Cortex necessary for pain — but not in sense that matters

*Commentary on **Key** on Fish Pain*

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Abstract: Certain cortical regions are necessary for pain in humans in the sense that, at particular times, they play a direct role in pain. However, it is not true that they are necessary in the more important sense that pain is never possible in humans without them. There are additional details from human lesion studies concerning functional plasticity that undermine Key's (2016) interpretation. Moreover, no one has yet identified any specific behaviors that mammalian cortical pain regions make possible that are absent in fish.

Keywords: pain, sentience, neuroethics, cortical regions, affect, fish, mammals, vertebrates, consciousness, brain plasticity

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Key's (2016) target article, "Why fish do not feel pain" is the strongest yet in a series of recent papers arguing that fish are incapable of consciously experiencing pain. Key does an excellent job bringing a wide range of evidence from the neurosciences to bear on the challenging question of consciousness in other species. Nevertheless, I think his conclusion oversteps the available evidence and fails to address adequately the contrary evidence provided by lesions to cortical areas involved in pain in humans.

Key claims that the cortex is both "necessary and sufficient for the feeling of pain in humans." Before delving further into the evidence, it is worth noting that there are different ways in which a brain region might be "necessary" for the feeling of pain in humans. On one interpretation, when we say that "region X is necessary for pain" what we mean is that, at a particular point in time, if region X is prevented from performing its usual activities, pain will not be possible. But on a stronger notion of "necessary," saying "region X is necessary for pain" means that at *any* point in time for a human, if region X is prevented from performing its usual activities, pain will not be possible.

Like Key, I have argued that there is good evidence that certain cortical regions are necessary for pain in the former, weaker, sense of necessity (Shriver 2006, 2016). As Key notes, there is ample evidence from lesion studies — bolstered by single-unit recording, direct stimulation, and fMRI — that the primary somatosensory cortex, the anterior cingulate cortex, and the insula cortex all play a central role in humans' typical experiences of pain, and that interfering with their functioning will selectively impair aspects of painful experience. Since studies have shown that impairing these areas in other mammals results in behaviors that indicate a similar lack of pain (Allen 2005, Shriver 2006), I believe the argument for pain in other species is strongest when it is directed at other mammals, since they have the same core brain regions involved in the experience of pain as humans.

But although the argument is strongest for mammals in virtue of shared cortical areas, it is a mistake to conclude that other species lack the conscious experience of pain in virtue of lacking those same cortical areas. This is because, despite the fact that certain cortical regions appear to be "necessary for pain" at particular times for humans, lesion studies indicate that there are no cortical areas that are *always* necessary for the conscious experience of pain, even in humans.

To his credit, Key discusses all of the studies that provide the evidence supporting his argument. However, I believe he pays insufficient attention to important details of the studies that ultimately undermine his argument. Since I take it that it has been sufficiently established that new pains are possible even after lesions to the anterior cingulate cortex (Davis et al. 2014), and that both lesion studies (Ploner et al. 1999) and anatomical evidence (direct spinothalamic pathways to affective brain regions) show that the primary somatosensory cortex is not required for the unpleasantness of pain, I will focus my arguments on Key's discussion of the lesion studies involving the insula cortex, an important region involved in pain affect in mammals.

The two most discussed recent lesion studies involving the insula are those of Damasio et al. (2013) and Feinstein et al. (2015). Both examine patients with extensive bilateral damage to the insula cortex who report that they still experience pain. A natural interpretation of these results is that the insula is not necessary for the experience of pain in these patients. Key resists this conclusion, however, by arguing several points: (1) we can't be sure in any of the cases that the insula was completely obliterated, and other evidence has suggested that even highly damaged areas of the cortex can still play a functional role in cognitive processes; (2) two other studies by Berthier et. al (1987, 1988) have shown that damage to the insula does interfere with the experience of pain; (3) the authors failed to obtain fMRI evidence showing that the insula was not active during pain; and finally and most importantly: (4) even if the insula was damaged, other cortical regions were intact and might therefore still be necessary for pain.

Regarding (1) and (2), it is worth noting that Key is holding the Damasio et al. and Feinstein et al. studies to standards that are not met by the Berthier studies. All the patients with pain asymbolia described by Berthier et al. (1987, 1988) had unilateral lesions only (that is, lesions to the insular cortex in one hemisphere), whereas the more recent studies both involved bilateral lesions (lesions to the insular cortex in both hemispheres). The insula lesions in Damasio et al.

and Feinstein et al. were far more extensive than those reported in Berthier's studies. If it were the case that all lesions involving a certain amount of damage to the insula, or lesions to a particular subdomain of the insula, reliably prevented the experience of pain, that would be a strong argument for the role of the insula. What we are left with, however, is a much weaker and more complicated body of evidence: Sometimes damage to the insula interferes with the experience of pain, and sometimes even greater damage to the insula does not; it is not entirely clear what the explanation for the discrepancy is (but see below for one possible explanation). Thus, the insula lesion studies, considered together, do not seem to be strong support for the claim that the insula is necessary for the experience of pain.

As noted in (3) above, Key also criticized the Damasio et al. and Feinstein et al. studies for failing to use fMRI to confirm that the insula was not active during noxious stimulation. However, a study from Robert Coghill's lab (Starr et al. 2009) did just that, and in fact should clearly be included alongside the Damasio and Feinstein studies based on what was reported. The Starr et al. studies examined patients with unilateral lesions to the insula who were hence more like the ones in the Berthier studies than those in the recent studies involving more extensive damage. However, the researchers performed fMRI on the patients during noxious stimulation of the side of the body contralateral to the lesion and found that not only were the patients still able to report on both the sensory and affective components of pain during long-duration noxious stimulation, but the patients also exhibited "no detectable activity in either the contralateral or ipsilateral insular cortex" during brain imaging (p. 2690). Thus, the insula lesion study that did use fMRI during noxious stimulation confirmed that the insula was not playing a role despite the patients' reports of pain.

