Recent advances and future prospects in neuroimaging of acute and chronic pain

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Keywords: allodynia, FM R1, functional, hyperalgesia, neuroimaging, pain, perception, PET

The advent of modern functional brain imaging has created new possibilities for exploring the brain mechanisms that underly acute and chronic pain. It is now possible to explore how specific aspects of the pain experience are represented in the brain and the impact of individual attributes on these representations. This review provides an overview of the capabilities of positron emission tomography and functional magnetic resonance imaging and their utility in identifying pain-evoked forebrain responses in both acute and chronic pain conditions. Also presented are sophisticated approaches to the design and implementation of such studies, with the ability to isolate cortical responses related to specific pain constructs, the complexities of interpreting hemodynamic-based responses in consideration of the underlying neurophysiology and the impact of imaging pain for diagnostic considerations. Finally, it is predicted that the ability to identify functional brain abnormalities will challenge classical boundaries between neurology, gastroenterology and psychiatry.

Pain is one of the most common patient complaints for the physician to address. Chronic pain can lead to great suffering and is also an enormous economic drain on society. Despite its impact, we only have a rudimentary knowledge of the mechanisms underlying pain, and much of what we do understand is based primarily on research in experimental animal models. However, over the last 15 years, modern neuroimaging has provided exciting opportunities to explore the basic central mechanisms underlying acute and chronic pain in humans. Early neuroimaging studies of pain used relatively simple methodologies and designs and established the capacity of these emerging technologies in the study of pain. These early results were primarily confirmatory, in that they identified pain-related activations in forebrain regions that, for the most part, had already been associated with the classical pain system. However, there were some surprising findings in these studies, such as pain-evoked activation in motor areas (e.g., the cerebellum and striatum) and emotional areas and inconsistent activation in the somatosensory cortex [1]. These findings set the stage for more recent studies over the last few years, in which there has been a transition to more sophisticated neuroimaging approaches for studying mechanisms of both acute and chronic pain. This review will summarize the main findings from these studies. In the future, neuroimaging may also be developed to assist with diagnostics and to test the effectiveness of analgesic therapies. Therefore, the review will focus on the innovative approaches in the design and statistical analysis of imaging data as they impact the future utility of neuroimaging for basic studies and clinical pain assessment and diagnostics.

Multidimensional nature of pain
Pain is defined as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' [2]. The pain experience is multidimensional, comprised of sensory-discriminative, motivational-affective and evaluative components leading to reactions to pain [3]. Thus, a pain experience can be described in terms of the pain quality (e.g., burning, shooting, throbbing or pricking), its intensity (e.g., mild, moderate or intense) and its perceived location on or within the body. Furthermore, this sensory experience is associated with attentional, emotional and motivational factors.

Prior to the advent of modern neuroimaging, knowledge of the central neural mechanisms underlying pain was based primarily on experimental studies in animals, with limited information regarding pain mechanisms in humans derived from psychophysical and clinical studies. The general framework derived from those studies is one comprising multiple nociceptive pathways, including a medial and lateral system. These systems are thought to subserve different types of pain perceptions. Figure 1 illustrates the main cortical areas implicated in pain and nociception, which include the primary and secondary somatosensory cortex (S1, S2), insula, anterior cingulate cortex (ACC) and prefrontal cortex (PFC) [4].
Over the last 15 years, modern neuroimaging technologies have provided opportunities to noninvasively investigate the mechanisms underlying different aspects of the pain experience, both in acute and chronic pain. Furthermore, neuroimaging also provides a window into the response of these systems to analgesic therapies.

Overview of modern neuroimaging techniques

The two most common techniques used to image pain in humans are positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). These techniques provide indirect measures of neuronal activity [5–8].

