Comparing Painful Stimulation vs Rest in Studies of Pain

To the Editor

A recent Research Letter in *JAMA Neurology* presented results of a functional magnetic resonance imaging study of individuals with rare loss-of-function *SCN9A* mutations that abolish sensory neuron sodium channel Nav1.7 activity, resulting in congenital pain insensitivity. The study compared brain responses to a brief pinprick stimulus between patients (n = 2) and control individuals (n = 4). The authors reported activation of areas that have previously been implicated in pain processing and observed “no significant difference between patients and control individuals...across the entire pain matrix.” Although studying patients with loss-of-function *SCN9A* mutations is important and could potentially be highly informative, the conclusions to be drawn from the current study are limited for several reasons.

Adopting a forward-inference mask from Neurosynth (http://www.neurosynth.org) (based on studies mentioning the term painful) does not provide a set of pain-specific regions because many of these studies compare painful stimuli with a resting baseline. This comparison is confounded by unspecific effects such as orienting or response preparation. To overcome this limitation, the authors could have adopted a more insightful experimental design such as a parametric design with different pain intensities. Previously, this approach was able to dissociate pain-related areas based on their individual response functions: subregions of the secondary somatosensory cortex and anterior insula showed an increase of activity with increasing pain stimulus intensity, whereas regions in the parietal and frontal cortices showed an increase in activation when comparing mild painful stimulation with a resting baseline. However, the latter regions showed no further increase with increasing pain intensity, suggesting a nonpain-related function.

Given that areas such as the thalamus, S2, and the insula respond to nociceptive and tactile stimulation, it is no surprise that pinprick stimulation did not produce any difference between patients and control individuals. In addition, averaging across large regions of interest does not account for important spatial and functional subdivisions of gross anatomical regions. Finally, the absence of a difference between the patients and the control group (with n = 2 and n = 4, respectively) might be simply due to insufficient statistical power and not necessarily due to the absence of a difference.

In summary, the authors try to refute an ill-defined concept (“pain matrix”) by using a weak experimental design that led to the existence of the concept in the first place. We would argue that it is time to use informative experimental designs to characterize complex brain functions, thus allowing assertive conclusions.

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In Reply We thank Büchel and colleagues for their letter, and we are pleased to see that their considerations are based on a viewpoint almost entirely in agreement with our own. Their statement that pain matrix responses generated using traditional analysis methods and experimental designs are “confounded by unspecific effects” is a concise summary of our letter and a theme of much of our previous work.² Büchel and colleagues point out that because of our experimental/analytical approach and sample size, only limited conclusions can be drawn from our observed lack of group differences. If we were claiming this null finding as evidence that specific neural representations of pain do not exist, or to preclude the possibility that functional magnetic resonance imaging could be used to detect such representations, these

Figure. Pain Matrix Responses in a Reverse Inference Mask of Pain

A, Red indicates Neurosynth-based pain matrix (reverse inference, feature set pain; N = 420 studies). Blue indicates conjunction of control individuals’ responses to noxious stimulation. B, Activation levels (z scores) of single participants within the pain matrix. C, Neurosynth-based pain matrix (red) and conjunction of patients’ responses to noxious stimulation (yellow). ACC indicates anterior cingulate cortex.

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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 and widely accepted. We wish this were true, but recent scientific debate over the “selectivity” of subsets of the pain matrix, controversy over the use of neuroimaging as medicolegal evidence of pain, and popular media reports conflating pain matrix activation with the experience of pain 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. 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.

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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, 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.