Thermal Pain and Electrical Stimulation: neuromodulation of C- and Aδ-fibre afferents in the central nervous system

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List of abbreviations

CGRP	Calcitonin gene related peptide
CHEPS	Contact Heat Evoked Potentials
CTQ	Child Trauma Questionnaire
HFS	High Frequency Stimulation
HPT	Heat Pain Threshold
LFS	Low Frequency Stimulation
LTD	Long Term Depression
LTP	Long Term Potentiation
MPT	Mechanical Pain Threshold
PCS	Pain Catastrophizing Scale
STAI-S	The State-Trait Anxiety Inventory (State)
STAI-T	The State-Trait Anxiety Inventory (Trait)
TENS	Transcutaneous Electrical Nerve Stimulation
VAS	Visual Analogue Scale
WDT	Warm Detection Threshold

1. Introduction

1.1 Acute and chronic pain

Pain is an essential sensation signalling danger for the human body (Woolf, 2010). The intensity of pain differs not only depending on the trigger but also depending on many inter-individual variables ranging from mental state to gender (Keefe et al., 2000). Although pain can express itself very differently, a working definition of acute pain has been suggested by the American Academy of Pain Medicine: “Acute pain is the physiologic response to and experience of noxious stimuli that can become pathologic, is normally sudden in onset, time limited, and motivates behaviours to avoid potential or actual tissue injury.” (Kent et al., 2017). In contrast to time limited acute pain, patients suffering from chronic pain experience this feeling on a regular, often daily basis (Mills, Nicolson, & Smith, 2019). Chronic pain is a societal burden and people affected experience a strongly reduced quality of life (Galvez-Sanchez & Montoro, 2022). In Germany, in 2014 an estimated number of 3.25 million people suffered from some sort of chronic pain (GEK, 2016). That is nearly 4% of Germany´s population at that time ("Germany´s population 2016,"). Defining chronic pain is very complex due to its heterogeneity. Pain is considered to be chronic when lasting longer than 3 months (Cohen, Vase, & Hooten, 2021). It is a result of learning mechanisms that misinterpret long-lasting acute pain (Galvez-Sanchez & Montoro, 2022). (Imminent) tissue damage triggers a chain reaction in chemical, mechanical or thermal receptors. It also activates leucocytes and macrophages which transduce the noxious stimuli to the dorsal horn of the spinal cord, where amino acid and peptide transmitters activate spinal neurones. Spinal neurones then transmit signals to the brain. The individual´s conclusions involve sensory-discriminative, motivational-affective and modulatory processes in an attempt to limit the painful process (Voscopoulos & Lema, 2010). When acute pain lasts long enough, the above described changes occurring in neuronal signalling and immune response after sensation of acute pain can become persistent and lead to chronic pain sensation (Treede et al., 2019). One can conclude two things from this theory of chronic pain development. Firstly, it is crucial to treat acute pain sufficiently in order to impede the development of chronic pain (Fricton et al., 2015) and secondly, causal chronic pain treatment should aim at reversing the changes in pain signalling to a default mode where only noxious stimuli lead to a time limited pain response (Voscopoulos & Lema, 2010).

Treatment of chronic pain should always consist of pharmaceutical and non-pharmaceutical therapy options (Mills, Torrance, & Smith, 2016). As pharmaceutical therapy is often not enough to alleviate pain sufficiently and side effects limit the therapeutic window of medication, complementary therapeutic approaches become more important (Busse et al., 2018). In order to ameliorate chronic pain treatment, it is crucial to study mechanisms and systems that exhibit the capacity to alter acute and chronic pain perception and complement pharmaceutical therapy. To this end, we need a better understanding of mechanisms and techniques modulating pain perception. This is the aim of the current study.

1.2 Pain signalling from periphery to the brain

Wide-dynamic range neurons are found in the dorsal horn of the spinal cord (Beauchene, Sacre, Yang, Guan, & Sarma, 2019). They receive action potentials from peripheral nociceptors and low-threshold mechanoceptors and transmit these inputs to the sensory cortex (Giere, Melchior, Dufour, & Poisbeau, 2021). Thus, wide-dynamic range neurons are the first part of central pain projection to the central nervous system. Wide-dynamic range neurons can react to stimuli in different intensities which is responsible for coding the intensity of a painful stimulus (sensory discrimination) (Sandkuhler, 2007). The synapse between wide-dynamic range neurons and nociceptors is possibly subject to modulations (Zhang, Janik, & Grill, 2014). There is substantial evidence that the synaptic strength can be modulated by either high-frequency stimulation or low-frequency stimulation (van den Broeke, Urdi, Mouraux, Biurrun Manresa, & Torta, 2021; Whitlock, Heynen, Shuler, & Bear, 2006). Changes in synaptic strength are thought to alter pain signal transfer by either enhancing the signal of pain (stronger synaptic cohesion) or extenuating it (weaker synaptic cohesion) (Chen & Sandkuhler, 2000). These mechanisms are called long-term potentiation (LTP, stronger synaptic transmission) and long-term depression (LTD, weaker synaptic transmission) (Malenka & Bear, 2004).

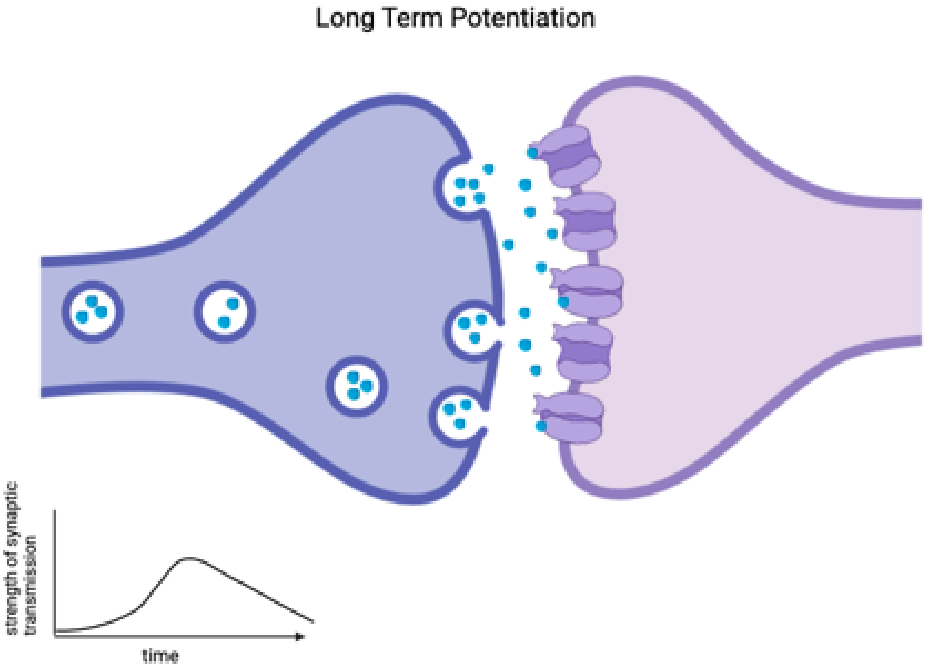

Figure 1: Schematic diagram: synapse modulated by LTP and strength of synaptic transmission over course of time. Postsynaptic neuron displays high density of channels, thus facilitating postsynaptic response. Figure modulated after “Langzeitpotenzierung, Taschenatlas Physiologie 8th edition, Stefan Silbernagl, Agamemnon Despopoulos page 359”. Diagram is not exhaustive.

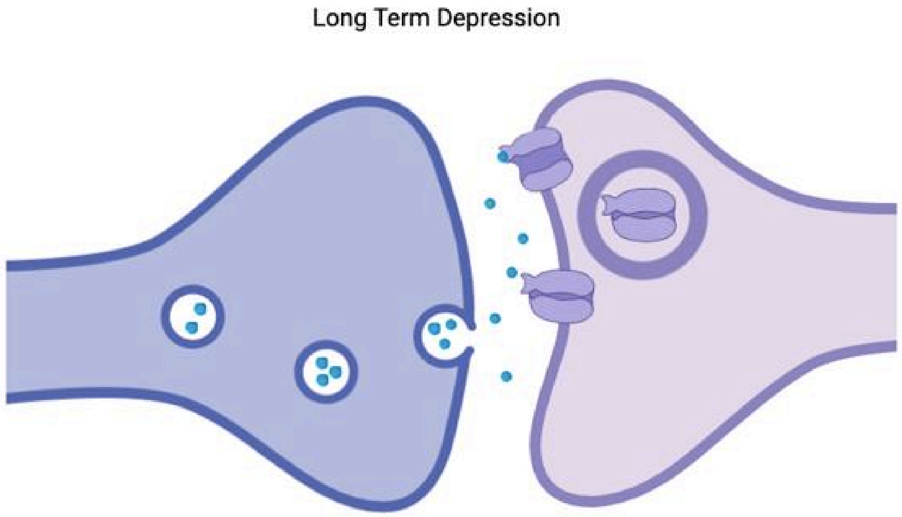

Figure 2: Schematic diagram: synapse modulated by LTD. Postsynaptic neuron displays low density of channels, thus impeding postsynaptic response. Diagram is not exhaustive.

1.3 Long Term Depression and Long Term Potentiation in pain processing

LTP and LTD are lasting changes in synaptic signalling, induced by specific patterns of synaptic activity (Woolf & Salter, 2000). As cellular models of learning in the central nervous system, they have been studied extensively (Malenka, 1994). In response to a variety of induction protocols, chemical synapses have a reliable capacity for enduring changes in synaptic transmission (Bliss & Cooke, 2011). This has been studied in various regions of the central nervous system from the spinal cord to the cerebral cortex (Mantyh & Hunt, 2004). LTP is believed to play a crucial role in the development of chronic pain (Bliss & Cooke, 2011). In turn, LTD has been targeted as a potential mechanism to disable nociceptive signalling (Jung et al., 2012). Targeting synaptic plasticity in chronic pain treatment is thought to be promising because changes in synaptic plasticity such as LTP and LTD have been shown to last and exhibit therefore the potential for a more permanent effect (Muecke, Cuhls, Radbruch, Weigl, & Rolke, 2014). This is further supported by the theory that LTP might play a crucial role in the development of chronic pain (Bliss, Collingridge, Kaang, & Zhuo, 2016) and that LTP and LTD are key mechanisms in learning (Levy & Steward, 1983). In order to retain information and resort to it later, reliable and permanent neuronal signalling is essential. One major objective in pain research is therefore to find reliable induction protocols to induce LTD in the dorsal horn of the spinal cord which exhibits the potential to reduce pain perception in humans (Jung, Rottmann, & Ellrich, 2009). In the long run, achievements could be to alleviate strong pain such as cancer patients often experience or to reduce pain in chronic pain patients.

1.4. Electrical stimulation of nociceptors

In recent years, researchers have used electrical stimulation to induce LTD and LTP (Jung et al., 2012; Muecke et al., 2017). In contrast to electrical nerve stimulation (TENS) (Johnson, Paley, Jones, Mulvey, & Wittkopf, 2022) matrix array or concentric electrodes favour the stimulation of nociceptors (C- and Aδ-fibres) and are therefore thought to influence the synapse between nociceptors and wide-dynamic range neurons in the dorsal horn of the spinal cord (Klein, Magerl, Hopf, Sandkuhler, & Treede, 2004; Sandkuhler, 2007). Stimulation with a matrix electrode has already been tested successfully on healthy subjects and cancer patients (Muecke et al., 2017; Muecke et al., 2018). The mentioned study (2017) in healthy participants (“ Neuromodulation mittels Matrixstimulation”, Muecke et al., 2017) investigated whether the pain experienced during a blood draw could be alleviated using low-frequency stimulation with a matrix electrode. The authors assessed pain during blood draw before, during and after electrical stimulation. In the study investigating tumour pain, low-frequency matrix stimulation (4 Hz) was applied to the skin within the Head’s zones referring to the tumour localisation of cancer pain patients. Pain at baseline was compared to a 3-day treatment interval consisting of 5 min of matrix stimulation in the morning and evening followed by a 3-day follow-up period without therapy. Low-frequency stimulation was effective in reducing nociceptive pain in cancer patients by 30% on average and in the blood draw experiment in healthy subjects by 77% after the stimulation while the only side effect observed was temporary erythema of the stimulated skin area (Mucke et al., 2017; Mucke et al., 2018). The present work aims at replicating the finding of pain relief after low-frequency stimulation. In addition, the current study investigates whether the matrix electrode also alters thermal pain processing, in form of a pain reduction. This would extend the previous findings to the modification or the perception of a different pain quality and thus increase generalisability of the stimulation technique.

