Behavioral and neural underpinnings of positive and negative treatment expectations and their effects on pain

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Treatment Expectation
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PREREGISTERED

INTRODUCTION

- Pain can be **modulated by positive and negative treatment expectations** induced by a combination of verbal instructions and classical conditioning[1,2].
- More research is needed to **identify shared and distinct neural mechanisms underlying placebo and nocebo effects** in the same paradigm and individual.
- Especially the **formation and temporal dynamics** of placebo and nocebo effects need to be further investigated[3,4].

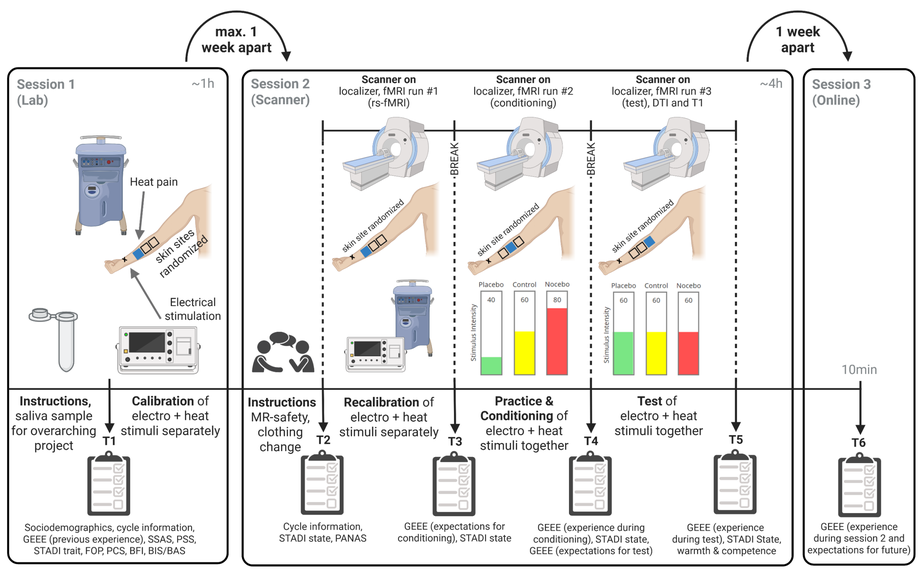
Research Objective

What are the **temporal dynamics and neural mechanisms** underlying the formation and effects of positive and negative treatment expectations in pain?

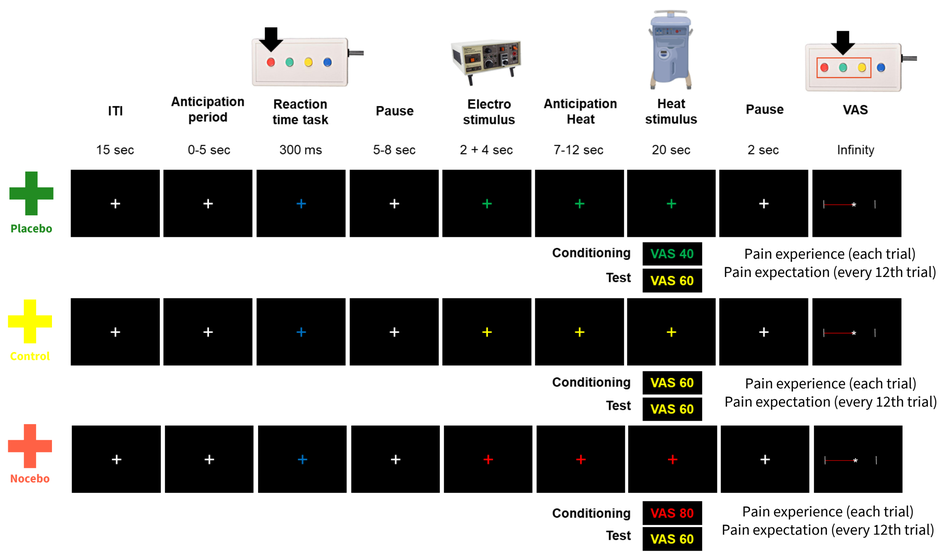
METHODS

- Established **model of verbally instructed and conditioned placebo hypoalgesia and nocebo hyperalgesia**[5]
- Within-subject study design
- Two fMRI tasks:
  - **Expectation formation run** during conditioning with reinforcement of positive or negative treatment experience
  - **Placebo/nocebo test run** without such reinforcement
- **Outcomes**: BOLD responses, expectation ratings, pain ratings, and questionnaire data
- **Sample:** *n* = 67 participants
  - Mean age ± SD = 24 ± 3 years, range: 19-37
  - Gender distribution: 33 males & 34 females
- Ongoing **fMRI data analysis** (fmriprep & SPM)
- **10-12 month follow-up data** (*n* = 37) and an additional **control group without conditioning** are being collected (*n* = 30)

