Do patterns matter?

Inspecting the patterns containing majority of cold or warm bars in TGI research

Patrik Molnar (202104687@post.au.dk)

Perception & Action – 3rd semester BSc. Cognitive Science

Aarhus University

Abstract

Sample: n=9 (f=55%), Age_m= 21.6, Age_{SD}=1.6

The thermal grill illusion causes an illusionary perception of heat or pain when in reality the temperatures used in the experiment are innocuous. It is still unclear what causes this phenomenon and most of the studies produce conflicting results about neuromechanics. However, as described later in this paper, a great amount of research suggests that due to neurophysiology of thermal perception, cold and warm stimuli might be perceived differently. This raises a question; Is there a possibility of getting different results in TGI research when utilising thermal grill devices configured with different patterns having majority of cold bars or majority of warm bars?

Keywords: TGI, Illusionary pain, TCS, QST, bar patterns

AARHUS UNIVERSITY

Table of Contents

Introduction

Note

At the outset, it is important to ensure that the terminology is understood correctly. Francesca Fardo, PhD. noted in the research on population coding of TGI (2018)[1] that the term "TGI" is often an unreliable terminology for the observed effects in this field of research. She argued that it encompasses a range of concepts such as warm/cold illusions, innocuous reactions, and other concepts, and thus may lead to misunderstanding or confusion. Hence, she proposed the use of the terms “illusionary pain” or ”illusionary heat” (depending on the measured effect), in order to reduce the risk of misunderstanding of the studied effects. This paper acknowledges that and follows this important note.

Thermal Grill Illusion

Thermal Grill Illusion (TGI) is a popular phenomenon that has been studied since the late 19th century. One of the first documented research was done by Thorsten Thunberg in 1896. He found that when the skin was exposed to steady temperatures that differentiate enough, the subject perceived an illusionary pain or noxious heat[2]. Simply said, when the two temperatures cold and warm were presented together, an “illusion of pain/heat” occured.

Since then, dozens of studies have been conducted to explore the phenomenon, focusing on various aspects such as the factors affecting the magnitude of the illusion, the effects of varying temperatures or the neuromechanics causing the illusion (Bouhassira et al., 2005; Craig & Bushnell, 1994; Adam et al., 2014; Fardo et al., 2020, among others)[3456].

This phenomenon is of particular interest because neither of the two stimuli is noxious in isolation, yet the thermal-nociceptive illusion is evoked when combined. By investigating how the nervous system processes and responds to TGI stimuli, researchers believe they can better understand how to target and manipulate the pathways involved in the transmission of pain signals (Craig, A. D. in 2008)[7]. Other studies suggest that investigating and analysing TGI may provide insight into the underlying mechanisms and processes associated with neuropathic pain (Raafat, K., & Hdaib, F., 2017)[8] or spinal inhibitory network disinhibition of pain (Osumi, Michihiro, et al. 2022)[9]. Some research even suggests improving diagnostic accuracy in MS patients, as well as the possibility of optimising pain management (Rivel, Michal, et al. 2022)[10].

Devices used to inspect this illusion

Based on the extensive review of the thermal grill devices by Fardo, F., Finnerup, N. B., & Haggard, P. (2018)[11], it was easy to summarize the review of the thermal grill devices in the following paragraph.

Studies have employed thermal grill devices to induce TGI sensations with different patterns of alternating bars, hence the term "grill illusion" (Bouhassira et al., 2005; Craig and Bushnell, 1994; Leung et al., 2005; Harper and Hollins, 2014 2014)[12 13 14 15 16].

Alternatively, other devices have been used such as alternating cold and warm spiral tubes (Bach et al., 2011; Thunberg, 1896)[17 18], warm-cold-warm patterns using three probes (Kammers et al., 2010; Marotta et al., 2015)[19 20], or one single cold and one single warm probes. Some research even inspected the effect at large distances between the stimulated area (Defrin et al., 2008; Fardo et al., 2018)[21 22].

As Craig, A. D., 2008[23] noted, inspecting the TGI-related processes is a great way to gain a deeper understanding of neuropathic pains or pain in general. Prior to the development of modern devices, "handcrafted/hobby" methods made it challenging to replicate the studies or follow up in the research.

Currently we possess better devices to inspect the illusions, such as the TCS by QST.lab or other manufacturers, which will hopefully bring a bit more unification of methods in the future and a way to replicate the studies under the same conditions. Conversely, since these devices permit the adjustment of the patterns of presenting the stimuli, it is essential to evaluate how different patterns affect the illusion.

Research on patterns in Thermal Grill Devices

There has been limited research into the effect of various patterns on stimuli. However, Li et al. (2009)[24] conducted an important study in this area which created a solid ground for further research using TGI devices.

They aimed to investigate the importance of stimulus parameters (distance between, and number of stimulation bars) in determining its effect on the experience of the TGI. They compared different patterns of alterating bars but concluded that there is no significance difference among them and their effect on the TGI perception. The distance and number of stimulation bars were not important to the sensation of TGI. These results are useful for future TGI studies with respect to experimental design.

However, the study did not consider the effect of two identical conditions where an odd amount of the bars is presented only differentianing in the amount of cold or warm bars presented.