2. Objectives

The main objective of the study was to find out whether a matrix array electrode low-frequency stimulation and high-frequency stimulation alter heat pain perception. We expected high-frequency stimulation to enhance thermal pain or at least attenuate the effect of habituation to repetitive thermal stimuli and low-frequency stimulation to alleviate thermal pain, exceeding the effect of habituation. We also tested the effect of high-frequency- and low-frequency stimulation via the matrix electrode on mechanical pain perception. Based on the results of previous studies, we expected that high-frequency stimulation would increase mechanical pain perception and low-frequency stimulation would decrease mechanical pain perception.

Only stimulation protocols that induce LTD are tested for potential clinical use. In contrast a facilitation of pain-sensitivity resulting from induced LTP is especially undesired in pain patients. Understanding the mechanisms of LTP helps us, however, to understand the process underlying the modulation of pain in general. Beyond that, LTP serves as a positive control.

3. Materials und methods

3.1 Study design

Healthy male volunteers were included in a prospective, randomized, controlled cross-over monocentric study. Subjective thermal pain was investigated as primary outcome variable in a post-between and pre/post-between electrical stimulation design. The order of low-frequency stimulation, high-frequency stimulation and sham condition had been randomized by a computer program before the start of the study. The study depicts a pilot which includes that the study protocol was adjusted after eleven participants. Both protocols are described. Data are pooled for the analyses described here.

3.2 Ethical requirements

The study design and protocol were reviewed and approved by the Ethics Committee of the Medical Faculty, RWTH Aachen University (EK 313-18). The study was in accordance with the ethical principles originating from the Declaration of Helsinki ((WMA), amended in 2008) and in compliance with Good Clinical Practice. Participation was voluntary and could be withdrawn at any time without any disadvantage for the participant. Protection of data privacy was ensured by coding information that is attributable to a person.

3.3 Study population

In total, 16 healthy male volunteers (mean age 27.8) were included in this study. Participants received a compensation for their participation in the study. Eleven participants were included in our first cohort (protocol A) and five were included in the second cohort (protocol B). After evaluation of the data obtained from protocol A, we decided to alter the electrical stimulation paradigm according to results of previous studies using the matrix or concentric electrodes (Jung et al., 2009; Muecke et al., 2017) Additionally, we applied the heat stimulation paradigm twice, once before electrical stimulation, and once after electrical stimulation, creating a pre-post design.

Recruitment was conducted using flyers in the University hospital in Aachen and on social media. We posted a call for participation in a Facebook network group and on our social media accounts, such as Instagram and WhatsApp.

Inclusion criteria were minimum age of 18 years and male sex. Participants had to sign a consent form after a thorough explanation of the investigation. Exclusion criteria were contraindications to the use of electrical stimulation such as the presence of cardiac pacemakers or other implanted electronic devices, severe cardiac arrhythmia, malignant tumors, neurological diseases such as but not limited to multiple sclerosis, stroke and neuropathies, peripheral vascular diseases, hemophilia, skin or soft tissue disease or chronic pain syndromes such as migraine or chronic back pain. Previous experience with electrical stimulation methods was also an exclusion criterion in order to avoid expectation bias.

3.4 Quantitative Sensory Testing

Three tests of the Quantitative Sensory Testing protocol of the German Research Network on Neuropathic Pain (DFNS) (Rolke et al., 2006) were used to evaluate the effects of stimulation with the matrix electrode 10 min after stimulation. Thermal detection thresholds, heat pain thresholds and mechanical pain thresholds were measured.

Thermal testing was conducted using the Pathway thermode, Model CHEPS provided by the company Medoc. This device is a computer-based system for recording the functionality of thinly myelinated Aδ- and non-myelinated C-fibers. Using a contact thermode on the lower left forearm of the subject, the warm detection threshold (WDT) and heat pain threshold (HPT) were determined. The contact area of the thermode was 572 mm². By pressing a stop button that is connected to a computer unit, thresholds can be determined starting at 33 °C with a continuously increasing ramp of temperature (1 °C/s). The actual thermal detection and pain thresholds were calculated as the mean from four consecutive threshold determinations.

Mechanical pain threshold (MPT) was determined using a set consisting of blunt needles (pinprick, MRC Systems GmbH, Germany) with a skin contact area of 0.25 mm diameter and fixed stimulation intensities between 8 and 512 mN with a stepwise increase of force intensities by a factor of 2. Mechanical pain threshold was calculated as the geometric mean of five straight above and five below pain threshold stimulation intensities.

3.5 Heat stimulation paradigm

The mean heat pain threshold obtained earlier in Quantitative Sensory Testing was used to determine the temperature applied in the heat stimuli paradigm. In order to ensure that the heat stimuli activated Aδ- and C-fibres (Benoliel, 2008), we added 4 °C to the individual heat pain threshold of each subject. As this potentially included stimulating the participants with heat stimuli up to 50 °C, we always tested the temperature in two single applications of heat stimuli with the participants before applying the complete paradigm. If the participant reported that the stimulus was too hot, the temperature was reduced by one or maximally two degrees Celsius. Moreover, if participants rated the heat stimuli higher than 70 (on visual analogue scale, VAS) we asked them if the stimuli were too painful. For an illustration of how we determined stimulation temperature, see Figure 3. For ethical reasons and individual differences in heat pain perception we could not always apply heat pain threshold temperature +4 °C but the temperature used in the heat paradigm was always above heat pain threshold and for each person differed by a maximum of two degrees Celsius between the three measurement days. We conducted this procedure in every experimental session.

Heat paradigm

During the heat pain paradigm subjects were sitting in front of a desktop connected to a computer unit that regulated the experiment. The previously determined temperature was applied 30 times for a duration of one second in random intervals of 5-8 seconds. Between every applied heat stimulus, participants had to rate the painfulness of the stimulus on a visual analogue scale. After entering the rating, a random inter-trial interval (5-8 seconds) followed. The appearance of a white cross on a black screen indicated that the next stimulus was to be expected. This was the anticipation phase followed by the heat stimulus. After completing the paradigm, the thermode was removed and subjects answered a short questionnaire about how they experienced the heat paradigm.

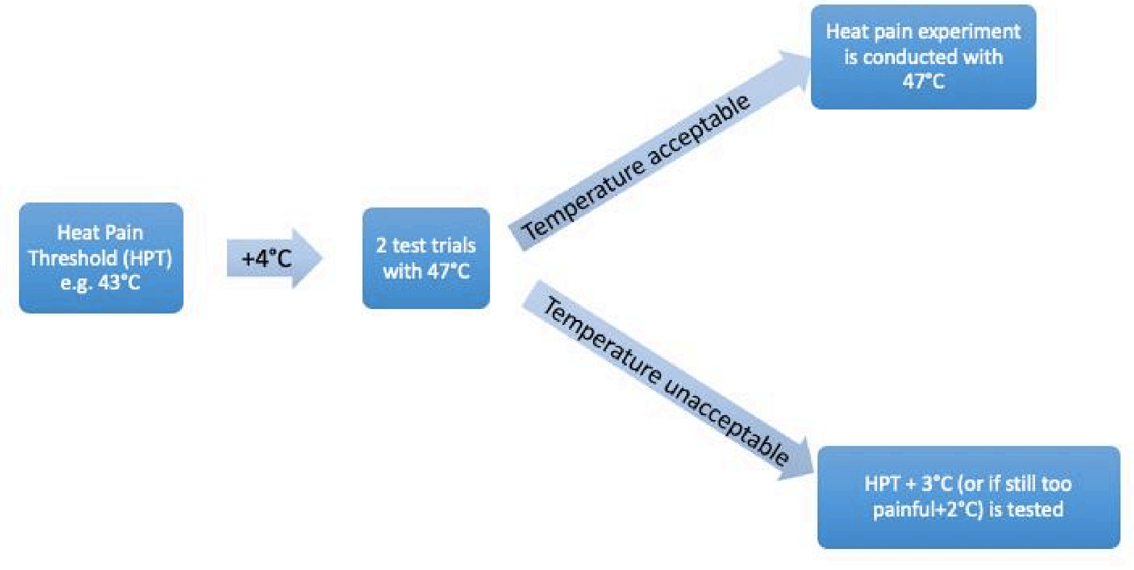

Figure 3: Illustration of how we determined stimulation temperature in the heat pain experiment.

3.6 Electrical stimulation paradigms

For electrical stimulation of epidermal nociceptive Aδ- and C-fibres, we used a matrix array electrode provided by the company BIOPAC Systems, Inc. The matrix array electrode is a three-dimensional electrode array. It is comprised of a central cathode (negative pole) and a perimetric anode (positive pole). By

coating it with so-called ball grids (ball grid array), point-wise contact with the skin is ensured. Using these point-wise small diameter (0.5 mm) skin contacts, high current densities are reached under each pin. In a depth of 1mm a current density of 20 mA/cm² is reached (Muecke et al., 2017). Maximal penetration depth is estimated to be at 5.5 mm. This favours stimulation of intraepidermal nociceptive C- and Aδ-fibres and not Aβ-fibres (Muecke et al., 2017).
We used 4 Hz low-frequency stimulation in order to induce long-term depression and 100 Hz stimulation to induce long-term potentiation. As sham condition we did not stimulate the subjects but told them that they were being stimulated but might not necessarily perceive it.

Protocol A

In the first protocol electrical stimulation was applied for 10 minutes. Stimulation was intermitted, 10 seconds of stimulation followed by a stimulation free interval of 5 seconds both in low-frequency stimulation and high-frequency stimulation protocol. See Figure 4 below for an illustration of the stimulation protocol. This resulted in a total number of 1440 stimuli applied in low-frequency stimulation and 40.000 stimuli applied in high-frequency stimulation. For the electric current, we tested the stimulation with the participants shortly to find out what electric current each participant perceived as slightly painful. We then used the resulting individual electric current on the respective participant.

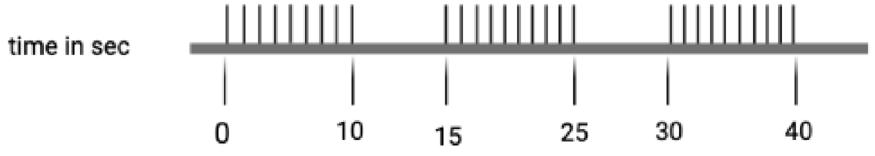

Figure 4: Illustration of stimulation protocol A for HFS and LFS. The number of stimuli shown in the illustration is not representative of the number of stimuli applied in the experiment. This illustration has the purpose of showing the timeline of the stimulation protocol only.

Protocol B

A 4 Hz stimulation was applied for five minutes continuously without pause resulting in a total number of 1200 stimuli (compare Figure 5). 100 Hz stimulation was applied in trains of five times a one-second stimulation with a stimulation-free interval of 9 seconds after each one-second stimulation period (see Figure 6). This resulted in a stimulation period of 50 seconds and a total number of 500 stimuli applied in the 100 Hz condition. We used a current strength of 2 mA for low-frequency stimulation and 5 mA for high-frequency stimulation.

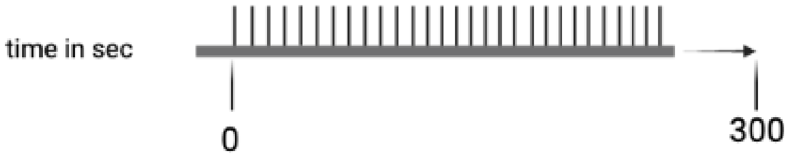

Figure 5: Illustration of stimulation protocol B for LFS. The number of stimuli shown in the illustration is not representative of the number of stimuli applied in the experiment. This illustration has the purpose of showing the timeline of the stimulation protocol only.

