EDITORIAL

Pain Perception
Multiple Matrices or One?

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Acute or transient pain activates a large set of brain regions, including thalamus, primary and secondary somatosensory areas, insula, anterior cingulate cortex (ACC), and periaqueductal gray matter, areas collectively referred to as the *pain matrix*, with variable activation of striatum (dorsal and ventral), amygdala, and medial and dorsolateral prefrontal cortex (**Figure**).[1] Activity in areas of the pain matrix has been consistently observed in hundreds of studies irrespective of the modality used to elicit nociceptive input (eg, thermal heat, painful pressure, intramuscular injections, visceral balloon inflation), leading some investigators to propose that this matrix of regions mediates the conscious perception of pain.[2] In addition to the consistency of activation across studies, proponents of the pain matrix advance the argument that subjective reports of pain intensity correlate with neural response magnitude within some areas of the pain matrix, mainly insula and ACC, and suggest as a corollary that modulation of pain experience leads to a corresponding modulation of the neural response within the pain matrix. More recently, Wager et al[3] added strength to these arguments by showing,

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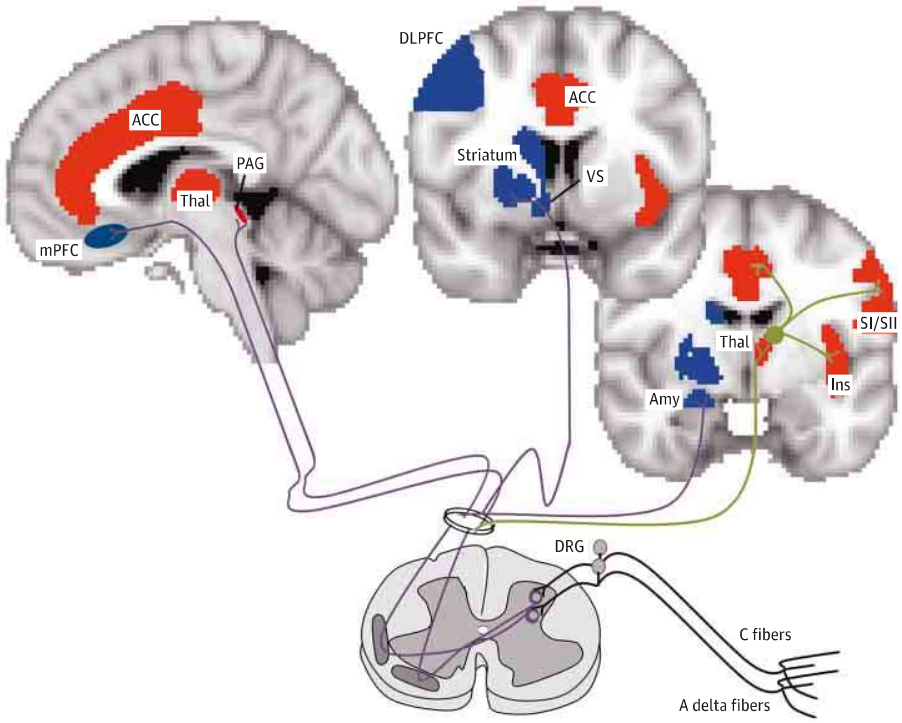
Figure. Brain Areas Activated by Painful Stimulation



Nociceptive input is relayed from peripheral C fibers and A delta fibers via second-order neurons in the spinal cord either directly (fibers shown in purple) to cortical areas like the medial prefrontal cortex (mPFC) or indirectly (fibers shown in green) via subcortical nuclei like the thalamus (Thal), the periaqueductal gray matter (PAG), the striatum (including the ventral striatum [VS] and the dorsal striatum), the amygdala (Amy), or the parabrachial nucleus (not shown). The thalamus in turn relays pain signals via direct projections to the primary somatosensory cortex (SI) and secondary somatosensory cortex (SII), insula (Ins), and anterior cingulate cortex (ACC). Brain areas shown in red collectively depict the pain matrix. Brain areas shown in blue are often activated during functional magnetic resonance imaging experiments in response to painful stimulation, although less consistently than the components of the pain matrix. Large areas of the prefrontal cortex are often activated in response to pain; the mPFC encodes the subjective value of pain and the dorsolateral prefrontal cortex (DLPFC) mediates executive control and decision making. DRG indicates dorsal root ganglion.

using a machine-learning approach, that a weighted pattern of brain activity within the areas presented in the Figure in red can be derived from one group of individuals and used to predict pain intensity in a new group or can differentiate somatosensory pain from nonnoxious thermal heat or the pain of social rejection. The pain matrix has therefore been considered sufficient to generate the conscious perception of pain elicited by peripheral nociceptive input via A delta and C fibers. However, serious challenges have been raised against this view. In a series of experiments using nociceptive, somatosensory, auditory, and visual stimuli, Mouraux et al[4] demonstrated that activation within the pain matrix is multimodal rather than pain specific, and they suggested that the magnitude of neural activation can be explained by the saliency of the stimulus independent of modality. Using evoked potentials, the same authors had previously demonstrated how the context of nociceptive stimulus presentation, eg, comparing repetitive monotonous stimuli vs novel stimuli, can decorrelate the brain response in ACC and insula from the perceived pain intensity, providing counterexamples to the concept of the pain matrix.[5] More recently, they showed that patterns of brain activity elicited in response to nociceptive, visual, tactile, or auditory stimuli derived from the noncorresponding primary sensory cortex, eg, response to pain derived from the auditory cortex or the visual cortex, is sufficient to differentiate between different types of peripheral input, including pain.[6] These results suggest that even the traditional view of primary sensory cortices, let alone large-scale matrices like the pain matrix, being specialized in processing information exclusively from 1 sensory modality has to be abandoned for a more multisensory or multimodal view.

