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Insights for clinicians from brain imaging studies of pain

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In Kumbhare et al.(1), a selective review of brain imaging studies is presented that focuses on chronic pain. The stated aim of the review is to provide clinicians with information deemed important to the utility of functional and structural MRI to understand the brain abnormalities across the spectrum of chronic pain conditions. Towards this goal, the review provides an overview of MRI approaches and data from studies that have used these methods to study chronic pain. The authors then discuss the clinically important topic of how these methods have been used to study brain predictors of chronic pain chronification and treatment response. Overall, the review provides a good sense of what has been done in the field to demonstrate that brain abnormalities exist across a spectrum of chronic pain conditions, and notes some of the developments that are needed in the future to make neuroimaging have direct impact on patient care.

To identify the brain imaging studies that have been published to examine chronic pain, Kumbhare et al. (1) performed a literature search of papers published from 2000–May 2014 based on the key words “chronic pain” and “neuroimaging” and “MRI” and excluded “anecdotal, reviews, speculative and editorial articles”, animal studies, and studies with fewer than 4 patients. Many studies were we missed though because they included the general term “chronic pain” in the search, which excluded most studies on migraine and many studies by research groups who refer to specific pain conditions rather than “chronic pain” more generally. Furthermore, many studies that specify a method (such as gray matter, white matter, connectivity, etc.) were not captured because they did not have “neuroimaging” or “MRI” as a key word. Thus, the review is not a “comprehensive scoping review” as claimed because the very limited search terms used and timeframe restricted the review to only 78 published papers with the exclusion of several hundred relevant studies. We encourage authors of future reviews to cast a wide net using more and broader key words to ensure important studies are not missed.

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Conflict of Interest Statement

The authors have no conflict of interests to report.

Despite the limitation of this review to a selection of studies, some general trends and points of interest to clinicians can certainly be gleaned. Here, we highlight some points made in the paper as well as some additional important take away points for pain management clinicians.

1. Neuroimaging has taught us a lot about the brain in chronic pain, but individual variability means that these findings cannot be generalized across conditions

The first point to take away from the Kumbhare et al. (1) review is that there were no specific abnormalities in common across the studies, likely owing to the variability between studies, including differences in chronic pain condition, age, sex, and co-occurring symptoms and diseases. The authors conclude that there is general disruption of anatomical and functional brain networks across multiple chronic pain conditions, with varying types of abnormalities between studies. Even the finding that seemed to be the most consistent across studies, gray matter volume (GMV) decreases in chronic pain, was somewhat inconsistent, with some studies showing increases and others decreases. Widespread structural brain abnormalities with distinct patterns for different chronic pain conditions have previously been shown (2;3). Changes in GMV in sensory areas could either increased or decreased depending on the associated sensory loss (or gain) that may accompany some chronic pains. GMV changes can be further confounded by co-occurring disorders, age, and many other factors. Further discussion of these issues can be found in a review by Davis and Moayedi (3).

Individual and sex differences is a key issue to consider to understand the variability that clinicians no doubt observe first hand in their patients, how they cope with chronic pain and how they respond to different treatments. Kumbhare et al. (1) do note age effects in their discussion, but clinicians should be aware of how age can impact the assessment of gray matter. The age effect was not fully realized in early gray matter studies but the findings of Kuchinad et al. (4), Moayedi et al. (5), and Ceko et al. (6) brought the issue to the attention of the imaging community. The effect of sex differences is not always often fully considered in brain imaging studies despite chronic pain conditions being more prevalent in women (e.g., fibromyalgia, IBS, TMD) or men (e.g., back pain, anklyosing spondylitis).

Thus, it is important for a clinician to know that there is vast intersubject variability (including sex differences) in the general response to and coping with painful stimuli (7–10), brain circuitry and connectivity (10–14). To understand the brain structural and functional abnormalities for a given disease, we recommend referring to literature on that specific condition, rather than looking for commonalities across chronic pain disorders. For example, there are important anatomical considerations, particularly involving brainstem and subcortical brain regions that will be specific for the type of pain.

2. Neuroimaging can be used to assess structural and functional abnormalities, and the number of techniques and analysis approaches is growing

Kumbhare et al. (1) focused on studies examining GMV and pain-related functional MRI, but there are many other MRI techniques that have been used in chronic pain neuroimaging studies. It is often difficult to link together the results from different imaging modalities and analysis techniques across studies. The choice of analysis approach (e.g., voxel-based morphometry vs cortical thickness analysis; probabilistic vs deterministic tractography vs tract based spatial statistics), and metric used (e.g., fractional anisotropy vs mean/radial/axial diffusivity) not only impact the outcome of the study but also can provide insight into potential mechanism underlying the finding (e.g., cell type, plasticity, inflammation/edema, etc.). A discussion of such issues can be found in DeSouza et al. (15), Davis and Moayedi (3) and in Moayedi et al. (16).

