CORRESPONDENCE

Evidence against pain specificity in the dorsal posterior insula [v1; ref status: indexed, http://f1000r.es/5o3]

Karen D. Davis[1-3], M. Catherine Bushnell[4], Gian Domenico Iannetti[5], Keith St. Lawrence[6,7], Robert Coghill[8]

[1]Institute of Medical Science and Department of Surgery, University of Toronto, Toronto, ON, M5T 2S8, Canada
[2]Division of Brain Imaging and Behaviour - Systems Neuroscience, Toronto Western Research Institute, Toronto, ON, M5T 2S8, Canada
[3]Joint Department of Medical Imaging, University Health Network, Toronto, ON, M5T 2S8, Canada
[4]Pain and Integrative Neuroscience Branch, Division of Intramural Research, National Center for Complementary and Integrative Health (NCCIH), National Institutes of Health, Bethesda, MD, 20892-1302, USA
[5]Department of Neuroscience, Physiology and Pharmacology, University College London, London, WC1E 6BT, UK
[6]Lawson Health Research Institute, London, ON, N6A 4V2, Canada
[7]Department of Medical Biophysics, The University of Western Ontario, London, ON, N6A 4V2, Canada
[8]Department of Anesthesiology, Cincinnati Children's Hospital, Cincinnati, OH, 45229-3026, USA

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Abstract

The search for a "pain centre" in the brain has long eluded neuroscientists. Although many regions of the brain have been shown to respond to painful stimuli, all of these regions also respond to other types of salient stimuli. In a recent paper, Segerdahl *et al.* (Nature Neuroscience, 2015) claims that the dorsal posterior insula (dpIns) is a pain-specific region based on the observation that the magnitude of regional cerebral blood flow (rCBF) fluctuations in the dpIns correlated with the magnitude of evoked pain. However, such a conclusion is, simply, not justified by the experimental evidence provided. Here we discuss three major factors that seriously question this claim.

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1 **David Borsook**, Massachusetts General Hospital USA

2 **Apkar Vania Apkarian**, Northwestern University USA

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Corresponding author: Karen D. Davis (kdavis@uhnres.utoronto.ca)

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There are three major factors that we feel negate the claims of the recent study by Segerdahl *et al.*[1] that the dorsal posterior insula (dpIns) is a pain-specific area of the brain.

First, the evidence that the dpIns is specific is lacking based on the experimental design and data analysis employed. The methodological approach used by Segerdahl *et al.*[1] was to induce an ongoing pain with capsaicin and then to correlate pain intensity ratings with brain perfusion changes using arterial spin labeling (ASL). ASL is an MRI-based perfusion method that can measure fluctuations in rCBF (akin to PET imaging) without the need for a stimulus, and so its application to study ongoing pain is promising. ASL has been previously used by others[2,3] to identify acute and chronic pain-related changes in regional cerebral blood flow (rCBF) but the way Segerdahl *et al.*[1] applied it has several shortcomings. The choice of Segerdahl *et al.*[1] to collect multi-delay ASL data resulted in rCBF images sampled at infrequent intervals of ~45s, which represents a statistically challenging condition because of the small number of data collected. The control experiment using vibrotactile stimuli comprised a very short scan with even fewer data points in only seven subjects – a design that did not match the already low statistical power of the capsaicin experiment. Therefore, the analysis was underpowered and does not constitute a valid control for the pain experiment. This likely contributed to the minimal activation detected anywhere in the brain during the vibrotactile stimulation. The skin is richly innervated by rapidly adapting, low-threshold mechanoreceptors, so this absence of activation is of substantial concern. Even very early PET studies of regional cerebral blood flow (CBF) found robust vibrotactile activation of primary and secondary somatosensory cortex (S1, S2), and the adjacent posterior insula[4,5]. Most importantly, unlike previous investigations where CBF was directly and statistically compared between pain and innocuous stimulation to evaluate specificity of activation[5,6], the Segerdahl *et al.*[1] study performed no such key statistical comparison. Without this direct comparison, and in the absence of a control for vibration intensity, or for stimulus saliency, claims of specificity and pain intensity coding simply cannot be made[7]. This comparison is crucial given the evidence of a vast predominance of low threshold mechanoreceptive neurons in the posterior insula[8] and robust vibrotactile activation of the insula (e.g., see 4).

