

The “pain matrix” in pain-free individuals

Article

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1 **The “Pain Matrix” in Pain-Free Individuals**

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21 591 words

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28 INTRODUCTION

29 Human functional imaging provides a correlative picture of brain activity during pain. A particular set of
30 CNS structures (e.g. ACC, thalamus, insula) consistently respond to transient nociceptive stimuli causing
31 pain. Activation of this so-called “pain matrix” or “pain signature” has been related to perceived pain
32 intensity, both within and between-individuals^{1,2} and is now considered a candidate biomarker for pain
33 in medico-legal settings, as well as a tool for drug discovery. The pain-specific interpretation of such
34 fMRI responses, although logically flawed^{3,4}, remains pervasive. For example, a recent review states
35 that “the most likely interpretation of activity in the pain matrix seems to be pain”⁵. Demonstrating the
36 non-specificity of the “pain matrix” requires ruling out the presence of pain when highly-salient sensory
37 stimuli are presented. Here we administer noxious mechanical stimuli to individuals with congenital
38 insensitivity to pain and sample their brain activity with fMRI. Loss-of-function *SCN9A* mutations in these
39 individuals fully impairs sodium channel Nav1.7 activity in peripheral neurons, resulting in loss of the
40 ability to experience pain through impaired peripheral drive that leaves tactile percepts fully intact.⁵
41 This allows complete experimental disambiguation of sensory responses and painful sensations.

42 METHODS

43 3-Tesla fMRI was performed on two pain-free individuals (one female) and four age-matched controls.
44 Subjects received twenty-four mechanical stimuli (465mN, 0.2mm tip, 1s duration) to their right hand
45 dorsum. fMRI results from thermal stimuli are not reported due to motion artifacts. Subjects rated the
46 intensity of both subjective sensation (0=no sensation, 10=most intense sensation imaginable) and pain
47 (0=no pain, 10=most intense pain imaginable). GLM analysis of fMRI data were performed using FSL
48 (<http://fsl.fmrib.ox.ac.uk/fsl>), using a cluster correction for multiple comparisons ($z=1.96$, $p<0.05$) at
49 single-subject level and a conjunction analysis at group-level, such that group activations represent
50 regions significantly activated in all individuals. To compare results to a canonical “pain matrix”, a meta
51 analysis of pain studies ($n=139$) was performed with Neurosynth (www.Neurosynth.org) using forward
52 inference with the feature set “painful”. Group comparisons were conducted by extracting activation z -
53 scores from the Neurosynth-defined pain matrix and from key pain matrix regions (thalamus, insula, S2
54 and ACC - defined using the Harvard Oxford 25% probability atlas).

55 RESULTS

56 In response to identical noxious stimuli, pain-free subjects reported similar levels of sensation to healthy
57 controls [patients: 4.6 ± 0.5 ; controls: 4.4 ± 1.2 (mean \pm SD), $F=0.53$, $p=0.51$]. Unlike controls, who uniformly
58 reported the stimuli as painful (3.2 ± 1.8), the patients’ percepts were devoid of any painful quality.
59 Strikingly, fMRI revealed normal activation of brain regions commonly activated by painful stimuli in
60 both pain-free individuals (Figure 1a,c). There was no significant difference between patients and
61 controls either across the entire “pain matrix” or in key “pain matrix” regions (Figure 1b; thalamus,

62 F=0.66, p=0.46; ACC, F=0.02, p=0.89; S@, F=0.01, p=0.93, Insula: F=0.09, p=0.78; pain matrix: F=0.3,
63 p=0.61).

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66 DISCUSSION

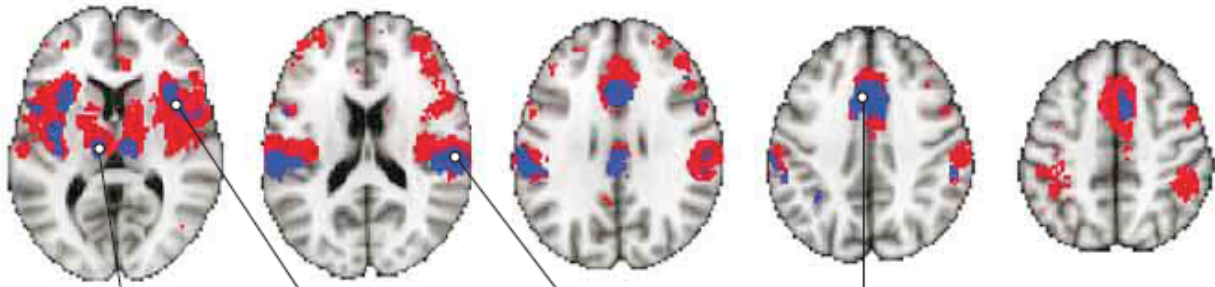
67 Previous work³ interpreting “pain matrix” activation as a response to salient sensory stimuli rather than
68 perceptual qualities unique to pain has been challenged on the basis that the presence of pain in
69 response to these stimuli could not be fully ruled out.⁵ Here we address this challenge by demonstrating
70 intact “pain matrix” responses in individuals congenitally unable to experience pain.