PET involves measuring the distribution of an intravenously injected radioactive tracer as it decays or binds to a receptor [9,10]. In pain research, the most popular type of PET application measures regional cerebral blood flow (rCBF) following the injection of H2O15. Blood flow studies provide an opportunity to assess both the resting (baseline) blood flow within brain areas of interest and also the response of those areas to a stimulus or task. Since PET can also measure receptor binding to specific radiolabeled ligands, it has also been used to investigate mechanisms of opiate analgesia (e.g., using radiolabeled remifentanil or carfentanil) [11–14]. Therefore, PET provides the unique opportunity to assess rCBF and opiates binding before, during and after a noxious stimulus. However, the invasive nature of PET (owing to the necessity of injecting a radioactive compound) imposes limitations on its repeated use in the same subject. This restriction, coupled with the relatively poor temporal resolution and high cost of PET studies, has contributed to the popularity of fMRI, a noninvasive, less expensive and more widely available technique with finer temporal and spatial resolution. Most fMRI studies use the blood oxygenation level detection (BOLD) technique [15]. This is essentially a method to identify differences in the ratio of deoxyhemoglobin to oxyhemoglobin between two conditions; for example, a nonpain versus a pain state. Both fMRI and PET rely on statistical tests to determine the location and magnitude of an evoked response in the brain.

Application of fMRI to the study of pain

Pain studies often employ mechanical, electrical or thermal devices to deliver experimental stimuli. Figure 2 provides an overview of some of the main features of a typical fMRI pain study. Usually, the stimulus is delivered in blocks of time at a predetermined intensity to evoke a particular amount of pain. The stimulus blocks are interleaved with either stimulus-free or control stimuli (e.g., a nonpainful stimulus) blocks of time. The imaging data are then interrogated to locate regions of statistically significant signal changes during the noxious stimulus blocks, compared with the rest or control stimulus blocks. In fMRI, a characteristic hemodynamic response function (HRF) describes the general temporal dynamics of a BOLD response to a brief stimulus [16]. The temporal profile of the stimulus is usually mathematically convolved with this HRF to create a predictor function. fMRI analysis software packages use this predictor function to locate areas of brain activation (or deactivation).

The simple block stimulus paradigm described was used in most of the early imaging studies of acute pain with fMRI, and in virtually all PET imaging studies of pain. The results demonstrated that the cortical areas classically considered to be part of pain networks (i.e., S1, S2, insula, ACC and prefrontal cortex), were indeed activated by noxious stimuli [17–19]. Soon after, more sophisticated neuroimaging approaches were developed to study the mechanisms of both acute and chronic pain. One important development was the use of a single epoch design [20,21], particularly in combination with the online pain rating (discussed later). The advantage of single epoch and short single trial designs is that subjects experience shorter pain stimuli which can be more tolerable. This design can also facilitate the perceptual assessment of pain after each stimulus. This type of online pain assessment is useful for following the temporal effects of analgesic agents [22,23]. Further enhancements in fMRI studies of pain include correlation analysis incorporating the context of the experiment (e.g., attentional state and anticipation period) or individual subject characteristics (e.g., personality factors and percepts) (Figure 2) and network analyses of connectivity among brain regions [19,24–26]. These approaches are imperative due to the individual variability in cortical responses to noxious stimulation [27–30].

As noted here, there are several ways in which information regarding pain experienced during the presentation of noxious stimuli can be considered in an fMRI study. After each stimulus, subjects can provide an overall rating (e.g., a number from 0 to 5) of pain experienced during the preceding stimulus. This provides some basic information regarding the subjective experience. However, this approach does not provide precise information regarding perceptions on a
second-by-second basis as they occur. Also, this approach requires the subject to remember their experience. These, and other considerations concerning the pain experience, led to the development of an approach called percept-related fMRI [31]. First, the pain experience (intensity, quality and affect) evoked by a noxious stimulus can be different from one person to the next. Second, the pain experience may consist of more than one quality of sensation, each presumably due, at least in part, to a specific cortical mechanism. Third, repeated noxious stimulation may invoke temporal summation or habituation so that perceived pain intensity changes over time. Fourth, in some situations (particularly in the case of pathological pain), the temporal dynamics of each evoked sensation may not coincide with the presence of the evoking stimulus. Therefore, to integrate this information into a fMRI experiment, it is necessary to acquire continuous online ratings of sensation during fMRI [31,32]. Thus, percept-related fMRI was developed to delineate brain activity, specifically related to particular qualities of pain rated by the subject continuously during acquisition of the fMRI data [31,33,34]. In a percept-related study, the predictor function used to interrogate the fMRI brain activity is created from the time course (and in some cases, magnitude) of the sensation of interest (Figure 2). This approach has been used successfully to identify forebrain activity related to prickle sensations (Figure 3) [31], paradoxical heat sensations in the insula [33], cutaneous pain intensity coding in S1 [35,36] and pain salience in the ACC, temporoparietal and inferior frontal cortex [37]. Percept-related fMRI has also been used in patients with chronic pain conditions, such as chronic back pain [38] and irritable bowel disorder [34]. Therefore, with percept-related fMRI, we can begin to parcellate brain activity related to a specific attribute from the general activity evoked by a stimulus, and look at specific modulatory effects of analgesic agents. The distinction between stimulus- and percept-related brain activity is important because repeated or prolonged noxious stimuli may produce temporal summation or habituation of the evoked percept. In addition, some of the stimulus-related activity may be related to nonconscious, homeostatic or reflexive activity and does not contribute to an actual sensation. Hence, future studies of targeted therapeutics will need to consider these factors. Many other factors inherent to an individual subject (e.g., personality factors) or experimental condition (e.g., attention vs distraction) can also be used as regressors in pain imaging studies.
example, two recent studies, one in fibromyalgia patients and one in healthy subjects, have identified pain-evoked cortical responses correlated to an individual's catastrophizing [39,40].

