Central Neuroimaging of Pain

Central neuroimaging of pain has emerged as an effective way to assess central nervous system correlates and potentially also to characterize mechanisms of human pain perception, modulation, and plasticity. Central neuroimaging has allowed us to open windows into the brain to observe the roles of attention, anticipation, fear/anxiety, placebo, direct control, and other factors. We now better understand the changes in the brain associated with chronicity of pain, the effects of opioids, and effects of nonopioid therapies. The benefits we have gained from using central neuroimaging clearly advance our scientific knowledge of pain. However, the authors of 2 articles in this issue of the Journal of Pain suggest that perhaps our use of neuroimaging overreaches in our attempt to address 2 important questions: 1) Does brain neuroimaging replace self-reporting of pain or will it do so in the future? and 2) Do central neuroimaging findings alone define pain as a disease? The authors of these articles make compelling arguments about the positive psychometrics and merits of using self-report; then, they outline the weaknesses of replacing self-report with central neuroimaging. Given their overriding premise that brain imaging should not replace self-report of pain, they argue quite effectively. I would, however, submit that their arguments are so forcefully presented that readers may lose sight of the real value of central neuroimaging—a way to augment self-report of pain and a potential, objective biomarker of pain and pain treatment.

Clearly we need to improve subjective assessments of pain and determine pain’s objective biomarkers. Even Robinson et al agree that pain self-reporting is not perfect. The beneficial idea that identifying a biomarker that correlates with self-reported pain is not a new one. Researchers have long sought to develop a physiology-based pain assessment that does not depend on self-report. They have focused on various biological signals, such as skin conductance, heart rate, and electroencephalography. Several physiologic-based measurements have shown statistically significant correlations with pain intensity or the presence of pain. However, no measure has provided a sufficiently high relationship with pain to be used as a valid surrogate for self-reports. Neuroimaging might be just such a surrogate.

However, we have many issues to address first. The first issue concerns the study subjects themselves. Almost all neuroimaging studies to date have studied subjects known to have pain (based on self-report) and attempted to determine the neural correlates of that pain experience. Until recently, no investigators have taken brain images and attempted to decode them to determine whether a person is experiencing either acute or chronic pain. Recent developments in applying machine-learning algorithms to neuroimaging have changed that situation. For example, multivariate pattern analyses (MVPA) can be used to...
decide perceptual states and intentions, opening up a new era of brain imaging to perform “mind reading.” Many reports describe using machine-learning approaches to determine what a person is hearing, seeing, planning, or even thinking.\textsuperscript{3,7,13}

Investigators are applying these functional magnetic resonance imaging (fMRI) MVPA techniques to pain research. Marquand et al\textsuperscript{12} recently used them to predict self-reported, thermally induced pain for each participant. In other words, for each individual, a machine classifier trained on that individual could discriminate whether that person was experiencing pain. More broadly, we have applied these techniques to show that a group pattern of brain activity can predict with 87% accuracy whether a novel individual (ie, someone not trained in the classifier) is experiencing thermally evoked pain or just heat.\textsuperscript{5} Of note, and contrary to the closing statement by Sullivan et al,\textsuperscript{23} our work was not meant to suggest that these techniques would substitute for self-report.

Most recently, we have extended MVPA techniques to classifying chronic low back pain with a resulting prediction accuracy of 76% for classifying chronic low back pain versus healthy matched controls.\textsuperscript{25} It is important to comment also that these studies were carefully controlled and do not presume that the same results would occur in typical clinical and less controlled conditions. Nonetheless, these studies are but the first in what is expected to now be a large number of applications of MVPA techniques to classify and predict pain. Future work will focus on classifying multiple pain states, determining the influences of psychological factors on pain detection, and classifying chronic pain and other comorbid conditions (eg, depression, anxiety, posttraumatic stress disorder, and addiction).

A second issue is the need to validate MVPA techniques as a biomarker or surrogate measure of pain. These techniques must establish both analytical validity (ie, to what extent do the techniques measure what they claim to measure) and clinical validity (ie, how well do the techniques, using standard statistical concepts such as sensitivity, specificity, and positive and negative predictive value, predict the presence or absence of pain).

