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A brain signature for acute pain

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Abstract

Wager and colleagues developed an fMRI-based spatial and magnitude pattern for perception of acute pain, which seems to generalize across many task conditions and subjects. This is a strong demonstration of the existence of a pain signature and raises important questions regarding what pain and perception are.

Localization of the representation of pain in the brain and the existence of specific neocortical circuits that underlie pain have been a matter of debate since the beginning of the 20th century. Henry Head and Roger Penfield were the most vocal representatives of the position that the neocortex does not have any tissue specifically dedicated to pain [1, 2], whereas many others asserted otherwise. A naïve bystander would presume that this debate would have faded away after more than 20 years of noninvasive brain imaging studies of the human brain in pain (a PubMed search on May 1st, 2013 for the terms ‘brain imaging AND pain’ identified 7084 human studies) and a large number of studies that have shown a consistent brain activity pattern, especially for acute/experimental painful stimuli [3, 4]. Yet, it remains as topical as ever. For example, at the 2012 meeting of the International Association for the Study of Pain (IASP) in Milan (http://bit.ly/13fwpV8), Garcia-Larrea presented human cortical recording and lesion data to argue that the posterior insular cortex contains nociceptive neurons, the activation of which gives rise to pain perception in humans [5]. In contradistinction, in a separate session Iannetti presented human brain imaging results showing that brain activity for acute thermal pain, although present in a large network of brain regions, cannot be differentiated from brain activity for loud noises or for bright light (non-painful), and concluded that functional MRI activity for acute pain reflects a saliency response rather than pain specifically [6]. Between the two extreme positions, there are ample human neuroimaging data that point to a consistent brain activity pattern for acute painful stimuli. This is perhaps best illustrated by the term-based meta-analysis tool developed by Yarkoni and colleagues, which on the basis of approximately 200 studies shows that about 10% of the cortex is reproducibly related with the term ‘pain’ [4]. Nonetheless, the persisting question is the extent to which this pattern is specific to the pain percept, given that many regions identified to be part of the network are observed to be involved in multitudes of other states or cognitive conditions and that electrophysiological studies have identified only a handful of nociceptive neurons in the cortex [5, 7, 8].

Wager and colleagues [9] recently addressed the critical question of the existence of a specific brain activity pattern for acute pain. The authors assessed this question in a rigorous

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and systematic approach. First, they developed what they call a 'neural pain signature' (NPS) by defining a brain pattern of voxels with appropriate weights that predict pain perception for a series of thermal stimuli of increasing intensity. They then tested its generalizability with a second group of subjects and also evaluated the ability of NPS to discriminate pain in other tasks and its sensitivity to the presence of an opiate analgesic. The approach used is elegant in its simplicity, as it relies primarily on general linear modeling (GLM) for the stimulus, followed by a data reduction approach using a standard machine learning algorithm. The latter reduced membership to the NPS, removing redundant as well as noisy elements, and calculated optimum weighting functions for the input–output relationship. Thus, the NPS is a template to which individual subject GLM outputs are compared, for a variety of task conditions, and tested as to its ability to identify or discriminate pain from non-pain conditions. The authors rigorously assessed sensitivity and specificity across multiple conditions and demonstrated very impressively accurate results. Thus, they affirmed the existence of a specific brain signature for pain, at least for the task conditions tested. They also showed that this signature is not temperature dependent, can be dissociated from a salience signal, and correlates better with pain perception than temperature. Thus, the authors argued that there is a universal signature for pain.

As is typical for a high quality study, this paper raises a long list of exciting questions. How can these results be reconciled with the competing ideas outlined above? Regarding the nociceptive-specific brain 'real estate' viewpoint, because the NPS is composed of elements in regions that do not contain nociceptors, for example primary visual cortex, as well as many brain areas that one suspects may have nociceptive neurons (somatosensory, insula, and cingulate cortices), the NPS cannot be considered nociceptive specific. This raises a question as to the extent to which NPS accuracy would degrade if it were spatially restricted to nociceptive tissue. Alternatively, such an approach can be used to assign weights to the components of the NPS on the basis of their information contribution. A related question is the extent of redundancy versus uniqueness of the NPS. For example, if the voxels involved are all dropped, is it possible to find a second set and how well would this set perform? Variants of these questions would be fascinating to tackle and all provide insights into the mechanisms that underlie pain perception, as well as the mechanisms by which perception more generally is constructed. Can Wager and colleagues' approach also shed further light into the viewpoint that cortical fMRI responses to pain may be non-specific? Mouraux, A. *et al.*'s position [6] is based on the observation that a GLM-based contrast – between pain and bright light – results in minimal differences. Given that the NPS is a weighted spatial map, the question then reduces to the extent to which the weights are critical to NPS performance. Thus, the study has several important implications and answers to the preceding questions will lead rapidly to new understanding.

Overall, the study advances our understanding of pain perception in several ways: first, by identifying a general NPS that seems to be valid across subjects and tasks; second, by beginning to address what perception itself is. The study moves the discussion away from the contribution of cortical 'real estate' dedicated to nociceptors to a network that incorporates afferent inputs with memory traces that give rise to pain. Farmer *et al.* [10] suggested that an NPS derived from acute pain most likely will not generalize to chronic pain. Yet, the extent to which it might or might not, and the identification of the number of NPS's needed for diverse chronic pain conditions, is now testable.

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