

Letters

COMMENT & RESPONSE

To the Editor Linnman and Morales-Quezada recently questioned why the neurologic pain signature (NPS)¹ is largely unresponsive to placebo treatment.² They suggest it may be because the NPS was trained on pain ratings elicited by heat applied to the left forearm,¹ but tested on studies involving various body sites and stimulation types.² 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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Published Online: May 20, 2019. doi:10.1001/jamaneurol.2019.1232

Conflict of Interest Disclosures: Dr Zunhammer receives personal fees from Takeda Pharmaceutical. Dr Bingel receives grant support from the German Research Foundation. Dr Wager receives personal fees from GSK, grant support from WaviMed and PainQX, and research collaboration fees from Cliexa; serves on the scientific advisory board for Curable; and had a patent to US 2016/0054409 issued and a patent to US 2018/0055407 issued.

Additional Contributions: We thank the members of the Placebo Imaging Cohort: Lauren Atlas, PhD, National Center for Complementary and Integrative Health; Fabrizio Benedetti, MD, University of Turin; Christian Büchel, MD, University Medical Center Hamburg-Eppendorf; Jae Chan Choi, MD, PhD, Yonsei University; Luana Colloca, MD, PhD, University of Maryland; Davide Duzzi, PhD, University of Modena e Reggio Emilia; Falk Eippert, PhD, University of Oxford; Dan-Mikael Ellingsen, PhD, Harvard Medical School; Sigrid Elsenbruch, PhD, Essen University Hospital; Stephan Geuter, PhD, Johns Hopkins University; Randy L. Gollub, MD, PhD, Massachusetts General Hospital; Ted J. Kaptchuk, Beth Israel Deaconess Medical; Simon S. Kessner, MD, University Medical Center Hamburg-Eppendorf; Irving Kirsch, PhD, Harvard Medical School; Jian Kong, MD, Massachusetts General Hospital; Claus Lamm, PhD, University of Vienna; Siri Leknes, PhD, University of Oslo; Alexa Müllner-Huber, PhD, University of Vienna; Fausta Lui, MD, University of Modena e Reggio Emilia; Carlo A. Porro, MD, PhD, University of Modena e Reggio Emilia; Markus Rütgen, PhD, University of Vienna; Lieven Schenk, PhD, University of Maryland; Julia Schmid, PhD, Essen University Hospital; Nina Theysohn, MD, Essen University Hospital; Irene Tracey, PhD, University of Oxford; Nathalie Wrobel, PhD, Karolinska Institute; and Fadel Zeidan, PhD, Wake Forest School of Medicine for their contributions to the original article.

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