Expectation and placebo effect in pain experience

: tracking the degree of belief and its transition

Human Brain Mapping with fMRI

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Introduction

Placebo effects have been known as one of effective treatments for pain relief in clinical settings, and a lot of studies have suggested an understanding of placebo effects in a neuroscience perspective (Benedetti et al, 2014). Bayesian and predictive coding framework provides one way to illustrate placebo effects (Büchel et al., 2014, Geuter et al., 2017). Although it is well known that a cue information which gives rise to expectation modulates pain perception (Atlas et al., 2010), accurate cues would not be enough to understand placebo in the uncertain and noisy environment of real life. Instead, dynamic probabilistic cues might help manipulate the environment to be naturalistic. The dynamic change of probability of the cues has been studied in some previous studies (Roy et al., 2014), but it was not in the context of placebo effect.

In the present study, we aim to investigate how pain perception is changed by the dynamic probabilistic cues, which elicit expectation of low or high painful thermal stimulation. Also, the interaction between dynamic cue conditions and placebo effect would be figured out. There are two hypotheses in this study. First, the difference of belief level would have some impact on placebo effects. In terms of brain activation, when the participants expect high pain, there would be more activation in the pain processing areas, such as anterior cingulate (ACC), primary somatosensory cortex(S1), secondary somatosensory cortex(S2), Insular cortex, thalamus, and prefrontal cortex (PFC), which were commonly activated for pain across diverse studies (Apkarikan et al., 2005). Anticipation and belief related brain areas-medial orbitofrontal cortex (OFC) and ventral striatum (Atlas et al., 2010)-would mediate this correlation. Second, the belief update would be divergent in the aspect of slope and latency according to the dynamic probabilistic pain, and this would be represented in Periaqueductal Grey (PAG). PAG is known to be important for pain related learning, and generates predictive error signals (Roy et al., 2014).

Methods

Participants

A total of two participants were recruited at the Center for Neuroscience Imaging Research in

Sungkyunkwan university, and a male and a female were recruited. Both of them were right-handed and were not sensitive to heat pain.

Procedures

The participants were instructed to do a 'Belief tracking task', in which there were two different cues indicating high or low pain, and the cue's accuracy could be changed over a period of time. The participants rated the belief on the cue before the stimuli was presented and rated perceived pain after the stimuli was given. Additionally, along with high and low pain, to measure the placebo effect, there were hidden moderate pain intermittently, and the moderate thermal intensity was never informed to the participants. Thus, the participants would think they were only on a task about belief and perceived pain. The figure below is the structure of a single trial that participants experienced. The intensity of pain for high, low, and medium(hidden) were calibrated per person before the fMRI experiment (see *Thermal calibration*).

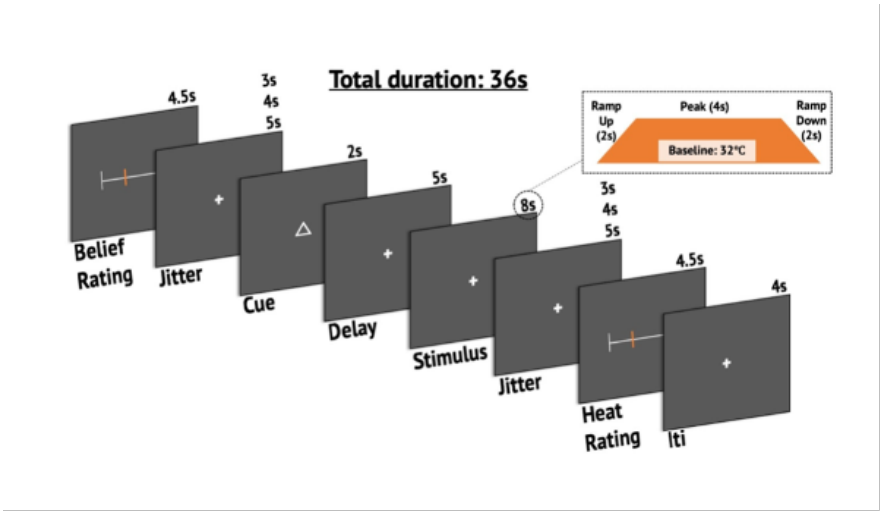

Figure 1

The probability of match and mismatch between cue and actual pain intensity varied in three conditions: high confidence, medium confidence, and low confidence. In the high confidence condition, the pain of a trial was matched to the cue in the probability of 90%, 50% match was given to the medium condition, and 10% for low confidence condition. Whether the cue and pain intensity were matched in the probability of each confidence condition was determined by generating a random number in Matlab. Each trial had independent probability of matching. The low confidence condition means the cue is

more likely to represent the opposite pain stimuli (high cue-low pain, low cue-high pain). This exact relationship was not informed to the participants.