In this issue of *JAMA Neurology*, Salomons et al[7] buttress this argument, presenting interesting data from 2 patients with congenital insensitivity to pain due to *SCN9A* loss-of-function mutations. Gene *SCN9A* encodes the $Na_V1.7$ sodium channel, which is preferentially expressed in peripheral neurons such as dorsal root ganglion (DRG) neurons. The channel regulates the threshold and acts at or near central synaptic terminals to facilitate synaptic transmission from DRG neurons to second-order sensory neurons within the spinal cord dorsal horn.[8] Gain-of-function mutations of *SCN9A*, which produce $Na_V1.7$ channels that activate more readily than wild-type channels, make DRG neurons hyperexcitable and thereby produce an excruciatingly painful disorder, inherited erythromelalgia.[9] Loss-of-function mutations of *SCN9A* conversely result in a failure to produce functional $Na_V1.7$ channels. This presumably results in attenuated or absent signaling from DRG neurons to the spinal cord in response to noxious stimuli, thereby producing a syndrome of congenital insensitivity to pain. Individuals with this disorder present a remarkable picture of painless fractures, painless burns, painless dental extractions, and painless childbirth.

In the study by Salomons et al,[7] the brain response to tactile mechanical stimuli was measured with functional magnetic resonance imaging (fMRI) and compared between the 2 patients and 4 age-matched controls. The stimuli presented to both groups were rated of equal intensity; however, only the control participants perceived them as painful. Interestingly, the 2 groups showed no difference in the magnitude of activation of thalamus, secondary somatosensory cortex, insula, and ACC, major components of the pain matrix, again presenting a challenge to the specificity of this network of areas in mediating pain perception. Salomons and colleagues present the findings as evidence of pain matrix activity without pain despite equal intensity of mechanical stimulation between the groups, and they call for caution in interpreting activity within the pain matrix as a reflection of pain perception without causal inference or more invasive animal work. Their results certainly add momentum to the criticism raised against the concept of the pain matrix. In fact, their demonstration of activity in the pain matrix without pain is in line with the observation that areas of the pain matrix are highly interconnected at rest, in the absence of any peripheral input, and form parts of one of the major resting-state brain networks.[1] Nevertheless, studies of patients with congenital insensitivity to pain pose several important challenges. We know, for example, that different individuals carrying the same $Na_V1.7$ variant (even within a single family) can present different pain phenotypes, possibly due to effects of modifier genes and/or epigenetic factors,[10] raising the question of whether additional patients with *SCN9A*-related congenital insensitivity to pain might display different patterns of brain activation when studied by fMRI. Second, it is likely that lifelong learning associated with nociceptive stimuli ultimately, along with many other genetic and social factors, shapes our pain behavior. Painful stimuli induce robust learning and memory formation[11]; patients with congenital insensitivity to pain presumably experience a reduced peripheral afferent barrage in response to noxious stimuli beginning in infancy and would be expected to lack the lifelong entraining of brain circuitry that shapes pain behavior in otherwise pain-sensitive individuals. Given the lack of pain-related learning, the pain matrix itself might be insensitive to pain, nevertheless responding normally to stimuli it receives from the periphery such as mechanical stimuli, while mediating a different function in a brain persistently faced with a different perceptual input.

This argument brings us back to the brain pattern predictive of pain perception.[3,6] To derive brain activity, Salomons and colleagues used a general linear model approach, which is sensitive to the magnitude of activation but not as much to the functional information exchange between different areas of the pain matrix or their individual weights in determining the perception of different sensory experiences. The network traffic within the pain matrix may have completely different properties in individuals insensitive to pain compared with those with a lifelong normal experience of pain. Both groups would still show brain response to stimulation within the same areas but experience different perceptions.

Recent findings from studies using fMRI in patients with chronic pain present further challenges to both views outlined. We have demonstrated stimulus-free brain activity within the pain matrix while patients with chronic pain rated their ongoing spontaneous pain.[12,13] Hashmi et al[14] showed that the brain correlates of spontaneous, stimulus-free back pain shift from areas of the pain matrix when pain is still subacute

(6-12 weeks' duration) toward an emotional circuitry encompassing the amygdala and medial prefrontal cortex as it becomes chronic (after 1 year). In addition, we recently assessed the effect of carbamazepine vs placebo on pain in 2 patients carrying an *SCN9A* gain-of-function mutation with fMRI. Our treatment was genomically guided by in vitro work pointing to a specific effect of carbamazepine on the mutated $Na_V1.7$ channel carried by both patients. Clinical pain improvement was observed with carbamazepine but not placebo and was accompanied by a decrease in activity of valuation areas involved in emotional and reward-related decision making, mainly ventral striatum and medial prefrontal cortex, without a change within most parts of the pain matrix except ACC.[13] Taken together, brain imaging data in chronic pain show that the pain matrix can be activated during pain perception without any outside salient stimulation; however, the same perception of pain, which persists unchanged from the subacute to the chronic phase, can correlate to activity in totally different brain networks. These observations suggest that the nature of the network activated with pain and responding to analgesic treatment depends on the chronicity of the experience, which could lead to new learning. In fact, Apkarian et al[15] recently showed that hippocampal neurogenesis in areas important to learning is necessary for the expression of pain behavior in rodents.

Although major progress has been made in the past 2 decades, we are still unable to understand how conscious perception of pain arises, especially since there is no specialized brain tissue responding specifically to nociceptive input, like the primary somatosensory cortex responds to touch. As Salomons and colleagues conclude in their article, methods relying on causal inference and pattern analysis will help advance the field. An understanding of conscious processing of pain also falls within the larger framework of understanding how conscious subjective experience arises in the brain, which is still incompletely understood.

ARTICLE INFORMATION

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