Study Design

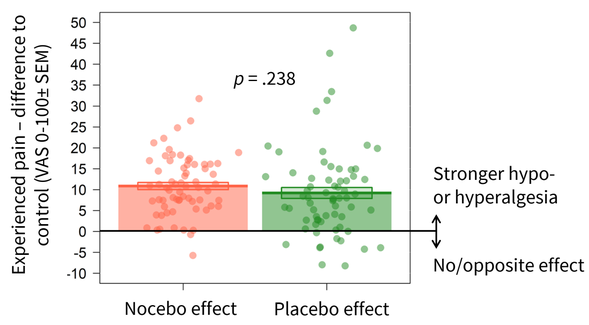


Experimental Task



RESULTS

FIG. 1 Placebo & Nocebo Effects



Questionnaire measuring Treatment Expectations, and Treatment Effects (G-EEE)[6]

FIG. 4A – Placebo

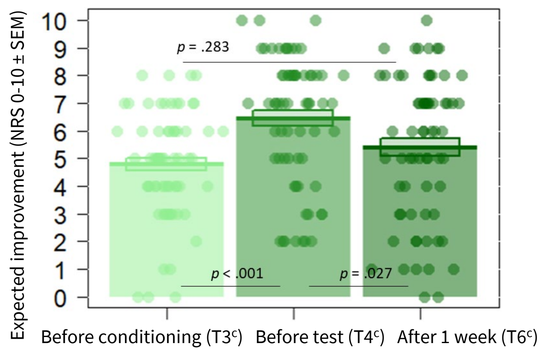
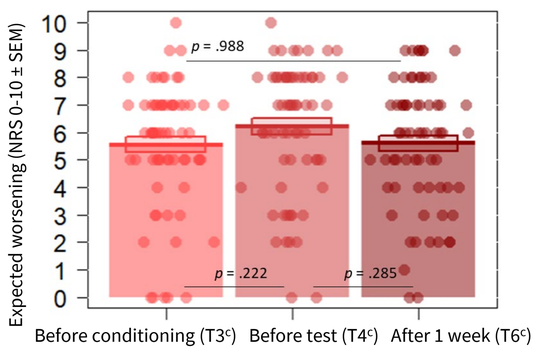


FIG. 4B – Nocebo



Relationship between Expectations and Effects

FIG. 3A – Placebo[a]

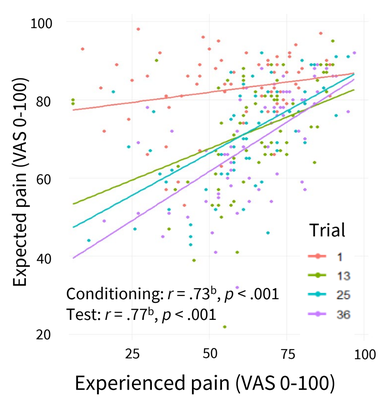
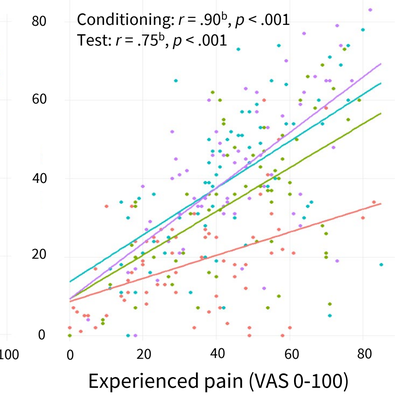


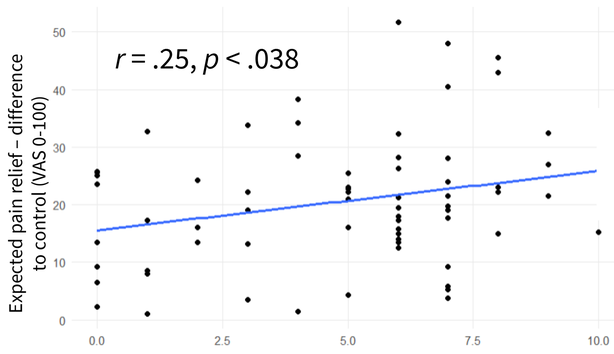
FIG. 3B – Nocebo[a]



[a] Displayed for the test phase separate for the four time points for visualization purposes (for trials 1, 13, and 25 the expectation rating right before the next pain rating, for trial 36 the expectation rating directly after the last pain rating was used).
[b] Correlations averaged over all trials.
[c] See study design figure for time points of questionnaires.

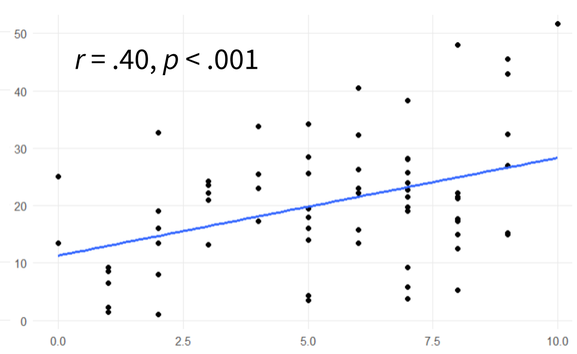
Relationship between Expectation Ratings during the Test Phase and G-EEE Ratings after one Week

FIG. 5A – Placebo



G-EEE **Retrospective improvement** after one week (T6c, NRS 0-10)