Second, the proposition of a very specific "spot" dedicated to pain is critically dependent on the ability of the methodology to localize findings precisely. However, it is challenging to derive an accurate, group-averaged localization of activation within the dpIns given 1) the large intersubject anatomical variability of the insula, in particular the posterior gyri[9] and 2) the method of realignment and morphing of brain anatomy into a common space to produce group maps. Inspection of the reported dpIns peak coordinate in the Juelich histologic atlas reveals that this peak activation has a 63% probability of being in the parietal operculum (S2, OP2), and only a 31% probability of being in the insular cortex. These areas are in close approximation, but S2 has a well-documented involvement in both nociceptive and innocuous somatosensory processing (e.g., see 8). No additional procedures were performed to functionally distinguish these two regions.

Third, the interpretation of the findings and proposition of a specific pain center was made without taking into consideration a large body of scientific evidence addressing the brain mechanisms that contribute to pain. Theories of pain have been debated for centuries[10], and we still do not know how pain is represented in the brain despite decades of searching for a pain specific brain center. This pursuit for a simple, single pain center however is no longer necessary given the enormity of human neuroimaging data indicating that there is no such dedicated center. Each and every brain area that contains nociceptive neurons also contains non-nociceptive neurons, and neuroimaging has shown that each brain area that responds to noxious stimuli can also respond to non-noxious stimuli[11]. Rather, multiple, converging lines of evidence strongly indicate that the experience of pain - as any other conscious experience - is constructed from highly distributed cortical processes[5,12]. For example, many brain regions exhibit activity related to pain intensity (e.g., 12,13). Furthermore, there are several clinical cases of preserved pain perception despite lesions of critical regions including the insula, anterior cingulate, and even the entire contralateral hemisphere[14,15]. Other studies have shown that interactions among multiple brain regions are critical for distinguishing a state of pain from other highly salient events[16].

It is also useful to place the findings of Segerdahl *et al.*[1] in context given the historical view of insular function. Morphological, physiological and imaging studies throughout the 1980s and 1990s, divided the insula into anterior agranular and posterior granular subregions, with pain-related function attributed to the anterior part, and a variety of other functions, including tactile recognition, attributed to the posterior part (e.g., see 8). Since that time, the anterior insula has been established to be part of a non-specific network related to attention and salience. In addition, there is anatomical and electrophysiological evidence for thermoreceptive processing in the dpIns via a spinal cord lamina 1 pathway[17]. Although neuroimaging has shown that the dpIns likely has a role in pain and intensity coding, it is critical to reiterate that intensity-coding has also been found for non-pain modalities in this region, including C-fiber mediated pleasant-touch[18–20]. The last decades have seen several theories of insula function being put forward[21]. This balanced view of potential dpIns functions is surprisingly absent from the discussion of Segerdahl *et al.*[1]. One important theory to consider, put forth by Apkarian's group[13], is that of the "how much" general magnitude-detector function of the insula. Another important theory developed by Craig and colleagues[17], proposes the dpIns to be a center for interoceptive integration and awareness. Thus, there are several important issues[22] that need to be considered to fully interpret the findings of Segerdahl *et al.*[1]. One assumption that drove the approach taken was that of the critical role of intensity-coding as being central to finding a "pain specific" center. We challenge this because although intensity certainly is one classic dimension of pain, there are many other dimensions including location, quality, and unpleasantness that together comprise the experience of pain. Furthermore, none of these dimensions are actually required for a fundamental feeling of pain (see the recent theory put forth by Davis *et al.*[23]).

In conclusion, the extensive evidence about the role of the dpIns is not considered by Segerdahl *et al.*[1] and we note that they do not refute this evidence in their claim to have identified a novel, specific pain center in the dpIns. Such simplistic notions of a specific pain center are incorrect, and therefore dangerous at both an intellectual as well as a clinical level. Here, we suggest an alternate concept of the function of the dpIns based on previous theories and a large body of data that strongly indicate that the dpIns likely is involved in pain but overall is a non-specific perceptual way-station, rather than a specific pain centre. Failure to recognize that many regions activated during nociceptive stimulation are engaging in computational processes related to many things other than pain, lead to interpretations that are fraught with reverse inference[11], and they encourage neurosurgeons to pursue lesions for pain control, an approach that has largely been shown to be ineffective since the 1960's[24]. Their promotion of the concept of a single spot in the brain for pain is even more surprising given the enormous amount of data emerging over the last decade showing the representation of brain function in functional networks, rather than "spots" and the newer view of a "dynamic pain connectome"[25]. Implications of their concept are far-reaching – from basic theories of pain, to development of "pain-o-meter" type diagnostic tests, to establishing a therapeutic target for clinical pain management[26,27].

