44	0.5	0.78	0.87
Unaffected Palm				
R value	-0.14	0.057	-0.17	-0.057
P value	0.55	0.82	0.47	0.81
Affected Palm				
R value	0.29	0.12	0.15	-0.14
P value	0.22	0.61	0.53	0.56
Unaffected Palm				
R value	0.21	0.13	0.29	-0.3
P value	0.39	0.59	0.21	0.2

All analysed with Spearman's correlation. Significance level < 0.0125.

Table 11.4.6 Correlations Between Salivary Cortisol and Cold and Heat Pain Thresholds: Patients with Sciatica

R and *P* values from the correlation analysis performed between patients early morning salivary cortisol levels, both awakening and 30 mins post awakening, and their cold and heat pain thresholds (listed horizontally) at patients affected and unaffected side cheek, palm and calf (listed vertically). Significant values represented by bold text.

	Awakening		30 mins Post-Awakening	
	Cold Pain Threshold	Heat Pain Threshold	Cold Pain Threshold	Heat Pain Threshold
Affected Cheek				
R value	0.39	-0.56	0.26	-0.67
P value	0.33	0.15	0.53	0.054
Unaffected Cheek				
R value	0.31	-0.21	0.63	-0.18
P value	0.45	0.62	0.092	0.68
Affected Palm				
R value	-0.034	-0.58	0.49	**-0.9**
P value	0.94	0.13	0.21	**0.0022**
Unaffected Palm				
R value	0.4	-0.4	0.56	-0.72
P value	0.33	0.33	0.15	0.045
Affected Calf				
R value	-0.016	-0.74	-0.58	-0.11
P value	0.97	0.037	0.13	0.79
Unaffected Calf				
R value	-0.21	-0.48	0.62	-0.3
P value	0.62	0.23	0.1	0.48

All analysed with Pearson's correlation. Significance level < 0.00833.

Table 11.4.7. Correlations Between Salivary Cortisol and the Thermal Grill Response: Pain-free Participants

R and *P* values from the correlation analyses performed at participants affected and unaffected side cheek, palm and calf are presented (described previously on page 94).

		Awakening			30 mins Post-Awakening		
	Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Affected Cheek	Intensity of Pain						
	R value	-0.054	-0.089	-0.22	-0.12	-0.16	0.17
	P value	0.83	0.72	0.36	0.6	0.49	0.48
	Intensity of Heat						
	R value	-0.17	-0.14	-0.39	-0.083	0.097	0.1
	P value	0.48	0.56	0.1	0.73	0.68	0.66
	Intensity of Heat						
	R value	-0.38	-0.27	-0.37	-0.19	-0.12	-0.043
	P value	0.11	0.26	0.12	0.41	0.61	0.86
	Unpleasantness						
	R value	-0.18	-0.26	-0.47	0.16	-0.07	0.042
	P value	0.46	0.28	0.043	0.5	0.77	0.86
	Tolerability						
	R value	-0.26	-0.18	-0.4	-0.076	-0.29	-0.0072
	P value	0.28	0.45	0.086	0.75	0.21	0.98
Unaffected Cheek	Intensity of Pain						
	R value	-0.17	-0.18	-0.18	-0.11	-0.066	-0.14
	P value	0.5	0.46	0.45	0.66	0.78	0.56
	Intensity of Heat						
	R value	0.097	-0.29	-0.11	0.067	0.094	0.19
	P value	0.69	0.24	0.65	0.78	0.69	0.43
	Intensity of Heat						
	R value	-0.076	-0.25	-0.3	-0.13	-0.11	-0.19
	P value	0.76	0.3	0.22	0.59	0.65	0.43
	Unpleasantness						
	R value	-0.2	-0.21	-0.16	-0.075	-0.15	-0.054
	P value	0.42	0.39	0.52	0.75	0.53	0.82
	Tolerability						
	R value	-0.10	-0.15	-0.19	0.036	-0.087	-0.099
	P value	-0.68	0.53	0.43	0.88	0.72	0.68

		Awakening			30 mins Post-Awakening		
	Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Affected Palm	Intensity of Pain						
	R value	0.0066	0.053	-0.19	-0.19	-0.023	-0.096
	P value	0.98	0.83	0.44	0.42	0.92	0.69
	Intensity of Heat						
	R value	-0.29	-0.12	-0.27	0.2	0.23	0.14
	P value	0.22	0.63	0.26	0.4	0.33	0.55
	Intensity of Heat						
	R value	-0.23	-0.34	-0.34	-0.074	-0.075	-0.023
	P value	0.35	0.16	0.15	0.76	0.75	0.92
	Unpleasantness						
	R value	0.042	-0.085	-0.1	0.003	-0.0087	-0.017
	P value	0.86	0.73	0.68	0.99	0.97	0.94
	Tolerability						
	R value	-0.13	-0.023	-0.13	-0.27	-0.033	-0.033
	P value	0.59	0.93	0.6	0.26	0.89	0.89
Unaffected Palm	Intensity of Pain						
	R value	-0.17	0.048	0.038	-0.19	-0.0034	-0.097
	P value	0.49	0.85	0.87	0.42	0.99	0.68
	Intensity of Heat						
	R value	-0.19	-0.19	-0.087	0.098	0.065	0.11
	P value	0.44	0.43	0.72	0.68	0.78	0.64
	Intensity of Heat						
	R value	-0.31	-0.29	-0.13	-0.2	-0.043	0.012
	P value	0.2	0.22	0.6	0.4	0.86	0.96
	Unpleasantness						
	R value	-0.21	-0.04	-0.014	-0.14	-0.053	-0.1
	P value	0.39	0.87	0.95	0.55	0.82	0.67
	Tolerability						
	R value	-0.18	-0.21	0.00044	-0.25	-0.2	-0.16
	P value	0.46	0.4	1.0	0.28	0.4	0.51

		Awakening			30 mins Post-Awakening		
	Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Affected Calf	Intensity of Pain						
	R value	-0.02	-0.069	-0.058	-0.14	-0.14	-0.077
	P value	0.94	0.78	0.81	0.55	0.56	0.75
	Intensity of Heat						
	R value	-0.38	-0.22	-0.096	0.03	0.17	0.1
	P value	0.11	0.36	0.7	0.9	0.49	0.66
	Intensity of Heat						
	R value	-0.43	-0.35	-0.21	-0.081	-0.0026	0.014
	P value	0.063	0.14	0.38	0.74	0.99	0.95
	Unpleasantness						
	R value	-0.14	-0.38	-0.078	0.18	0.19	0.17
	P value	0.58	0.11	0.75	0.44	0.42	0.47
	Tolerability						
	R value	0.054	-0.15	-0.036	0.017	0.15	0.0027
	P value	0.83	0.53	0.89	0.94	0.53	0.99
Unaffected Calf	Intensity of Pain						
	R value	-0.19	-0.0022	-0.18	-0.18	-0.16	0.026
	P value	0.44	0.99	0.47	0.44	0.5	0.91
	Intensity of Heat						
	R value	-0.074	-0.12	-0.18	0.083	0.077	0.25
	P value	0.76	0.63	0.46	0.73	0.75	0.3
	Intensity of Heat						
	R value	-0.24	-0.23	-0.35	0.0015	-0.03	0.059
	P value	0.32	0.35	0.14	1.0	0.9	0.8
	Unpleasantness						
	R value	-0.1	-0.34	-0.39	0.14	0.038	0.079
	P value	0.68	0.15	0.095	0.55	0.87	0.74
	Tolerability						
	R value	0.054	-0.15	-0.036	0.017	0.15	0.0027
	P value	0.83	0.53	0.89	0.94	0.53	0.99

ºC: degrees Celcius. All analysed with Spearman's correlation. Significance level < 0.000833.

Table 11.4.8. Correlations Between Salivary Cortisol and the Thermal Grill Response: Patients with Sciatica

R and *P* values from the correlation analyses performed at patients affected and unaffected side cheek, palm and calf are presented (described previously on page 94).

		Awakening			30 mins Post-Awakening		
	Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Affected Cheek	Intensity of Pain						
	R value	-0.27	-0.14	0.073	0.084	-0.036	-0.12
	P value	0.49	0.72	0.87	0.85	0.92	0.76
	Intensity of Heat						
	R value	0.052[P]	0.39[P]	0.5[P]	0.22[P]	0.035[P]	0.03[P]
	P value	0.9[P]	0.34[P]	0.21[P]	0.59[P]	0.93[P]	0.94[P]
	Intensity of Heat						
	R value	-0.4[P]	0.0052[P]	-0.13[P]	-0.13[P]	-0.23[P]	-0.39[P]
	P value	0.33[P]	0.99[P]	0.77[P]	0.76[P]	0.59[P]	0.33[P]
	Unpleasantness						
	R value	-0.51[P]	0.12[P]	0.11[P]	0.026[P]	-0.23[P]	-0.41[P]
	P value	0.19[P]	0.78[P]	0.8[P]	0.95[P]	0.59[P]	0.31[P]
	Tolerability						
	R value	-0.57	0.19	-0.19	0.0	-0.33	-0.52
	P value	0.087	0.66	0.6	0.88	0.33	0.18
Unaffected Cheek	Intensity of Pain						
	R value	0.14[P]	0.44[P]	0.27[P]	-0.47[P]	-0.068[P]	-0.21[P]
	P value	0.73[P]	0.27[P]	0.51[P]	0.23[P]	0.87[P]	0.62[P]
	Intensity of Heat						
	R value	0.36[P]	0.47[P]	0.24[P]	-0.3[P]	-0.042[P]	0.021[P]
	P value	0.38[P]	0.24[P]	0.57[P]	0.47[P]	0.92[P]	0.96[P]
	Intensity of Heat						
	R value	0.42[P]	0.085[P]	-0.43[P]	-0.23[P]	-0.24[P]	-0.27[P]
	P value	0.3[P]	0.84[P]	0.29[P]	0.58[P]	0.56[P]	0.51[P]
	Unpleasantness						
	R value	-0.03	0.21	-0.31	-0.36	-0.2	-0.21
	P value	0.9	0.61	0.43	0.36	0.61	0.62
	Tolerability						
	R value	-0.28	-0.079	-0.55	-0.52	-0.55	-0.18
	P value	0.45	0.81	0.15	0.18	0.15	0.65

		Awakening			30 mins Post-Awakening		
	Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Affected Palm	Intensity of Pain						
	R value	-0.049[P]	0.1[P]	-0.0077[P]	-0.53[P]	-0.097[P]	0.014[P]
	P value	0.91[P]	0.81[P]	0.99[P]	0.18[P]	0.82[P]	0.973[P]
	Intensity of Heat						
	R value	0.48[P]	0.29[P]	0.088[P]	-0.07[P]	-0.099[P]	0.074[P]
	P value	0.23[P]	0.48[P]	0.84[P]	0.87[P]	0.82[P]	0.86[P]
	Intensity of Heat						
	R value	-0.15[P]	-0.25[P]	-0.33[P]	-0.17[P]	-0.11[P]	-0.2[P]
	P value	0.72[P]	0.56[P]	0.42[P]	0.69[P]	0.8[P]	0.64[P]
	Unpleasantness						
	R value	0.11[P]	0.26[P]	-0.036[P]	-0.54[P]	-0.42[P]	-0.42[P]
	P value	0.79[P]	0.53[P]	0.93[P]	0.16[P]	0.31[P]	0.3[P]
	Tolerability						
	R value	-0.054	0.2	-0.3	-0.47	-0.51	0.0
	P value	0.88	0.65	0.45	0.23	0.18	1.0
Unaffected Palm	Intensity of Pain						
	R value	0.073[P]	0.18[P]	0.24[P]	-0.074[P]	-0.19[P]	-0.14[P]
	P value	0.86[P]	0.66[P]	0.56[P]	0.86[P]	0.65[P]	0.73[P]
	Intensity of Heat						
	R value	0.13[P]	0.47	0.47	0.031[P]	-0.094[P]	-0.13[P]
	P value	0.77	0.24	0.24	0.94[P]	0.83[P]	0.77[P]
	Intensity of Heat						
	R value	-0.52[P]	-0.29[P]	-0.33[P]	-0.15[P]	-0.31[P]	-0.26[P]
	P value	0.19[P]	0.49[P]	0.42[P]	0.72[P]	0.46[P]	0.54[P]
	Unpleasantness						
	R value	-0.1[P]	0.33[P]	0.33[P]	-0.16[P]	-0.35[P]	-0.3[P]
	P value	0.81[P]	0.42[P]	0.42[P]	0.71[P]	0.4[P]	0.47[P]
	Tolerability						
	R value	0.2	0.16	0.3	-0.51	-0.43	-0.43
	P value	0.65	0.69	0.47	0.18	0.27	0.27

		Awakening			30 mins Post-Awakening		
	Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Affected Calf	Intensity of Pain						
	R value	-0.0061	-0.15	-0.067	-0.54	-0.42	-0.59
	P value	0.95	0.52	0.83	0.16	0.21	0.12
	Intensity of Heat						
	R value	0.4	0.46	0.42	-0.036[P]	-0.012[P]	-0.14[P]
	P value	0.32[P]	0.25	0.31	0.93[P]	0.98[P]	0.75[P]
	Intensity of Heat						
	R value	0.2[P]	0.096[P]	-0.045[P]	-0.29[P]	-0.39[P]	-0.44[P]
	P value	0.64[P]	0.82[P]	0.92[P]	0.48[P]	0.34[P]	0.28[P]
	Unpleasantness						
	R value	-0.7	-0.46	-0.71	-0.098	-0.012	-0.098
	P value	0.046	0.23	0.048	0.76	0.96	0.76
	Tolerability						
	R value	0.15	-0.24	-0.31	-0.35	-0.57	-0.64
	P value	0.73	0.42	0.27	0.27	0.1	0.057
Unaffected Calf	Intensity of Pain						
	R value	-0.12	-0.15	-0.54	-0.26	-0.51	-0.06
	P value	0.73	0.66	0.16	0.48	0.18	0.87
	Intensity of Heat						
	R value	0.11	0.25	-0.03	-0.16	-0.12	0.18
	P value	0.78	0.55	0.92	0.69	0.76	0.67
	Intensity of Heat						
	R value	0.18[P]	0.3[P]	-0.26[P]	-0.28[P]	-0.24[P]	-0.31[P]
	P value	0.67[P]	0.47[P]	0.53[P]	0.5[P]	0.56[P]	0.46[P]
	Unpleasantness						
	R value	-0.6	-0.54	-0.28	0.049	0.036	-0.2
	P value	0.1	0.17	0.47	0.93	0.94	0.61
	Tolerability						
	R value	-0.39	-0.39	-0.39	-0.44	-0.44	-0.41
	P value	0.28	0.28	0.28	0.25	0.25	0.28

ºC: degrees Celcius; [P]: analysed with Pearson's correlation. Significance level < 0.000555.

Table 11.4.9. Correlations Between Body Mass Index and Cold and Heat Pain Thresholds: Pain-free Participants

R and *P* values from the correlation analysis performed between participants body mass index and their cold and heat pain thresholds (listed horizontally) at participants affected and unaffected side cheek, palm and calf (listed vertically).

	Cold Pain Threshold	Heat Pain Threshold
Affected Cheek		
R value	0.29	-0.026[P]
P value	0.22	0.91[P]
Unaffected Cheek		
R value	0.15	0.018[P]
P value	0.54	0.94[P]
Affected Palm		
R value	0.066[P]	-0.017[P]
P value	0.78[P]	0.94[P]
Unaffected Palm		
R value	0.12[P]	-0.055[P]
P value	0.62[P]	0.82[P]
Affected Calf		
R value	0.17	0.3
P value	0.48	0.19
Unaffected Calf		
R value	0.25	0.23[P]
P value	0.28	0.34[P]

[P]: analysed with Pearson's correlation. Significance level < 0.0125

Table 11.4.10. Correlations Between Body Mass Index and Cold and Heat Pain Thresholds: Patients with Sciatica

R and *P* values from the correlation analysis performed between patients body mass index and their cold and heat pain thresholds (listed horizontally) at patients affected and unaffected side cheek, palm and calf (listed vertically).

	Cold Pain Threshold	Heat Pain Threshold
Affected Cheek		
R value	-0.69	0.73[S]
P value	0.039	0.031[S]
Unaffected Cheek		
R value	-0.53	0.59
P value	0.14	0.096
Affected Palm		
R value	-0.26	0.72
P value	0.51	0.03
Unaffected Palm		
R value	-0.6	0.53
P value	0.086	0.14
Affected Calf		
R value	0.41[S]	0.36
P value	0.27[S]	0.34
Unaffected Calf		
R value	-0.21	0.48
P value	0.59	0.19

[S]: analysed with Spearman's correlation. Significance level < 0.0083

Table 11.4.11. Correlations Between Body Mass Index and the Thermal Grill Response: Pain-free Participants

R and *P* values from the correlation analyses performed at participants affected and unaffected side cheek, palm and calf are presented (described previously on page 94).

		Affected Side			Unaffected Side		
	Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Cheek	Intensity of Pain						
	R value	0.21	0.13	0.22	0.36[P]	0.33[P]	0.49[P]
	P value	0.37	0.57	0.36	0.12[P]	0.15[P]	0.028[P]
	Intensity of Heat						
	R value	-0.015[P]	0.18[P]	-0.026[P]	0.18[P]	0.2[P]	0.13[P]
	P value	0.95[P]	0.44[P]	0.91[P]	0.45[P]	0.41[P]	0.59[P]
	Intensity of Heat						
	R value	-0.015	-0.0038	-0.058	0.083[P]	0.2[P]	0.95[P]
	P value	0.95	0.99	0.81	0.73[P]	0.39[P]	0.69[P]
	Unpleasantness						
	R value	0.14	0.28	0.13	0.29	0.3	0.42
	P value	0.55	0.23	0.59	0.21	0.21	0.065
	Tolerability						
	R value	-0.0015	0.27	0.22	0.18	0.29	0.4
	P value	0.99	0.25	0.36	0.46	0.21	0.082
Palm	Intensity of Pain						
	R value	0.4	0.45	0.39	0.39	0.43	0.47
	P value	0.079	0.044	0.091	0.085	0.059	0.035
	Intensity of Heat						
	R value	-0.16	0.082	0.014	0.15	0.13	0.21
	P value	0.5	0.73	0.95	0.53	0.58	0.38
	Intensity of Heat						
	R value	-0.099[P]	-0.021[P]	-0.023[P]	0.037[P]	0.093[P]	0.095[P]
	P value	0.68[P]	0.93[P]	0.92[P]	0.88[P]	0.7[P]	0.69[P]
	Unpleasantness						
	R value	0.2[P]	0.16[P]	0.21[P]	0.28	0.32	0.41
	P value	0.4[P]	0.5[P]	0.38[P]	0.23	0.17	0.071
	Tolerability						
	R value	0.2	0.22	0.2	0.36	0.34	0.47
	P value	0.4	0.35	0.4	0.12	0.14	0.038

		Affected Side			Unaffected Side		
	Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Calf	Intensity of Pain						
	R value	0.34	0.36	0.28	0.26	0.17	0.1
	P value	0.14	0.12	0.24	0.27	0.48	0.67
	Intensity of Heat						
	R value	0.076[P]	0.064[P]	0.11[P]	0.034	0.039	-0.0045
	P value	0.75[P]	0.79[P]	0.65[P]	0.89	0.087	0.98
	Intensity of Heat						
	R value	-0.084	0.075	-0.036	-0.11[P]	-0.097[P]	-0.075[P]
	P value	0.72	0.75	0.89	0.64[P]	0.68[P]	0.75[P]
	Unpleasantness						
	R value	0.021	0.012	0.12	0.11	-0.011	-0.099
	P value	0.93	0.96	0.6	0.65	0.96	0.68
	Tolerability						
	R value	0.16	0.19	0.15	0.16	0.19	0.15
	P value	0.51	0.43	0.54	0.51	0.43	0.54

°C: degrees Celcius; [P]: analysed with Pearson's correlation. Significance level < 0.000833.

Table 11.4.12. Correlations Between Body Mass Index and the Thermal Grill Response: Patients with Sciatica

R and *P* values from the correlation analyses performed at patients affected and unaffected side cheek, palm and calf are presented (described previously on page 94).

		Affected Side			Unaffected Side		
	Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Cheek	Intensity of Pain						
	R value	-0.11	-0.22	-0.38	-0.38[P]	-0.48[P]	-0.33[P]
	P value	0.76	0.56	0.3	0.32[P]	0.19[P]	0.39[P]
	Intensity of Heat						
	R value	-0.3[P]	-0.46[P]	-0.5[P]	-0.52[P]	-0.49[P]	-0.41[P]
	P value	0.44[P]	0.21[P]	0.17[P]	0.15[P]	0.18[P]	0.27[P]
	Intensity of Heat						
	R value	0.26[P]	0.089[P]	0.34[P]	-0.4[P]	-0.035[P]	0.4[P]
	P value	0.5[P]	0.82[P]	0.38[P]	0.28[P]	0.93[P]	0.28[P]
	Unpleasantness						
	R value	-0.0085[P]	-0.41[P]	-0.3[P]	-0.29	-0.51	-0.13
	P value	0.98[P]	0.28[P]	0.43[P]	0.42	0.15	0.74
	Tolerability						
	R value	0.0	-0.42	-0.059	-0.084	-0.37	-0.017
	P value	0.91	0.21	0.87	0.8	0.31	0.96
Palm	Intensity of Pain						
	R value	-0.33	-0.19	-0.28	-0.36	-0.39	-0.5
	P value	0.36	0.6	0.46	0.33	0.28	0.18
	Intensity of Heat						
	R value	-0.51[P]	-0.47[P]	-0.3[P]	-0.37[P]	-0.45[P]	-0.5[P]
	P value	0.16[P]	0.2[P]	0.43[P]	0.32[P]	0.23[P]	0.17[P]
	Intensity of Heat						
	R value	0.043[P]	0.051[P]	0.32[P]	0.25[P]	0.25[P]	0.22[P]
	P value	0.91	0.9[P]	0.41[P]	0.51[P]	0.51[P]	0.57[P]
	Unpleasantness						
	R value	-0.39[P]	-0.52[P]	-0.32[P]	-0.35[P]	-0.53[P]	-0.52[P]
	P value	0.31[P]	0.16[P]	0.41[P]	0.35[P]	0.14[P]	0.16[P]
	Tolerability						
	R value	-0.28	-0.49	-0.34	-0.53	-0.42	-0.61
	P value	0.44	0.17	0.35	0.14	0.25	0.082

		Affected Side			Unaffected Side		
	Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Calf	Intensity of Pain						
	R value	-0.034	0.044	0.12	-0.15	0.11	0.31
	P value	0.92	0.92	0.76	0.64	0.78	0.41
	Intensity of Heat						
	R value	-0.41	-0.35	-0.28	-0.42	-0.44	-0.15
	P value	0.24	0.34	0.45	0.25	0.23	0.68
	Intensity of Heat						
	R value	-0.2[P]	0.089[P]	0.24[P]	-0.082[P]	-0.15[P]	0.37[P]
	P value	0.96[P]	0.83[P]	0.53[P]	0.83[P]	0.7[P]	0.33[P]
	Unpleasantness						
	R value	0.14	0.0	0.23	0.19	0.14	0.017
	P value	0.71	0.99	0.55	0.64	0.72	0.97
	Tolerability						
	R value	-0.43	-0.087	0.053	0.077	0.077	0.68
	P value	0.19	0.74	0.9	0.85	0.85	0.87

[o]C: degrees Celcius; [P]: analysed with Pearson's correlation. Significance level < 0.000555.

Table 11.4.13. Correlations Between Average Pain Intensity and Cold and Heat Pain Thresholds: Patients with Sciatica

R and *P* values from the correlation analysis performed between patients average pain intensity from their sciatica pain and their cold and heat pain thresholds (listed horizontally) at patients affected and unaffected side cheek, palm and calf (listed vertically).

	Cold Pain Threshold	Heat Pain Threshold
Affected Cheek		
R value	-0.18	-0.11
P value	0.71	0.84
Unaffected Cheek		
R value	0.9	0.43
P value	0.86	0.35
Affected Palm		
R value	0.054	-0.25
P value	0.92	0.59
Unaffected Palm		
R value	0.25	-0.21
P value	0.59	0.66
Affected Calf		
R value	-0.82	0.54
P value	0.027	0.24
Unaffected Calf		
R value	0.054	0.54
P value	0.92	0.24

All analysed with Spearman's correlation. Significance level < 0.00833.