Additional issues we must also address are the social and ethical implications surrounding use of these techniques, as tremendous potential exists for them to be misused by legal practitioners and medical payers. For example, simply look at the controversy over using MVPA for lie detection. Commercial entities (eg, http://www.noliemri.com/) already provide fMRI-based lie-detection services, a move that many say is premature. There is significant potential for commercial abuse of this type of technology—abuse that could have negative consequences for our patients with chronic pain.

This new field of neuroimaging-based pain prediction and classification is gaining significant interest in the research, commercial, and legal fields. We need to have thoughtful discussions among neuroscientists, psychologists, clinicians, and representatives from the legal community about this technology’s strengths and weaknesses, as well as when and how it should be used for pain applications. I suggest that the timing is right for our professional societies to develop one or more position papers on appropriate and inappropriate uses of this technology. We should start with a clear statement that these neuroimaging techniques should not replace self-report.

Sullivan et al close with “…the assertion that ‘objective brain images’ would greatly benefit measuring treatment efficacy involves magical thinking.” With this, I respectfully disagree. Brain imaging can and will greatly benefit our ability to measure treatment efficacy because it will provide richer information than self-report alone. Brain imaging will help us to understand 1) why some patients respond better to one treatment and not another; 2) why certain patients have side effects to some treatments and not others; 3) why some patients are placebo responders and others are not and how to distinguish the placebo response from the active treatment; and 4) what the targets should be for pharmacologic, stimulation, and psychological therapies. These ideas would indeed have been considered magical thinking several years ago. However, we are already seeing sophisticated MVPA techniques being successfully used for these purposes in other medical fields.\textsuperscript{9,10,14,17} Pain is next.

The Promise of Using Neuroimaging to Determine Pain as a Disease

In Sullivan et al,\textsuperscript{23} the authors are concerned that “…we believe that defining chronic pain as a brain disease on the basis of neuroimaging studies may have negative effects on 1) the therapeutic dialogue between clinicians and patients, 2) the social dialogue about reimbursement for pain treatments and disability due to pain, and 3) the chronic pain research agenda.” I will confine my comments to the first point for the sake of space.
The authors correctly raise potentially negative consequences for discussing neuroimaging and the concept of pain as a disease in the patient-clinician dialogue. However, I would submit that conceiving of many chronic pain conditions as a brain disorder or disease has been incredibly helpful in educating and empowering our patients with chronic pain. Simply look to all the women with fibromyalgia inappropriately labeled as histrionic and over-stressed housewives because science could not clearly identify a source of the pain in their muscles, tendons, ligaments, and joints. Central neuroimaging (and other research techniques) has now helped us identify fibromyalgia as a disorder or “disease” of the central nervous system with augmented peripheral facilitation and decreased inhibition. This knowledge has helped validate the experiences of millions of people suffering from this condition. A similar situation has occurred with patients suffering from complex regional pain syndrome.

Overall, I would submit that the advent of brain neuroimaging has only improved the clinician-patient dialogue. There is, however, a potential danger in using neuroimaging information to overpathologize chronic pain, by presenting it in a way that leads patients to think their brain changes are fixed or immutable. Fortunately, recently investigators have demonstrated that treatment of pain normalizes brain function and structure. This early research promises to further empower our patients with chronic pain. In the end, it will be up to clinicians as to how they use the information to educate patients and engage them in the therapeutic relationship. It is up to all of us to help education clinicians in what this neuroimaging information does and does not mean.

Finally, one of Sullivan et al’s primary premises is that neuroimaging changes in the brain do not define chronic pain as a disease. I would agree that we cannot look at neuroimaging in isolation and state that it defines pain as a disease. On the contrary, neuroimaging is but one way to capture growing evidence that chronic pain does, in fact, affect the whole organism. Neuroimaging proves that functional, structural, and chemical changes in the brain do occur in response to pain. There is also mounting evidence that pain causes disorders in the brainstem, the spinal cord, and peripheral nerve function. Additionally, in chronic pain there is glial cell disorder and impairments in immune, endocrine, and inflammatory functions. Taken together, these pieces of evidence argue that while pain can be a symptom of another disease, it can become a disease in its own right—a biopsychosocial disease that meets many definitions of disease, including one that the authors use in which a disease restricts the ability of an organism to function in its environment.

References


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