Why there might be a different effect of patterns containing majority of cold or warm bars?

Li et al. (2009) identified that the intensity of the thermal grill illusion increased when the temperature of the stimulus was lowered, suggesting that cold temperatures may be more likely to evoke the illusionary pain. That generated a valid thought whether there couldn't be an effect of the majority of either warm or cold bars on the intensity of the illusionary pain.

Hence, I decided to review the literature discussing the individual influence of cold and warmth on the illusion.

Fardo et al. (2020)[25] conducted a study with an extensive summary of the theories that are thought to cause the illusionary pain elicited by TGI including inhibition theory, the disinhibition theory and subsequently they propose framework of population coding.

They introduced a review of studies that have suggested the perception of cold, warmth, and pain may be mediated by fibers with different amounts of myelination. Thinly myelinated Aδ-fibers are thought to be primarily responsible for innocuous cold sensations, while C-fibers, which are unmyelinated, are thought to be primarily responsible for warm and burning pain sensations. They referred to previous authors suggesting that Aδ-fibers (cold fibers) may inhibit C-fibers (pain fibers). That would suggest that the warm stimuli should modulate the illusion more than cold.

On the other hand, in the section describing the disinhibition theory, they introduce an assumption that cold inhibits pain at a thalamo-cortical level through inhibitory effect of Aδ-

fibers on C-fibers. This assumption was based on Craig and Bushnell (1994)[26] where they indicated that the decrease in inhibition elicited by the heat nociceptors thermoreceptive-specific cells channels expose the cold-sensitive activity of the “heat, pinch, and cold” channel. The “heat, pinch, and cold” often occurs in the illusionary pain perception. Furthermore, the study suggests that the intensity of the thermal grill illusion is greater when the temperature of the stimulus is lower, as lower temperatures may result in more intense activation of the unmyelinated C-fibers.
They hypothesized that based on these findings, there is a specific effect of cold on the TGI induced pain.

There are numerous studies that focus on the effect of temperature stimuli and the processing on the neurophysiological level; however, due to the character limit and my limited knowledge of neuroscience, I will proceed to the following section of this paper and took the previously presented knowledge as sufficient to support my hypothesis.
Nonetheless, it is safe to say that the theory is ununified, which makes difficult to set reliable design for the future studies without examining the possibility of warmth/called influence in different patterns.

Spatial summation and Lateral inhibition

There is ongoing research on how spatial summation and lateral inhibition may influence the perception of the TGI induced illusionary pain. Fardo, F., Finnerup, N. B., & Haggard, P. (2018)[27] suggested that some of the perception processes are dependent on the single spinal segment and it’s proximal areas, which supports the possibility that there may be an effect of what temperature is used in patterns in TGI research as majority.
For better understanding of these concepts, I will offer a brief overview; however, due to my limited knowledge in the field of neuroscience, I will not make any advanced conjectures. Nonetheless it is important to acknowledge that these processes might have an influence on perception of the TGI.
Lateral inhibition is described as “a proccess in which a neuron’s response to a stimulus is inhibited by the excitation of a neighboring neuron” (Bakshi, A., & Ghosh, K., 2017)[28]. This means that the effect of the TGI can be influenced by stimulated area or possibly, as later

hypothesized, by the pattern of presented stimulus due to the excitement of the adjacent neurons.

"Spatial summation is one important characteristic, whereby increasing area of a stimulus, or distance between multiple stimuli, results in more intense pain—not only greater area of pain" as cited in paper by Holbert, Maleea D., et al., (2017)[29].

Methodological and theoretical aspects

A major challenge in advancing research in this field is the lack of uniformity in methods and the narrow focus of many studies on isolated components of the illusion or specific contributory factors. Consequently, it is not even certain, and there is no agreement, if the illusion is created spinally, supraspinally, or from both.

This paper, along with the research by Craig et al., (1994)[30] and others, attempts to take into consideration the neurophysiological aspects that different nerve fibers perceive different temperatures and inspects the methodological consequences. The findings of this paper hopefully provide more understanding in the methodologies of TGI devices. Specifically, whether there is a chance that human neurophysiology influence perception of the illusion when choosing multiple patterns containing majority of warm or cold bars.

Summary

The previously discussed knowledge suggests that the various processes underlying the perception of the TGI may interact with the illusion and shape it. Even though the theory is not yet unified and the mechanisms causing this illusion remain unclear, it is plausible that the majority of cold or warmth bars in the presented pattern will have a different effect on the perception of this illusion.

Hypothesis

I hypothesize that the perception of illusionary pain induced by the thermal grill illusion will be affected by the presence of a majority of either cold or warm bars.

H_0: *There is no difference in ratings of burning between a pattern containing a majority of cold bars and a pattern containing a majority of warm bars.*

H_1: *There is a difference in ratings of burning between a pattern containing a majority of cold bars and a pattern containing a majority of warm bars.*

Methods

Subjects:

A total number of 10 participants took place in this experiment with the mean age of 21.6 and SD of 1.6. All the participants were healthy individuals without any skin or pain related health conditions. All declined any use of pain medication. Participants were connected to either Cognitive Science or Center of Functionally Integrative Neuroscience, as required by the head examiner and program director Joshua Skews, PhD., due to the pain-related nature of this research. Only left forearms had been used to receive stimulations. Right hands were used to answer. No monetary compensation was received by participants.