Table 11.4.14. Correlations Between Average Pain Intensity and the Thermal Grill Response: Patients with Sciatica

R and *P* values from the correlation analyses performed at patients affected and unaffected side cheek, palm and calf are presented (described previously on page 94). Significant values represented by bold text.

		Affected Side			Unaffected Side		
	Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Cheek	Intensity of Pain						
	R value	-0.16	-0.29	-0.36	-0.59	-0.36	-0.68
	P value	0.7	0.56	0.44	0.15	0.44	0.12
	Intensity of Heat						
	R value	0.14	-0.36	-0.36	-0.45	-0.43	-0.18
	P value	0.78	0.44	0.44	0.29	0.35	0.71
	Intensity of Heat						
	R value	-0.36	-0.21	-0.072	-0.11	-0.57	0.071
	P value	0.44	0.66	0.86	0.84	0.2	0.91
	Unpleasantness						
	R value	0.32	-0.29	-0.57	-0.61	-0.23	0.11
	P value	0.5	0.56	0.2	0.14	0.58	0.84
	Tolerability						
	R value	0.074	-0.59	-0.71	-0.68	-0.22	0.29
	P value	0.89	0.15	0.088	0.087	0.62	0.56
Palm	Intensity of Pain						
	R value	-0.54	-0.34	-0.39	-0.29	-0.81	-0.82
	P value	0.24	0.43	0.4	0.56	0.02	0.034
	Intensity of Heat						
	R value	-0.36	-0.32	-0.11	-0.32	-0.51	-0.29
	P value	0.44	0.5	0.84	0.5	0.2	0.56
	Intensity of Heat						
	R value	-0.21	0.14	-0.071	0.21	-0.25	-0.036
	P value	0.66	0.76	0.91	0.66	0.56	0.92
	Unpleasantness						
	R value	-0.39	-0.41	-0.54	0.14	-0.43	-0.38
	P value	0.4	0.33	0.24	0.78	0.35	0.38
	Tolerability						
	R value	-0.64	-0.41	-0.018	-0.41	-0.69	-0.41
	P value	0.14	0.33	0.95	0.33	0.086	0.33

		Affected Side			Unaffected Side		
	Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Calf	Intensity of Pain						
	R value	-0.88	-0.85	-0.85	-0.74	-0.82	-0.29
	P value	0.0095	0.014	0.017	0.052	0.025	0.56
	Intensity of Heat						
	R value	-0.69	-0.64	-0.68	-0.54	-0.58	-0.11
	P value	0.086	0.14	0.12	0.24	0.17	0.84
	Intensity of Heat						
	R value	-0.72	-0.89	-0.68	-0.64	-0.68	-0.36
	P value	0.071	0.033	0.12	0.14	0.12	0.44
	Unpleasantness						
	R value	-0.018	0.071	-0.018	-0.13	-0.13	-0.43
	P value	0.95	0.91	0.95	0.76	0.76	0.35
	Tolerability						
	R value	-0.58	-0.74	-0.67	-0.55	-0.55	-0.63
	P value	0.13	0.057	0.081	0.2	0.2	0.13

ºC: degrees Celsius. All analysed with Spearman's correlation. Significance level < 0.000555.

Table 11.4.15. Correlations Between Duration of Pain and Cold and Heat Pain Thresholds: Patients with Sciatica

R and *P* values from the correlation analysis performed between patients duration of sciatic pain and their cold and heat pain thresholds (listed horizontally) at patients affected and unaffected side cheek, palm and calf (listed vertically).

	Cold Pain Threshold	Heat Pain Threshold
Affected Cheek		
R value	0.17	-0.15[S]
P value	0.66	0.68[S]
Unaffected Cheek		
R value	0.29	0.067
P value	0.44	0.86
Affected Palm		
R value	0.036	-0.16
P value	0.93	0.68
Unaffected Palm		
R value	-0.17	-0.23
P value	0.67	0.55
Affected Calf		
R value	0.18[S]	0.32
P value	0.63[S]	0.4
Unaffected Calf		
R value	0.48	-0.24
P value	0.19	0.54

[S]: analysed with Spearman's correlation. Significance level < 0.00833.

Table 11.4.16. Correlations Between Duration of Pain and the Thermal Grill Response: Patients with Sciatica

R and *P* values from the correlation analyses performed at patients affected and unaffected side cheek, palm and calf are presented (described previously on page 94). Significant values represented by bold text.

		Affected Side			Unaffected Side		
	Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Cheek	Intensity of Pain						
	R value	0.29	-0.063	-0.063	-0.41[P]	-0.61[P]	-0.35[P]
	P value	0.45	0.85	0.84	0.27[P]	0.08[P]	0.35[P]
	Intensity of Heat						
	R value	-0.14[P]	-0.54[P]	-0.46[P]	-0.53[P]	-0.64[P]	-0.46[P]
	P value	0.71[P]	0.13[P]	0.22[P]	0.15[P]	0.063[P]	0.21[P]
	Intensity of Heat						
	R value	0.14[P]	-0.26[P]	-0.14[P]	-0.37[P]	-0.39[P]	0.26[P]
	P value	0.71[P]	0.5[P]	0.72[P]	0.33[P]	0.3[P]	0.51[P]
	Unpleasantness						
	R value	0.068[P]	-0.6[P]	-0.59[P]	-0.068	-0.41	-0.14
	P value	0.86[P]	0.088[P]	0.093[P]	0.82	0.25	0.7
	Tolerability						
	R value	0.45	-0.13	0.14	0.11	-0.27	0.19
	P value	0.22	0.64	0.72	0.78	0.45	0.62
Palm	Intensity of Pain						
	R value	0.063	0.2	0.22	0.067	-0.3	-0.36
	P value	0.87	0.59	0.57	0.87	0.42	0.33
	Intensity of Heat						
	R value	-0.45[P]	-0.43[P]	-0.022[P]	-0.36[P]	-0.53[P]	-0.6[P]
	P value	0.22[P]	0.25[P]	0.96[P]	0.34[P]	0.14[P]	0.087[P]
	Intensity of Heat						
	R value	0.16[P]	0.2[P]	0.25[P]	0.24[P]	0.3[P]	0.12[P]
	P value	0.67[P]	0.61[P]	0.52[P]	0.54[P]	0.43[P]	0.76[P]
	Unpleasantness						
	R value	-0.52[P]	-0.49[P]	-0.23[P]	-0.37[P]	-0.59[P]	-0.67[P]
	P value	0.15[P]	0.18[P]	0.55[P]	0.33[P]	0.098[P]	0.049[P]
	Tolerability						
	R value	0.0042	-0.4	0.31	-0.29	-0.025	-0.27
	P value	0.99	0.25	0.42	0.4	0.92	0.46

		Affected Side			Unaffected Side		
	Thermal grill configuration	22/38 ºC	20/40 ºC	18/42 ºC	22/38 ºC	20/40 ºC	18/42 ºC
Calf	Intensity of Pain						
	R value	-0.03	0.022	-0.042	0.12	0.12	0.49
	P value	0.91	0.94	0.88	0.77	0.75	0.18
	Intensity of Heat						
	R value	-0.37	0.0042	-0.5	-0.15	-0.21	0.37
	P value	0.3	0.99	0.17	0.69	0.56	0.32
	Intensity of Heat						
	R value	-0.086[P]	0.058[P]	0.15[P]	0.00097[P]	0.04[P]	0.42[P]
	P value	0.83[P]	0.89[P]	0.7[P]	1.0[P]	0.92[P]	0.27[P]
	Unpleasantness						
	R value	0.5	0.16	0.34	0.49	0.46	0.4
	P value	0.17	0.69	0.36	0.19	0.21	0.28
	Tolerability						
	R value	-0.079	0.21	0.25	0.38	0.38	0.49
	P value	0.72	0.59	0.5	0.3	0.3	0.19

[o]C: degrees Celcius; [P]: analysed with Pearson's correlation. Significance level < 0.000555.

Figures

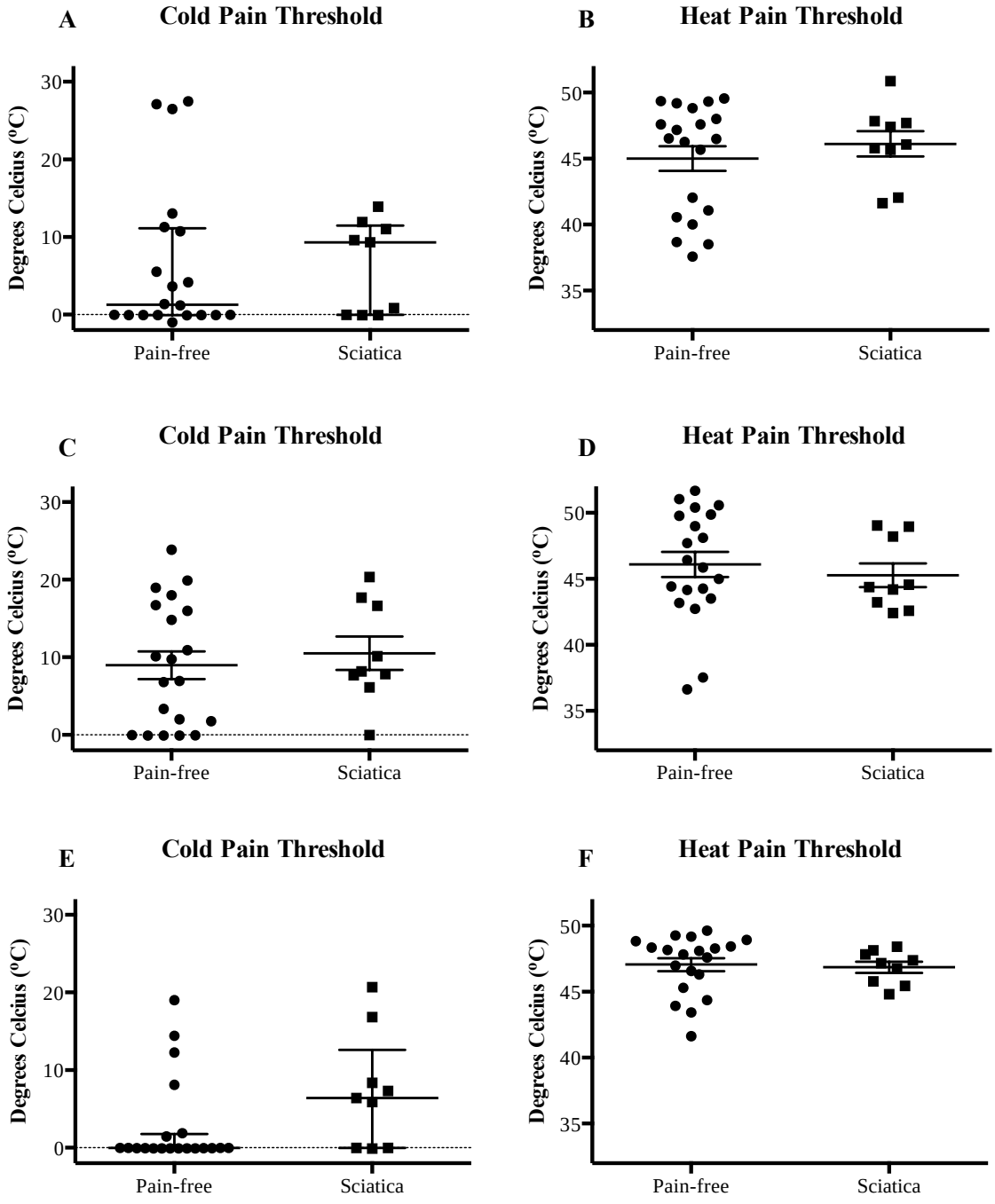
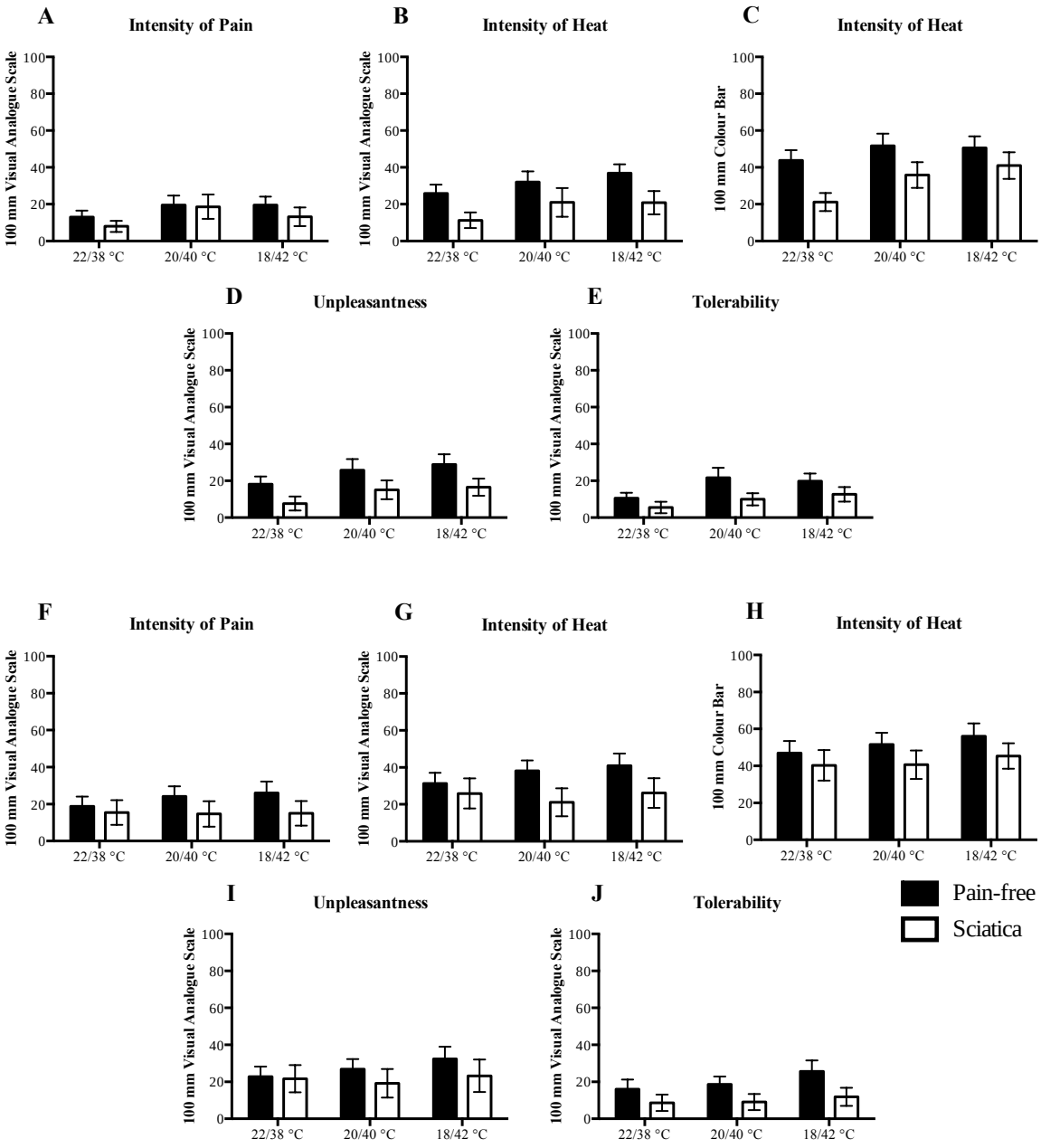


Figure 11.4.1. Pain-free participants versus patients with sciatica: cold and heat pain thresholds.

Cold and heat pain thresholds at the unaffected/non-dominant side cheek (A, B), palm (C, D) and calf (E, F) in pain-free participants and patients with sciatica. No significant differences were observed between pain-free participants and patients with sciatica for cold or heat pain threshold at the unaffected/non-dominant side cheek ($p = 0.63$, A and $p = 0.48$, B), palm ($p = 0.62$, C and $p = 0.6$ D) or calf ($p = 0.13$, E and $p = 0.81$, F). Cold pain thresholds on the unaffected/non-dominant side cheek (A) and calf (E) are represented as median and

interquartile range. Cold pain thresholds on the unaffected/non-dominant side palm (C) and heat pain thresholds on the unaffected/non-dominant cheek (B), palm (D) and calf (F) are represented as mean ± SEM.


A
Intensity of Pain
100 mm Visual Analogue Scale
B
Intensity of Heat
100 mm Visual Analogue Scale
C
Intensity of Heat
100 mm Colour Bar
D
Unpleasantness
100 mm Visual Analogue Scale
E
Tolerability
100 mm Visual Analogue Scale
F
Intensity of Pain
100 mm Visual Analogue Scale
G
Intensity of Heat
100 mm Visual Analogue Scale
H
Intensity of Heat
100 mm Colour Bar
I
Unpleasantness
100 mm Visual Analogue Scale
J
Tolerability
100 mm Visual Analogue Scale
0
20
40
60
80
100
22/38 °C
20/40 °C
18/42 °C
Pain-free
Sciatica

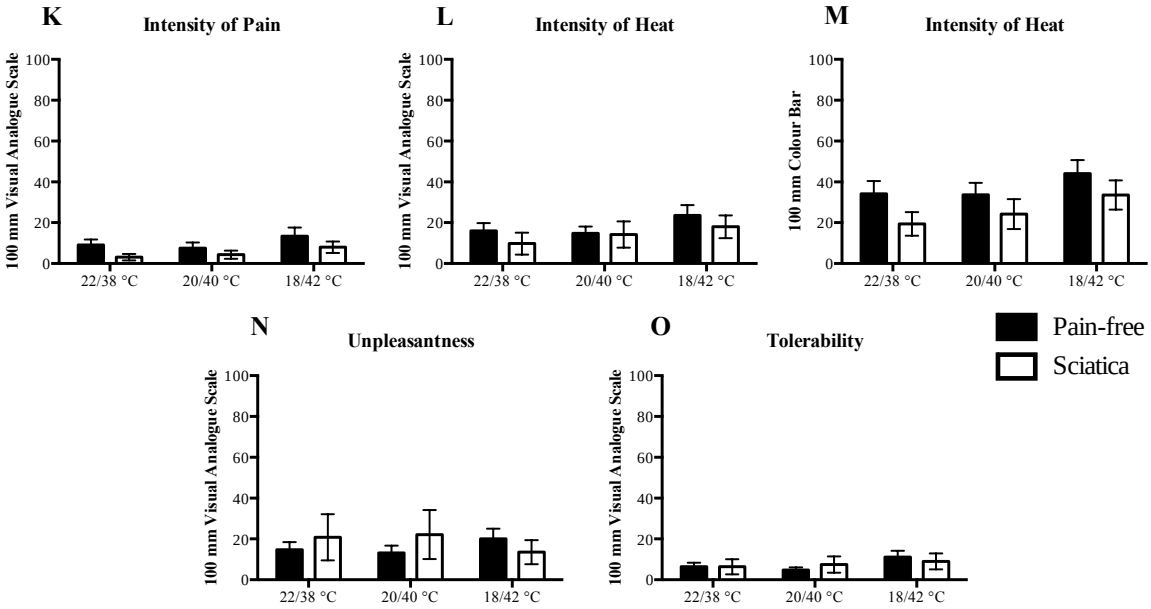


Figure 11.4.2. Pain-free participants versus patients with sciatica: thermal grill illusion.

The response to the thermal grill illusion at the unaffected/non-dominant side cheek (A-E), palm (F-J) and calf (K-O) in pain-free participants (black bars) and patients with sciatica (white bars). The response to the thermal grill did not differ between pain-free participants and patients with sciatica at the unaffected/non-dominant side cheek (A-E), palm (F-J) or calf (K-O) for all thermal grill outcomes. All graphs are represented as mean ± SEM.

Chapter 5

Table 11.5.1. Correlations Between Morphine Equivalent Dose and Cold and Heat Pain Thresholds

R and *P* values from the correlation analysis performed between patients morphine equivalent dose and their cold and heat pain thresholds (listed horizontally) at patients affected and unaffected side cheek, palm and calf (listed vertically).

	Cold Pain Threshold	Heat Pain Threshold
Right Cheek		
R value	0.015	0.01
P value	0.93	0.95
Left Cheek		
R value	-0.26	0.35
P value	0.15	0.049
Right Palm		
R value	-0.27	0.083
P value	0.13	0.65
Left Palm		
R value	-0.17	0.069
P value	0.37	0.71

All analysed with Spearman's correlation. Significance level < 0.01.

Table 11.5.2. Correlations Between Morphine Equivalent Dose and Thermal Grill Response

R and *P* values from the correlation analyses performed at patients right and left cheek and palm are presented (described previously on page 94).

	Right Cheek			Left Cheek			Right Palm			Left Palm		
Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Intensity of Pain												
R value	0.16	0.3	0.34	0.13	0.11	0.13	0.17	0.11	0.3	0.044	-0.031	0.11
P value	0.38	0.091	0.055	0.48	0.53	0.47	0.36	0.57	0.097	0.81	0.86	0.55
Intensity of Heat												
R value	0.086	0.091	0.12	-0.0057	-0.14	0.12	0.059	-0.028	0.022	-0.074	-0.068	0.035
P value	0.64	0.62	0.51	0.98	0.44	0.5	0.75	0.88	0.91	0.68	0.71	0.84
Intensity of Heat												
R value	-0.056	-0.046	-0.12	-0.13	-0.24	0.049	0.098	-0.019	-0.085	-0.049	0.065	0.0042
P value	0.76	0.8	0.51	0.47	0.19	0.79	0.59	0.92	0.64	0.79	0.72	0.98
Unpleasantness												
R value	0.087	0.21	0.17	-0.016	-0.1	0.1	0.083	0.027	0.096	0.0059	-0.067	0.13
P value	0.64	0.27	0.34	0.93	0.58	0.59	0.65	0.88	0.6	0.97	0.71	0.48
Tolerability												
R value	-0.033	0.17	0.17	0.072	0.023	0.16	0.21	0.16	0.1	0.022	0.013	0.12
P value	0.86	0.34	0.35	0.7	0.9	0.37	0.24	0.38	0.59	0.9	0.94	0.51

All analysed with Spearman's correlation. Significance level < 0.000667.

Table 11.5.3. Correlations Between Pain Intensity on Study Day and Cold and Heat Pain Thresholds

R and *P* values from the correlation analysis performed between patients pain intensity from their headache and their cold and heat pain thresholds (listed horizontally) at patients affected and unaffected side cheek, palm and calf (listed vertically).

	Cold Pain Threshold	Heat Pain Threshold
Right Cheek		
R value	0.13	-0.11
P value	0.49	0.55
Left Cheek		
R value	-0.23	-0.016[P]
P value	0.2	0.93[P]
Right Palm		
R value	-0.12	-0.0046[P]
P value	0.51	0.98[P]
Left Palm		
R value	0.14[P]	0.0058[P]
P value	0.46[P]	0.98[P]

[P]: Analysed with Pearson's correlation. Significance level < 0.01.

Table 11.5.4. Correlations Between Pain Intensity on Study Day and Thermal Grill Response

R and *P* values from the correlation analyses performed at patients right and left cheek and palm are presented (described previously on page 94).

	Right Cheek			Left Cheek			Right Palm			Left Palm		
Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Intensity of Pain												
R value	0.16	0.21	0.17	0.3	0.14	0.21	0.12	0.062	0.17	0.14	0.035	0.062
P value	0.4	0.24	0.35	0.1	0.45	0.26	0.52	0.74	0.34	0.44	0.85	0.73
Intensity of Heat												
R value	0.14[P]	0.16[P]	0.13[P]	0.1	-0.039	0.057	-0.11	-0.061	0.071	-0.16	-0.081	-0.054
P value	0.44[P]	0.4[P]	0.48[P]	0.58	0.83	0.75	0.54	0.74	0.7	0.36	0.66	0.77
Intensity of Heat												
R value	0.24[P]	0.14[P]	0.12[P]	0.2[P]	-0.081[P]	0.051[P]	-0.1[P]	-0.05[P]	-0.035[P]	-0.089[P]	-0.051[P]	-0.15[P]
P value	0.2[P]	0.44[P]	0.51[P]	0.26[P]	0.66[P]	0.78[P]	0.58[P]	0.78[P]	0.85[P]	0.62[P]	0.78[P]	0.4[P]
Unpleasantness												
R value	0.27[P]	0.24[P]	0.19[P]	0.078	0.021	0.14	0.065[P]	0.038[P]	-0.0091 [P]	-0.064	-0.011	-0.015
P value	0.14[P]	0.18[P]	0.29[P]	0.67	0.91	0.45	0.72[P]	0.84[P]	0.96[P]	0.72	0.95	0.93
Tolerability												
R value	0.31[P]	0.36[P]	0.19[P]	0.32	0.24	0.35	0.14	0.15	0.19	0.031	0.039	0.1
P value	0.084[P]	0.041[P]	0.3[P]	0.07	0.18	0.053	0.44	0.41	0.3	0.86	0.83	0.57

[o]C: degrees Celcius; [P]: analysed with Pearson's correlation. Significance level < 0.000667.

