Generalization of placebo pain relief

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Abstract:

Placebo pain relief refers to perceived pain relief due to cognitive modulation induced by mechanisms such as expectation and experience. Here, we formally study the transfer of previous treatment experiences to novel situations, investigating how similarity between original and novel situation can explain carry-over effects. Using a placebo pain paradigm in healthy human volunteers during functional MRI, we treated heat pain on capsaicin pretreated skin by cooling. We conditioned participants to expect better treatment from one face cue, CS+, by associating it with more cooling, i.e. pain relief, than treatment from another face cue (CS-). We tested participants on a total of eight perceptually highly similar faces from a circular similarity continuum from CS+ to CS-. Pain relief ratings in the test phase showed a significant placebo effect as well as decaying placebo effects with increasing dissimilarity to the CS+, i.e. generalization of placebo relief. Modelling these profiles by a Gaussian curve explained data better than a flat null-model. On the neuronal level, we observed Gaussian generalization gradients in the rostral anterior cingulate cortex and the right hippocampus. Our results indicate that experienced treatment success generalizes to novel situations as a function of its perceptual similarity to previous experience.

Keywords: placebo; pain relief; generalization, hypoalgesia

Pain relief can be subject to placebo effects as part of the treatment outcome, when perceived pain relief is modulated by mechanisms such as expectation and experience. In the present work, we explored how previous experiences are transferred to future situations, studying how similarity between original and novel situations can explain carry-over effects from one situation to another. Having experienced a substantial pain relief in one treatment context in the past, humans might expect similar outcomes in novel contexts - if the features of a novel treatment resemble the ones experienced before. We created differential treatment experiences using an experimental placebo paradigm in N = 35 healthy humans during functional MRI. We treated heat induced tonic pain on capsaicin pretreated skin by subtly lowering the applied temperature. We used 8 different face cues to announce the treatment, that were taken from a circular, well-controlled similarity gradient (Onat & Büchel, 2015). After a short baseline phase, in which all faces were paired with the same relief, we had participants experience better treatment from one human face cue (CS+) by associating it with a stronger temperature decrease, i.e. pain relief, than another human face cue (CS-), followed by a more subtle decrease. Following this conditioning procedure, participants were tested on a circular continuum of eight face cues ranging from CS+ to CS, all paired with the subtle treatment.

Results

Pain relief ratings in the test phase showed a significant placebo effect given by stronger relief ratings for the CS+ vs. CS-. Importantly, this was accompanied by placebo relief to similar but not identical faces. Here we observed that placebo was decaying as a function of increasing dissimilarity to the CS+, forming a Gaussian shaped profile of the induced placebo relief. On the neurobiological level, we tested regions of interest (ROIs) for Gaussian tunings after the conditioning procedure. The ROIs were based on previous research on placebo analgesia and pain, as well as generalization of aversive and appetitive learning and comprised the rostral anterior cingulate cortex (rACC), bilateral hippocampus as well as the bilateral amygdala (Bingel, Lorenz, Schoell, Weiller, & Büchel, 2006; Dunsmoor, Prince, Murty, Kragel, & LaBar, 2011; Geuter, Eippert, Hindi Attar, & Büchel, 2013; Kahnt & Tobler, 2015; Wimmer, Daw, & Shohamy, 2012). For the ACC as well as the right hippocampus (rHC) we found profiles of estimated evoked activity in the expected bell-shape, for which a Gaussian model explained the data better than a flat null-model (p_{corr} <.05, log-likelihood ratio test) and which was not present before conditioning.

While the hippocampus replicates findings on generalization both in the aversive as well as appetitive learning domain, the ACC is a key region in pain modulation and more specifically in placebo analgesia. We found that the connectivity, i.e. correlation of

individual time courses of ACC and rHC increased from before to after learning. This suggests a functional interplay of these regions, in which they work together in retrieving, modulating and updating experiences of pain relief.

Concluding, we find that learned analgesic associations are transferred to novel situations to the degree they resemble previous experiences, thus following the generic learning principle of generalization. Moreover, generalization profiles on the neuronal level allow further insight on the underlying mechanisms of how experience and related expectancies modulate novel pain experiences.

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