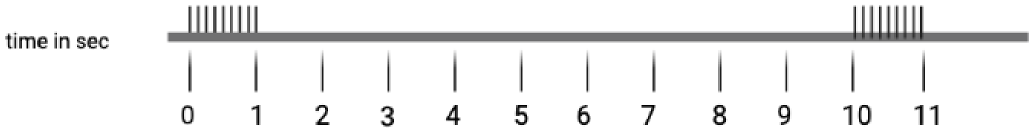

Figure 6: Illustration of stimulation protocol B for HFS. The number of stimuli shown in the illustration is not representative of the number of stimuli applied in the experiment. This illustration has the purpose of showing the timeline of the stimulation protocol only.

3.7 Procedure

Protocol A

In protocol A (11 participants) we used a post/between design. This means we conducted the heat pain experiment only once during an experimental session (see Figure 7) and compared the pain severity ratings between sessions.

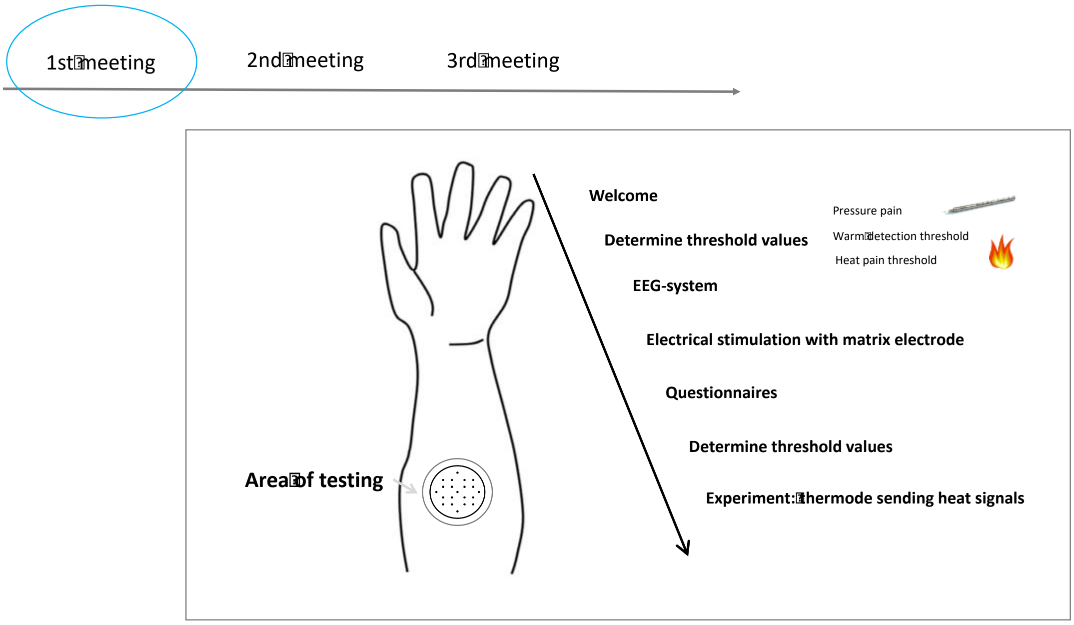

Figure 7: Experimental set-up in the post/between cohort

Protocol B

In protocol B (5 participants) we used a pre/post/between design. We conducted the heat pain experiment twice during a session, before and after electrical stimulation (see Figure 8) and compared it before and after stimulation and between sessions.

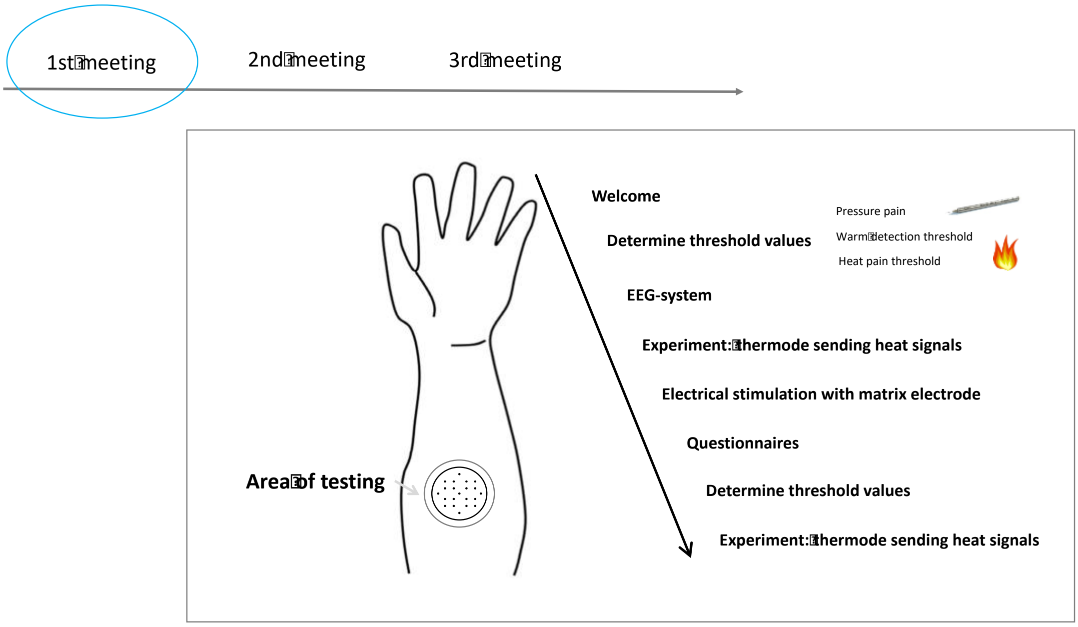

Figure 8: Experimental set-up in the pre/post/between cohort

For both protocols, participants came to the lab three times. A mandatory interval of three days between two sessions was ensured at all times because the above mentioned study with cancer patients has proposed that the effects of LTD and LTP last from several hours up to several days (Muecke et al., 2018).

After removing all electronic and metal devices from the body, participants sat down in a comfortable chair. At the beginning of each experimental session, we measured skin temperature in the area of testing. If skin temperature was below 30° Celsius participants warmed up first to ensure similar experimental conditions (Benoliel, 2008). The infrared thermometer TriTemp by the company TriMedika measured skin temperature. Additionally, we measured room temperature to be able to take that into consideration as well when analyzing our data. Room temperature was measured with a thermometer in our EEG-lab. During the experiments, all instructions for participants were read to them to ensure a standardized procedure at each session.

We first examined mechanical pain threshold at the left lower forearm, then placed the thermode at the area of mechanical pain testing (homotopic zone) and performed warm detection threshold and heat pain threshold testing. After installing the EEG recording system, in protocol B, we started the first of two heat paradigms, while in protocol A we continued with electrical stimulation. The thermode was then removed and subjects answered a short questionnaire about how they perceived the heat paradigm (protocol B). We placed the matrix electrode at the exact same area on the left lower forearm where the thermode had been placed before (homotopic zone) and applied either low-frequency stimulation, high-frequency stimulation or sham protocol. We removed the matrix electrode and participants filled out various psychological questionnaires such as PCS, CTQ, STAI-S, STAI-T, demographic data. After 10 minutes we re-examined mechanical pain threshold, warm detection threshold and heat pain threshold in that order. We conducted the (second) heat paradigm, followed by the heat questionnaire. At the end, we removed the EEG-system and the thermode and showed the participants where to wash their hair if they wanted. This course was unaltered in all three measurements except for the electrical conditioning stimulation. The experimental course is shown in Figures 7 and 8 for the first and second cohort respectively. One experimental session lasted between two to three hours.

Figure 9: Experimental set-up

Figure 10: EEG-recording cap

3.8 Statistical analysis

Statistical analysis was conducted using R studio 4.0.2. In order to check whether the residuals were normally distributed, we inspected the frequency distribution of the data, skewness, and kurtosis values and applied the Wilk-Shapiro test. Assumptions were given only for stimulation temperature and heat experiment temperature. For skewed data, we applied logarithmic transformation thereby creating a normal distribution. Residuals for mechanical pain threshold were normally distributed after logarithmic transformation.

Statistical comparison of the intensity of percept (mechanical, thermal) in our behavioral data before and after electrical stimulation was performed using a linear mixed model with the fixed effect of temperature using the lme4 package.

For post hoc tests, we applied the Satterthwaite´s method. For both, the mechanical pain and thermal pain model we included a random intercept at subject level and stimulation condition (4Hz, 100 Hz and sham) as well as session (1,2,3), time (before and after stimulation) and experiment type (protocol A and B). We included all interactions due to our hypotheses.

For the mechanical pain threshold, the data were transformed with a logarithmic function. We selected the model out of 4 theoretically plausible models based on the best empirical fit. We firstly checked the fit of random effects and in a second step the fit of fixed effects. Models were compared via chi-square tests.

The winning model code for random effects was written in R as

```
rand_1MPT= lmer(ln_MPT ~  (1|code) , data=Tempest)
```

The winning model code for fixed effects was written in R as

```
MPT lmer(ln_MPT ~   repetition + condition + (1|code) + (1|repetition)  ,
data=Tempest)
```

For the thermal pain threshold model, we tested 6 different theoretically plausible types of models and selected the winning model based on the best empirical fit. We firstly checked for random effects and then for fixed effects, using chi-square tests. All tested models are listed in the annex.

The winning model code for random effects was written in R as

```
rand_1Tempest= lmer(hot ~  (1|code) , data=Tempest
```

We then tested the fixed effects against the winning model code of random effects. All tested models are listed in the annex.

The winning model code for fixed effects was written in R as

```
Temp6 = lmer(hot ~  condition * repetition + session + warm + (1|code) , data=Tempest
```

For the heat pain experiment model, we tested 4 different theoretically plausible types of models and selected the winning model based on the best empirical fit. We firstly checked for random effects and then for fixed effects, using chi-square tests. All tested models are listed in the annex.

The winning model code for random effects was written in R as

```
HeatRandom2 = lmer(pain ~ (1 + session|code),data = HeatData)
```

The winning model for fixed effects was written in R as

```
HeatFixed6 = lmer(pain ~ condition * session + trial + temperature + (1|code),data = HeatData)
```

The level of significance was set at $p < 0.05$ (2-sided).

4 Results

4.1 Mechanical pain threshold

Mechanical pain was perceived as more painful after the stimulation independent of the condition we used (*F*(1,103.86) = 25.66, *p*<.001, Figure 11). The stimulation condition, session, and the type of experiment had no effect on pain perception. Interaction effects were not significant either (see Table 1 for all statistical effects).

