Is the Insula the "How Much" Intensity Coder?

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The perception of all sensations includes some sort of magnitude estimate used to calibrate behavior. However, it is not known whether unique intensity coding mechanisms exist for specific modalities or whether a common, centralized magnitude estimator operates for all sensations. Here, we discuss findings regarding pain intensity coding and the role of the insula in pain in light of the recent article by Baliki and colleagues that proposes the insula as a multimodal magnitude estimator.

In a recent article published in *Journal of Neurophysiology*, Baliki and colleagues (2009) adopted an innovative approach to search for a magnitude estimator (magINS) in the brain. Toward this goal, the authors used functional magnetic resonance imaging (fMRI) to examine brain responses to a visual task and to painful stimuli. Herein lies the *pièce de résistance* of the article: the psychophysics used in the article relies on the postulation that the amount of information perceived—in this case visual magnitude and pain intensity—is equivalent to the variance of the stimulus magnitude ratings. The authors state that a functional network that correlates to both the variance and the ratings of a given stimulus would represent a magnitude estimator of stimulus modality. Further, using tract tracing of white matter in the brain, the authors elucidated a structural basis for their functional data. Their findings contribute to two different and ongoing debates among pain scientists: the first is the issue of whether there is a specific region of the brain that is responsible for intensity coding of pain and the second is the more hotly debated issue of the role of the insula in pain perception. Here, we present some of the key concepts for each of these debates and discuss how the central magnitude perception regions presented by Baliki and colleagues correspond with these other ideas.

Intensity coding

All sensory modalities, including pain, require a magnitude estimator to evaluate the appropriate response. Classically, each system was believed to have its own intensity coding mechanism. Baliki et al. (2009) suggest that because different systems share this feature, perhaps a common brain structure has evolved to undertake the task—that is, that there is a central, multimodal magnitude estimator. The question, in essence, Baliki and coinvestigators address in their study—"Is there a 'how much' region of the brain?"

The concept of a region that codes pain intensity in the brain is by no means novel. There is converging evidence from several studies of intensity coding in the pain system that all dimensions of pain gauge the intensity of their relevant dimension of the stimulus. For instance, the intensity of pain is thought to be encoded in the so-called sensory-discriminative pain pathway that includes the primary and secondary somatosensory cortices (S1, S2) (Treede et al. 1999), whereas the unpleasantness of a noxious stimulus is thought to involve other areas in the pain pathway underlying affect, such as the anterior cingulate cortex (ACC) (Rainville et al. 1999).

Although there is contradictory brain imaging findings concerning the role of S1 in human pain perception, animal studies have irrevocably shown the involvement of S1 in nociception. Electrophysiological studies in S1 have demonstrated a somatotopic organization, correlation of neuronal activity with the duration and intensity of noxious stimuli, and correlation with the perceived stimulus intensity (Kenshalo et al. 2000). In contrast, Baliki and colleagues (2009) do not show S1 activation in the acute pain paradigm, although S1 is later used as a seed region for the white matter tractography analysis. A caveat of the paper is that they used classical pain regions to determine connectivity in the brain, despite the lack of S1 activation in their functional analysis. Further, if S1 is both functionally and anatomically connected to a nociceptive magnitude estimator—and is indeed a pain region of the cortex—then the lack of S1 activation is perplexing and casts some doubts on the pain paradigm of the study. Similarly, the authors fail to identify the ACC as a region of pain intensity coding.

Several imaging studies in humans have found that the activation of S1 and that of other cortical areas seem to be graded with intensity of experimental pain. For example, Porro et al. (1998) identified cortical areas with temporal profile changes that correlated with perceived pain intensity using fMRI. They identified areas showing activation graded with noxious stimulus intensity, specifically S1, supplementary motor area (SMA), primary motor cortex (M1), and ACC. Similarly, Davis et al. (1997) showed that the ACC activations were graded to painful stimulus intensity. Subsequently, Coghill and colleagues (1999) reported stimulus-evoked increases in regional cerebral blood flow that correlated with pain intensity in the insula ACC, S2, S1, and—similar to the findings of Baliki et al.—the ipsilateral anterior insula and ventral premotor area (VPC). Coghill and colleagues propose the redundancy of intensity coding may provide a compensatory mechanism to maintain pain intensity coding in lieu of neuronal loss or brain lesions. In addition, strong evidence for S1 as a pain intensity coding area comes from the fMRI study by Moulton et al. (2005), showing that S1 was particularly sensitive to changes in stimulus intensity compared with that of other regions. Moreover, Rainville et al. (1999) used hypnosis to manipulate the perception of pain intensity and unpleasantness and found that S1 and possibly S2 responses coded pain intensity, whereas the ACC was strongly correlated with the unpleasantness of pain perception. They further state that the ACC may also encode some intensity information, although it is more closely related to affective magnitude rating. However, it is

