Commentary

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Advances in multivariate pattern analysis for chronic pain: an emerging, but imperfect method

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Brain imaging has substantially advanced our understanding of chronic pain. Many studies have investigated the structure and function of the brain in chronic pain and have identified abnormalities in various distributed sets of brain regions.[1,3,5] However, there are few, if any, patterns of abnormalities that have been identified that are specific to pain; the pattern of functional brain activity related to nociceptive processing derived by univariate statistical approaches can largely be accounted for by the salience content of the stimulus.[4,9,16] One potential reason for the lack of specificity of brain imaging findings of chronic pain could be that pain is thought to be an emergent property of network activity, and this cannot be captured or modeled by traditional univariate statistics. Novel sophisticated analysis methods can account for distributed patterns of activity. These multivariate statistical approaches are more suitable for the complex pattern of brain activity related to nociceptive processing and pain modulation, both in health and disease (for a review, see Ref. 15).

One complex, ambiguous, and heterogeneous set of chronic pain conditions is temporomandibular disorders (TMDs), comprising of pain in the temporomandibular joint and/or the muscles of mastication. Temporomandibular disorders represent the most common orofacial chronic pain disorder and are more prevalent in women. Several studies have now reported structural and functional brain abnormalities in TMDs.[12–14,20,21] There is some evidence that TMD may, in part, have a central etiology. However, there are no clear patterns of brain activity specific to TMD. Harper et al.[6] set out to investigate whether they could use multivariate statistical methods to distinguish TMD-related brain activity from that of an experimental pressure pain. Specifically, the authors used functional magnetic resonance imaging (fMRI) to image the brains of ten patients with myofascial-type TMD and ten healthy subjects, whereas they received experimental pressure pain on the temporalis muscle or on the thumb.

Multivariate statistics typically use algorithms to learn patterns of activity related to different states (machine learning) to make predictions of brain states. For example, an algorithm can be trained to differentiate between the pattern of brain activity elicited by a noxious stimulus, and an auditory one. Once the algorithm is trained, it is presented with patterns of either auditory or noxious stimuli, and it attempts to predict which modality is being presented. The challenge is to optimize the algorithm to increase its classification accuracy without rendering the classifier ecologically invalid.[7]

Several studies have used multivariate techniques–namely multivariate pattern analysis (MVPA) to search for "fingerprints" specific for acute pain processing[10,19] and for chronic pain conditions.[2,8,11,17,18] Although these studies usually have reported low-levels of specificity, such approaches are important as they have the potential to improve our understanding of the neural information processing of complex perceptions such as pain. For example, one important recent finding is that primary sensory regions in the cortex (which are traditionally believed to be unimodal) uniquely encode stimuli of all modalities.[10] This study highlights the potential of MVPA to uncovering the central mechanisms of chronic pain disorders, and, in the future, the development of biomarkers.

Harper et al. use MVPA to test 3 different questions about central processing of pain. First the authors compare an acute experimental pressure pain stimulus on the temporalis muscle (or the face) to rest (nonstimulus, baseline fMRI) scans. The algorithm could successfully differentiate acute nociceptive stimuli from rest in healthy controls, and from spontaneous pain in TMD. The regions that encoded these differences were regions typically activated by nociceptive stimuli. Notably, the algorithm performed poorer in subjects who rated their clinical pain higher. This finding is important, as it suggests that, although MVPA is sensitive enough to differentiate between acute and chronic pain processing, these processes have common neural substrates.

Next, the authors compared the ability of MVPA to distinguish between experimental pressure pain on the temporalis region and on the thumb. The algorithm successfully differentiated brain activity from these 2 stimuli in patients with TMD, but not in controls. This finding suggests that the brain pattern associated with nociceptive processing of experimental pain in the temporalis region is different than that of pressure pain in the thumb in TMD. In addition, the algorithm performed better in patients with higher levels of clinical pain, suggesting that the algorithm is sensitive to both the spatial pattern of the signal and the amplitude of the fMRI signal. In other words, pain evoked over

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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PR9 1 (2016) e580

http://dx.doi.org/10.1097/PR9.0000000000000580

the temporalis muscle has a greater signal than pain evoked on the thumb, either because of mechanical hyperalgesia in the temporalis muscle in TMD or because of the additive nociceptive drive between TMD and evoked pressure pain.

In a third analysis, the authors tested whether the algorithm could differentiate between patients with TMD and controls while they received evoked pressure pain on the face. The algorithm was only slightly better than chance. Together, these sets of findings demonstrate that, although MVPA was able to differentiate between sources of pain within patients, it could not yet be used to correctly classify patients from healthy, pain-free subjects.

In sum, the study by Harper et al. highlights that MVPA is an emerging technique with great promise in elucidating the central mechanisms of acute and chronic pain processing. However, the technique is still clearly limited. With the development of higher resolution brain imaging techniques, such as MRIs with higher field strengths, and the combination of different imaging modalities (such as EEG and fMRI), future MVPA studies could become invaluable research tools.

Conflicts of interest statement

The author has no conflicts of interest to declare.

Article history:
Received 7 October 2016
Received in revised form 24 October 2016
Accepted 27 October 2016

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