Conditions:

Choice of temperatures

One aspect of the illusion that has been studied extensively is the temperature of the stimuli needed to produce the illusionary heat or pain. It was first observed by Alrutz, S in 1898[31], that an approximate temperature of 20 and 40 degrees Celsius could elicit the illusion. Subsequent studies (Leung, Albert Y., et al. 2005, Harper, D. E., & Hollins, M. (2017), Bouhassira, Didier, et al., 2005)[32][33][34] have continued in inspection of the different temperature combinations. Research agreed that small variations of 10-15 °C can create the feeling of "illusory heat", while larger discrepancies of 20 °C and more are needed to generate "illusory pain" sensations (precisely 21.5 ± 5.5 in the large study examining the temperatures by Adam, Frédéric, et al., 2014)[35].

Based on the knowledge gained from the literature review, the in-depth research of studies focused on the illusionary pain and guidance provided from the BPP lab, CFIN, Aarhus, I chose to use 20°C as a cold stimulus and 40°C as a warm stimulus. The temperature of 30°C was chosen based on Fardo, F., Finnerup, N. B., & Haggard, P. (2018)[36] as baselines for controls, in order to maintain consistency with other research in the BPP lab as well as general research on TGI.

Pattern of the conditions

In order to test the hypothesis, I presented 4 conditions of the patterns using the QST probe. The patterns were chosen to contain majority of either cold or warm temperatures as well as cold and warm control. For better understanding *Figure 1.* visualizes all the below mentioned conditions.

To make the description of the patterns easier, the following system will be used:
c=cold, w=warm, b=baseline

Condition #1 – *c-b-c-b-c* – this condition was used as a control in order to inspect how the participants perceived the cold stimuli accompanied by baseline

Condition #2 – *c-w-c-w-c* – this condition was used to measure and inspect the effect of majority of cold bars and its effect on perception

Condition #3 – *w-b-w-b-w* – this condition inspected how the participants perceived the warm stimuli accompanied by baseline

Condition #4 – *w-c-w-c-w* - this condition was used to inspect and measure the effect of majority of warm bars and its effect on perception

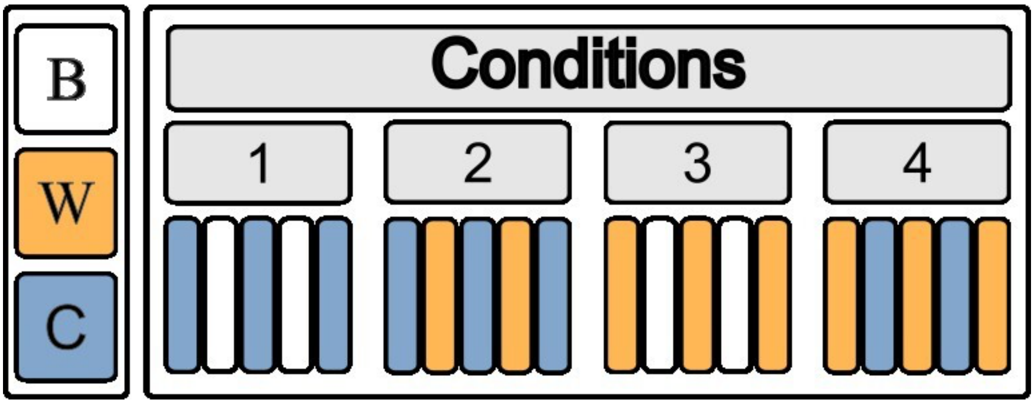

Figure 1 - patterns

Procedure:

The concepts of burning

In my research on “illusionary pain”, I chose to use the word "burning" to describe the sensation created by the illusion instead of the word "pain". This is because the perception of the illusion is not strictly a physical pain, but rather a perception modulated by the uncovered processes in our neurophysiology. By using the word "burning" instead of "pain," I was able to more accurately describe the sensation without implying physical pain.

Hardware and Software

All of the trials took place in an allocated room in the CFIN South, Aarhus during the week 51 of 2022. Only one participant was tested at a time. The same equipment has been used throughout the experiment, specifically TCS II device and T06 probe both by QST.Lab Strasbourg. Each zone of the probe is 7 x 28mm, a total stimulation surface of $10cm^2$. The internal ideentification of the TCS device and the T06 probe was for both “T06 #2”. The paradigm ran on Lenovo ThinkPad with internal identification “ECG lab”. The probe was placed next to participants always from the left side. Three different locations on the forearm were stimulated to account for varying perception and sensitivity in different skin areas. The trials were divided evenly among the 3 locations and paradigm was programmed to notify the participant automatically to move the probe to the following location.
The paradigm was coded using python (version 3.8) and Psychtoolbox-3, the script was based on the previous work of the assigned supervisor PhD student Camilla Eva Andersen.