noteworthy that this study has not yet been replicated. It has been shown that pain intensity and pain affect ratings are strongly correlated (Rainville et al. 1992). Taken together, these findings show that a number of regions code for magnitude relevant to their dimension—e.g., S1 activations correlate with pain intensity and ACC activations correlate with pain unpleasantness.

In Baliki et al.'s study, the subjects perform a pain-rating task and a visual-rating task. The authors identified the bilateral VPC, the posterior parietal cortex, the dorsal premotor cortex, the SMA, and the insula as regions in which activity correlates with variance of both tasks. According to the basic tenet of the study, these regions form a bimodal functionally connected network that encodes the *amount* of information perceived or, simply put: the perceived intensity of the stimulus. To further assess the function of these regions, the areas are discriminated based on whether they code for magnitude or variance: the activity of each region was correlated to magnitude ratings, although they did not correct for multiple comparisons. The authors found the insula and VPC as the regions of bimodal magnitude estimation. Also a second network specific to pain intensity coding is identified. They provide further evidence for this finding by showing functional connectivity of these regions with areas commonly activated in acute pain paradigms, including S1. The insular subregion of the nociceptive-specific magnitude estimator has a shorter latency than that of the bimodal magnitude network. The authors provided evidence toward an integrative role for insula in pain perception by demonstrating that the regions are connected, both anatomically and functionally, to sensorimotor regions, basal ganglia and amygdala. Thus the authors have identified two areas that they propose are magnitude estimators in the brain: a bimodal one and a more-rapidly responding pain-specific one.

The findings of Baliki et al. (2009) are compelling. However, there are issues related that are inherent to the finger-spanning rating method for this type of study, especially considering that the regions that correlated with the variance of both rating tasks subserve sensorimotor functions. The rating task requires error prediction of value estimations of the stimulus magnitude. This concept has recently been described in the neuroeconomic literature and is attributed to a subregion of the insula (Preuschoff et al. 2008). Parsing error estimation from magnitude encoding is very difficult. Thus the magINS network identified may, in reality, function as part of the magnitude prediction error network. Another possible confound is that the findings may represent the motor planning and performance required to rate the stimulus using a finger-spanning device. Therefore the motor component (and its variance) may be the common feature of both tasks, rather than the stimulus intensity variance. To overcome such an obstacle a task-free finger-spanning paradigm could have been included to control for this artifact. Moreover, the authors did not test a stimulus with the same saliency as that of the pain task.

We suggest that an alternative method of establishing a multimodal intensity encoder would be to apply a paradigm requiring magnitude estimation in a number of different sensory modalities (e.g., loudness, image brightness, temperature, smell, and taste). In this type of fMRI experiment, subjects could be asked to focus on and rate the intensity/magnitude of a stimulus using a finger-spanning device, on the same scale (e.g., between 0 and 10). Because there would be a number of

modalities tested, the visual task could serve as a control for motor performance. Specifically, the rating magnitudes from previous modalities would be displayed on a screen and the subject would be asked to match the magnitude of these previous ratings using the finger-spanning device. The brain activity recorded during the control session would then be subtracted from the other tasks' hemodynamic responses. The conjunction of these different sensory modality paradigms could determine what common regions these ratings activate in the cortex, thus identifying a central magnitude estimator—should one exist.

Although Baliki et al. (2009) provide a complex framework to identify a general (or bimodal) magnitude estimator and a nociceptive specific magnitude estimator in the insula, there is an abundance of literature providing strong evidence that supports intensity coding in other regions of the brain—that is, S1. Therefore brain areas involved in pain perception each may have an intrinsic intensity estimator, which may provide necessary, albeit redundant, dimension-specific intensity information that can serve as a compensatory mechanism in case of damage to S1 (Coghill et al. 1999; Starr et al. 2009). Nonetheless, the findings suggesting an integrative role for the insula in pain perception are noteworthy.