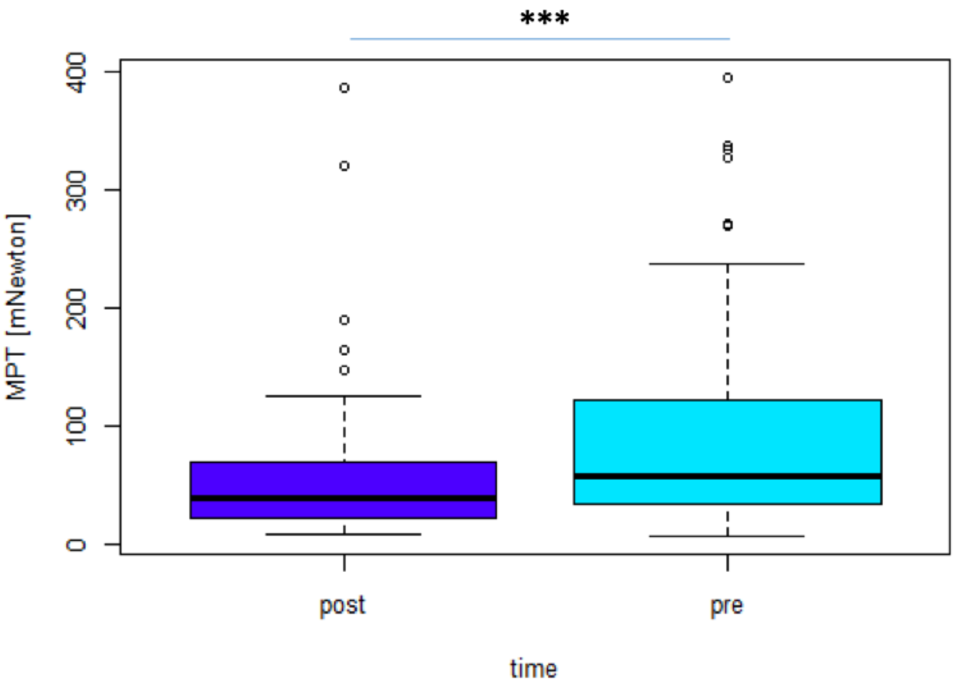

Figure 11: Box plot for mechanical pain threshold (MPT) in milli-Newton before and after electrical stimulation. Notes: *** p < .001

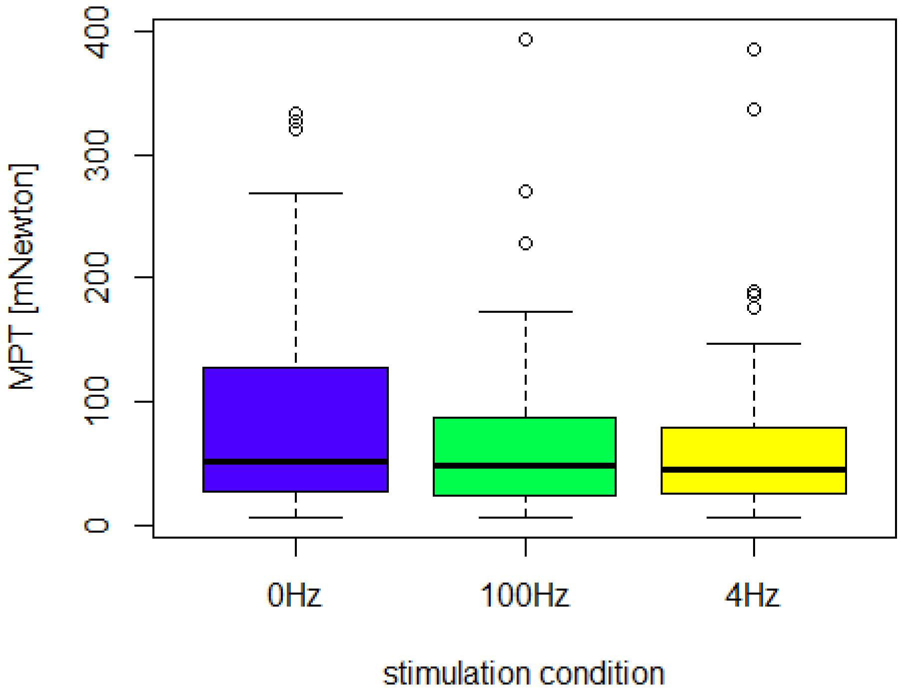

Figure 12: Box plot for MPT in milli-Newton in respective conditions (sham, 100Hz and 4Hz). No significant differences.

Table 1: Statistical measures of the linear mixed model for mechanical pain type III Analysis of Variance Table with Satterthwaite´s method.

Sum Sq = sum of squares, Mean Sq = mean squares, df num = numerator degrees of freedom, df den = denominator degrees of freedom, F = F-value, p = p-value

	Sum Sq	Mean Sq	df num	df den	F	p
repetition	8.59	8.59	1	103.86	25.66	<.001
condition	0.02	0.02	2	89.82	1.89	.160

4.2. Heat pain threshold

Heat pain thresholds did not significantly differ depending on the stimulation condition (*F*(2, 99.07) = 0.16, *p*= .85). Across participants and across conditions, the HPT became lower after the stimulation compared to before electrical stimulation, almost reaching statistical significance (*F*(1, 100.97) = 3.91, *p*= .051). We also observed a trend towards the threshold increasing from session 1 to session 3 (*F*(2, 99.16) = 3.03, *p*= .053). Additionally, the threshold for perceiving stimuli as warm, was positively associated to the threshold for perceiving stimuli as hot (*F*(1, 110.47) = 13.5, *p*= <.001). There were no further main effects or interactions (see Table 2 for full statistics on the heat threshold).

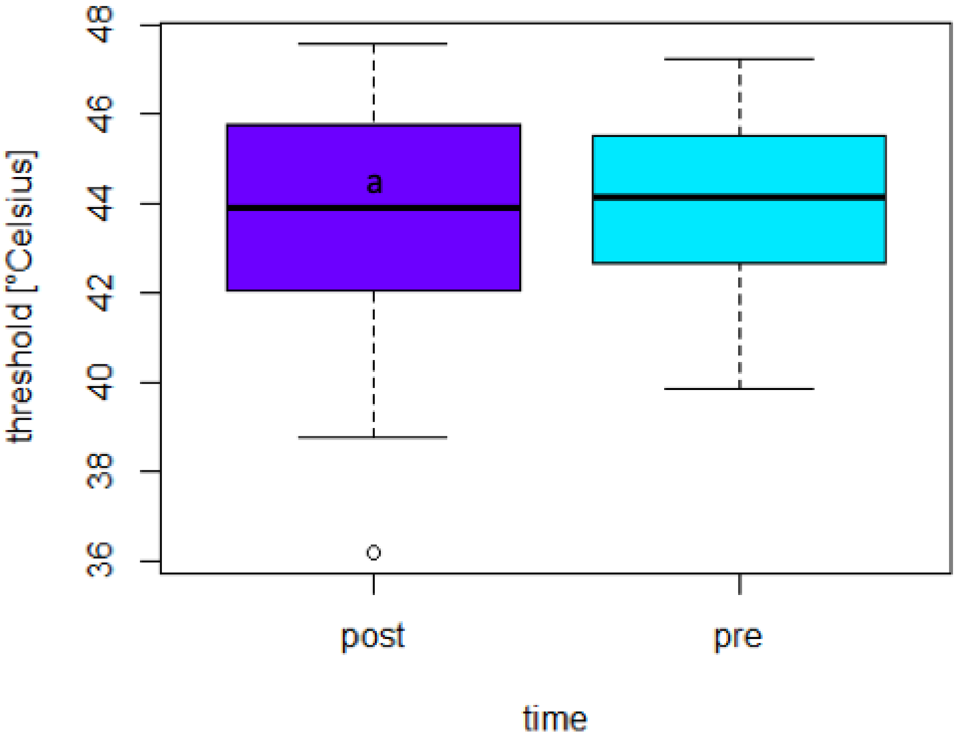

Figure 13: Box plot for heat pain threshold (HPT) in degree Celsius before and after electrical stimulation. Notes: a = trend towards significance p = .051

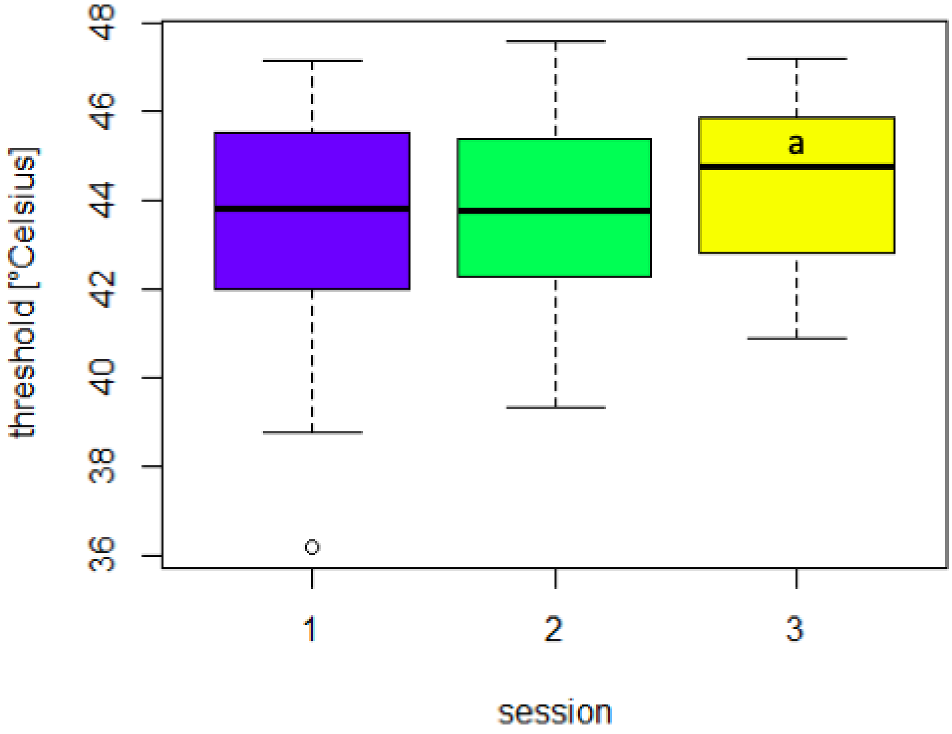

Figure 14: Box plot for Heat pain threshold (HPT) in degree Celsius in respective sessions. Notes: a = trend towards significance p = .053

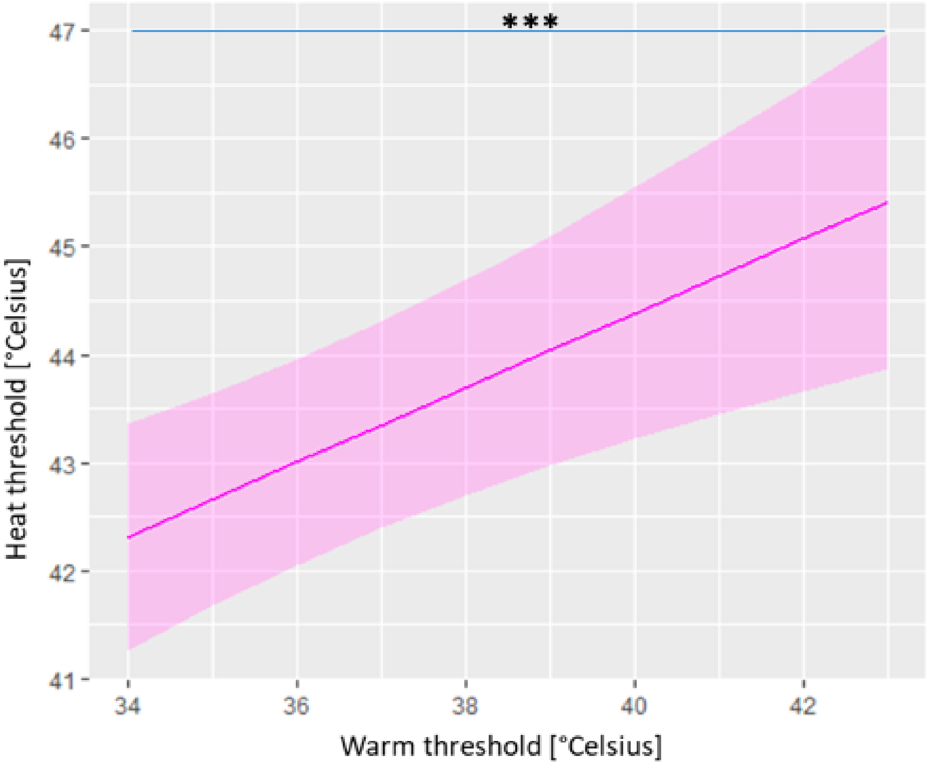

Figure 15: Predicted linear trend for warm threshold and heat threshold in degree Celsius. Notes: *** p < .001

Table 2: Statistical measures of the linear mixed model for heat pain threshold

	Sum Sq	Mean Sq	df num	df den	F	p
condition	0.60	0.30	2	99.07	0.16	.850
repetition	7.46	7.46	1	100.97	3.91	.051
session	11.57	5.78	2	99.16	3.03	.053
warm	25.77	25.77	1	110.47	13.50	<.001
Condition: repetition	4.65	2.32	2	99.22	1.22	.300

4.3. Heat pain rating experiment

In the final model all main effects (condition, session, trial and temperature) and the interaction of condition by session were significant (Table 3). For this analysis only data from protocol A (n = 11) were used (see Table 3 for full statistics on heat pain rating experiment).