A run was composed of two confidence condition blocks: every possible combination was presented. There were eight runs, and a confidence condition was maintained for 10 trials: eight low or high pain trials + two hidden trials with moderate pain. Thus, 160 trials in total were given, including 32 placebo trials.

Measurements

1) Thermal stimulation and pain ratings

Thermal stimulation was delivered using 16 x 16mm ATS thermode Pathway (Medoc) to the left inner forearm. As there were eight runs, the thermode was located at eight different sites per run. The baseline temperature was 32°C, ramped up to the target temperature for 2 seconds, maintained for 4 seconds, and ramped down to the baselines for 2 seconds. Therefore, the thermal heat was delivered for eight seconds. To rate the subjective pain in MRI, the participants used VAS (visual analogue scale), which is a linear and continuous scale of pain, while gLMS (general labeled magnitude scale), a nonlinear scale, was used for calibration (Bartoshuk et al., 2004). In both ratings, a trackball mouse was used.

VAS gLMS

Figure 2

2) Belief rating

For rating the belief level, a continuous bar was given with a phrase of “how much do you believe the meaning of cues below” and an illustration of two cues: high pain and low pain.

Thermal calibration

Three pain types are necessary in this experiment: low pain, high pain, and medium pain. As the perceived pain has variation across people, the temperature of each pain type was decided per person by using pain calibration procedure. A total of 18 pain was given to find the three temperatures that the participants stably rated as weak, moderate, and strong in gLMS. Each target intensity indicates 6, 17, and 34.7 in the range of 0-100. Each pain was delivered with 1.5 seconds ramp up, 5 seconds peak, and 1.5 seconds ramp down. After the procedure, it is possible to find a regression line per participant, and the three temperatures matched to the score of 17(moderate), 34.7(strong), 43.6(middle of strong and very strong) in gLMS are selected.

fMRI acquisition and preprocessing

The fMRI data were collected using 3T Siemens Prisma scanner at the Center for Neuroscience Imaging Research, Institute for Basic Science, Sungkyunkwan University. Structural T1-weighted images were obtained using magnetization-prepared rapid gradient echo sequence (0.7 × 0.7 × 0.7 mm3 voxel size, repetition time (TR): 2,400 ms, echo time (TE): 2.34 ms, slice thickness: 0.70 mm, flip angle: 8°, field of view (FoV): 224 × 224 mm2, inversion time (TI): 1,150 ms). Functional data were acquired using gradient echo-planar imaging (EPI) sequence (2.7 × 2.7 ×2.7 mm3 voxel size, repetition time (TR): 460 ms, echo time (TE): 27.20 ms, flip angle: 44° slice thickness: 2.7 mm, field of view (FoV): 220 × 220 mm2, slice orientation: 15 degree off of AC-PC axis, order of slice accession: interleaved)

Structural and functional MRI data were preprocessed using Cocoan Lab preprocessing pipeline (https://github.com/cocoanlab/humanfmri_preproc_bids), which is based on SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12) and FMRIB Software Library (FSL) (https://fsl.fmrib.ox.ac.uk). Structural T1-weighted images were co-registered to the functional image for each subject and then normalized to the Montreal Neurological Institute (MNI) space. For functional EPI images preprocessing pipeline included the following steps: motion correction (realignment), distortion correction using FSL's top-up, co-registration, spatial normalization to MNI space using structural T1-weighted images with the interpolation to 2x2x2 voxels, spatial smoothing with a Gaussian kernel (5 mm Full-Width Half-Maximum).

Analysis

The Independent variables were the confidence condition, which were implicitly given to participants, pain cue, which was explicit, and thermal heat pain, which was implicitly delivered. The dependent variables were pain rating, belief rating, and brain activation.

One of the two participants was excluded in the further analysis. The participant not only misunderstood the instruction of the experiment, but also rated the belief level in an inconsistent manner that it did not properly reflect his mind. In addition, the first run of the included participant was excluded as it has big variability in the belief rating and pain rating. The variability of the first run would be due to the unfamiliarity to the task, the absence of anchors to refer to, or the delivery of inexperienced thermal pain.

