PAIN IN EUROPE XIV

COMORBIDITY OF CHRONIC PAIN AND MENTAL HEALTH DISORDERS: BREAKING THE CYCLE

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3	I-A.27	THE MISMATCH HYPOTHESIS FOR CHRONIC PAIN – INSIGHTS FROM ANCIENT, COMPARATIVE AND NEUROIMAGING GENOMICS **Ole Goltermann,** Germany
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8	II-A.21	PREOPERATIVE SUSCEPTIBILITY TO DEVELOPING SECONDARY HYPERALGESIA IS ASSOCIATED WITH POST-THORACOTOMY PAIN AT TWO MONTHS **Solenn Gousset,** Belgium
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10	III-A.45	THE DYNAMIC BALLET OF NAV1.8 TRAFFICKING IN CHRONIC PAIN **Nicolas Dumaire,** United States

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I-A.30

Altered Gut Microbiome Composition and Function in Individuals with Complex Regional Pain Syndrome

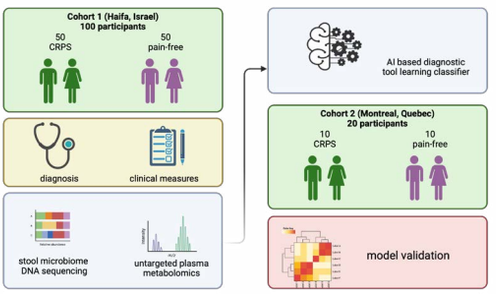
Emmanuel Gonzalez, Tali Sahar, May Haddad, Sylvie Toupin, Ramzi Zioud, Muhammad Zoabi, Lilach Eyal Waldman, Zohar Tal Leshinsky, Maayan Ben Sasson, Vibhu Kumar, Yosefa Marom, Ayelet Midbari, Nicholas JB Brereton, Yoram Shir, Amir Minerbi

Introduction

Our team has recently demonstrated the significant role of the gut microbiome in fibromyalgia.
This study aims to address the following questions:

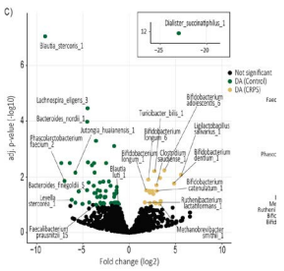
- Do individuals with Complex Regional Pain Syndrome (CRPS) exhibit alterations in their gut microbiome?
- Are these microbiome changes consistent across different environments?

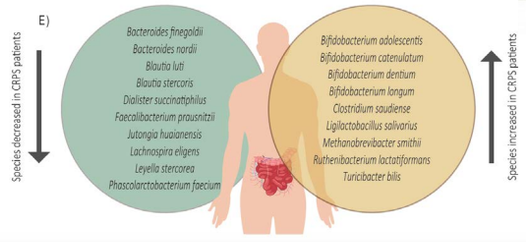
Design

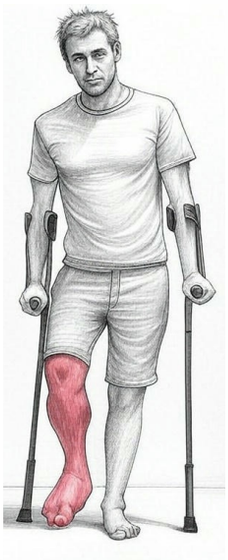


Results

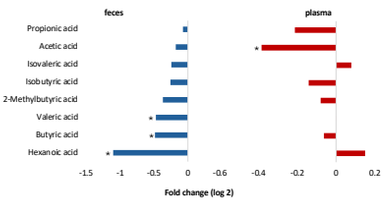
1. Certain bacterial taxa were differentially abundant in individuals with CRPS, using 16S rRNA sequencing.







2. Measurable changes were observed in the concentrations of bacterial-derived short-chain fatty acids (SCFA) in the feces and plasma of CRPS patients using mass spectrometry.



3. A machine learning algorithm (Generalized Linear Model) accurately identified patients with CRPS based solely on the composition of their gut microbiome. The model achieved over 90% sensitivity and specificity when tested on a geographically discordant validation cohort.

Conclusions

1. Patients with CRPS exhibit a unique gut microbiome composition and function.
2. These microbiome changes are independent of environmental factors.
3. Machine learning algorithms can accurately diagnose CRPS patients based solely on the composition of their gut microbiome.

Minerbi Lab

Clinical Research Institute at Rambam

TECHNION Israel Institute of Technology

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III-C.42

Dynamics of Electroencephalographic Peak Alpha Frequency in Capsaicin-Induced Pain and Resolution

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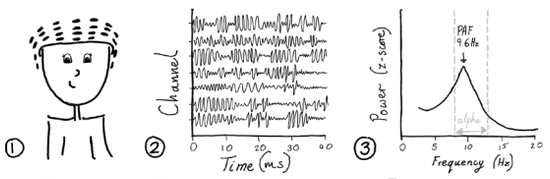
2 Department of Health Science and Technology, Aalborg University, Aalborg, Denmark

INTRODUCTION

- Electroencephalographic (EEG) peak alpha frequency (PAF) may be associated with chronic pain presence [1,2] but also may predict acute post-operative [3] and experimentally-induced prolonged pain [4,5].
- **However, we don't know whether lower PAF would serve better as a prospective marker of pain risk or metric of ongoing chronic pain.**
- Prolonged experimental pain can decrease PAF [6,7,8,9], without reversal upon pain resolution [7]. Thus, might PAF dynamics reflect **pain-associated states** rather than ongoing pain?



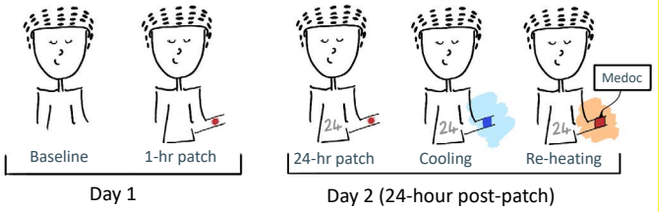
EEG cap | EEG signal (brainwaves) | Frequency spectra

AIMS

To understand mechanisms relating PAF to pain, by investigating effects of capsaicin-induced pain on PAF during i) 1- and ii) 24-hours of pain, and iii) resolution via cooling and facilitation via re-heating

STUDY DESIGN & METHODS

- **Pre-registered** Bayesian secondary analysis (https://osf.io/5ekxs/) using data from two **placebo-controlled, cross-over** studies (N=52).



- **Study 1:** Capsaicin- & placebo-patch sessions. 5-min EEG at baseline & 1-hour post-patch (n=28) [10]. Numerical rating scale (NRS) pain every 5 mins.
- **Study 2:** Also included sessions 24-hour post patch (n=24), with EEG during rest, cooling & reheating [11]. NRS every hour.
- Global PAF (center of gravity) extracted using DISCOVER-EEG [12].

RESULTS

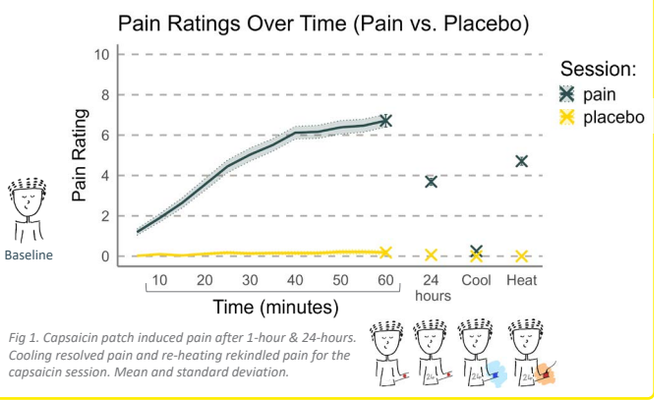
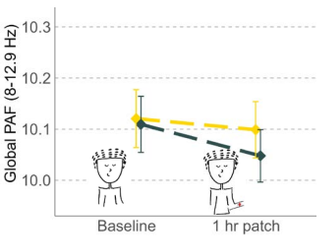


Fig 1. Capsaicin patch induced pain after 1-hour & 24-hours. Cooling resolved pain and re-heating rekindled pain for the capsaicin session. Mean and standard deviation.

RESULTS (CONT.)

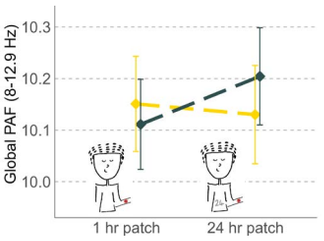
i) 1-hour post-patch



Moderate evidence for PAF decrease during 1-hour capsaicin pain vs. placebo

(b=-0.04, 96% CrI: [-0.11, 0.02], evidence ratio [ER]=8.8, 90% posterior probability, n=52).

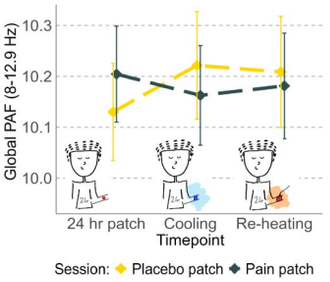
ii) 24-hours post-patch



Strong evidence for PAF increase from 1-hour to 24-hours in capsaicin vs. placebo

(b=0.14, 96% CrI: [0.05, 0.24], ER=443.4, 100% posterior probability, n=24).

iii) Cooling and re-heating



Strong evidence for PAF decrease from 24-hour application to cooling

(b=-0.10, 96% CrI: [-0.19,-0.01], ER=50.3, 98% probability, n=24).

Modest/unclear evidence for PAF decrease from 24-hour application to re-heating

(b=-0.04, 96% CrI: [-0.13,0.06], ER=3.39, 77% probability, n=24).

Fig 2. Mean & standard error bars for global peak alpha frequency (PAF) across 5 timepoints

Baseline PAF **did not correlate** with current pain after 1-hour or 24-hours of capsaicin patch application.

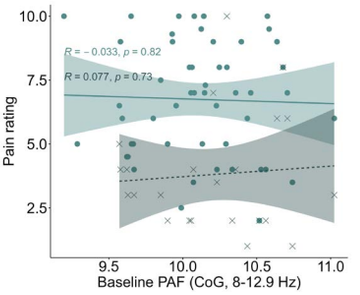


Fig 3. Correlations between baseline peak alpha frequency (PAF) using the centre of gravity method (CoG) & pain after 1-hour (green) and 24-hours (grey) of capsaicin.

CONCLUSIONS

Capsaicin-induced pain affects PAF, with acute decreases then increases after 24 hours, possibly reflecting compensatory attention mechanisms, since a decrease was also found with pain resolution.

Findings demonstrate clear temporal PAF dynamics and underscore the complexity of pain adaptation during prolonged pain.

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12. Gil Avila et al., 2023 – Scientific Data.

The authors declare no conflict of interest

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I-A.27

The Mismatch Hypothesis for Chronic Pain – Insights from Ancient, Comparative and Neuroimaging Genomics

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2 Max Planck School of Cognition, Leipzig, Germany

INTRODUCTION

- An evolutionary perspective on chronic pain offers unique insights into the **adaptive origins** and **vulnerabilities** of the pain system.[1]
- The **mismatch-hypothesis** posits that the gradual processes of evolution have failed to keep pace with the rapid changes and challenges of modern society, resulting in a **mismatch** between our biological **predisposition** and the demands of our **environment.**[2]
- A key prediction of this hypothesis is that chronic pain is under **current selection pressure** and strongly **shaped** by **epigenetic mechanisms.**
- In this study, by combining methods from ancient, comparative and neuroimaging genomics, we investigate the **evolutionary history** of common **genetic variations** linked to chronic pain conditions and associated brain morphology, **evaluating** central predictions of the **mismatch hypothesis**.

DATA / METHODS

More details here

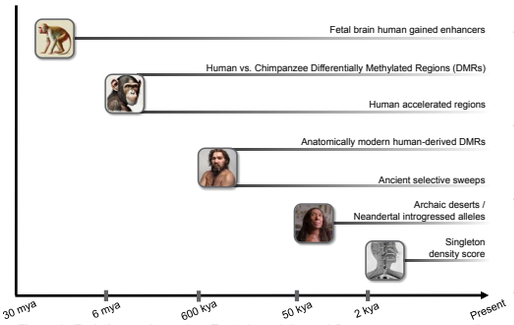

Figure 1: Evolutionary timescales. To study evolutionary influences on common genetic variations of COPC, we used seven genome annotations, covering the last 30 million years.

- We obtained genome-wide associations study (**GWAS**) data for **chronic overlapping pain conditions**[3] (COPC, ***N* = 164,778**) using partitioned heritability analysis (LDSC[5]), gene-set enrichment analysis (MAGMA[6]) and singleton density scores (SDS[7]).
- As a first step, we tested for shared genetic influences of these 46 brain regions with COPC (Fig. 2). Regions with a **shared genetic architecture** were selected for further analysis.
- Next, we explored the **evolutionary history** (spanning the **past 30mya**, see Fig. 1) of **common genetic variations** using partitioned heritability analysis (LDSC[5]), gene-set enrichment analysis (MAGMA[6]) and singleton density scores (SDS[7]).
- Additionally, we tested heritability enrichment for **epigenetic influences**, including epigenetic activity related to immune-diseases[8], and active marks in fetal human brain development[9].

RESULTS

Shared genetic architecture

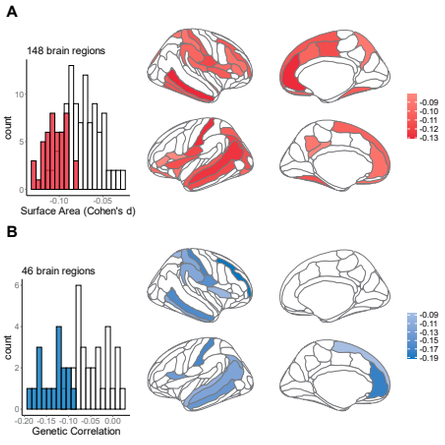

Figure 2: Selected brain regions. (**A**) Brain regions with reduced surface area between COPC individuals and controls, in red statistically significant ones. (**B**) Genetic correlation between chronic pain and surface area, in blue statically significant ones.

Positive selection pressure on chronic pain

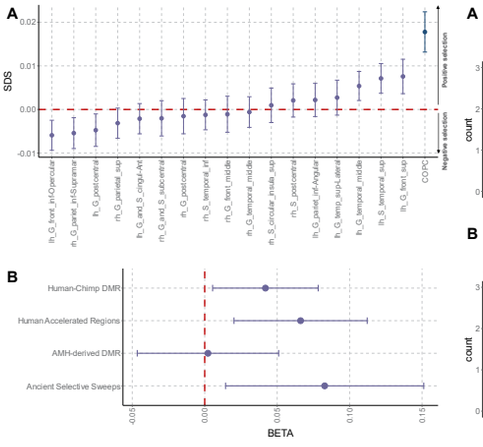

Figure 3 (A) Singleton density scores. SDS are used to detect selection pressure acting over the past ~100 generations (~2000-3000 years). For chronic overlapping pain we found a statistically significant positive SDS, indicating positive selection of this trait. **(B) MAGMA results.** None of the four investigated evolutionary annotations revealed a statistically significant enrichment in gene-set analysis.

Deep evolutionary and epigenetic signals

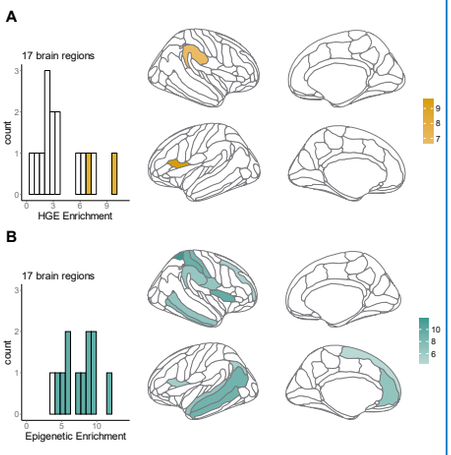

Figure 4: Partitioned heritability analysis. (**A**) The left inferior operculum and the right parietal inferior supramarginalis showed statistically significant heritability enrichment for the fetal human gained enhancer elements. (**B**) Except of the left postcentral gyrus, all selected brain regions showed statistically significant enrichment for fetal human brain active marks.

CONCLUSIONS

- **Deep** (~30mya) and **recent** (past ~2000 years) **evolutionary influences** have shaped genetic variations of chronic overlapping pain and associated brain morphology.
- We observed **no heritability enrichment** for epigenetic activity related **to immune diseases**. However, we found **strong heritability enrichment** for **epigenetic marks** active during fetal human brain development, highlighting the **involvement** of **early epigenetic mechanisms** in chronic overlapping pain conditions.
- These findings align with the mismatch hypothesis, suggesting that chronic overlapping pain is under **ongoing selection pressure** and is strongly **influenced by epigenetic factors.**

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CODE AND DATA

Code / ReadME

Imaging data

Chronic pain data

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I-B.14

Cortical excitability measured by EEG aperiodic exponent shapes the brain's response to painful laser stimulation

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2 Institute of Neuroscience (IoNS), UCLouvain, Brussels, Belgium

INTRODUCTION

The intensity and character of pain evoked by external activation of the nociceptive system can be modulated centrally at the level of the spinal dorsal horn via descending pain modulatory pathways[1]. The key role in this process has been previously attributed to the prefrontal cortex (PFC)[2]. It is therefore likely, that the momentary functional state of the PFC influences the brain's response to a painful stimulus.

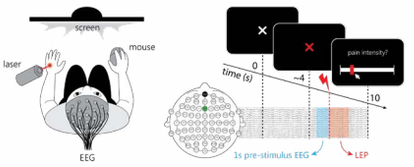
The level of activation and functional integration of a cortical network is governed by the local ratio of neuronal excitation (E) and inhibition (I)[3]. Previous studies suggested that the E/I in the human brain can be estimated from the power spectrum density (PSD) of electroencephalogram (EEG)[4], specifically from the slope of its aperiodic component defined by the exponent β [5,6]. We propose that the excitability of functionally specific cortical areas can be approximated by β extracted from neural activity modelled at anatomically relevant source locations.

AIMS

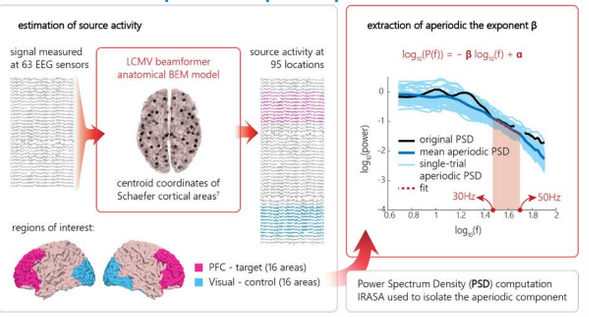
Presented study aimed to test, whether the E/I within the PFC approximated by β can predict the readout of cortical activity evoked by a painful stimulus (laser-evoked potentials; LEP) and/or the intensity of elicited pain. To pinpoint the origin of analyzed signals, the extraction of β was performed in the source-space. The PFC values were tested against values obtained from control visual cortex, which presumably has a minimal impact on the processing of painful stimuli.

