

Persistence of placebo analgesia and nocebo hyperalgesia: evidence from pooled data

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INTRODUCTION

- Treatment expectations shape pain:** Positive and negative expectations can produce **placebo analgesia (PA)** and **nocebo hyperalgesia (NH)**, respectively.
- Despite their **fundamental translational potential**¹, considerably less is known about **how long these effects last**.
- Previous work indicates that **PA and NH can extend beyond their initial acquisition**^{2,3}, with some findings suggesting that **NH may be more enduring than PA**⁴.
- It remains unclear whether PA and NH persist over time, whether the magnitude of their persistence differs and which factors predict their maintenance.



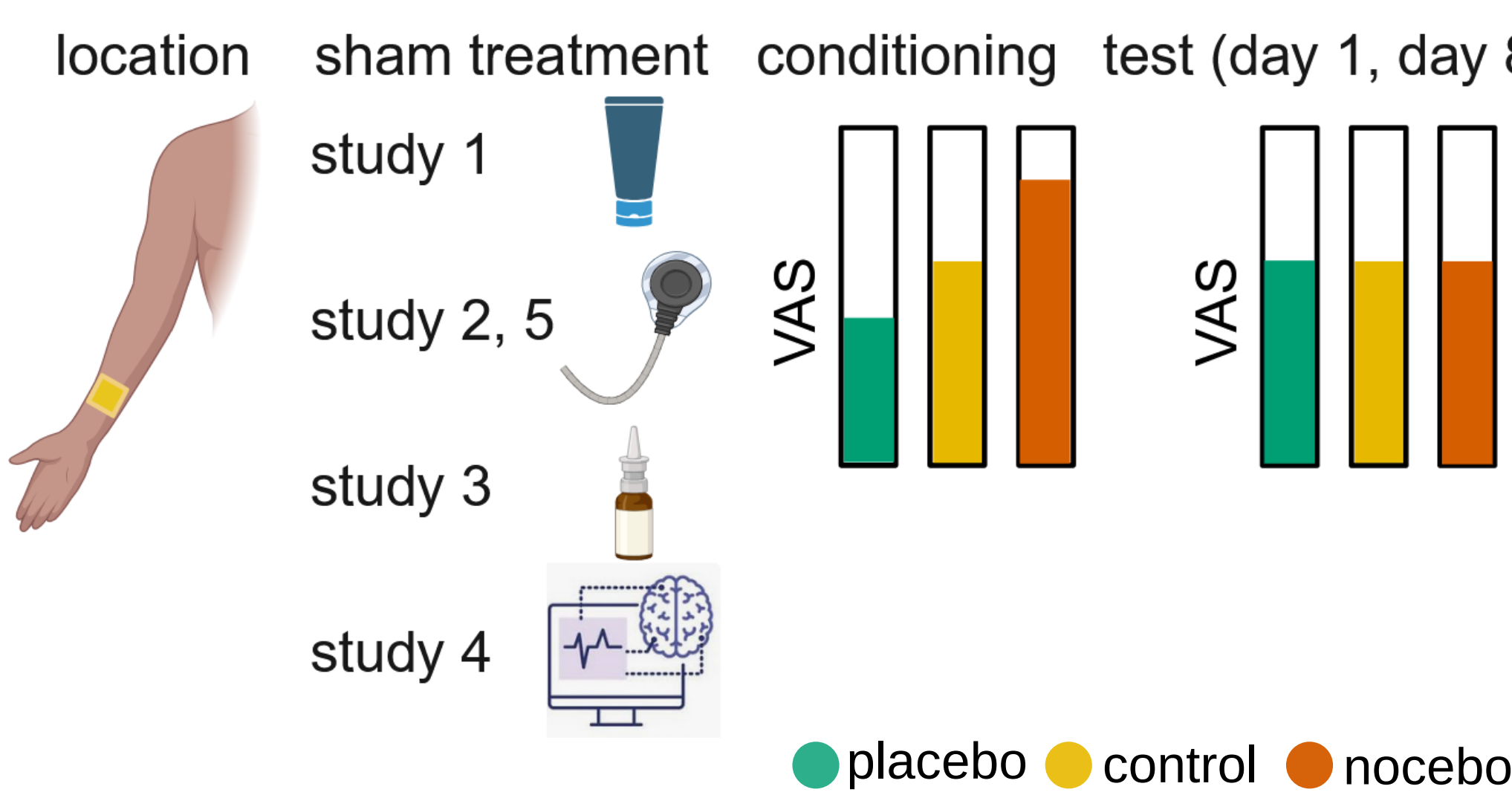
Research Questions

- Do PA and NH persist over time?
- Do PA and NH differ in their magnitude over time?
- Which factors predict their maintenance?

