Neuroimaging: How Can Clues from the Brain Help Pain Management?

Magnetic resonance imaging (MRI) is routinely used in the clinical setting to identify pathologies. However, functional MRI (fMRI) can also be used to improve our understanding of pain mechanisms, develop objective measures of clinical pain and therapeutic outcomes (ie, biomarkers), and even predict treatment response.[1] fMRI research might act as a bridge between neurophysiologic studies and clinical findings, providing principled input for diagnosis, management, and treatment.[2] To succeed in that ambition, however, we must catalyze the growing awareness of these technologies to our colleagues "at the chalkface" in pain clinics. Exciting developments in orofacial pain and headache fMRI research are providing us with some key findings and new lines of investigation.

fMRI studies have focused on how the healthy brain responds to acute, evoked noxious stimulation in order to identify core pain perception circuitry. Thanks to these efforts, we now know that regions such as the brainstem and the hypothalamus include important hubs for endogenous pain control, and recent reports have described perturbations in these top-down modulation systems in chronic pain conditions. For example, brainstem functional connectivity and responses to noxious orofacial stimulation in migraineurs fluctuate throughout the migraine cycle, suggesting attacks are not solely caused by external triggers but also by endogenous factors.[3] Another good illustration is how fMRI has highlighted the role of the hypothalamus and midbrain in the generation of cluster headache attacks,[4] contributing to the development of efficacious treatments in the clinic such as midbrain deep brain stimulation.[5] Of course, one of the hallmarks of clinical pain is not just pain in use, but background pain that is ever-present and inescapable. Traditional evoked-response fMRI methods are poorly suited to studying ongoing pain, but in the last decade or so, alternative fMRI techniques, namely arterial spin labeling (ASL) fMRI and resting-state fMRI, have come to the fore to meet this need.[6] We have published several ASL reports of changes in regional cerebral blood flow (rCBF) in patients suffering from ongoing pain following third molar extraction surgery, a model commonly used in the development of novel analgesics as a means of initiating moderate to severe ongoing pain. We and other groups have demonstrated rCBF as an index of resting-state brain activity relating to ongoing pain, showing quantifiable changes in brain regions including the thalamus, insula, anterior cingulate, and somatosensory cortices.

ASL fMRI has allowed us to investigate ongoing pain pathophysiology and improve our understanding of the mechanisms of action of putative treatments, pharmacologic and otherwise. Using a randomized double-blind placebo-controlled design and an open method of drug administration, we provided new insights on the mechanism of action of treatment for postsurgical pain with ibuprofen. Ibuprofen treatment following third molar surgery produced increased rCBF in descending pain control circuitry, including the periaqueductal grey and rostral ventromedial medulla, and normalized rCBF values in brain areas previously associated with the representation of ongoing pain. Importantly, rCBF changes were unique to experiencing ongoing pain, as delivering ibuprofen to the same individuals when they were pain free resulted in no measurable effects on brain activity.[7] In another recent study on patients with cluster headache, we demonstrated treatment-induced rCBF changes following greater occipital nerve blockade.[8] Treatment responders showed relative increases in rCBF compared to nonresponders in the medial prefrontal cortex and lateral occipital cortex, but relatively reduced rCBF in the cingulate and middle temporal cortices. These differences between responder groups were visible prior to treatment, offering the enticing potential of predicting treatment response.

The question of whether fMRI techniques can help predict treatment outcomes for chronic pain is increasingly becoming a primary line of investigation. Moreover, recent efforts have focused on identifying early signs of risk of developing chronic pain pathology—awareness of early warning signs may have an effect on clinical decision-making, helping us to direct health care resources efficiently. Which patients will benefit most from surgery, pharmacology, and/or psychologic interventions? Resting-state fMRI studies have provided important insights as to how the way brain regions communicate with one another (their functional connectivity) differs in individuals with chronic pain, as brain systems involved in motivation switch away from attempts to escape pain to finding ways to cope and achieve pain relief. In an important 3-year longitudinal study,[9] changes in corticolimbic functional and structural connectivity between the nucleus accumbens, amygdala, and medial prefrontal cortex differentiated, at initial clinical presentation, between low back pain patients who

would recover and those who would ultimately transition to suffering from persistent pain. Investigating changes in brain connectivity is an active area for research, and already we know multiple brain networks beyond corticolimbic circuits are involved, including but not limited to descending control and medial temporal lobe systems.