Table 3: Statistical measures of the linear mixed model for heat pain experiment

	Sum Sq	Mean Sq	df num	df den	F	p
condition	5241.90	2620.90	2	940.67	19.25	<.001
session	3550.10	1775.10	2	942.93	13.04	<.001
trial	607.20	607.20	1	938.67	4.46	.035
temperature	9603.30	9603.30	1	882.08	70.53	<.001
Condition: session	16702.90	4175.70	4	948.75	30.67	<.001

Pain ratings significantly differed between all conditions (*F(*2, 940.67) = 19.25, *p*= <.001, with the highest pain ratings in the 100 Hz condition and the lowest in the placebo condition (see Figure 16, Table 4).

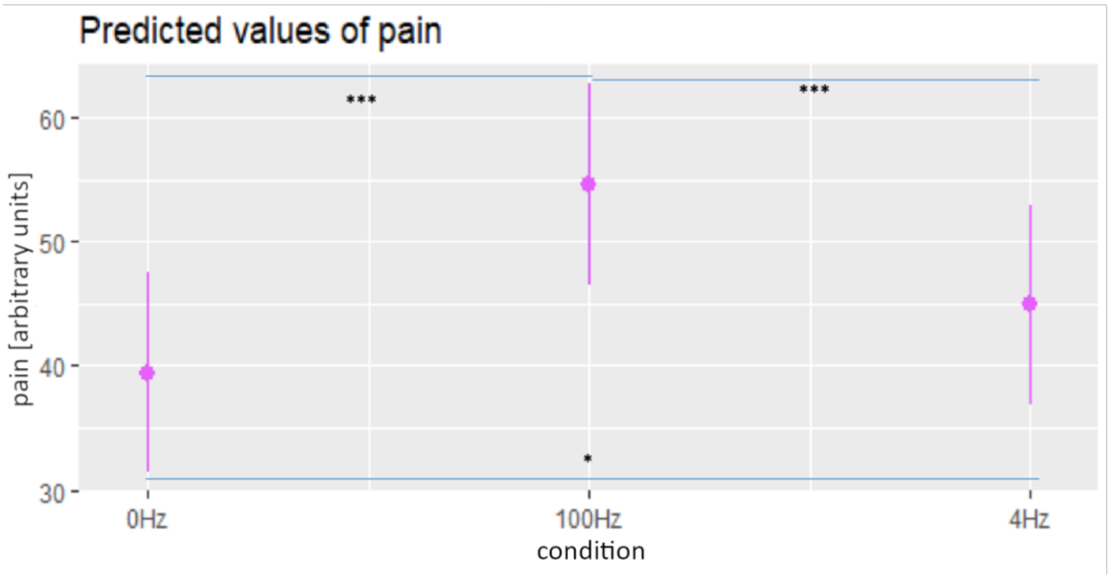

Figure 16: Estimated marginal means and standard error for pain rating plotted for each condition. Notes: * p < .05, *** p < .001

Table 4: Statistical measures of the post hoc comparisons for the different stimulation conditions. EMM = estimated marginal mean, SE = standard error, df = degrees of freedom, t = t-value, p = p-value

contrast	EMM	SE	df	t	p
0Hz – 100Hz	-5.95	0.96	941	-6.18	<.001*
0Hz – 4Hz	-2.23	0.92	940	-2.42	.04*
100Hz – 4Hz	3.72	0.97	942	3.83	<.001*

* p < .05, Bonferroni corrected

Pain ratings also significantly differed depending on the session (*F(*2, 942.93) = 13.04, *p* = <.001, Figure 17, Table 5). Post hoc tests showed that pain ratings in all sessions differed significantly except for session two compared to session three (see Table 5 for post hoc tests on session).

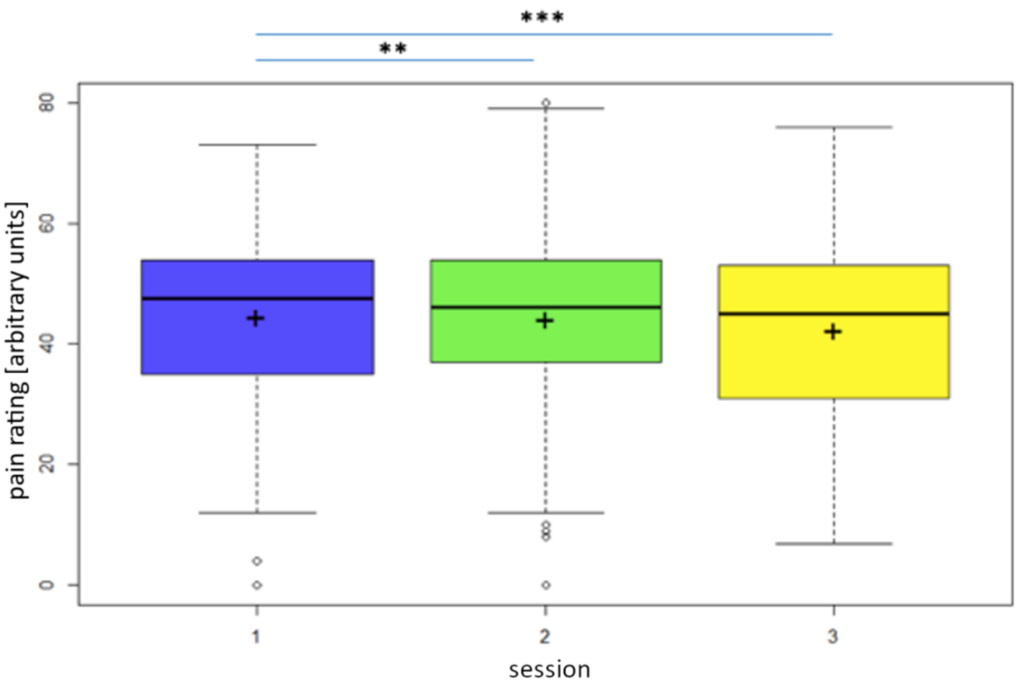

Figure 17: Box plot with depicted mean of pain ratings plotted for each session. Notes: ** p < .01, *** p < .001

Table 5: Statistical measures of the post hoc comparisons for session

Contrast	EMM	SE	df	t	p
session					
1 – 2	2.93	0.94	942	3.12	.005
1 – 3	5.08	1.00	945	5.05	<.001
2 – 3	2.14	0.98	943	2.19	.07

* p < .05, Bonferroni corrected

The main effects of condition and session have to be interpreted with caution as there was an interaction of condition and session on the pain ratings during the heat pain experiment (*F*(4, 948.75) = 30.67, *p* = <.001, Table 3). Post hoc tests show that the 4 Hz and 100 Hz condition did not differ if they were applied in session 2 or 3 (Table 6). All other conditions differed significantly, but without a clear pattern, depending on the session (Figure 18). Values in session 1 and 3 did not differ in the 4Hz condition but in all other conditions ratings varied over the session (see Table 6 for full statistics on post hoc tests for session:condition).

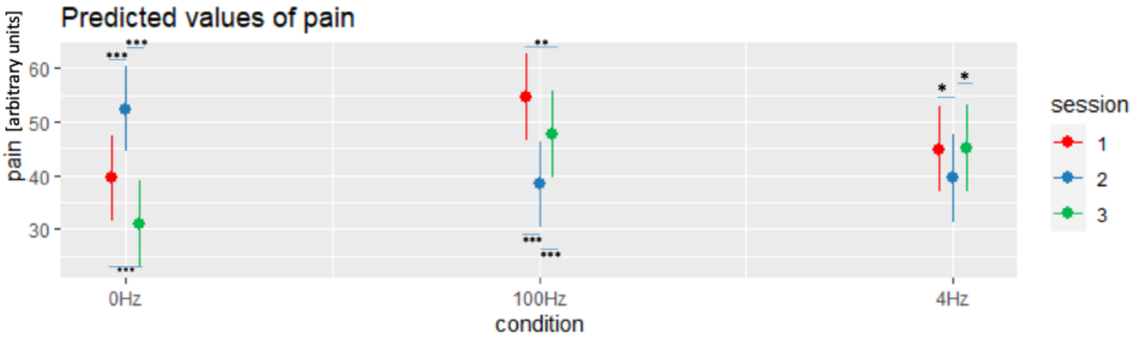

Figure 18: Estimated marginal means and standard error for pain rating plotted for each condition and session. Notes: * p < .05, ** p < .01, *** p < .001

Table 6: Statistical measures of the post hoc test for session:condition

contrast	EMM	SE	df	t	p
Session = 1					
0Hz – 100 Hz	-15.11	2.14	949	-7.07	<.001*
0Hz – 4 Hz	-5.42	2.04	949	-2.65	.02*
100Hz – 4Hz	9.69	2.12	949	4.56	<.001*
Session = 2					
0Hz – 100 Hz	13.98	1.99	949	7.04	<.001*
0Hz – 4 Hz	12.88	2.20	949	5.85	<.001*
100Hz – 4Hz	-1.11	2.16	949	-0.51	.87
Session = 3					
0Hz – 100 Hz	-16.73	2.24	948	-7.48	<.001*
0Hz – 4 Hz	-14.15	2.11	948	-6.70	<.001*
100Hz – 4Hz	2.58	2.14	948	1.21	.45
Condition = 0 Hz					
1 – 2	-12.87	2.06	949	-6.26	<.001*
1 – 3	8.53	2.16	948	3.95	<.001*
2 – 3	21.39	2.12	948	10.09	<.001*
Condition = 100Hz					
1 – 2	16.23	2.11	948	7.70	<.001*
1 – 3	6.90	2.26	948	3.06	.006*
2 – 3	-9.32	2.16	949	-4.32	<.001*
Condition = 4Hz					
1 – 2	5.44	2.23	949	2.44	.04*
1 – 3	-0.20	1.99	949	-0.10	.99

2 – 3	-5.64	2.15	949	-2.63	.02*

Notes: *p<.05 Bonferroni corrected

Based on the trial-by-trial analysis in the heat pain experiment, we were also able to detect differences in the ratings over time. We observed a significant linear effect reflecting a decrease of pain ratings over the course of 30 trials (*F*(1, 938.67) = 4.46, *p* = .035, Figure 19).

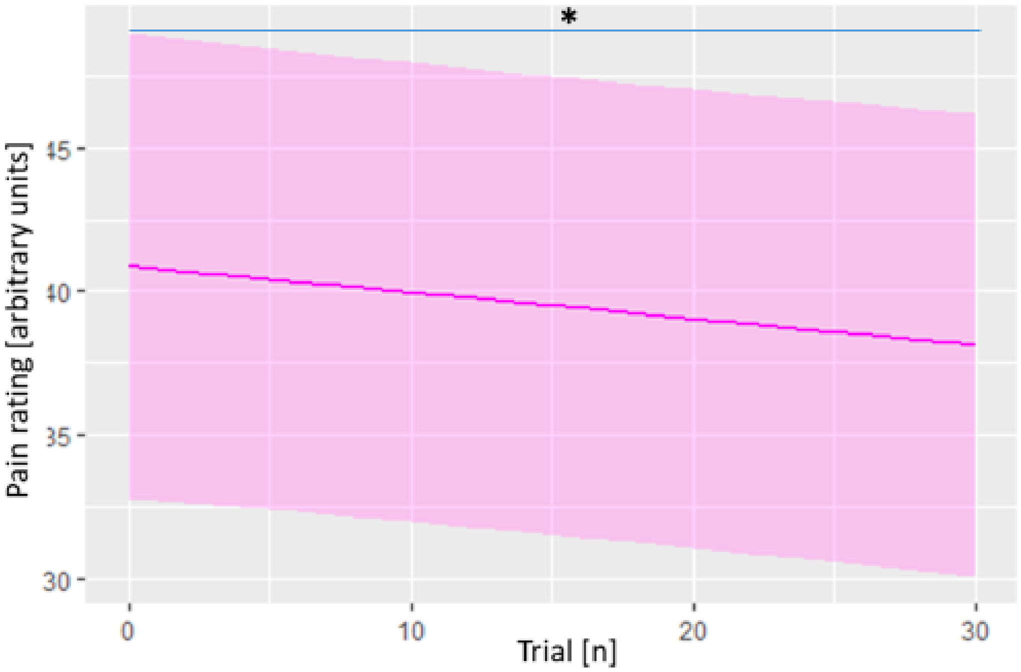

Figure 19: Linear trend and confidence interval for the pain rating of heat stimuli depending on the trial in the experiment. Notes: * p < .05

Furthermore, there was a linear correlation between stimulation temperature and painfulness rating, meaning that the higher the temperature the more painful subjects rated the thermal stimulation (*F*(1, 882.08) = 70.53, *p* = <.001, see Table 3 for full statistics on heat pain experiment).

