concerns would be critical. As no such claims were made, however, these concerns largely miss the point of our letter. We concluded that pain matrix activation is insufficient evidence for the presence of pain. This conclusion does not hinge on the null finding (lack of group differences). Rather, it requires demonstrating robust pain matrix activation in the absence of pain. Patients with loss-of-function *SC9A* mutations are extremely rare (limiting sample size), but studying this population allows us to conclusively rule out pain as an explanation of the measured neural response. Testing for significant differences and displaying group scatter plots merely allows us to demonstrate that patient responses are within the same range as those observed in individuals who experienced pain in response to an identical stimulus. To strengthen inferences about nonspecificity, we include an analysis based on a reverse (rather than forward) inference mask of pain (**Figure**).

Many in the neuroimaging field feel the nonspecificity of the pain matrix has already been conclusively demonstrated[2] and widely accepted. We wish this were true, but recent scientific debate over the "selectivity" of subsets of the pain matrix,[3] controversy over the use of neuroimaging as medicolegal evidence of pain,[4] and popular media reports conflating pain matrix activation with the experience of pain[5] demonstrate that pain matrix activation continues to be used as evidence for pain, both in the scientific community and in the court of public opinion.

Finally, we disagree that parametric designs are a remedy for unspecific confounds. We have used these powerful designs in our own work to isolate responses that track the perceptual transition from nonpainful to painful levels of sensation.[6,7] However, the question remains whether these responses are attributable to the painful percept or increases in nonspecific effects, such as "orienting or response preparation." For this purpose, we advocate the use of equisalient stimulus designs, where stimuli are carefully matched for nonspecific effects (eg, sensation, unpleasantness, and/or attentional capture). Such designs, while requiring careful instruction and measurement, are necessary for isolating neural responses specifically associated with painful percepts.

Tim V. Salomons, PhD

Author Affiliation: School of Psychology and Clinical Language Sciences, Centre for Integrative Neuroscience & Neurodynamics, University of Reading, Reading, England.

Corresponding Author: Tim V. Salomons, PhD, School of Psychology and Clinical Language Sciences, Centre for Integrative Neuroscience & Neurodynamics, University of Reading, PO Box 238, Reading RG6 7BE, England (t.v.salomons@reading.ac.uk).

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1. Salomons TV, Iannetti GD, Liang M, Wood JN. The "pain matrix" in pain-free individuals. *JAMA Neurol*. 2016;73(6):755-756.

2. Iannetti GD, Salomons TV, Moayedi M, Mouraux A, Davis KD. Beyond metaphor: contrasting mechanisms of social and physical pain. *Trends Cogn Sci*. 2013;17(8):371-378.

3. Wager TD, Atlas LY, Botvinick MM, et al. Pain in the ACC? *Proc Natl Acad Sci U S A*. 2016;113(18):E2474-E2475.

4. Reardon S. Neuroscience in court: the painful truth. *Nature*. 2015;518:474-476. doi:10.1038/518474a.

5. Spencer B. Very young babies can feel pain and have a lower threshold that adults, say experts at Oxford. *Daily Mail*. http://www.dailymail.co.uk/sciencetech/article-3047901/Babies-feel-pain-lower-threshold-adults.html. Published April 20, 2015. Accessed July 28, 2016.

6. Johnstone T, Salomons TV, Backonja MM, Davidson RJ. Turning on the alarm: the neural mechanisms of the transition from innocuous to painful sensation. *Neuroimage*. 2012;59(2):1594-1601.

7. Hu L, Cai MM, Xiao P, Luo F, Iannetti GD. Human brain responses to concomitant stimulation of Aδ and C nociceptors. *J Neurosci*. 2014;34(34):11439-11451.

CORRECTION

Omitted Author Affiliation: In the Original Investigation article by Santos-Santos et al titled "Features of Patients With Nonfluent/Agrammatic Primary Progressive Aphasia With Underlying Progressive Supranuclear Palsy Pathology or Corticobasal Degeneration," published online April 25, 2016, and also in the June 2016 print issue of *JAMA Neurology*,[1] there was an omission in the Author Affiliations section in the Article Information. The following affiliation should have been included: "Department of Medicine, Autonomous University of Barcelona, Bellaterra, Barcelona, Spain (Santos-Santos)." This article was corrected online.

1. Santos-Santos MA, Mandelli ML, Binney RJ, et al. Features of patients with nonfluent/agrammatic primary progressive aphasia with underlying progressive supranuclear palsy pathology or corticobasal degeneration. *JAMA Neurol*. 2016;73(6):733-742.

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