Testing the predictive processing model of placebo hypoalgesia using multivariate hierarchical models: evidence for precision weighted effects of expectations and Bayesian updating of expectations accounting for volatility

Arthur S. Courtin (arthur.courtin@cfin.au.dk)
Center for Functionally Integrative Neuroscience (CFIN), Aarhus University, Aarhus (Denmark)
Institute of Neuroscience (IoNS), UCLouvain, Brussels (Belgium)
Jesper Fischer Ehmsen (jesperfischer@cfin.au.dk)
Center for Functionally Integrative Neuroscience (CFIN), Aarhus University, Aarhus (Denmark)
Micah G. Allen (micah@cfin.au.dk)
Center for Functionally Integrative Neuroscience (CFIN), Aarhus University, Aarhus (Denmark)
Cambridge Psychiatry, Cambridge University, Cambridge (United Kingdom)
Francesca Fardo (francesca@cfin.au.dk)
Center for Functionally Integrative Neuroscience (CFIN), Aarhus University, Aarhus (Denmark)
Danish Pain Research Center, Aarhus University, Aarhus (Denmark)

Abstract

Placebo hypoalgesia is often explained by predictive processing theories, in which perception arises from a form of (approximate) Bayesian integration of expectations (prior) and sensory evidence (likelihood). However, few studies have formally tested this model and uncertainty remains regarding its implementation in the nervous system.
Here, we use a probabilistic pain learning task and computational modelling to test a series of hypotheses about how healthy volunteers form and update expectations about the painfulness of upcoming thermal stimuli and how these expectations shape the way they perceive these stimuli. Of note, our models jointly account for all response types collected during the task, constituting a first step towards a comprehensive computational model of pain perception.
Our results support the full Bayesian predictive processing model, in which 1) the update of expectations is calibrated on different sources of uncertainty (posterior belief variance, sequence volatility), which are tracked continuously by the agent, and 2) the effect of expectations on perception is proportional to the relative uncertainty of predictions and sensory evidence (precision weighting).

Keywords: placebo, hypoalgesia, predictive coding, pain, nociception, thermosensation, learning, expectation, hierarchical models

Expectations shape pain perception. A prime example of this is placebo hypoalgesia, when the expectation of pain relief leads to a decrease of perceived pain even in the absence of exogenous analgesic molecules (Buchel et al., 2014).
This phenomenon nicely aligns with the predictive processing framework, which postulates that perceptions are the result of a form of (approximate) Bayesian inference in which the nervous system uses expectations derived from context and past experience to make sense of the noisy bottom-up sensory evidence it receives from the periphery (Walsh et al., 2020).
This predictive processing account of placebo hypoalgesia has become quite popular in the field, even though few experiments have formally tested it (Buchel et al., 2014).
With this study, we aimed to directly test this model using the data of 34 healthy volunteers who performed a probabilistic reversal learning task during which they had to learn the association between two arbitrary visual cues and the probability of receiving either a painful or a non-painful heat stimulus. Reversing the cue-stimulus association was used as a way to periodically modulate the participant's expectations.

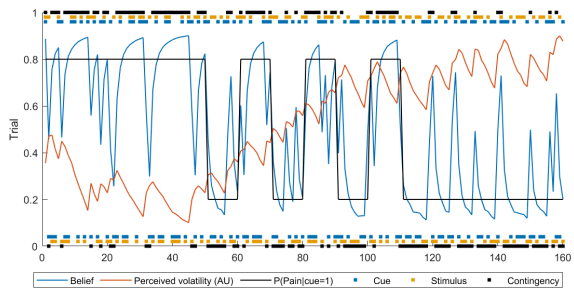

Figure 1: Task structure and belief trajectories of a sample participant

Using model comparison, we aimed to test different hypotheses about the way participants update their beliefs about the likelihood of painful events and how these expectations are integrated with sensory evidence to form the final percept.

An optimal Bayesian learner would calibrate the update of their belief on different sources of uncertainty: the inherent uncertainty of their belief (posterior variance) but also the uncertainty of their perceptions (stochasticity) and uncertainty linked to changes in the sequence (volatility) (Pulcu & Browning, 2019). Here we assess whether our participants dynamically track and calibrate their learning rate on the uncertainty of their belief and the volatility of the sequence (binary Volatile Kalman Filter;VKF), only the uncertainty of their belief (binary Kalman Filter; KF), or use a constant learning rate (Rescoral-Wagne; RW) (Piray & Daw, 2020).