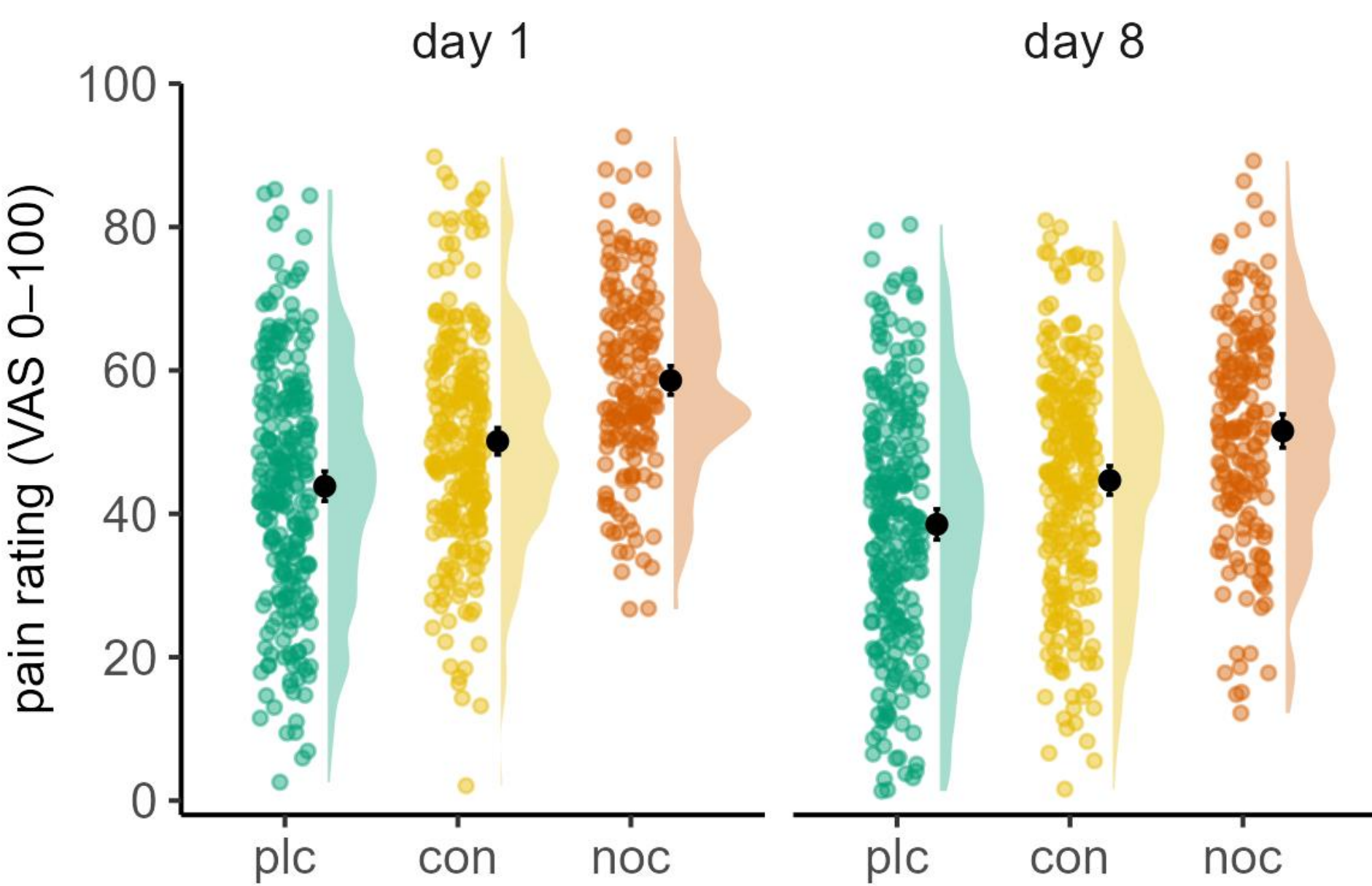
METHODS

- Pooled data from five studies**³⁻⁷ conducted between 2020–2024 within the CRC/TRR 289 “Treatment Expectation”
- Sample:** 252 participants (104 men & 146 women; mean ± SD = 28 ± 11 years old, range: 18 – 82)
- Experimental paradigms:** Variations of established models inducing PA and NH through verbal instructions and conditioning (studies 2, 4, 5), or PA only (studies 1, 3).
- Impact of expectations on pain perception** (pain ratings on a VAS from 0 = not painful at all, 100 = unbearably painful) was tested after conditioning and one week later (day 1, day 8).
- Outcomes of interest:** pain ratings and questionnaire data