71 These observations reinforce the need for caution in using “pain matrix” responses for diagnosis or drug
72 discovery and corroborate evidence that reported correlations between neuroimaging data and
73 perceived pain have largely relied on non-pain-specific activities.⁴³ Examining how the brain gives rise to
74 the unique perceptual experience of pain will require human neuroimaging to be supplemented by
75 techniques that allow for causal inferences. These include studies in non-human species where cell
76 populations and circuitry can be genetically or chemically modified, as well as human studies of
77 individuals with relevant lesions or genetic mutations.

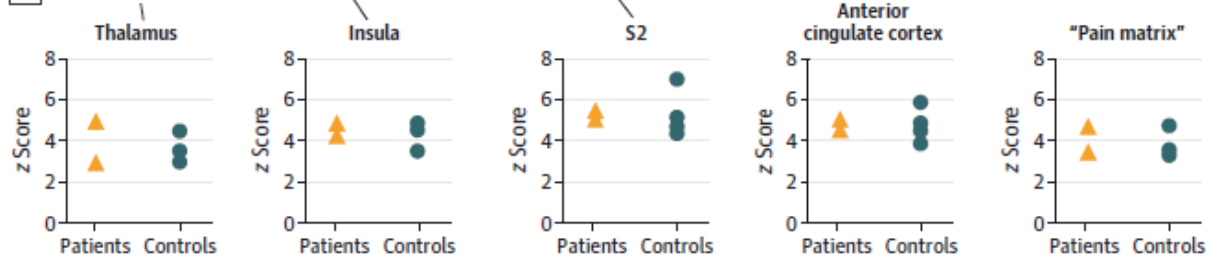
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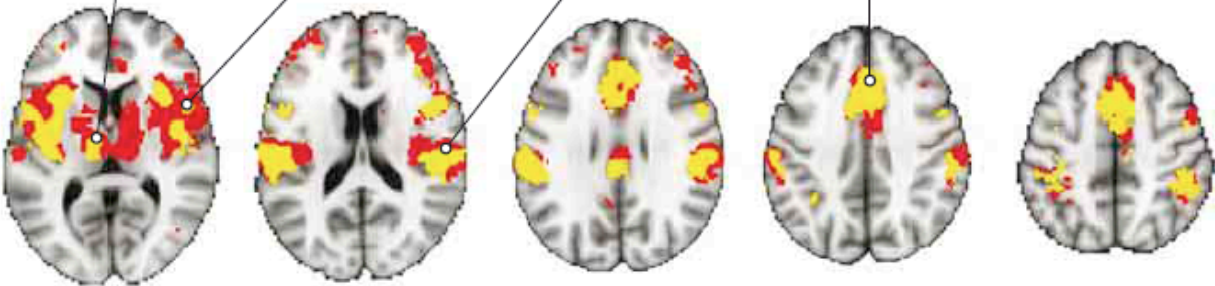
A Controls and neurosynth



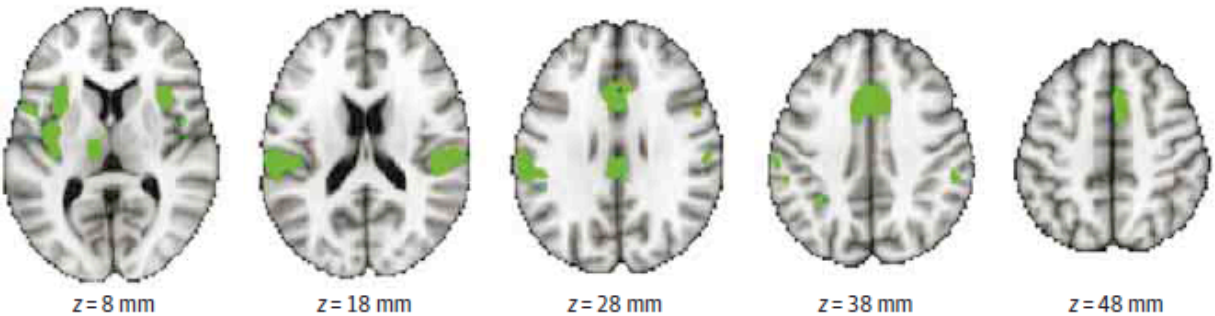
B Cluster mean activation



C Pain-free patients and neurosynth



D Patients and controls conjunction



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83 **FIGURE 1:** (A) shows the Neurosynth-based "pain matrix" (red) and the regions where all control
84 subjects had significant activation in response to noxious stimulation (blue). (B) shows activation levels
85 (z-scores) of single subjects within regions of the "pain matrix" (C) shows the Neurosynth-based "pain
86 matrix" (red) and "pain matrix" regions where pain-free individuals had significant activation (yellow).

87 (D) shows the conjunction (green) of pain-free and control activations within the Neurosynth-based
88 “pain matrix” regions.

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