Table 11.5.5. Correlations Between Duration of Pain and Cold and Heat Pain Thresholds

R and *P* values from the correlation analysis performed between patients duration of headache pain and their cold and heat pain thresholds (listed horizontally) at patients affected and unaffected side cheek, palm and calf (listed vertically).

	Cold Pain Threshold	Heat Pain Threshold
Right Cheek		
R value	-0.035	-0.33
P value	0.85	0.057
Left Cheek		
R value	0.0092	-0.21[P]
P value	0.96	0.25[P]
Right Palm		
R value	-0.11	-0.18[P]
P value	0.54	0.33[P]
Left Palm		
R value	-0.0062[P]	-0.15[P]
P value	0.97[P]	0.42[P]

[P]: Analysed with Pearson's correlation. Significance level < 0.01.

Table 11.5.6. Correlations Between Duration of Pain and Thermal Grill Response

R and *P* values from the correlation analyses performed at patients right and left cheek and palm are presented (described previously on page 94).

	Right Cheek			Left Cheek			Right Palm			Left Palm		
Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Intensity of Pain												
R value	0.12	0.23	0.19	0.019	0.1	-0.03	0.028	0.014	0.2	0.13	0.037	0.26
P value	0.52	0.21	0.3	0.92	0.57	0.87	0.88	0.94	0.28	0.48	0.84	0.15
Intensity of Heat												
R value	0.069[P]	0.0094[P]	-0.013[P]	-0.183	-0.12	-0.23	-0.19	-0.16	0.089	-0.074	-0.09	0.004
P value	0.71[P]	0.96[P]	0.94[P]	0.317	0.5	0.2	0.3	0.39	0.63	0.68	0.62	0.98
Intensity of Heat												
R value	0.27[P]	0.37[P]	0.28[P]	0.14[P]	0.15[P]	0.15[P]	0.09[P]	0.055[P]	0.25[P]	0.21[P]	0.097[P]	0.084[P]
P value	0.13[P]	0.035[P]	0.19[P]	0.45[P]	0.41[P]	0.42[P]	0.63[P]	0.77[P]	0.17[P]	0.25[P]	0.59[P]	0.64[P]
Unpleasantness												
R value	0.057[P]	0.036[P]	0.1[P]	-0.1	-0.057	-0.17	-0.093[P]	-0.097[P]	0.019[P]	0.063	-0.076	0.094
P value	0.76[P]	0.85[P]	0.58[P]	0.59	0.76	0.36	0.61[P]	0.6[P]	0.92[P]	0.73	0.68	0.6
Tolerability												
R value	0.13[P]	0.124[P]	0.15[P]	-0.017	0.026	-0.08	0.0019	-0.0028	0.2	0.097	0.018	0.14
P value	0.47[P]	0.5[P]	0.42[P]	0.93	0.89	0.66	0.99	0.99	0.28	0.59	0.92	0.43

°C: degrees Celcius; [P]: analysed with Pearson's correlation. Significance level < 0.000667.

Table 11.5.7. Correlations Between Anxiety Score (HADS-A) and Cold and Heat Pain Thresholds

R and *P* values from the correlation analysis performed between patients anxiety score and their cold and heat pain thresholds (listed horizontally) at patients affected and unaffected side cheek, palm and calf (listed vertically). Significant values represented by bold text.

	Cold Pain Threshold	Heat Pain Threshold
Right Cheek		
R value	**0.5**	-0.4
P value	**0.0031**	0.022
Left Cheek		
R value	0.23	-0.29[P]
P value	0.2	0.1[P]
Right Palm		
R value	0.37	-0.39[P]
P value	0.036	0.027[P]
Left Palm		
R value	0.39[P]	-0.39[P]
P value	0.029[P]	0.027[P]

[P]: Analysed with Pearson's correlation. Significance level < 0.01.

Table 11.5.8. Correlations Between Anxiety Score (HADS-A) and Thermal Grill Response

R and *P* values from the correlation analyses performed at patients right and left cheek and palm are presented (described previously on page 94). Significant values represented by bold text.

	Right Cheek			Left Cheek			Right Palm			Left Palm		
Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Intensity of Pain												
R value	0.39	0.52	0.49	0.41	0.4	0.39	0.37	0.43	0.34	0.41	0.35	0.4
P value	0.026	0.0025	0.0048	0.021	0.023	0.026	0.038	0.014	0.058	0.017	0.043	0.023
Intensity of Heat												
R value	0.31[P]	0.4[P]	0.53[P]	0.29	0.39	0.33	0.36	0.29	0.18	0.34	0.41	0.32
P value	0.089[P]	0.023[P]	0.0018[P]	0.11	0.027	0.065	0.043	0.1	0.33	0.05	0.018	0.069
Intensity of Heat												
R value	0.39[P]	0.33[P]	0.39[P]	0.27[P]	0.21[P]	0.23[P]	0.26[P]	0.22[P]	0.15[P]	0.12[P]	0.25[P]	0.00053[P]
P value	0.027[P]	0.068[P]	0.028[P]	0.13[P]	0.26[P]	0.2[P]	0.15[P]	0.22[P]	0.41[P]	0.51[P]	0.17[P]	1.0[P]
Unpleasantness												
R value	0.5[P]	**0.65[P]**	0.52	0.433[P]	0.5[P]	0.5[P]	0.51[P]	0.53[P]	0.37[P]	0.38	0.52	0.4
P value	0.004[P]	**<0.0001[P]**	0.0021	0.0134[P]	0.0036[P]	0.0035[P]	0.0027[P]	0.0019[P]	0.036[P]	0.028	0.0019	0.022
Tolerability												
R value	0.53[P]	**0.72[P]**	**0.63[P]**	0.408	0.38	0.46	0.45	0.46	0.35	0.26	0.46	0.41
P value	0.0017[P]	**<0.0001[P]**	**<0.0001[P]**	0.0205	0.032	0.0086	0.01	0.0083	0.05	0.15	0.0076	0.017

°C: degrees Celcius; [P]: analysed with Pearson's correlation. Significance level < 0.000667.

Table 11.5.9. Correlations Between Depression Scores (HADS-D) and Cold and Heat Pain Thresholds

R and *P* values from the correlation analysis performed between patients depression score and their cold and heat pain thresholds (listed horizontally) at patients affected and unaffected side cheek, palm and calf (listed vertically).

	Cold Pain Threshold	Heat Pain Threshold
Right Cheek		
R value	0.15	-0.25
P value	0.41	0.16
Left Cheek		
R value	-0.1	-0.099[P]
P value	0.57	0.58[P]
Right Palm		
R value	0.11	-0.14[P]
P value	0.54	0.44[P]
Left Palm		
R value	0.14[P]	-0.26[P]
P value	0.44[P]	0.14[P]

[P]: Analysed with Pearson's correlation. Significance level < 0.01.

Table 11.5.10. Correlations Between Depression Scores (HADS-D) and Thermal Grill Response

R and *P* values from the correlation analyses performed at patients right and left cheek and palm are presented (described previously on page 94). Significant values represented by bold text.

	Right Cheek			Left Cheek			Right Palm			Left Palm		
Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Intensity of Pain												
R value	0.44	**0.58**	**0.64**	0.31	0.38	0.41	0.36	0.38	0.41	0.43	0.32	0.34
P value	0.011	**0.0005**	**<0.0001**	0.085	0.03	0.021	0.041	0.032	0.019	0.014	0.065	0.054
Intensity of Heat												
R value	0.37[P]	0.36[P]	0.52[P]	0.054	0.073	0.3	0.16	0.073	0.12	0.16	0.17	0.16
P value	0.039[P]	0.041[P]	0.0025[P]	0.77	0.69	0.098	0.39	0.69	0.52	0.37	0.33	0.38
Intensity of Heat												
R value	0.033[P]	0.29[P]	0.39[P]	0.12[P]	0.11[P]	0.32[P]	0.13[P]	0.12[P]	0.098[P]	0.027[P]	0.18[P]	-0.012[P]
P value	0.066[P]	0.11[P]	0.026[P]	0.52[P]	0.54[P]	0.076[P]	0.47[P]	0.5[P]	0.6[P]	0.88[P]	0.32[P]	0.95[P]
Unpleasantness												
R value	0.5[P]	0.51[P]	**0.64[P]**	0.25	0.28	0.31	0.41[P]	0.4[P]	0.32[P]	0.3	0.22	0.33
P value	0.0039[P]	0.003[P]	**<0.0001[P]**	0.16	0.13	0.08	0.02[P]	0.023[P]	0.075[P]	0.9	0.22	0.063
Tolerability												
R value	0.4[P]	0.55[P]	**0.68[P]**	0.23	0.21	0.26	0.34	0.37	0.21	0.2	0.28	0.31
P value	0.024[P]	0.001[P]	**<0.0001[P]**	0.2	0.26	0.15	0.054	0.0393	0.24	0.27	0.12	0.075

°C: degrees Celcius; [P]: analysed with Pearson's correlation. Significance level < 0.000667.

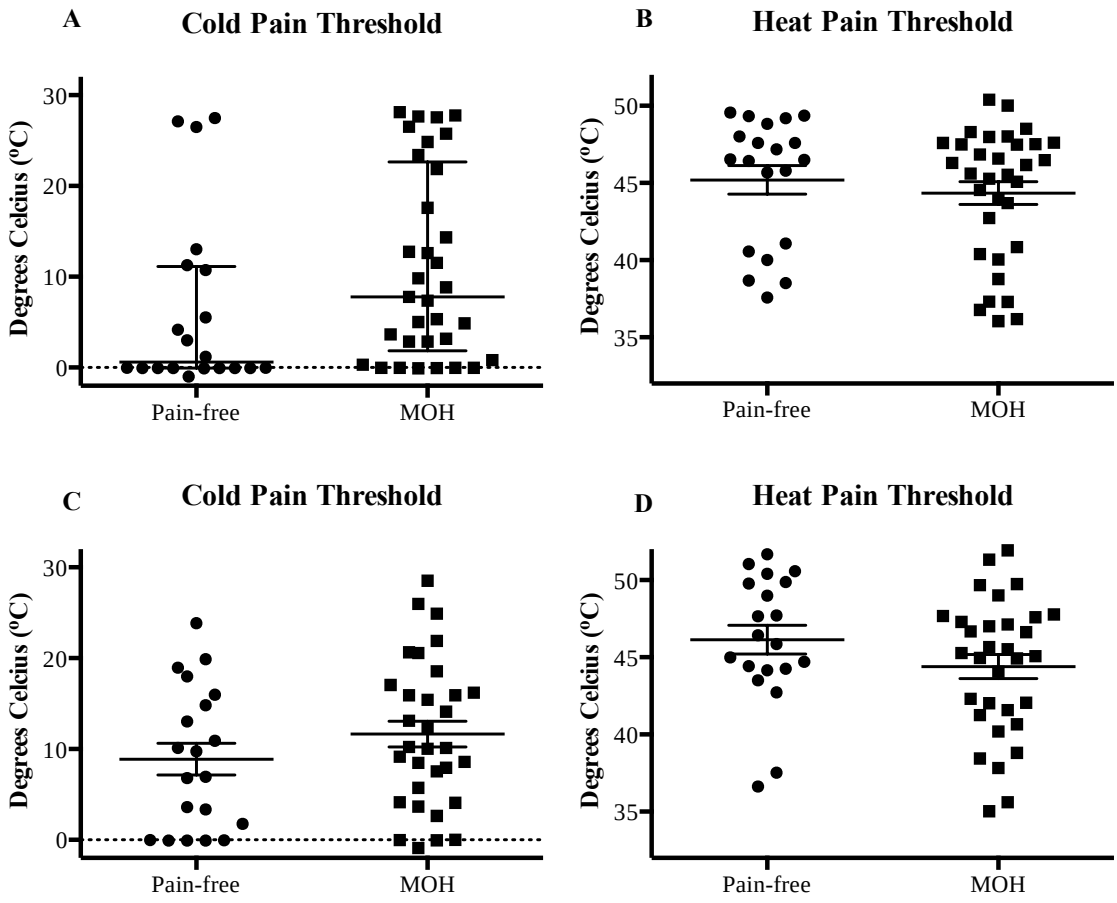


Figure 11.5.1. Pain-free participants versus patients with medication overuse headache: cold and heat pain thresholds.

Cold and heat pain thresholds at the left cheek (A, B) and palm (C, D) in pain-free participants and patients with medication overuse headache. No significant differences were observed between pain-free participants and patients with medication overuse headache cold and heat pain threshold on the left cheek ($p = 0.11$, A and $p = 0.48$, B) or palm ($p = 0.23$, C and $p = 0.16$, D). Graph A is represented as median and interquartile range. Graphs B, C and D are represented as mean ± SEM. MOH: medication overuse headache.

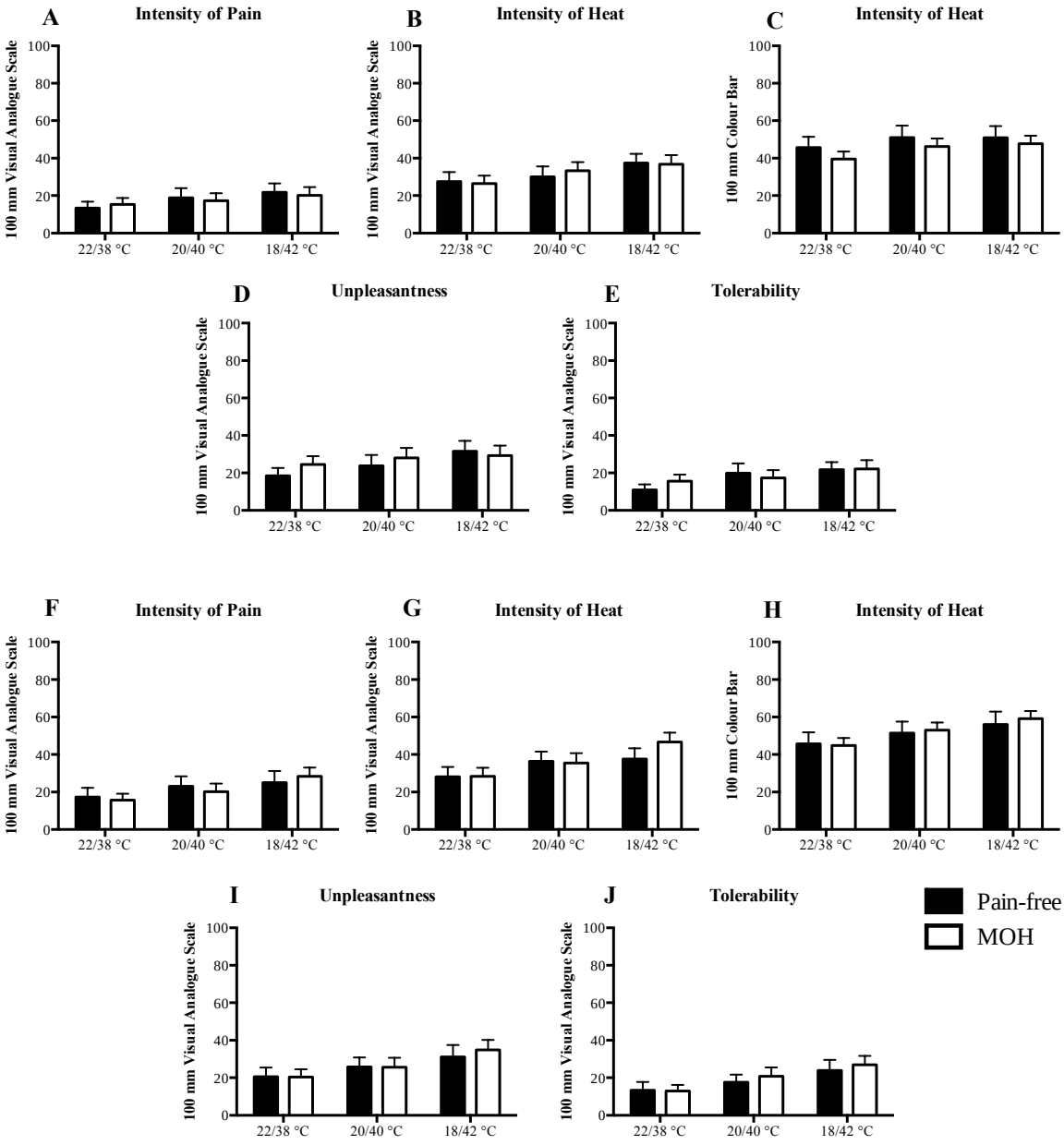


Figure 11.5.2. Pain-free participants versus patients with medication overuse headache: thermal grill response.

The response to the thermal grill illusion at the left cheek (A-E) and palm (F-J) in pain-free participants and patients with medication overuse headache. The response to the thermal grill did not differ between pain-free participants and patients with medication overused headache on either the left cheek (A-E) or left palm (F-J) for all thermal grill outcomes. All graphs are represented as mean ± SEM. MOH: medication overuse headache.

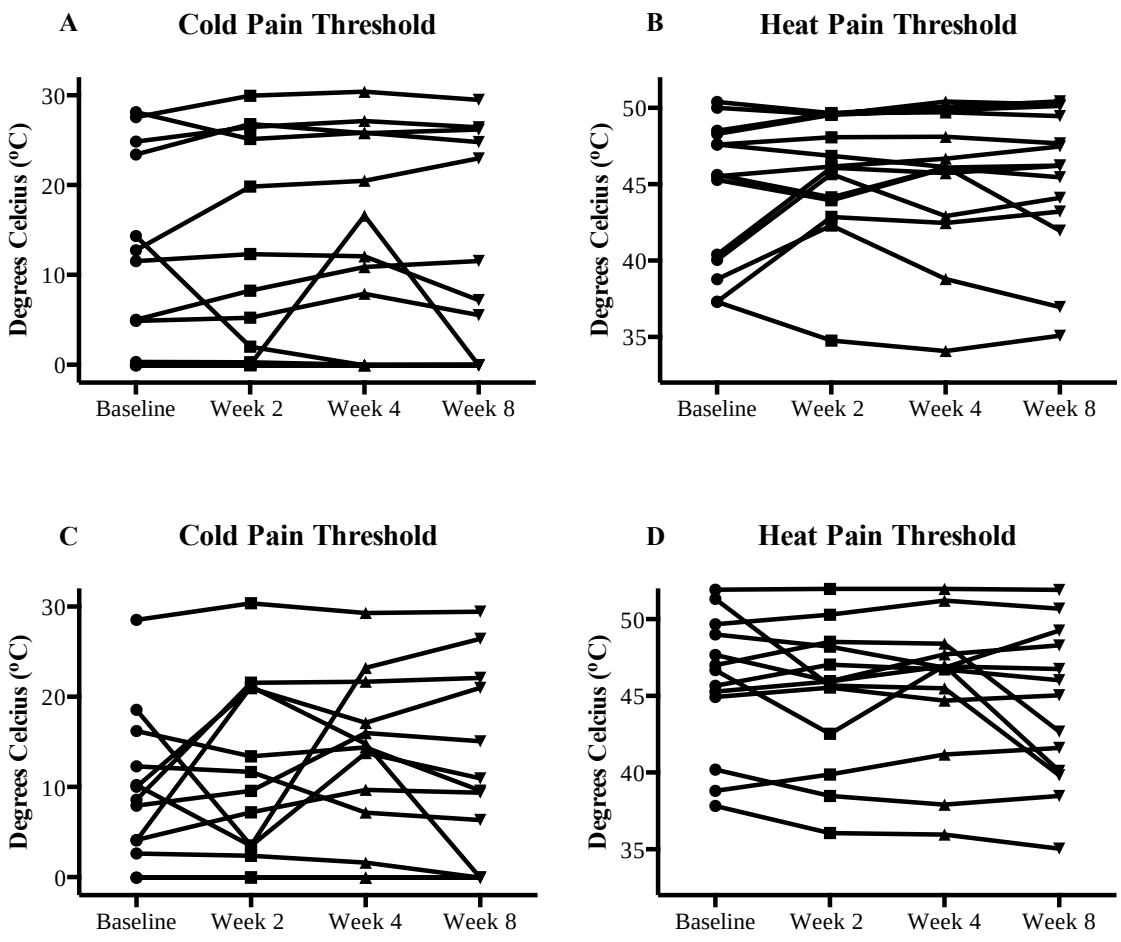


Figure 11.5.3. Repeatability of cold and heat pain thresholds over 8 weeks of placebo treatment.

Cold and heat pain thresholds at the left cheek (A, B) and palm (C, D) across four testing sessions conducted over 8 weeks in patients assigned to the placebo group. No significant differences across the 8 weeks of placebo treatment were observed for cold (A, C) and heat (B, D) pain thresholds on the left cheek (A, B) or palm (C, D).

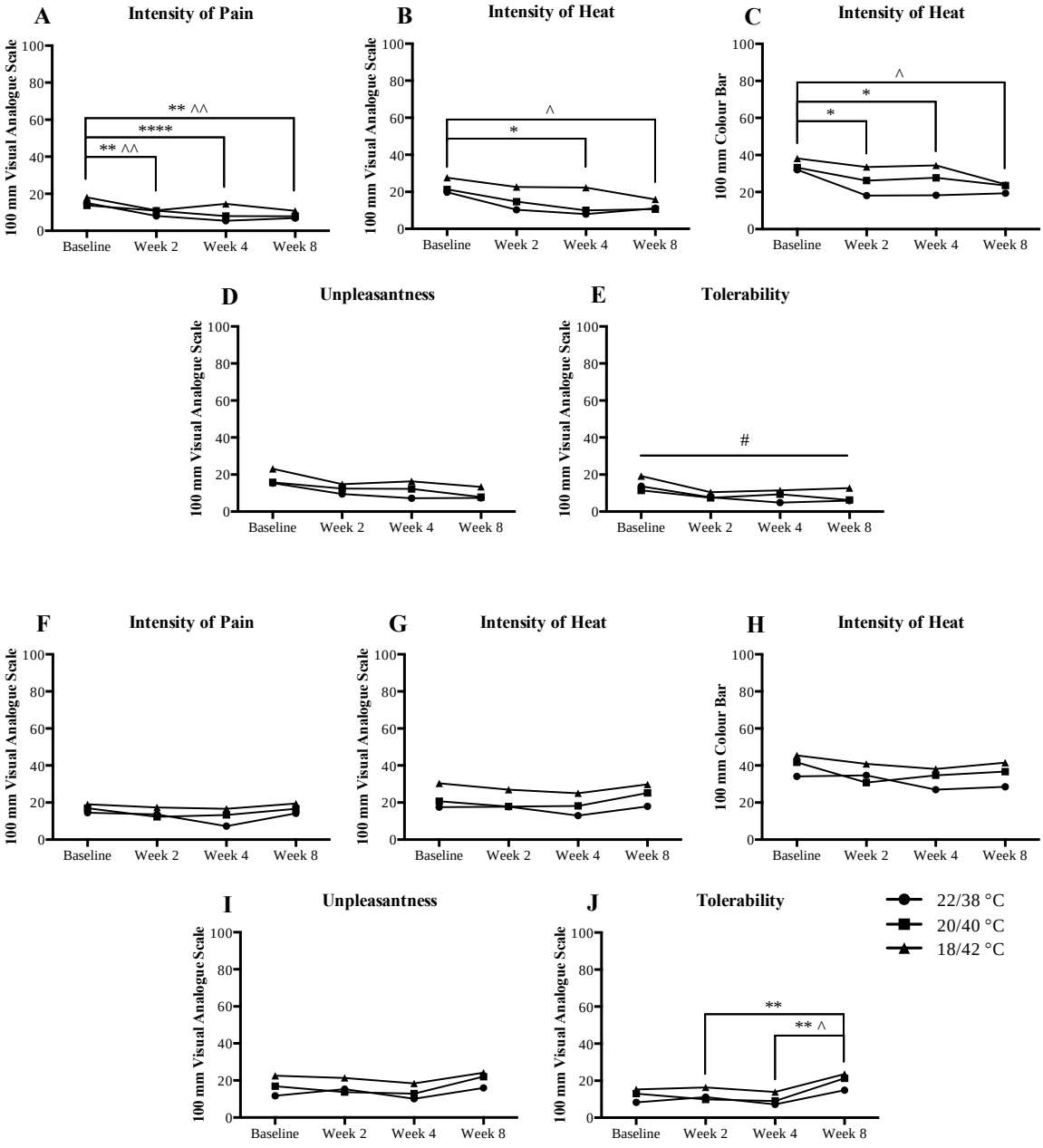


Figure 11.5.4. Repeatability of thermal grill illusion over 8 weeks of placebo treatment.