From this, Starr et al. concluded that "insular activation, although frequently observed in studies of pain, may not be necessary to elicit a conscious pain experience," (p. 2691). Moreover, they also noted that the dorsolateral prefrontal cortex and the somatosensory cortex showed increased activation in the patients with insula lesions and that this "may suggest increased burden on the remaining neural networks to process nociceptive information in the face of insular damage," (p. 2690). This suggests one possible answer to the previous question about why some patients with insula lesions lack aspects of painful experience while others do not: the brain can rewire after certain lesions so that processes that were previously performed in one brain region can later be performed in different regions. The differences in pain behavior between patients with insula lesions might be due to the fact that the brains of some of the patients with insula lesions have rewired in a way that allows other brain regions to process affective pain information. Thus, at a particular point in time, it may be true that damaging a person's insula would result in that person being incapable of feeling the unpleasantness of pain. However, it might also be true that, given enough time for the brain to adapt and reorganize, the person could later feel pain that is mediated by different brain regions that fulfill the role of the insula. The insula may thus be "necessary for pain" in the weaker sense, but not "necessary for pain" in the stronger sense — the sense that is more relevant to the question of whether animals without insular cortices could be capable of feeling pain.

Since the two areas that appear to have compensated for the insula damage in Starr et al. study are both cortical, this leads us directly to Key's final criticism of the lesion study responses: (4) that other cortical regions might be responsible for pain even when the insula is impaired. One could argue that even though no one particular cortical region is necessary for pain, it is nevertheless only cortical regions (or "structurally similar" regions) that are able to play the role in pain typically occupied by the insula. Key seems to endorse this idea when he writes that even if it were true that pain is possible with the loss of the whole insula, all this would show is that "the network of brain regions associated with pain can function when one, or more, of its nodes are lost." An alternative hypothesis, of course, is that since no particular cortical region is necessary for pain, non-cortical regions can play a role in non-mammalian species similar to the one that cortical regions play in pain perception in mammals. How can we decide between these possibilities?

My suggestion is to examine whether there are any behaviors that cortical pain regions enable that are not present in other, non-mammalian species. Many nonhuman studies of pain have been criticized for relying on measures such as paw withdrawal, tail flicks, and vocalizations that do not appear to require the conscious experience of pain; these studies have had a poor track record predicting the clinical efficacy of various analgesics (Vierk et al. 2008). Many researchers have accordingly argued that better predictions of human pain can be found using conditioned place aversion tasks, which require the animal to learn to avoid areas associated with painful stimuli (Vierk et al. 2008, Roughan et al. 2013, Gregory et al. 2013). These findings have been crucial for understanding the significance of various cortical areas in painful experience; just as humans with lesions to the anterior cingulate or insula cortices or those given certain doses of morphine will report feeling pain but no longer finding it unpleasant, mammals with lesions to these areas who are given opiates will still show some pain behavior but will no longer choose to avoid areas where they previously received noxious stimulation (Shriver 2015). Thus, conditioned place aversion appears to be one of the best measures of pain behavior in nonhuman animal models.

Of course it would be a mistake to assume that there's something magical about conditioned place aversion that facilitates conscious experience, but we can further drill down by noting that certain forms of aversive conditioning appear to require conscious awareness while others do not. Clark and Squire (1998), for example, found that trace conditioning required conscious awareness, whereas delay conditioning did not (Allen 2004). A recent paper by Descalzi et al. (2012) found that the synaptic potentiation of the anterior cingulate, one of the crucial cortical areas involved in pain affect, mediated trace conditioning in response to noxious stimuli.

So where does this leave us with regard to the previous two options? Birds, reptiles, and fish are all capable of conditioned place aversion. Given that (1) the best model we have for pain in nonhuman mammals involves a behavior that is shared with fish and that (2) no other behaviors appear to be made possible exclusively by mammalian pain circuitry, I suggest that this pushes us toward the interpretation that other brain regions can and do play the same role in non-mammalian species that the cingulate and insula play in mammals. Unless we think that the conscious experience of pain is epiphenomenal (i.e., causally superfluous), a strong argument

would be needed to show that conscious pain makes certain behaviors possible in mammals that are not possible in other species.

Of course, the cingulate and insula are involved in some processes in mammals that have no equivalent in other species, and Key makes the case that neural structures that enable signal amplification and global integration are required for consciousness. But since there is certainly no deductive argument that can take us from signal amplification or global integration to qualia, the claims about their importance are based primarily on research correlating them with self-reports about conscious experience. But even these correlations (as Seth, 2016, notes in his commentary) do not seem to be as robust as was originally supposed. Moreover, *when it comes to pain specifically*, it does not appear that these brain regions are making possible any particular form of behavior that is unavailable to other vertebrates. Given the adaptive importance of avoiding life- and tissue-threatening features of the environment, it certainly would be strange if the ability to experience injury consciously as pain resulted in no new behavioral responses to injury.

Perhaps there are important properties of the brain regions that mediate conditioned place aversion and other pain behaviors of non-mammalian species that would lead us to conclude that these are fundamentally different processes in mammals. But we currently do not know anything about those mechanisms that would warrant such a conclusion. Given the similarity of behavior, and the lack of a clear, unique role of cortical processes in pain, I think the evidence currently points to the (cautious) conclusion that cortical areas involved in pain, though necessary in one sense, are actually elaborations of similar processes in other species, rather than processes that should be thought of as fundamentally different in kind. As such, there is no reason to believe particular cortical regions or indeed the entire cortex to be necessary for pain in the sense that really matters.

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