Conventional analysis methods for fMRI data like the ones described above are limited to inferences from groups of individuals rather than the more desirable level of a single patient. However, multivariate machine-learning techniques do not have this limitation, bringing closer the possibility of personalized diagnostic, prognostic, and therapeutic predictions for pain. Early machine-learning pain reports have largely focused on predicting responses of pain intensity derived during acute pain experiences evoked in healthy volunteers.[10] But that landscape is changing, and these methods are starting to be applied to real-world patients experiencing intractable ongoing pain. Tonic pain classifiers are being developed and applied to clinical data that provide early indications that multivariate fingerprints derived from healthy volunteers may usefully translate to real-world pain patients. Predicting treatment response also shows early promise. A recent study evaluated patients with fibromyalgia, reporting that brain functional connectivity patterns used in a machine-learning framework differentially predict clinical response to pregabalin and milnacipran.[11] Nonetheless, we need more clinical data to refine these methods and these data, and the methods under development to analyze them should be shared to facilitate testing across institutions and laboratories. The OpenPain initiative in the US (https://www.openpain.org) and the new Advanced Pain Discovery Platform (https://mrc.ukri.org/research/initiatives/advanced-pain-discovery-platform-apdp/) are excellent examples of these pioneering endeavors.

In conclusion, available neuroimaging techniques have a promising future in early identification of brain pathology, particularly inflammation and following trauma. Neuroimaging offers relevant adjunctive information that can help in the clinic, but further efforts are needed from clinicians and research teams to ensure best use of these advances in our patients' care plans. Despite the excitement generated by these novel developments, we urge perspective. Pain is, and always will be, experienced by an individual. Neuroimaging measures can and should add value, but not attempt to replace our patients' subjective reports.

Sonia Medina, PhD(c)
Matthew A. Howard, PhD
Tara F. Renton, BDS, MDSc, PhD

References

1. Tu Y, Cao J, Bi Y, Hu L. Magnetic resonance imaging for chronic pain: Diagnosis, manipulation, and biomarkers. Sci China Life Sci 2021;64:879–896.
2. Kumbhare DA, Elzibak AH, Noseworthy MD. Evaluation of chronic pain using magnetic resonance (MR) neuroimaging approaches: What the clinician needs to know. Clin J Pain 2017;33:281–290.
3. Marciszewski KK, Meylakh N, Di Pietro F, et al. Changes in brainstem pain modulation circuitry function over the migraine cycle. J Neurosci 2018;38:10479–10488.
4. DaSilva AF, Goadbsy PJ, Borsook D. Cluster headache: A review of neuroimaging findings. Curr Pain Headache Rep 2007;11:131–136.
5. Nowacki A, Schober M, Nader L, et al. Deep brain stimulation for chronic cluster headache: Meta-analysis of individual patient data. Ann Neurol 2020;88:956–969.
6. Loggia ML, Segerdahl AR, Howard MA, Tracey I. Imaging clinically relevant pain states using arterial spin labeling. Pain Rep 2019;4:e750.
7. Hodkinson DJ, Khawaja N, O'Daly O, et al. Cerebral analgesic response to nonsteroidal anti-inflammatory drug ibuprofen. Pain 2015;156:1301–1310.
8. Medina S, Abu Bakar NAF, O'Daly O, et al. Regional cerebral blood flow as predictor of response to occipital nerve block in cluster headache. J Headache Pain 2021;22:91.
9. Tracey I. A vulnerability to chronic pain and its interrelationship with resistance to analgesia. Brain 2016;139:1869–1872.
10. van der Miesen MM, Lindquist MA, Wager TD. Neuroimaging-based biomarkers for pain: State of the field and current directions. Pain Rep 2019;4:e751.
11. Ichesco, E, Peltier SJ, Mawla I, et al. Prediction of differential pharmacologic response in chronic pain using functional neuroimaging biomarkers and a support vector machine algorithm: An exploratory study. Arthritis Rheumatol 2021;73:2127–2137.