The response to the thermal grill at the left cheek (A-E) and palm (F-J) across four testing sessions conducted over 8 weeks in patients assigned to the placebo group. The response to the thermal grill illusion differed significantly across the 8 weeks of placebo treatment on both the left cheek (A-E) and left palm (F-J) for the outcomes "intensity of pain" (A), "intensity of heat" (B), "intensity of heat (colour bar)" (C), and tolerability (E, J) to the thermal grill illusion. Graphs are represented as mean. * $P < 0.05$ (22/38 ^{o}C); ** $P < 0.01$ (22/38 ^{o}C); **** $P < 0.0001$ (22/38 ^{o}C); ^ $P < 0.05$ (18/42 ^{o}C); ^^ $P < 0.01$; # $P < 0.05$ for an overall main effect.

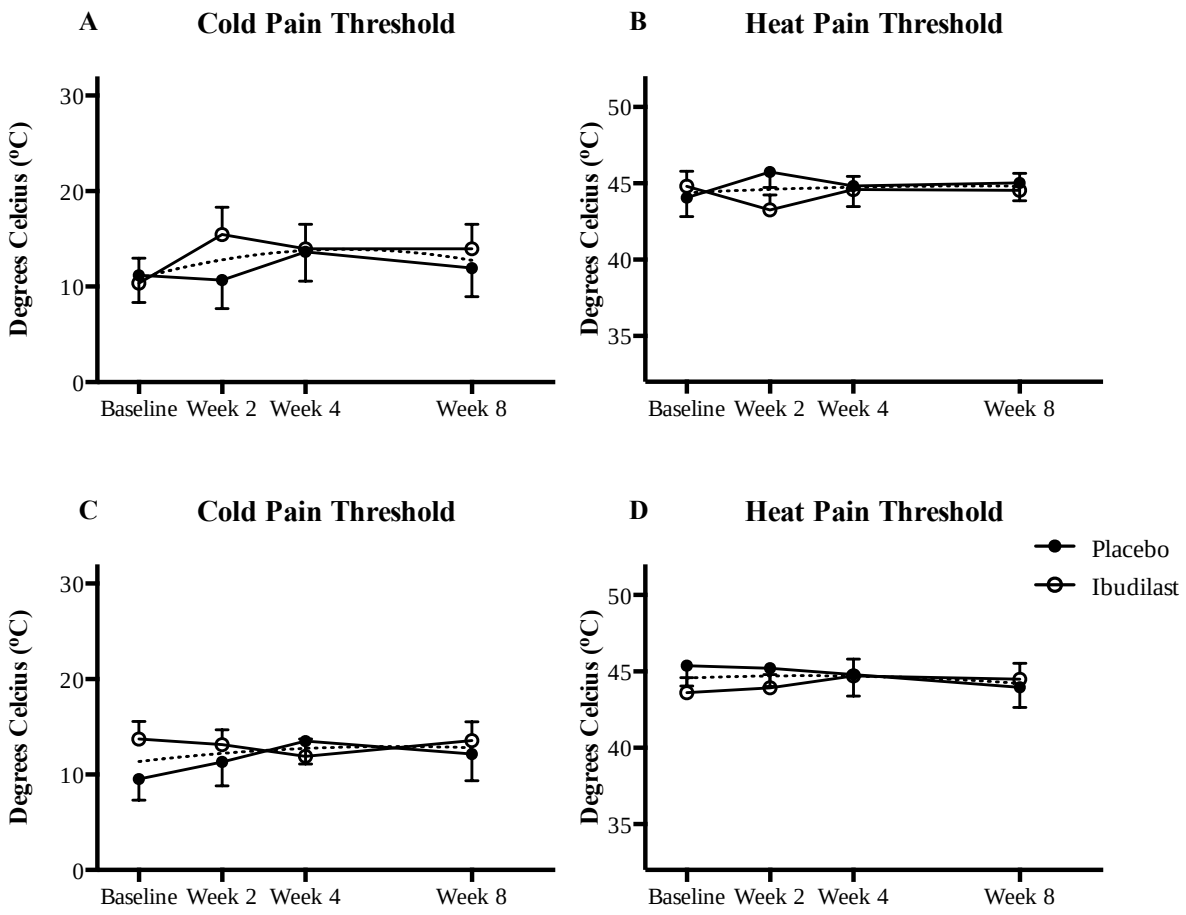


Figure 11.5.5. Response to ibudilast: cold and heat pain thresholds.

Cold and heat pain thresholds at the left cheek (A, B) and palm (C, D) across four testing sessions conducted over 8 weeks in patients assigned to the placebo and ibudilast groups. Comparing ibudilast and placebo, no significant differences were observed between the effect time curves for cold pain thresholds on the left cheek (A)($p = 0.86$) or palm (C)($p = 0.49$) or heat pain thresholds on the left cheek (B)($p = 0.77$) or palm (D)($p = 0.63$). Graphs are represented as mean ± SEM.

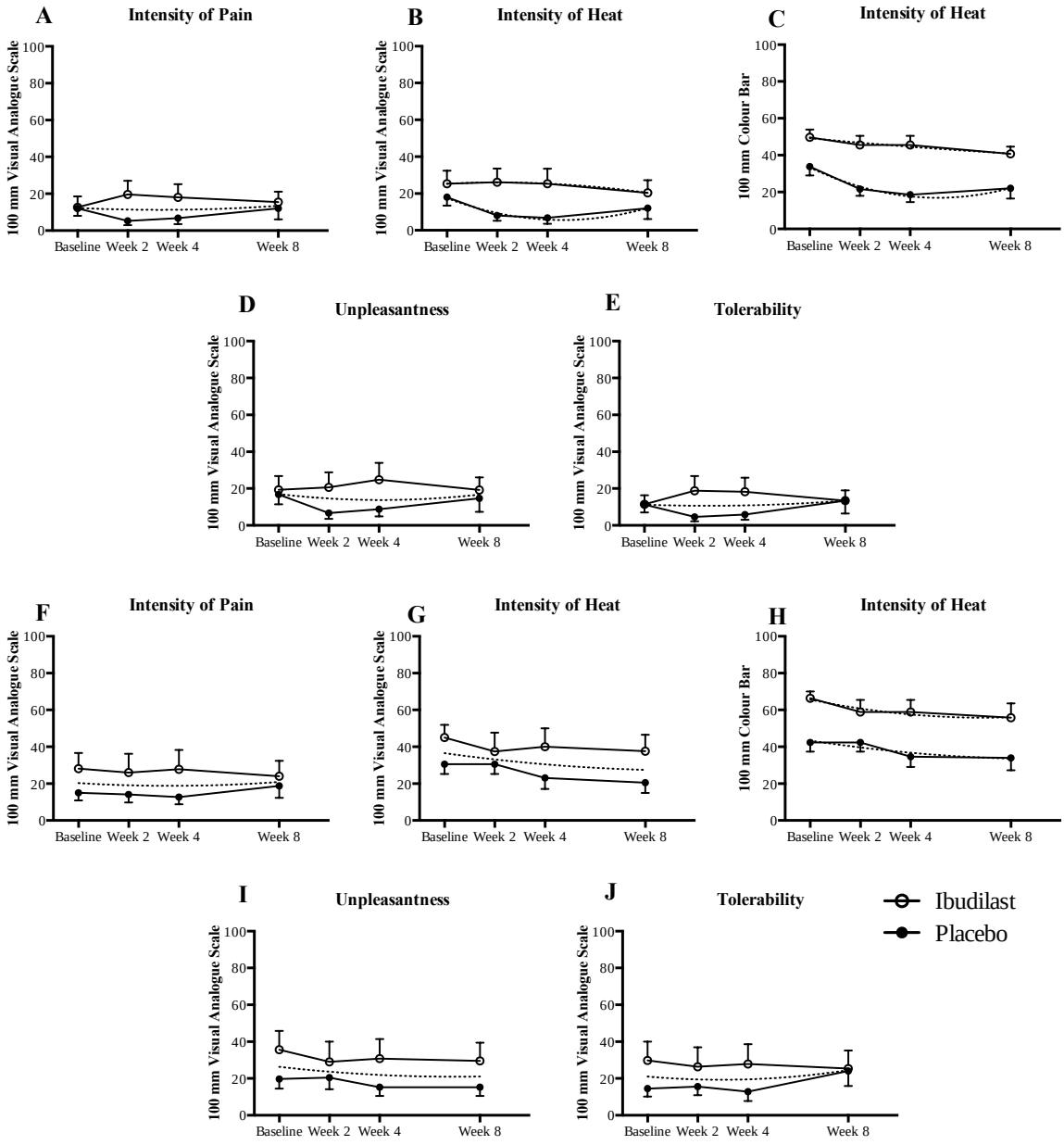


Figure 11.5.6. Response to ibudilast: thermal grill response.

The response to the thermal grill illusion at the right cheek across four testing sessions conducted over 8 weeks in patients assigned to the placebo and ibudilast groups at the 22/38 ºC (A-E) and 18/42 ºC (F-J) thermal grill configurations. Comparing ibudilast and placebo, no significant differences were observed between the effect time curves for all thermal grill outcomes on the right cheek when tested at the 22/38 ºC (A-E) and 18/42 ºC (F-J) thermal grill configurations. Graphs are represented as mean ± SEM.

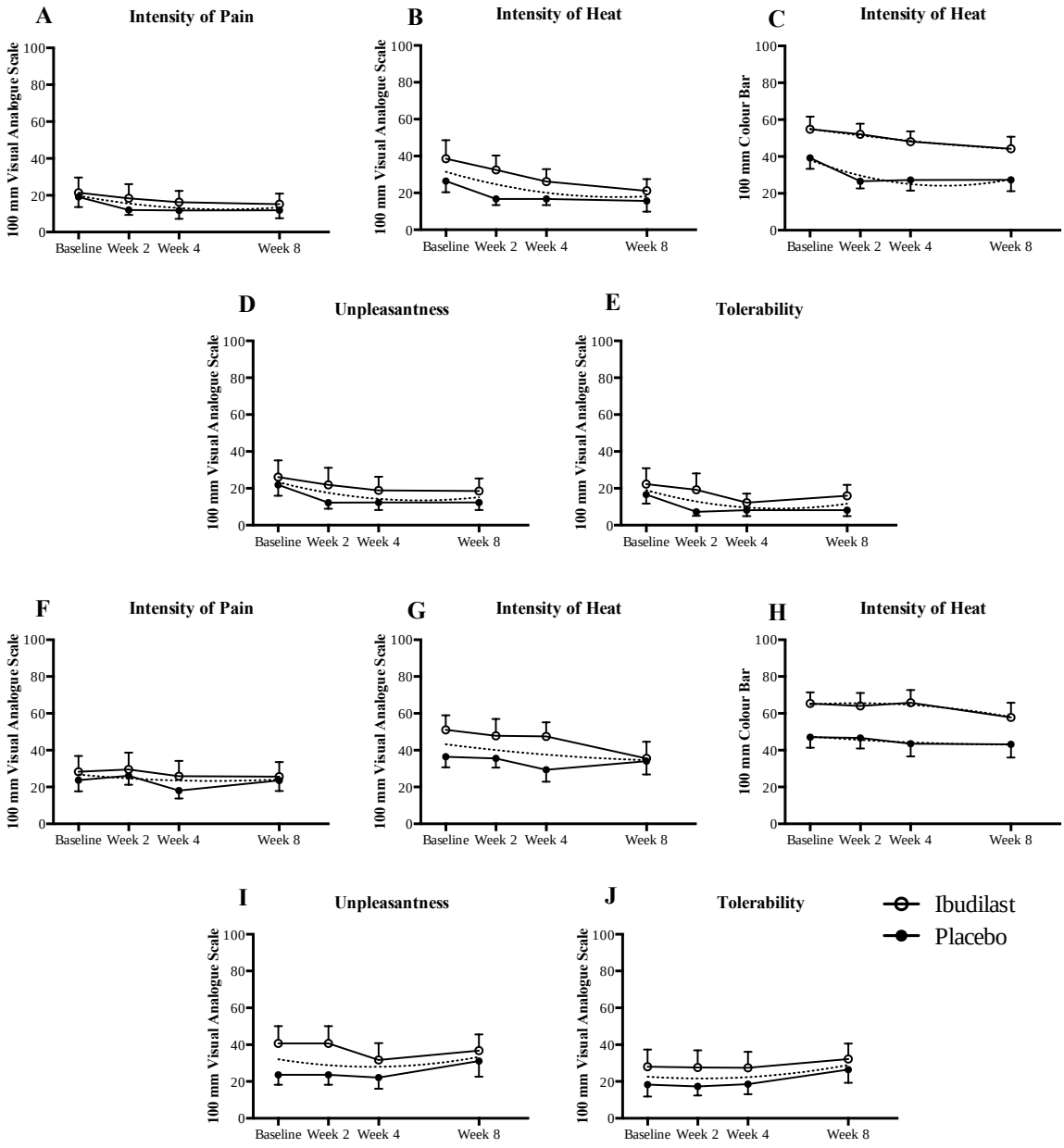
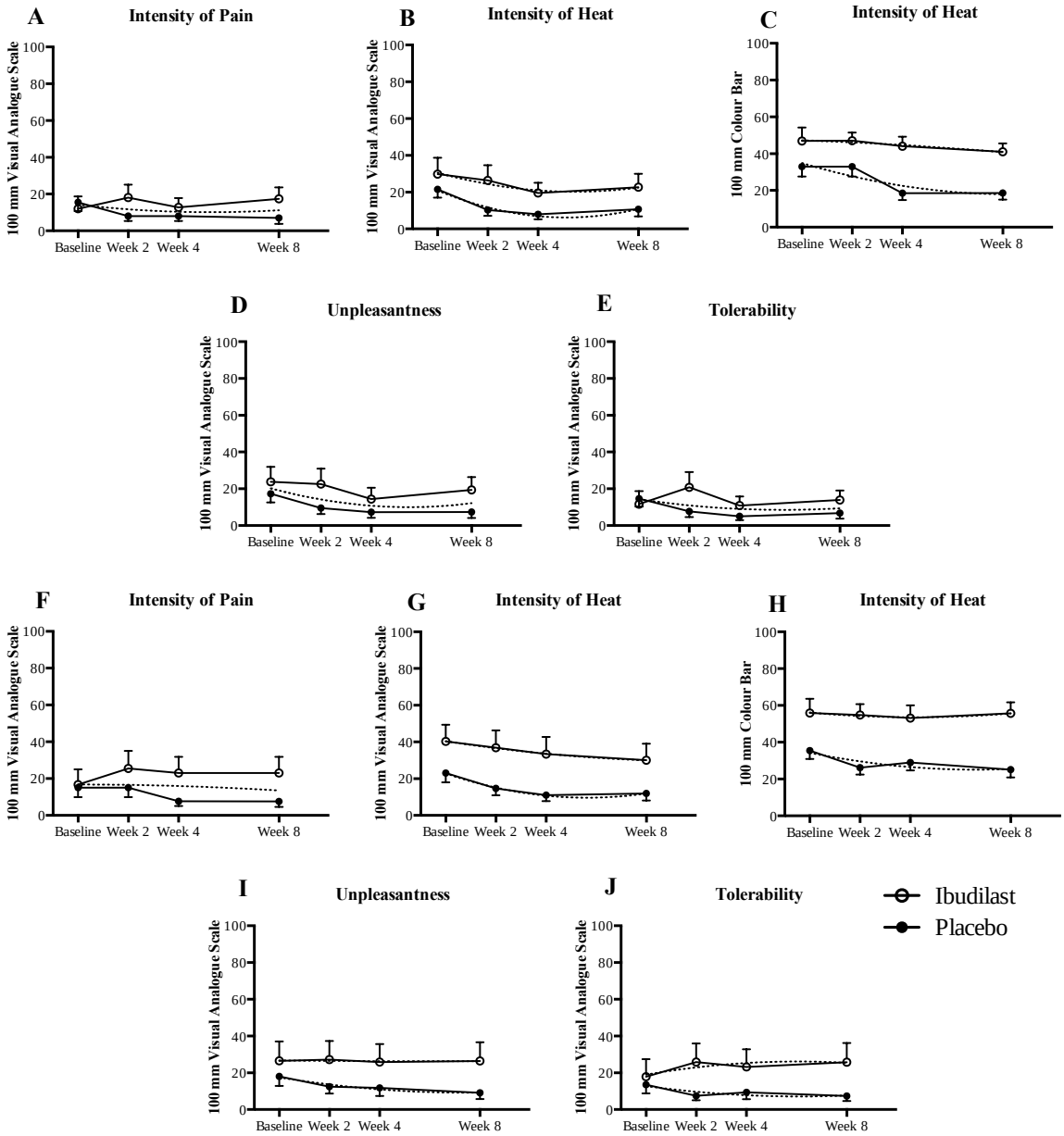


Figure 11.5.7. Response to ibudilast: thermal grill response.

The response to the thermal grill illusion at the right palm across four testing sessions conducted over 8 weeks in patients assigned to the placebo and ibudilast groups at the 22/38 ºC (A-E) and 18/42 ºC (F-J) thermal grill configurations. Comparing ibudilast and placebo, no significant differences were observed between the effect time curves for all thermal grill outcomes on the right palm when tested at the 22/38 ºC (A-E) and 18/42 ºC (F-J) thermal grill configurations. Graphs are represented as mean ± SEM.


A
Intensity of Pain
100 mm Visual Analogue Scale
B
Intensity of Heat
100 mm Visual Analogue Scale
C
Intensity of Heat
100 mm Colour Bar
D
Unpleasantness
100 mm Visual Analogue Scale
E
Tolerability
100 mm Visual Analogue Scale
F
Intensity of Pain
100 mm Visual Analogue Scale
G
Intensity of Heat
100 mm Visual Analogue Scale
H
Intensity of Heat
100 mm Colour Bar
I
Unpleasantness
100 mm Visual Analogue Scale
J
Tolerability
100 mm Visual Analogue Scale
0
20
40
60
80
100
Baseline
Week 2
Week 4
Week 8
Ibudilast
Placebo

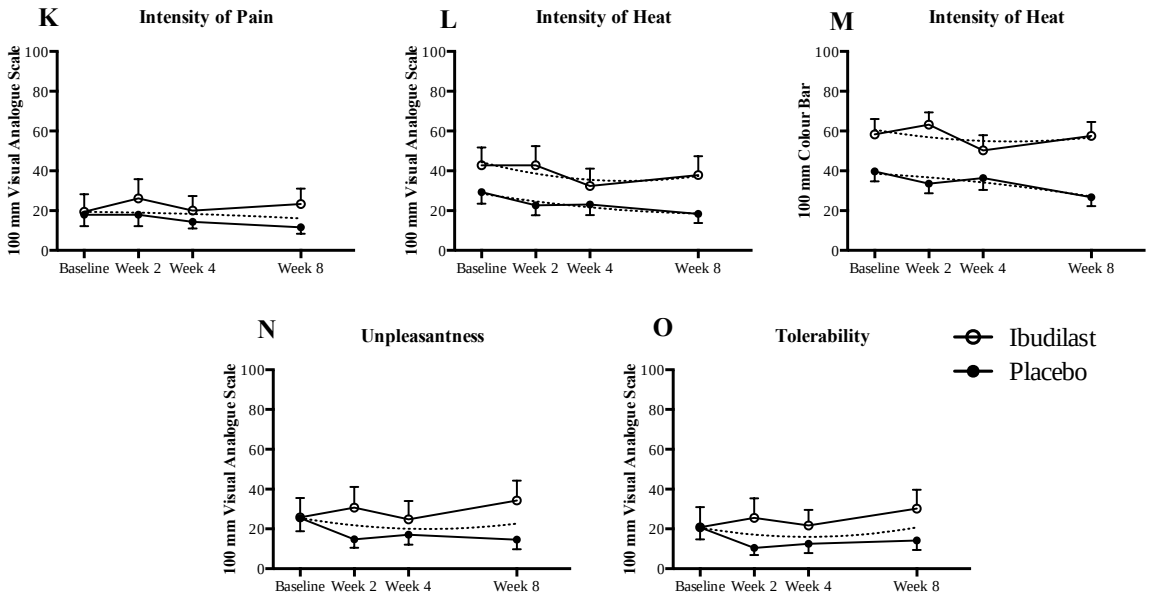
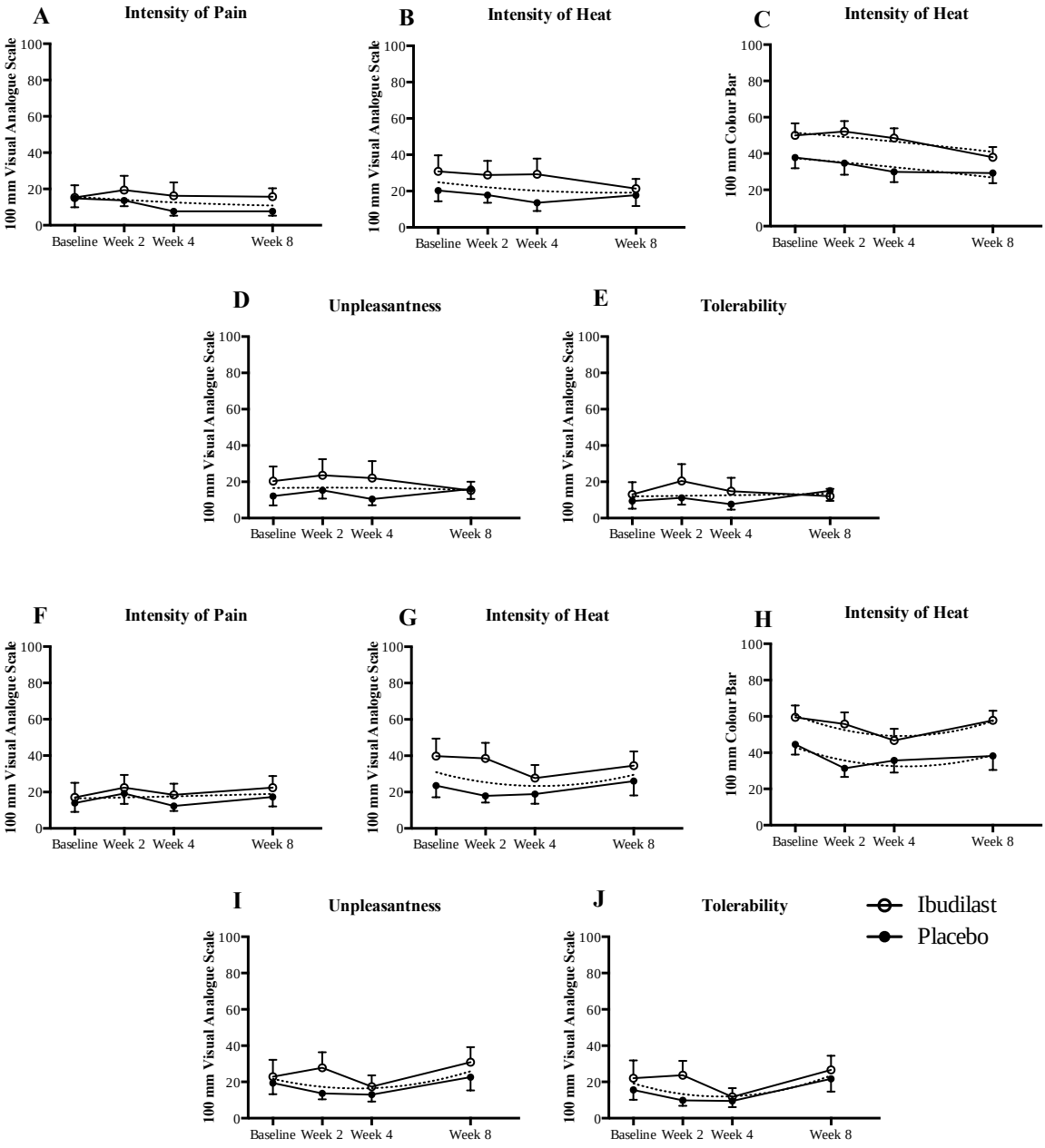


Figure 11.5.8. Response to ibudilast: thermal grill response.