Experimental paradigm common to all studies



Perceived pain over time: all studies



RESULTS

Fig 1. Persistent placebo and nocebo effects across days

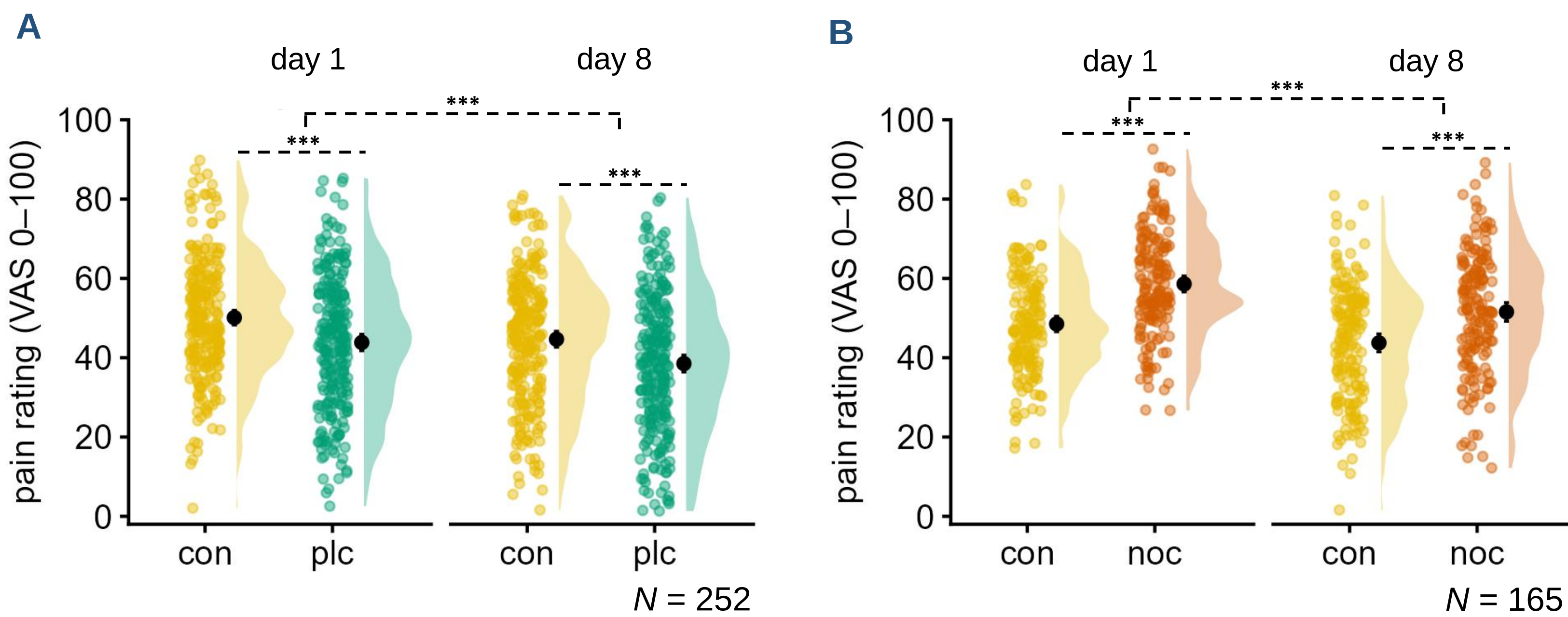
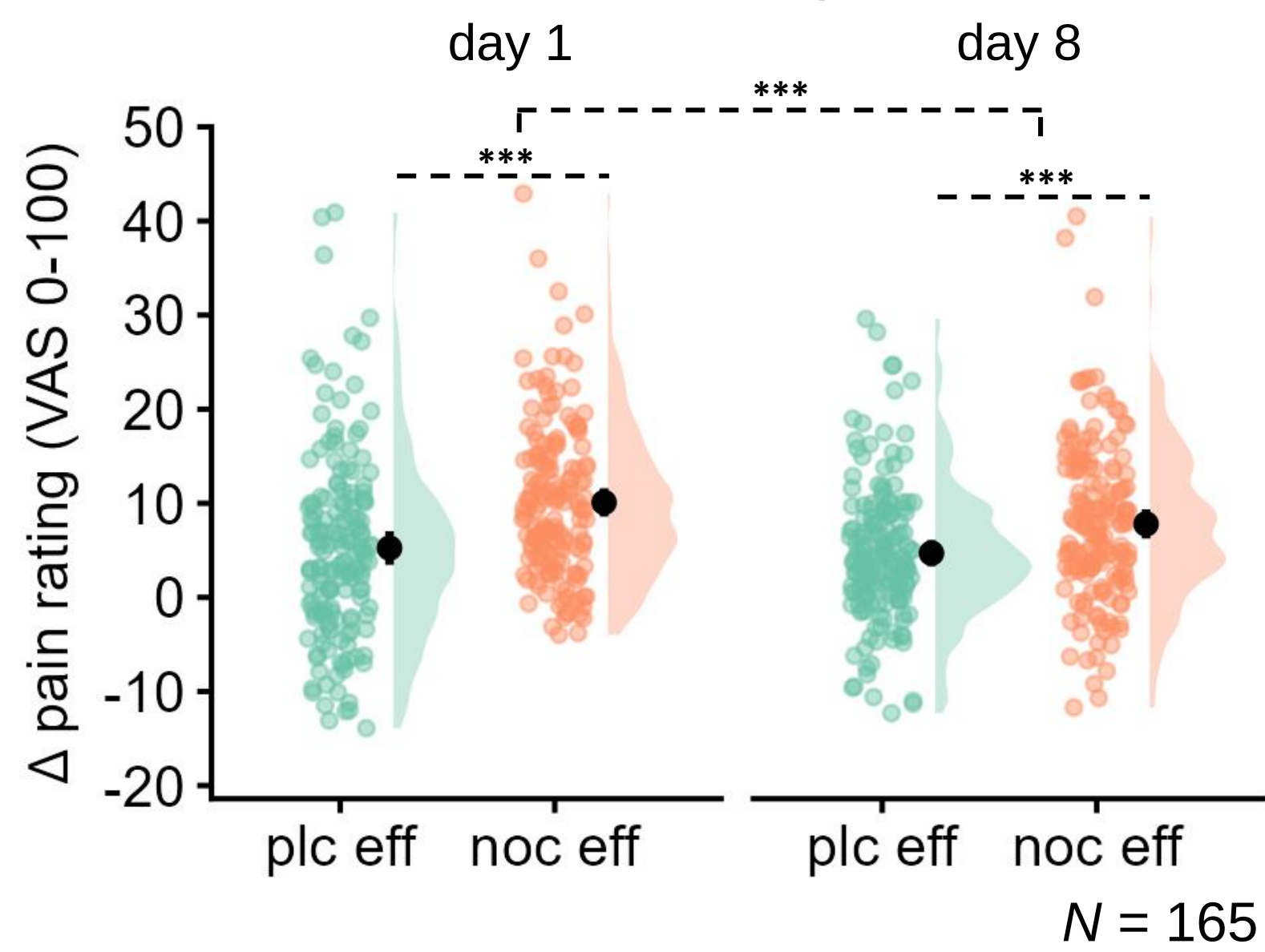


Fig 2. Stronger nocebo than placebo effects across days



Predictors of persistence^a

	PA	NH
Day 1 effect	✓	✓
Treatment expectation	✗	✗
Negative affect	✗	✗
Warmth & competence	✗	✗

^a Hierarchical multiple regression models tested whether the predictors were associated with day 8 effects. Only the initial magnitude of PA/NH predicted the corresponding effect one week later.