Several other emerging technologies warrant note here because of their potential utility in pain studies. The first variant introduces a pharmacological agent into the fMRI study [18] and, coupled with percept-related fMRI, can be useful to study the effects of analgesics [41]. The second is a group of statistical approaches to model cortical (and subcortical) networks [42,43]. Functional and effective connectivity analyses provide an insight into how brain areas are functionally connected and affect each another [44-46]. These approaches have clear applicability to pain studies [24]. In one recent study, it was demonstrated that hypnosis to induce analgesia modulated the functional connectivity between the ACC and several cortical areas during noxious stimulation [47]. Functional connectivity may have great utility in the future to identify abnormal cortical resting activity (default mode) in chronic pain patients [48-50].

Extracting abnormal patient responses
Brain imaging can be used to identify abnormal pain responses in experimental models of pain and hyperalgesia and also in patients with various types of chronic pain. Nociceptive pain is defined as 'pain initiated or caused by a primary lesion or dysfunction in the nervous system' [2]. Therefore, a diagnosis of neuropathic pain requires the identification of an anatomical or functional abnormality. Most significant anatomical lesions can be identified on computed tomography (CT)/MRI, but identifying functional abnormalities can be problematic. Classically, abnormal sensations associated with any type of pain condition are assessed using simple mechanical and thermal devices. More sophisticated psychophysical assessments can also be used to identify more subtle abnormalities of pain and temperature sense. However, it is also possible that there are functional brain abnormalities that are not detectable with clinical electrophysiological tests, such as electroencephalography (EEG), evoked potentials and conduction velocity measures. Advances in fMRI, PET and magnetoencephalography (MEG) technologies may provide such information, although there is currently no standard method/criteria to identify all types of functional brain abnormalities with these methods.

Towards this goal, it is critical to determine the criteria by which we base our decisions regarding abnormal responsiveness. A typical fMRI study of pain consists of alternating epochs of painful stimulation with a control nonpainful stimulus and/or rest. The pain activation is derived from a statistical analysis of the MRI signal intensity within each brain voxel during the painful state compared with the control or rest state. To identify an abnormal pain response, it is then necessary to compare the pain activation of interest with a normal pain activation response. This is a relatively straightforward concept. However, there are many fundamental criteria that can be used to identify and characterize activations.

The six main attributes of fMRI data that can be used to characterize and compare functional brain activations between states A and B are presented in Figure 4. In a simple experiment, these two states represent a control or rest condition and an experimental condition. In a more complex study, the fMRI attributes can be used to compare responses between conditions (e.g., a
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...non-noxious stimulus vs a noxious stimulus), between groups of subjects (e.g., healthy controls vs chronic pain patients) or between sessions with the same subjects (e.g., before vs after an injury). The most basic approach is simply to determine whether or not a response exists at a certain statistical threshold. After this is determined, the activation within a region of interest (ROI) can be characterized in terms of its peak or mean response magnitude (i.e., signal intensity), the location of the peak response (e.g., x, y and z coordinates from a common stereotactic atlas) and the spatial extent of the activation. More advanced analyses can also be performed to identify functional or effective connectivity between activations, or correlations between the activations and a behavioral or perceptual feature of interest [42]. Alternatively, an unthresholded approach can be used to interrogate the overall signal intensity within a ROI to circumvent the problem of setting a threshold. It is important to point out that there is no gold standard in the choice of a statistical threshold or any one specific attribute as being indicative of true activations. This is owing not only to statistical issues and noise; a variety of neuronal changes can also contribute to fMRI differences between states A and B. For example, these two states may be associated with different neuronal properties (e.g., action potential firing frequency or patterns or synaptic activity), different numbers or populations of active neurons and/or different locations of active neurons [51].