The response to the thermal grill illusion at the left cheek across four testing sessions conducted over 8 weeks in patients assigned to the placebo and ibudilast groups at the 22/38 ºC (A-E), 20/40 ºC (F-J) and 18/42 ºC (K-O) thermal grill configurations. Comparing ibudilast and placebo, no significant differences were observed between the effect time curves for all thermal grill outcomes on the left cheek when tested at the 22/38 ºC (A-E), 20/40 ºC (F-J) and 18/42 ºC (K-O) thermal grill configurations. Graphs are represented as mean ± SEM.


A
Intensity of Pain
B
Intensity of Heat
C
Intensity of Heat
D
Unpleasantness
E
Tolerability
F
Intensity of Pain
G
Intensity of Heat
H
Intensity of Heat
I
Unpleasantness
J
Tolerability
100 mm Visual Analogue Scale
100 mm Colour Bar
0
20
40
60
80
100
Baseline
Week 2
Week 4
Week 8
Ibudilast
Placebo

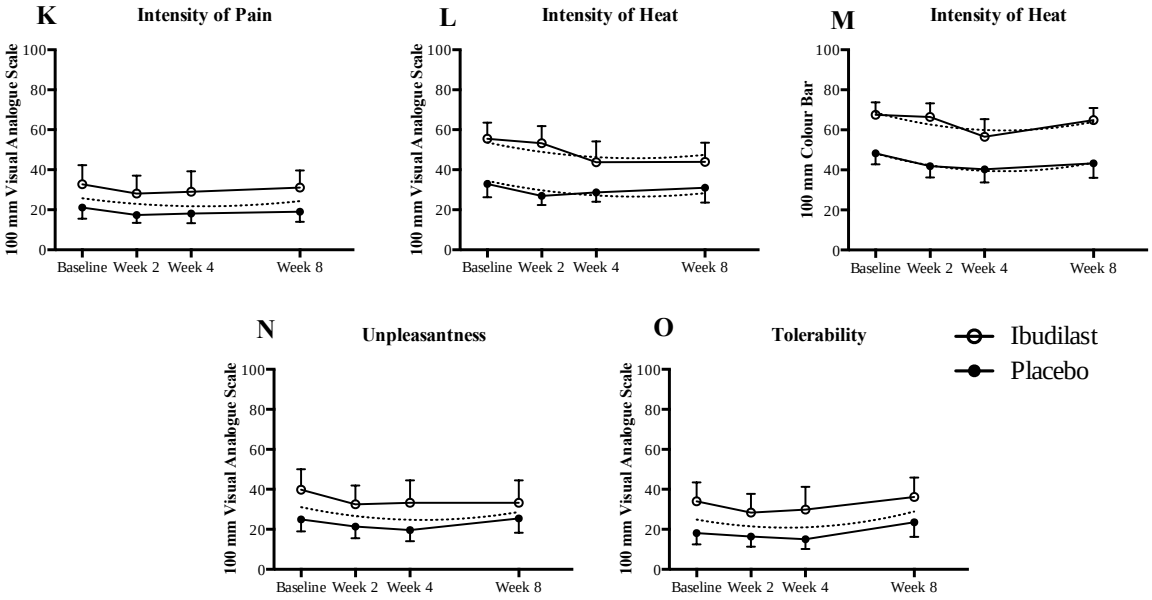


Figure 11.5.9. Response to ibudilast: thermal grill response.

The response to the thermal grill illusion at the left palm across four testing sessions conducted over 8 weeks in patients assigned to the placebo and ibudilast groups at the 22/38 ºC (A-E), 20/40 ºC (F-J) and 18/42 ºC (K-O) thermal grill configurations. Comparing ibudilast and placebo, no significant differences were observed between the effect time curves for all thermal grill outcomes on the left palm when tested at the 22/38 ºC (A-E), 20/40 ºC (F-J) and 18/42 ºC (K-O) thermal grill configurations. Graphs are represented as mean ± SEM.

Chapter 6

Table 11.6.1. Correlations Between Average Pain Intensity and Cold and Heat Pain Thresholds

R and *P* values from the correlation analysis performed between patients average pain intensity from their headache pain and their cold and heat pain thresholds (listed horizontally) at patients affected and unaffected side cheek, palm and calf (listed vertically).

	Cold Pain Threshold	Heat Pain Threshold
Right Cheek		
R value	-0.067	-0.14[S]
P value	0.84	0.65[S]
Left Cheek		
R value	0.4	-0.34
P value	0.2	0.29
Right Palm		
R value	0.032[S]	-0.45
P value	0.93[S]	0.14
Left Palm		
R value	0.11	-0.3
P value	0.74	0.34

[S]: analysed with Spearman's correlation. Significance level < 0.025.

Table 11.6.2. Correlations Between Average Pain Intensity and Thermal Grill Response

R and *P* values from the correlation analyses performed at patients right and left cheek and palm are presented (described previously on page 94).

	Right Cheek			Left Cheek			Right Palm			Left Palm		
Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Intensity of Pain												
R value	0.24	0.16	0.18	0.12	0.81	0.099	0.15[P]	0.27[P]	0.15[P]	0.053[P]	-0.17[P]	0.24[P]
P value	0.45	0.62	0.57	0.71	0.8	0.76	0.65[P]	0.4[P]	0.64[P]	0.87[P]	0.61[P]	0.45[P]
Intensity of Heat												
R value	0.42	0.23	0.22	0.24[P]	0.21[P]	0.29[P]	0.18[P]	0.21[P]	0.055[P]	0.046[P]	0.0063[P]	0.14[P]
P value	0.17	0.47	0.49	0.45[P]	0.52[P]	0.37[P]	0.59[P]	0.52[P]	0.87[P]	0.89[P]	0.98[P]	0.67[P]
Intensity of Heat												
R value	-0.076[P]	-0.11[P]	-0.027[P]	0.086[P]	-0.088[P]	-0.073[P]	-0.066[P]	0.032[P]	-0.1[P]	-0.32[P]	-0.24[P]	-0.073[P]
P value	0.82[P]	0.75[P]	0.93[P]	0.79[P]	0.79[P]	0.82[P]	0.84[P]	0.92[P]	0.75[P]	0.32[P]	0.45[P]	0.82[P]
Unpleasantness												
R value	0.041	0.083	0.12	0.13	0.0053	0.032	-0.041	0.13	-0.12	0.02[P]	0.13[P]	0.095[P]
P value	0.9	0.8	0.7	0.69	0.97	0.92	0.88	0.67	0.69	0.95[P]	0.69[P]	0.77[P]
Tolerability												
R value	0.33[P]	0.26[P]	0.39[P]	0.023	0.11	0.091	0.067	-0.011	-0.14	-0.12	-0.092	-0.11
P value	0.29[P]	0.41[P]	0.21[P]	0.94	0.74	0.78	0.84	0.93	0.64	0.68	0.74	0.73

°C: degrees Celcius; [P]: analysed with Pearson's correlation. Significance level < 0.00167.

Table 11.6.3. Correlations Between Duration of Pain and Cold and Heat Pain Thresholds

R and *P* values from the correlation analysis performed between patients duration of headache pain and their cold and heat pain thresholds (listed horizontally) at patients affected and unaffected side cheek, palm and calf (listed vertically).

	Cold Pain Threshold	Heat Pain Threshold
Right Cheek		
R value	-0.55	0.51[S]
P value	0.062	0.094[S]
Left Cheek		
R value	**-0.71**	**0.74**
P value	**0.01**	**0.0059**
Right Palm		
R value	**-0.82[S]**	**0.8**
P value	**0.0015[S]**	**0.0019**
Left Palm		
R value	**-0.85**	**0.74**
P value	**0.0005**	**0.0063**

[S]: analysed with Spearman's correlation. Significant values represented by bold text. Significance level < 0.025.

Table 11.6.4. Correlations Between Duration of Pain and Thermal Grill Response

R and *P* values from the correlation analyses performed at patients right and left cheek and palm are presented (described previously on page 94).

	Right Cheek			Left Cheek			Right Palm			Left Palm		
Thermal grill configuration	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C	22/38 °C	20/40 °C	18/42 °C
Intensity of Pain												
R value	-0.37	-0.18	-0.3	-0.59	-0.43	-0.43	-0.41[P]	-0.33[P]	-0.46[P]	-0.3[P]	-0.037[P]	-0.23[P]
P value	0.21	0.53	0.34	0.045	0.15	0.15	0.18[P]	0.29[P]	0.13[P]	0.34[P]	0.91[P]	0.46[P]
Intensity of Heat												
R value	-0.24	-0.78	-0.53	-0.5[P]	-0.45[P]	-0.68[P]	-0.51[P]	-0.45[P]	-0.53[P]	-0.47[P]	-0.45[P]	-0.49[P]
P value	0.44	0.0035	0.073	0.098[P]	0.14[P]	0.015[P]	0.094[P]	0.14[P]	0.078[P]	0.12[P]	0.14[P]	0.1[P]
Intensity of Heat												
R value	0.033[P]	-0.66[P]	-0.65[P]	-0.43[P]	-0.4[P]	-0.64[P]	-0.5[P]	-0.62[P]	-0.72[P]	-0.54[P]	-0.47[P]	-0.73[P]
P value	0.92[P]	0.019[P]	0.022[P]	0.16[P]	0.2[P]	0.026[P]	0.094[P]	0.031[P]	0.0078[P]	0.07[P]	0.12[P]	0.0074[P]
Unpleasantness												
R value	-0.31	-0.46	-0.11	-0.64	-0.47	-0.57	-0.44	-0.33	-0.4	-0.36[P]	-0.19[P]	-0.35[P]
P value	0.3	0.12	0.71	0.027	0.11	0.052	0.15	0.26	0.19	0.25[P]	0.56[P]	0.26[P]
Tolerability												
R value	-0.15[P]	-0.21[P]	-0.13[P]	-0.48	-0.35	-0.59	-0.39	-0.52	-0.59	-0.45	-0.23	-0.27
P value	0.64[P]	0.52[P]	0.69[P]	0.11	0.25	0.041	0.19	0.079	0.044	0.14	0.45	0.38

°C: degrees Celcius; [P]: analysed with Pearson's correlation. Significance level < 0.00167.

Figures

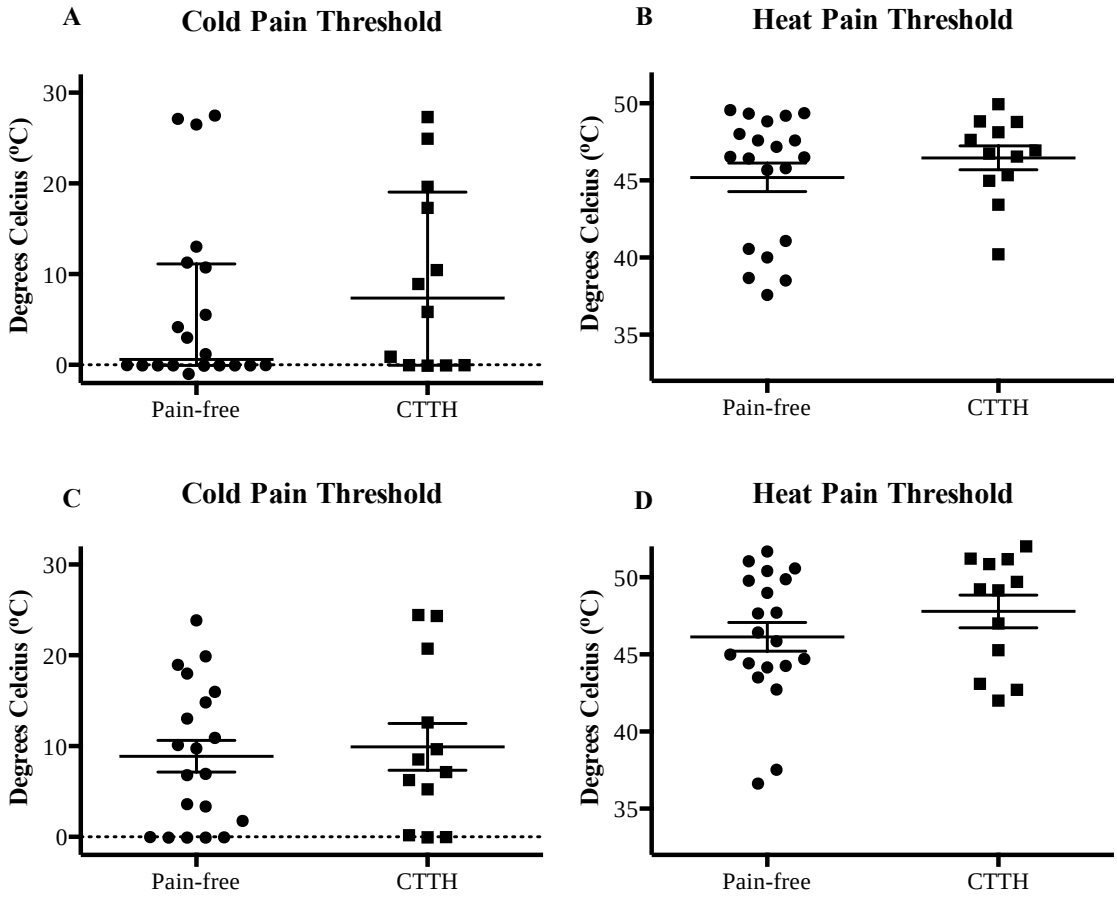


Figure 11.6.1. Pain-free participants versus patients with chronic tension-type headache: cold and heat pain thresholds.

Cold and heat pain thresholds at the left cheek (A, B) and palm (C, D) in pain-free participants and patients with CTTH. Cold and heat pain thresholds did not differ between pain-free participants and patients with CTTH at both the left cheek ($p = 0.58$, A and $p = 0.35$, B) and left palm ($p = 0.73$, C and $p = 0.27$, D). Graph A is are represented as median and IQR. Graphs B, C and D are represented as mean ± SEM. CTTH: chronic tension-type headache.

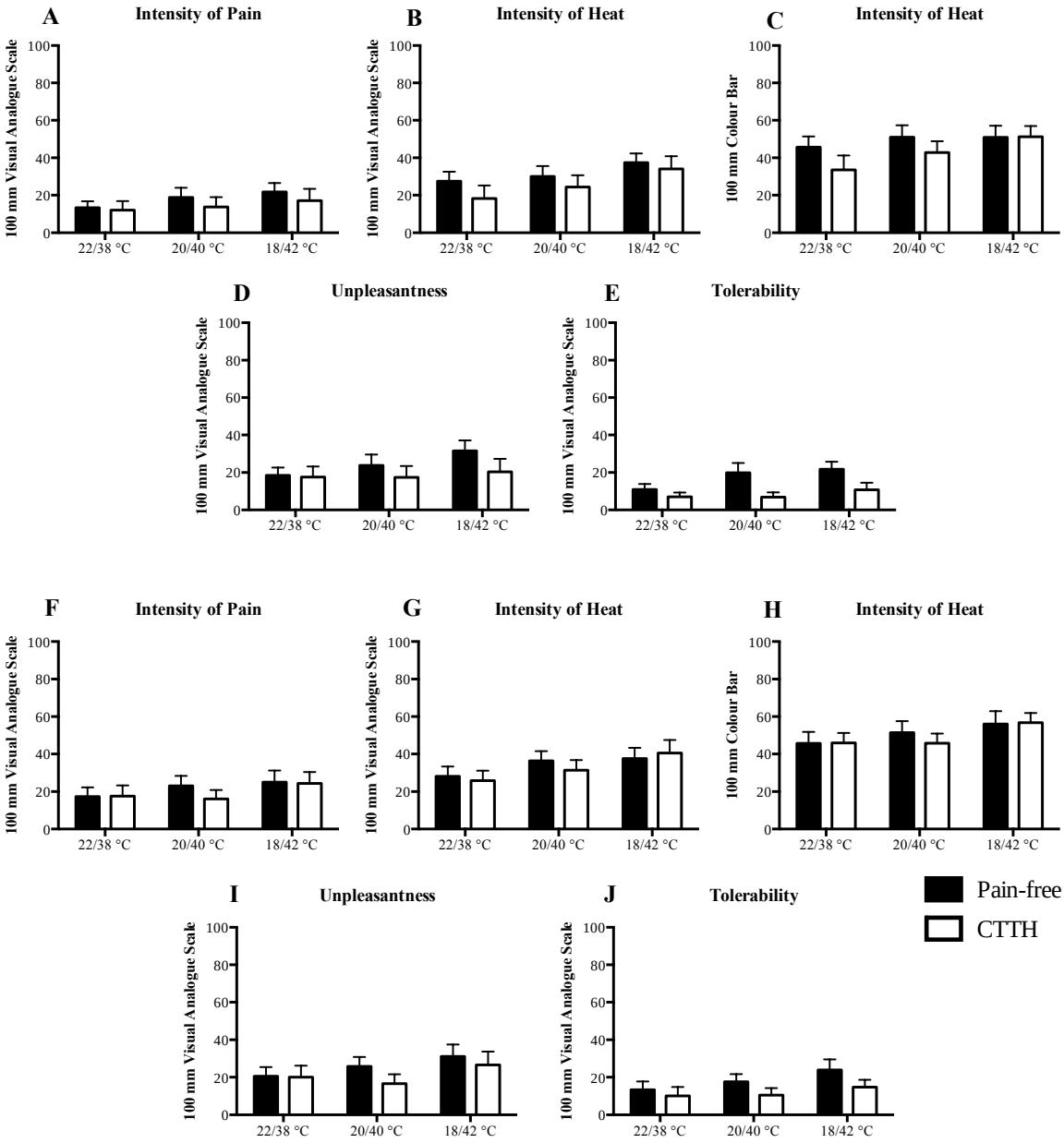


Figure 11.6.2. Pain-free participants versus patients with chronic tension-type headache: thermal grill response.

The response to the thermal grill illusion at the left cheek (A-E) and palm (F-J) in pain-free participants (black bars) and patients with CTTH (white bars). The response to the thermal grill did not differ between pain-free participants and patients with medication overused headache on either the left cheek (A-E) or palm (F-J) for all thermal grill outcomes. All graphs are represented as mean ± SEM. CTTH: chronic tension-type headache.

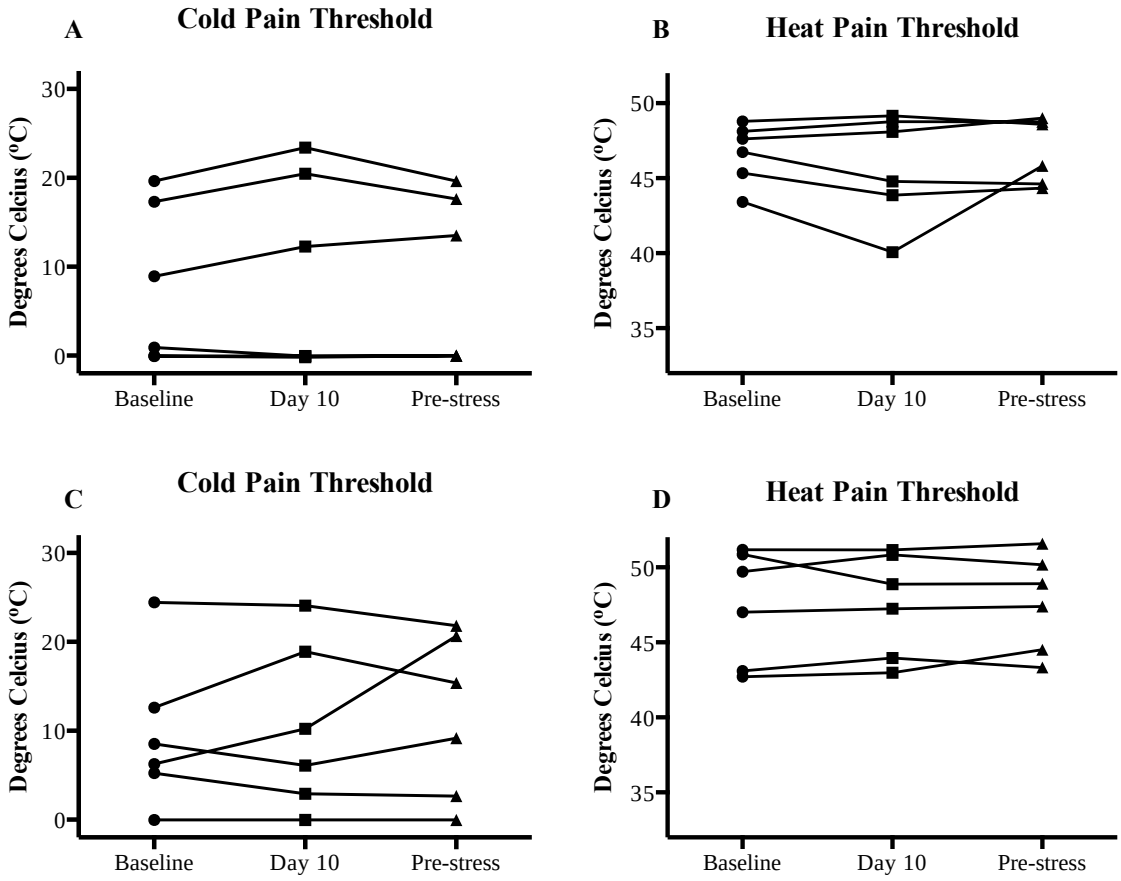


Figure 11.6.3. Repeatability of cold and heat pain thresholds across 15 days in patients assigned to the sham group.

Cold and heat pain thresholds at the left cheek (A, B) and palm (C, D) across three testing sessions conducted over 15 days in patients assigned to the sham treatment group. Both cold and heat pain thresholds did not significantly differ between testing session at both the left cheek ($p = 0.43$, A and $p = 1.0$, B) and palm ($p = 1.0$, C and $p = 0.25$, D).

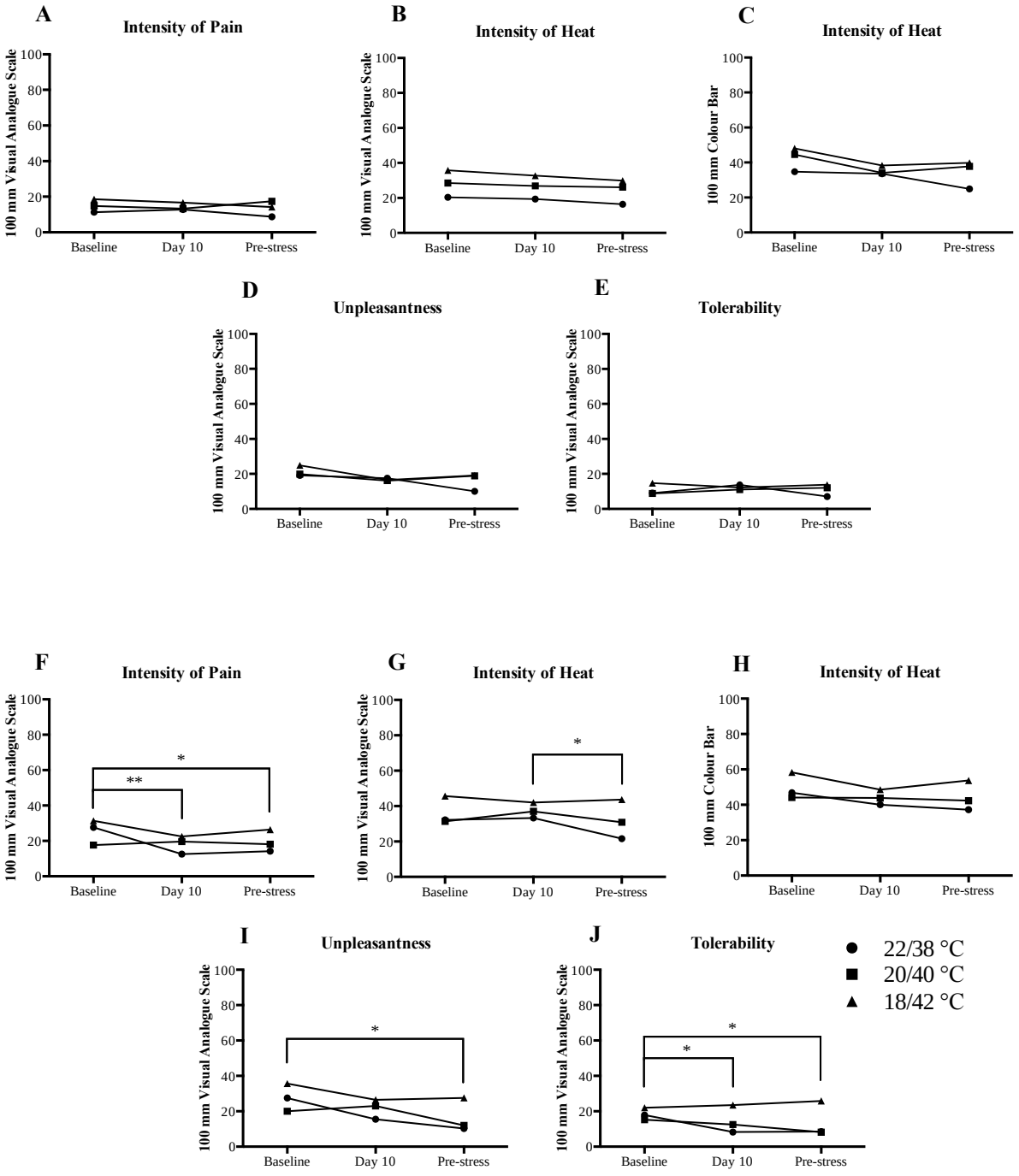


Figure 11.6.4. Repeatability of thermal grill illusion across 15 days in patients assigned to the sham group.