Author contributions

KDD and RC prepared the first draft of the manuscript. All authors (KDD, MCB, GI, KSL, and RC) were involved in the revision of the draft manuscript and have agreed to the final content.

Competing interests

No competing interests were disclosed.

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Apkar Vania Apkarian
Department of Surgery and Anesthesia, Northwestern University, Chicago, IL, USA

The correspondence by K. Davis and colleagues regarding the recently published study by Segerdahl *et al*. raises important and valid concerns regarding the conclusion of the paper. The issue is important as the report appeared in a high visibility journal, and the authors make the strong claim that they have identified a single "pain center" in the cortex. The latter has been a quest sought by many pain researchers since the advent of neuroimaging technology. Most importantly a lack of adequate statistical power and a proper control are the most obvious technical weaknesses pinpointed by Davis *et al*.. Perhaps it would be informative to elaborate on this issue, specifically regarding how an underpowered study can lead into discovering a brain "specific center" for pain perception, the validity of which is doubted by senior scientists in the field.

Neuroimaging studies, whether based on BOLD or ASL, when attempting to identify brain activity relative to a task commonly first identify in each participant brain activity related to the task, average these patterns across all participants, and then use a set of statistical criteria to determine what brain areas are statistically significantly conveying information about the task. In the present study only one brain region passed the specific criteria used and thus we have a single brain area related to the task. Not surprisingly the area is the posterior insula. A brain region that 10 years ago was described to be most commonly observed activated area to any painful stimuli[1] and currently in a PubMed term-based meta-analysis, neurosynth (www.neurosynth.org), it is identified (together with the secondary somatosensory cortex) as the region with highest reverse inference probability (z-score > 13.0) for association with the term “pain”, based on 420 publications. Thus, there is good evidence for this region being involved in pain related studies, and in an underpowered study where high thresholds becomes necessary to identify brain activity it is not surprising that only this one region is identified. Additionally one fully expects that with increased power most of the extended set of brain regions identified in neurosynth, whether called ‘neuromatrix’ or ‘pain connectome’, would also be observed independent of the neuroimaging technology used (tip of the iceberg phenomenon). A simple analogy can be derived from astronomy. Modern telescopes provide us with a picture of the sky full of millions of stars and galaxies. However, even today if we look at the sky by a telescope manufactured by Galileo, or having an equivalent resolution, we will still only observe the handful of stars that Galileo was describing 450 years ago.

The other important issue of the paper by Segerdahl *et al*. regards the conceptual implications, an issue that Davis *et al*. mention and again is important to elaborate. In the effort of proving that pain is in and of itself a unique sensory system, a large number of pain scientists have espoused the notion of dedicated real estate in the cortex for pain. Yet, isolation of such a single region has the strong implication that the conscious, subjective, and affective perception of pain is all captured in this one brain area. The latter

implies the thought experiment of excising the region and placing it in a dish (perhaps also keeping all the tissue that connects it to the periphery), with which act we can claim to recapitulate pain consciousness in a dish, which seems absurd and inconsistent with modern theories relating the brain to perception[2].

Borsook's commentary on the problems associated with Segerdahl *et al*. publication is also very astute[3]. He points that the competition to publish in high end journals pushes the scientist into making more extravagant conclusions than even the author herself or himself actually does not trust. Yet ultimately responsibility rests on the peer review process, and the latter is not guaranteed to be full proof.

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I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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David Borsook
Department of Radiology, Massachusetts General Hospital, Boston, MA, USA

When Research Reports may be Painful - Open Discourse should Prevail

Karen Davis and coauthors, including notable researchers in the pain imaging field, including Robert Coghill and Catherine Bushnell [1], argue strongly against the concept reported in Nature Neuroscience by Segerdahl and colleagues [2]; a paper that has quickly proven to be highly controversial for many in the field. The Segerdahl report utilizes an MRI technique known as arterial spin labeling (ASL) to measure quantitative cerebral blood flow as a surrogate marker for neuronal activation [3], which in this case, was combined with a model of capsaicin application to the skin to induce a hypersensitivity to heat stimuli in healthy patents [4,5] as a surrogate model of allodynia in chronic pain.