Paradigm

Participants were first familiarised with the task and with the position that needed to be maintained throughout the experiment. The stimulation areas were marked by a marker. One of the 4 conditions was randomly presented, and participants were asked to respond to the 3 following questions:

1.) **Cold or Warm** – this question inspected whether the presented stimulus was perceived as a cold or warm one. Arrows on a keyboard were used to record the answer.

2.) **How cold/warm did it feel?** – depending on the previous answer, participants were asked to rate how cold/warm the stimulus was. Participants answered on a VAS using mouse to allow them for the most precise answer.

3.) **How much burning did you experience?** – this question inspected how burning the stimulus was. As previously explained, the concept of "burning" is used to inspect the illusionary pain created by the TGI illusion. Participants answered on a VAS using mouse to allow them for the most precise answer.

The *Figure 2* visualize the whole paradigm process.

Divided in 5 blocks with breaks depending on the participants decision. Over 1400 observations were collected. The whole experiment took roughly 15 to 25 minutes depending on the participant's ability to understand the the "burning" concept, the speed of answering and the total number of breaks.

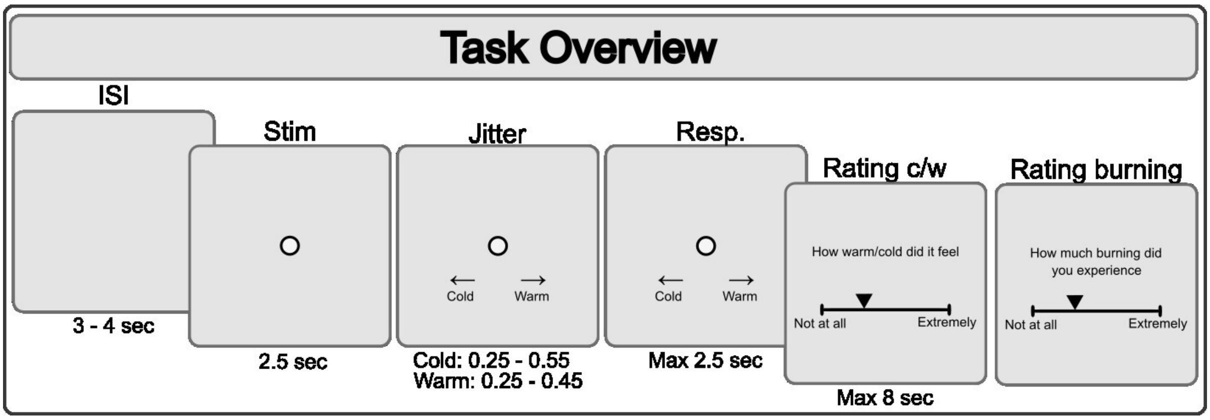

Figure 2 - paradigm

Analysis

I chose to use zero-inflated beta distribution modelling to analyse the collected data, because it was an appropriate choice for dataset with a dependent variable measured on a scale with high expectation of answers containing zero as well as the expectation that the distribution will hardly follow normal distribution. This decision was made based on Tang, Becky, et al. (2022)[37] and the recommendation of the BPP lab members.

The data analysis was conducted in R (R Core Team, 2020)[38] using following packages: tidyverse(Wickham, H., 2017)[39], brms (Bürkner, P.-C., 2017)[40], glmmTB(Bates, D., Maechler, M., Bolker, B., & Walker, S., 2015)[41] and zoib (Dey, D.K., & Choudhury, D., 2019)[42]

Variables used to model

Manipulation – This variable measured whether the presented condition was TGI or Control.
Quality – This variable measured whether the presented stimulus contained majority of cold or warm bars.

Modeling these variables and their interaction allowed me to model in a way where I could see the interaction of the different condition without having to present the variable of "Configuration" where I would have to face factor variable with four levels due to 4 configurations of the bar patterns.
Ratings – This variable measured the intensity of ratings of how cold/warm the presented stimulus was. Collected through VAS.
Burning ratings – This variable measured the rating intensity of the presented stimuli for burning. Collected through VAS.

Analysis framework

First, I uploaded the data into R using the read_tsv() function and combined them into a single data frame. I cleaned the data and removed NAs to ensure that the dataset doesn't contain any unnecessary variables and datapoints that could influence the following analysis in a negative way.
The variable Manipulation was converted to a factor, as well as the variable Quality.

Both ratings of temperature and burning were scaled by a simple arithmetics where the 100 ratings in the Rating_Burn column were assigned a value of 0.9999 and afterwards the whole variable was scaled to a range of 0 – 1. This has been done due to the chosen way of modelling, since zero inflation does not deal with 100 ratings too good, therefore it is a common practice to avoid using values of 100 (or 1 after the conversation).

A boxplot was constructed to visually inspect the data, followed by using the glmmTMB() function to model the data. The function was chosen due to its ability to include zero inflated modelling using beta distribution.
The following model was used:

Burning ratings ~ Manipulation *Quality+ (1|ID)

The model is examining the interaction effect of Manipulation and Quality on ratings of burning and allowing individual intercept.

Results

The model showed that the burning ratings are significantly predicted by the Manipulation condition, which of course, was expected as the illusionary pain was induced by design with well-researched temperatures.