1) Behavioral analysis

The continuous belief rating was reprocessed into a discrete scale, and the categorization was based on the histogram of all the belief ratings. As a result, the score from 0 to 0.3 was the low belief condition, from 0.3 to 0.7 was the middle belief condition, and from 0.7 to 1 was the high belief condition.

2) fMRI analysis

General Linear model analyses

We modeled the fMRI data using the single-trial design and analysis approach. The single-trial response magnitude for each voxel was estimated using a general linear model design matrix with separate regressors for each trial.

First, because our main focus was brain representations during pain experience, we created separate event regressors per each pain stimulus (20 trials x 8 runs = 160 event regressors) and the other events such as belief rating, cue, and pain rating were included as one regressor per each one in the design matrix. Next, boxcar regressors, convolved with the canonical hemodynamic response function (HRF), were constructed to model belief rating, cue, pain stimulus, and pain rating periods. Then, a regressor for each trial and nuisance covariates, for example, head motion parameters x, y, z, roll, pitch and yaw, were included.

In order to investigate whether the neural correlates of pain perception during the medium heat stimulus between a pair of belief levels, all possible pairwise contrasts (e.g., in high cue, high belief > low belief) were estimated.

Mediation analyses

Mediation analyses extend the univariate model in that it could examine the relationship between experimental manipulations and brain activity or between brain activity and behavior by incorporating an additional outcome. We presented three different conditions and heat stimulus, and then measured belief rating and heat rating. Using these variables, we constructed the structure of mediation analysis. The initial variable (X) in the path model was the experimentally manipulated belief based on belief rating (which opposite belief, low belief, and high belief) or the three levels of heat stimulus, and the outcome variable (Y) is the response variable of heat stimulus (i.e., pain rating). The total effect of X on Y reflects the observed behavioral effects of belief or heat level on reported pain and is usually referred to as path c. The path c is mediated by the brain response, M and the controlling path is referred to as path c'. M is the estimated brain activity measured over a large number of different voxels in a single region. We assume that the values of M are either parameters or contrasts (linear combinations of parameters) obtained by fitting the single-trial analysis (i.e., GLM). The brain region candidates were selected from Wager-combined atlas-2018 (github.com/canlab/Neuroimaging_Pattern_Masks/tree/master/Atlases_and_parcellations/2018_Wager_combined_atlas).

Results

Calibration

For subject 1, 42.4°C, 46.2°C, 28.2°C were chosen for low pain, medium pain, and high pain, and 44.8°C, 46.2°C, 47°C were chosen for subject 2. As there was a big variability of the temperature and the range, the calibration procedure is thought to be helpful for the experiment.

Behavior data

1) placebo

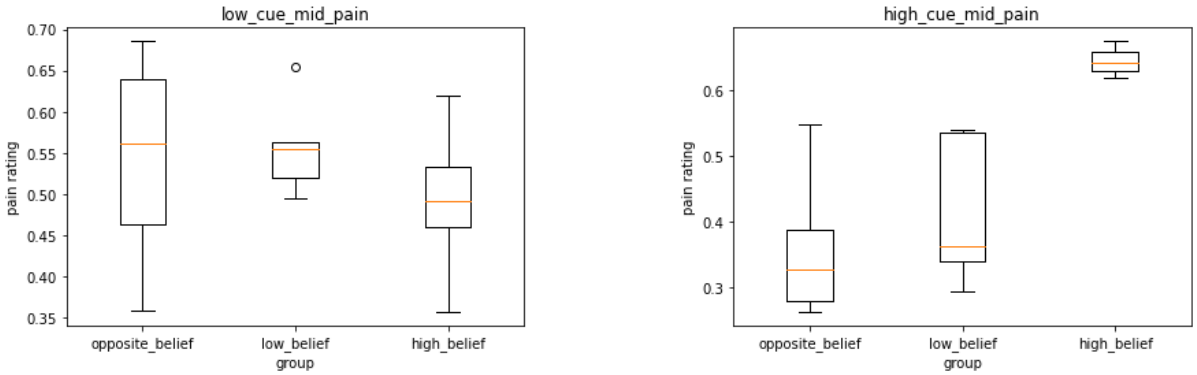

Figure 3

An ANOVA test was performed to see if a placebo with a different pain rating depending on the belief rating under the same cue and pain conditions was presented. More significant placebo effect was observed after high cue was presented (F = 8.4, p = 0.00607) than low cue condition (F = 0.6, p = 0.59119).

