

It's All in Your Head: Context-Dependent Cortical Pain Processing in the Orbitofrontal Cortex

Pain is processed in a complex, hierarchical manner in the brain. Its variegated clinical manifestations, including poorly understood entities such as somatic symptom disorder¹ and chronic pain syndrome,² speak to this underlying complexity. Previous studies have demonstrated that processing of pain occurs throughout a “pain matrix,” including, among other areas, the cingulate cortex, insula, and thalamus.³⁻⁵ These regions encode an “absolute value” of the painful stimulus; in effect, they create a baseline neural correlate of the objective stimulus. Yet, subjective experiences of a given painful stimulus differ markedly not only between individuals but also within the same individual. The willingness-to-pay paradigm, which entails a theoretical monetary amount given by a subject to avoid a painful stimulus during a task, is an oft-used metric in neuroeconomic studies in studying this phenomenon.⁶⁻⁸ Its utility arises in determining a concrete value for avoiding a given painful experience: How much money will you give to stop the pain? Indeed, studies using willingness-to-pay to assess pain valuation have demonstrated that context is crucial when it comes to guiding behavior.^{7,8} Stimulus A, when experienced after stimulus B, may result in an entirely different behavior than if it were given after stimulus C. In their recent article in *The Journal of Neuroscience*, Winston and colleagues⁹ from University College London used a willingness-to-pay paradigm with functional magnetic resonance imaging (fMRI) in an attempt to disentangle the neural correlates of the contextual effect of pain processing. Specifically, they asked where the context of a painful stimulus is encoded and what its relation to the objective pain matrix is.

The authors used a task paradigm consisting of 1 of 3 possible painful stimuli (low, medium and high) and then allowed the subject to offer a certain monetary amount to avoid another

painful stimulus, as alluded to above. The subject was then shown what the “market value” of avoiding the stimulus was; only if that subject had offered more than the market value would he or she avoid a painful stimulus. The authors confirmed the established pain matrix by noting fMRI activation in conventional regions, including the cingulate, insula, somatosensory cortices, and thalamus. Consistent with previous studies,⁶ they found context-based differences in pain valuation (specifically, decreased sensitivity to a medium stimulus preceded by a high one compared with a medium stimulus preceded by a low one). Their important, new finding demonstrated that differences in valuation of painful stimuli reliably tracked with left lateral orbitofrontal cortex (OFC) fMRI activity after

analysis of variance and bayesian modeling (Figure, A and B). They found no similar effect of context of painful stimulus in any other brain region.

What this finding suggests is that there are multiple levels of pain processing in the brain, with earlier ones faithfully representing the objective properties of the stimulus (encoded by the pain matrix) and later levels modulating that representation to give meaning to the present stimulus in the context of recent stimuli. The latter representation elaborates how pain is being processed on a cognitive level and, ultimately, how it influences behavior. In fact, the authors found that increased propensity to health complaints in subjects was correlated with greater sensitivity to context of pain in the

