Letters

COMMENT & RESPONSE

To the Editor Linnman and Morales-Quezada recently questioned why the neurologic pain signature (NPS) is largely unresponsive to placebo treatment. They suggest it may be because the NPS was trained on pain ratings elicited by heat applied to the left forearm, but tested on studies involving various body sites and stimulation types. Predictive models like the NPS can be expected to be more sensitive in settings similar to the training situation, although the degree to which they generalize is an empirical question.

Linnman and Morales-Quezada estimate placebo effects on the NPS by body site (left: Hedges $g = -0.09$; midline/bilateral, $-0.09$; right, $-0.05$) and by stimulus type (heat/laser, $g = -0.08$; electrical, $-0.11$; visceral, 0.01). However, body site and stimulus type were not independent in this data set. To account for this, we performed a meta-regression with body site and stimulus type as simultaneous predictors of study-level effect sizes. We found comparable effect sizes within the very small range but no statistically significant effect of body site ($P = .65$; left $[n = 10]$: $g = -0.09$; midline/bilateral $[n = 5]$, $g = -0.09$; right $[n = 5]$, $g = -0.05$) or stimulus type ($P = .51$; heat/laser $[n = 16]$, $g = -0.09$; electrical $[n = 2]$, $g = -0.12$; rectal distension $[n = 2]$, $g = 0.01$). Even considering that 7 studies with a combined 229 participants involved heat on the left upper limb, the placebo effect sizes were very small ($g = -0.07$; 95% CI, $-0.19$ to 0.04). These analyses support our original conclusions.

The analysis of placebo effect sizes is further complicated by variations in placebo treatment (eg, contact heat studies involved conditioning, whereas rectal distension studies did not). The issue of how biased NPS responses are toward particular body sites and stimulus types is therefore better addressed by examining effect sizes for responses to painful stimulation. We repeated the meta-regression mentioned previously using effect sizes for the pain vs baseline comparison. Studies using painful heat/laser yielded smaller NPS responses ($g = 1.87$) than electrical ($g = 3.04$) and rectal distension ($g = 2.41$) studies ($P = .04$). Body site effects were not statistically significant ($P = .18$) but were numerically smaller for left ($g = 1.95$) and right ($g = 1.99$) body sites than midline/bilateral sites ($g = 2.61$). These results should be interpreted with caution, as pain levels and stimulus timings varied across studies; for example, pain/discomfort might have been greater in midline studies. However, these analyses suggest that the NPS generalizes across body sites and types of evoked pain. Given the interstudy variation in this data set, the effects of these and other moderating variables might best be evaluated in new, fit-for-purpose studies.

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