For Control: $\beta = -1.61481$, $SE = 0.24274$, z-value = -6.652, $p < 0.01$,
For TGI: $\beta = 0.980450$, $SE = 0.088941$, z-value =11.024, $p < 0.01$.

However, the configuration of the bars modeled using Manipulation*Quality hadn't significant effect on burning ratings with crossing the p-value threshold of .05. In order to follow good science manners, I refrain from making any assumptions about the results, however I propose options in the discussions. The visual inspection supports the statistical findings from the modelling quite clearly, with boxplots overlapping heavily. The area of stimulation had no significant effect on the perception either as can be seen on the *Figure 3*.

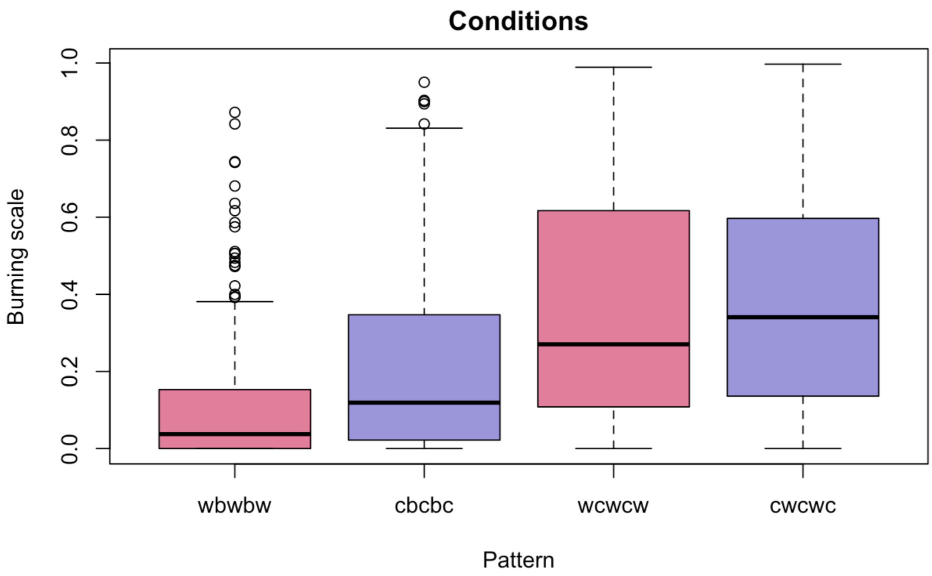

Figure 3 – VAS Burning scale ~ pattern of bars

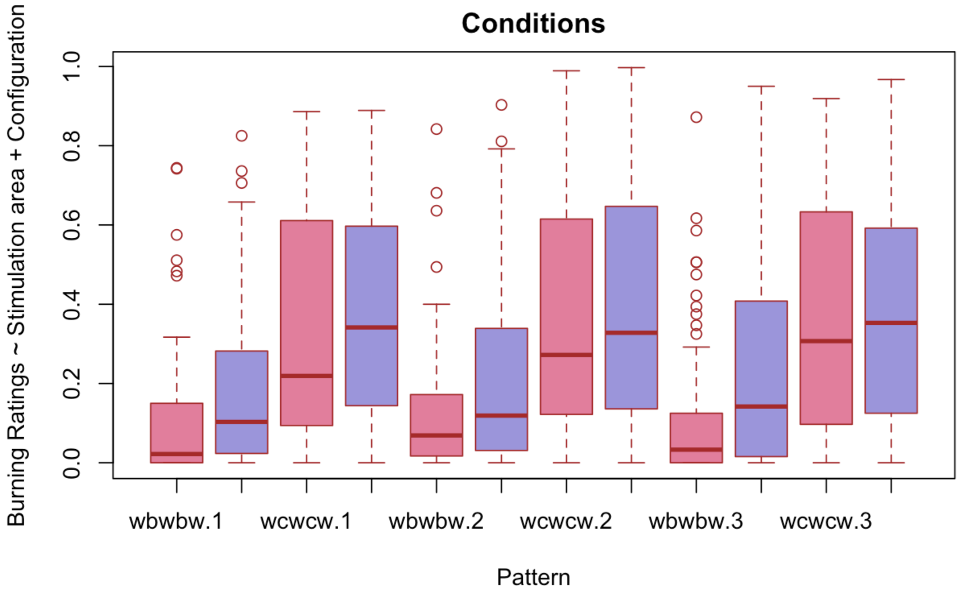

Figure 4 – VAS Ratings of burning by configuration, sorted by stimulation area – from left to right follows from the wrist to an upper forearm