METHODS

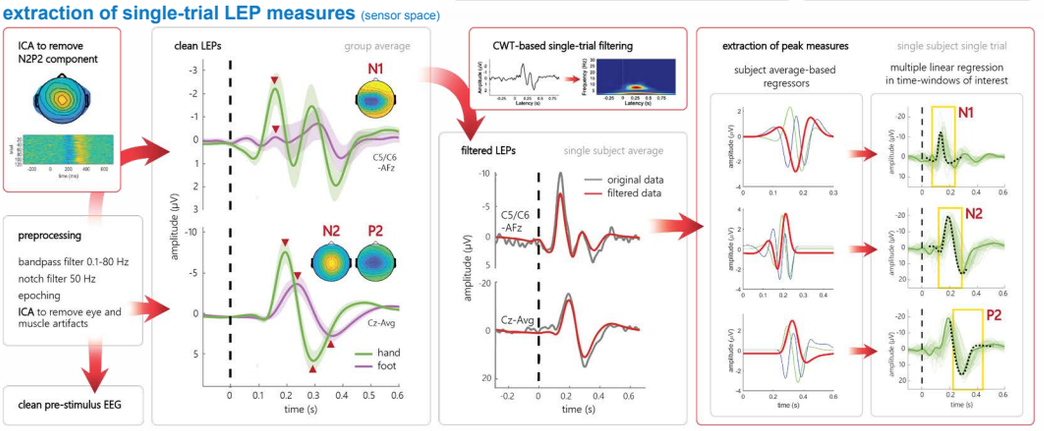
- **45 healthy volunteers:** 14 males, mean age 25.9 ± 6.2 (SD), 39 right-handed)
- **laser stimulation**: Nd-Yap laser, wl 1340 nm, energy 1,75J, pulse 3ms, Ø 5mm
- delivered to dorsum of both hands, both feet, or hand and foot – 60 stimuli/area
- **EEG recording**: 63-channel Brain Products system with active electrodes, ref Fz
- **pain intensity ratings:** taken after each stimulus using a visual analogue scale (no pain – maximum imaginable localized pain)



extraction of the aperiodic exponent β

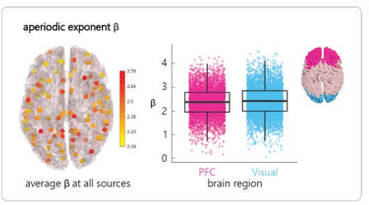


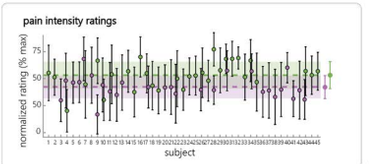
extraction of single-trial LEP measures (sensor space)

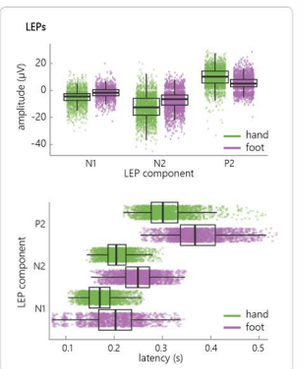


RESULTS

Mean values (± SD) of **β** reached 2.37 ± 0.60 in the PFC area and 2.42 ± 0.63 in the control Visual cortex (no statistical difference). For LEP measures and pain ratings, significant differences were found across stimulated areas. **N1** peaked at 172 ± 30 ms and reached -5.29 ± 5.29 μV when hand was stimulated, foot stimulation led to latency 199 ± 54 ms and amplitude -1.98 ± 4.23 μV. In **N2,** hand stimulation led to latency 206 ± 27 ms and amplitude -12.65 ± 8.75 μV, foot stimulation to latency 248 ± 37 ms and amplitude -7.32 ± 7.02 μV. **P2** peaked at 307 ± 43 ms and reached 9.76 ± 6.76μV following hand stimulation, foot stimulation led to latency 373 ± 50 ms and amplitude 5.14 ± 5.18 μV. **Pain ratings** reached on average 27 ± 17.5/100 (= 53.3 ± 23.3% normalized to maximum individual rating) after hand stimulation, foot stimulation led to mean rating 25.8 ± 18.8/100 (normalized value 42.2 ± 24.3 %max).







The effect of β was evaluated using Linear Mixed Models with random intercept: ***outcome variable ~ exponent * region + area + (1 | subject)***
We found significant, but very small (d < 0.1) positive association between β and **N1 latency** and negative association between β and **amplitude of N2 and P2.** The directions of the effects correspond to our predictions. No effect of brain region, nor interaction between brain region and exponent, was found.

outcome variable	factor	df	F value	p value
N1 latency	**β**	**1, 7661.808**	**7.331**	**0.007**
	brain region	1, 7646.209	0.030	0.862
	stimulated area	1, 7680.997	3648.948	< 0.001
	β * brain region	1, 7646.207	0.018	0.893
N2 amplitude (log-transformed)	**β**	**1, 10009.802**	**5.825**	**0.016**
	brain region	1, 9967.961	0.013	0.908
	stimulated area	1, 9844.477	322.410	< 0.001
	β * brain region	1, 9967.983	0.007	0.932
P2 amplitude (log-transformed)	**β**	**1, 9983.314**	**17.376**	**< 0.001**
	brain region	1, 9969.000	0.013	0.910
	stimulated area	1, 8915.747	178.672	< 0.001
	β * brain region	1, 9969.049	0.031	0.860

CONCLUSIONS

Our findings show that larger values of the aperiodic exponent measured in the pre-stimulus EEG are associated with a slower N1 and smaller N2 and P2 LEP amplitudes. This is in line with previous claims that more negative slope of the aperiodic component indicates a shift of E/I towards cortical inhibition – in this aspect, our study presents another piece of evidence supporting the relevance of β as a measure of cortical excitability. However, we were not able to demonstrate any selective association between the functional state of the PFC and the processing of a painful stimulus. As it is usually the case – more research is needed.

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ICAN

I-C.35

Investigating corticospinal excitability in response to experimentally induced acute pain and itch

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INTRODUCTION

- Acute **pain** and **itch** evoke **different bilateral motor behaviors**: Pain triggers withdrawal, whereas itch induces a scratching behavior [1].
- **Despite** these motor response **differences**, pain and itch share **similar sensory manifestations**, such as **hyperalgesia** for pain and **hyperknesis** for itch [2].
- Experimentally induced acute **pain decreases corticospinal excitability** [3], which is measured as motor-evoked potentials (MEPs) induced by transcranial magnetic stimulation (TMS).
- The effects of experimentally induced acute **itch** on TMS-evoked MEPs are **unknown**.

AIMS

- **Investigate whether acute experimental muscle pain and itch have opposite effects on MEPs when stimulated with TMS, pain being inhibitory and itch excitatory.**
- **Explore whether the induced pain and itch increase MEPs in the contralateral limb**

STUDY DESIGN & METHODS

- **Participants:** Twenty-one healthy volunteers (M: 11, F:10) in a two-session, crossover study.
- **Acute pain and itch:** Hypertonic saline injection and cutaneous histamine application to the right first dorsal interosseous (FDI) muscle.
- **Numeric rating scale** (NRS) to measure pain/itch every ~30 seconds.
- **TMS:** Stimulation of **both left and right** motor cortices (120% of resting motor threshold), targeting the right and left FDI muscles, inducing **MEPs** every ~7 seconds (Figure 1) .

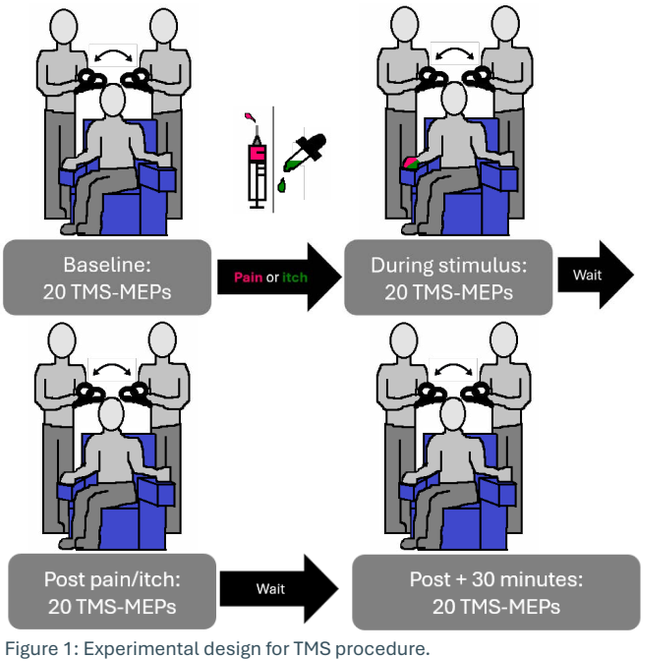

Figure 1: Experimental design for TMS procedure.

STATISTICAL ANALYSIS:

- **Two-way repeated measures ANOVA.** Post hoc pairwise analyses with Bonferroni-corrected multiple comparisons.
- **Pearson's correlation** analysis

RESULTS

- **NRS** scores **were higher** for acute **pain** than itch **immediately after** application up to 120 seconds **but higher for acute itch** after 390 seconds (p<0.05, Figure 2).

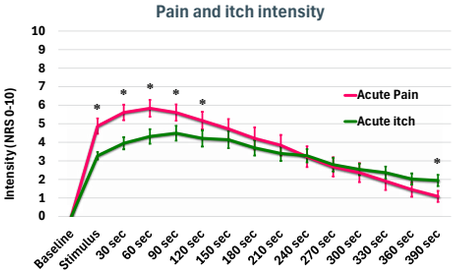

Figure 2: Mean ± SEM of pain- and itch NRS scores over time.

- **Both** acute pain and acute itch **reduced right-FDI MEPs** compared to baseline (p<0.05, Figure 3). **No changes** in left-FDI MEPs.

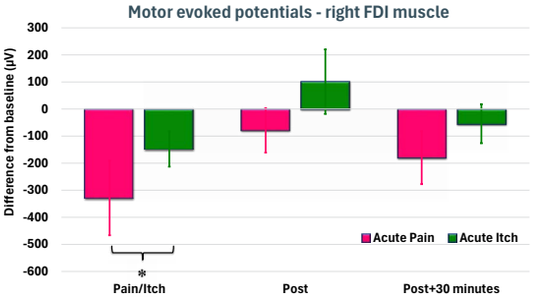

Figure 3: Mean ± SEM of absolute changes from baseline in the right FDI-MEPs.

- **Correlations** between **MEP reductions** in the **left and right** FDI muscles were found during itch (p<0.001) and pain (p<0.05, Figure 4)

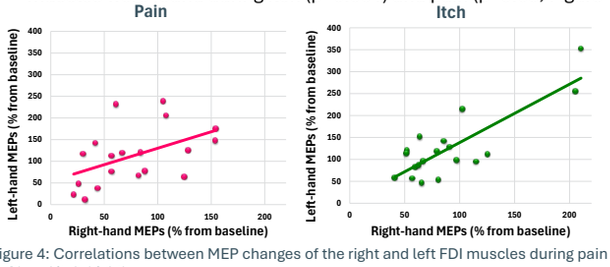

Figure 4: Correlations between MEP changes of the right and left FDI muscles during pain (left) and itch (right).

CONCLUSIONS

- **Contrary to the hypothesis, acute experimental pain and itch produced corticospinal inhibition, suggesting non-significantly different effects on motor output in the affected limb.**
- **Both modalities had a bilateral effect on corticospinal tract excitability, suggesting interhemispheric communication during acute pain and itch.**

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The authors declare no conflict of interest

I-B.06

Temporal contrast enhancement during auditory and thermal stimulation

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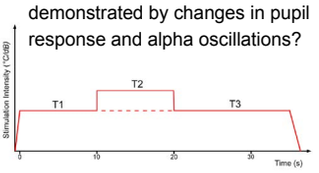
INTRODUCTION

- Offset analgesia, mediated by temporal contrast enhancement (TCE), is often used to assess endogenous pain inhibition. [1]
- It is characterized by a disproportionate reduction in pain following a subtle decrease in a thermal stimulus. [2]
- It remains unclear whether TCE can be induced independently of the nociceptive system and whether it is processed by similar neural pathways. [3-4]

AIM

Can thermal and auditory stimulation induce TCE, and do they correlate? Can this effect be demonstrated by changes in pupil response and alpha oscillations?



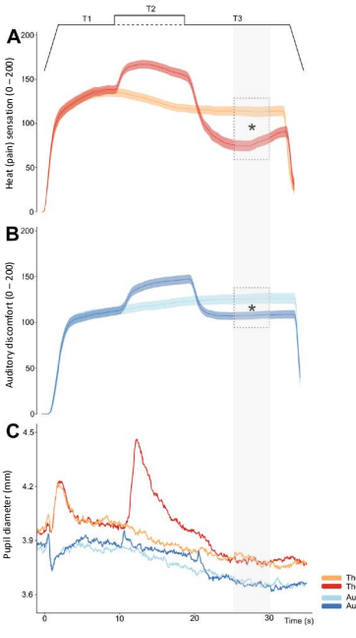
▲ ***Figure 1.*** *Overview of the stimulation paradigm. Three time intervalls were used: T1 (0-9s), T2 (10-19s) and T3 (20-35s).*

METHOD

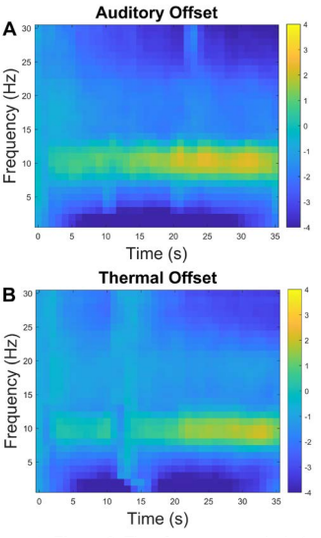
- Healthy participants (n = 33) evaluated the sensation of heat or sound in constant and offset trials with an electronic visual scale.
- Auditory stimulation with over-ear headphones was applied using a 1000Hz sine tone with a maximum of 100dB. Thermal stimulation was applied using a thermal stimulator (temperatures up to 48.5°C). Offset trials consisted of three different time points (T1-T3) and two different stimulus intensities. An example can be seen in **Figure 1**.
- Additionally, a study (n = 29 healthy participants) replicated the stimulation paradigm while concurrently acquiring electroencephalography (EEG) and pupillometry data.

RESULTS

- A significant TCE effect was observed for both thermal ($p<0.01$) and auditory ($p < 0.01$) stimulation, as illustrated in **Figure 2A/B**.
- However, TCE effects across these two stimulation modalities did not exhibit a significant correlation ($r = 0.26$, $p = 0.14$).
- Preliminary visual inspection of pupillometric data suggests that both modalities elicit changes in pupil diameter, particularly at the onset of stimulation and during the transition to T2 in the offset trial (**Figure 2C**). However, these differences are not visible in T3.
- Furthermore, time-frequency analysis indicates that both stimulation modalities influence alpha-band activity (8–12 Hz), with inducing a change in alpha power during T2.



▶ ***Figure 2.*** *TCE effects for thermal stimulation (**A**) and for auditory stimulation respectively (**B**) (n = 33). Displayed are offset and constant trials (OT, CT) for each modality as well as for the time intervals (T1 (0-10s), T2 (11-20s) and T3 (21-35s)). Average pupillometry for both modalities and trials (**C**). Heat pain, and auditory discomfort were measured using an eVAS (0: no sensation, 100: threshold, 200: maximum pain/discomfort).*



▲ ***Figure 3.*** *Time frequency analysis (n = 29) of the auditory offset trial (**A**) and the thermal offset trial (**B**). The area of interest are alpha oscillations (8-12Hz) throughout the 35 seconds stimulus interval.*

CONCLUSIONS

- Both auditory and thermal stimulation effectively induced TCE, though their effects were uncorrelated.
- Preliminary analysis shows no TCE-driven pupillary response, suggesting marginal autonomic nervous system involvement.
- Both stimulation modalities display changes in alpha oscillations, underscoring their influence on cortical dynamics.

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Pre-registration to both studies can be accessed using the following Link(s):

https://osf.io/643kg

https://osf.io/v37mp

II-B2.W.01

Investigating the role of affective touch by romantic partners in modulating secondary hyperalgesia

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INTRODUCTION

Cutaneous tissue injury can lead to heightened pain sensitivity in the surrounding uninjured areas, referred to as "**secondary hyperalgesia**" (SH). SH occurs as a result of heightened responsiveness of nociceptive neurons in the central nervous system, a process also known as central sensitization[1].

Affective interpersonal touch activates C-fiber afferents called C-Tactile (CT)[2]. It plays a crucial role in modulating pain perception and providing emotional comfort[3]. This type of touch attenuates the salience of impending noxious stimuli by signaling the presence of a socially supportive and nurturing environment[4].

AIM

This study aimed to examine **how interpersonal touch**, when applied by a romantic partner at an optimal velocity to activate CT receptors, **influences the development of secondary hyperalgesia** induced by high-frequency electrical stimulation (HFS)[5].

METHOD

64 Participants (31 ♀ and 33 ♂, N=28 romantic couples)

Age 18-40 years (mean ± SD = 25,3 ± 5,7)

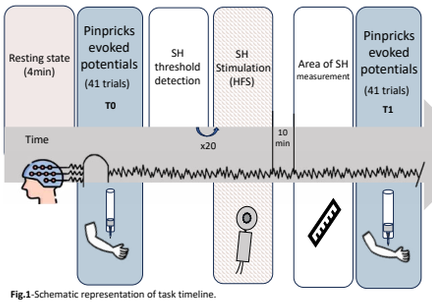

Fig.1-Schematic representation of task timeline.

Statistical Analysis
- Paired sample t-test (Student and Wilcoxon signed-rank)

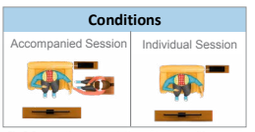

Fig.2-Schematic representation of task conditions

Behavioral Measures:
Pain levels (VAS scale 1-100):
During the pinprick:
Before SH (T0)
After SH (T1)
During the induction of SH
Area of SH

EEG Recording:
- BioSemi ActiveTwo EEG system (64-electrode)
- Sampling rate 512Hz

EEG Pre-processing:
- EEGLAB
- 2-30 Hz band-pass filter

Peak amplitude of Analyzed Components

N-P complex = P peak (100-300ms) -N peak (20-100ms)

RESULTS

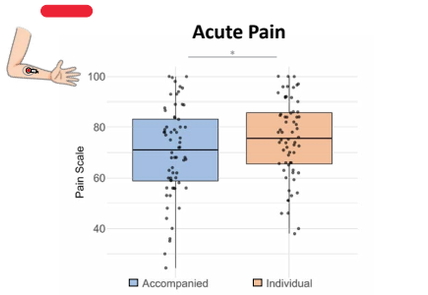

Fig.3- Pain levels during HFS are shown for both conditions. Receiving stroking by their romantic partner **decreases the reported acute pain level** during the moments of stimulation compared to being alone (t(62)=-2.68, p=.009).

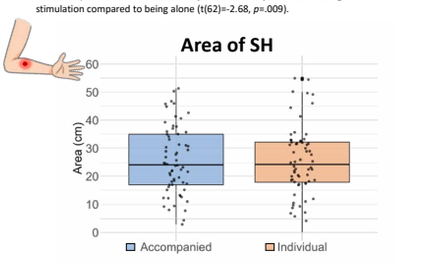

Fig.4- Receiving stroking by their romantic partner **does not decrease** the area of Secondary mechanical hypersensitivity (t(63)=0.176 p=.86).

Induction of SH

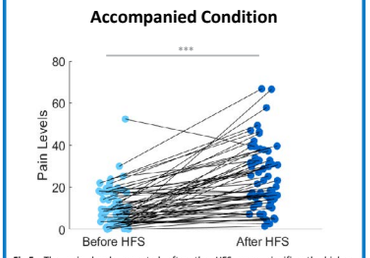

Fig.5- The pain levels reported after the HFS were significantly higher compared to those recorded prior HFS in the **accompanied setting** indicating successful induction of secondary mechanical hypersensitivity (Z=-6,452, p<.001)

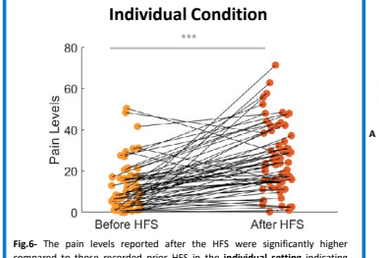

Fig.6- The pain levels reported after the HFS were significantly higher compared to those recorded prior HFS in the **individual setting** indicating successful induction of secondary mechanical hypersensitivity (Z=-5,785, p<.001)

Reported Pain during pinprick stimulation

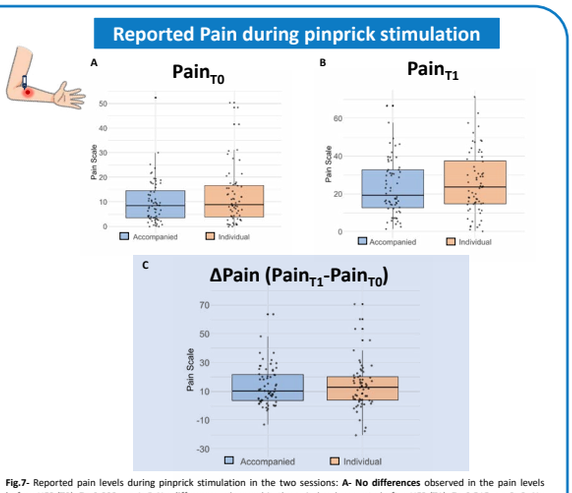

Fig.7- Reported pain levels during pinprick stimulation in the two sessions: **A- No differences** observed in the pain levels **before** HFS (T0), Z=-0.803, p=.4; **B-No differences** observed in the pain levels reported **after** HFS (T1), Z=-0.515, p=.6; **C- No differences** in the computed difference of the pinpricks pain levels (T1-T0), Z=0.31, p=.76.