Insula

The site of pain percept integration proposed by Baliki et al. (2009) is the insula. The insula (and S2) is consistently activated in pain paradigms. However, the insula is a very large region and receives a wide range of inputs from a number of sensory modalities, limbic, motor, and other brain areas (Augustine 1996). As such, the insula has been divided into anterior, mid, and posterior subregions, based on functional and anatomical features.

A number of roles of the insula have been postulated in terms of pain perception. Brooks and Tracey (2007) postulated that the insula is a multidimensional integration site for pain. In this perspective, the insula integrates the many dimensions of pain perception and serves as a gate of behavioral outcome. Alternatively, Craig (2002) suggested that the mid/posterior insula is a multimodal homeostatic or interoceptive integration area. Although these ideas are similar, the distinction of one being a homeostatic area, whereas the other is a multidimensional pain integrator is key: one establishes pain as a subset of homeostatic function and the other maintains pain as a separate modality.

Apkarian's group, specifically in the Baliki et al. study, suggests a new role for the insula, in addition to that of an integrator of pain perception. Because of its multimodal input (Augustine 1996) they suggest that the insula is the ideal site for a central magnitude estimator. In line with Coghill's finding (Coghill et al. 1999) that the insula encodes pain intensity, Baliki et al. (2009) show that the insula can be parcelated into a multimodal magnitude estimator (magINS) (albeit they tested only two modalities and thus bimodal is a more appropriate appellation) and a nociceptive-specific magnitude estimator. The magINS is the hub of a cortical network of regions, whereas the nociINS is a node of a subcortical network. The magINS is, in essence, a salience detector. Similarly, a study by Downar et al. (2001) established a multimodal sensory stimulus salience detection network, which included the tem-

poroparietal junction, the ACC, the inferior frontal gyrus, and, most interestingly, the right anterior insula. However, in a later study by Downar et al. (2003), the insula showed differential activations to a sustained painful task versus a sustained nonpainful task, suggesting that the insula may be involved in both salience detection and pain per se. In a recent study, Mouraux and Iannetti (2009) showed that areas believed to encode sensory stimulus magnitude in the brain may in fact be coding salience and reorienting attention appropriately. Further work is required to properly disentangle pain perception and salience detection in the insula. The study reported by Baliki and colleagues falls prey to this conundrum: because the study fails to appropriately control for salience we cannot conclude that the nociINS identified therein is not simply a node of the salience network.

As mentioned earlier, studies have found that the insula is implicated in the sensory-discriminative aspect of pain perception. Furthermore, a number of imaging studies have demonstrated that the posterior operculoinsular complex responds to peripherally applied noxious stimuli and codes for both intensity and location of the stimuli (for a review, see Peyron et al. 2002). In corroboration with these findings, Afif et al. (2008) showed that the middle short gyrus of the insula is involved in pain perception: stimulation of this region is one of the only regions of the cortex that will elicit a painful sensation in the periphery.

In a more recent examination of patients with insular lesions, Starr et al. (2009) found that patients were still able to rate the magnitude of evoked acute pain. However, the patients showed increased S1 activation ipsilateral to the insular lesion and contralateral to the stimulation, as well as increased pain ratings (hyperalgesia). Therefore the authors conclude that the insula may play a modulatory role in pain, that is to say, that with the loss of the insula patients developed unilateral hyperalgesia, attributed to a loss of descending pain modulation. Furthermore, the authors suggest that the insula may not be required for conscious pain percept and, even further, that there are a number of pain regions within the cortex that can compensate for one another, in case of injury or damage. This, they suggest, is the case with the increased S1 activation when the insula is absent. These findings, however, should be considered in light of the fact that the patients studied had suffered from ischemic strokes, leading to large unilateral lesions. These are neither exactly within a cortical region, nor are they limited to the insula. These findings suggest that there is redundancy in magnitude estimation in the cortex—i.e., both S1 and the insula are involved—and further support Coghill's theory of "backup" pain intensity coding areas (Coghill et al. 1999; Starr et al. 2009).

In conclusion, Baliki et al. (2009) offer a novel method to evaluate regions encoding the amount of information perceived by either a painful stimulus or a visual stimulus. Because of the novel approach to evaluating perceived stimulus intensity, we can expect that some of the findings differ from those of studies applying a more straightforward method—i.e., correlating stimulus intensity and cortical activations. However, a follow-up to their study could be to control for motor functions to extract the intensity coding regions without the possibility of a motor confound. Further, to support their findings, several other sensory modalities could be tested. Nonetheless, the commonality of certain findings, such as the insula, provides insight into this intriguing multimodal structure and its role in pain percept.

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