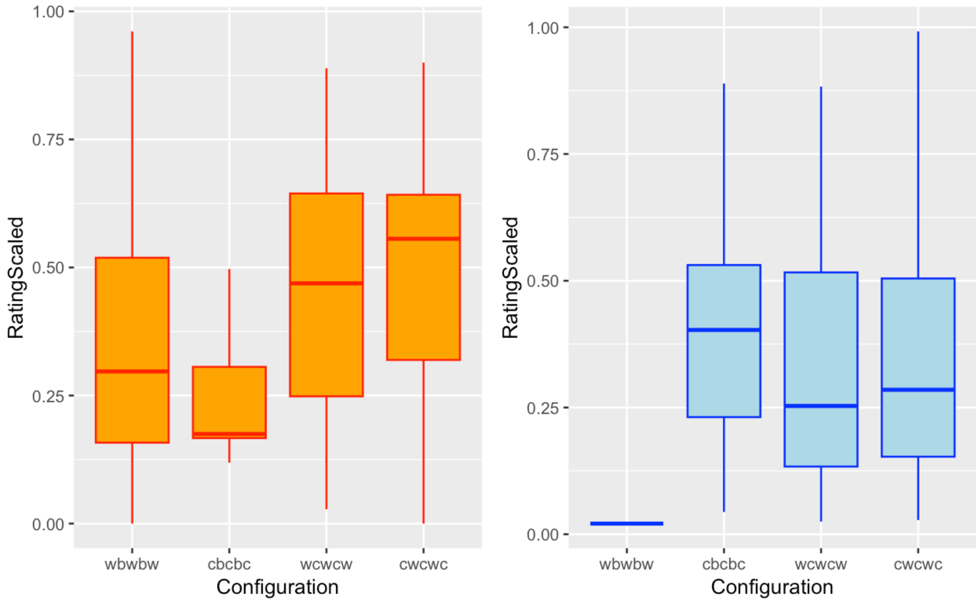

Figure 5 & 6 – VAS Ratings of warm and cold stimuli

Discussions

The modelling made clear that the patterns with a majority of either cold or warm bars have no effect on the perception of TGI. As mentioned before, in order to adhere to the standards of good science, no assumptions will be made based on the results where p-value was above the threshold due to the analysis being of a frequentist nature. However, from the Figure 3, it is apparent that, despite the baseline being set to 30 degrees with a difference of 10 degrees in both directions, cold is perceived to be colder than warm is warmer; or, at least, it is safe to say that the variance and median of *c-b-c-b-c* suggest this to be the case.

When inspecting the data, the model output, or the visual plotting, questions arise as to whether a Bayesian framework of modeling could be adopted in order to analyze the collected data and make assumptions based on inverted conditional probability rather than frequentist inference. Nonetheless, the scope of this paper and my knowledge does not currently allow that.

A larger sample size would also be needed in order to achieve precise results due to the multiple outlying ratings that seem to be either a mistake or the result of participants losing interest. The small dataset did not allow for the data to be cleaned extensively or to infere any pattern of outliers.

Visually inspecting Figure 4 confirms the zero hypothesis even across the different stimulation areas, but it is visible that cold was scored more intensively. This observation has been verified by Francesca Fardo, PhD, in her research, whereby it has been noticed that when both stimuli are innocuous, cold sensitization and warm habituation can be observed.

The figures 5 & 6 show the ratings when only warm and only cold stimuli were chosen and their VAS intensity ratings. Observations of cold being scored more intensively can be seen as well.

Conclusion

The burning ratings were not statistically different, indicating that the presence of a majority of either cold or warm bars did not influence the perception of illusionary pain induced by the thermal grill illusion. This finding is contrary to my original hypothesis that there will be a difference in perception based on the presented pattern. These findings benefit future research, as experimental designs no longer have to be concerned with the potential of creating an unwanted effect due to the presentation of stimuli in a pattern with an odd number of bars when the thermal grill device is constructed in such a manner.

Acknowledgments

I would like to express my sincere gratitude to Camilla Eva Andersen for her invaluable knowledge and support provided during my thesis writing process, both academically and personally. I would also like to thank the BPP Lab team for making this possible.

References

[1] Fardo, F., Beck, B., Allen, M., & Finnerup, N. B. (2020). Beyond labeled lines: A population coding account of the thermal grill illusion. *Neuroscience & Biobehavioral Reviews*, *108*, 472-479.

[2] Thunberg T (1896) Förnimmelserna vid till samma ställe lokaliserad, samtidigt pågående köld-och värmeretning. Uppsala Läkfören Förh 2: 489–495.

[3] Adam, F., Alfonsi, P., Kern, D., & Bouhassira, D. (2014). Relationships between the paradoxical painful and nonpainful sensations induced by a thermal grill. PAIN®, 155(12), 2612-2617.

[4] Craig, A. D., & Bushnell, M. C. (1994). The thermal grill illusion: unmasking the burn of cold pain. *Science*, *265*(5169), 252-255.

[5] Adam, F., Alfonsi, P., Kern, D., & Bouhassira, D. (2014). Relationships between the paradoxical painful and nonpainful sensations induced by a thermal grill. *PAIN®*, *155*(12), 2612-2617.

[6] Fardo, F., Beck, B., Allen, M., & Finnerup, N. B. (2020). Beyond labeled lines: A population coding account of the thermal grill illusion. *Neuroscience & Biobehavioral Reviews*, *108*, 472-479.

[7] Craig, A. D. (2008). Can the basis for central neuropathic pain be identified by using a thermal grill?

