Letters

RESEARCH LETTER

The "Pain Matrix" in Pain-Free Individuals

Human functional imaging provides a correlative picture of brain activity during pain. A particular set of central nervous system structures (eg, the anterior cingulate cortex, thalamus, and insula) consistently respond to transient nociceptive stimuli causing pain. Activation of this so-called *pain matrix* or *pain signature* has been related to perceived pain intensity, both within and between individuals,[1,2] and is now considered a candidate biomarker for pain in medicolegal settings and a tool for drug discovery. The pain-specific interpretation of such functional magnetic resonance imaging (fMRI) responses, although logically flawed,[3,4] remains pervasive. For example, a 2015 review states that "the most likely interpretation of activity in the pain matrix seems to be pain."[4] Demonstrating the nonspecificity of the pain matrix requires ruling out the presence of pain when highly salient sensory stimuli are presented. In this study, we administered noxious mechanical stimuli to individuals with congenital insensitivity to pain and sampled their brain activ-

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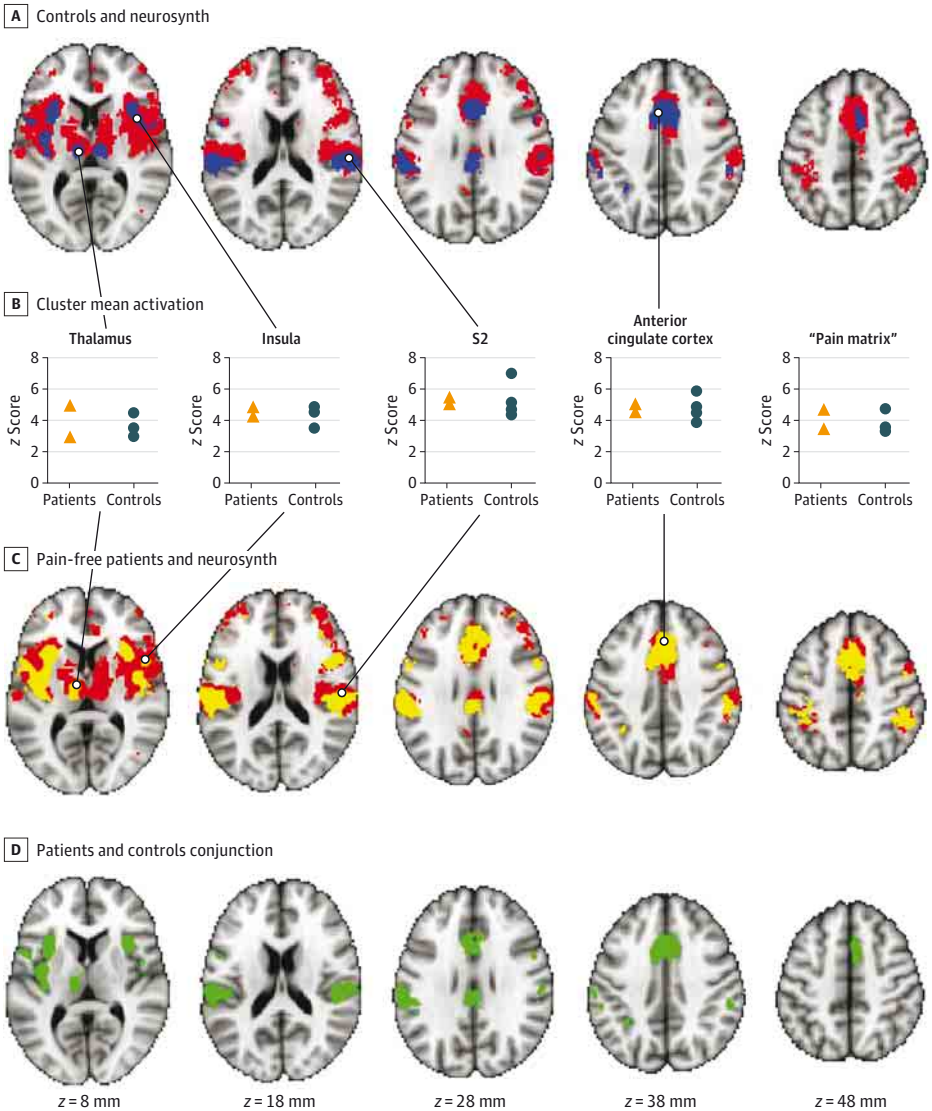
Figure. Pain Matrix Activation in Pain-Free People



A, Neurosynth-based pain matrix (red) and the regions where all control participants had significant activation in response to noxious stimulation (blue). B, Activation levels (*z* scores) of single participants within regions of the pain matrix. C, Neurosynth-based pain matrix (red) and pain matrix regions where pain-free individuals had significant activation (yellow). D, Conjunction (green) of pain-free and control activations within the Neurosynth-based pain matrix regions.

ity with fMRI. Loss-of-function *SCN9A* mutations in these individuals abolishes sensory neuron sodium channel Nav1.7 activity, resulting in pain insensitivity through an impaired peripheral drive that leaves tactile percepts fully intact.[5] This allows complete experimental disambiguation of sensory responses and painful sensations.