Many of the arguments raised by Davis *et al*. relate to the validity of the Segerdahl report, and are of a technical nature. Hopefully, these technical problems can be easily addressed (e.g., in future experiments) or challenged by an understanding of the field and its limitations (as Davis *et al* so eloquently do - see First and Second Arguments in their paper). What is still unclear is why Segerdahl and colleagues, seem to have overlooked considerable prior work using ASL in experimental pain [6-8], post-surgical pain [9-11], and chronic pain [12-16]. There is also a noticeable lack of consideration for the

limitations of both the imaging technique and the experimental pain model [5], which itself in healthy volunteers, has some issues relating to reproducibility and its clinical relevance [4].

The concept of discovering or defining a pain specific area in pain patients has to be understood in terms of a long history searching for such an area to target with various therapeutic modalities, most notably, neurosurgery has led the charge. The evaluation of putative pain specific areas in acute pain models probably has little if any bearing on the clinical condition of chronic pain. More modern concepts of brain-wide integrative processes are now in vogue. Davis authors use the definition of "*Pain-Connectome* " [17] which while conceptually is not new, adds to the growing literature of Connectomics [18], and should help rid the often used and probably not useful concept or term '*pain matrix*' from use, given the modern understanding of brain networks.

At best, the Segerdahal contribution has raised a vibrant discussion in the field, at is worst it is setting the field back not only because of its purported methodological inaccuracy (as evaluated by Davis *et al.*), lack of acknowledgement of what has come before, perhaps being too enthusiastic about the results and therefore pushing a notion that is unlikely to be true – finding a single brain area that is a pain specific region. Publications in high impact journals such as *Nature Neuroscience* (http://www.nature.com/neuro/index.html) carry a great responsibility, since they can (and usually) contribute to a field moving forward, or in a few cases the field becoming 'stuck' because of potentially false concepts that then take time for any field to undo. Hopefully this is not one of those issues relating to how high profile papers may occasionally be problematic as previously commented on, for example: " *How journals like Nature, Cell and Science are damaging science*" (http://www.theguardian.com/commentisfree/2013/dec/09/how-journals-nature-science-cell-damage-scien). Having the finding being replicated in the context of chronic pain conditions will be interesting to observe; perhaps Segerdahl *et al*., have these in the planning stage. This is of particular importance since having reproducible data from chronic pain patients may provide important therapeutic opportunities.

What is still to be defined, through a more detailed connectomic understanding, is whether such brain areas may be important through integration of processes such as chronic pain with other brain regions, in remodeling or reconstituting normalization of brain circuits following treatment for chronic pain. Such a notion could perhaps be the real excitement of where the field is headed. A healthy discourse in science can only lead to further evolution in the field and should be open and honest. I believe Davis and colleagues have made such a contribution in their review of the Segerdahl paper.

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Competing Interests: No competing interests were disclosed.

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Version 1

Reader Comment 04 Sep 2015

Petra Schweinhardt, Faculty of Dentistry and Department of Neurology and Neurosurgery, McGill University, Canada

Many things said in the Nature Neuroscience article by Segerdahl *et al.* are correct – a huge body of literature supports the view that the dorsal posterior insular cortex plays an important role in the processing of nociceptive information and possibly, in the processing of the conscious experience of pain. At the same time, the criticisms noted by Davis *et al.* are equally justified – methodologically, the Segerdahl *et al.* study was not in a position to test 'a fundamental role [...] of the dorsal posterior insula' in pain, as claimed by the title of the article. In my view, the Segerdahl *et al.* study is an imaging study that, like previous ones, provides support for the involvement of the dorsal posterior insula in the processing of nociceptive stimuli. As already mentioned, this is in line with existing literature, including evidence from methodologies that allow more direct conclusions than neuroimaging, such as intracerebral stimulation (Mazzola *et al.* Brain. 2012 Feb;135(Pt 2):631-40). Other experimental approaches are needed to meet the objective to establish 'a fundamental role' of the insula in the experience of pain. Because the parietal operculum (including the posterior insula and S2) is the only cortical region that has been found to provoke the sensation of pain when stimulated (Mazzola *et al.* Brain. 2012 Feb;135(Pt 2):631-40), a key question is whether activation of this area is sufficient for the sensation of pain or if subsequent activation of other brain areas, as discussed by Davis *et al.* with the concept of a 'pain connectome', is required. This could be tested with a combination of cerebral stimulation and inhibition.

I conclude that the Segerdahl *et al.* study presents supporting evidence for a role of the dorsal posterior insula in nociceptive processing but that the approach taken cannot provide evidence for one of its main claims. Given the interest that neuroimaging generates in the general public, often paired with high levels of faith for the method, researchers, reviewers, and journals have a responsibility to present balanced views that aspire to be as close to the underlying truth as possible.

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