[8] Raafat, K., & Hdaib, F. (2017). Neuroprotective effects of Moringa oleifera: Bio-guided GC-MS identification of active compounds in diabetic neuropathic pain model. Chinese journal of integrative medicine, 1-10.

[9] Osumi, M., Sumitani, M., Nobusako, S., Sato, G., & Morioka, S. (2022). Pain quality of thermal grill illusion is similar to that of central neuropathic pain rather than peripheral neuropathic pain. Scandinavian Journal of Pain, 22(1), 40-47.

[10] Rivel, M., Achiron, A., Dolev, M., Stern, Y., Zeilig, G., & Defrin, R. (2022). Unique features of central neuropathic pain in multiple sclerosis: Results of a cluster analysis. European Journal of Pain, 26(5), 1107-1122.

[11] Fardo, F., Finnerup, N. & Haggard, P. (2017). The encoding of the thermal grill illusion in the human spinal cord. Scandinavian Journal of Pain, 16(1), 171-171. https://doi.org/10.1016/j.sjpain.2017.04.022

[12] Bouhassira, D., Kern, D., Rouaud, J., Pelle-Lancien, E., & Morain, F. (2005). Investigation of the paradoxical painful sensation (‘illusion of pain’) produced by a thermal grill. Pain, 114(1-2), 160-167.

[13] Craig, A. D., & Bushnell, M. C. (1994). The thermal grill illusion: unmasking the burn of cold pain. Science, 265(5169), 252-255.

[14] Leung, A. Y., Wallace, M. S., Schulteis, G., & Yaksh, T. L. (2005). Qualitative and quantitative characterization of the thermal grill. Pain, 116(1-2), 26-32.

[15] Harper, D. E., & Hollins, M. (2014). Coolness both underlies and protects against the painfulness of the thermal grill illusion. *PAIN®*, *155*(4), 801-807.

[16] Harper, D. E., & Hollins, M. (2017). Conditioned pain modulation dampens the thermal grill illusion. *European Journal of Pain*, *21*(9), 1591-1601.

[17] Bach, P., Becker, S., Kleinböhl, D., & Hölzl, R. (2011). The thermal grill illusion and what is painful about it. Neuroscience letters, 505(1), 31-35.

[18] Thunberg T (1896) Förnimmelserna vid till samma ställe lokaliserad, samtidigt pågående köld-och värmeretning. Uppsala Läkfören Förh 2: 489–495.

[19] Kammers, M. P., de Vignemont, F., & Haggard, P. (2010). Cooling the thermal grill illusion through self-touch. Current Biology, 20(20), 1819-1822.

[20] Marotta, A., Ferrè, E. R., & Haggard, P. (2015). Transforming the thermal grill effect by crossing the fingers. Current Biology, 25(8), 1069-1073.

[21] Defrin, R., Benstein-Sheraizin, A., Bezalel, A., Mantzur, O., & Arendt-Nielsen, L. (2008). The spatial characteristics of the painful thermal grill illusion. Pain, 138(3), 577-586.

[22] Fardo, F., Finnerup, N. B., & Haggard, P. (2018). Organization of the thermal grill illusion by spinal segments. Annals of neurology, 84(3), 463-472.

[23] Craig, A. D. (2008). Can the basis for central neuropathic pain be identified by using a thermal grill?

[24] Li, X., Petrini, L., Wang, L., Defrin, R., & Arendt-Nielsen, L. (2009). The importance of stimulus parameters for the experience of the thermal grill illusion. Neurophysiologie Clinique/Clinical Neurophysiology, 39(6), 275-282.

[25] Fardo, F., Beck, B., Allen, M., & Finnerup, N. B. (2020). Beyond labeled lines: A population coding account of the thermal grill illusion. Neuroscience & Biobehavioral Reviews, 108, 472-479.

[26] Craig, A. D., & Bushnell, M. C. (1994). The thermal grill illusion: unmasking the burn of cold pain. Science, 265(5169), 252-255.

[27] Fardo, F., Finnerup, N. B., & Haggard, P. (2018). Organization of the thermal grill illusion by spinal segments. Annals of neurology, 84(3), 463-472.

[28] Bakshi, A., & Ghosh, K. (2017). A neural model of attention and feedback for computing perceived brightness in vision. In Handbook of neural computation (pp. 487-513). Academic Press.

[29] Holbert, M. D., Pedler, A., Camfermann, D., & Harvie, D. S. (2017). Comparison of spatial summation properties at different body sites. Scandinavian journal of pain, 17(1), 126-131.

[30] Craig, A. D., & Bushnell, M. C. (1994). The thermal grill illusion: unmasking the burn of cold pain. *Science*, *265*(5169), 252-255.

[31] Alrutz, S. (1898). On the temperature-senses. Mind, 7(25), 141-144.

[32] Harper DE, Hollins M. Conditioned pain modulation dampens the thermal grill illusion. Eur J Pain 2017;21:1591–1601.

[33] Defrin R, Benstein-Sheraizin A, Bezalel A, et al. The spatial characteristics of the painful thermal grill illusion. Pain 2008;138:577–586.

[34] Craig, A. D., & Bushnell, M. C. (1994). The thermal grill illusion: unmasking the burn of cold pain. *Science*, *265*(5169), 252-255.