Fig 3. Persistent treatment expectations across days (G-EEE⁹)

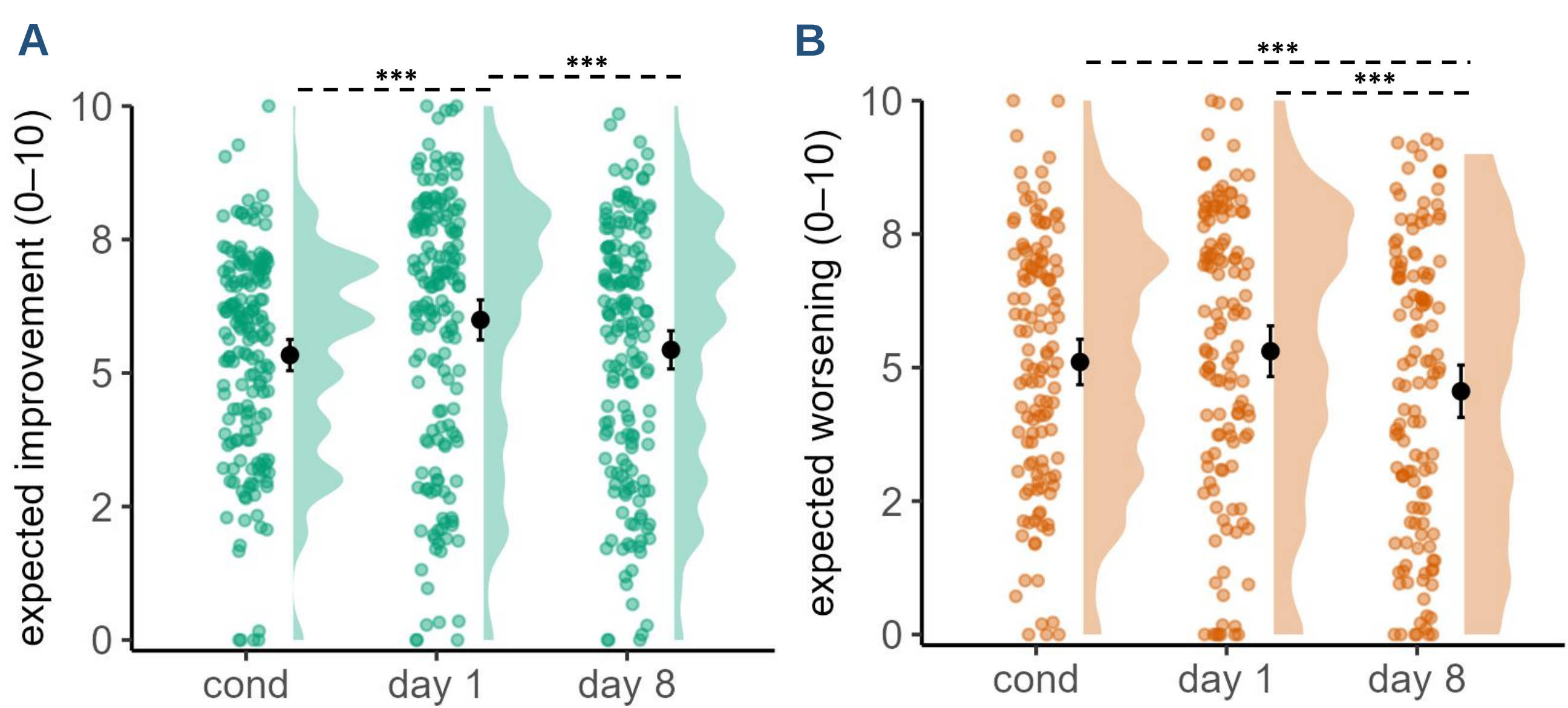
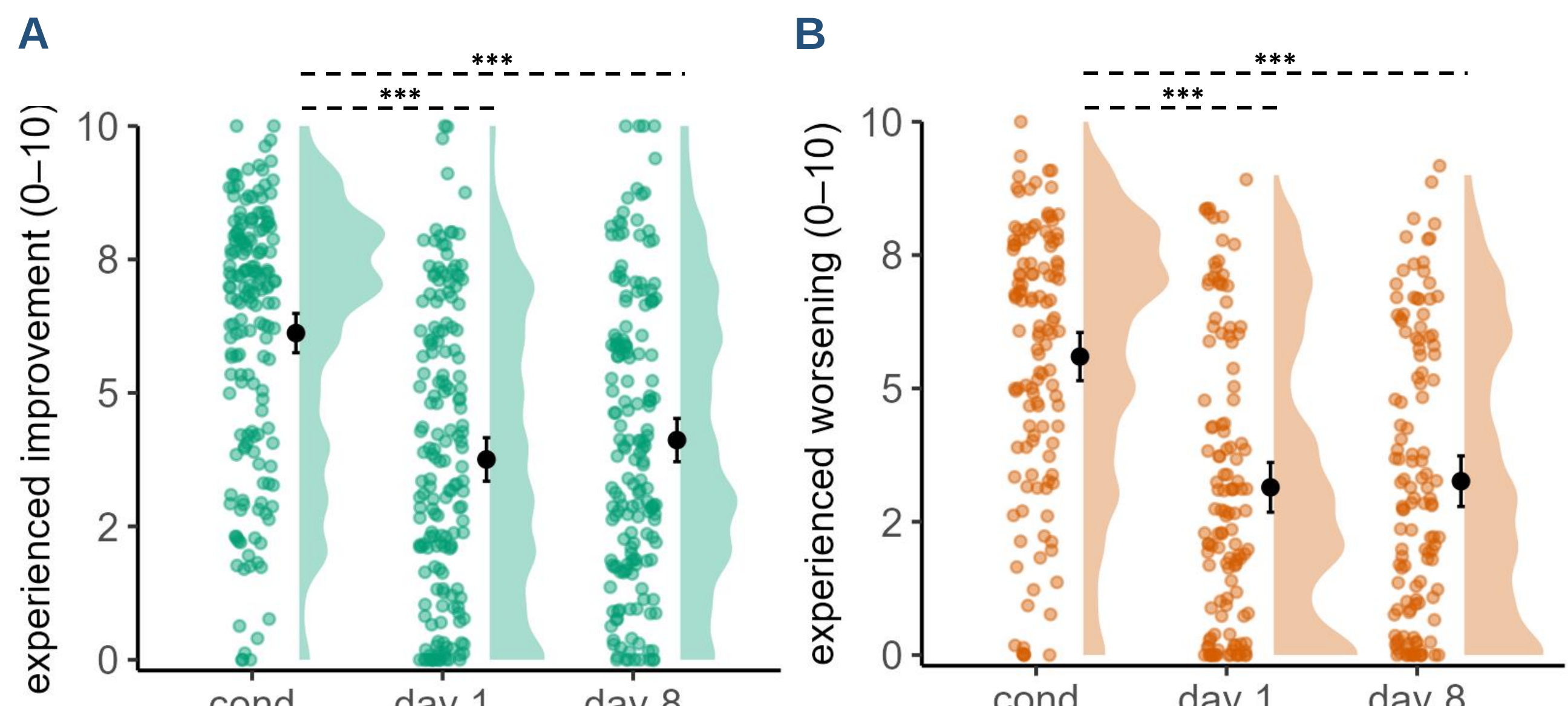