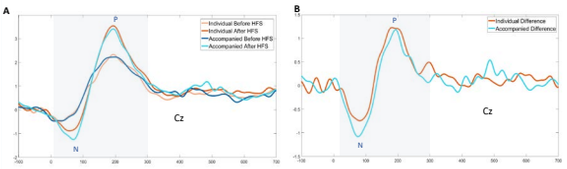

Fig. 8-Graphic of the pinprick evoked potentials measured at Cz electrode. A- Two conditions at T0 and T1; B- plotted difference waveform of Pinprick evoked potentials for both conditions (T1-T0; Z=0.258, p=.8)

CONCLUSIONS

- Touch of a romantic partner may help reduce the perception of pain in individuals experiencing **acute pain**.
- The present findings do not provide support for the hypothesis that the touch of a romantic partner affects sensitivity to mechanical pain stimuli.
- This study highlights the complex nature of pain modulation and the potential role of interpersonal touch in acute pain relief, but **not in pain sensitization**.

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II-A.21

Preoperative Susceptibility to Developing Secondary Hyperalgesia is Associated with Post-Thoracotomy Pain at Two Months

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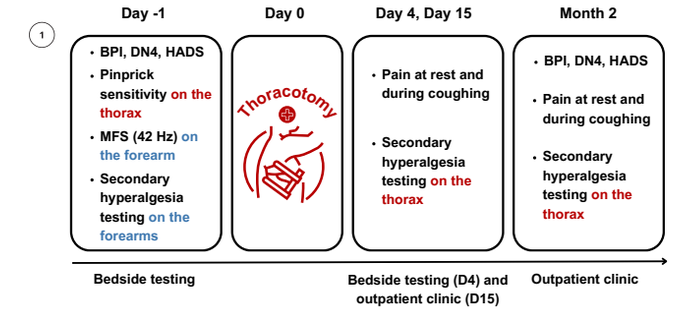
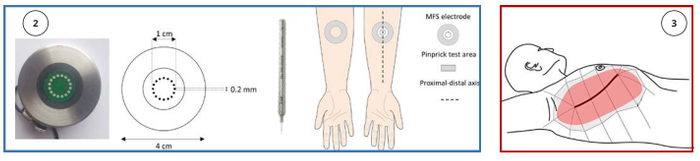
BACKGROUND AND AIM

Persistent pain after thoracotomy is common and significantly impacts quality of life [1,2]. Growing evidence suggests that central sensitization plays a key role in its development, and one of its clinical correlates is secondary hyperalgesia — an increased sensitivity to pain in uninjured surrounding tissue [3]. While prior studies have linked postoperative secondary hyperalgesia to persistent postoperative pain, the predictive value of experimentally induced secondary hyperalgesia before surgery remains unclear [4]. In this prospective study, **we investigated whether individual susceptibility to secondary hyperalgesia**, experimentally induced using middle-frequency electrical stimulation (MFS), **prior to thoracotomy is associated with the presence of persistent pain at two months after surgery**. This approach could shift pain prevention from reactive to truly proactive, enabling early, targeted interventions for vulnerable individuals. We hypothesized that patients with stronger MFS-induced secondary hyperalgesia before surgery would be more likely to develop persistent postoperative pain.

METHODS

Twenty patients undergoing posterolateral thoracotomy for lung cancer were included in the study. Preoperatively (D-1), we experimentally induced secondary hyperalgesia at one of the two forearms. Then, we measured the change in perceived pinprick intensity and the spread of secondary hyperalgesia. At postoperative Day 4, Day 15 and 2 Months, pain and incision-induced hyperalgesia around the scar were assessed.

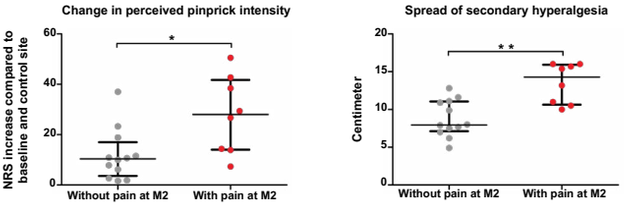




1: Design of the study. 2: Characteristics of the MFS electrode. MFS was applied on one forearm. Changes in pinprick sensitivity were assessed before and after MFS within the grey areas. The length of the area of secondary hyperalgesia was assessed along the proximal-distal axes at the arm that received MFS. 3: Assessment of incision-induced hyperalgesia around the scar (intensity of pinprick sensitivity and area of secondary hyperalgesia).

RESULTS

Patients **with persistent pain** at 2 months report significantly **higher preoperative experimentally-induced secondary hyperalgesia** compared to those without persistent pain.



*MFS-induced secondary hyperalgesia compared between patients with and without cough-evoked pain at the 2-month follow-up. Left: Median change in perceived pinprick intensity. Right: Median spread of secondary hyperalgesia. Shown are the median and interquartile ranges. Each dot represents a single patient. *p < 0.05, **p < 0.01. Significance refers to the Mann–Whitney U test.*

A binary logistic regression combining **the intensity and extent of preoperative hyperalgesia was a significant predictor of cough-evoked persistent pain at two months** (χ^2 = 12.4, p = .002). It showed a high predictive power (McFadden R^2 = 0.462) and an excellent discrimination (AUC = 0.938).

Model	Factors	Chi-squared (df)	p-value	McFadden R^2	AUC
1	Change in perceived intensity	6.639 (18)	0.010	0.247	0.833
2	Length of the area	11.968 (18)	0.0005	0.445	0.885
3	Change in perceived intensity AND Length of the area	12.439 (17)	0.002	0.462	0.938

Logistic regression model summary for cough-evoked pain 2 months after surgery. For each model the chi-squared, its p-value, the McFadden R2, and area under the receiver operating curve (AUC) are shown.

CONCLUSION

Our findings indicate for the first time that **the individual susceptibility to developing experimentally induced secondary hyperalgesia preoperatively may identify patients who are potentially vulnerable to develop persistent post-thoracotomy pain**. While promising, these results require validation in larger cohorts. Still, this study opens the door to a future where pain prevention is personalized — and starts even before the first incision.

FUNDING AND DISCOLSURE

ENvdB was supported by the Fonds de Recherche Clinique of UCLouvain (2018) and the ESA-BJA grant. S.G. has received funding from the European Union's Horizon2020 Research and Innovation Program under grant agreement no 848068. This publication reflects only the authors' view, and the European Commission is not responsible for any use that may be made of the information it contains. The authors declare that they have no conflict of interest.

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II-C.27

The Relationship Between Pain Modulation and Prediction Errors During Secondary Hyperalgesic States: A Novel Virtual Reality Protocol

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INTRODUCTION

- **The Predictive Coding Model**[1] suggests that the brain predicts sensory input based on prior learning. **Prediction errors (PEs)** arise when pain perception deviates from expectations, allowing for adjustments in future predictions.
- In chronic pain, **fear of pain and catastrophising** can lead to pain overestimation and reinforce negative expectations[2].
- The role of **central sensitisation (CS)**[3] in maladaptive persistence of PEs remains unclear.
- The **high-frequency stimulation (HFS) model**[4] induces prolonged secondary hyperalgesia in a well-defined heterotopic area, a hallmark of CS.
- **Virtual reality (VR)** and hand-tracking technology can deliver visual cues before stimulation to experimentally induce PEs inside and outside sensitised areas.

AIM

We explored pain modulatory responses due to experimentally induced PEs following HFS using VR in a healthy cohort.

Our preregistered hypotheses[5] were:

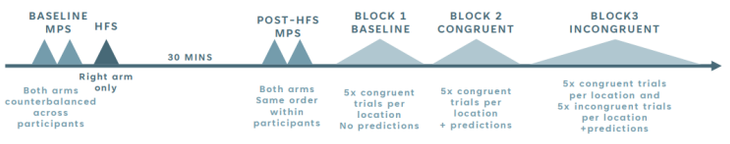
1. *HFS would increase mechanical pain sensitivity measures*
2. *If predicted pain at the attended location is lower than perceived pain, the result would be lower pain perception compared to a match between predicted and perceived pain, and vice versa*
3. *We explored how these bidirectional relationships vary depending on presence of absence of CS*

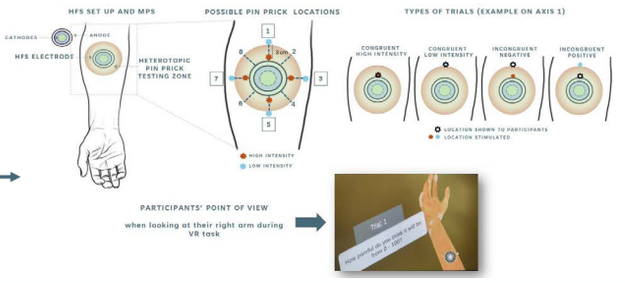
METHOD

- Cohort: **20 healthy individuals**, aged between 20 and 31 (mean age: 25, SD = 2, 15 males)
- **HFS**: 5 x 100 Hz 1-second trains delivered at 20x participants' electrical detection thresholds
- **Mechanical pain sensitivity (MPS)** measures were carried out in both forearms at baseline and 30 minutes post-HFS.
  - *MPS = geometric mean across all pain scores*
  - *Standard ΔMPS = delta MPS (post HFS – baseline)/ SD baseline MPS*
- **VR setup:** HTC VIVE 2 PRO headset, equipped with an Ultraleap hand-tracking camera
- **8 stimulus locations**: 4 x proximal to HFS area ('high intensity') and 4 x distally ('low intensity')
- **Types of trials**: congruent (high vs low intensity) and incongruent (negative vs positive). All delivered with a 512mN pinprick.
- **Experimental Blocks:**
  - **BLOCK 1:** 5 x trials per stimulus location (40 trials, randomised order). In each trial participants are shown a visual cue, then congruent location is stimulated, then participants provide a pain score
  - **BLOCK 2**: same trial order as Block 1, but participants are asked for a predicted pain score before stimulation (Figure 3)
  - **BLOCK 3:** 10 x trials per location, (80 trials, randomised order). Incongruent trials 50% of the time on each location. Same trial sequence as Block 2.

Experimental design

STUDY PROTOCOL. Total duration: ~ 75 mins

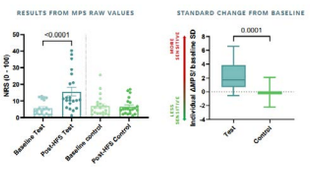




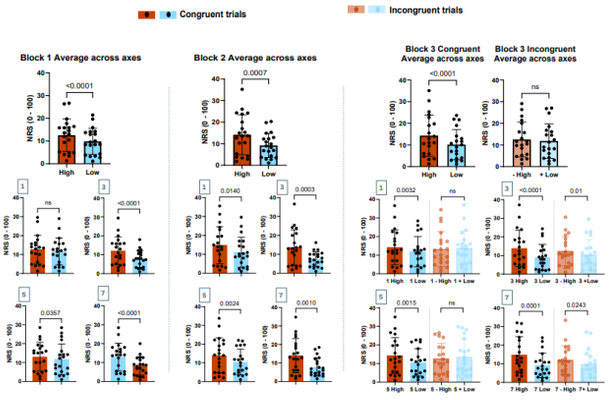
RESULTS

Changes in MPS following HFS

- **MPS increased significantly after HFS in the test arm only** (paired t-test)
- **Boxplots** show MPS changes from baseline (test: blue, control: green)
- **One-sample t-tests**: MPS changes were greater than zero only in the test arm
- **Paired t-test**: MPS changes differed significantly between arms

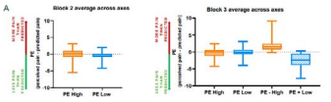


High intensity stimuli were perceived as significantly more painful than low intensity stimuli during congruent trials but not during incongruent trials

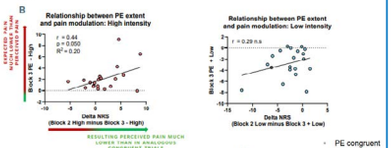


PE = perceived NRS – predicted NRS

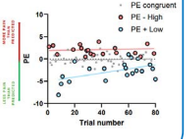
PEs in congruent trials ≈ 0, indicating high accuracy. PEs in incongruent trials showed greater pain than expected (negative) or lower pain than expected (positive)



Incongruent negative trials showed **placebo analgesia for highly positive expectations**. No significant effects in incongruent positive trials



PEs for stimuli in non hyperalgesic areas tended to 0 (learning effects). **PEs for stimuli within hyperalgesic areas persisted over time**



CONCLUSIONS

- This study introduces a novel VR-based approach to examine the **interplay pain expectations and central sensitisation**
- Findings suggest that PEs persist in sensitised states, potentially reflecting **maladaptive predictive coding mechanisms** seen in chronic pain
- This model provides a **controlled framework** to study interventions targeting maladaptive PE mechanisms and inform VR-based rehabilitation strategies

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III-A.45

The dynamic ballet of NaV1.8 trafficking in chronic pain

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INTRODUCTION

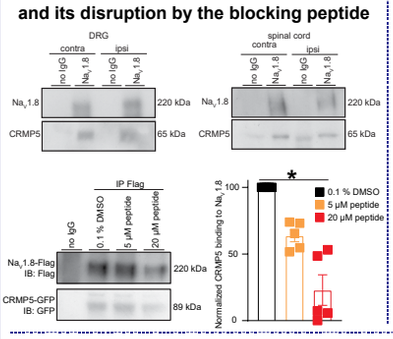
- The sodium channel $Na_V1.8$ is critical to conduct nociceptive signals from the periphery to the brain
- $Na_V1.8$ properties are upregulated in neuropathic pain, including its trafficking to the membrane
- CRMP5 is an understudied onconeural protein highly expressed in the developing brain
- We uncovered CRMP5 as a novel protein involved in neuropathic pain by controlling $Na_V1.8$ function

Hypothesis: CRMP5, by interacting with $Na_V1.8$, modulates the trafficking of the channel and thus the nociceptive signalization of the afferent fibers.

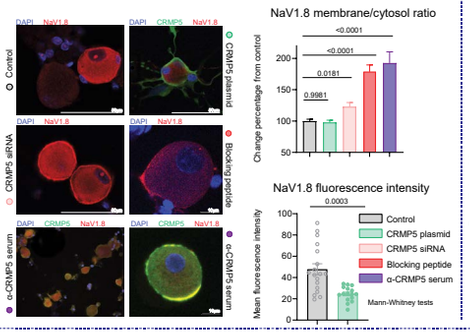
(Liu et al.,2014; Charrier et al., 2003; Moutal et al., 2015)

RESULTS

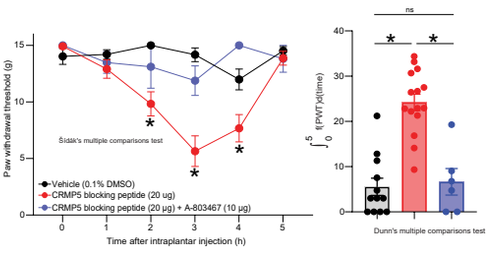
Validation of the CRMP5/NaV1.8 interaction and its disruption by the blocking peptide



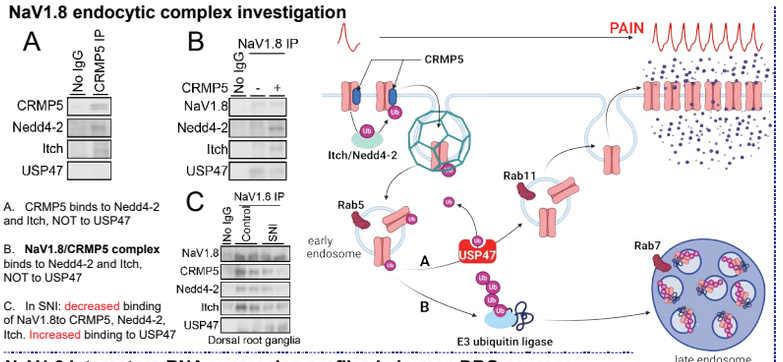
NaV1.8 trafficking is controlled by CRMP5



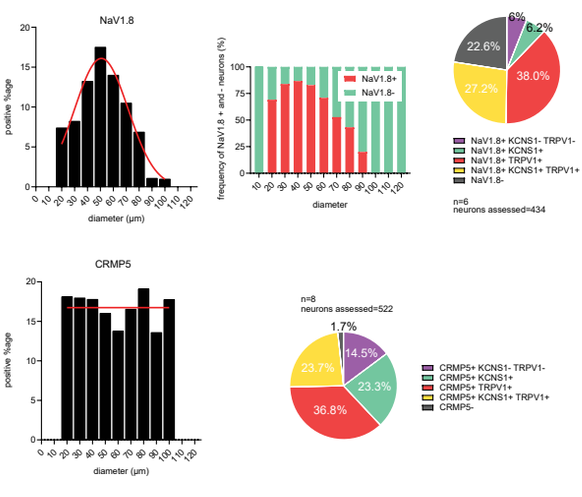
Inhibiting the CRMP5/NaV1.8 interaction creates a NaV1.8-dependent mechanical hypersensitivity



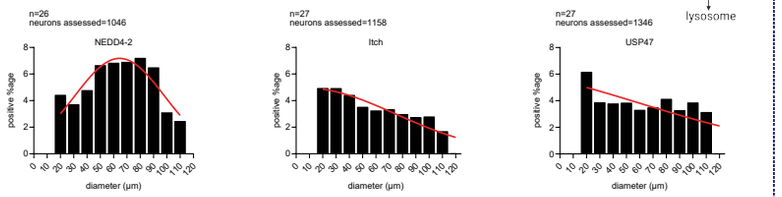
NaV1.8 endocytic complex investigation

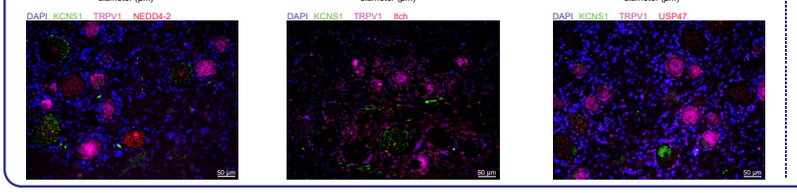


NaV1.8 and CRMP5 transcripts distribution in human DRG neurons



NaV1.8 interactors RNA expression profiles in human DRG neurons





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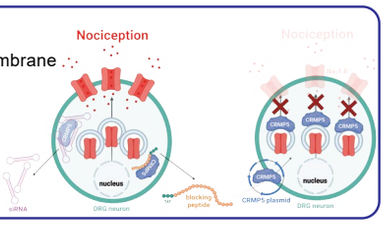
Saturday April 26th

12:30 pm 2:00 pm

CONCLUSION

- Protein-protein interaction between CRMP5 and $Na_V1.8$ = negative regulatory mechanism removing $Na_V1.8$ from the membrane
- Inhibiting CRMP5/$Na_V1.8$ interaction = increased $Na_V1.8$ membrane localization, DRG neurons sensitization and NaV1.8-dependant pain behavior
- Conversely, increasing CRMP5 = decreased total NaV1.8 in the neurons
- CRMP5 seems to act as the conductor of NaV1.8 trafficking by recruiting ligases Itch and Nedd4-2 and inhibiting deubiquitinase USP47 activity



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I-C.40

Effects of suppressed motor responses on neural pain signatures

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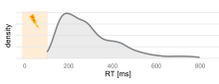
2 General Psychology and Cognitive Neuroscience, Charlotte Fresenius Hochschule - University of Psychology, Hamburg, Germany

INTRODUCTION

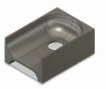
- **Motor responses** are crucial for the protective function of acute pain
- Most neuroimaging **pain paradigms require participants to suppress natural motor responses**, which might affect neural pain signatures[1,2]
- Here, we compared pain-related neural activations when natural **motor responses were either executed or suppressed**

METHOD

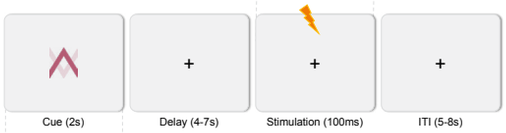
Two calibrated electrotactile stimulus intensities: non-painful vs. painful
Stimulus duration: 100ms



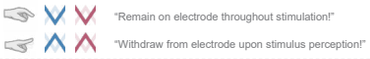
Stimulus duration was below the minimum RT, ensuring **identical stimulation across task conditions**



Participants placed their **left index finger** in a custom-made electrode frame, ensuring **consistent finger positioning**



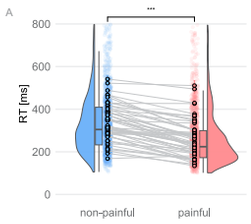
Cue indicated both task and stimulation intensity



- **53 participants**
  30 female, mean age: 24.83 (18-35)
- **2x2 within-subjects design**
  Stimulation Intensity: painful vs. non-painful
  Movement Task: suppression vs. execution
- **6 runs, 28 trials per run**
- **Readouts**
  fMRI, Reaction times (RT) and acceleration (via accelerometry), EDA, pain ratings (4 per run)

RESULTS

Faster RT following painful than non-painful stimuli



Faster acceleration following painful than non-painful stimuli

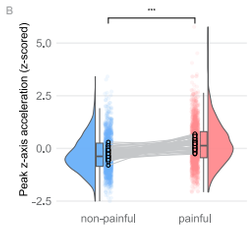


Figure 1: **A**: Reaction time differences for trials with painful vs. non-painful stimuli. Outlined points depict individual means. **B.** Peak z-axis acceleration difference for painful vs. non-painful trials.