[3535] Adam, F., Alfonsi, P., Kern, D., & Bouhassira, D. (2014). Relationships between the paradoxical painful and nonpainful sensations induced by a thermal grill. PAIN®, 155(12), 2612-2617.

[36] Fardo, F., Finnerup, N. B., & Haggard, P. (2018). Organization of the thermal grill illusion by spinal segments. Annals of neurology, 84(3), 463-472.

[37] Tang, B., Frye, H. A., Gelfand, A. E., & Silander, J. A. (2022). Zero-inflated Beta distribution regression modeling. *Journal of Agricultural, Biological and Environmental Statistics*, 1-21.

[38] R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/ Wickham, H. (2017).

[39] tidyverse: Easily install and load the 'tidyverse'. R package version 1.2.1. https://CRAN.R-project.org/package=tidyverse

[40] Bürkner, P.-C. (2017). brms: An R package for Bayesian multilevel models using Stan. Journal of Statistical Software, 80(1), 1–28. https://doi.org/10.18637/jss.v080.i01

[41] Bates, D., Maechler, M., Bolker, B., & Walker, S. (2015). Fitting linear mixed-effects models using lme4. Journal of Statistical Software, 67(1), 1–48. https://doi.org/10.18637/jss.v067.i01

[42] Dey, D.K., & Choudhury, D. (2019). zoib: Zero Inflated Beta Regression. R package version 0.1.3. https://CRAN.R-project.org/package=zoib

Appendix

AARHUS UNIVERSITY
DEPARTMENT OF CLINICAL MEDICINE

Ms Camila Eva Andersen
Center for Functionally Integrative Neuroscience
Aarhus University
camilaevaandersen@cfin.au.dk

Project: "Perception of warm and cold temperatures"

The Institutional Review Board at DNC has discussed the project "Perception of warm and cold temperatures" at its meeting on 28 November 2022.
Based on the submitted material, the committee has taken the following decision.

Decision:

Conditional on offering the participants several breaks during the project, the project is approved.

The approval applies to the notified locations, its notified investigators in Denmark and for the specified project period.

The approval is valid until 31 December 2023 and is based on the following documents:

- Microsoft Word - IRB-Application-rev1.0.docx kopi
- Project summery_08112022
- ParticipantInformation_ver1_140922
- ConsentForm_ver1_08112022
- DNC-ResponsibilityStatement-v1.0
- ForsøgspersonRettigheder_ver2_27092021
- RetningslinjerFrivilligeForsøgspersoner
- EthicsCommitteeResponseSS-1
- Advertisement material
- Response to IRB

Changes:

If significant changes to the protocol material are made during the implementation of the project, these must be reported to the committee in the form of protocols changes or amendments. The project may only resume after approval from the committee.

Department of Clinical Medicine - Center of Functionally Integrative Neuroscience

Leif Østergaard
Professor, director

Date: 28 November 2022

Email: leif@cfin.au.dk
Web: au.dk/leif@cfin

Case number: DNC-IRB-2022-014

Afs. CVR-nr.: 31119103

Page 1/3

Center of Functionally Integrative Neuroscience
Aarhus University
Universitetsbyen 3
DK-8000 Aarhus C
Denmark

Tel.: +45 7845 9001

E-mail: clin@au.dk
Web: cfin.au.dk

AARHUS
UNIVERSITY
DEPARTMENT OF CLINICAL MEDICINE

The following committee members participated in the meeting:

Neuroscience and modality experts
- Leif Østergaard (Chairman)
- Elvira Brattico
- Diego Vidaurre
- Dora Grauballe

Lay people
- Henriette Vuust (Vice chairman)
- Hella Kastbjerg

Yours sincerely

Leif Østergaard

AARHUS
UNIVERSITY
DEPARTMENT OF CLINICAL MEDICINE

Protocol changes and amendment must be submitted to the secretariat at DNC with the project's assigned notification number.

Significant changes include changes that may affect subjects' safety, interpretation of the scientific documentation on which the project is based, and implementation or management of the project. For example, there may be changes in in- and exclusion criteria, project design, number of subjects, project procedures, duration of treatment, effect parameters, changes regarding the investigators or locations and changes in the written information material to the subjects.

If new information causes the researcher to consider procedure changes or project termination, the committee shall be notified immediately.

Side Effects and Unexpected Incidents:

Ongoing reporting
The committee must be informed immediately if suspected serious, unexpected adverse incidents or serious incidents occur during the project.

The report must be accompanied by comments on any consequences for the experiment. Only side effects and incidents occurred in Denmark have to be reported. Notification shall be made no later than 7 days after the sponsor or the investigator has received knowledge of the case.

Reporting must be made to the chair of the Committee and the secretariat at DNC with the project's assigned notification number.

Completion:

Within 90 days after the completion of the project the investigator must send a final report to the committee. The project is considered as completed when the last subject is completed.

Reporting must be made to the secretariat at DNC with the project's assigned notification number.

If the project is not initiated, the committee must be informed of the reasons.

The Committee requests a copy of the final research report or publication. We note that there is a duty to publish both negative, positive and inconsistent test results.