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Letter to the Editor

## Response to the commentary "Multiple potential mechanisms for context effects on pain"

*To the Editor:*

We are grateful for the discussion and positive commentary by Jepma and Wager regarding our article [1], and agree that this area is ripe for investigation and discussion. We would, however, like to clarify one or two potential misunderstandings.

Jepma and Wager state that our findings are discrepant from the prior literature on expectation, and therefore seek alternative mechanistic explanations for our findings. However, as we discuss in the article, our study design differs significantly from these previous paradigms, and although related, asks a fundamentally different question predicting a different outcome. The literature Jepma and Wager cite on placebo and expectation involves a level of deception: participants are told to expect an intense stimulus, when the actual delivered stimulus is only moderate. This stimulus is subsequently perceived as more intense compared to a setting without the "intense" expectation. Our paradigm is designed to answer a very different question and does not involve any deception. Crucially, there was a context induced by setting an expectation: "there could be intense pain" followed either by fulfillment of this expectation (ie, intense pain), or in 50% of cases, a fully predictive cue that unequivocally signaled the correct outcome (ie, moderate pain). We explicitly predict and discuss in our paper that an alternative paradigm such as that of Atlas et al. [2] (to which Jepma and Wager refer) would not lead to relative relief effects. Therefore, we firmly hold that the results are not at odds, and hence the search for alternative explanations is perhaps unwarranted, although discussion is always a good thing.

That said, in seeking alternative explanations to the one we believe best fits the paradigm and data, Jepma and Wager propose peripheral habituation effects as a possible alternative explanation. We are cognizant of the problems related to peripheral habituation and sensitization effects, always controlling for them in our studies by psychophysical validation prior to functional imaging. This study was no exception, which is why two thermodes were used, placed 5 to 10 cm apart on the volar aspect of the forearm, and each thermode only delivering one of the destination temperatures (ie, one site only received moderate stimuli, whereas the other site received all intense stimuli in one session and all nonpainful warm stimuli in the other session). Therefore, their concern that the intensely painful stimulation followed by a moderate one at the same site may have led to habituation in the relative relief session is unfounded. The experiment was designed to avoid that very confound. We apologize if this was not clear from the methods by our terse description (relevant text from Methods: "We used two in-house thermal resistors [8], [12] and [66] to deliver noxious thermal stimuli (4 seconds at destination temperature) to the volar aspect of the participants' left arm").

As Jepma and Wager correctly point out, the correlational nature of all functional imaging studies limits the ability to infer causality and leaves open the possibility of alternative interpretations. However, although stress can reduce pain, we know of no examples where it has been shown to hedonically flip pain into pleasure. Therefore, having clarified some misunderstandings, we maintain that the relative relief and valuation mechanisms, as discussed in our article, provide the most compelling explanation for how pain can be rendered pleasant.

### References

[1] Leknes S, Berna C, Lee MC, Snyder G, Biele G, Tracey I. The importance of context: When relative relief renders pain pleasant. Pain 2013;154:402–10.

[2] Atlas LY, Bolger N, Lindquist MA, Wager TD. Brain mediators of predictive cue effects on perceived pain. J Neurosci 2010;30:12964–77.

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