Another important issue to consider when assessing potential abnormal responses concerns the meaning of contrasting states A and B. Statistical contrasts are used commonly to determine the relative effects of two states (e.g., A and B). Using this approach, when brain areas show a greater activity for state A compared with state B they are said to be activated by A (compared with B). However, there are many scenarios that could lead to a positive outcome of A versus B. Figure 5 illustrates that A can be greater than B, even when one or both states in and of themselves show a negative fMRI response (i.e., a signal intensity change with respect to a baseline/control state). Similarly, the B minus A contrast, used to identify deactivations, could arise from a combination of negative and positive fMRI signal intensities in A and B, compared with the resting or control state. Therefore, caution must be used in the interpretation of direct A/B contrasts. To avoid misinterpretation, it is advisable to first interrogate each state against a baseline or control level to determine whether the state itself causes increases or decreases in signal.

There are many other factors that may contribute to false negative or false positive results; an in-depth discussion of these factors is beyond the scope of this review. However, it is important to point out the potential for confounds owing to abnormal vascular reactivity [52], poor stimulus and task condition control, individual differences, statistical cut offs and imaging capabilities (magnetic resonance strength, susceptibility effects and pulse sequences, etc.). Finally, one must be knowledgeable about the physiological impact of the experimental conditions and stimulation devices in terms of the neural elements recruited from the level of the receptors through to the cortical pathways [51].

Neuroimaging in chronic pain conditions

Neuroimaging in patients suffering from chronic pain provides an opportunity to explore the fundamental abnormalities underlying chronic pain. Patients suffering from chronic pain conditions may experience ongoing, spontaneous...
They may also experience stimulus-evoked pain - sensitivity to normally nonpainful stimuli, such as a light brush (allodynia) or an increased pain response to innocuous and noxious stimuli (hyperalgesia).

Neuroimaging is best suited to activation studies, but stimulus-free (i.e., spontaneous or ongoing) pain can be investigated using PET or MRI. PET imaging can be used to observe baseline rCBF differences or receptor binding of opiate agents between chronic pain conditions and healthy controls. For example, rCBF studies in chronic pain patients have reported thalamic hypoperfusion. MRI spectroscopy can also be used to interrogate neurochemical abnormalities. For example, there is evidence for abnormal brain chemistry in the prefrontal cortex of chronic back pain patients. Furthermore, fMRI with a percept-related approach can be used if there are minute-by-minute fluctuations in the ongoing pain (e.g., back pain or migraine pain) [4].

Studies of alldynia and hyperalgesia in patients with neuropathic pain typically apply mechanical stimuli to an affected and non-affected body region [53–55]. The cortical responses to stimulation in the affected region is typically enhanced when compared with the unaffected region in terms of the signal magnitude and extent, resulting in a cortical response that resembles a pain-like rather than brush-like pattern in somatosensory, insula, cingulate and frontal regions. These alldynic and hyperalgesic responses may also include ipsilateral activations, and activations in medial pain areas and attention-related areas. In addition to these quantitative differences, there may also be qualitatively unique responses to the alldynic/hyperalgesic state in areas of the medial pain system [56].

Neuroimaging has also provided an opportunity to investigate brain activity in patients suffering from so-called ‘functional pain disorders’, such as irritable bowel syndrome, fibromyalgia and hysterical anesthesia [34,39,57]. Despite some variability across studies [4], it is clear that these patients show abnormal forebrain responses to somatic and/or visceral stimuli. The findings suggest that the patients suffer from either heightened sensitivity in cortical somatosensory processing, abnormal attentional processes, insufficient (endogenous) pain modulation and/or abnormal connectivity between normally connected cortical and subcortical networks subserving pain and analgesia. For example, several studies have found abnormal stimulus-evoked reactivity in the ACC and prefrontal cortex in chronic pain patients compared with healthy controls [4].

It is beyond the scope of this review to discuss in detail studies of plasticity in chronic pain conditions. However, it should be noted that neuroimaging provides a window into the cortical changes following a pain-inducing injury, amputation or due to treatment.

