Background & Aims

- Placebo hypoalgesia and nocebo hyperalgesia refer to pain decrease and increase, respectively, that occur after administering an inert intervention (a placebo).
- As placebo hypoalgesia and nocebo hyperalgesia are known to be learning phenomena, it seems essential to study their susceptibility to extinction, i.e. how long the effects last once established.
- The current systematic review and meta-analysis is the first to summarise and analyse the available data on the extinction of placebo effects in pain shaped by various learning procedures: classical conditioning, operant conditioning, verbal suggestion, and observational learning.
- This systematic review and meta-analysis specifically focus on quantitative data related to extinction but is part of a broader project examining the efficacy of various learning procedures in modifying placebo effects in pain.

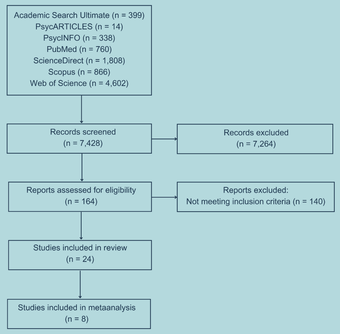
Methods

Data Sources: Seven databases were searched (Academic Search Ultimate, PsycArticles, PsycInfo, PubMed, ScienceDirect, Scopus, Web of Science) and references of included studies.

Inclusion Criteria: Studies were included if they were published in English and (1) enrolled healthy volunteers; (2) placebo or nocebo effects in pain were induced experimentally,
(3) learning procedures, i.e., counterconditioning, extinction, observational learning, operant conditioning or verbal suggestion were used to change previously induced effects.

Analyses: To investigate the extinction over time, trial-by-trial data from the testing phase (i.e., the phase in which learning effects were tested) were extracted and analyzed. Difference scores were calculated by subtracting the low cue pain rating from the high cue rating (i.e., nocebo - control or control - placebo). Risk of bias was assessed for all the included studies.

Figure 1. Study selection diagram



Results

Twenty-four articles (twenty-five experiments) were included in the systematic review with eight studies on extinction. Regarding extinction analysis, two studies [1, 2] aimed to induce placebo hypoalgesia by observational learning and in six studies nocebo hyperalgesia was induced via classical conditioning combined with verbal suggestion [3-7].

Nocebo hyperalgesia: significant differences were observed between high and low pain cues in the 1st trial (M_{dif} = 0.71; CI [0.49, 0.94]), 2nd trial (M_{dif} = 0.60; CI [0.40, 0.80]), 3rd trial (M_{dif} = 0.64; CI [0.33, 0.94]), and 4th trial (M_{dif} = 0.41; CI [0.21, 0.60]). Differences between high and low cues were insignificant from the 5th trial (M_{dif} = -0.13; CI [-0.55, 0.28]).

Placebo hypoalgesia: significant differences were found between high and low pain cues in the 1st trial (M_{dif} = 1.81; CI [1.37, 2.25]) and 2nd trial (M_{dif} = 1.39; CI [0.63, 2.15]). Differences between high and low cues were insignificant starting from the 3rd trial (M_{dif} = -0.04; CI [-0.78, 0.70]).

References:
[1] Bieniek, H., & Bąbel, P. (2022). The Effect of the Model's Social Status on Placebo Analgesia Induced by Social Observational Learning. Pain Medicine (Malden, Mass.), 23(1), 81–88.
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[3] Colagiuri, B., et al. (2021). Pre-Exposure, But Not Overshadowing, Inhibits Nocebo Hyperalgesia. The Journal of Pain, 22(7), 864–877.
[4] Skvortsova, A., et al. (2020). Effects of Oxytocin on Placebo and Nocebo Effects in a Pain Conditioning Paradigm: A Randomized Controlled Trial. The Journal of Pain, 21(3), 430–439.
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[6] Thomaidou, M. A., et al. (2021). An experimental investigation into the mediating role of pain-related fear in boosting nocebo hyperalgesia. Pain, 162(1), 287–299.
[7] Thomaidou, M. A., et al. (2020). Learning mechanisms in nocebo hyperalgesia: The role of conditioning and extinction processes. Pain, 161(7), 1597–1608.

Figure 2. Forest plots of the random-effects model comparison of the nocebo hyperalgesia (operationalized as the difference between high pain cue and low pain cue) in the 1st–5th trials, observed across the studies included in the meta-analysis