FIG. 5B – Placebo



G-EEE **Prospective improvement** after one week (T6c, NRS 0-10)

Conditioning Phase

FIG. 2A

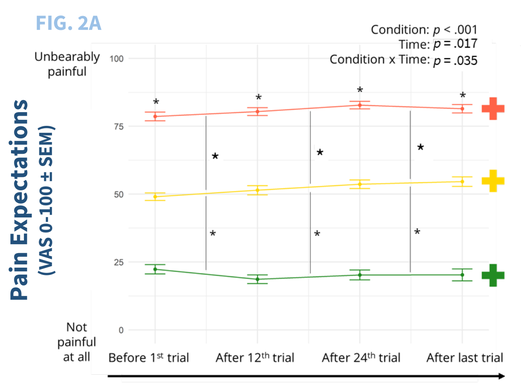
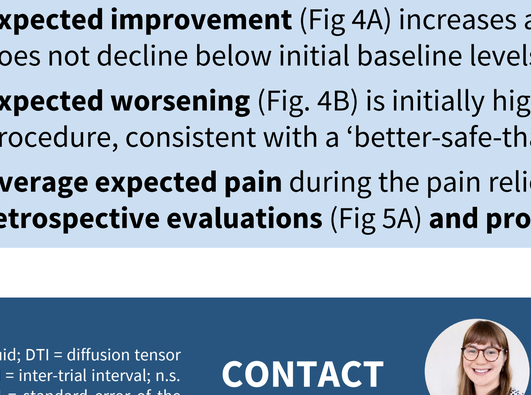


FIG. 2B



Test Phase

FIG. 2C

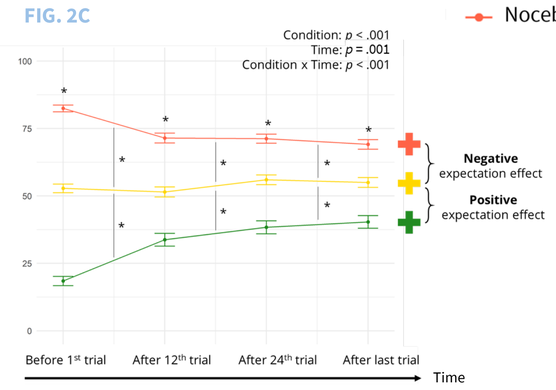
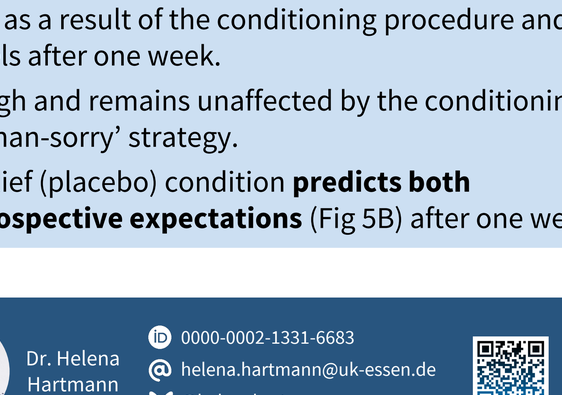


FIG. 2D



DISCUSSION

- **No difference between behavioral placebo and nocebo effect** in the Test phase, which differs from our previous study reporting a stronger nocebo than placebo effect[7] (Fig. 1).
- **Successful and equal conditioning of both positive and negative treatment expectations** for expected (Fig. 2A) and experienced (Fig. 2B) pain. These effects are still present when stimulation intensity is kept constant in the Test phase (Fig. 2C+D).
- Compared to positive expectations, **negative expectations develop more quickly, are more stable, and extinguish more slowly,** as indicated by their temporal slopes (Fig. 2).
- **Strong association between expected and experienced pain** in both conditioning and test phase, which seems to increase with time (NOC: Fig. 3A, PLA: Fig. 3B).
- **Expected improvement** (Fig 4A) increases as a result of the conditioning procedure and does not decline below initial baseline levels after one week.
- **Expected worsening** (Fig. 4B) is initially high and remains unaffected by the conditioning procedure, consistent with a 'better-safe-than-sorry' strategy.
- **Average expected pain** during the pain relief (placebo) condition **predicts both retrospective evaluations** (Fig 5A) **and prospective expectations** (Fig 5B) after one week.

REFERENCES

1) Benedetti et al., 2022
2) Colloca & Barsky, 2020
3) Colagiuri et al., 2015
4) Rooney et al., 2023
5) Colloca et al., 2010
6) Rief et al., 2021
7) Kunkel et al., 2025

Statistical models: Expectation or Pain rating ~ Condition*Time + (1 | Subject)

Abbreviations: BOLD = blood oxygen level dependent; CSF = cerebrospinal fluid; DTI = diffusion tensor imaging; (rs-)fMRI = (resting-state) functional magnetic resonance imaging; ITI = inter-trial interval; n.s. = not significant; NRS = numeric rating scale; SD = standard deviation; SEM = standard error of the mean; T1 = T1-weighted anatomical; VAS = visual analogue scale; WM = white matter.

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