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Commentary

All roads lead to the insula

The multidimensional concept of pain, as proposed by Melzack and Casey [24], has stood the test of time, as well as that of rigor of the scientific method [25]. The concept of pain as a multidimensional experience has been described in ancient texts, dating as far back as the Syriac Empire (ca 200 BCE) [5]. The current definition comprises 3 dimensions: the sensory-discriminative (intensity, location, quality, and duration); the affective-motivational (unpleasantness and the subsequent flight response); and the cognitive-evaluative (appraisal, cultural and/or religious values, context, and cognitive state). Although these 3 dimensions interact to form the pain experience, they are experimentally dissociable [27,28], which allows the investigation of the unique neural underpinnings of individual dimensions.

As of yet, no study has demonstrated that any single brain area is both necessary and sufficient to elicit the pain experience. As Marshall suggested, S1 (and likely other cortical regions) receives and processes nociceptive input (likely sensory-discriminative information) [22]; however, this is not the region where the nociceptive input is perceived as pain; rather, this information is processed and "sent" to other brain regions where the percept of pain occurs. To address this point, Melzack suggested that a network of brain regions working together is required for the percept of pain [23]. This pain "neuromatrix," as he called it, can account for the multidimensional experience of pain. This theory proposed that to have a conscious experience of pain, many brain regions, each related to a dimension of pain, are required. For example, the sensory–discriminative dimension of pain has been associated with somatosensory areas, such as the primary and secondary somatosensory cortices (S1, S2) and the posterior insula [17]. The affective–motivational dimension has been associated with the insula, the cingulate and other limbic regions; the cognitive–evaluative dimension has been associated with the prefrontal cortices, the cingulate and the insula [31]. However, no single dimension is sufficient to elicit a painful experience. This theory provides an explanation for the finding that stimulating a single brain region does not consistently produce pain. However, the concept of the so-called "pain matrix" idea has been discredited, and other theories about cortical brain regions have been postulated (for a review, see Davis and Moayedi [9] and Farmer et al. [14]).

Thus, a fundamental question that remains in pain research is to elucidate how and where these various dimensions converge and are integrated to elicit pain, sometimes referred to as the *binding problem*. One brain region that is commonly associated with all of the dimensions of pain is the insula—and for this reason, among others, it has been proposed to be the site of pain integration.

The insula is a very large, heterogeneous region implicated in a variety of functions. It comprises 2 long sulci in the posterior portion, and 3 short sulci in the anterior portion [1,2]. The insula can be divided into 3 subregions: the anterior, middle, and posterior insula, based on functional and anatomical features [2]. Several studies have found that the insular subregions have differential structural and functional connectivity [6,10,19,26,30,32].

The paper by Wiech et al. [33] investigates the structural and functional connectivity of the 3 insular subregions to pain-related brain regions. The study confirmed previous findings that the 3 subregions showed largely congruent patterns of connectivity, but with some notable differences between subregions and pain-related regions. Specifically, the investigators found that the posterior insula had greater connectivity to somatosensory regions—and is thus likely related to the sensory dimension of pain; the anterior insula had greater connectivity to the ventrolateral prefrontal cortex, and is thus likely related to the cognitive–motivational aspects of the pain experience. Further support for this comes from the investigators' finding that structural connectivity between the anterior insula and the amygdala was positively correlated with pain vigilance and awareness, whereas anterior insula–rostral anterior cingulate cortex structural connectivity was negatively correlated with pain vigilance and awareness. Interestingly, rather than having a unique connectivity pattern, the mid-insula was connected to both somatosensory and prefrontal regions. The authors speculate that the differential connectivity may be related to the different roles of the insular subregions in pain perception, that is, the various dimensions of pain. The study did not, however, investigate measures uniquely related to the other dimensions of pain.

A number of theories about the role of the insula in pain perception have been postulated. For instance, Coghill et al. reported that the insula responds in a graded fashion to increasing intensity of noxious stimuli, suggesting that it encodes pain intensity [7]. Brooks and Tracey suggested that the insula is a multidimensional integration site for pain [4]. An alternative hypothesis about the role of the insula proposed by Craig [8] suggested that the mid-posterior insula was a multimodal homeostatic or interoceptive area. The former hypothesis maintained pain as a separate modality, whereas Craig's hypothesis established pain as a subset of homeostatic function. Garcia-Larrea has posited that the posterior insula is akin to tertiary somatosensory cortex (S3), which receives direct input from the spinothalamic system and produces pain through network interaction with other brain regions [16]. Baliki and colleagues have posited another hypothesis suggesting that, in addition to integrating the dimensions of pain perception, the insula is a central, multimodal magnitude estimator and a nociceptive-specific magnitude estimator [3]. The findings in the

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Wiech et al. study support the concept that nociceptive information is processed serially along the insula, along the posterior–anterior axis, each segment related to a different dimension of pain, and becoming fully integrated in the anterior insula. Recent findings by Frot et al. support this model [15].

However, there are some notable problems with many of these interpretations: (1) The anterior insula has been implicated in a multimodal sensory stimulus salience detection network, where salience stimuli are encoded and processed to appropriately orient attention [11–13,21]. It is also one of the most commonly activated brain regions across *all* neuroimaging studies [34]. Given that pain is inherently salient, it is possible (or more likely) that the processes encoded in the insula reflect the salience of the stimulus. (2) There are other multimodal regions in the brain that are related to the various dimensions of pain (eg, the cingulate cortex) [18,20,29]. Thus, future studies will need to investigate how insular connections contribute to the experience of pain and its various dimensions, and parse these responses from generalized salience-related responses.

Conflict of interest statement

The author is aware of no conflicts of interest regarding this commentary.

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