Fig 4. Persistent treatment experiences across days (G-EEE⁹)



*** p < .001

DISCUSSION

- PA and NH persisted over one week**, although their magnitude declined over time (Fig 1).
- NH was consistently stronger than PA:** NH exceeded PA in magnitude at both assessment days (Fig 2). This is in line with previous evidence showing stronger NH than PA, and with a *better-safe-than-sorry* strategy¹⁰.
- Initial effect magnitude predicted persistence of PA and NH:** Participants showing stronger PA or NH immediately after conditioning also showed stronger effects one week later. This suggests that the strength of the initial placebo and nocebo response is relevant for its subsequent maintenance.
- Treatment expectations persisted:** Expected pain improvement (Fig 3.A) and worsening (Fig 3.B) persisted over time, despite differences in their temporal course.
- Retrospective evaluations of treatment effects persisted:** Ratings of retrospectively experienced pain improvement (Fig 4.A) and worsening (Fig 4.B) declined from post-conditioning levels but remained detectable after one week.

- Bingel, 2020
- Colloca & Benedetti, 2020
- Wolf et al., 2024
- Kunkel, Schmidt et al., 2025
- Kunkel, Asan et al., 2024
- Schenk et al., 2024
- Wittkamp et al., 2024
- Schlitt-Nguyen et al., *in prep*
- Rief et al., 2021
- DeKay et al., 2009

Statistical models: e.g., pain rating – condition*time + (1 | study) + (1 | participant)
Abbreviations: G-EEE = Generic Rating Scale for Previous Treatment Experiences, Treatment Expectations, and Treatment Effects; SD = standard deviation, VAS = visual analogue scale.

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