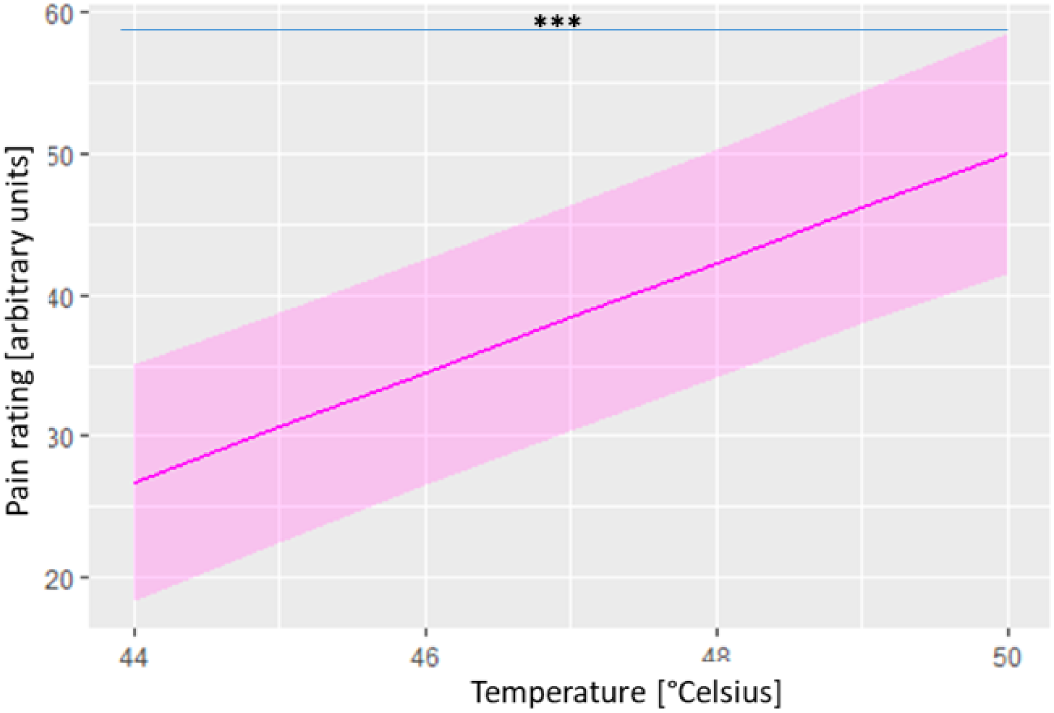

Figure 20: Linear positive trend and confidence interval for temperature of applied heat stimuli (in degree Celsius) as predictor for pain ratings of heat stimuli. Notes: *** p < .001

The findings of EEG recording are not part of this work. Due to low data quality, it was decided that they do not advance our understanding of the presented behavioral data.

5. Discussion

Our objective was to find out whether low-frequency stimulation with a matrix array electrode led to pain reduction and whether high-frequency stimulation led to pain increase. The underlying mechanisms behind the modulation of pain with a matrix electrode in the central nervous system are hypothesized to be LTP and LTD. While LTP (via increased synaptic transmission, thought to be facilitated by high frequency) reflects an increase in pain perception clinically, LTD (reduced synaptic transmission, thought to be inhibited via low frequency) reflects a decrease in pain perception and is therefore a possible target for pain management in acute and chronic pain patients. Summarizing our main findings, participants did not perceive our pain experiments as less painful after low-frequency stimulation, therefore, we deduce that we did not induce LTD. However, there is evidence for increased synaptic transmission, LTP, after electrical stimulation independent of the frequency as participants indicated increased pain perception.

Intervention effects

The mechanical pain threshold and heat pain threshold decreased after electrical stimulation independent of the stimulation frequency (or placebo), thus not presenting evidence for LTD. In contrast, we cautiously consider this finding to indicate that we induced LTP for mechanical pain within the experiment but not via stimulation. In the heat pain experiment, the stimulation affected pain ratings. High-frequency stimulation led to the highest pain perception of the three applied frequencies, supporting the idea that LTP had been produced. Interestingly, participants had a higher pain perception after low-frequency stimulation compared to the placebo condition as well, thus again rather producing LTP. This data suggests a stimulation dependent LTP, observed by higher pain ratings, with no modulation via the applied frequency. None of the pain experiments pointed towards an effect of lowering pain (increasing the pain threshold). Our data therefore critically question the applicability of electrical stimulation for pain reduction.

LTP or LTD and heat pain

LTP is described as lasting change in synaptic signalling, induced by specific patterns, meaning enhanced synaptic signalling. LTP is hypothesised to be the mechanism behind an increase in pain perception clinically. On the other hand, LTD is induced by a low-frequent stimulation of the synapse and results in a weaker synaptic transmission, supposedly leading to pain reduction compared to baseline. In our heat pain experiment we found that pain ratings differed between all stimulation conditions, with the highest pain ratings occurring after electrical stimulation at 100 Hz, which should indeed induce LTP. However, it was not lowest after 4 Hz stimulation, which is thought to induce LTD, but was lowest after placebo stimulation. We have to be careful in interpreting the results of the electrical stimulation as there was an interaction effect between the applied condition (stimulation frequency) and the session in which it was applied. The painfulness ratings in this experiment with the high-frequency condition being the most painful, points to LTP as the biochemical explanation. However, looking at the results of the low-frequency condition and linking the overall findings in the experiment, synaptic transmission is either increased after electrical stimulation independent of the frequency or possible pain-increasing factors other than LTP have influenced pain ratings.

The fact that low-frequency stimulation increased heat pain compared to placebo in the heat pain experiment and increased pain perception in the threshold tests was rather unexpected. One hypothesis that may explain the pain increase is based on a phenomenon called axon reflex (Barnes et al., 1986). Peripheral nociceptors can release neuropeptides when stimulated, such as calcitonin gene related peptide (CGRP) and substance P. These in turn lead to mast cell activation and discharge of histamine which can lead to higher pain susceptibility (Fuller, Conradson, Dixon, Crossman, & Barnes, 1987).

Interestingly, this mechanism could potentially be responsible for the temporary erythema observed after electrical stimulation in our experiment as well. Histamine leads to vasodilatation (Fuller et al., 1987) which results in erythema. Low-frequency stimulation might have activated the axon-reflex to a higher extent than it induced LTD, therefore potentially neutralising the effect expected by LTD. Future investigators of reliable induction protocols for LTD should take this into consideration.

This biochemical explanation would also be in line with the placebo condition (frequency at 0 Hz) being the least painful while still increasing in painfulness after the electrical stimulation compared to the painfulness before the experiment. In this consideration, placebo had the smallest effect of axon-reflex induction while a significant change in perception was still measurable. It may be interesting to analyse whether the respective stimulation frequencies induce an axon-reflex response to different extents by comparing the extent of erythema after application of the respective stimulation conditions.

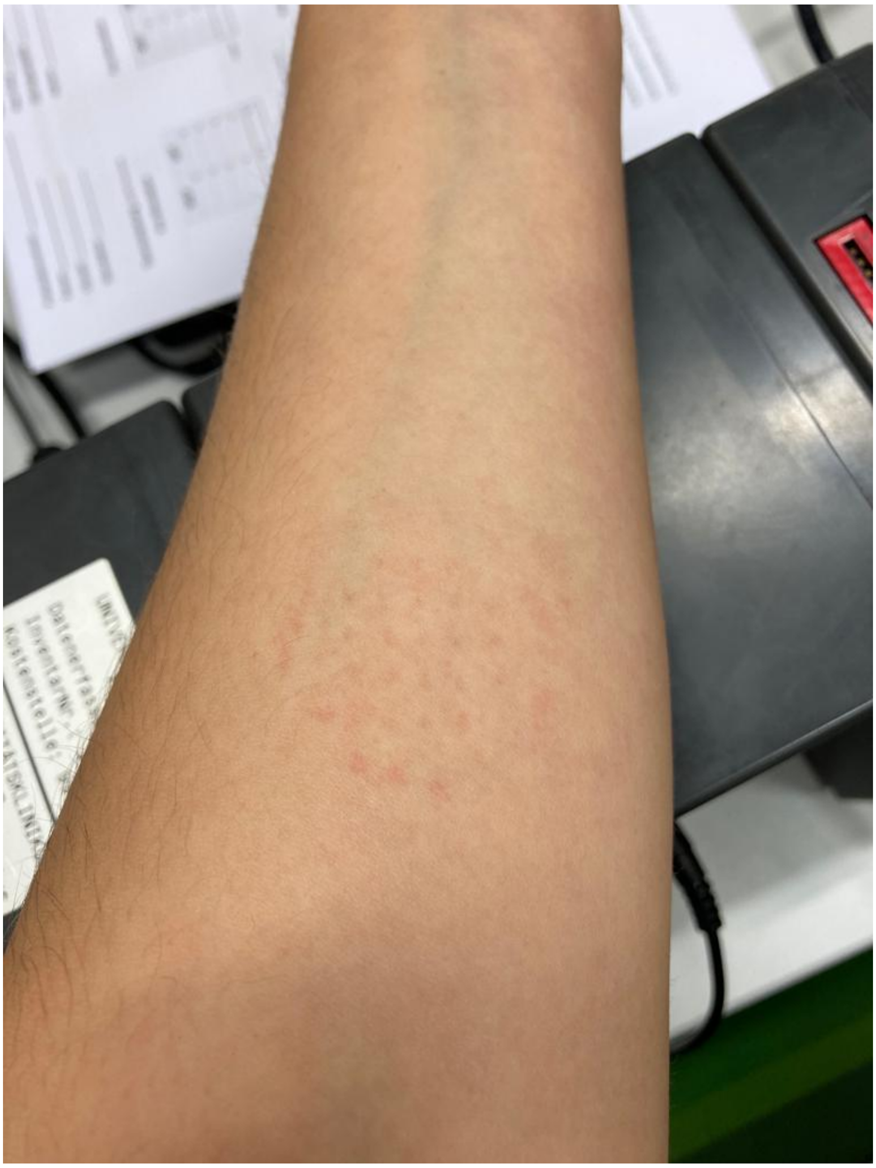

Figure 21: Temporary erythema after electrical stimulation

In a nutshell, our findings do not support the results of other research groups who found a clear pattern of low-frequency stimulation leading to LTD and thus alleviating pain (Arendsen, Guggenberger, Zimmer, Weigl, & Gharabaghi, 2021;

Mucke et al., 2014; Mucke et al., 2017; Mucke et al., 2018). However, we observed important changes in pain ratings within our experiment, partly relating to the stimulation. We would strongly recommend to increase research investigating the association of electrical stimulation and the modulation of pain perception as the links between the stimulation frequency and the pain ratings seem to be more complicated than originally assumed.