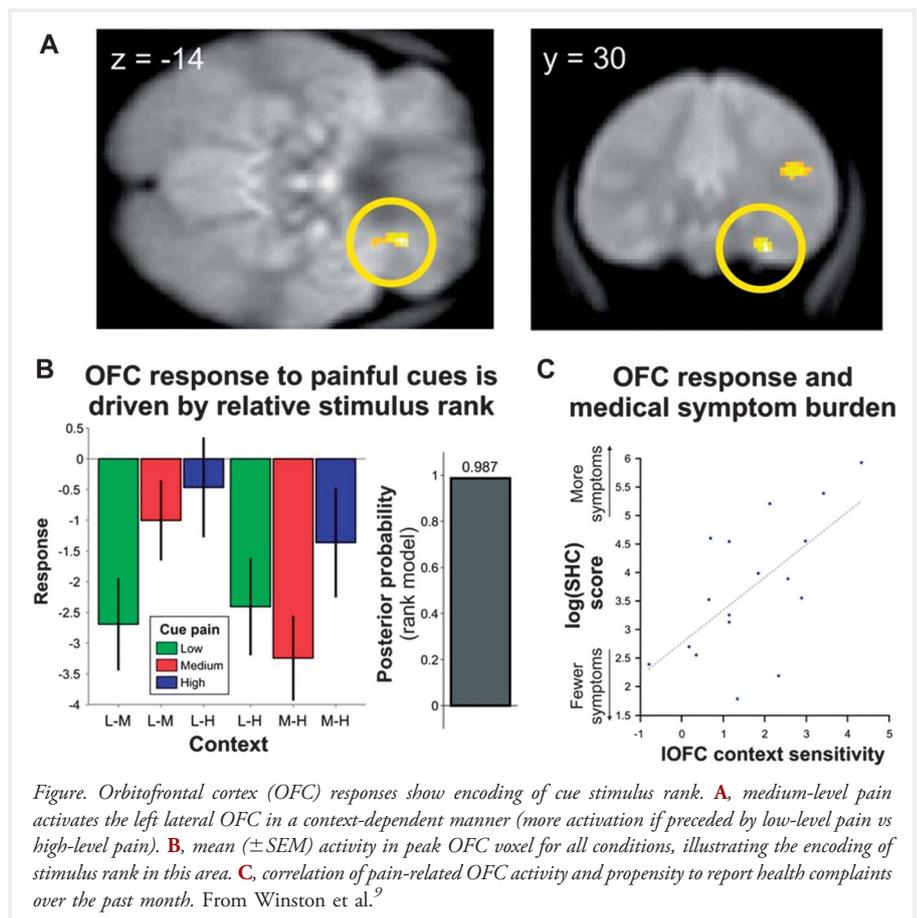


Figure. Orbitofrontal cortex (OFC) responses show encoding of cue stimulus rank. **A**, medium-level pain activates the left lateral OFC in a context-dependent manner (more activation if preceded by low-level pain vs high-level pain). **B**, mean (\pm SEM) activity in peak OFC voxel for all conditions, illustrating the encoding of stimulus rank in this area. **C**, correlation of pain-related OFC activity and propensity to report health complaints over the past month. From Winston et al.⁹

lateral OFC (Figure, C), suggesting a behavioral link to differential lateral OFC activity.

Along with processing of the context of pain in the lateral OFC, the authors found that bid value, ie, the amount offered to avoid another painful stimulus, was negatively correlated with activity in a region in the right OFC more medial to that activated contralaterally by the context of the painful stimulus. Distinct regions of processing for stimulus context and bid value could be linked by a pathway through which context-dependent pain processing influences bidding behavior. Although this potential pathway needs further elucidating, one can appreciate the influence that the context of pain has on the activity of different brain regions that ultimately govern specific behaviors.

From a clinical perspective, given the presence of an integrated, objective pain matrix and higher-order contextual processor, there is potential for a deficit to arise in the communication between these processes. In concrete terms, deficits would manifest as differences between objective stimuli and perceived symptomatology, similar to what might be seen in somatic symptom disorder or chronic pain syndrome. Specifically, the patient processes an objective stimulus (be it visceral, somatic, or neuropathic), but the higher-order cognitive representation of that stimulus is transmuted so as to be immensely problematic for the patient. Patients with somatic symptom disorder, with prevalence estimates ranging from 10% to 20%,¹⁰ may experience pain that does not respond to a long list of conventional medical therapies. For these patients, the lateral OFC may represent a target for therapy. Along with processing contextual correlates of pain as demonstrated by Winston and colleagues, the lateral OFC performs related higher-order functions such as the reception of integrated afferent sensory information¹¹ and the processing of alterations in expected outcome values.¹² Neurosurgically, the convergence of these higher-order functions in the lateral OFC presents a node with therapeutic potential for disorders such as somatic symptom disorder or chronic pain syndrome that possess troublesome, hard-to-treat cognitive components. Neuromodulation of the lateral OFC (and other associated nodes in the circuit as they are delineated) may thus provide logically defined therapeutic avenues for patients suffering from debilitating disorders who have exhausted all other options.

Saurabh Sinha, BS

*Rutgers-Robert Wood Johnson Medical School
New Brunswick, New Jersey*

Robert A. McGovern, MD

Sameer A. Sheth, MD, PhD

Guy M. McKhann II, MD
*Columbia University Medical Center
New York, New York*

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A Novel Vehicle for the Delivery of Exogenous Neurotrophic Factors in Spinal Cord Injury

The relatively permanent nature of central nervous system injury is a great scientific dilemma, specifically as it pertains to spinal cord injury (SCI). Over the

past several decades, significant advances have been made in the understanding of the pathophysiological mechanisms of SCI. Furthermore, the basic science literature is rife with promising studies investigating the effects of novel therapeutic interventions targeted to alter the disease process and to restore neurological function. Unfortunately, translating this progress into effective clinical treatment modalities has proved to be a major challenge and lags far behind. Despite the advances in basic science research, severe SCI continues to carry a poor prognosis with respect to restoration of neurological function and creates a major burden on our society.

As is the case for any disease process, to develop effective therapeutic interventions for SCI, it is first necessary to gain a thorough understanding of the pathophysiology of SCI. In broad terms, neurological recovery after SCI is impeded by a multitude of processes that occur both immediately after the injury and in a delayed fashion. Such processes include myelin-associated inhibitors, a paucity of neurotrophic factors, the inability of mature neurons to overcome inhibitory signals, and delayed formation of glial scar. No single process is responsible for blocking neuronal regeneration; therefore, effective therapies should be multimodal. Methods to promote neuronal regeneration range from genetic alterations and stem cell transplantation to administration of exogenous neurotrophic factors. However, the lack of feasible and realistic strategies for successful administration of these interventions in humans has limited their translation to clinical medicine.

In a recent article, Wang et al¹ explored the advantages and effectiveness of administering exogenous neurotrophic factors, specifically ciliary neurotrophic factor (CNTF), to promote neuroregeneration after SCI. The development of realistic application strategies for genetic and stem cell-based therapies, although potentially effective, is rather challenging. Comparatively, delivery of exogenous neurotrophic factors is theoretically less complicated. The authors have focused on the cytokine CNTF because dramatic increases in expression of CNTF after central nervous system injury have been detected and because it may play an important role in neuroregeneration. Simple injection of exogenous compounds generally leads to poor results owing to rapid diffusion, insufficient concentration at the site of injury, and systemic side effects. One solution to this dilemma involves implantation of a pump to deliver high concentrations of the desired cytokine to the injury site. Alternatively, the authors used sodium hyaluronate as a vehicle for sustained CNTF release by implanting gelatinous