2) belief update

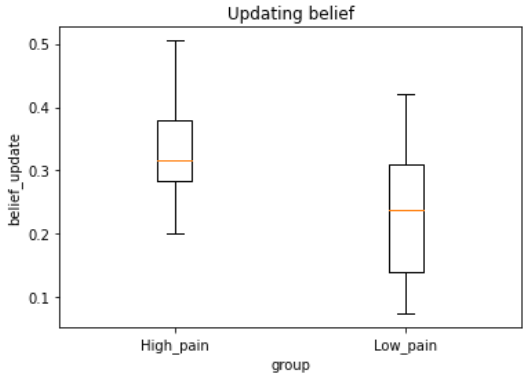

Figure 4

When pain that does not match one's own belief was presented, it was observed that the amount of update relatively increased when the pain was high (t = -1.7701, p = 0.0970).

3) belief tracking model

We modeled belief rating through applying four parameters frequently used in reinforcement learning. Memory size indicates how many recent trials the subject considers for the next belief update, and discount rate is decreasing influence of trial through time difference. Learning rate is the average sensitivity to which the belief rate varies for trial results. Lastly, ratio is the ratio of the sensitivity slope

when the belief rating rises and falls. The higher the ratio, the slower the belief rises and the easier it falls.

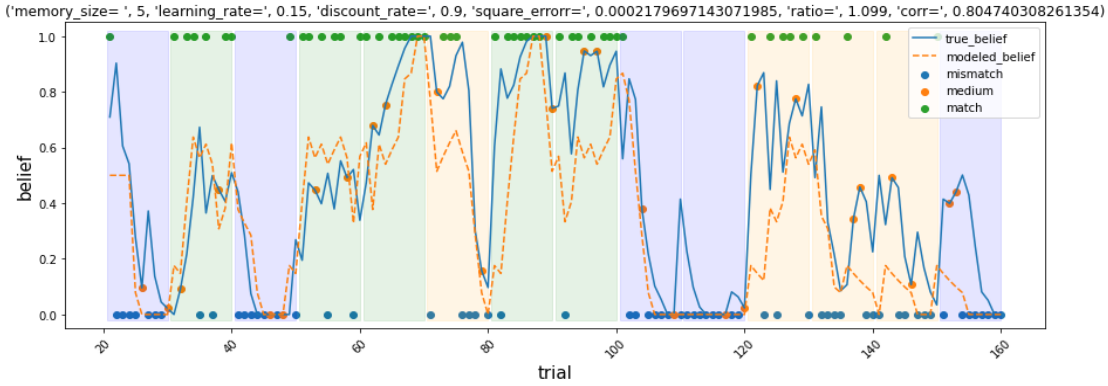

Figure 5

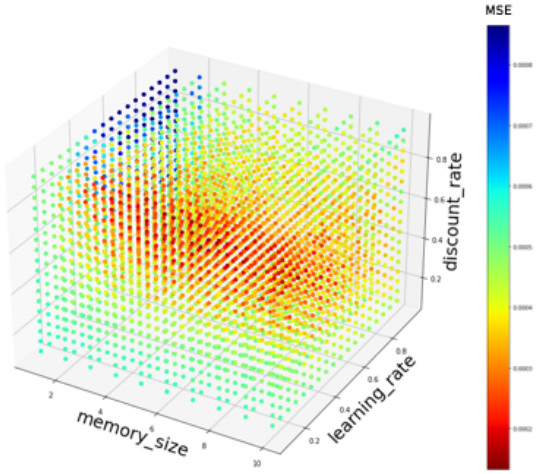

Figure 6

As a result of the greedy search algorithm, the MSE changes in a gradient depending on the value of each parameter, and a pattern converging to one global optimum point was observed.

