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The "Pain Matrix" in Pain-Free Individuals

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INTRODUCTION

Human functional imaging provides a correlative picture of brain activity during pain. A particular set of CNS structures (e.g. ACC, thalamus, 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 medico-legal settings, as well as a tool for drug discovery. The pain-specific interpretation of such fMRI responses, although logically flawed [3,4], remains pervasive. For example, a recent review states that "the most likely interpretation of activity in the pain matrix seems to be pain"[5]. Demonstrating the non-specificity of the "pain matrix" requires ruling out the presence of pain when highly-salient sensory stimuli are presented. Here we administer noxious mechanical stimuli to individuals with congenital insensitivity to pain and sample their brain activity with fMRI. Loss-of-function *SCN9A* mutations in these individuals fully impairs sodium channel Nav1.7 activity in peripheral neurons, resulting in loss of the ability to experience pain through impaired peripheral drive that leaves tactile percepts fully intact.[5] This allows complete experimental disambiguation of sensory responses and painful sensations.

METHODS

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

RESULTS

In response to identical noxious stimuli, pain-free subjects reported similar levels of sensation to healthy controls [patients: 4.6±0.5; controls: 4.4±1.2 (mean±SD), $F=0.53$, $p=0.51$]. Unlike controls, who uniformly reported the stimuli as painful (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 1a,c). There was no significant difference between patients and controls either across the entire "pain matrix" or in key "pain matrix" regions (Figure 1b; thalamus,

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, p=0.61).

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.[5] Here we address 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.[43] 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 non-human species where cell populations and circuitry can be genetically or chemically modified, as well as human studies of individuals with relevant lesions or genetic mutations.

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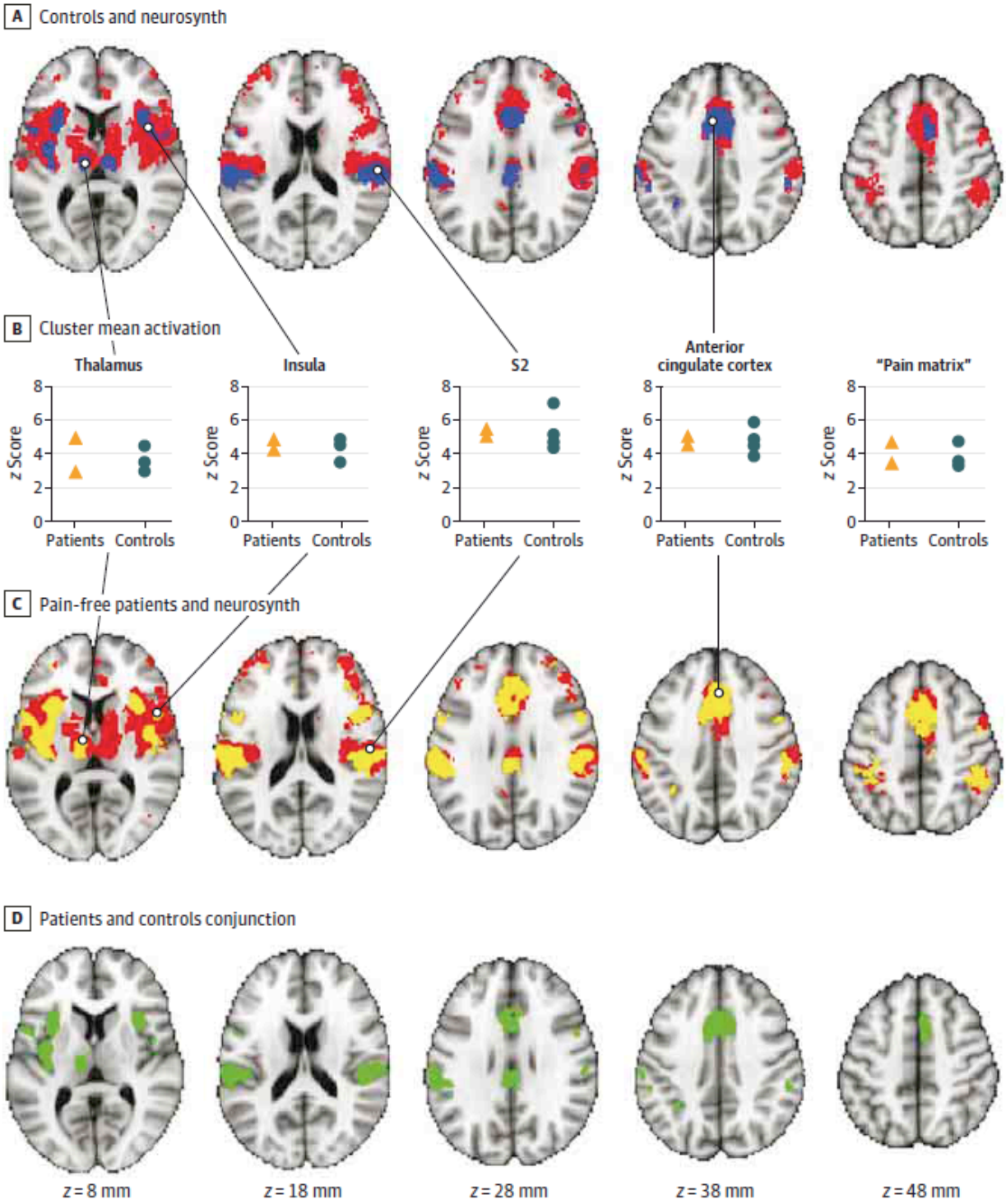

FIGURE 1: (A) shows the Neurosynth-based "pain matrix" (red) and the regions where all control subjects had significant activation in response to noxious stimulation (blue). (B) shows activation levels (z-scores) of single subjects within regions of the "pain matrix" (C) shows the Neurosynth-based "pain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

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

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