Several regions are only sensitive to pain when natural motor responses are suppressed

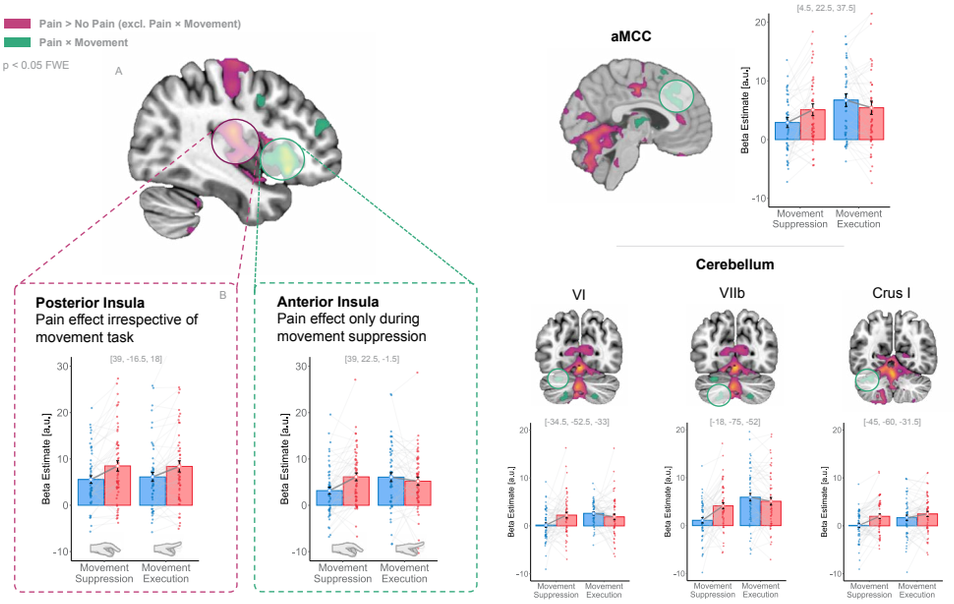


Figure 2: **A**: Group-level brain activations for painful vs. non-painful stimuli (highlighted in magenta), excluding interactions between pain and movement. Activations for pain × movement interactions (cyan) show greater differences between painful and non-painful stimuli during movement suppression compared to movement execution **B:** Peak voxel mean beta estimates across experimental conditions for different clusters (coordinates in MNI space). Individual beta estimates are represented as points. Error bars indicate the standard error of the mean.

CONCLUSIONS

- **Acute pain facilitates motor responses** (faster RTs and acceleration)
- "Pain-related regions"[3,4] show **pain-specific activation only in contexts that restrict natural motor responses** (typical pain paradigm)
- Such pain-motor-interactions highlight the need to **study pain in more ecologically valid contexts**

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PREREGISTRATION

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III-B.30

Critical Contribution of Nav1.7 and Nav1.9 to Action Potential Upstroke in Mechanoinsensitive C-Fibers

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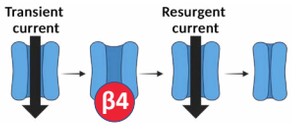
3 Institute for Computational Biomedicine and Disease modelling with focus on phase transitions between phenotypes, Uniklinik RWTH Aachen University, Aachen, Germany; 4 Center for Computational Life Sciences, RWTH Aachen University, Aachen, Germany;
5 Institute for Clinical Pharmacology, Uniklinik RWTH Aachen University, Aachen, Germany; 6 Department of Anesthesiology and Intensive Care and CBBM-Center of Brain, Behavior and Metabolism, University of Lübeck, Lübeck, Germany

INTRODUCTION

The voltage-gated sodium channels Nav1.1-Nav1.3 and Nav1.5-Nav1.9 are crucial for sensory neuron excitability. Each channel isoform exhibits a distinct behaviour during an action potential (AP).[1]

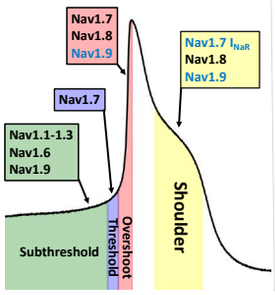
Mutations in Nav1.7 linked to the painful channelopathy Paroxysmal Extreme Pain Disorder (PEPD) show increased resurgent currents (I_{NaR}).

It is not yet fully understood how I_{NaR} influences AP dynamics, neuronal excitability, and pain perception.

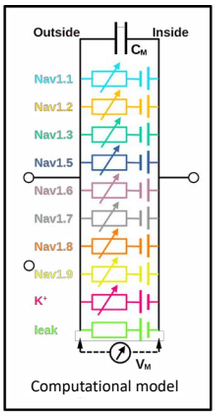


AIM

Using computational models, we aim to identify the influence of sodium channel isoforms and Nav1.7 I_{NaR} on AP morphology in mechanoinsensitive C-fibers (CMi) and Aδ-fibers, both of which play a key role in neuropathic pain.



METHODS



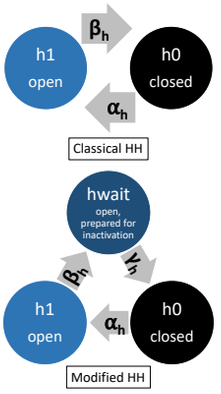
We propose a computational model, which is based on modified Hodgkin-Huxley equations and parameterized using patch-clamp experiments.

Hodgkin-Huxley models (HH) are modified to include waiting states in the h-gate which delay inactivation and improve the model's fit to experimental data.[1]

To account for I_{NaR}, Hodgkin-Huxley models are translated to equivalent Markov models and extended with an open-channel-blocked (OCB) state.[2]

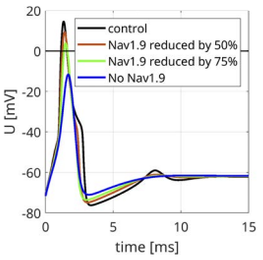
Markov models are fitted using high-throughput patch-clamp data (Qube384, Sophion) of HEK cells stably expressing wild-type Nav1.7 or the PEPD-associated mutation M1628K in the presence of the Navβ4-peptide.

AP recordings of nerve fiber subclasses in pig dorsal root ganglia[3] were employed as voltage-clamp stimuli.

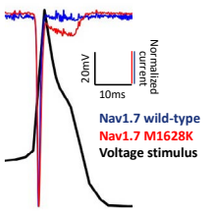


RESULTS

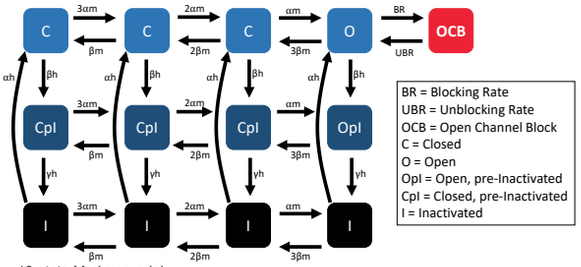
- For CMi- and Aδ-fibers, our simulations suggest a critical contribution of Nav1.7 and Nav1.9 to the AP upstroke.[1]
- Nav1.9 is the main contributor to the shoulder of the AP in both fiber types.[1]
- A hyperpolarizing shift in the activation of Nav1.7 reduces the threshold for AP generation.[1]
- PEPD mutations show increased resurgent currents, which develop during the shoulder of an AP.
- A 13-state Markov model can simulate transient and resurgent currents.



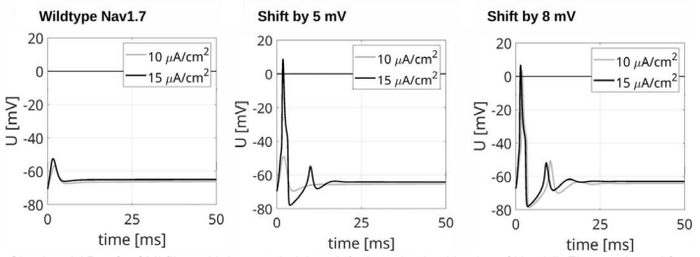
Simulated APs of a CMi-fiber with varied conductance levels of Nav1.9 during current injection of 30 μA/cm². Figure adapted from (1)



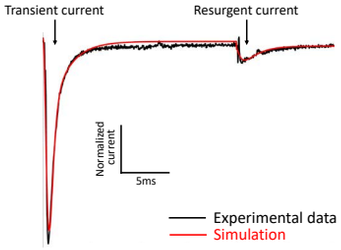
Exemplary traces of Nav1.7 wild-type and M1628K in response to the AP of a CMi-fiber



13-state Markov model



Simulated APs of a CMi-fiber with hyperpolarizing shifts in activation kinetics of Nav1.7. Figure adapted from (1)



Experimental data from Nav1.7 M1628K overlaid with simulated transient and resurgent current

CONCLUSIONS & OUTLOOK

Nav1.9 contributes to AP upstroke and shoulder in CMi- and Aδ-fibers.

Shifted gating kinetics of Nav1.7 increase excitability, potentially driving neuropathic pain.

Patch-clamp data suggest Nav1.7 I_{NaR} contributes to AP shoulder formation.

Markov models incorporating an OCB state can emulate resurgent currents.

Integrating I_{NaR} into a sensory nerve fiber model will further elucidate its impact on AP morphology, firing patterns and neuropathic pain.

Computational models aid in understanding the complex interplay of ion channels in chronic pain.

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Some figures created with https://BioRender.com.

AL has a consultancy contract with Grünenthal.

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II-C2.W.01

Uncover ing the funct ional relat ionship between pain perception and the modulation of ongoing oscillations in the human posterior insula using intracerebral EEG

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2 Department of Neurology, Saint-Luc University Hospital , Brussels, Belgium;

3 Department of Neurosurgery, Saint-Luc University Hospital, Brussels, Belgium

INTRODUCTION

- The insula is an important spinothalamic relay point, but its exact role in nociception and pain perception is not yet fully elucidated.[1]
- **Preferential modulation** for thermonociceptive stimuli compared to vibrotactile stimuli in the **posterior insula** (intracerebral EEG), particularly in the **theta and alpha** frequency bands.[2]

AIM

- Functional relationship between pain perception and the modulation of ongoing oscillations in the insula?
- Does modulating attention using an arithmetic task lead to a **congruent change of ongoing oscillations and perceived stimulus intensity?**

METHODS

- 8 patients undergoing presurgical evaluation of refractory epilepsy were recruited (age: 30 ± 8 years old, 2 female)
- Insular electrode contacts: **44 anterior, 16 posterior**

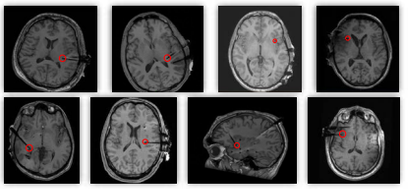

*Figure 1. **Examples of the localization of the depth electrodes** implanted in the insula. One example is shown for each patient.*

- **Sustained periodic somatosensory stimuli were delivered at frequency of 0.2 Hz**
- An unrelated **arithmetic task** was used to **distract** patients from the stimuli
- **Frequency-tagging** to investigate the modulation of ongoing oscillations

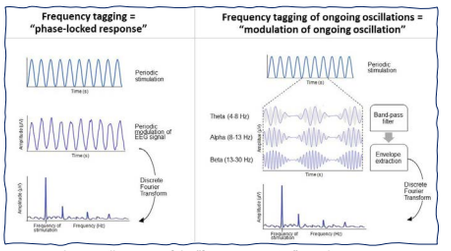

*Figure 2. **Schematic illustration of the "frequency-tagging" paradigm.***

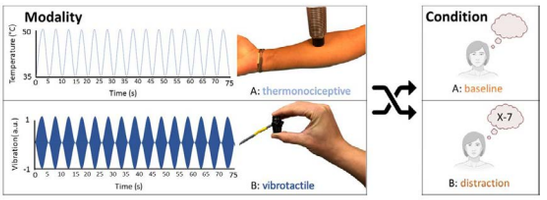

*Figure 3. **Description of the experimental setup**, adapted from Leu et al. (2023)[3]. Each modality was presented for 10 trials per block, either without (baseline) or with an arithmetic task (distraction).*

RESULTS

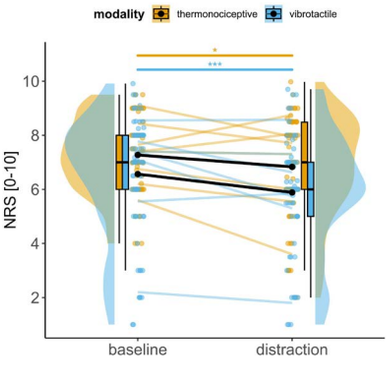

*Figure 4. **Ratings of intensity perception** on a numerical rating scale (NRS) from 0 (no perception) to 10 (most intense perception imaginable). Post-hoc paired t-test results are indicated: *p<0.05, ***p<0.001.*

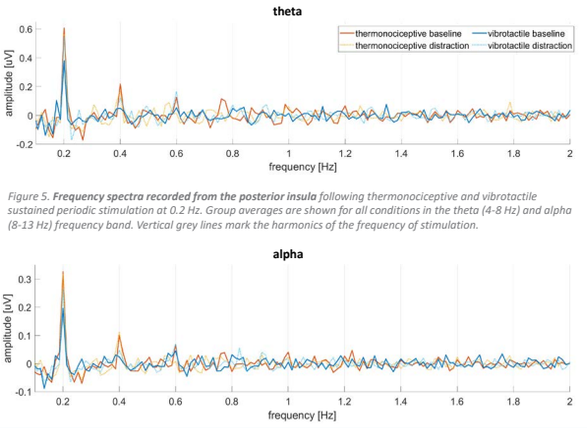

*Figure 5. **Frequency spectra recorded from the posterior insula** following thermonociceptive and vibrotactile sustained periodic stimulation at 0.2 Hz. Group averages are shown for all conditions in the theta (4-8 Hz) and alpha (8-13 Hz) frequency band. Vertical grey lines mark the harmonics of the frequency of stimulation.*

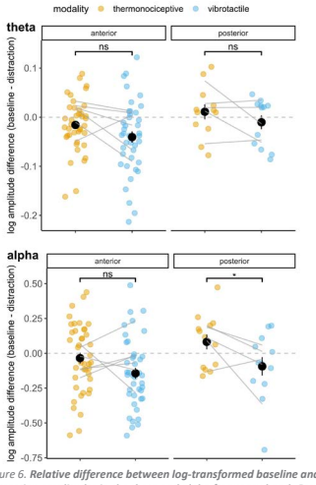

*Figure 6. **Relative difference between log-transformed baseline and distraction amplitudes in the theta and alpha frequency band.** Grey horizontal lines indicate subject means. Pairwise comparison: *p<0.05*

CONCLUSIONS

- The **arithmetic task was successful** in modulating the perceived level of stimulus intensity in both modalities by distracting patients.
- Observed a tendency in the alpha frequency band of a **modulation of ongoing oscillations congruent to the decrease in perception during the distraction task** in the posterior insula.
- These results could suggest a functional relationship between the modulation of ongoing oscillations and pain perception in the human posterior insula, predominantly in the alpha frequency band.
- Extension of the sample with inclusion of **additional electrode contacts** in the posterior insula to confirm observed trend and increase validity of statistics.

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II-B1.W.01

Alterations of peripheral blood mononuclear cell and dorsal root ganglia transcriptomics and plasma metabolite profile in the chronic restraint stress-induced pain model of mice

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2 Hungarian Research Network (HUN-REN) Chronic Pain Research Group at the University of Pécs;
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6 University of Pécs Szentágothai Research Centre, Pécs, Hungary

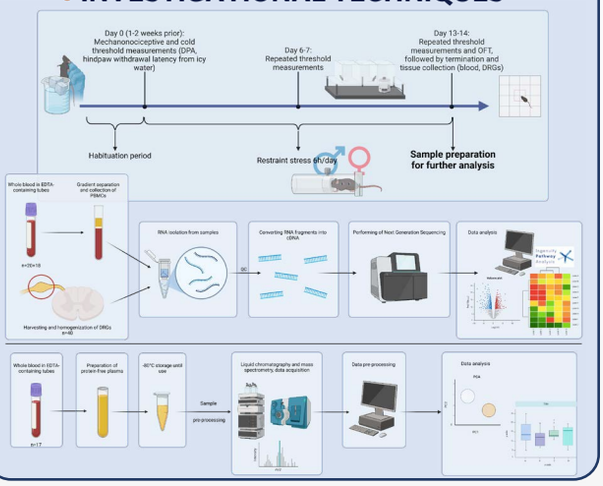
INTRODUCTION

Chronic psychosocial distress is an etiological and/or aggravating factor of several pain conditions including fibromyalgia, a widespread musculoskeletal chronic primary pain condition. The chronic restraint stress (CRS)-induced pain model in mice appears to be appropriate for investigating the pathophysiological mechanisms to identify key mediators and potential drug targets.

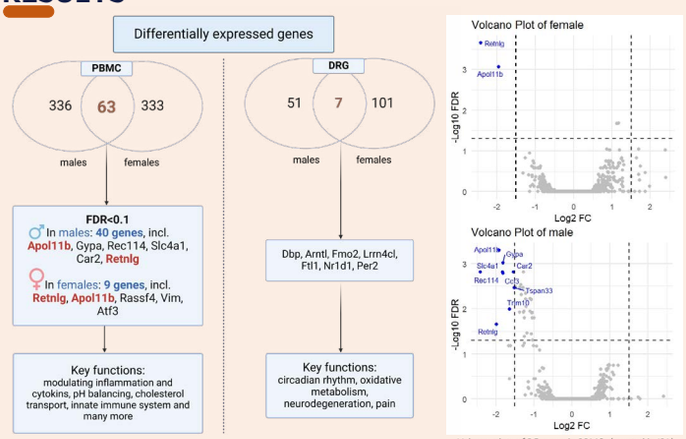
AIM

To explore key transcriptomic and metabolomic alterations, networks and pathways in the CRS-induced model using and unbiased approach and combined bioinformatic platform

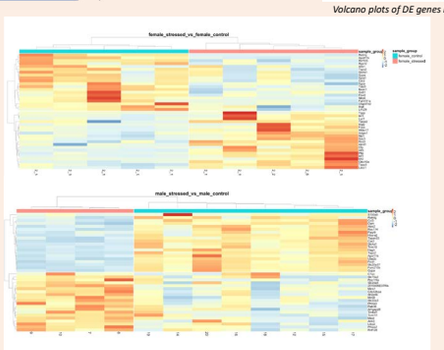
EXPERIMENTAL PROTOCOL AND INVESTIGATIONAL TECHNIQUES



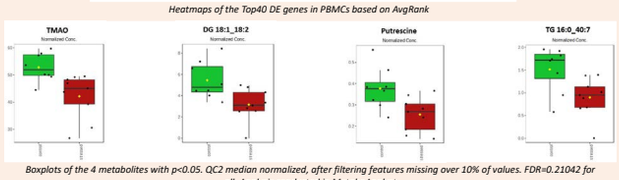
RESULTS



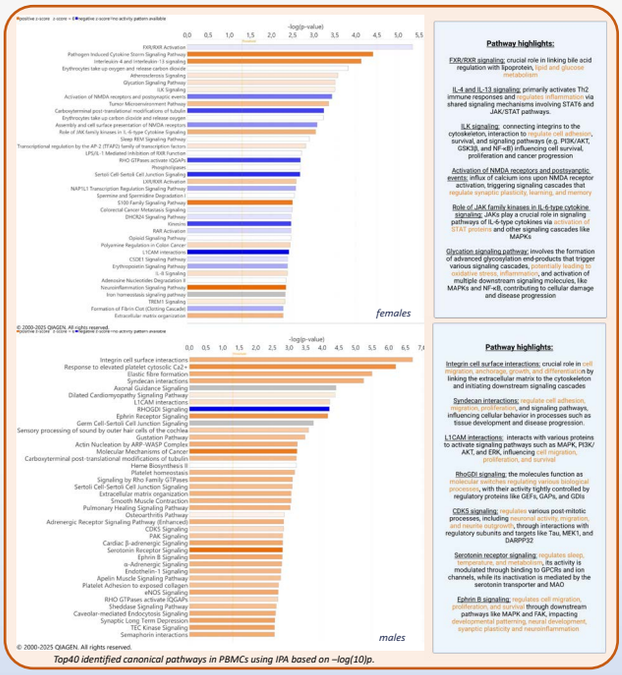
Volcano plots of DE genes in PBMCs (created in IPA)



Heatmaps of the Top40 DE genes in PBMCs based on AvgRank



Boxplots of the 4 metabolites with p<0.05. QC2 median normalized, after filtering features missing over 10% of values. FDR=0.21042 for all. Analysis conducted in MetaboAnalyst



Top40 identified canonical pathways in PBMCs using IPA based on –log(10)p.