The response to the thermal grill at the left cheek (A-E) and palm (F-J) across three testing sessions conducted over 15 days in patients assigned to the sham treatment group. Generally, a decline in response to the thermal grill illusion was observed over time. Graphs are represented as mean. * $P < 0.05$ (22/38 ^{o}C).

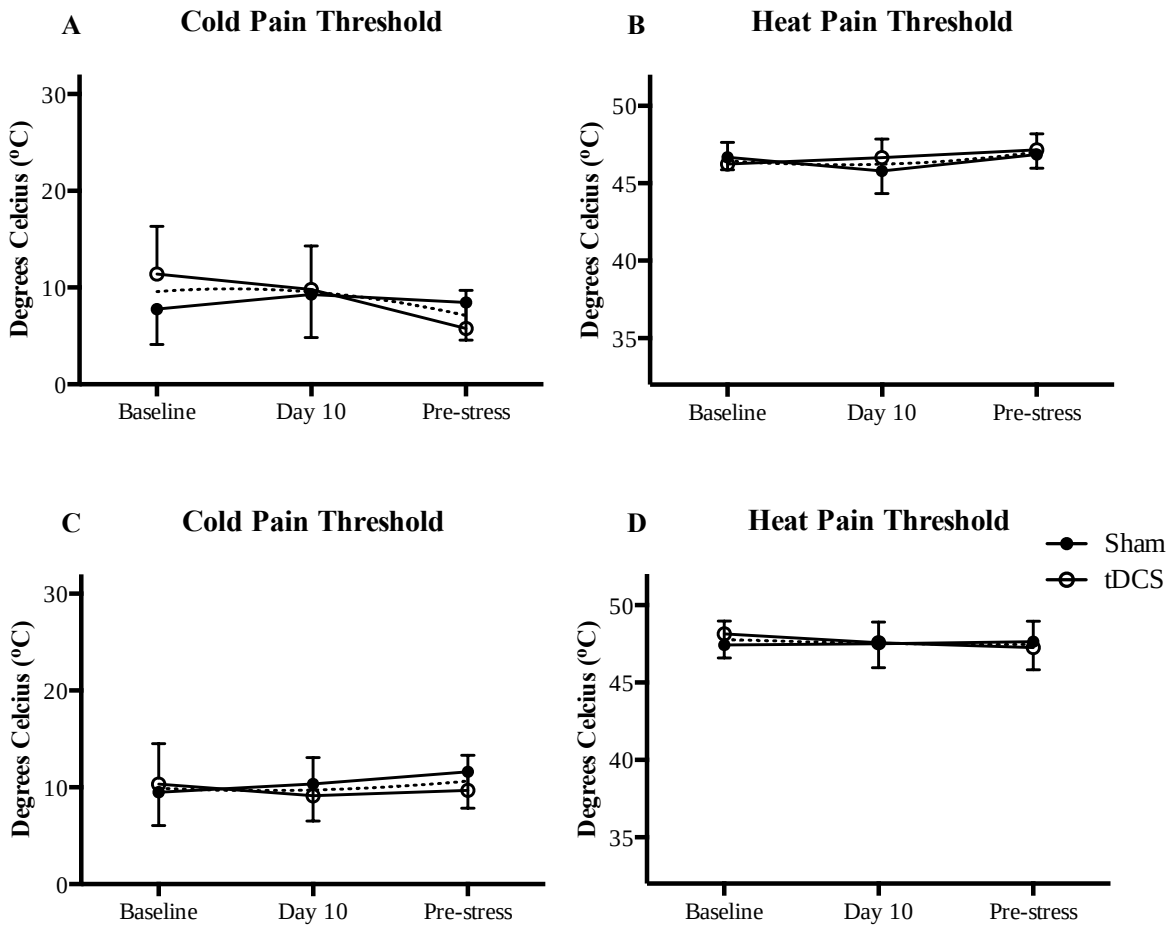


Figure 11.6.5. Response to tDCS (baseline to pre-stressful mental task): cold and heat pain thresholds.

Cold and heat pain thresholds at the left cheek (A, B) and palm (C, D) across three testing sessions conducted over 15 days in patients assigned to the sham and tDCS treatment groups. Comparing the tDCS and sham groups, no significant differences were observed between the effect time curves for cold pain thresholds on the left cheek (A)($p = 0.91$) or palm (C)($p = 0.98$) or heat pain thresholds on the left cheek (B)($p = 0.94$) or palm (D)($p = 0.98$). Graphs are represented as mean ± SEM.

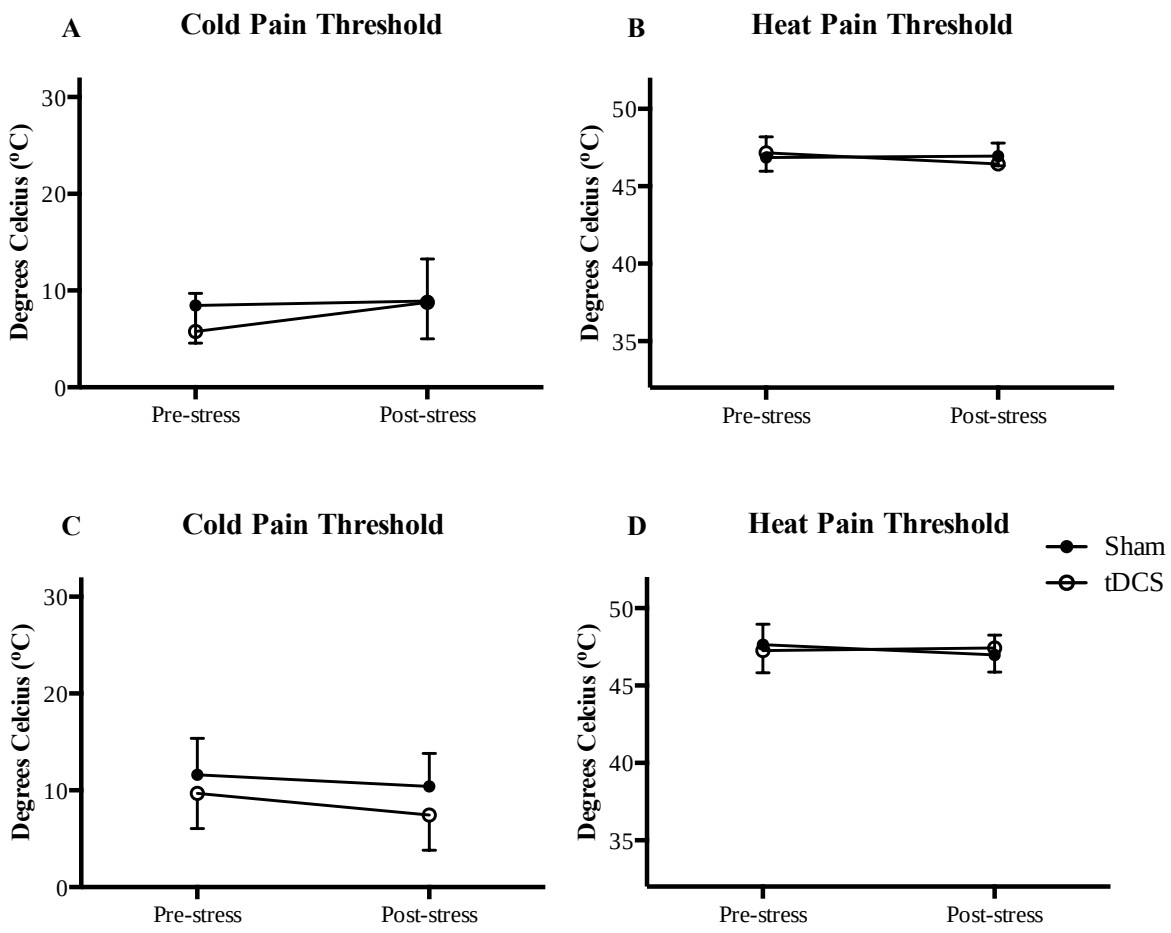


Figure 11.6.6. Response to tDCS (pre- to post-stressful mental task): cold and heat pain thresholds.

Cold and heat pain thresholds at the left cheek (A, B) and palm (C, D) pre- and post-stressful mental task in patients assigned to the sham and tDCS treatment groups. Comparing the tDCS and sham groups, no significant differences were observed between the effect time curves for cold pain thresholds on the left cheek (A)($p = 0.81$) or palm (C)($p = 0.63$) or heat pain thresholds on the left cheek (B)($p = 0.95$) or palm (D)($p = 0.99$). Graphs are represented as mean ± SEM.

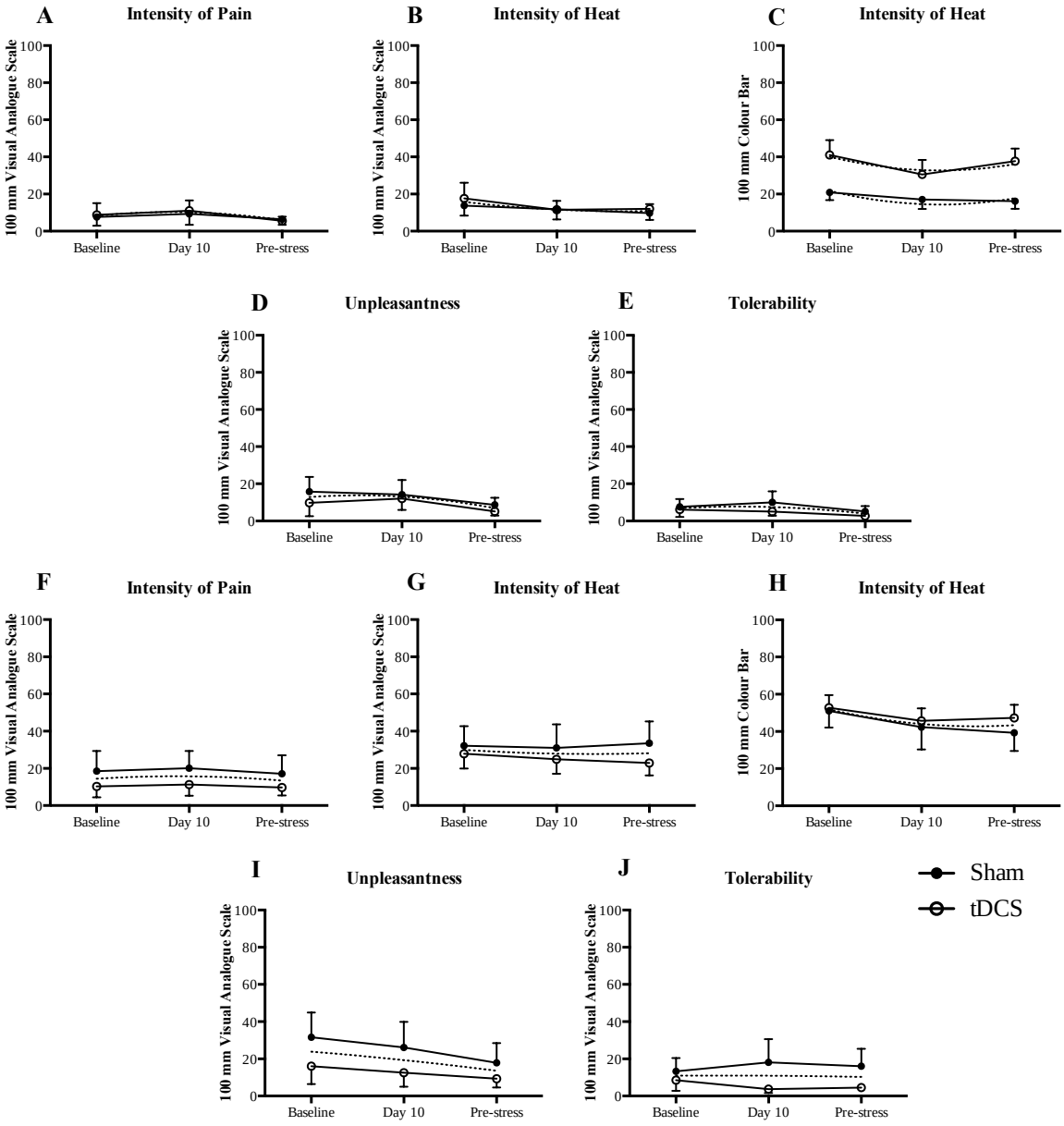


Figure 11.6.7. Response to tDCS (baseline to pre-stressful mental task): thermal grill response.

Response to the thermal grill illusion at the right cheek across three testing sessions conducted over 15 days in patients assigned to the sham and tDCS treatment groups at the 20/40 ºC (A-E) and 18/42 ºC (F-J) thermal grill configurations. Comparing the tDCS and sham groups, no significant differences were observed between the effect time curves for all thermal grill outcomes at both the 20/40 ºC (A-E) and 18/42 ºC (F-J) thermal grill configurations. Graphs are represented as mean ± SEM.

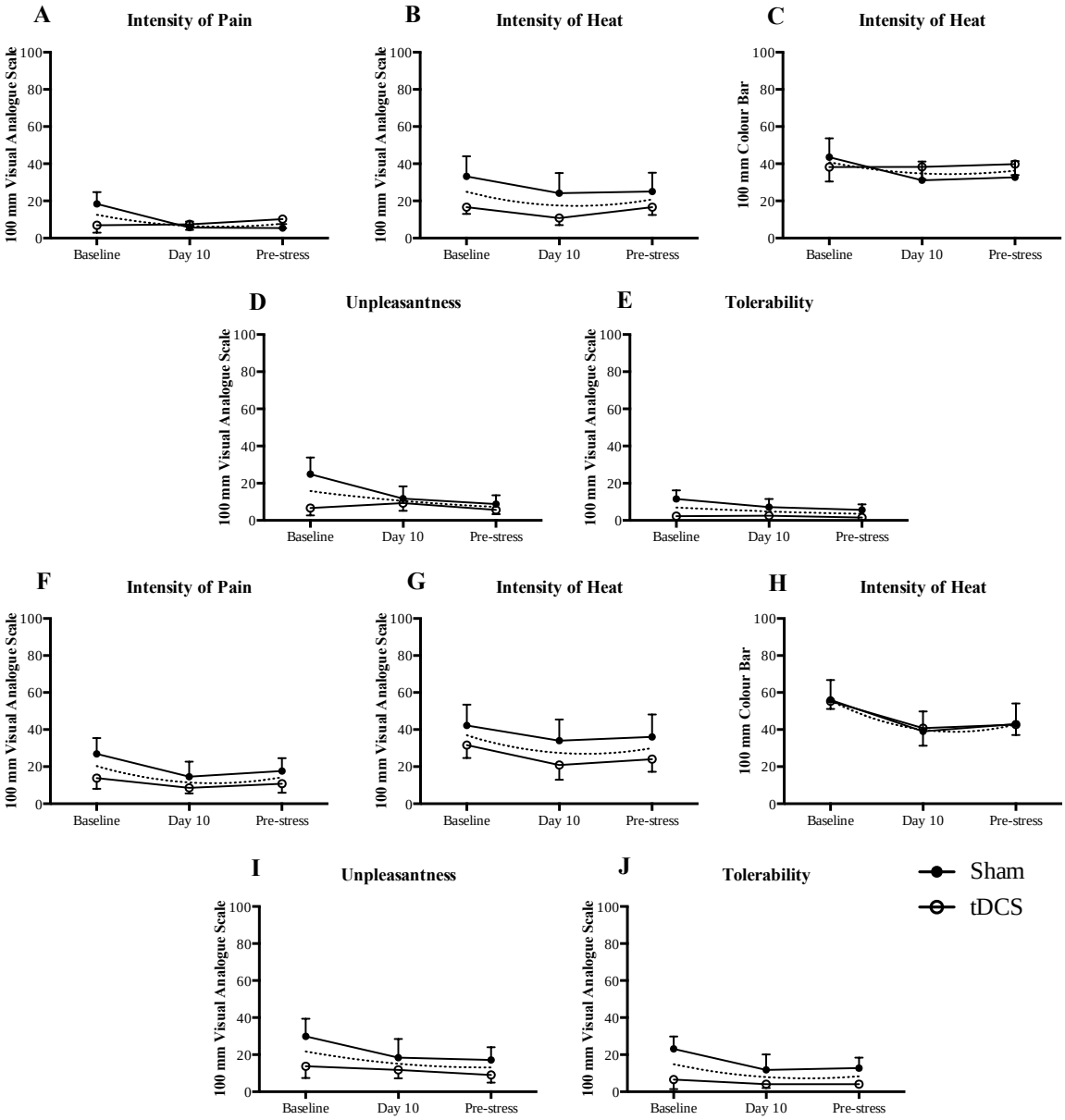
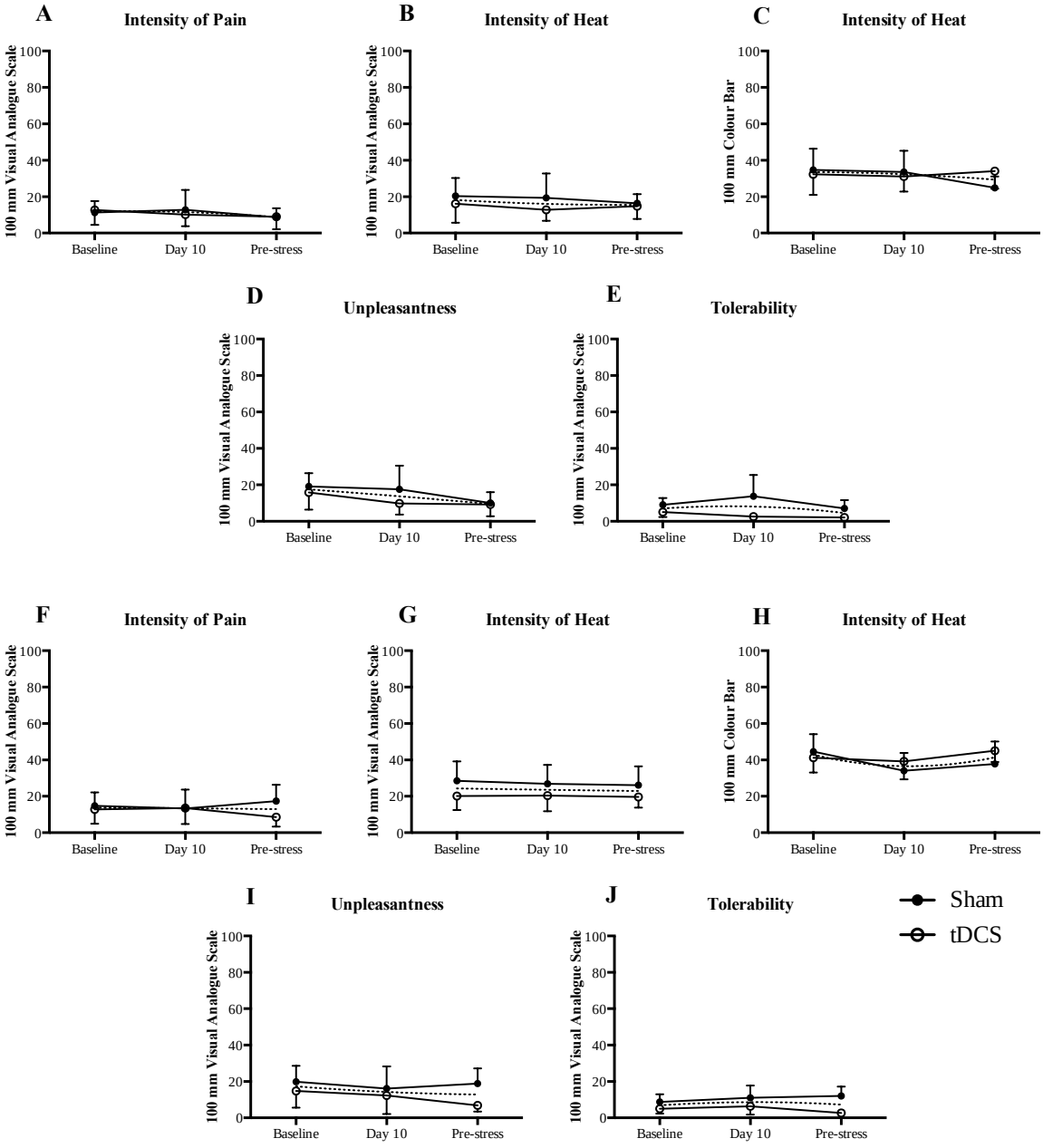


Figure 11.6.8. Response to tDCS (baseline to pre-stressful mental task): thermal grill response.

Response to the thermal grill illusion at the right palm across three testing sessions conducted over 15 days in patients assigned to the sham and tDCS treatment groups at the 20/40 ºC (A-E) and 18/42 ºC (F-J) thermal grill configurations. Comparing the tDCS and sham groups, no significant differences were observed between the effect time curves for all thermal grill outcomes at both the 20/40 ºC (A-E) and 18/42 ºC (F-J) thermal grill configurations. Graphs are represented as mean ± SEM.