Stimulation protocol

Another possible explanation as to why we did not induce LTD in our experiments is that our stimulation procedure in protocol A was unsuitable for that purpose. Protocol A was designed to fit the use in an MRI scanner. Therefore, pauses and a longer duration of the stimulation were considered essential for an optimal functional MRI signal. These adjustments altered the induction protocol used by other groups (protocol B) substantially as depicted graphically under paragraph 3.6 “Electrical stimulation paradigms”. However, as the study was not run in an MRI scanner due to technical problems, and after completing a first analysis of the results, we decided to alter the protocol. We resorted to a protocol that has been shown to induce LTD and LTP in other studies, using a matrix electrode (Arendsen et al., 2021; Muecke et al., 2014; Muecke et al., 2017). Only a handful of studies on pain modulation published results about stimulation with the matrix electrode (Arendsen et al., 2021; Muecke et al., 2014; Muecke et al., 2018). Induction protocols are not yet widely studied. Reviews on reliable induction protocols do not exist yet. More basic research on the topic is needed to determine a standardized induction protocol.

Sensitisation and Habituation

In our heat pain experiment we observed a decrease in heat pain perception over the course of 30 trials reflecting fast habituation to repetitive heat stimuli. We also observed that higher stimulation temperatures led to higher pain ratings.

The heat pain threshold testing revealed that subjects had a decreased pain threshold from the first to the second testing within one session. Thus participants indicated pain more quickly. In contrast, participants' heat pain thresholds increased from sessions one to three. This suggests an effect of in-session sensitisation but between-session habituation to heat stimuli, as previously described by May and colleagues (May et al., 2012). Studying a control group and patients with chronic back pain and depression, May et al. hypothesised that the central nervous system becomes more susceptible to repetitive heat stimuli at first, likely in order to prevent tissue damage. When tissue damage does not occur it becomes more resistant to heat stimuli in order to protect the brain from unimportant information. Interestingly, in our experiment, electrical stimulation did not seem to interfere with sensitisation or habituation as sham stimulation elicited the same response as electrical stimulation. However, our study is not completely comparable to the study of May and colleagues because they described the effects of sensitisation and habituation to repetitive heat stimuli (contact-heat evoked potentials), not heat pain thresholds.

Heat pain thresholds were obtained by rating an increasing ramp of temperature. The heat stimuli in our experiment present a different modality as they were presented as repetitive short heat stimuli. During our heat pain experiment, participants indicated decreased subjective pain over the course of 30 trials. This suggests a repetition effect and supports the idea of a rapid habituation effect (Greffrath, Baumgartner, & Treede, 2007).

To some extent this is a contradiction compared to the effect of in-session sensitisation described by May and colleagues (2012). Differences in stimulation temperature possibly account for the different outcomes comparing our study and the study of May and colleagues. Although the stimulation protocols of both studies are comparable, May and colleagues applied a stimulation temperature of 48 °C for all participants whereas we used an individual stimulation temperature. Greffrath and colleagues, however, reported habituation to contact-heat evoked potentials for pain threshold temperature, mildly noxious temperature and peak temperature at 51 °C especially when applied at fixed skin areas. Treede and colleagues postulate that pain thresholds are mediated by C-fibres and contact-heat evoked potentials are mediated by Aδ-fibres (Treede, Meyer, Raja, & Campbell, 1995). In the same paper they further describe that pain thresholds are higher for Aδ-fibres than C-fibres. Applying this theory to our study, our participants sensitised to threshold testing because the C-fibres evoked a robust pain signal in the central nervous system, indicating possible tissue damage but habituated to contact-heat evoked potentials because Aδ-fibres did not fire to the same extent as they have a higher threshold. We were able to show that the threshold for perceiving stimuli as warm was positively associated with the threshold for perceiving stimuli as hot which means that subjects who perceived lower temperatures as warm also perceived lower temperatures as hot. This suggests that warmth and heat signalling are associated in a linear way (Schepers & Ringkamp, 2009).

The role of electrode type

Looking more closely at heat pain pathways, it is possible that electrical stimulation with the matrix electrode does not alter heat pain perception in our experiment because humans have rather few thermal sensors in their skin (1-3/ cm2) (Schmelzer, 2005). Other studies using the matrix electrode presented a similar result to our study concerning heat pain while one study using a concentric electrode showed that stimulation with this type of electrode did alter heat pain perception (Jung et al., 2012). This points to a more favourable impact on thermal sensory neurons by a concentric electrode than a matrix array electrode. This idea is supported only by the study mentioned before. More research is needed to understand which type of electrode alters heat pain the most effectively.

External influence factors

Other possible explanations as to why we increased pain perception in all tests and in the heat pain experiment in all frequencies applied, include that our experimental session was rather long and uncomfortable for the participants. They had to sit still for several hours in order to ensure good quality of EEG recordings. It is possible that the uncomfortable posture over several hours led to higher pain susceptibility (Jennings, Okine, Roche, & Finn, 2014) and thus explaining the post-stimulation increase in pain. In addition, the application of the EEG-system itself was often described as mildly painful by the participants. We deduce that this could partly be responsible for the increase in pain perception as well.

We considered using the same stimulation temperature for all participants in order to have more comparable results as most other groups did who investigated heat pain (Albu & Meagher, 2019; Hullemann et al., 2019; May et al., 2012; Roberts et al., 2008). However, we decided for an individual stimulation temperature, mainly due to ethical concerns and to accommodate for individual differences in pain perception (Fillingim, 2017). In our results we see that the stimulation temperature did indeed influence pain perception. Higher temperatures led to higher pain and vice versa. Therefore, we suggest to use one stimulation temperature for all participants to exclude this confounder while referring to procedures that ensure patient security. There is evidence that a temperature of 44-45 °C robustly induces a mild feeling of pain while still tolerable to most individuals (Greffrath et al., 2007). Researchers have to ensure to stay in accordance with the declaration of Helsinki and the guidelines on Good Clinical Practice, so we suggest to ask participants about tolerability. If participants cannot tolerate the applied temperature, the temperature must be lowered or participants will be excluded. However, it has to be taken into consideration that, when excluding participants who are more susceptible to pain, one creates a selection bias.

Limitations

One methodological limitation is that we used two different stimulation protocols. Protocol B is the more promising one as it showed effective alterations of pain processing in previous studies and should be used in the future. If other pain assessment tools such as the MRI scanner are going to be used, one should take the importance of the stimulation protocol into consideration. By using two protocols we created two small study groups instead of one big group therefore limiting the informative value of our findings.

In our study, we used an individual stimulation temperature in every session for every individual, making the results less comparable. Higher temperatures lead to higher pain and vice versa and therefore a standardised stimulation temperature is desirable.

The study had a gender selection bias because we only included men. We did so in order to have a comparable and homogeneous group but ideally a larger group size including men and women should be used because men and women experience pain differently (Greenspan et al., 2007; Osborne & Davis, 2022). It is not possible to generalise the findings to both sexes when only investigating men. Furthermore, there is evidence that gender affects pain as well (Wise, Price, Myers, Heft, & Robinson, 2002), so ideally gender should be taken into consideration as well.

More research needs to be done on the question of how electrical stimulation with a matrix electrode and LTD and LTP in pain modulation are related. The study is currently still in progress so we will conduct the final analyses after completion of the study.

6. Conclusion

We did not find support for low-frequency stimulation to alleviate heat pain but found some evidence for high-frequency stimulation to increase heat pain. A number of other pain increasing factors likely account to some extent for the increase in heat pain as well (e.g axon reflex, experimental setting). We further observed that heat-pain thresholds decreased independent of the stimulation condition, reflecting in-session sensitisation while the application of repetitive stimuli led to rapid and between-session habituation. We conclude from our study that we did not find support for low-frequency stimulation with the matrix electrode to effectively treat heat or mechanical pain. In order to replicate previous findings that support the effect of the matrix electrode a standardized stimulation protocol is needed.

7. Summary

„Thermal Pain and Electrical Stimulation: neuromodulation of C- and Aδ-fibre afferents in the central nervous system“

by Daniela Pravdic

Acute and chronic pain attenuate the quality of life of patients and cause immense costs for society. Therefore, health professionals continuously try to ameliorate pain treatment concepts. A crucial part of pain treatment is pharmacological pain therapy. It is, albeit, limited by side effects of the medications used and insufficient pain reduction. For this reason, we need complementary approaches for pain treatment. A promising method is pain modulation by electrical stimulation. The method presented in this study influences the transmission of neuronal signals to the first synapse in the central nervous system by facilitating (LTP) or inhibiting (LTD) it.

Attenuating synaptic transmission through low-frequency stimulation (4 Hz) is thought to reduce the sensation of pain in the central nervous system while high-frequency stimulation (100 Hz) should increase the sensation of pain in the experimental setting. In order to investigate our hypothesis, 16 men underwent low-frequency, high-frequency and sham stimulation in a randomized placebo-controlled cross-over study. Pain perception was evaluated with Quantitative Sensory Testing and Visual Analogue Scale. The main findings of our study do not support the promising results of previous studies that low-frequency stimulation led to pain reduction. Our study found that the pain ratings of participants increased after low-frequency stimulation as well as high-frequency stimulation. A possible explanation for this finding compared to the findings of other studies is that our stimulation protocol differed from that of other groups. We conclude from our study that a standardized, reliable stimulation protocol is required to further study the capacity for pain modulation of afferent pain fibres by electrical stimulation with the matrix electrode and potentially use it on a regular basis for pain treatment in patients.

8. Zusammenfassung

„Hitzeschmerz und elektrische Stimulation: Neuromodulation von C- und Aδ-Nervenfaserenden im zentralen Nervensystem“

von Daniela Pravdic

Da akute und chronische Schmerzen viele Menschen betreffen und ihre Lebensqualität mindern sowie hohe Kosten für die Gesellschaft verursachen, ist es wichtig, die Konzepte in der Schmerztherapie fortlaufend zu verbessern, um die zuvor genannten negativen Auswirkungen zu minimieren. Ein zentraler Bestandteil der Schmerztherapie ist die medikamentöse Therapie. Diese ist häufig mit Arzneimittelnebenwirkungen verbunden und kann das Ausmaß der Schmerzen selten auf ein erträgliches Niveau reduzieren. Daher sind ergänzende Maßnahmen zur Schmerzreduktion notwendig. Ein vielversprechendes Verfahren stellt die Schmerzbeeinflussung mittels elektrischer Stimulation dar. Das in dieser Studie vorgestellte Verfahren beeinflusst die Weiterleitung neuronaler Reize an Synapsen im zentralen Nervensystem durch Stärkung (LTP) oder Schwächung (LTD) der synaptischen Übertragung. Durch eine Schwächung synaptischer Übertragung mittels niederfrequenter elektrischer Stimulation (4 Hz) soll die Weiterleitung von Reizen, die im zentralen Nervensystem als Schmerz wahrgenommen werden, reduziert werden. Eine hochfrequente elektrische Stimulation (100 Hz) soll im experimentellen Setting die Schmerzwahrnehmung erhöhen. Dazu wurden bei 16 männlichen Probanden in einem cross-over, randomisierten placebokontrollierten Design die niederfrequente, hochfrequente und eine Placebo-Stimulation angewendet. Die Schmerzwahrnehmung wurde anhand der QST sowie der VAS gemessen. Die Ergebnisse der Studie können die vielversprechenden Ergebnisse vorausgegangener Studien größtenteils nicht unterstreichen. So kommt unsere Studie zu dem Ergebnis, dass die niederfrequente elektrische Stimulation die Schmerzempfindung nicht reduziert, sondern gesteigert hat, ebenso wie die hochfrequente Stimulation. Ein möglicher Grund für die unterschiedlichen Ergebnisse im Vergleich zu vorausgegangenen Studien sind die unterschiedlichen Stimulationsprotokolle. Es lässt sich zusammenfassend aus den Ergebnissen herleiten, dass ein einheitliches, verlässliches Stimulationsprotokoll helfen kann, die therapeutischen Möglichkeiten der elektrischen Stimulation afferenter Schmerzfasern besser zu untersuchen und sie gegebenenfalls zu einem festen Bestandteil der Schmerztherapie von Patientinnen und Patienten zu machen.