CONCLUSIONS

CRS induced significant changes at the level of peripheral blood mononuclear cells and primary sensory neurons in the dorsal root ganglia in mice. Metabolomic differences are few, but correlate with findings in human studies concluding alterations in lipid metabolism and involvement of polyamines (like putrescine) in ion channel function modulation in pain states. DRG transcriptomics suggested alterations in oxidative metabolism and circadian rhythm, while PBMC transcriptomics suggested the involvement of lipid transport, inflammation and pH regulation, cell adhesion, JAK/STAT signaling, and inflammasome formation providing hypotheses for further investigations and functional validation.

ACKNOWLEDGEMENT

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I-C1.W.01

Trajectories of School Absenteeism Longitudinal Associations with Pain and Stress in Childhood, and Sick Leave and Disability Pension in Adulthood

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BACKGROUND

Pain and stress often co-occur during adolescence.

Adolescents with pain and stress problems are more absent from school than healthy peers.

Absenteeism might continue into adulthood as sick leave and disability pension.

AIM & QUESTIONS

To investigate longitudinal relationships among pain and stress during adolescence, absenteeism from school, and work-life absenteeism.

Q1: Is childhood pain and stress related to patterns of absenteeism during adolescence?

Q2: Are patterns of absenteeism during adolescence related to sick leave and disability pension later in life?

Q3: Are pain and stress throughout life-span related to **(1)** sick leave and **(2)** disability pension?

METHODS

- Data from the **longitudinal IDA program** (1965-2023)

Age 10 13 15 ... 43/48 68

1965 2023

- **Sick leave and disability pension** during ages 48 to 67 (2003 to 2022), the MiDAS register, Sweden

- Hierarchical cluster analysis of patterns of absenteeism during adolescence
- Multinomial regression, logistic regression, and the Kruskal-Wallis H test for associations among childhood pain and stress, patterns of school absenteeism, adult pain, distress, and work-life absenteeism

RESULTS

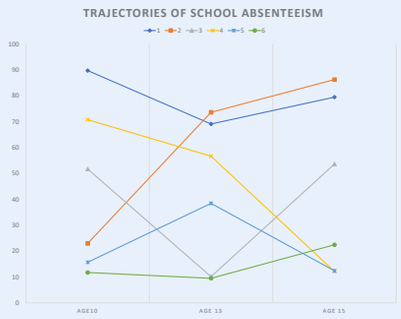

Figure 1. Trajectories of school absenteeism (N=678).
Clusters:
- *1. Consistently high absenteeism (n=112);*
- *2. Consistently increasing absenteeism (n=162);*
- *3. Increasing at age 10 and 15 (n=138);*
- *4. Decreasing absenteeism (n=64);*
- *5. Increasing at age 13 only (n=72).*
- *6. Consistently low absenteeism (n=135)*

Q1: Adolescents with **consistently high school absenteeism** (Cluster 1) reported significantly **more pain and stress (age10)** compared to adolescents with:

- Consistently low absenteeism (Cluster 6)*

  $B = 0.700$, $p = 0.025$, 95%CI [1.09; 3.72]
- Increasing at age 13 only absenteeism (Cluster 5)*

  $B = 0.899$, $p = 0.017$, 95%CI [1.17; 5.15]
- Decreasing absenteeism (Cluster 4)

  $B = 0.919$, $p = 0.023$, 95%CI [1.14; 5.53]
- Increasing at age 10 and 15 (Cluster 3)*

  $B = 0.907$, $p = 0.008$, 95%CI [1.32; 4.65]

*Remained significant when controlled for gender and SES

Q2: Trajectories of school absenteeism during adolescence were not associated with number of pain locations ($\chi^2(5) = 1.677$, $p = 0.892$) and distress ($\chi^2(5) = 5.290$, $p = 0.382$) in midlife (age43/48)

Q3 (1): Individuals with **long sick leave (>365days)** have significantly **more pain locations in midlife** (age 43/48) compared to those with medium long sick leave (<366 days) (p=0.001) and those with no sick leave (p=0.010) during age 48-67.

Q3 (2): Pain and stress in childhood (age10), number of pain locations, and distress in midlife (age 43/48) were associated with probability of **disability pension:**

Table 1. Logistic regression predicting disability pension (age 48-67)

	B	*Wald*	*P*	*Odds Ratio*
Gender	0.484	1.915	0.166	1.622
SES	-0.079	0.233	0.629	0.924
Pain and stress (age10)	0.830	4.766	0.029	2.294
School absenteeism clusters				
Cluster 6 (ref)				
Cluster 1	-0.104	0.028	0.866	0.901
Cluster 2	0.121	0.055	0.814	1.128
Cluster 3	-0.426	0.530	0.467	0.653
Cluster 4	0.810	1.921	0.166	2.247
Cluster 5	-0.244	0.148	0.700	0.784
Distress (age 43/47)	0.631	4.002	0.045	1.880
Number of pain locations (age 43/47)	0.577	10.022	0.002	1.780
Constant	-5.056	28.627	<0.001	0.006

Omnibus test = χ2 (10) = 38.014, p < 0.001. Cox & Snell R square =0.091. Nagelkerke R square = 0.178

CONCLUSIONS

- Limited evidence for relation between pain and stress and school absenteeism trajectories in adolescence
- Earlier life school absenteeism trajectories did not predict later life work-life absenteeism
- Pain and stress across the life-span, from childhood to midlife, were related to work-life disability
- Future research addressing accumulation of pain, stress, and work-life disability over life-span is warranted

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I-D1.W.08

Effects of Iatrogenic Opioid Withdrawal Nested in a Cognitive Behavioral Treatment for Chronic Pain

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2 Vrije Universiteit Brussel, Pain in Motion Research group, Belgium

INTRODUCTION

Prevention of long-term use of opioids is essential to avoid long term side effects.

Side effects are:
-hyperalgesia (pain)
-mental health problems (depression)
-sleep disturbances
-social & behavioural consequences
-physically dependency
-long-term gastrointestinal issues
-fatigue & cognitive disfunction

AIM

To investigate the effects of a program for withdrawal of iatrogenic opioid use nested in a cognitive-behavioural treatment (CBT) for patients with long-term opioid use for chronic pain.

(METc : 202200318)

METHOD

1. transdisciplinary bio-psycho-social matched care assessment
2. pain education including the explanation of central sensitization (CS) in chronic pain and the negative effects of opioids on pain
3. personal shared decision-making withdrawal program combined with CBT-chronic pain.

A clinical mixed method study including pre- and post-measurements and interviews was conducted on opioid use and health-related quality of life.

RESULTS

29 patients were included.

23 (79 %) were no longer using opioids!

None of the patients reported more pain after opioid withdrawal!

Withdrawal is difficult but it was worth it!

SF-36	N = 24	N =16
General Health	36.6%	36.8%
Health changes	41.1 %	75.0%
Physical functioning	35.0 %	46.0%
Social functioning	41.5%	61.7%
Role limitations physical	50.0%	82.1%
Role limitation emotional	76.2 %	90.0%
Mental health	58.0%	65.8%
Vitality	34.8%	43,8%
Pain	26.2%	42.6%
Satisfaction with treatment results (0-10)	n.a.	8.3

Population:

Opioid use M = 4,8 y (Sd 4.0 y, min 1 / max 18)
Gender: F: 16 / M: 13
Age: M: 49,9 y (Sd 13 y)

Opioids included: Oxycodone (14), Fentanyl (4), Tramadol (8) Buprenorphine (1) Morphine (3), Codeine (2)

Quote:
"Same pain experience without and with medication, much better energy, back to work, like coming out of a cloud, quality of life much better."

Quote:
"Better mood, better mobility, better concentration (e.g., able to read again), more active, better sleep"

Quote:
"Significant decreased pain, much better mood, can move again, stomach issues are gone, can concentrate, watch things on TV and work again. Got my life back."

CONCLUSIONS

Withdrawal of opioid use nested in CBT for patients with chronic pain seems effective.

PAIN IN MOTION

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VUB PAIN IN MOTION RESEARCH GROUP

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Centralised Pain Predicts Worse Pain Outcomes in Early Rheumatoid Arthritis: A Prospective Cohort Study with Embedded Neuroimaging Study

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INTRODUCTION

- **Rheumatoid Arthritis (RA)**: An autoimmune condition causing joint inflammation, particularly in the hands and wrists.
- Pain persists in ~50% of RA patients despite effective DMARD therapy.
- **Centralised pain** can be measured with **PainDETECT** questionnaire.
- May contribute to persistent pain in established RA, but its role in *early* RA remains unclear

AIMS

- Evaluate **centralised pain** as a predictor of poor pain outcomes in *newly diagnosed* RA patients.
- Investigate neural correlates of **centralised pain** in early RA.

METHOD

- **Design**: Prospective cohort study of 158 adults with newly diagnosed RA in Oxfordshire, UK.
- **Pain Assessment**: Centralised pain measured with **PainDETECT** questionnaire at baseline.
- **Neuroimaging**: Task-based **fMRI** in 27 participants to assess brain responses to evoked pressure pain at joint (left wrist) and non-joint (left nailbed) sites.
- **Outcomes**: Primary outcome was **bodily pain** measured by the **SF-36 Bodily Pain Scale (BPS)** at baseline, 3, 6, and 12 months. **CRP levels** were measured as a marker of inflammation as a secondary outcome.
- **Analysis**: **Linear mixed-effects models** examined associations between PainDETECT scores, BPS, and CRP over time, adjusting for age, sex, symptom duration, employment status, tobacco use, comorbidities, depression, and anxiety.
- **Whole-brain analysis** explored associations between PainDETECT scores and pain-related brain activity.

RESULTS

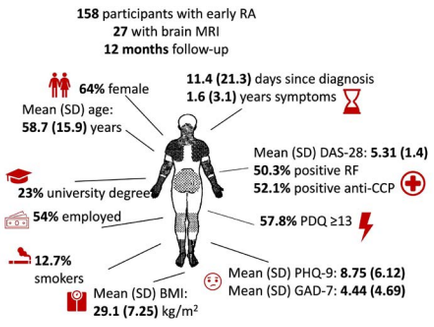

Figure 1. Over half of patients with a new diagnosis of RA have centralised pain (PainDETECT ≥13)

- **Over half** of participants had centralised pain at time of diagnosis (*Figure 1*)
- **Baseline PainDETECT scores** were significantly associated with **worse bodily pain** during follow-up (β = -0.52; 95% CI -0.88 to -0.16; P = 0.005) (*Table 1A & Figure 2*).
- This association remained significant after adjusting for **socio-demographics**, **lifestyle factors**, **depression**, and **anxiety** (β = -0.41; 95% CI -0.79 to -0.03; P = 0.034) (*Table 1A*).
- Centralised pain was **not associated with inflammation** during follow-up (*Table 1B*).
- In the **neuroimaging sub-study**, higher **PainDETECT scores** were linked to increased activation in the **left insula**, **dorsal anterior cingulate cortex (dACC)**, and **left amygdala** during evoked pain (Figure 3).

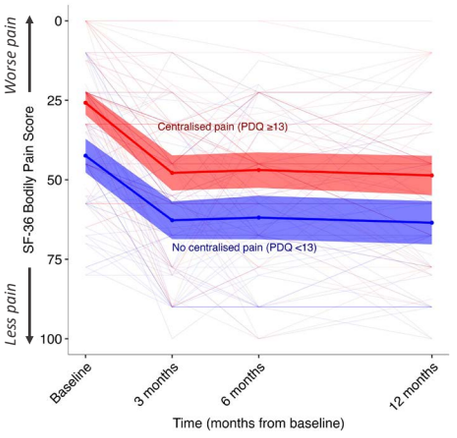

Figure 2. Patients with centralised pain at baseline had worse pain prognosis during follow-up
Lines represent individual raw patient trajectories of bodily pain over time, with mean values in bold. Shaded areas indicate 95% confidence intervals.

	β	95%CI	P
A. SF36 Bodily Pain score during follow-up			
Minimally adjusted	-0.52	-0.88 to -0.16	0.005
Fully adjusted	-0.41	-0.79 to -0.03	0.034
B. CRP during follow-up			
Minimally adjusted	0.090	-0.20 to -0.38	0.55
Fully adjusted	0.011	-0.33 to 0.36	0.95

Table 1. Baseline centralised pain is associated with worse bodily pain, but not inflammation, during follow-up
Results from linear mixed effects model for association between baseline PainDETECT with (A) bodily pain (SF36 Bodily Pain score, *lower* values indicate *worse* pain) and (B) inflammation (C-reactive protein) over 12 months' follow-up.
Minimally adjusted model includes age, sex, time, and bodily pain at baseline. Fully adjusted model further includes symptom duration, employment, smoking, comorbidities, depression (PHQ-9), and anxiety (GAD-7)

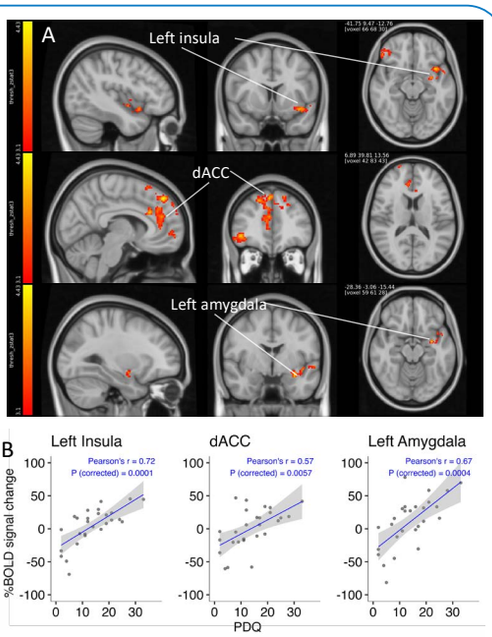

Figure 3. Centralised pain correlates with neuronal activity in early RA
Higher PainDETECT (PDQ) scores are associated with greater activity in the left insula, dorsal anterior cingulate cortex (dACC), and left amygdala after whole brain correction.

A. Whole brain group-level activation maps for painful vs. non-painful stimulation of the left wrist vs. left nailbed contrast with PDQ scores. Maps are overlaid on a standard MNI152 T1-weighted brain template and thresholded at Z > 3.1.

B. The y-axes show the induced effects of painful stimulation to the left wrist as a percentage BOLD signal change, defined as $X = (X_{pain\ (wrist)} - X_{no\ pain\ (wrist)}) - (X_{pain\ (nailbed)} - X_{no\ pain\ (nailbed)})$. Shaded areas represent the 95% confidence interval. Pearson correlation coefficients (r) are reported.

CONCLUSIONS

- In **newly diagnosed** RA patients, **centralised pain** at diagnosis predicted **worse bodily pain** over 12 months, independent of inflammation, even after adjusting for socio-demographics, lifestyle, and psychological factors
- Centralised pain was associated with increased neuronal activity in the **left mid-posterior insula**, **left amygdala**, and **dorsal ACC** in response to pain in the affected wrist.
- **PainDETECT** may help identify patients at high risk for persistent or severe pain despite adequate anti-inflammatory therapy.

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Neural Correlates of Affective Symptoms in Juvenile Fibromyalgia: A Multisensory FMRI Study

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INTRODUCTION

Juvenile fibromyalgia (JFM) is a chronic pain syndrome [1].

- **Core symptoms:** Widespread musculoskeletal pain, physical fatigue, nonrestorative sleep and headaches.
- **Affective symptoms:** Anxiety and depression.

Previous studies:

- JFM patients report reduced tolerance to non-painful multisensory stimuli [2].
- Depressive patients showed altered neural processing of sensory stimulation [3].

AIM

- To investigate whether non-painful multisensory sensitivities were linked to affective symptoms in juvenile fibromyalgia patients.
- To investigate whether brain responses to multisensory stimulation were significantly associated with affective symptoms in patients.

METHOD

46 JFM girls (16.56 ± 1.01 years)

44 Healthy girls (16.09 ± 1.06 years)

- **Validated measures** of multisensory hypersensitivities in daily life and affective symptoms.
- **Statistical analysis:**
  - Two-sample t-tests were used to see the differences between groups.
  - Bivariate Pearson correlations.
- **Multisensory task**

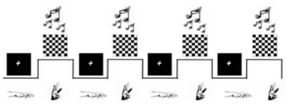

Figure 1. Schematic representation of the Multisensory fMRI task.

- **fMRI analysis:**
  - **Pre-process:** CONN Toolbox running on MATLAB.
  - **First levels:** General Lineal Model approach (GLM) implemented in SPM12 software.
  - **Second levels:** Regression (JFM patient's group): Association between self-reported measures and brain functional activity.

RESULTS

Table 1. Demographic, affective symptoms and sensory sensitivity variables.

	Healthy Controls (N=44)	JFM Patients (N= 46)	Statistics	
Demographic variables	**Mean ± SD**	**Mean ± SD**	**T**	**p-value**
Age (years)	16.09 ± 1.06	16.43 ± 1.10	1.51	0.13
Race (C / NC)	2.06 ± 0.25	2.10 ± 0.43	0.54	0.58
Yearly Household Income (1–7)	5.18 ± 1.90	4.80 ± 1.96	-0.76	0.44
Education Level of the Primary Caregiver (1–5)	4.41 ± 0.86	3.95 ± 0.89	- 0.38	0.39
Education Level of the Secondary Caregiver (1–5)	3.80 ± 0.84	3.80 ± 1.03	0	1
Affective variables	**Mean ± SD**	**Mean ± SD**	**T**	**p-value**
Child Depression Inventory (CDI)	5.10 ± 5.34	19.55 ± 10.06	8.22	<0.0001
CDI Negative Mood	1.35 ± 1.82	8.11 ± 3.75	10.50	<0.0001
CDI Negative Self Esteem	0.84 ± 1.15	2.95 ± 2.63	4.75	<0.0001
CDI Ineffectiveness	2.43 ± 2.46	6.46 ± 3.60	5.94	<0.0001
CDI Interpersonal Problems	0.46 ± 0.82	2.02 ± 1.51	5.85	<0.0001
Sensory sensitivity variables	**Mean ± SD**	**Mean ± SD**	**T**	**p-value**
AASP Visual	10.82 ± 3.44	16.23 ± 5.34	5.50	<0.0001
AASP Touch	12.38 ± 3.90	21.00 ± 6.86	7.06	<0.0001
AASP Auditory	8.51 ± 2.97	15.18 ± 5.42	6.99	<0.0001

Note: Yearly income is shown using a scale of 1–7 that goes from $25K to $150K in intervals of $25K. Caregiver education level is shown using a scale of 1–5, where 1=less than high school; 2=high school/GED; 3=partial college or trade school; 4=college graduate; 5=postgraduate degree. C1, caregiver 1; C2, caregiver 2; FMSS, Fibromyalgia Symptom Severity; JFM, juvenile fibromyalgia; WPI, Widespread Pain Index.