Similarly, an optimal Bayesian agent would calibrate the influence of their expectations on their perception based on the relative uncertainty of these expectations and of the sensory information. In situations in which sensory evidence is ambiguous/clear, expectations would have more/less weight. Here, we test models which assume no effect of expectations (N) on stimulus recognition (classification as painful or not), constant weighting of expectations and sensory evidence (KW), and optimal precision-weighted integration (PW).

Combining the different learning and recognition models, we built a series of eight joint models (precision-weighted integration and RW learning are incompatible). Importantly, rather than modelling these processes separately, we built integrated multivariate models that jointly explain binary predictions and response times, binary postdictions and response times, and VAS intensity ratings (Figure 2). These models are built hierarchically to reflect the structure of the data: trial within participant within population.

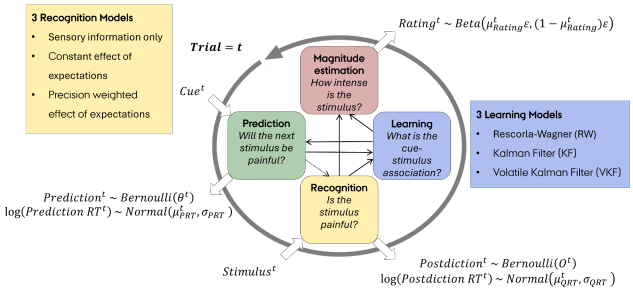

Figure 2: Architecture of the multivariate model

We wrote and estimated these models in Stan. We ensured internal validity and model discriminability through parameter and model recovery. Conventional diagnostics were used to ensure proper sampling of the models (Stan Development Team, 2019). Two of the models (VKF N & VKF KW) could not be properly sampled (divergent transitions even when using .99 adapt_delta and 2000 warm-up iterations) and were excluded from model comparison.

Using approximate leave-one-out cross-validation with moment matching, we compared the ability of the different models to explain our data (Vehtari et al., 2024). As can be seen in Table 1, the best model (highest expected log-pointwise predictive density - ELPD) included the VKF learning algorithm and precision-weighted integration of expectations and sensory evidence when forming perceptions.

Table 1. Model comparison results

Learning	Recognition	Δ ELPD	P(Δ ELPD>0)
VKF	PW	0.0	NA
KF	N	-60.0	0.025
KF	PW	-62.3	0.000
KF	KW	-64.8	0.000
RW	KW	-120.9	0.000
RW	N	-131.3	0.000

Additional hypothesis tests built into the models revealed that perceived intensity was biased towards expected pain level beyond the effect of expectations on recognition (P(θ>0)=0.003) and that

this effect appeared to be similar regardless of the type of stimulus (P(θ>0)=0.743).

These findings provide direct empirical support for a Bayesian predictive processing account of placebo hypoalgesia, showing that both the update of pain expectations and their integration with sensory evidence appear to be dynamically calibrated to uncertainty. Additionally, by jointly modelling all behavioural responses rather than fitting separate models for each, we move closer to a comprehensive computational model of pain perception. This approach avoids the pitfalls of sequential model fitting and provides a more unified account of the mechanisms shaping pain perception. It also lays the groundwork for future studies investigating how these computations may be altered in clinical populations or modulated by neuromodulatory interventions.

References

Buchel, C., Geuter, S., Sprenger, C., & Eippert, F. (2014). Placebo analgesia: A predictive coding perspective. Neuron, 81(6), 1223–1239. https://doi.org/10.1016/j.neuron.2014.02.042

Piray, P., & Daw, N. D. (2020). A simple model for learning in volatile environments. PLOS Computational Biology, 16(7), e1007963. https://doi.org/10.1371/journal.pcbi.1007963

Pulcu, E., & Browning, M. (2019). The Misestimation of Uncertainty in Affective Disorders. Trends in Cognitive Sciences, 23(10), 865–875. https://doi.org/10.1016/j.tics.2019.07.007

Stan Development Team. (2019). Stan Modeling Language Users Guide and Reference Manual 2.21.0.

Vehtari, A., Gabry, J., Magnusson, M., Yao, Y., Bürkner, P.-C., Paananen, T., & Gelman, A. (2024). loo: Efficient leave-one-out cross-validation and WAIC for Bayesian models. https://mc-stan.org/loo/

Walsh, K. S., McGovern, D. P., Clark, A., & O'Connell, R. G. (2020). Evaluating the neurophysiological evidence for predictive processing as a model of perception. Annals of the New York Academy of Sciences, 1464(1), 242–268. https://doi.org/10.1111/nyas.14321