Laterality and Stimulation Bias in Meta-analysis of Placebo Responses

To the Editor—Zunhammer et al. claim that the effects of placebo are small in terms of changes in bottom-up nociceptive processing based on an analysis of participant-level neuroimage contrast maps from 603 healthy participants in 20 placebo pain imaging studies. We commend the authors and the contributing groups for sharing their findings. However, we have found a bias in how they analyzed this source. Briefly, they computed the dot product of individual placebo contrast images with a predefined weighted set of brain regions called the neurological pain signature (NPS). From this computation, they calculated the effect size (Hedges’ $g$) within each of the 20 placebo studies. Their results indicated a large effect for noxious stimulation ($g = 2.30$) on the NPS outcome and a moderate effect of placebo on pain ratings ($g = -0.66$), but only weak evidence that placebo altered the NPS ($g = -0.08$).

The NPS is based on 4 functional magnetic resonance imaging studies on healthy controls, encompassing pain, social exclusion, and remifentanil infusion manipulations. The 4 studies used thermal pain delivered to the left forearm, thus biasing the NPS to the right hemisphere. In the meta-analysis, 9 studies (45%) applied pain to a left limb (6 to the forearm, 2 to the hand, and 1 to the middle finger), 6 (30%) applied pain to a right limb (3 to the forearm, 2 to the calf, and 1 to the wrist), and 5 (25%) used midline or left and right pain stimuli (2 on rectal distension, 1 on hands, 1 on arms, and 1 on feet). Segregating the obtained placebo effect sizes on the NPS by left-sided, right-sided, and midline/bilateral pain stimulation, indicates a larger effect size on left-sided ($g = -0.09$) and midline/bilateral studies ($g = -0.09$) than on right-sided studies ($g = -0.05$). Similarly, segregating the effect sizes by stimulation type indicates a larger effect for heat/laser (15 studies [75%]; $g = -0.08$) and electrical stimulation (3 studies [15%]; $g = -0.11$) than rectal distention (2 studies [10%]; $g = 0.01$). Thus, by using NPS, which does not account for stimulation site or type, the magnitude of the placebo effect on bottom-up nociceptive processes is likely underestimated.

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