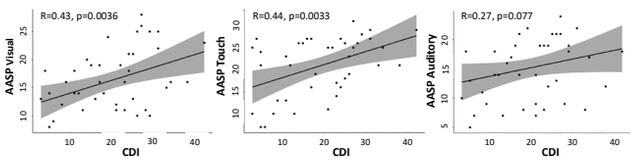

Figure 2. Correlations between affective symptoms and sensory sensitivity variables. Significant positive correlations between the scores from all the subscales of the AASP questionaire (visual, touch and auditory) and CDI.

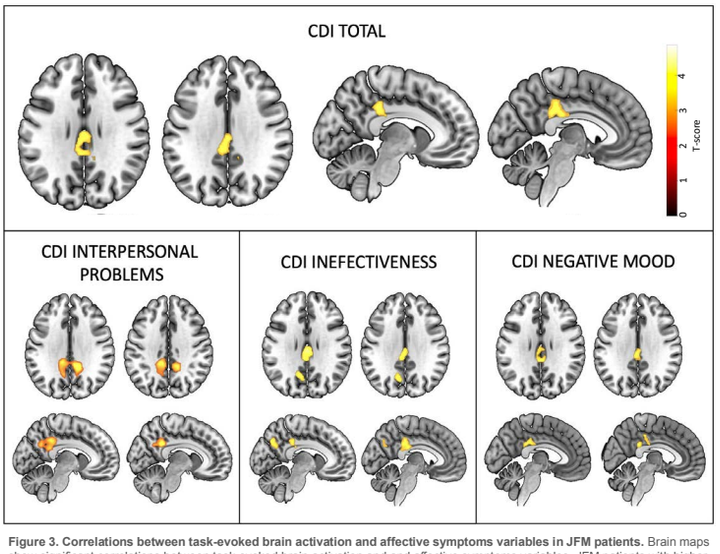

Figure 3. Correlations between task-evoked brain activation and affective symptoms variables in JFM patients. Brain maps show significant correlations between task-evoked brain activation and and affective symptoms variables. JFM patients with higher scores on the CDI showed augmented activation in the posterior cingulate cortex (PCC) during the multisensory task Results are presented at a significant level of whole-brain FWE cluster-corrected level (voxel-level p<0.001).

CONCLUSIONS

The findings strengthen the association between augmented nonpainful multisensory hypersensitivities and affective symptoms in juvenile patients with fibromyalgia.

JFM patients with enhanced depressive symptoms showed amplified cortical responses in a region that is crucial for self-referential processes, autobiographical memories, and internally-vs-externally oriented attention shifting (PCC).

This study highlights the potential role of sensory processing alterations when studying, diagnosing, and treating JFM.

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Repetitive Transcranial Magnetic Stimulation Hinders Functional Recovery in a Subgroup of Patients with Chronic Low Back Pain and Clinical Features of Central Sensitization

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INTRODUCTION

Exercises are recommended for chronic low back pain (CLBP) management, but its effects remain modest (1). This may be due because exercises may not influence brain alteration, potentially involved in chronicity.

Repetitive transcranial stimulation (rTMS) can influence brain alteration, but its effects in CLBP is unsure (2). Considering CLBP is multifactorial, exercises and rTMS can be more effective in subgroups of patients with specific clinical profile.

AIM

The **aim** of this study was to determine if subgroups of patients with CLBP can best respond to exercise and to rTMS using a secondary moderation analysis of the ExTraStim factorial randomized controlled trial (RCT) (3).

Table 1: Moderators and a priori hypotheses

Moderators	A priori hypothesis
Sex	rTMS: female > male
Kinesiophobia	High: exercise > no exercise
Self-efficacy	Low: exercise > no exercise
"Central sensitization"	High: active rTMS > sham Low: exercise > no exercise
"Spine instability"	High: exercise > no exercise
Expectations	High: active rTMS > sham

METHODS

PARTICIPANTS

Table 2: Eligibility criteria

Inclusion criteria	Exclusion criteria
• 18 -65 years old • non-specific CLBP (> 3 months) • pain intensity > 3 out of 10 • pain-related disability >10% (Oswestry Disability Index - ODI)	• neuropathic pain (>4 on DN4) • specific cause of LBP (e.g. fracture, tumor) (4) • any unstable medical disorder • any contraindication to rTMS (5) • no prior rTMS treatment

STUDY DESIGN

- Factorial design (4 groups)
  - Active rTMS + exercises
  - Sham rTMS + exercises
  - Active rTMS
  - Sham rTMS

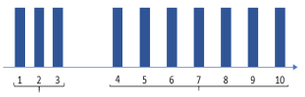

Figure 1. Treatment schedule for all groups.

METHODS (cont'd)

INTERVENTIONS

- Motor control exercises (MCE):
  - Assessment of posture, movement, muscle activation
  - Consideration of strength, endurance and psychosocial features
- Active rTMS
  - 40 trains of 5 s. at 10 Hz over the primary motor cortex (M1) lasting 20 min
  - 95% of the resting motor threshold of a finger muscle
- Sham rTMS: identical but a shield blocks the magnetic field

OUTCOMES

- Pain intensity and pain-related disability (ODI) at 8 weeks

POTENTIAL BASELINE MODERATORS (dichotomized)

- Pain self-efficacy → Chronic pain self-efficacy scale (45.5 median split)
- Kinesiophobia → Tampa Scale for Kinesiophobia (TSK: cut-off: 33)
- Clinical features of "central sensitization" → Central Sensitization Inventory (CSI - cut-off: 40)
- "Spine instability" → Lumbar Spine Instability Questionnaire (cut-off: 9)
- Expectations → cut-off: 2
- Sex at birth → male / female

STATISTICAL ANALYSIS

- Separate linear mixed models for Exercises (Yes, No) and rTMS (active vs. sham)
  - Fixed factors: Moderators (e.g. low vs. high), Intervention and Moderators x Intervention
  - Random factor: participant's intercept
  - Covariates: pain or disability at baseline for pain and disability outcomes, respectively

RESULTS

PARTICANTS: 140 participants recruited [mean age: 38.4 (13.0); baseline pain: 5.2 (1.6)]

- **rTMS**: active (n=70) / sham (n=70) | **MCE:** Yes (n=72) / No (n=68)

MODERATORS (interaction with Intervention):

- **rTMS:** Intervention x CSI interaction ($F_{(1, 123.96)}$=4.34 ; p=0.04) for ODI
  - CSI high: sham rTMS less disability than active rTMS (5.66% [95%CI, 0.11,11.21])
  - active rTMS: CSI low less disability than CSI high (-7.28% [95%CI, -12.06,-2.50])
  - No interaction for pain intensity (p>0.11)

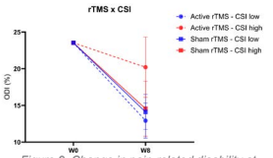

Figure 2. Change in pain-related disability at 8 weeks for the four groups

- **MCE**:
  - no Intervention x CSI interaction (p>0.10) for ODI
  - no Intervention x CSI interaction (p>0.27) for pain intensity

PREDICTORS OF BEST OUTCOMES (main effects of Moderators)

- **rTMS:**
  - CSI ($F_{(1, 123.96)}$=5.43 ; p=0.02) and Expectations ($F_{(1, 105)}$=9.80; p=0.002) for ODI
  - No significant main effect for pain intensity
- **MCE:**
  - Self-efficacy ($F_{(1, 123.96)}$=)=6.35 ; p=0.013) and CSI ($F_{(1, 123.96)}$=4.21; p=0.042) for ODI
  - No significant main effect for pain intensity

CONCLUSIONS

- In opposition with *a priori* hypothesis, rTMS prevented disability improvement in patients with CLBP and clinical features of "central sensitization" (CSI >40). If confirmed, it will be imperative to strongly advocate against rTMS use in this subgroup since it may hinder natural recovery. The underlying mechanisms remain unclear.
- For MCE, no treatment effect modifier was found in contrast to a study reporting that LSIQ may be one (6).
- Clinical features of "central sensitization, pain self-efficacy and expectations predict change in pain-related disability regardless of the allocated intervention.

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II-B.17

The role of pain expectancy and its confidence in pain perception

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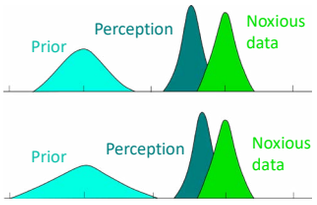
INTRODUCTION

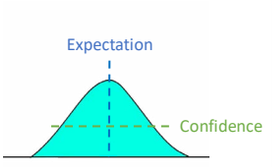
Positive and negative expectations can bias pain perception, e.g., placebo hypoalgesia and nocebo hyperalgesia[1,2].

Bayesian Brain Hypothesis: Perception results from the integration between a prior, incoming sensory data, and their precision[3,4].

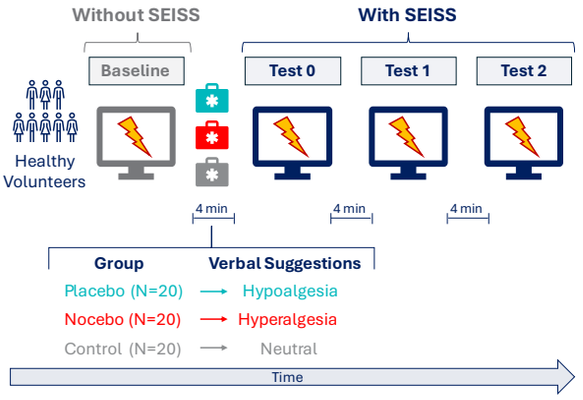


AIM

To investigate whether **placebo hypoalgesia** and **nocebo hyperalgesia** can both be described under the same **Bayesian framework** assessed at the **metacognitive level.**



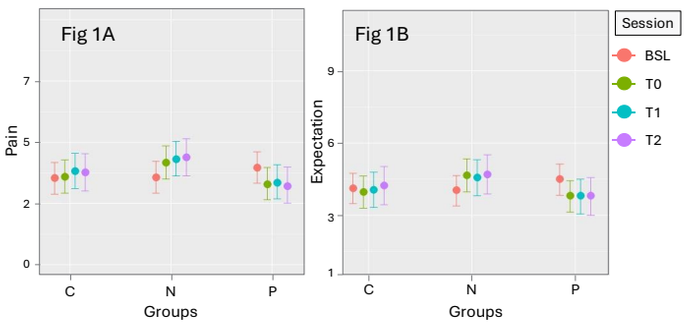
METHOD



RESULTS

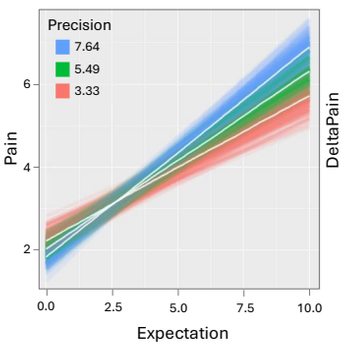
✓ Where there placebo and nocebo effects? YES!

- **Pain** was modulated and the effect lasted over time.
- **Expectations** were modulated and the effect lasted over time.



BLMM Analyses including Groups and Session as fixed effects and Pain (Fig A) and Expectation (Fig B) as DVs. Sequential contrast used to track updating over time (BSL vs T0; T0 vs T1; T1 vs T2).

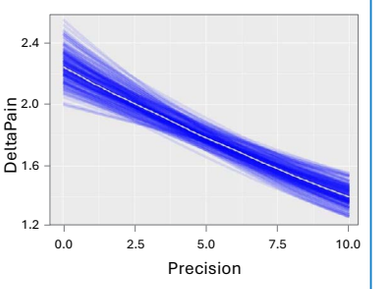
✓ Did the data follow Bayesian rules? YES!



BLMM Analysis

Pain ~ Expectation*Precision

- Small but consistent **interaction** effect.



BLMM Analysis

DeltaPain ~ Precision

- Strong and consistent main effect of **Precision on DeltaPain** (|Expected – Perceived Pain|)

CONCLUSIONS

- ✓ Once triggered both placebo hypoalgesia and nocebo hyperalgesia lasted over time.
- ✓ Placebo hypoalgesia and nocebo hyperalgesia can be unified under the same Bayesian predictive model assessed at the metacognitive level.
- ✓ **Expectation precision (confidence) as a potential new target for pain modulation and treatment developments.**

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ACKNOWLEDGEMENT

We thank Carlo Toneatto for his technical expertise and support in setting up the experiment.

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SCAN ME!

III-C.08

Machine learning clinical decision support for interdisciplinary multimodal chronic musculoskeletal pain treatment: prospective pilot study of patient assessment and prognostic profile validation

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INTRODUCTION

Chronic musculoskeletal pain (CMP) impacts around 20% of people globally.

Interdisciplinary multimodal pain treatment (IMPT) provides positive and sustained outcomes where other interventions have failed.

IMPT programs combined with **multidimensional machine learning** predictive patient profiles aim to improve clinical decision support and personalized patient assessments, potentially leading to better treatment outcomes.[1]

AIM

This prospective pilot study [2] aimed to:

1. Externally validate **machine learning** prognostic patient profiles and examine how they may assist clinicians and patients during IMPT assessment.
2. Review and **consolidate** the IMPT outcome framework.
3. Assess **presentation** and interpretation of the patient profiles and develop new profile summary indicators to better assist clinicians and patients in making informed treatment decisions.

METHOD

This prospective pilot study utilized a machine learning prognostic patient profile of 7 outcome measures across 4 clinically relevant domains including activity/disability, pain, fatigue and quality of life.

Prognostic profiles were created for new IMPT patients in the Netherlands in November 2023 (N=17).

New summary indicators were developed:

- Categories for positive, negative, and mixed prognostic profiles
- Accuracy indicator with high, medium, and low levels based on weighted true or false positive values
- Indicator for consistently positive or negative outcomes.

The consolidated reporting guidelines checklist for prognostic machine learning modelling provided transparency of data quality, model development methodology and validation.

RESULTS

The machine learning IMPT prognostic patient profiles demonstrated high accuracy and consistency in predicting patient outcomes.

The profiles combined with extended new prognostic summary indicators provided improved identification of patients with predicted positive, negative and mixed outcomes supporting more comprehensive IMPT assessment.

Overall, 82.4% (14/17) of prognostic patient profiles were consistent with clinician assessments.

Notably, clinician case notes indicated the stratified prognostic profiles were directly discussed with around half (47.1%, 8/17) of patients.

Clinicians found the prognostic patient profiles helpful in 88.2% (15/17) of initial IMPT assessments, to support shared clinician and patient decision making and discussion of individualised treatment planning.

Pilot study prognostic patient profiles with 7 outcome measures and new summary indicators

Outcome domain / outcome	% Positive	AUC	TPR	TNR
Activity / Disability				
1 Pain Disability Index (PDI)	58.2	0.63	0.89	0.23
2 General Perceived Effect (GPE): disability <3	39.7	0.65	0.32	0.83
Pain				
3 General Perceived Effect (GPE) pain	68.7	0.62	0.97	0.09
4 Pain Numeric Rating Scale (NRS)	42.4	0.65	0.37	0.81
Fatigue				
5 Fatigue Numeric Rating Scale (NRS)	36.3	0.61	0.09	0.96
6 Checklist Individual Strength (CIS) total	52.3	0.60	0.72	0.42
Health Related Quality of Life (PCS)				
7 SF12 - Physical Component Score (PCS)	59.7	0.58	0.94	0.10

Source: Machine learning IMPT prognostic patient profile pilot study (N=17). AUC=area under the curve, TPR=true positive rate, TNR=true negative rate. Profile accuracy H=high, M=medium, L=low

IMPT – Prognostic patient profile

Patient data		Activity / Disability	TPR	TNR	Prognostic prediction
	1	Pain Disability Index (PDI)	0.89	0.23	Negative
	2	General Perceived Effect (GPE): disability <3	0.32	0.83	Positive
		Pain			
	3	General Perceived Effect (GPE) pain	0.97	0.09	Positive
	4	Pain Numeric Rating Scale (NRS)	0.37	0.81	Positive
		Fatigue			
	5	Fatigue Numeric Rating Scale (NRS)	0.09	0.96	Negative
	6	Checklist Individual Strength (CIS) total	0.72	0.42	Negative
		Health Related Quality of Life			
	7	SF12 - Physical Component Score (PCS)	0.94	0.10	Positive
	8	SF12 - Physical Component Score (MCS)			Planned inclusion

IMPT Prognostic profile summary indicators		
Number of outcomes positive		4
Prognostic profile summary	(Positive / Negative / Mixed)	Positive
Profile accuracy category	(High / Medium / Low)	High
All outcomes positive or negative	(Yes / No)	No

Example patient prognostic profile with actual pilot testing study data results. PDI, pain disability index; GPE, global perceived effect (disability); NRS, numeric rating scale; CIS, checklist individual strength; SF-12 PCS, short-form quality of life survey physical component score; SF-12 MCS, short-form quality of life survey mental component score. TPR, true positive rate; TNR, true negative rate; patient data section is shown for illustrative purposes representing the 55 baseline prognostic variables and values that would appear on the patient profile.

CONCLUSIONS

Machine learning prognostic patient profiles showed promising contributions for IMPT clinical decision support and improving treatment outcomes for CMP patients.

Further research is needed to validate these findings in larger, more diverse populations.

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III-C.09

Efficacy of two psychological therapies for different indices of painrelated outcomes derived from ecological momentary assessment

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INTRODUCTION

Average pain intensity is the most used index for assessing the effectiveness of therapies. However, this index may not capture dynamic changes in the outcomes.

Schneider et al[1] proposed alternative indices of pain intensity obtained through ecological momentary assessment (EMA).

This study explores alternative indices in evaluating Acceptance and Commitment Therapy (ACT) and Behavioral Activation Therapy for Depression (BATD) for individuals with chronic low back pain (CLBP) plus depressive symptoms using EMA.

AIM

To analyze the treatment effects of two psychological therapies (ACT and BATD) compared to treatment as usual (TAU) using 6 indices: Average, Maximum, Minimum, Variability, % Time in high, and % Time in low.

The outcomes are pain intensity, pain interference, pain control, sleep disturbance, and depressed mood.

Specifically, this study seeks to answer two key questions: (1) Which indices are most sensitive in general? And (2) Do ACT and BATD have a different impact on the indices of the outcomes?

METHOD

- **Design:** Secondary analysis of the IMPACT study[2] (NCT04140838), a RCT with three study arms: ACT, BATD, and TAU.
- **Participants:** 82 Spanish participants (77% women, mean age = 56 years) with CLBP plus clinically relevant depressive symptoms (ACT = 23; BATD = 27; TAU = 32). No significant baseline between-group differences were found.
- **Interventions:** 8-week group-based ACT or BATD delivered via videoconference.
- **Data collection:** 5,361 EMA data points were collected twice daily over 70 days with the Pain Monitor app.
- **Outcomes:** Pain intensity, pain control, pain interference, sleep disturbance, and depressed mood. Each outcome was assessed using 6 indices: Average, Maximum, Minimum, Variability, % Time in high, and % Time in low.
- **Analysis:** Linear mixed models to assess group differences over time were computed using SPSS v29 and R (lme4, multcomp libraries).

RESULTS

Which indices are most sensitive in general?

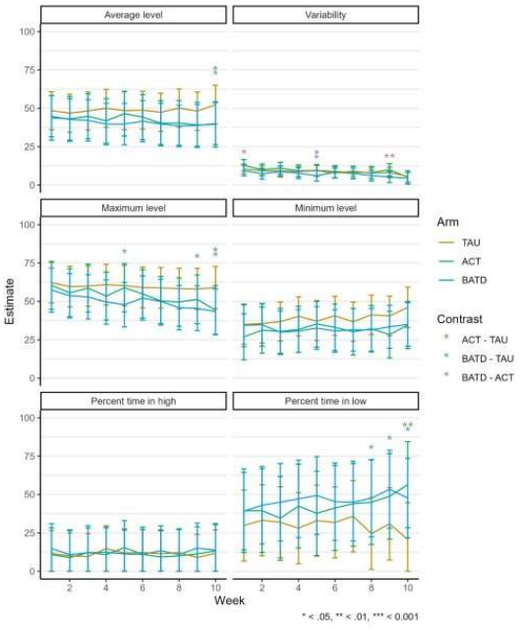
- "% Time in low" emerged as the most sensitive index for change in pain interference, sleep disturbances, and depressed mood.
- "Average intensity", the most common index in the literature, was not a sensitive index across all study outcomes.

