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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

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Nicole M. Sumracki

Date
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## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT</td>
<td>Serotonin</td>
</tr>
<tr>
<td>5-HTT</td>
<td>Serotonin transporter</td>
</tr>
<tr>
<td>ACC</td>
<td>Anterior cingulate cortex</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>AMHs</td>
<td>A-δ mechano-heat nociceptive afferents</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>ASI</td>
<td>Anxiety severity index</td>
</tr>
<tr>
<td>BAC</td>
<td>Breath alcohol concentration</td>
</tr>
<tr>
<td>BDI-II®</td>
<td>Beck Depression Inventory®-II</td>
</tr>
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<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>C-warm</td>
<td>C-fibres responsive to warm</td>
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<tr>
<td>C2</td>
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<td>CAP</td>
<td>Capsaicin</td>
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<td>CH</td>
<td>C-fibres responsive to noxious heat</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CMH</td>
<td>C-fibres responsive to noxious mechanical and heat stimuli</td>
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<td>CMHC</td>
<td>C-fibres responsive to noxious mechanical, heat and noxious cold stimuli</td>
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<tr>
<td>COLD</td>
<td>Lamina I thermoreceptive specific cells</td>
</tr>
<tr>
<td>CPT</td>
<td>Cold pain threshold</td>
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<tr>
<td>CRPSI</td>
<td>Chronic regional pain syndrome type I</td>
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<tr>
<td>CTTH</td>
<td>Chronic tension-type headache</td>
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<tr>
<td>CU</td>
<td>Clinical unit</td>
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<tr>
<td>CWC</td>
<td>Warm stimulus flanked by two cool stimuli</td>
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<tr>
<td>EEG</td>
<td>Electroencephalography</td>
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<tr>
<td>EPT</td>
<td>Electrical pain threshold</td>
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<td>F</td>
<td>Female</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
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<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
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<tr>
<td>HADS</td>
<td>Hospital anxiety and depression scale</td>
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<tr>
<td>HADS-A</td>
<td>Hospital anxiety and depression scale (anxiety)</td>
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<tr>
<td>HADS-D</td>
<td>Hospital anxiety and depression scale (depression)</td>
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<tr>
<td>Hep C</td>
<td>Hepatitis C</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>HPA</td>
<td>Hypothalamo-pituitary-adrenal</td>
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<td>HPC</td>
<td>Lamina I multimodal cells</td>
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<tr>
<td>i.d.</td>
<td>Intradermal</td>
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<td>IQR</td>
<td>Interquartile range</td>
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<td>LFTs</td>
<td>Liver functions tests</td>
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<td>M</td>
<td>Male</td>
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<td>mA</td>
<td>Milliampere</td>
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<tr>
<td>MDD</td>
<td>Major depressive disorder</td>
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<td>MDvc</td>
<td>Ventral caudal medial dorsal nucleus</td>
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<tr>
<td>MOH</td>
<td>Medication overuse headache</td>
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<tr>
<td>MS</td>
<td>Multiple sclerosis</td>
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<tr>
<td>NNT</td>
<td>Number needed to treat</td>
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<td>NRS</td>
<td>Numerical rating scale</td>
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<td>NSAIDs</td>
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<td>°C</td>
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<td>OIH</td>
<td>Opioid induced hyperalgesia</td>
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<td>PARC</td>
<td>Pain and anaesthesia research clinic</td>
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<td>PET</td>
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<td>QST</td>
<td>Quantitative sensory testing</td>
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<td>Spearman</td>
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<td>S1</td>
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<tr>
<td>S2</td>
<td>Secondary somatosensory cortex</td>
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<td>Symptom checklist-90-R</td>
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<td>SD</td>
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<td>SMT</td>
<td>Spinomesencephalic</td>
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<td>SRT</td>
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<td>STAI-T</td>
<td>State trait anxiety index (trait)</td>
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<td>tDCS</td>
<td>Transcranial direct current stimulation</td>
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<tr>
<td>TG</td>
<td>Thermal grill</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>TGI</td>
<td>Thermal grill illusion</td>
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<td>Transient receptor potential vanilloid 4</td>
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<td>Visual analogue scale</td>
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<td>VMpo</td>
<td>Posterior aspects of ventral medial nucleus</td>
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<tr>
<td>VP</td>
<td>Ventral posterior nucleus</td>
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<tr>
<td>VPI</td>
<td>Ventro-posterior-inferior nuclei</td>
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<td>VPL</td>
<td>Ventro-posterior-medial thalamic nuclei</td>
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<tr>
<td>WARM</td>
<td>Lamina I warm cells</td>
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<tr>
<td>WCW</td>
<td>Cool stimulus flanked by two warm stimuli</td>
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<tr>
<td>β-CD</td>
<td>Hydroxypropyl-β-cyclodextrin</td>
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