Cautionary notes
First, neuroimaging, particularly with fMRI, has evolved quickly from a tool for exploring the basic mechanisms underlying brain function to the realm of pre-surgical mapping and even diagnostics. The major MRI manufacturers all now provide fMRI paradigm presets for online, real-time analyses of fMRI data. However, the protocols are rather simple, block designs with little flexibility to change the number of blocks or their duration or incorporate perceptual ratings or other physiological measures. They also rely on simple statistical measures at set thresholds. Therefore, these exciting clinical opportunities should be used with particular caution for pain studies, for it is important to consider...
more sophisticated designs; statistical analyses beyond A–B contrasts; potential altered resting state activity and deactivations, individual characteristics and percepts.

Second, before a pain abnormality can be diagnosed with certainty, solid understanding of the normal range of individual noxious stimulus- and pain-evoked responses across different populations must first be established, as is known for other vital signs.

Third, the impact of the test conditions and limitations of a hemodynamic, response-based technology need to be considered in the interpretation of pain-imaging evaluations.

Finally, we need to be cognizant of privacy issues and the impact of using fMRI for diagnostic purposes, given the emerging field of neuroethics and neuroeconomics.

Conclusion
The brain mechanisms underlying the multidimensional nature of pain can be interrogated using the modern neuroimaging technologies of fMRI and PET. Many centers are now asking more targeted questions concerning specific aspects of the acute pain experience, individual differences in pain perception and brain activity and connectivity between cortical areas. In the immediate future, these approaches will begin to address hypotheses concerning mechanisms of chronic pain in a variety of clinical conditions. Further developments over the next 10 years may provide a new opportunity to assess therapeutic efficacy or provide a new diagnostic measure of CNS dysfunction underlying chronic pain.

Future perspective
Neuroimaging of pain is now entering a more mature era whereby we can now ask sophisticated questions concerning both individual pain responses and fundamental abnormalities in specific chronic pain conditions. This new era is fostered not only by better analytical models but also by advances in other fields, such as genetics, computational neuroscience, cognitive psychology and even nanotechnology. Over the next 5–10 years, this will undoubtedly lead to new concepts of the brain mechanisms of pain and analgesia. However, a large effort is needed to establish the range of normal pain responses before pain imaging can be used as a clinical diagnostic test.

As we move closer to this eventuality, we should contemplate how a diagnosis of brain abnormality impacts patients with functional pain disorders. Patients suffering from chronic pain for which there is no structural demonstrable cause are often deemed to have a functional pain disorder – a psychiatric term. Despite the utility in dividing patients into categories based on their underlying causes, this particular classification has a strong negative connotation. A psychiatric label can have consequences for patients in terms of their care, societal and workplace acceptance, compassion and financial compensation. Therefore, let us for a moment consider why a particular symptom or disorder lies within the realm of neurology, psychiatry or even gastroenterology (in the case of functional bowel diseases). Gastroenterology tends to concentrate on peripheral etiologies but is now beginning to discuss the issue of brain–gut communication. Strictly speaking, neurology deals with diseases of the nervous system and psychiatry with diseases of the mind. However, the ability to see the inner workings of the brain with neuroimaging is now challenging the concepts of the mind as being separate from the brain,
thus blurring the traditional boundaries between these disciplines. This situation is not without precedence. Neurosyphilis was classified as a psychiatric illness until its underlying biological (organic) cause was found. Hallucinations and other symptoms, which were once considered just matters of the mind in conditions, such as Alzheimer’s disease and schizophrenia, are now being revealed as abnormalities associated with specific brain areas or thalamo-cortical networks\(^{[58,59]}\). Therefore, in the future, neuroimaging will provide a window into the health of the CNS in patients suffering from chronic pain in a way that could not have been captured with traditional methods. This information can then be used to develop targeted therapeutics.

Acknowledgements
These studies were funded by the Canadian Institutes of Health Research, Ontario Mental Health Foundation and the Canada Research Chair Program. The author is a Canada Research Chair in Brain and Behavior. The author would like to thank Jonathan Downar, Chun L Kwan, David Seminowicz, Keri Taylor and Geoff Pope for their scientific and technical contributions.

### Executive summary

**Introduction**
- Classical pain models are based primarily on experimental animal models.
- Modern neuroimaging allows for the investigation of CNS mechanisms of acute and chronic pain states in humans.