Do ACT and BATD have a different impact on the indices of the outcomes?

- Compared to TAU, both therapies significantly improved more than one index of some outcomes.
- Compared to BATD, ACT showed a stronger impact on reducing sleep disturbances and pain interference.

The example of depressed mood (see graph on the right)

- The "Average" depressed mood level was lower in ACT and BATD compared to TAU at Week 10 (β = -12.90 and β = -12.38, respectively).
- BATD showed less "Variability" in depressed mood compared to TAU at Week 5 (β = -3.34) and compared to ACT at Week 1 (β = -3.44), Week 5 (β = -3.47), and Week 9 (β = -4.71).
- The "Maximum" depressed mood levels were lower in ACT compared to TAU at Week 10 (β = -14.71) and in BATD compared to TAU at Week 5 (β = -12.46), Week 9 (β = -12.65), and Week 10 (β = -35.88).
- ACT had a higher "% of Time in low" depressed mood compared to TAU at Week 10 (β = 35.74) and BATD had a higher "% Time in low" compared to TAU at Week 8 (β = 23.07), Week 9 (β = 22.56), and Week 10 (β = 27.01).



CONCLUSIONS

"% Time in low" is a promising index to be considered for detecting therapy effects.

This study provides new insights into the differential effects of ACT and BATD on clinically relevant pain-related outcomes.

Our work offers valuable contributions by enhancing the understanding of dynamic, individualized therapy responses, and refining pain management practices.

However, our results should be interpreted with caution due to the small sample size.

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I-D.30

Is There a Need for Peer-Education in Interdisciplinary Multimodal Pain Therapy (IMPT)? Results of Focus Group Interviews with Chronic Pain Patients

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INTRODUCTION

Peer Education refers to the provision of credible and reliable information about specific health topics to patients by individuals who are themselves affected by those issues. It is assumed that peer education has more chance of permeating the peer-group and changing health behaviour than information-giving just by professionals (Topping 2022, Thompson et al. 2022).

Also in chronic pain-management it is suggested that peer education may be a useful therapeutic supplement to improve patients self-management and self-efficacy (Arnott et al. 2023, Wilson et al. 2024). In interdisciplinary multimodal pain therapy (IMPT), education is an important intervention for improving patients' knowledge about chronic pain as a prerequisite for successful behavioural change to manage pain (Kaiser et al. 2017).

To date, there are still no specific recommendations for implementing peer education in IMPT.

AIM

The inclusion of the patient's perspective is considered essential for the successful implementation of peer education in various therapeutic settings (Thompson et al. 2022).

The aim of the present study is therefore to identify the

1. **need for peer education**
2. **required characteristics of a peer**
3. **topics for peer education**
4. **additional benefits of peer education** and
5. **potential risks of peer education**

from the perspective of patients who have participated in an IMPT.

METHOD

Setting
- Inpatient IMPT in group setting in a tertiary hospital in Switzerland

Participants
- Patients suffering from chronic pain disorder and have completed the IMPT

Data collection and analysis
- Semi-structured focus group interviews
- Interview moderation and recording through "knowledge mapping" (Pelz et al. 2004, Burgess-Allen et al. 2010) by two professionals from the IMPT team
- Data analysis by qualitative content analysis (Mayring 2019) with inductive categorisation by three authors

RESULTS

Population

14 focus groups with a total of 76 patients
- average 47.6 years
- 56,9% female

Need for peer education in IMPT?

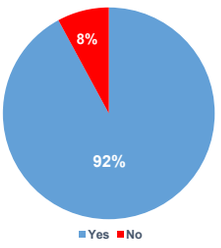

Figure 1:
Patients' responses to the question "Would you consider it useful to include peer-led educational sessions in the IMPT programme?"

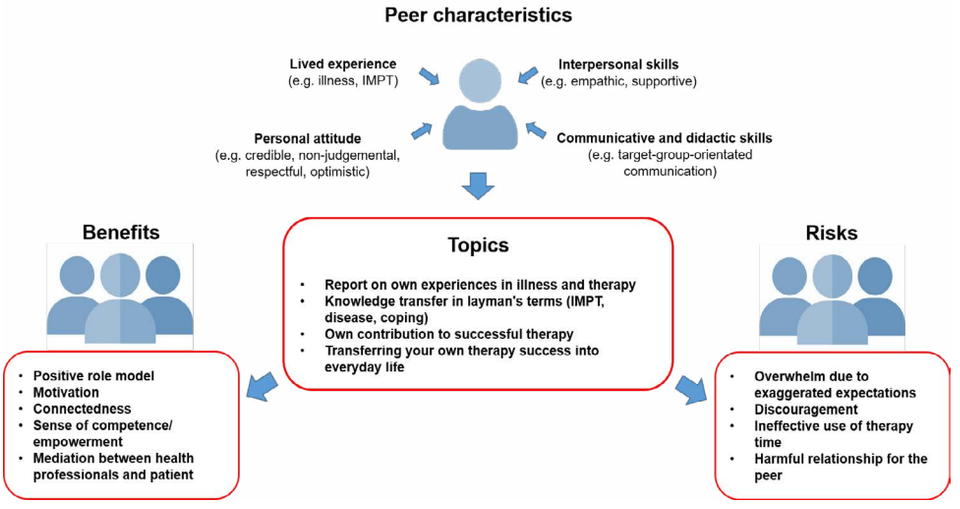

Figure 2:
Categories of qualitative content analysis on the characteristics of the peer, the topics of the peer education and the benefits and potential risks from the patient's perspective.

CONCLUSIONS

From the patient's perspective, there is a need to integrate peer education into IMPT.

Patients anticipate an additional therapeutic benefit in managing their chronic pain through the connection with a peer and the exchange of experiences on an equal footing.

Nevertheless, it is essential to consider certain potentially negative impacts when implementing peer education. In particular, the peer-characteristics required from the patients' perspective, along with the mentioned potential risks, suggest that peers should undergo specific training for an effective implementation in IMPT.

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II-C2.W.01

Sleep Disruptions & Immune Markers Predict Longitudinal Pain Outcomes Following Orthopedic Surgery

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INTRODUCTION

- Up to 50% of individuals with upper extremity joint-related conditions requiring surgery experience insufficient and poor sleep.[1]
- While the bidirectional nature of sleep and pain is well-known, sleep characteristics may serve as better predictors of pain outcomes than pain intensity is of sleep outcomes.[2,3]
- Yet, there is a dearth of research examining how changes in postoperative sleep are associated with post-surgical pain outcomes with much of the literature based on cross-sectional studies or discerning risks utilizing preoperative sleep presentations.[4,5]
- One pathway through which poor sleep may contribute to the development of post-surgical chronic pain is increased systemic inflammation.[2,5]
- Shortened sleep and increased sleep disturbances can induce, and even exacerbate, an outsized inflammatory reaction that propagates nociception after surgery.[2,5]

AIM

This longitudinal pilot study aimed to **discern the association between postoperative sleep presentations and inflammation on longitudinal postoperative pain** outcomes following orthopedic surgery.

METHOD

- Between December 2021 and January 2023 patients undergoing upper extremity surgery were recruited from an academic medical center.
- Eligibility criteria included adult patients without a history of sleep apnea, insomnia, chronic pain conditions, cancer, or autoimmune diseases, individuals not taking opioid or steroidal medications in the 30 days before surgery, and patients who were not undergoing a revision procedure.
- After providing consent, blood samples and following surveys were collected 2-weeks before surgery and again at 2-, 6-, 12-, and 24-weeks after:
  - Numeric Pain Rating Scale: assessed average pain from 0, no pain, to 10, worst pain imaginable.
  - PROMIS Sleep Disturbance: self-perceived sleep quality over the past week captured on a series of Likert scales that are summed and transformed to a T-score from 0 to 100 (i.e., higher scores indicate worse sleep quality).
- Assays were run on aliquoted plasma to ascertain inflammatory markers, including levels of tumor necrosis factor-α (TNF), interleukin-1β (IL-1β), interleukin-6 (IL-6) and corresponding receptors (i.e., IL-1ra and IL-6sr).

RESULTS

- The sample (N=40) was mostly female (72.5%) with an average age of 61.8 years (±12.3).
- Over a quarter of participants identified as Black/African American (27.5%) and most participants identified as white (72.5%)
- Approximately, half of participants underwent arthroplasty (57.5%) or arthroscopic procedures (42.5%) on their shoulder (85.0%) or elbow (15.0%).
- Preoperative pain scores in this sample were 6.1 (2.3), on average, and decreased by 4.3-points postoperatively (±3.5). Preoperative PROMIS Sleep Disturbance scores were above national norms, with an average of 56.2 (±9.2).
- Changes in sleep disturbance scores predicted changes in postoperative average pain when accounting for surgery type, changes in inflammatory markers, preoperative sleep, and pain scores.
- A standard deviation increase in PROMIS Sleep Disturbance scores was linked to a 1-point increase in postoperative average pain (β=0.11; p<.001) (Figure).
- Elevated postoperative IL-6sr levels were also associated with increased pain in the adjusted model (β=0.01; p=.036) (Table).
- Changes in other inflammatory markers were not associated with pain scores.

Figure. Mixed-effects model showing sleep estimating postoperative 24-hour average pain, by study visit

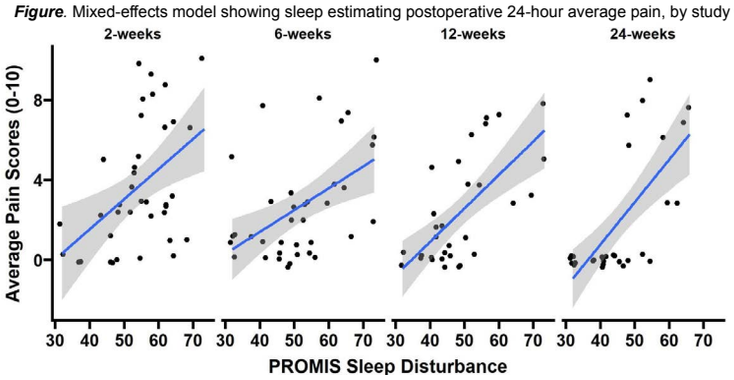

Table. Mixed-effects model estimating postoperative 24-hour average pain

Variable	β	*P* Value
Intercept	-6.93 (-11.52, -2.35)	0.008*
Change in PROMIS Sleep Disturbance T-Score Postoperatively	0.11 (0.07, 0.16)	<.001*
PROMIS Sleep Disturbance T-Score Preoperatively	0.05 (-0.03, 0.12)	0.250
Past 24-hour Average Pain (0-10) Preoperatively	0.25 (-0.05, 0.54)	0.130
Study Visit (Time)	-0.19 (-0.52, 0.17)	0.290
Surgery Type		
Arthroscopy (Reference)		
Arthroplasty	-0.85 (-1.66, 0.04)	0.060
Interleukin 6 Receptor (IL-6sr) pg/mL	0.01 (0.01, 0.01)	0.036*

CONCLUSIONS

- In this study postoperative sleep disturbances and elevated postoperative IL-6 receptor levels predicted postoperative pain scores out to 6 months following orthopedic surgery.
- The IL-6 trans-signaling system has been found to contribute to both pain perception and impact sleep architecture.[6]
- Given the shared influences on both postoperative pain and sleep, continued research on changes in the IL-6 trans-signaling system is warranted.[6,7]
- This study's longitudinal design, use of repeated measures, and ability to account for markers of potential mechanistic pathways that may drive the relationship between sleep disruption and pain outcomes builds upon previous cross-sectional studies and studies utilizing patient-reported outcomes alone.[2,8]

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EMORY

III-B1.W.09

Borders that hurt: The global spread of anti-immigration attitudes linked to the epidemic of chronic pain in adolescence

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INTRODUCTION

281 Million
International migrants worldwide in 2020
10% children

IOM UN MIGRATION

- Migration is fundamental to society.
- While migration is often safe and beneficial, some migrate due to conflict, economic instability, or climate disasters.
- Upon arrival, they may encounter additional health challenges stemming from racism, xenophobia, and discrimination, compounding pre-migration stressors.
- Immigrant youth in some European countries (e.g., Spain; Roman-Juan et al., 2024) are disproportionately affected by chronic pain (≥3 months; Treede et al., 2019).

European Commission

"The debates concerning the response to rising levels of migrants and refugees have become substitutes for debates on exclusion, racialisation and global inequality."

"Politicians and political/media commentators have delivered anti-migrant statements and racist hate speech with impunity."

"The anti-migrant rhetoric and political positions at a national or EU level over the course of 2015/2016 were played out through the media, and this had an impact on public opinion on the ground."

AIMS & HYPOTHESES

To examine the associations between country-level anti-immigration attitudes on chronic pain in immigrant adolescents across European countries using an intersectional approach.

Hypotheses:

1. Anti-immigration attitudes would be positively and significantly associated with chronic pain.
2. This association would be stronger among girls and adolescents with lower socioeconomic status, as compared to boys and adolescents with higher socioeconomic status, respectively.

METHODS

hbsc HEALTH BEHAVIOUR IN SCHOOL-AGED CHILDREN

- Survey: 2018
- 46 countries
- N = 240,951

European Social Survey

Procedure

Data were obtained from a **large cross-sectional, school-based survey** conducted every four years in collaboration with the **WHO Regional Office for Europe**. Nationally representative samples of **11-, 13-, and 15-year-old adolescents** were selected using a **cluster sampling method**, with **schools or school classes** as the primary sampling unit. Data collection followed a **rigorously standardized protocol**, including **translation and back-translation** of questionnaires. **Ethical approval** was secured from national ethics boards in each participating country.

Measures

Immigration background	Self-reported country of birth
Gender	Self-reported gender
Socioeconomic status (SES)	Family Affluence Scale IV (Torhseim et al., 2016)
Chronic Pain	HBSC Symptom Checklist (Haugland & Wold, 2001)

Anti-immigration attitudes

Item	Score
"Would you say it is generally bad or good for [country]'s economy that people come to live here from other countries?"	Good for the economy = 0 Bad for the economy = 10
"Is [country] made a worse or a better place to live by people coming to live here from other countries?"	Cultural life enriched = 0 Cultural life undermined = 10
"Would you say that [country]'s cultural life is generally undermined or enriched by people coming to live here from other countries?"	Better place to live = 0 Worse place to live = 10

Data analysis

Country-level data on anti-immigration attitudes (European Social Survey, 2018) and Gross Domestic Product (GDP) per capita (World Bank, 2018) were linked to HBSC 2018 data. Non-European countries and those lacking country-of-birth information were excluded. Weighted multilevel logistic regression models, accounting for clustering at the school and national levels, were conducted with chronic pain as the outcome variable.

RESULTS

Table 1. Descriptive statistics on key variables.

Variable	*N* (weighted %)
Individual characteristics (*n* = 5,621)	
Gender	
Boys	2,885 (51.39)
Girls	2,736 (48.61)
Missing	0,00 (0.00)
Age group	
11 years	1,661 (29.40)
13 years	1,960 (34.36)
15 years	1,912 (34.70)
Missing	88 (1.54)
SES	
Low	1,579 (28.07)
Middle-high	3,772 (67.15)
Missing	270 (4.78)
Chronic pain	
No	4,767 (84.74)
Yes	701 (12.52)
Missing	153 (2.74)
	M (Range)
Age	13.62 (10.5-16.5)
FAS	8.44 (0-13)
Country characteristics (*n* = 20)	
GDP per capita, US$000s	54.04 (17.7-84.9)
Anti-immigration attitudes	4.32 (2.8-6.2)

Abbreviations. SES = Socioeconomic Status; FAS = Family Affluence Scale; M = mean; SD = standard deviation GDP = Gross Domestic Product.

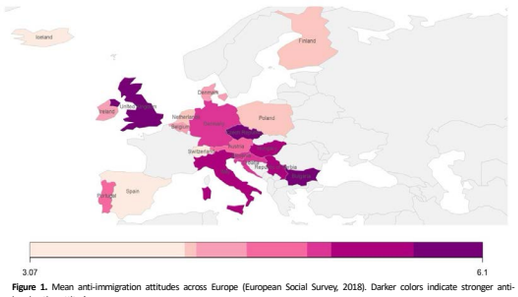

Figure 1. Mean anti-immigration attitudes across Europe (European Social Survey, 2018). Darker colors indicate stronger anti-immigration attitudes.

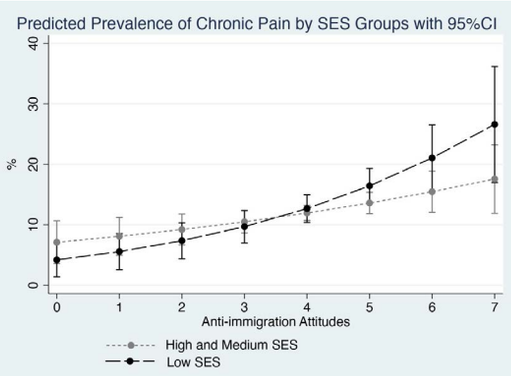

Figure 2. Predicted prevalence of chronic pain with 95% confidence intervals by socioeconomic status groups across increasing levels of anti-immigration attitudes.

Table 2. Weighted multilevel logistic regression models predicting chronic pain.

	Model 1	Model 2	Model 3	Model 4
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Fixed components				
Constant	**0.07 (0.02 - 0.24)‡**	**0.02 (0.01 - 0.10)‡**	**0.02 (0.04 – 0.14)‡**	0.02 (0.00 – 0.14)‡
Gender (ref:male)	**1.74 (1.41 - 2.15)‡**	**1.74 (1.42 – 2.16)‡**	2.72 (0.68 – 10.94)	2.71 (0.68 – 10.86)
Age	**1.11 (1.03 – 1.19)†**	**1.10 (1.03 – 1.19)†**	**1.10 (1.02 – 1.18)†**	1.10 (1.03 – 1.18)†
Low SES (ref:middle-high SES)	1.14 (0.94 - 1.37)	1.14 (0.95 – 1.37)	0.57 (0.26 – 1.26)	0.55 (0.25 – 1.22)
GDP per capita	**0.98 (0.97 - 0.99)†**	**0.99 (0.98 – 0.99)†**	**0.98 (0.98 – 0.99)†**	**0.98 (0.98 – 0.99)†**
Anti-immigration attitudes		**1.19 (1.03 – 1.38)***	1.20 (0.92 – 1.58)	1.20 (0.92 – 1.58)
Gender X Anti-immigration attitudes			0.91 (0.67 – 1.22)	0.90 (0.66 – 1.22)
SES X Anti-immigration attitudes			**1.17 (1.11 – 1.38)***	1.16 (0.97 – 1.39)
SES X Gender X Anti-immigration attitudes				1.02 (0.97 – 1.01)
Random components				
σ^2v0 (school)	0.12	0.12	0.12	0.12
σ^2v0 (country)	0.05	0.02	0.02	0.02
ICC (school)	0.05	0.04	0.04	0.04
ICC (country)	0.01	0.01	0.01	0.01
AIC	3860.27	3858.88	3860.39	3862.15
BIC	3906.10	3911.25	3925.85	3934.16
log-likelihood	-1923.13	-1921.44	-1920.19	-1920.07
df	7	8	10	11

Note: SES = Socioeconomic Status; GDP = Gross Domestic Product; OR=odds ratio; CI=confidence interval; ICC=intraclass correlations; BIC=Bayesian information criterion; AIC=Akaike's information criterion; df=degrees of freedom; number of schools=1,911; number of countries=20.
*$p<.05$; †$p<.01$; ‡$p<.001$

CONCLUSIONS

- Anti-immigration attitudes may act as a **modifiable driver** of health disparities among immigrant youth.
- **Public policies** should target social integration and public perception of immigrants to create inclusive environments and reduce chronic pain risk.
- The study underscores the importance of an **intersectional approach** that considers immigrant status, socioeconomic status, and systemic oppression in chronic pain research.