fMRI data

1) Pain

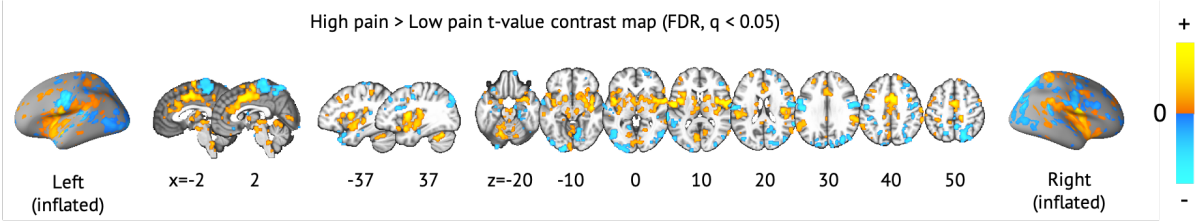

Figure 7

Using a standard GLM analysis, we found differential activity related to the heat levels in several brain regions. This contrast map of high pain and low pain shows pain related brain areas that we found. T-test was conducted with False discovery rate (FDR) correction ($q<0.05$) for multiple comparison. Pain related areas of ACC, S2, Insula, thalamus, and amygdala were activated, which was consistent with previous studies, but there was some deactivation of S1, which was inconsistent.

To test the hypothesis that these regions actually mediated the direct effect on heat stimulus levels on pain ratings, we used a multi-level mediation approach in one of multiple candidate anatomical regions.

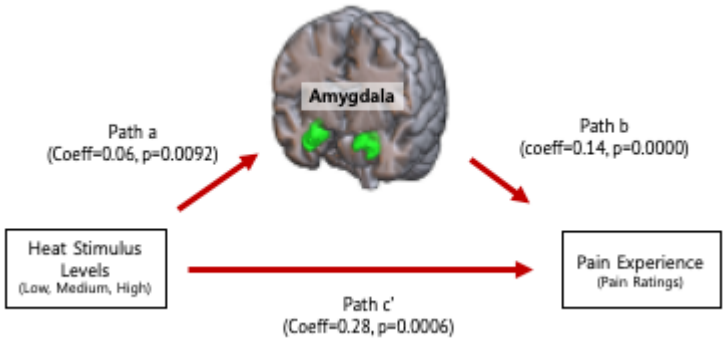

Figure 8

Our mediation analysis shows that amygdala showed a significant positive mediator (Path a x b) of relationship between heat stimulus levels and pain experience. We conducted this analysis on other candidate regions such as thalamus, S1, and nucleus accumbens and other variable X for belief levels. However, we did not obtain any significant correlation coefficient in the other relationships.

2) Placebo

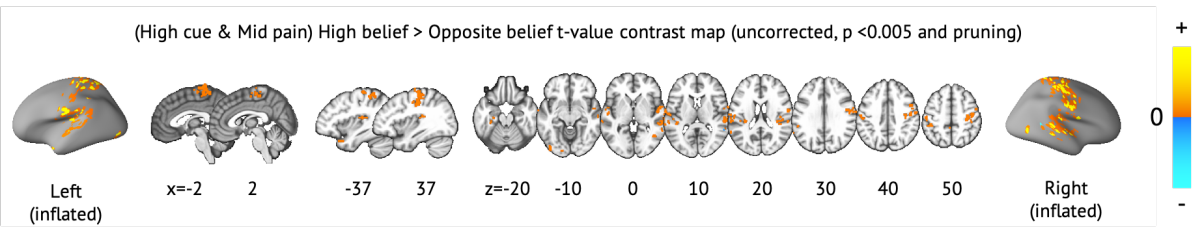

Figure 9

This contrast map indicates the placebo related regions, which are more activated when the high pain is expected. The uncorrected($p<0.005$) t-test was conducted with the process of pruning. Significantly activated brain areas involved posterior insula, parietal operculum, S1, and S2. The activation of posterior insula and parietal operculum is consistent with the result of meta-analysis (Fu et al., 2021). The more activation of S2 in high pain expected condition is also consistent with the previous research (Atlas & Wager, 2014). S1 is not a generally reported area related to placebo effect, but it is one of the most common pain areas (Apkarikan et al., 2005). Thus, the activation of S1 might reflect the sensory difference of pain induced by the placebo effect.

Discussion

Our study investigated the difference of perceived pain evoked by thermal stimulus in both certain and uncertain condition that what type of stimulus will be delivered was expected by using behavioral data and fMRI data of a participant. Using belief ratings, cues, thermal pain stimuli, and pain ratings, we manipulated a various of experimental conditions in order to impose many different environments.