**Multidimensional nature of pain**
- Pain is a multidimensional experience comprised of sensory-discriminative, motivational-affective and reactive-evaluative components.
- Multiple nociceptive pathways subserve different aspects of the pain experience. The main cortical areas implicated in pain perception are the primary and secondary somatosensory cortex, insula, anterior cingulate cortex and prefrontal cortex.

**Modern neuroimaging techniques**
- Positron emission tomography (PET) can be used to image resting and stimulus-evoked regional cerebral blood flow and opiate binding before, during and after exposure to a painful stimulus.
- Functional magnetic resonance imaging (fMRI) is the most commonly used imaging method to study pain because it is noninvasive, widely available and has finer spatial and temporal resolution than PET. fMRI uses blood oxygen level detection (BOLD) to identify differences in deoxyhemoglobin between conditions.

**Application of fMRI for the study of pain**
- fMRI activations related to nociception are identified by searching the brain for regions where activity is correlated to a predictor function. The predictor function is created by a mathematical convolution of a characteristic hemodynamic response function with the noxious stimulus time course.
- Percept-related fMRI can be used to identify brain activity correlated to the temporal dynamics of a specific attribute of the pain experience. These activations are identified by constructing a predictor function from online ratings of the percept of interest. Percept-related fMRI can distinguish brain activity associated with particular types of sensations from activity evoked by a stimulus that is not necessarily consciously perceived (possibly used for homeostatic or reflexive functions). Percept-related fMRI is particularly useful when there is a temporal disconnection between stimulus and sensation, as is the case in some chronic pain pathologies.
- Other types of correlative methods and network analyses can be used to investigate the contribution of attention and individual characteristics (e.g., personality) to pain-related brain activity.

**Extracting abnormal responses in patients with chronic pain**
- The statistical criteria used to establish the normality of pain responses determine the size and extent of neuroimaging activations; but there are no gold standards for these criteria. fMRI pain activations can be described in terms of their statistical probability, peak or mean response magnitude (signal intensity), location, spatial extent, connectivity with other regions and correlation with individual behavioral traits.
- Statistical contrasts are commonly used to identify the relative effects of two states (A, B). In pain studies, these states may represent a pain stimulus and a control stimulus or can represent two populations (e.g., chronic pain patients and healthy control subjects). There are many scenarios that can lead to a statistical outcome of A > B or A = B, including various levels of activations and deactivations. Thus, it is imperative to understand the effect of each state in and of itself, ideally against a rest baseline or appropriate control.
**Executive summary (cont.)**

- Neuroimaging studies of pain, particularly in chronic pain patients, need to consider many other factors to minimize false negatives and false positives, such as potential vascular reactivity insufficiencies, individual differences, experimental conditions, study designs and imaging capabilities.

**Abnormalities in chronic pain conditions**

- PET, fMRI and magnetic resonance spectroscopy studies have identified abnormalities in brain function in chronic pain patients suffering from neuropathic pain, back pain, cardiac pain, fibromyalgia, irritable bowel syndrome or headache/migraines.

- Neuropathic pain patients with allodynia and hyperalgesia can exhibit pain-like cortical responses to innocuous stimuli and also tend to show bilateral responses.

- Some chronic pain patients exhibit thalamic hypoperfusion.

- Chronic pain patients show abnormal forebrain responses to somatic and/or visceral stimuli, particularly in the anterior cingulate cortex and prefrontal cortex. These findings suggest heightened sensitivity in cortical somatosensory processing, abnormal attentional processes, insufficient (endogenous) pain modulation and/or abnormal connectivity between normally connected cortical and subcortical networks subserving pain and analgesia.

**Cautionary notes & future perspective**

- Quick, real-time fMRI based on the MRI manufacturer’s pre-set paradigms are too simplistic in experimental design and statistical analysis for pain diagnostic applications.

- The range of normal brain response to a noxious stimulus needs to be established before this imaging-based vital sign can be used for diagnostic purposes.

- The ability to identify and localize functional abnormalities in the brain challenges classical boundaries between neurology, gastroenterology and psychiatry.

**Bibliography**

Papers of special note have been highlighted as either of interest (+) or of considerable interest (+++) to readers.


• Review of data linking neuronal basis of the functional magnetic resonance imaging (fMRI) blood oxygenation level detection (BOLD) effect.


• Review of percept-related studies.


• Review and meta-analysis of pain-imaging studies.


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