A
Intensity of Pain
100 mm Visual Analogue Scale
B
Intensity of Heat
100 mm Visual Analogue Scale
C
Intensity of Heat
100 mm Colour Bar
D
Unpleasantness
100 mm Visual Analogue Scale
E
Tolerability
100 mm Visual Analogue Scale
F
Intensity of Pain
100 mm Visual Analogue Scale
G
Intensity of Heat
100 mm Visual Analogue Scale
H
Intensity of Heat
100 mm Colour Bar
I
Unpleasantness
100 mm Visual Analogue Scale
J
Tolerability
100 mm Visual Analogue Scale
0
20
40
60
80
100
Baseline
Day 10
Pre-stress
Sham
tDCS

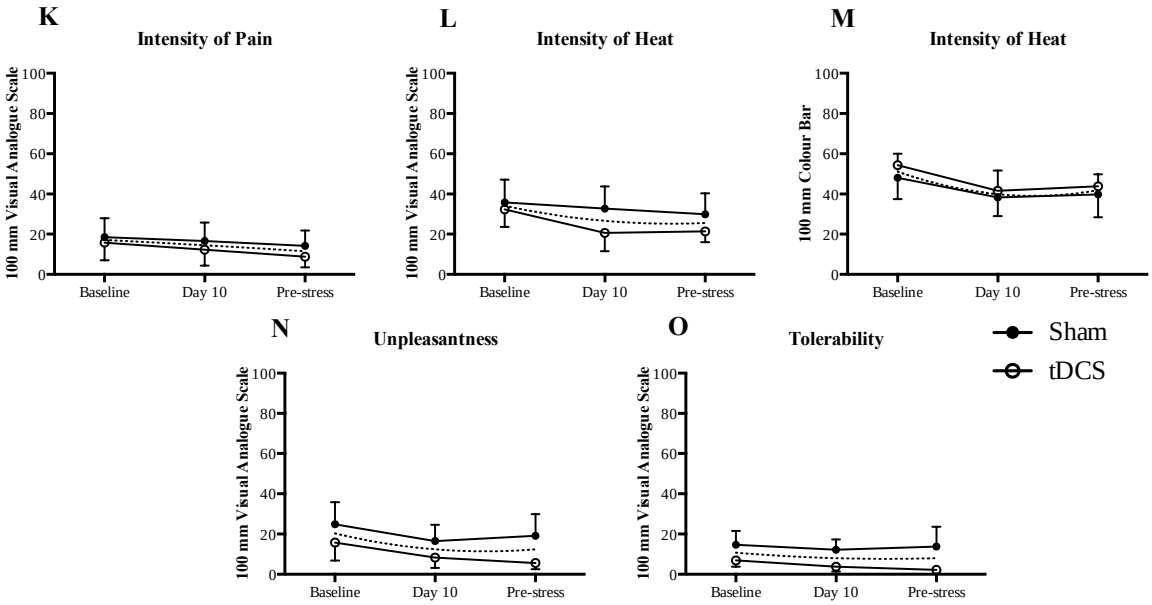
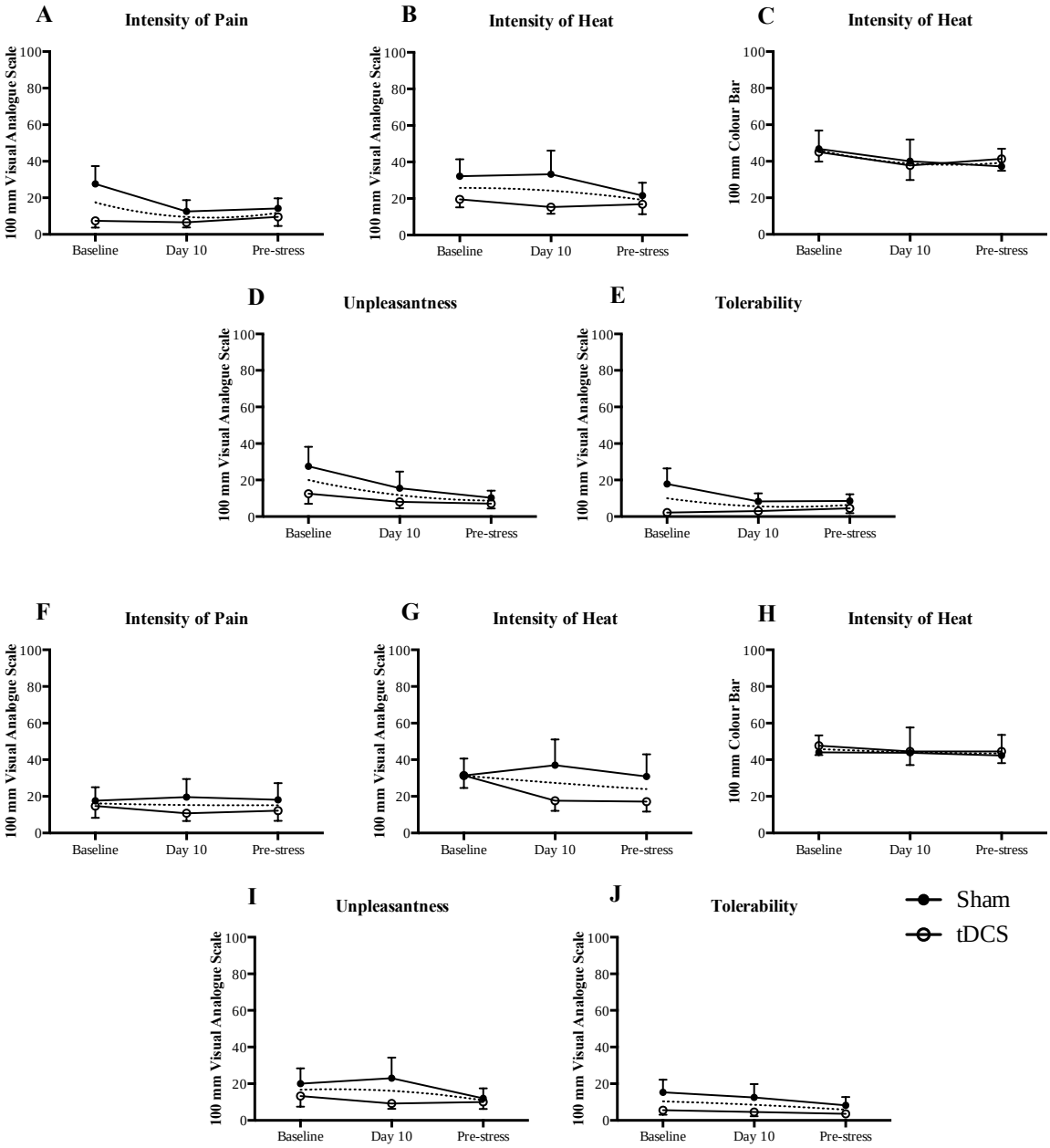


Figure 11.6.9. Response to tDCS (baseline to pre-stressful mental task): thermal grill response.

Response to the thermal grill illusion at the left cheek across three testing sessions conducted over 15 days in patients assigned to the sham and tDCS treatment groups at the 20/40 ºC (A-E), 20/40 ºC (F-J) and 18/42 ºC (K-O) thermal grill configurations. Comparing the tDCS and sham groups, no significant differences were observed between the effect time curves for all thermal grill outcomes at the 20/40 ºC (A-E), 20/40 ºC (F-J) and 18/42 ºC (K-O) thermal grill configurations. Graphs are represented as mean ± SEM.


A
Intensity of Pain
B
Intensity of Heat
C
Intensity of Heat
D
Unpleasantness
E
Tolerability
F
Intensity of Pain
G
Intensity of Heat
H
Intensity of Heat
I
Unpleasantness
J
Tolerability
100 mm Visual Analogue Scale
100 mm Colour Bar
0
20
40
60
80
100
Baseline
Day 10
Pre-stress
Sham
tDCS

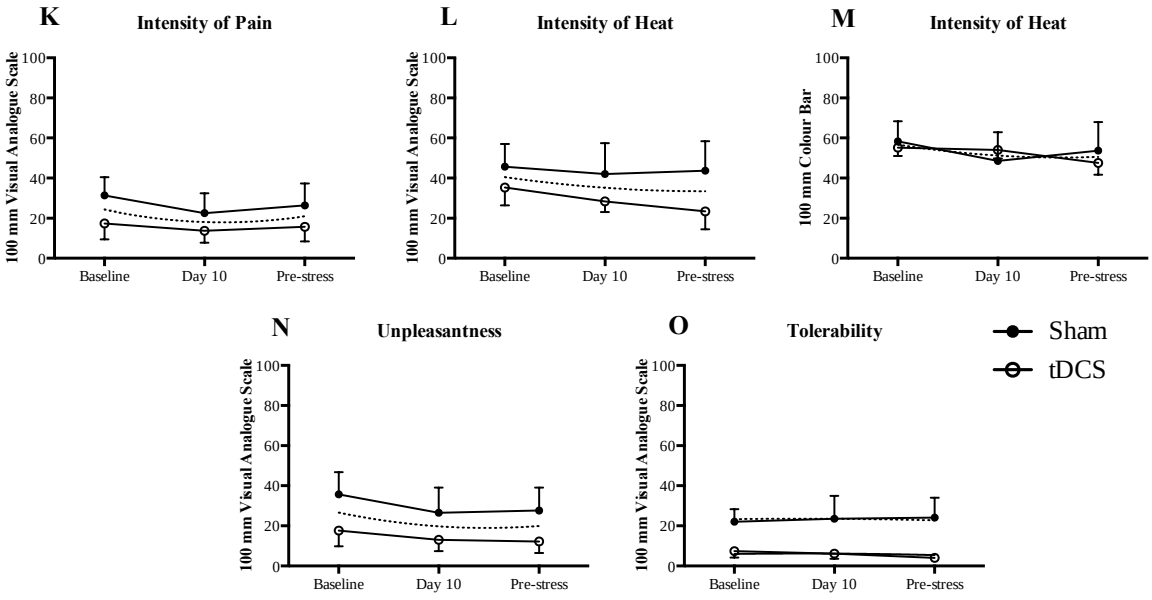


Figure 11.6.10. Response to tDCS (baseline to pre-stressful mental task): thermal grill response.

Response to the thermal grill illusion at the left palm across three testing sessions conducted over 15 days in patients assigned to the sham and tDCS treatment groups at the 20/40 ºC (A-E), 20/40 ºC (F-J) and 18/42 ºC (K-O) thermal grill configurations. Comparing the tDCS and sham groups, no significant differences were observed between the effect time curves for all thermal grill outcomes at the 20/40 ºC (A-E), 20/40 ºC (F-J) and 18/42 ºC (K-O) thermal grill configurations. Graphs are represented as mean ± SEM.

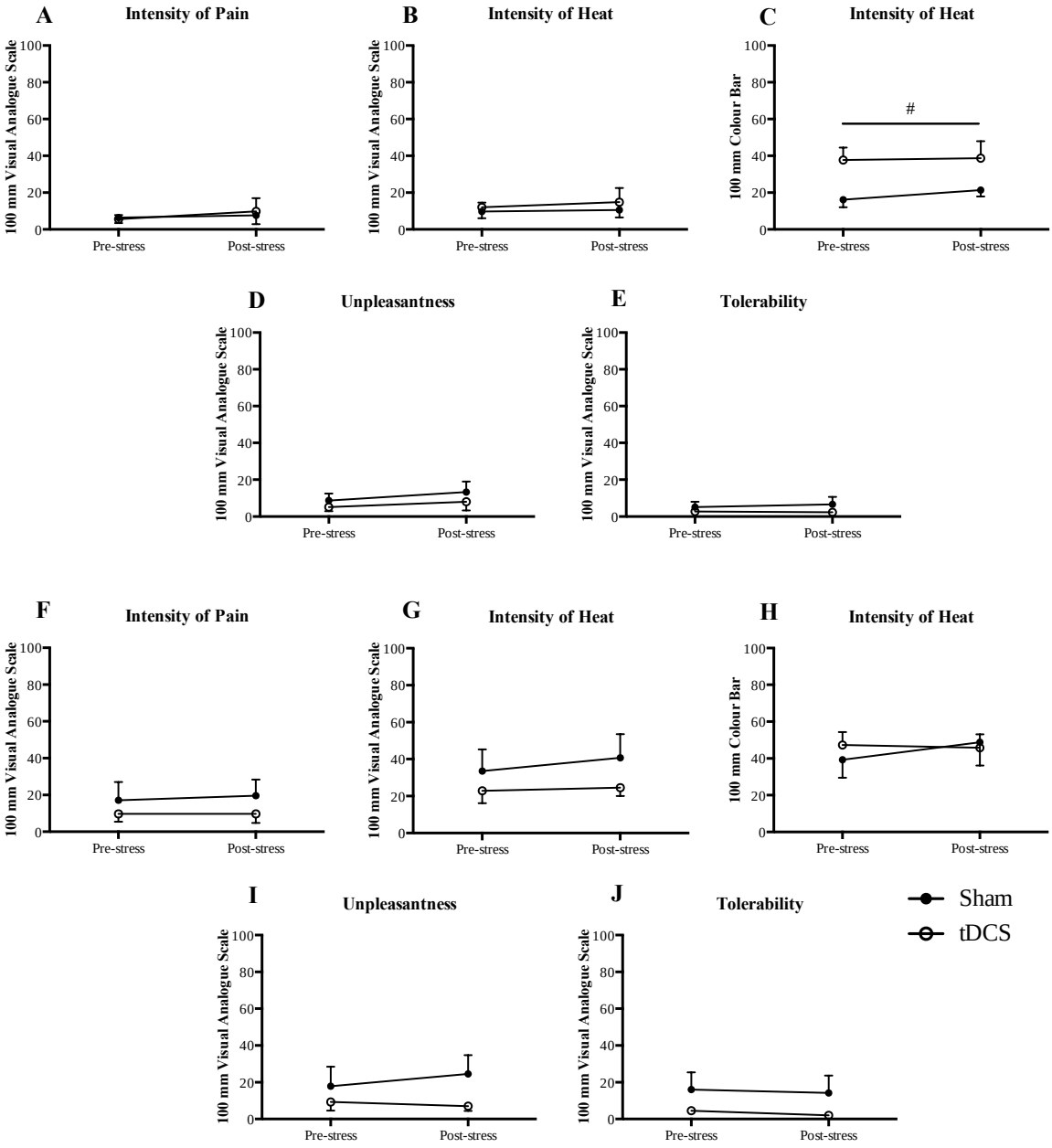


Figure 11.6.11. Response to tDCS (pre- to post-stressful mental task): thermal grill response.

Response to the thermal grill illusion at the right cheek pre- and post-stressful mental task in patients assigned to the sham and tDCS treatment groups at the 22/38 ºC (A-E) and 18/42 ºC (F-J) thermal grill configurations. Comparing the tDCS and sham groups, an overall main effect of group was observed for the outcome "intensity of heat" at the 22/38 ºC thermal grill configuration (C). No significant differences were observed for all other thermal grill outcomes at the 22/38 ºC (A-E) thermal grill configuration or for all outcomes at the 18/42 ºC (F-J) thermal grill configuration. Graphs are represented as mean ± SEM. # $P < 0.05$ for an overall main effect of group.

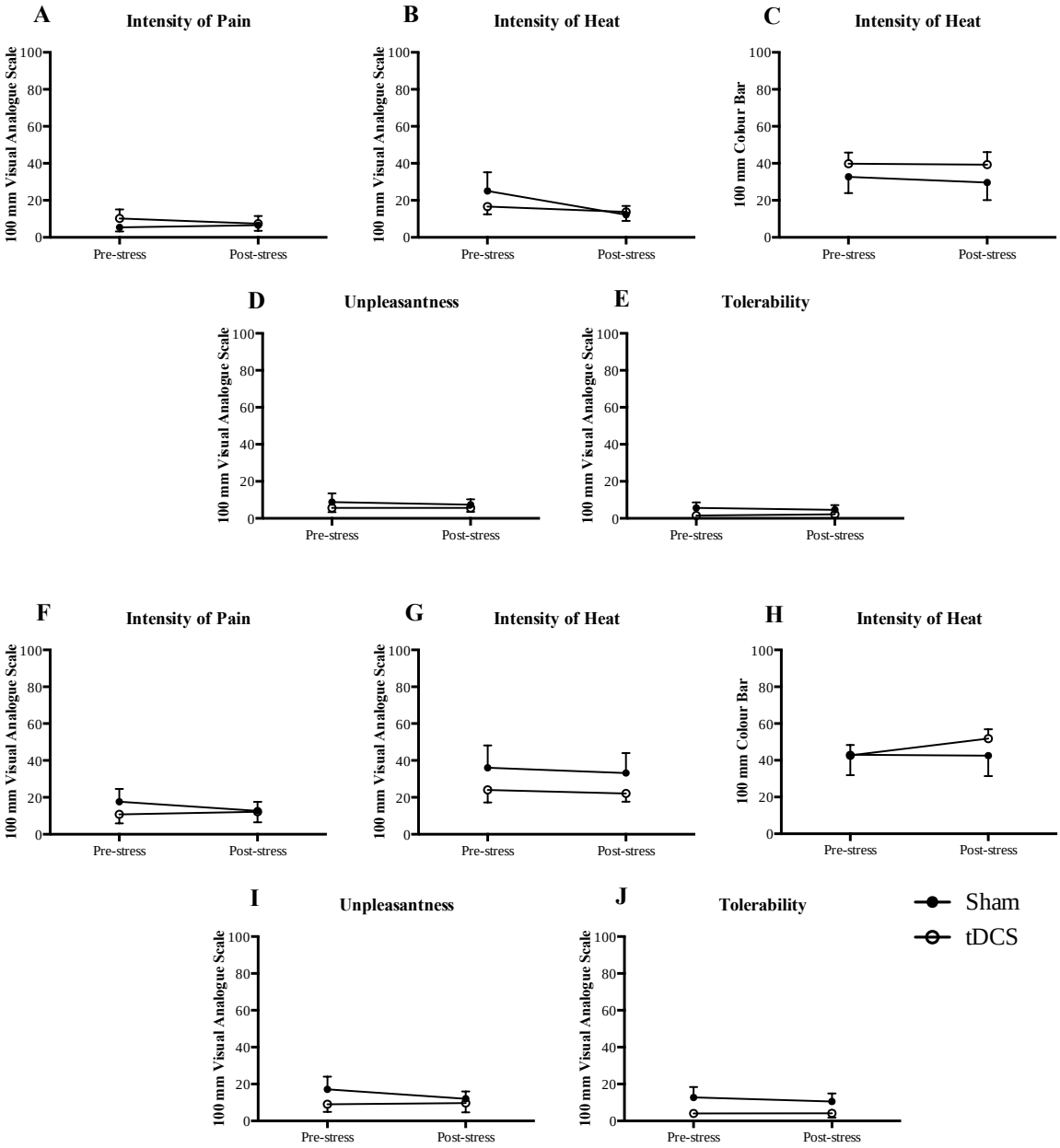
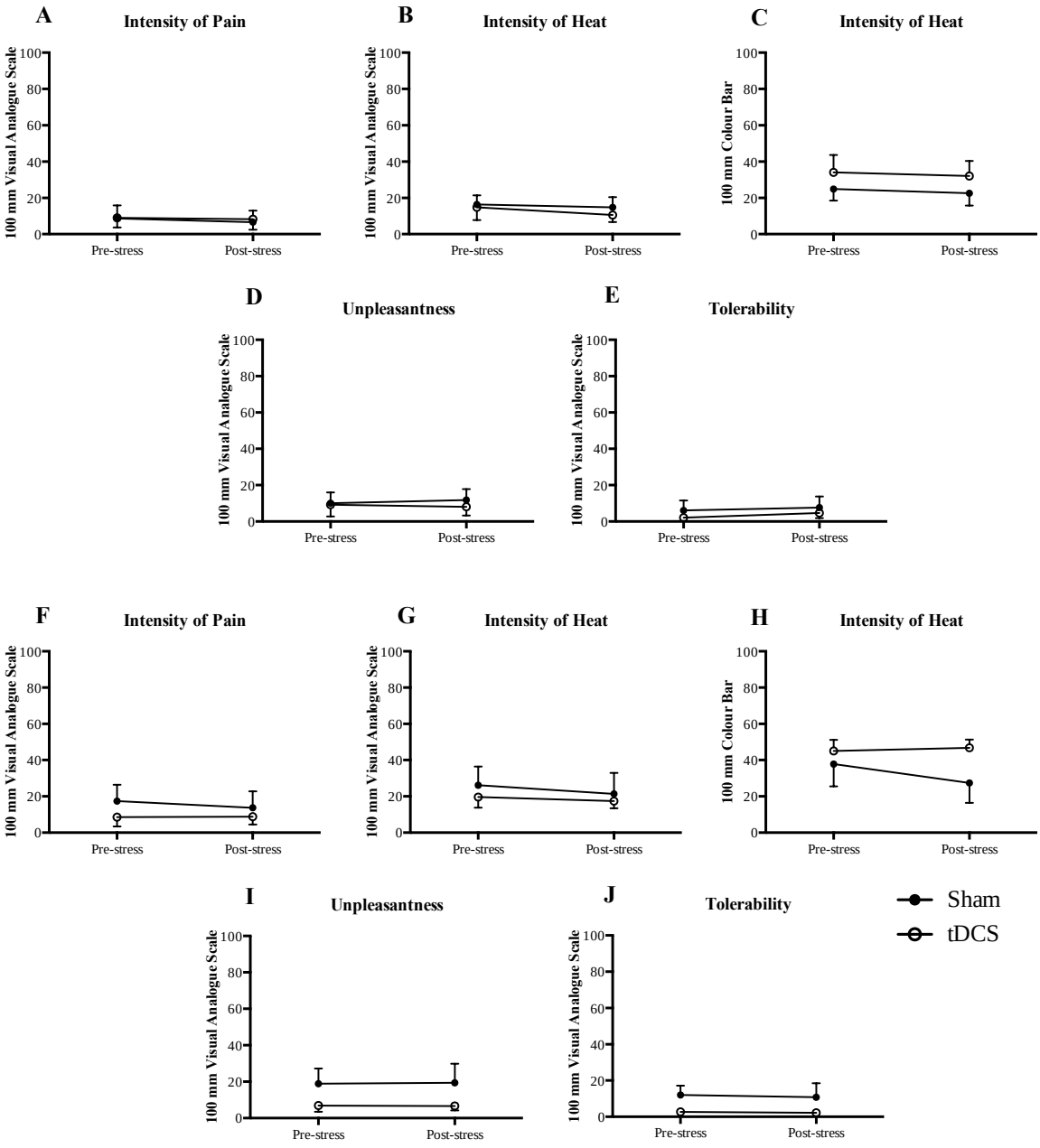


Figure 11.6.12. Response to tDCS (pre- to post-stressful mental task): thermal grill response.

Response to the thermal grill illusion at the right palm pre- and post-stressful mental task in patients assigned to the sham and tDCS treatment groups at the 22/38 ºC (A-E) and 18/42 ºC (F-J) thermal grill configurations. Comparing the tDCS and sham groups, no significant differences were observed for all thermal grill outcomes at the 22/38 ºC (A-E) and 18/42 ºC (F-J) thermal grill configurations. Graphs are represented as mean ± SEM.