Behavioral data

The most interesting finding in behavioral data was the ANOVA test on the groups of belief level within high cue and medium pain intensity condition (**Fig. 3**). The same stimulus intensity caused different perception of pain depending on the levels of belief. This might be the evidence that certainly or uncertainly expecting upcoming painful stimulus regulates pain perception. Also, another important finding was that the belief tracking model built by some parameters in reinforcement learning showed impressive performance (**Fig. 5**). It seems possible that this result is due to the similarity between stimulus-reward learning and belief learning in penalty. A note of caution is due here since the model might be overfitted given that there was no test set.

fMRI data

The most obvious finding to emerge from the analysis of fMRI data is the neural correlates of pain perception in the contrast map of high pain and low pain (**Fig. 7**). The regions related to pain were

activated such as ACC, S2, insula, thalamus, and amygdala. This result confirms the findings of previous studies. An unanticipated finding was that only amygdala showed significant correlation as a mediator of the effect of thermal pain levels on pain ratings (**Fig. 8**). The other regions showed no significance.

Limitations

Throughout the experiment and analyses, we've found several limitations and potential room for improvement for further study. First of all, we missed the data of one participant out of two because he misunderstood our experiment design in an unexpected way. That's why the amount of data was really insufficient for analysis. The no significant results might result from small sample size. Second, we subdivided the conditions in terms of belief levels, cues, intensities, and prediction error (e.g., match between cue and intensity). The trials were categorized in each condition and some condition contained only three trials for analysis. Additionally, we used probabilistic cue to impose uncertainty. However, this caused unequal sample size in conditions and gave difficulty to test t-test and ANOVA test. Third, the experimental task requires cognitive load during the period when the participant rated belief for the relationship between cues and intensities. For example, after a participant reports low belief and low cue is given, he or she will expect that the upcoming intensity would be high, and it requires reverse inference compared to high belief and high cue. This cognitive load might be more bias in pain perception than expected. We should have designed more straightforward cue-intensity table and collected belief rating data based on it. Lastly, the mediation analysis in the current study is basic level. We did not search significant voxels in whole-brain analysis because of time limitation.

Future directions

In the further study, participants at least more than one should be recruited and complete the experiment to maximize statistical power in both behavioral and fMRI analysis. Also, instead of probabilistic cue generated by a random number, it would be promising approach to use the belief tracking model. For example, before the scan, participants conduct the same task for a run out of the scanner, then the belief tracking model is built based on the data. In the scanner, cue is given to participants considering the ratio between match and unmatch trials from the pre-trained belief tracking

model. The balance between number of trials in each condition is important and the researcher could predict the result of ratio before all experiments are finished.

Contributions

Dong Hee, Hyemin and Jaeyoung designed the study. Dong Hee, Hyemin and Jaeyoung performed the study. Dong Hee analyzed the brain data. Jaeyoung analyzed the behavioral data. Dong Hee, Hyemin and Jaeyoung wrote the paper.

References

Apkarian, A. V., Bushnell, M. C., Treede, R. D., & Zubieta, J. K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. European journal of pain, 9(4), 463-484.

Atlas, L. Y., Bolger, N., Lindquist, M. A., & Wager, T. D. (2010). Brain mediators of predictive cue effects on perceived pain. Journal of Neuroscience, 30(39), 12964-12977.

Atlas, L. Y., & Wager, T. D. (2014). A meta-analysis of brain mechanisms of placebo analgesia: consistent findings and unanswered questions. In Placebo (pp. 37-69). Springer, Berlin, Heidelberg.

Bartoshuk, L. M., Duffy, V. B., Green, B. G., Hoffman, H. J., Ko, C. W., Lucchina, L. A., ... & Weiffenbach, J. M. (2004). Valid across-group comparisons with labeled scales: the gLMS versus magnitude matching. *Physiology & behavior*, *82*(1), 109-114.

Benedetti, F. (2014). Placebo Effects: From the Neurobiological Paradigm to Translational Implications. Neuron, 84(3), 623–637.

Büchel, C., Geuter, S., Sprenger, C., & Eippert, F. (2014). Placebo analgesia: a predictive coding perspective. Neuron, 81(6), 1223-1239.

Fu, J., Wu, S., Liu, C., Camilleri, J. A., Eickhoff, S. B., & Yu, R. (2021). Distinct neural networks subserve placebo analgesia and nocebo hyperalgesia. NeuroImage, 231, 117833.

Geuter, S., Boll, S., Eippert, F., & Büchel, C. (2017). Functional dissociation of stimulus intensity encoding and predictive coding of pain in the insula. Elife, 6, e24770.

Roy, M., Shohamy, D., Daw, N., Jepma, M., Wimmer, G. E., & Wager, T. D. (2014). Representation of aversive prediction errors in the human periaqueductal gray. Nature neuroscience, 17(11), 1607-1612.