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LETTER

Individual Differences in Placebo Analgesia: Functional Connectivity and Neural Mechanisms [Letter]

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Dear editor

We recently read with great interest the article by Nicholas J. Bush et al,[1] titled "Individual Differences in Placebo Analgesic Responses and Functional Connectivity During Painful Stimulation", which investigates the differential effects of placebo analgesia in healthy adults. This study provides valuable insights into how expectancy manipulations can modulate pain responses and highlights significant behavioral and neural differences between placebo responders and non-responders. The authors' use of functional magnetic resonance imaging (fMRI) and generalized psychophysiological interaction (gPPI) analysis to explore the neural mechanisms behind placebo responses is particularly noteworthy. However, we would like to suggest a few areas for further consideration.

First, while the study uses expectancy-enhancing instructions to induce placebo effects, the authors could explore additional placebo induction strategies, such as conditioning or social cues, to understand whether these different approaches may result in varying neural and behavioral responses. This could provide a more comprehensive understanding of the diverse mechanisms that underlie placebo analgesia.

Second, the study relies on heat stimuli as the sole method for inducing pain. While heat is a commonly used modality, it may not fully capture the complexity of pain experiences that individuals encounter in real-world settings, such as mechanical or chemical pain. Investigating placebo responses across multiple pain modalities would improve the generalizability of the findings and offer a more nuanced understanding of placebo analgesia.

Lastly, the study provides compelling evidence of differential functional connectivity between placebo responders and non-responders. However, the observational nature of the analysis makes it difficult to establish a causal link between changes in brain activity and pain reduction. Future research could benefit from experimental manipulation of brain activity (eg, through neuromodulation techniques) to more definitively explore the causal relationship between functional connectivity and placebo-induced analgesia.

In conclusion, this study makes an important contribution to the understanding of placebo analgesia and the role of brain connectivity in pain modulation. Addressing the suggestions mentioned would further strengthen the study's impact and clinical applicability.

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Reference

1. Bush NJ, Cushnie AK, Boissoneault J. et al. The Two Sides of Placebo Analgesia: differential Functional Connectivity Reveals Mechanisms of Placebo Analgesic Response. *J Pain Res*. 2025;18:189–201. doi:10.2147/JPR.S483157

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