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LAEF Louise & Alan Edwards Foundation | SickKids Pain Centre | PICH Pain in Child Health Global Research Training

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III-B1.W.01

From Breast Cancer Diagnosis to Survivorship: Analyzing Perioperative Biopsychosocial Phenotypes and Their Relationship to Pain on Long Term

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INTRODUCTION

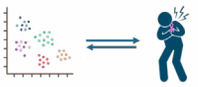
Pain affects up to 40% of breast cancer survivors decreasing their quality of life

Current research is focused on correlation and regression analysis to identify biopsychosocial phenotypes

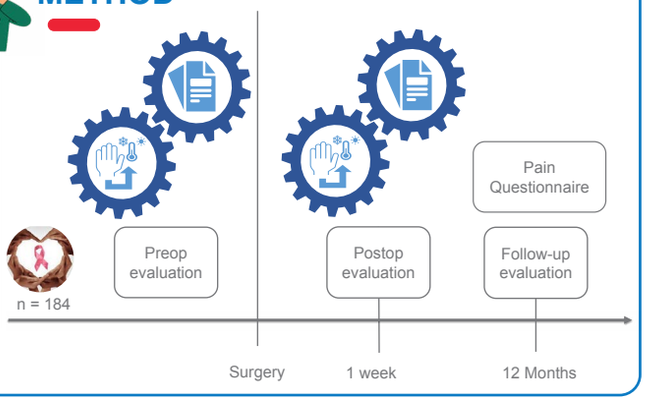
AIM

Identifying phenotypes before and one week post-surgery using latent class analysis

What is the relationship between the identified phenotypes and pain one year post-sugery?



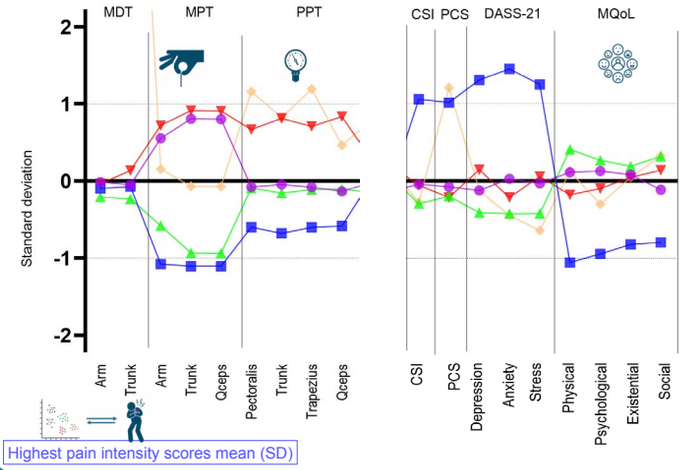
METHOD



RESULTS

Preoperative phenotypes

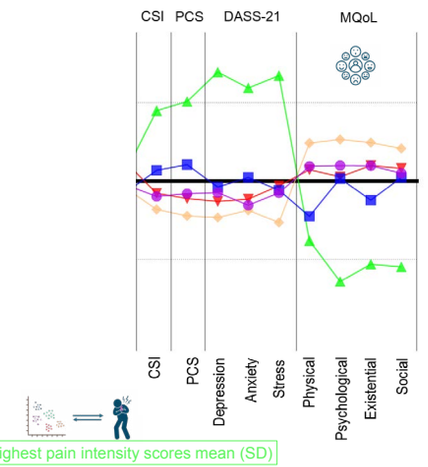
phenotype 1	phenotype 2	phenotype 3	phenotype 4	phenotype 5
n=65;35,7%	n=21;12,1%	n= 63; 33,6%	n=32;17,5%	n=2;1,1%
VAS: 22,8 (21,4)	VAS: 33,4 (24,1)	VAS: 22,6 (21,4)	VAS: 21,3 (20,2)	VAS: 24,0 (33,9)



Highest pain intensity scores mean (SD)

Postoperative phenotypes

phenotype 1	phenotype 2	phenotype 3	phenotype 4	phenotype 5
n= 27; 14,7%	n= 33; 17,9%	n= 31; 16,7%	n=34;18,4%	n=59;32,4%
VAS: 24,6 (14,7)	VAS: 26,6 (20,3)	VAS:37,7 (25,1)	VAS: 25,6 (24,1)	VAS: 15,2 (19,2)



Highest pain intensity scores mean (SD)

CONCLUSIONS

Presurgical mechanical and pain thresholds should be included

Using psychosocial questionnaires perioperatively

Be aware of patients psychosocial distress to intervene if necessary

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II-B2.W.02

Sensory Phenotypes of 612 Patients with Complex Regional Pain Syndrome

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Introduction and Aim

Complex Regional Pain Syndrome (CRPS) depends on a clinical diagnosis as defined by the Budapest criteria, which among other criteria include the assessment of pain continuity, sensory, vasomotor, sudomotor and trophic function. However, the clinical representation of the disease appears heterogenous and the exact underlying pathophysiological mechanism for Complex Regional Pain Syndrome (CRPS) has been under debate in recent years. Previous work has identified potential CRPS subtypes, which were characterized as “cold” and “warm” (Bruehl et al., 2016) or peripheral and central phenotypes (Dimova et al., 2020). Here, we aim to provide an additional cluster analysis of sensory CRPS data based on the highly standardized Quantitative Sensory Testing (QST) protocol of the DFNS (German Research Network on Neuropathic Pain) and thereby identify potential CRPS subgroups.

Results

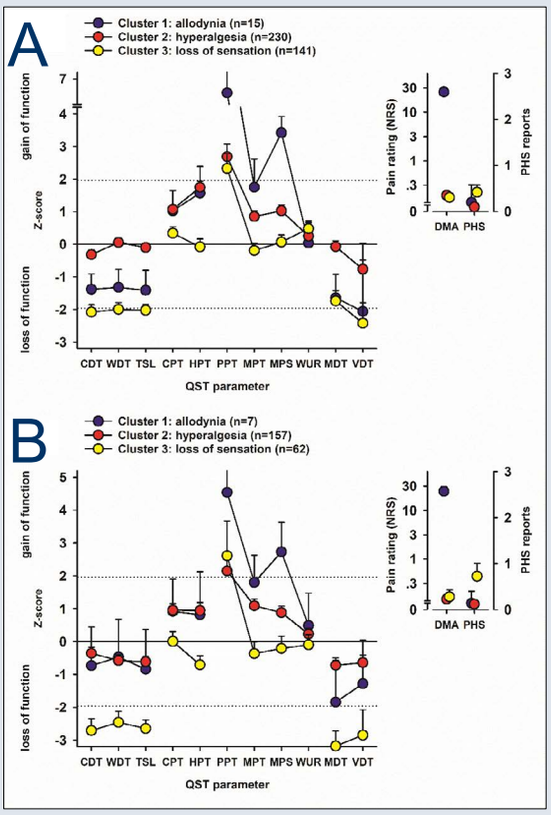
We identified three distinct sensory phenotypes, which were confirmed by the validation cluster analysis. The largest group was characterized by hyperalgesia (n=387), a second group was characterized by loss of sensation (n=203). A third, small, but consistent group exhibited strong allodynia and hyperalgesia (n=22).

CRPS Type	allodynia	hyperalgesia	loss	Total	p-value (chi² for three groups) or effect sizes (A/H; A/L; H/L)
n	**22**	**387**	**203**	**612**	
Age, Years ± SD	43.1 ± 13.9	51.6 ± 13.0	53.1 ± 14.0	51.8 ± 13.5	.63; .72; .12
Sex female, n(%)	18 (81.8%)	285 (73.6%)	138 (68.0%)	441 (72.1%)	0.202
CRPS I, n (%)	18 (81.8%)	342 (88.4%)	166 (81.8%)	526 (85.9%)	0.077
Lower extremity, n(%)	4 (18.2%)	50 (12.9%)	35 (17.2%)	89 (14.5%)	0.326
Foot, n(%)	4 (18.2%)	46 (11.9%)	34 (16.7%)	84 (13.7%)	0.219
Leg, n(%)	0 (0.0%)	4 (1.0%)	1 (0.5%)	5 (0.8%)	0.716
Upper extremity, n(%)	18 (81.8%)	337 (87.1%)	168 (82.8%)	523 (85.5%)	0.326
Hand, n(%)	18 (81.8%)	336 (86.8%)	166 (81.8%)	520 (85.0%)	0.242
Arm, n(%)	0 (0.0%)	1 (0.3%)	2 (1.0%)	3 (0.5%)	0.458
Duration, Years ± SD	2.8 ± 3.0	1.5 ± 3.3	1.8 ± 2.2	1.6 ± 3.0	.41; .38; .10
less than half a year, n(%)	6 (27.3%)	172 (44.4%)	65 (32.0%)	243 (39.7%)	**0.006**
less than 1 year, n(%)	0 (0.0%)	46 (11.9%)	31 (15.3%)	77 (12.6%)	0.096
less than five years, n(%)	7 (31.8%)	110 (28.4%)	63 (31.0%)	180 (29.4%)	0.778
less than ten years, n(%)	3 (13.6%)	10 (2.6%)	13 (6.4%)	26 (4.2%)	**0.008**
Ten or more years, n(%)	0 (0.0%)	6 (1.6%)	2 (1.0%)	8 (1.3%)	0.729
Average Pain, NRS ± SD	6.9 ± 1.9	6.0 ± 2.3	6.0 ± 2.4	6.0 ± 2.3	.45; .44; .00
Maximum Pain, NRS ± SD	8.6 ± 1.0	7.8 ± 2.2	7.5 ± 2.5	7.7 ± 2.3	.49; .62; .12
Current Pain, NRS ± SD	6.2 ± 2.5	4.7 ± 2.7	5.1 ± 2.7	4.9 ± 2.7	.57; .42; .14
Attacks only, n(%)	0 (0.0%)	49 (12.7%)	11 (5.4%)	60 (9.8%)	**0.006**
Ongoing Pain only, n(%)	7 (31.8%)	65 (16.8%)	49 (24.1%)	121 (19.8%)	**0.037**
Ongoing Pain + Attacks, n(%)	8 (36.4%)	134 (34.6%)	57 (28.1%)	199 (32.5%)	0.253
ADS, Score ± SD	25.9 ± 13.2	21.8 ± 11.0	21.9 ± 10.7	22.0 ± 11.0	.34; .33; .01

Tab. 1 Comparison of demographic data and pain specific data (localization, duration, average, maximum and current pain on NRS , presence of pain attacks/ongoing pain, ADS-score).

Methods

In total, 612 patients (age: 51.8 [±13.5], female: 441, see Tab. 1) with CRPS underwent Quantitative Sensory Testing according to the DFNS protocol. Thereby, 13 parameters including thermal and mechanical detection and pain thresholds were generated - indicating one distinct sensory profile for each participant. We conducted two separate hypothesis free cluster analysis (K-means clustering, no ad-hoc assumptions about cluster numbers, medium silhouette width as a decision criterion). First a training cluster analysis (**A**, n=386) and second a validation cluster analysis (**B**, n=226) was performed.



Conclusion

Here, we report a new way of stratifying patients with CRPS based on sensory phenotypes. The therapeutical implications for each subtype are unknown but still may add to a personalized pain treatment of CRPS in the future.

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I-A.09

Tripletreat vs Dynamic Duo for prolonged post-operative pain relief

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INTRODUCTION

Adductor canal block : contemporary, safe ,minimally invasive approach for postoperative pain management in knee surgery patients.

The duration of block : can it be prolonged, with **'Multimodal perineural analgesia' ???,** reducing the requirement of continuous catheters, parenteral or oral analgesics.

AIM

To compare duration of postoperative analgesia provided by addition of multiple adjuvants perineurally vs single adjuvant in adductor canal block

METHOD

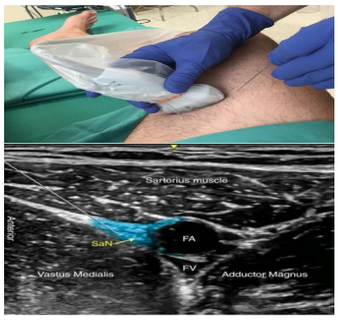
✅ **Setting & Participants**:
- A Randomized Controlled Double-Blind Study conducted at a tertiary care rural teaching hospital in Gujarat, India
- 70 patients (18–75 years, ASA I/II/III) undergoing knee surgeries
- Randomized into two groups using a web-based program

✅ **Intervention**: Ultrasound-guided single-shot adductor canal block given immediately post-operatively with 23 G Quinke's needle:
- Group A: 25 ml 0.25% Ropivacaine + 150 mcg Buprenorphine + 8 mg Dexamethasone
- Group B: 25 ml 0.25% Ropivacaine + 8 mg Dexamethasone

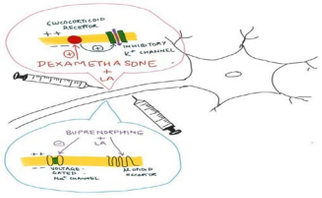
✅ **Outcomes Assessed**:

✓ Duration of analgesia (time until first rescue opioid needed) as Pain Scores (VAS) & Functional Activity Scores (FAS) over 24 hours

✅ **Statistical Analysis**:
- Data analyzed using STATA 14.2
- Independent sample t-test used to compare mean rescue analgesia time
- p-value < 0.05 was considered statistically significant



Ultrasound guided adductor canal block



Mechanism of action of multimodal perineural analgesia

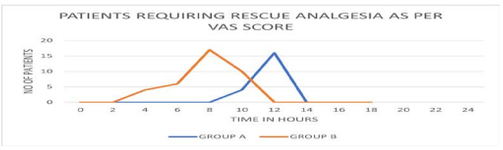
RESULTS

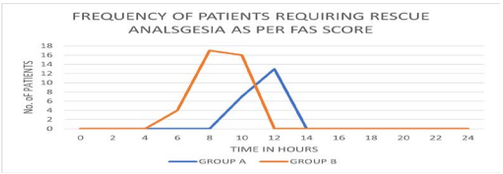
✅ Intergroup comparisons showed **statistically highly significant P value < 0.0001 in Group A** compared to Group B → '**Prolonged duration of analgesia in group A**'

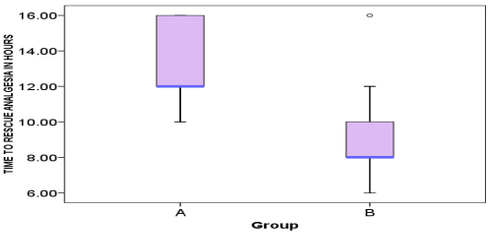
✅ Mean ± SD Time to First Rescue Analgesia:
- Group A: 12.91 ± 2.13 hours ⏳
- Group B: 9.14 ± 2.07 hours ⏳

✅ VAS and FAS profile was better in group A as compared to group B

✅ Zero Adverse Effects in both groups → Safe & Effective







Frequency of patients requiring rescue analgesia in both groups according to VAS and FAS score

CONCLUSIONS

Combining Buprenorphine and Dexamethasone with a local anesthetic perineurally significantly prolongs analgesia compared to using a single adjuvant.

This **triple treat** ensures longer-lasting pain control, reduced opioid need, and enhanced patient recovery—a game-changer in regional anesthesia!

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No conflicts of interest.

II-D2.W.01

The effects of rTMS on comorbidities in individuals with chronic neuropathic pain

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INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation technique recommended as a third-line treatment for **neuropathic pain** (NP) [1]. The analgesic efficacy has been demonstrated in randomized placebo-controlled clinical trials and in real life study [2].

NP regularly coexists with **comorbidities** which can significantly impact overall functioning, quality of life of individuals and treatment efficacy.

AIMS

Primary :

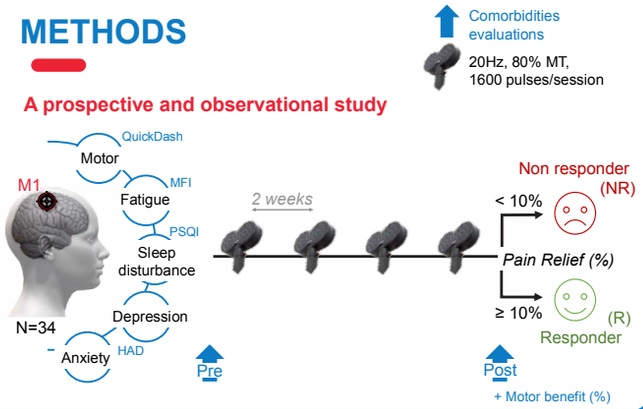
1. Assess the efficacy of four sessions of rTMS on comorbidities;

Secondary :

2. Explore the relations ships between rTMS's analgesic efficacy and its effects on comorbidities;
3. Evaluate the impact of baseline comorbidities on the analgesic efficacy of rTMS.

METHODS

A prospective and observational study



RESULTS

1 General and mental **fatigue**, subjective **sleep** quality, and sleep **latency** improved after 4 sessions of rTMS.

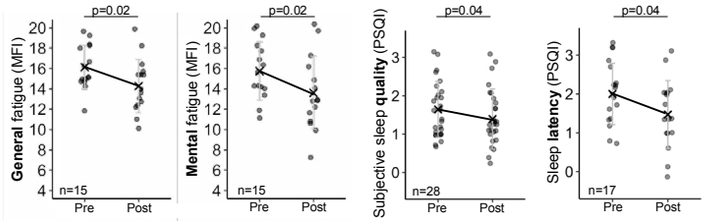


Fig.1 : **Changes** in comorbidities before and after the 4 rTMS sessions in subgroups of initially symptomatic patients. For the MFI, a threshold score based on age and sex was used to define the presence of pathological fatigue. For the PSQI, a score different from 0 was considered abnormal. Only the 4 outcomes with significant changes are represented.

2 The rTMS analgesia successful and the evolution of psychological and physiological variables are independent.

The relation between motor benefit and pain relief highlights 3 patient clusters.

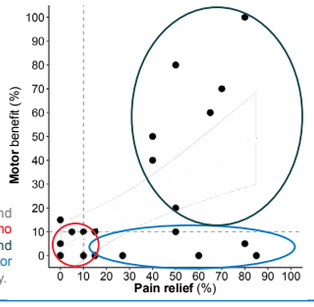


Fig.2: **Scatterplot** of individual patient data, with pain relief and motor benefit. Three patient clusters are identified: those with no benefit (neither analgesic nor motor), those with both analgesic and motor benefits, and those with analgesic benefit but no motor benefit. The benefit threshold is set at 10% for determining efficacy.

3 High levels of general and cognitive fatigue are predictive of analgesia successful of rTMS.

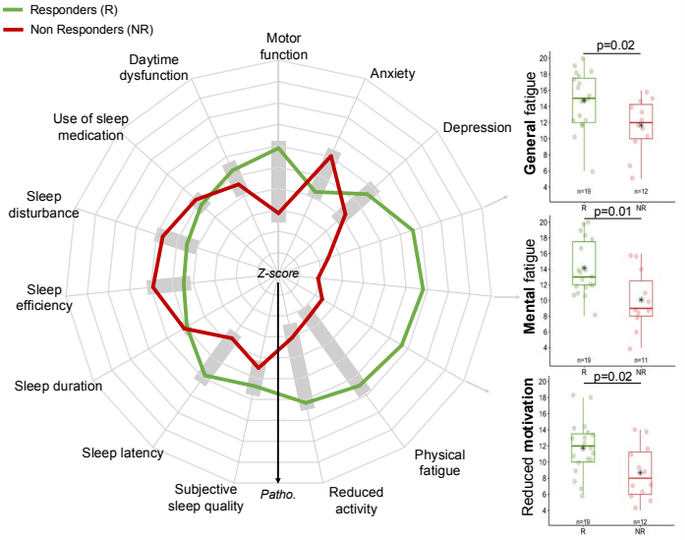


Fig.3 : **Radar plot** of the normalized mean values (z-score) of clinical variables at baseline in responders (R, Green) and non-responders (NR, Red). The further the score is from the center, the worse the value (scale: -1 > z-score > +1, tick mark: 0.2). The grey areas represent the lack of statistical significance in the comparative analyses, although a potential trend may be observed. *The first limitation is the small sample size analyzed*. On the right, distribution and **boxplot** of variables showing a significant difference based on pain relief status.

CONCLUSIONS

This cohort provides a first clinical assessment of the effects of rTMS on comorbidities in neuropathic pain, as well as the impact of these comorbidities on the analgesic efficacy of rTMS. Our study, consistent with previous literature [3], suggests that rTMS could be an effective holistic approach to managing both pain and associated comorbidities, such as motor dysfunction, fatigue, and sleep disturbances. The analysis of rTMS's analgesic efficacy and its effects on comorbidities underscores the complexity of the underlying mechanisms by which pain and comorbidities co-exist, emphasizing the need for further research to better understand these mechanisms as well as the mechanisms of rTMS itself. Additionally, general and cognitive fatigue may influence neuromodulation effectiveness.

These preliminary results highlight the importance of ongoing data collection in clinical practice and align with EFIC's strategy to prioritize research on comorbidities [4].

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