Methods | This study was approved by the ethics committee at University College London, and written informed consent was obtained from the participants. A 3-T fMRI scan was performed on 2 pain-free individuals (1 woman) and 4 age-matched control individuals. Participants received 24 mechanical stimuli (465 mN, 0.2-mm tip, 1-second duration) to their right hand dorsum. Functional MRI results from thermal stimuli are not reported owing to motion artifacts. Participants rated the intensity of both subjective sensation (0 = no sensation and 10 = most intense sensation imaginable) and pain (0 = no pain and 10 = most intense pain imaginable). General linear model analysis of fMRI data was performed using the Functional Imaging Statistics Library,[6] using a cluster correction for multiple comparisons ($z = 1.96$, $P < .05$) at single-participant level and a conjunction analysis at the group level such that group activations represented regions significantly activated in all individuals. To compare results with a canonical pain matrix, a meta-analysis of pain studies (N = 139) was performed with Neurosynth[7] (Neurosynth) using forward inference with the feature set at "painful." Group comparisons were conducted by extracting activation *z* scores from the Neurosynth-defined pain matrix and from key pain matrix regions (thalamus, insula, S2, and anterior cingulate cortex, defined using the Harvard Oxford 25% probability atlas).

Results | In response to identical noxious stimuli, pain-free participants reported similar levels of sensation to healthy control individuals. Patients had a mean (SD) level of 4.6 (0.5), and control individuals had a mean (SD) level of 4.4 (1.2) ($P = .51$). Unlike control individuals, who uniformly reported the stimuli as painful at a mean (SD) level of 3.2 (1.8), the patients' percepts were devoid of any painful quality. Strikingly, fMRI revealed normal activation of brain regions commonly activated by painful stimuli in both pain-free individuals (**Figure**, A and C). There was no significant difference between patients and control individuals either across the entire pain matrix or in key pain matrix regions (Figure, B; thalamus: $P = .46$; anterior cingulate cortex: $P = .89$; S2: $P = .93$; insula: $P = .78$; and pain matrix: $P = .61$).

Discussion | Previous work[3] interpreting pain matrix activation as a response to salient sensory stimuli rather than perceptual qualities unique to pain has been challenged on the basis that the presence of pain in response to these stimuli could not be fully ruled out.[4] In this study, we addressed this challenge by demonstrating intact pain matrix responses in individuals congenitally unable to experience pain.

These observations reinforce the need for caution in using pain matrix responses for diagnosis or drug discovery and corroborate evidence that reported correlations between neuroimaging data and perceived pain have largely relied on non-pain-specific activities.[3] Examining how the brain gives rise to the unique perceptual experience of pain will require human neuroimaging to be supplemented by techniques that allow for causal inferences. These include studies in nonhuman species where cell populations and circuitry can be genetically or chemically modified[5] and human studies of individuals with relevant lesions or genetic mutations.

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Published Online: April 25, 2016. doi:10.1001/jamaneurol.2016.0653.

Author Contributions: Dr Wood had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed equally to this study.
Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: Salomons, Iannetti, Liang,
Drafting of the manuscript: Salomons, Iannetti, Wood.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Salomons, Iannetti,
Obtained funding: Wood.
Administrative, technical, or material support: Liang, Wood.
Study supervision: Iannetti.

Conflict of Interest Disclosures: None reported.

Funding/Support: Dr Iannetti received support from The European Research Council. Drs Wood and Iannetti received support from the Wellcome Trust. Dr Wood received support from the Medical Research Council. Dr Salomons received support from an EC Marie Curie Fellowship.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript.

Additional Contributions: We thank Tom Johnstone, PhD (University of Reading), for statistical consultations. No funding was used for this contribution.

1. Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-based neurologic signature of physical pain. *N Engl J Med*. 2013;368(15):1388-1397.

2. Huang G, Xiao P, Hung YS, Iannetti GD, Zhang ZG, Hu L. A novel approach to predict subjective pain perception from single-trial laser-evoked potentials. *Neuroimage*. 2013;81:283-293.

3. 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.

4. Eisenberger NI. Social pain and the brain: controversies, questions, and where to go from here. *Annu Rev Psychol*. 2015;66:601-629.

5. Minett MS, Nassar MA, Clark AK, et al. Distinct Nav1.7-dependent pain sensations require different sets of sensory and sympathetic neurons. *Nat Commun*. 2012;3:791.

6. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*. 2004;23 (S1)(suppl 1):S208-S219.

7. Yarkoni T, Poldrack RA, Nichols TE, Van Essen DC, Wager TD. Large-scale automated synthesis of human functional neuroimaging data. *Nat Methods*. 2011;8(8):665-670.