A
Intensity of Pain
100 mm Visual Analogue Scale
B
Intensity of Heat
100 mm Visual Analogue Scale
C
Intensity of Heat
100 mm Colour Bar
D
Unpleasantness
100 mm Visual Analogue Scale
E
Tolerability
100 mm Visual Analogue Scale
F
Intensity of Pain
100 mm Visual Analogue Scale
G
Intensity of Heat
100 mm Visual Analogue Scale
H
Intensity of Heat
100 mm Colour Bar
I
Unpleasantness
100 mm Visual Analogue Scale
J
Tolerability
100 mm Visual Analogue Scale
Pre-stress
Post-stress
Sham
tDCS

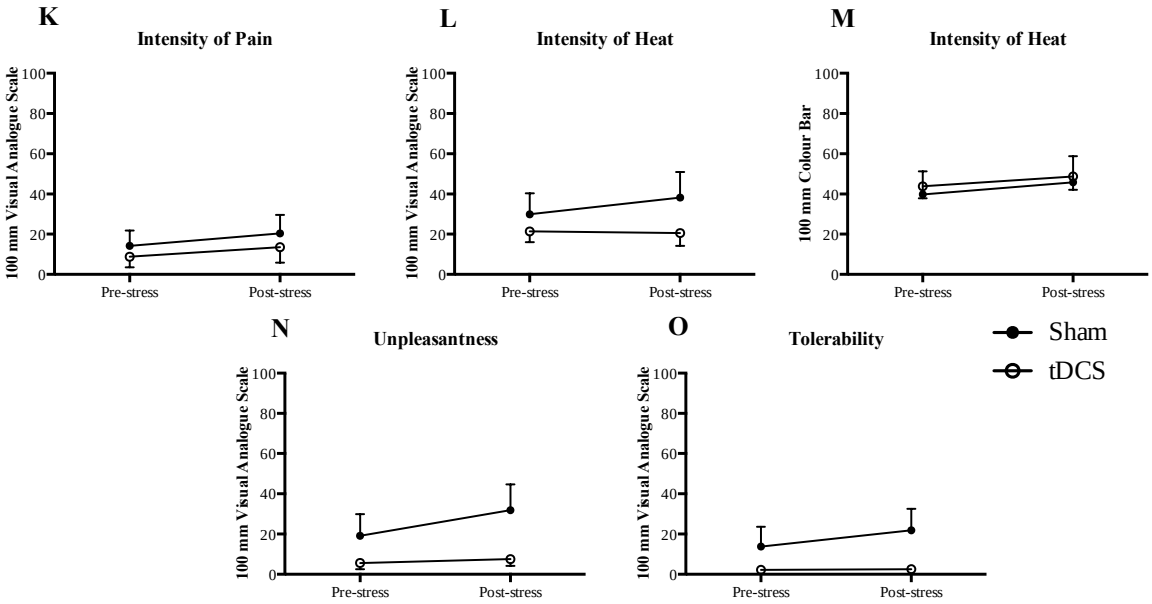
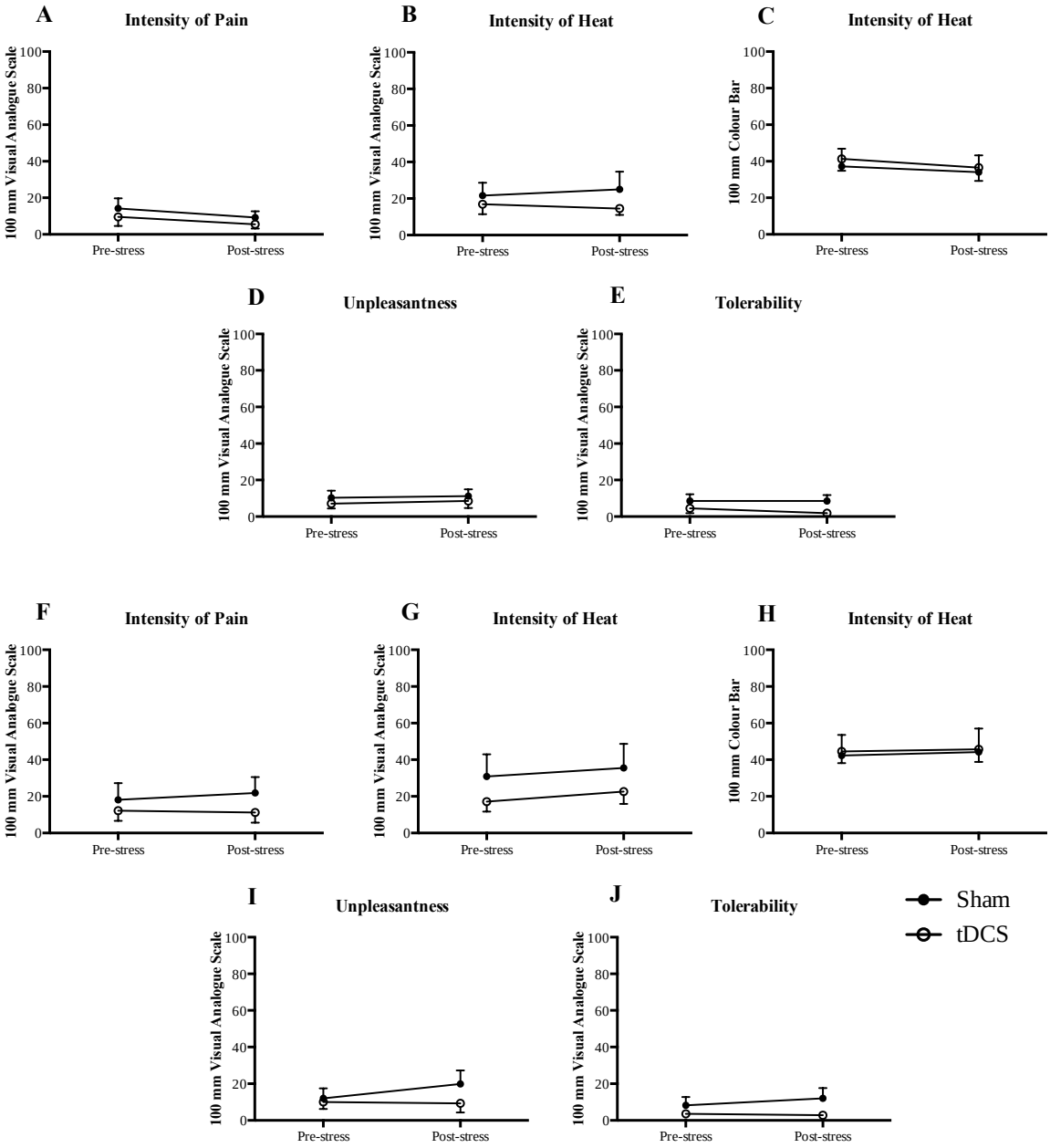


Figure 11.6.13. Response to tDCS (pre- to post-stressful mental task): thermal grill response.

Response to the thermal grill illusion at the left cheek pre- and post-stressful mental task in patients assigned to the sham and tDCS treatment groups at the 22/38 ºC (A-E), 20/40 ºC (F-J) and 18/42 ºC (K-O) thermal grill configurations. Comparing the tDCS and sham groups, no significant differences were observed for all thermal grill outcomes at the 22/38 ºC (A-E), 20/40 ºC (F-J) and 18/42 ºC (K-O) thermal grill configurations. Graphs are represented as mean ± SEM.


A
Intensity of Pain
100 mm Visual Analogue Scale
B
Intensity of Heat
100 mm Visual Analogue Scale
C
Intensity of Heat
100 mm Colour Bar
D
Unpleasantness
100 mm Visual Analogue Scale
E
Tolerability
100 mm Visual Analogue Scale
F
Intensity of Pain
100 mm Visual Analogue Scale
G
Intensity of Heat
100 mm Visual Analogue Scale
H
Intensity of Heat
100 mm Colour Bar
I
Unpleasantness
100 mm Visual Analogue Scale
J
Tolerability
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0
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40
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Pre-stress
Post-stress
Sham
tDCS

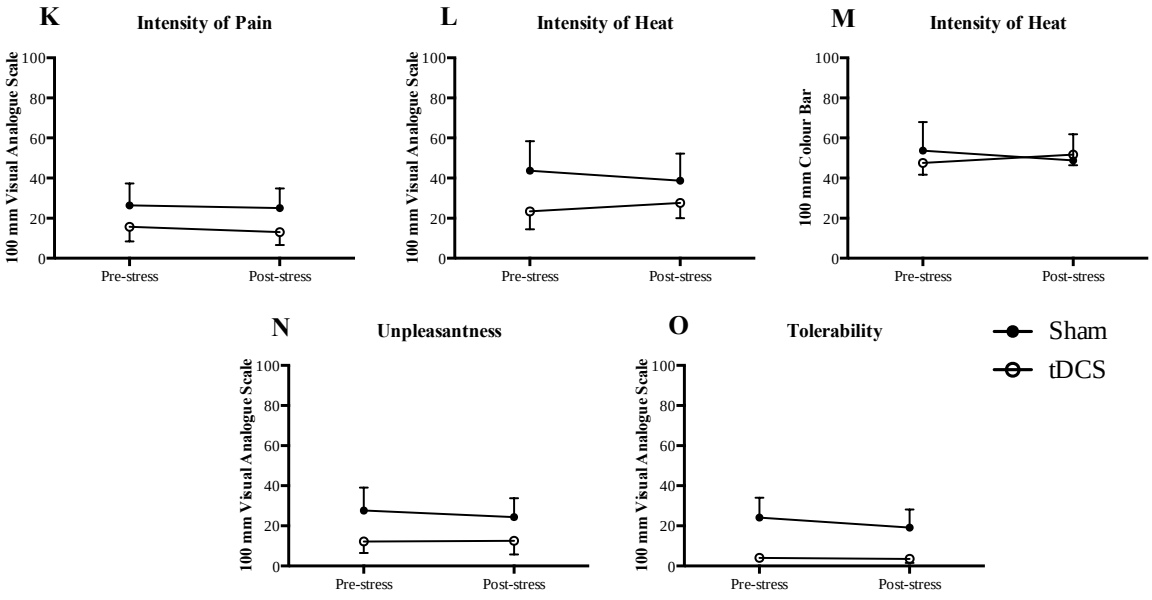

Figure 11.6.14. Response to tDCS (pre- to post-stressful mental task): thermal grill response.

Response to the thermal grill illusion at the left palm pre- and post-stressful mental task in patients assigned to the sham and tDCS treatment groups at the 22/38 ºC (A-E), 20/40 ºC (F-J) and 18/42 ºC (K-O) thermal grill configurations. Comparing the tDCS and sham groups, no significant differences were observed for all thermal grill outcomes at the 22/38 ºC (A-E), 20/40 ºC (F-J) and 18/42 ºC (K-O) thermal grill configurations. Graphs are represented as mean ± SEM.

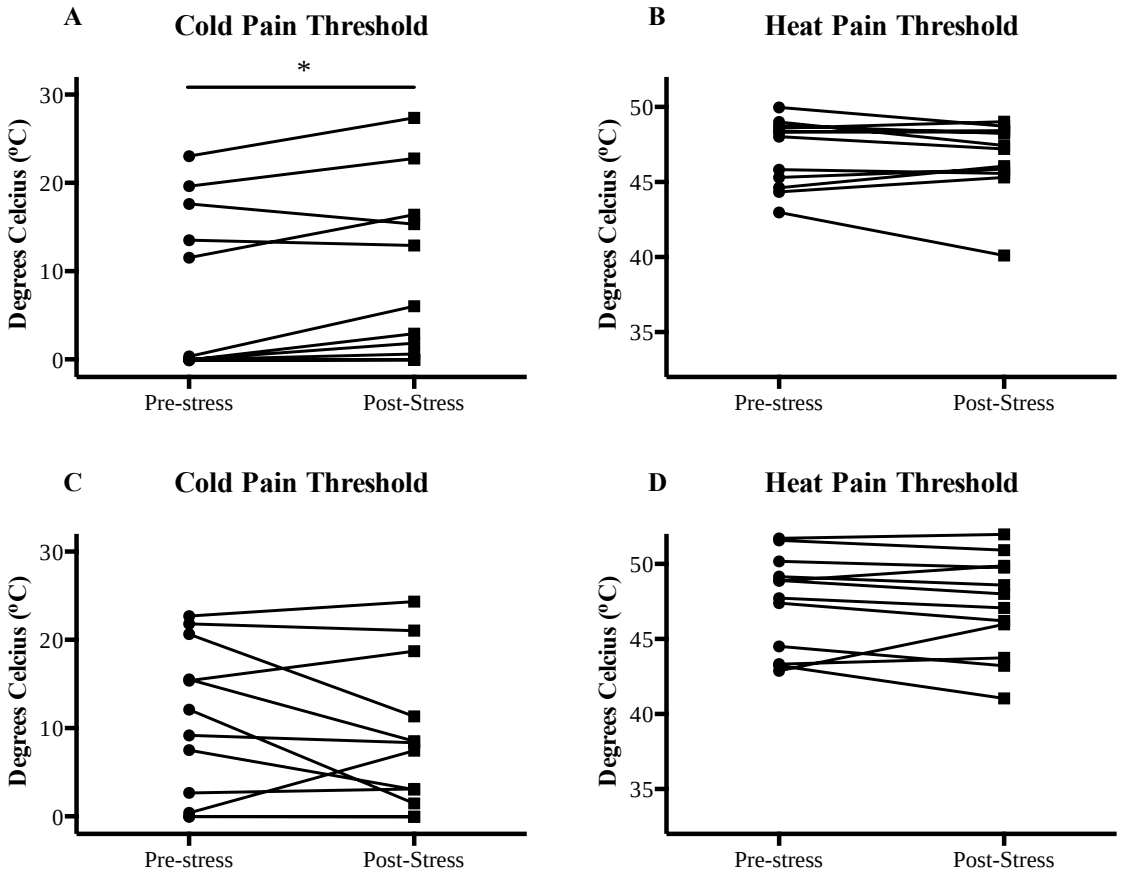

Figure 11.6.15. Effect of stressful mental task: cold and heat pain thresholds

Cold and heat pain thresholds at the left cheek (A, B) and palm (C, D) pre- and post-stressful mental task in all patients (tDCS and sham groups combined). Post-stressful mental task, cold pain thresholds were significantly increased (i.e. more sensitive) at the left cheek (A)(mean difference: 1.3 ºC, 95% CI for difference: 0.2 ºC to 3.3 ºC). Cold pain thresholds did not differ pre- to post-stressful mental task on the left palm (B)($p = 0.28$) nor did heat pain thresholds at the left cheek (B)($p = 0.57$) or palm (D)($p = 0.52$). * $P < 0.05$.

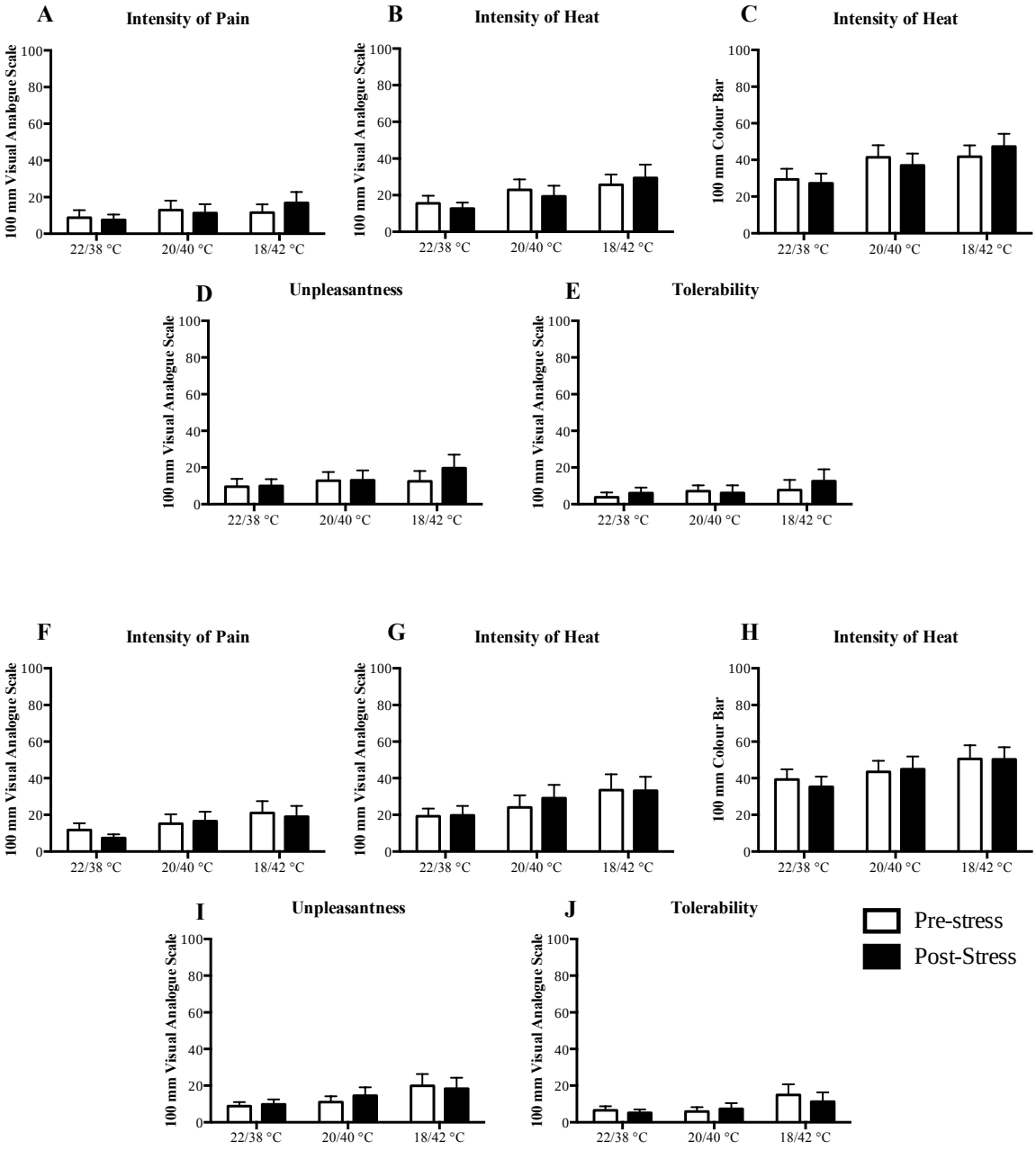

Figure 11.6.16. Effect of stressful mental task: thermal grill response

The response to the thermal grill illusion pre- and post-stressful mental task on the left cheek (A-E) and palm (F-J) in all patients (tDCS and sham groups combined). No significant differences pre- and post-stressful mental task were observed. Graphs are represented as mean ± SEM. * $P < 0.05$.

Chapter 7

Figures

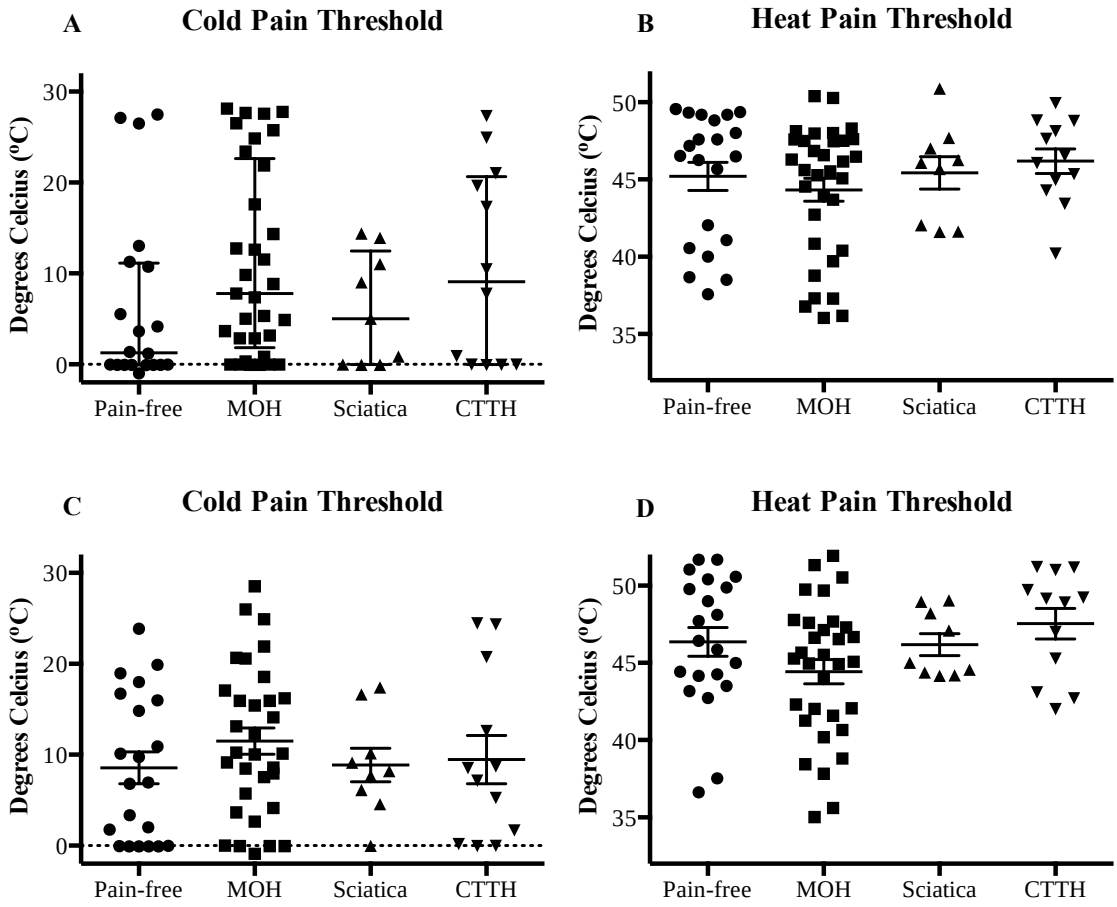

Figure 11.7.1. Cold and heat pain thresholds on the non-dominant side cheek and palm

Cold and heat pain thresholds on the non-dominant side cheek (A, B) and palm (C, D) in pain-free participants, patients with medication overuse headache, patients with sciatic pain and patients with chronic tension-type headache. Cold and heat pain thresholds did not differ on the non-dominant side cheek (A, $p = 0.503$; B, $p = 0.330$) and palm (C, $p = 0.594$; D, $p = 0.0631$). Graphs B, C and D are represented as mean ± SEM. Graph A is represented as median and interquartile range. MOH: medication overuse headache; CTTH: chronic tension-type headache.

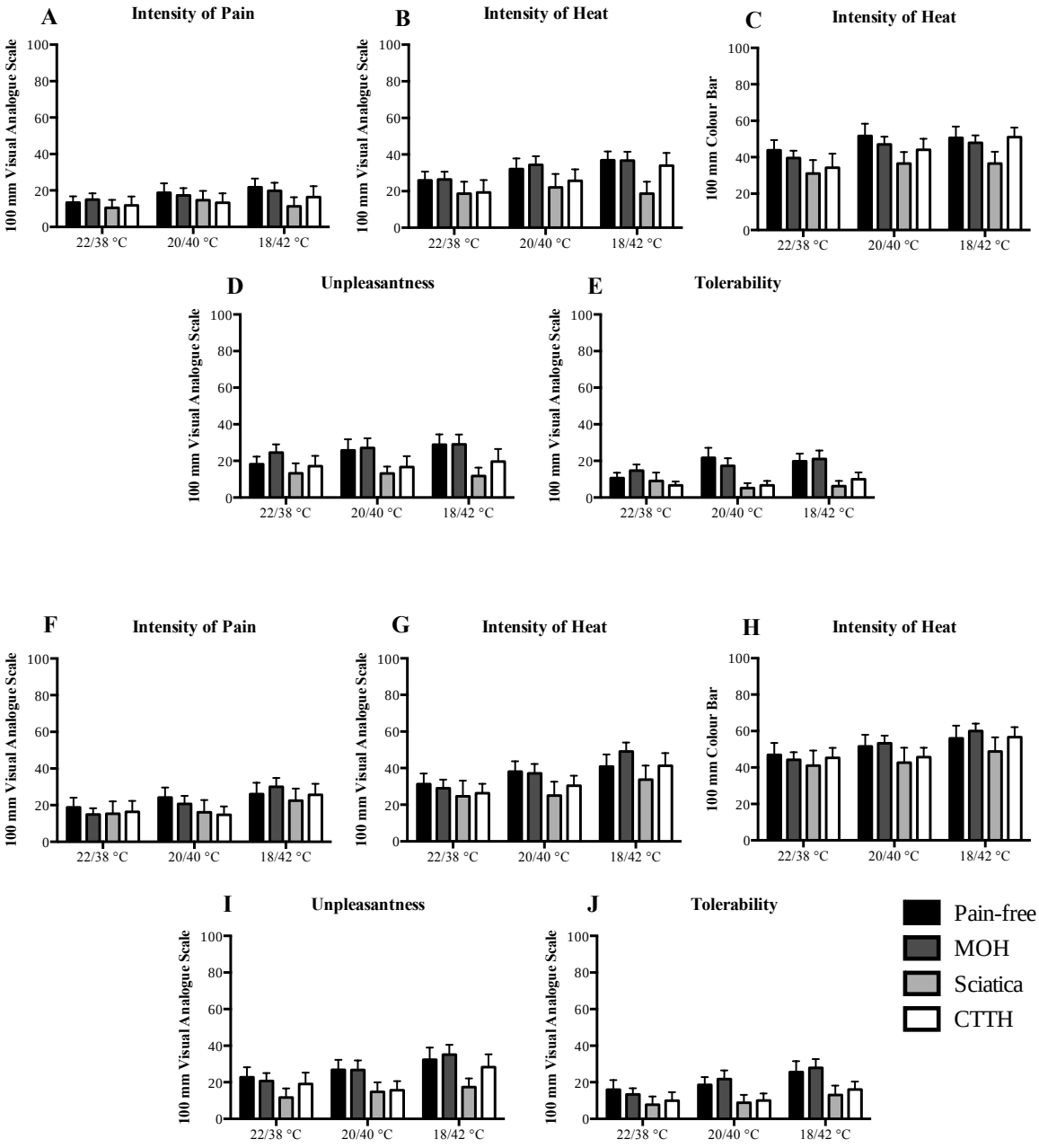

Figure 11.7.2. Response to the thermal grill illusion on the non-dominant side cheek and palm

The response to the thermal grill illusion on the non-dominant side cheek (A-E) and palm (F-J) in pain-free participants (black bars), patients with medication overuse headache (darker grey bars), patients with sciatic pain (lighter grey bars) and patients with chronic tension-type headache (white bars). The response to the thermal grill illusion did not differ on the non-dominant side cheek (A-E) or palm (F-J). Graphs are represented as mean ± SEM. MOH: medication overuse headache; CTTH: chronic tension-type headache.