Some methodologies are limited in the insight they can provide about a disease state. For example, the most common fMRI method to assess pain-related brain activity relies on the BOLD response. In chronic pain conditions there might be ceiling effects in BOLD because of an ongoing state of activation in nociceptive neurons. Percept-related fMRI was partially developed for this purpose and to identify brain activity related to the temporal pattern of pain rather than the timing of the evoking stimulus (see (3;17)). However, to avoid the ceiling effect more effectively, baseline BOLD activity can be assessed using resting state fMRI techniques (see section 3, below) and perfusion-based measures of cerebral activity, such as arterial spin labelling (ASL). ASL can measure baseline blood flow and thus can be useful for detecting differences in chronic pain patients and healthy controls at rest. However, ASL has lower spatial and temporal resolution than BOLD fMRI and has relatively lower signal-to-noise and high intersubject variability. Thus, most studies need to boost their ASL signal by having patients increase their pain (e.g., with a leg lift for back pain) which confound the chronic pain state (18;19).

3. Current pain neuroimaging research examines network connectivity, rather than identifying abnormalities in single brain regions

There is a vast literature that speaks to the mechanisms by which specific brain areas and their interactions and organization into networks and systems contribute to our pain experience. The Kumbhare et al. (1) review identifies many of the areas that are part of these networks, but their findings are complex and so it is challenging to extract the big picture. Thus, we feel that a few new overarching concepts may help to provide a useful framework. One emerging theme of late is the importance of dynamics in brain activity within a brain area (14) and dynamic functional connectivity between brain areas in shaping pain sensitivity and response during competing attentional demands (12) – findings that led to the concept of a “dynamic pain connectome” (20). Another concept concerns a basic pain “switch” that is the core of the feeling pain, aside from the associated sensory-discriminative, motivational-affective and cognitive-evaluative dimensions (21;21). These concepts are based a view that pain relies on the activation of and communication between

networks. In studies where an abnormality is identified in a single brain region, the bigger question is how that affects the function of the brain networks involved in cognitive, emotional, sensory, and motor processes.

4. Can brain biomarkers replace pain ratings?

Kumbhare et al. (1) state that “compared with self-reporting approaches, objective imaging techniques are expected to potentially lead to better pain management.” We find this statement problematic for several reasons. We argue that pain ratings are the best outcome measure we have for treating chronic pain and will likely always remain that way (imagine for example a patient who’s brain is deemed “recovered” based on our neuroimaging techniques, but still reports suffering intolerable pain most of the day). In addition, several other measures aside from neuroimaging, such as questionnaire data or psychophysical measures of pain modulation (22) have been shown to be predictive of treatment efficacy.

On the other hand, the use of neuroimaging as prognostic biomarkers and to guide treatment is an area that is growing and has great potential, such as to provide information useful for individualized treatment. That is, if, say, a patient shows abnormal structure or function in a circuit known to respond to a specific type of treatment, that treatment could be first-line for that patient. Thus, neuroimaging information could provide clinical outcome trajectories that could be assessed throughout an intervention. There are new analytical techniques driven by technological advances in machine learning that have now allowed researchers to predict – at least in healthy individuals – the intensity of pain an individual is experiencing, just by examining their brain activity (23). Research in this area is likely to continue and expand to chronic pain populations. The ethical and legal implications of this type of biomarker have been discussed elsewhere (24–31).

5. Time for translation

Kumbhare et al. (1) state that “one of the limitations of our study is that neuroimaging is currently still in its infancy with regards to its clinical applicability.” However, there is no reason that we cannot now begin to focus on translation given the new developments in neuroimaging and the wide availability of the technology used. In order for neuroimaging to have clinical utility, we need a conversation between clinicians and researchers about what technologies are available and what solutions are needed.

One promising ongoing direction in the field of pain neuroimaging, as Kumbhare et al. (1) point out, is in the development of prognostic biomarkers in studies assessing changes in either the transitions from acute to chronic pain or following treatment. We agree with this point and think this is where translation from basic research to clinical utility has the greatest potential. Studies such as those that have reported changes in corticolimbic connectivity and structure in subacute back pain that predict the transition to chronic back pain (32;33) point to brain circuits whose activity could be modified early to avoid the development of chronic pain. Treatment studies including surgery, anti-NGF, and cognitive behavioral therapy for various chronic pain disorders have indicated that many of the brain changes associated with chronic pain can be reversed (34–41). By pinpointing brain circuits that change during

effective treatment, new or improved existing therapies that target these circuits may be applied as novel interventions for chronic pain.

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