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10. Attachment

Datum:

VP-Code: ______________________

STAI – S – X1

Anleitung: Im folgenden Fragebogen finden Sie eine Reihe von Feststellungen, mit denen man sich selbst beschreiben kann. Bitte lesen Sie jede Feststellung durch und wählen Sie aus den vier Antworten diejenige aus, die angibt, wie Sie sich **jetzt,** d.h. **in diesem Moment,** fühlen. Kreuzen Sie bitte bei jeder Feststellung die von Ihnen gewählte Antwort an. Es gibt keine richtigen oder falschen Antworten. Überlegen Sie bitte nicht lange und denken Sie daran, diejenige Antwort auszuwählen, die Ihren **augenblicklichen** Gefühlszustand am besten beschreibt.	ÜBERHAUPT NICHT	EIN WENIG	ZIEMLICH	SEHR
001. Ich bin ruhig	1	2	3	4
002. Ich fühle mich geborgen	1	2	3	4
003. Ich fühle mich angespannt	1	2	3	4
004. Ich bin bekümmert.	1	2	3	4
005. Ich bin gelöst	1	2	3	4
006. Ich bin aufgeregt	1	2	3	4
007. Ich bin besorgt, dass etwas schiefgehen könnte	1	2	3	4
008. Ich fühle mich ausgeruht	1	2	3	4
009. Ich bin beunruhigt	1	2	3	4
010. Ich fühle mich wohl	1	2	3	4
011. Ich fühle mich selbstsicher	1	2	3	4
012. Ich bin nervös	1	2	3	4
013. Ich bin zappelig	1	2	3	4
014. Ich bin verkrampft	1	2	3	4
015. Ich bin entspannt	1	2	3	4
016. Ich bin zufrieden	1	2	3	4
017. Ich bin besorgt	1	2	3	4
018. Ich bin überreizt	1	2	3	4
019. Ich bin froh	1	2	3	4
020. Ich bin vergnügt	1	2	3	4

Datum:

VP-Code: ____________________

STAI – T – X2

Anleitung: Im folgenden Fragebogen finden Sie eine Reihe von Feststellungen, mit denen man sich selbst beschreiben kann. Bitte lesen Sie jede Feststellung durch und wählen Sie aus den vier Antworten diejenige aus, die angibt, wie Sie sich **im Allgemeinen** fühlen. Kreuzen Sie bitte bei jeder Feststellung die von Ihnen gewählte Antwort an. Es gibt keine richtigen oder falschen Antworten. Überlegen Sie bitte nicht lange und denken Sie daran, diejenige Antwort auszuwählen, die am besten beschreibt, wie Sie sich im **Allgemeinen** fühlen.	FAST NIE	MANCHMAL	OFT	FAST IMMER
001. Ich bin vergnügt	1	2	3	4
002. Ich werde schnell müde	1	2	3	4
003. Mir ist zum Weinen zumute	1	2	3	4
004. Ich glaube, mir geht es schlechter als anderen Leuten	1	2	3	4
005. Ich verpasse günstige Gelegenheiten, weil ich mich nicht schnell genug entscheiden kann	1	2	3	4
006. Ich fühle mich ausgeruht	1	2	3	4
007. Ich bin ruhig und gelassen	1	2	3	4
008. Ich glaube, dass mir meine Schwierigkeiten über den Kopf wachsen	1	2	3	4
009. Ich mache mir zu viel Gedanken über unwichtige Dinge	1	2	3	4
010. Ich bin glücklich	1	2	3	4
011. Ich neige dazu, alles schwer zu nehmen	1	2	3	4
012. Mir fehlt es an Selbstvertrauen	1	2	3	4
013. Ich fühle mich geborgen	1	2	3	4
014. Ich mache mir Sorgen über ein mögliches Missgeschick	1	2	3	4
015. Ich fühle mich niedergeschlagen	1	2	3	4
016. Ich bin zufrieden	1	2	3	4
017. Unwichtige Gedanken gehen mir durch den Kopf und bedrücken mich	1	2	3	4
018. Enttäuschungen nehme ich so schwer, dass ich sie nicht vergessen kann	1	2	3	4
019. Ich bin ausgeglichen	1	2	3	4
020. Ich werde nervös und unruhig, wenn ich an meine derzeitigen Angelegenheiten denke	1	2	3	4

Datum ___ / ___ / ___ (Tag / Monat / Jahr)
VP-Code: ________________________

CTQ

Diese Fragen befassen sich mit einigen Ihrer Erfahrungen während Ihrer Kindheit und Jugend. Auch wenn die Fragen sehr persönlich sind, versuchen Sie bitte, sie so ehrlich wie möglich zu beantworten. Streichen Sie dazu bitte für jede Frage die Zahl durch, die am besten beschreibt, wie Sie rückblickend die Situation einschätzen.

Antwortbeispiel: 1 ~~2~~ 3 4 5

Als ich aufwuchs...	**Trifft auf mich zu...**				
	über-haupt nicht	sehr selten	einige Male	häufig	sehr häufig
1. hatte ich nicht genug zu essen.	1	2	3	4	5
2. wusste ich, dass sich jemand um mich sorgte und mich beschützte.	1	2	3	4	5
3. bezeichneten mich Personen aus meiner Familie als “dumm”, “faul” oder “hässlich”.	1	2	3	4	5
4. waren meine Eltern zu betrunken oder von anderen Drogen “high”, um für die Familie zu sorgen.	1	2	3	4	5
5. gab es jemanden in der Familie, der mir das Gefühl gab, wichtig und jemand Besonderes zu sein.	1	2	3	4	5
6. musste ich dreckige Kleidung tragen.	1	2	3	4	5
7. hatte ich das Gefühl, geliebt zu werden.	1	2	3	4	5
8. glaubte ich, dass meine Eltern wünschten, ich wäre nie geboren.	1	2	3	4	5
9. wurde ich von jemandem aus meiner Familie so stark geschlagen, dass ich zum Arzt oder ins Krankenhaus musste.	1	2	3	4	5
10. gab es nichts, was ich an meiner Familie ändern wollte.	1	2	3	4	5
11. schlugen mich Personen aus meiner Familie so stark, dass ich blaue Flecken oder Schrammen davontrug.	1	2	3	4	5
12. wurde ich mit einem Gürtel, einem Stock, einem Riemen oder mit einem harten Gegenstand bestraft.	1	2	3	4	5
13. gaben meine Familienangehörigen aufeinander acht.	1	2	3	4	5
14. sagten Personen aus meiner Familie verletzende oder beleidigende Dinge zu mir.	1	2	3	4	5

Datum ___ / ___ / ___ (Tag / Monat / Jahr)
VP-Code: ________________________

PCS

Hier finden Sie verschiedene Fragen vor. Bitte lesen Sie jeweils die Einleitung und füllen Sie nachfolgenden Fragen aus.
Irgendwann im Leben erleidet jeder Mensch einmal Schmerzen. Dies können z.B. Kopf-, Zahn-, Gelenk- oder Muskelschmerzen sein. Menschen sind oft Situationen ausgesetzt, die Schmerzen verursachen, wie Krankheiten, Verletzungen, Zahnbehandlungen oder Operationen. Wir sind an den Gedanken und Gefühlen interessiert, die Sie haben, wenn Sie Schmerzen erleiden.
Die folgenden dreizehn Sätze beschreiben verschiedene Gedanken und Gefühle, die bei Schmerzen auftreten können. Bitte markieren Sie auf der folgenden Skala wie stark diese Gedanken und Gefühle auf Sie zutreffen, wenn Sie Schmerzen haben.

Antwortbeispiel: 0 [✓ 1] 2 3 4

Wenn ich Schmerzen habe, beschäftigen mich folgende Gedanken:

	Trifft überhaupt nicht zu	Trifft eher nicht zu	Teils-teils	Trifft eher zu	Trifft immer zu
1. Ich mache mir ständig Sorgen, ob die Schmerzen wohl jemals wieder aufhören werden?	0	1	2	3	4
2. Ich denke, ich kann nicht mehr.	0	1	2	3	4
3. Der Zustand ist schrecklich und ich denke, dass es nie mehr besser wird.	0	1	2	3	4
4. Der Zustand ist furchtbar und droht mich zu überwältigen.	0	1	2	3	4
5. Ich habe das Gefühl, ich halte es nicht mehr aus.	0	1	2	3	4
6. Ich bekomme Angst, dass die Schmerzen noch stärker werden.	0	1	2	3	4
7. Ich denke ständig an andere Situationen, in denen ich Schmerzen hatte.	0	1	2	3	4
8. Ich wünsche mir verzweifelt, dass die Schmerzen weggehen.	0	1	2	3	4
9. Ich kann nicht aufhören, an die Schmerzen zu denken.	0	1	2	3	4
10. Ich denke ständig daran, wie sehr es schmerzt.	0	1	2	3	4
11. Ich denke ständig daran, wie sehr ich mir ein Ende der Schmerzen herbeiwünsche.	0	1	2	3	4
12. Es gibt nichts was ich tun kann, um die Schmerzen zu lindern.	0	1	2	3	4

Danksagung

An dieser Stelle möchte ich meinen besonderen Dank nahestehenden Personen entgegenbringen, ohne deren Mithilfe die Anfertigung dieser Promotionsschrift nicht zustande gekommen wäre.

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Ich danke der Leiterin unserer Arbeitsgruppe Univ.-Prof. Dr. rer. soc. Dipl.-Psych. Ute Habel dafür, dass ich die Arbeit in ihrer Arbeitsgruppe durchführen durfte, für die fachliche Unterstützung und dafür, dass ich Räumlichkeiten und Materialien zur Verfügung gestellt bekommen habe.
Ein besonderer Dank gilt Max Röhl, der mich beim technischen Aufbau der Experimente, häufig auch zu später Stunde, unterstützt hat.
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Ich bin allen Probanden zu Dank verpflichtet, die an dieser Studie teilgenommen haben. Ohne sie wäre die Studie nicht zustande gekommen.

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geprägt. Ihr Vorbild hat mich ermutigt, die Dissertation mit Disziplin und Resilienz fertigzustellen.

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Erklärung zur Datenaufbewahrung

Erklärung § 5 Abs. 1 zur Datenaufbewahrung

Hiermit erkläre ich, dass die dieser Dissertation zu Grunde liegenden Originaldaten in der **Klinik für Psychiatrie, Psychotherapie und Psychosomatik** des Universitätsklinikums Aachen hinterlegt sind.

Erklärung zum Eigenanteil

Eidesstattliche Erklärung gemäß § 5 Abs. (1) und § 11 Abs. (3) 12. der Promotionsordnung

Hiermit erkläre ich, Daniela Pravdic an Eides statt, dass ich folgende in der von mir selbstständig erstellten Dissertation „Thermal Pain and Electrical Stimulation: neuromodulation of C- and Aδ-fibre afferents in the central nervous system“ dargestellten Ergebnisse erhoben habe.

Bei der Durchführung der Arbeit hatte ich folgende Hilfestellungen, die in der Danksagung angegeben sind.

	Daniela Pravdic	Ann-Kristin Röhr	Dr. Han-Gue Jo	Univ.-Prof. Dr. Roman Rolke	Max Röhl	Jun-Prof. Dr. Lisa Wagels	Univ.-Prof. Dr. Ute Habel	Summe (%)
Studienüberwachung		20				80		100
Studiendesign/Konzeption	20		80					100
Rekrutierung der Probanden	100							100
Datenvorverarbeitung und Datenmanagement	100							100
Durchführung der EEG-Aufzeichnung	100							100
Durchführung der Experimente zum Hitzeschmerz und der QST	100							100
Technischer Aufbau	50				50			100
Statistische Auswertung	50					50		100
Bereitstellung von Materialien				20			80	100
Interpretation der Datenauswertung	90					10		100

Unterschrift der Doktorandin

Als Betreuerin der obigen Dissertation bestätige ich die Angaben von Daniela Pravdic

Unterschrift der Doktormutter