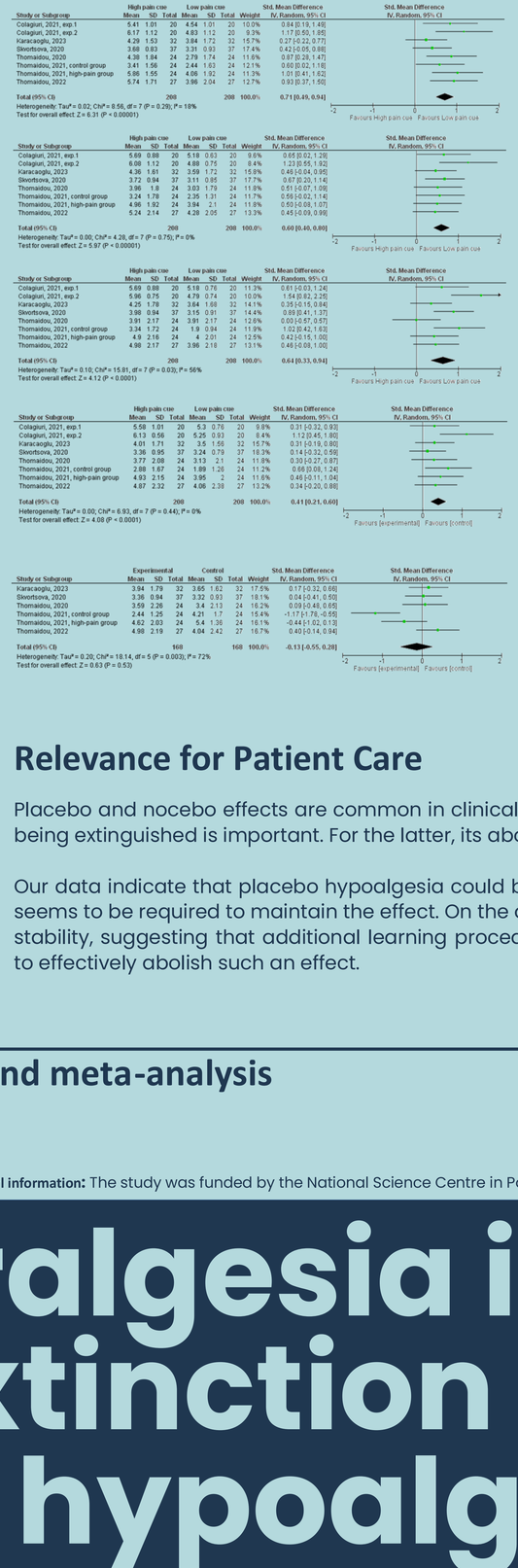
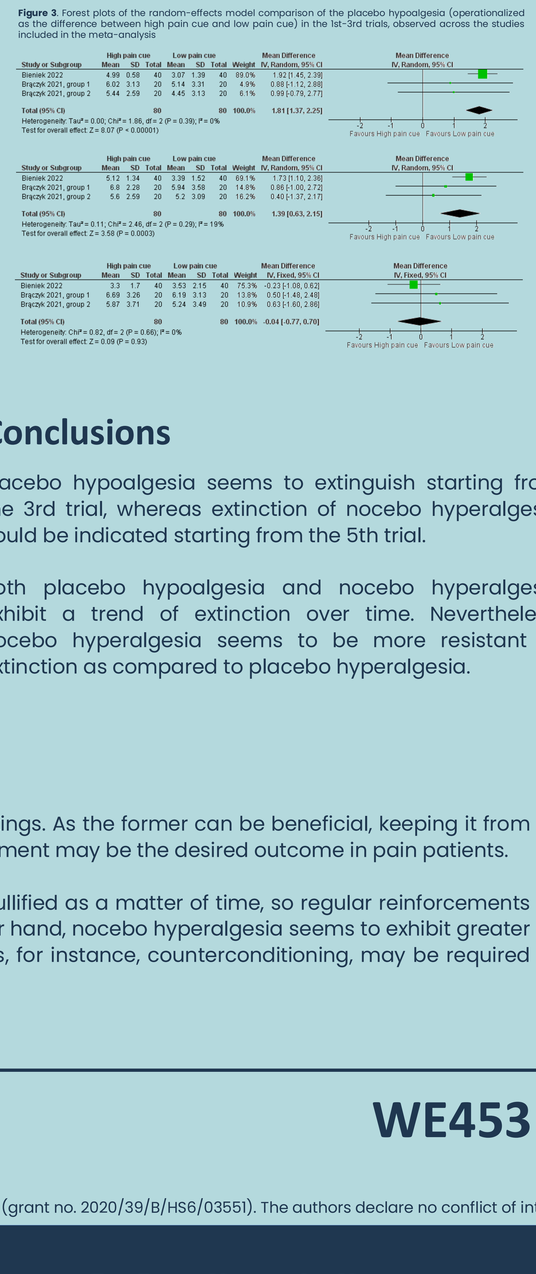


Figure 3. Forest plots of the random-effects model comparison of the placebo hypoalgesia (operationalized as the difference between high pain cue and low pain cue) in the 1st–3rd trials, observed across the studies included in the meta-analysis



Conclusions

Placebo hypoalgesia seems to extinguish starting from the 3rd trial, whereas extinction of nocebo hyperalgesia could be indicated starting from the 5th trial.

Both placebo hypoalgesia and nocebo hyperalgesia exhibit a trend of extinction over time. Nevertheless, nocebo hyperalgesia seems to be more resistant to extinction as compared to placebo hyperalgesia.

Relevance for Patient Care

Placebo and nocebo effects are common in clinical settings. As the former can be beneficial, keeping it from being extinguished is important. For the latter, its abolishment may be the desired outcome in pain patients.

Our data indicate that placebo hypoalgesia could be nullified as a matter of time, so regular reinforcements seems to be required to maintain the effect. On the other hand, nocebo hyperalgesia seems to exhibit greater stability, suggesting that additional learning procedures, for instance, counterconditioning, may be required to effectively abolish such an effect.

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Extinction of placebo hypoalgesia and nocebo hyperalgesia: a systematic review and meta-analysis

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Nocebo hyperalgesia is more resistant to extinction than placebo hypoalgesia