HHS Public Access

Author manuscript

Future Neurol. Author manuscript; available in PMC 2017 February 02.

Published in final edited form as:

Future Neurol. 2014 November ; 9(6): 615–626. doi:10.2217/FNL.14.57.

Neuroimaging chronic pain: what have we learned and where are we going?

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Abstract

Advances in neuroimaging have helped illuminate our understanding of how the brain works in the presence of chronic pain, which often persists with unknown etiology or after the painful stimulus has been removed and any wounds have healed. Neuroimaging has enabled us to make great progress in identifying many of the neural mechanisms that contribute to chronic pain, and to pinpoint the specific regions of the brain that are activated in the presence of chronic pain. It has provided us with a new perception of the nature of chronic pain in general, leading researchers to move toward a whole-brain approach to the study and treatment of chronic pain, and to develop novel technologies and analysis techniques, with real potential for developing new diagnostics and more effective therapies. We review the use of neuroimaging in the study of chronic pain, with particular emphasis on magnetic resonance imaging.

Keywords

brain-based therapy; chronic low back pain; CNS; fibromyalgia; fMRI; MRI; MVPA; real-time fMRI; resting state fMRI

Chronic pain is a widespread and growing problem in the USA, affecting more than 100 million adults at some point in their lives, and accounting for about US$600 billion annually in medical costs and lost productivity [1].

Chronic pain is complex, and the neural mechanisms that underlie chronic pain have been poorly understood. However, the evolution of various neuroimaging techniques has opened new windows into the brain and spurred new avenues of pain research that hold real promise for developing new, more effective treatments. Neuroimaging has shown us that chronic pain is different from acute pain, and that it can become a separate disease entity that may occur, in part, following changes in the entire CNS that cause chronicity and the development of comorbid symptoms. However, it is imperative to remember that despite the involvement of

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Competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

brain changes in chronic pain, the nervous system is not solely responsible for the initiation and/or maintenance of chronic pain, as addressed in a series of recent commentaries [2,3].

Nonetheless, neuroimaging has become an increasingly important and popular means of studying how the brain perceives and processes chronic pain. Various neuroimaging modalities have been used, including PET, EEG [4], magnetoencephalography (MEG), single-photon-emission computed tomography (SPECT/CT) [5] and MRI. These techniques have been used to study several chronic pain states, including, most commonly, chronic low back pain (cLBP) [6], fibromyalgia (FM) [7], osteoarthritis [8], complex regional pain syndrome (CRPS) [9,10], phantom-limb pain, chronic migraine [11], chronic pelvic pain (CPP) [12,13] and peripheral neuropathy [14], among others [15]. Experiments have evaluated acute pain processing mechanisms in healthy volunteers [16–18] and in animals [19] and in animal models of chronic pain [20]. Neuroimaging has helped elucidate many of the neural correlates regarding factors well known to modulate the experience of pain, including attention [21], anticipation [22], empathy [23,24], placebo [25], meditation [26], fear/anxiety [18] and reward [15]. Each factor impacts how we perceive pain, and an increasing number of functional neuroimaging studies are investigating how these factors affect pain perception and activity in the brain. Current pain research also uses various neuroimaging techniques to investigate a broad range of translational science that can eventually be tested in clinical trials.

The present review focuses specifically on the use of neuroimaging, and especially MRI, to study CNS changes in patients with a variety of chronic pain states.

How MRI has been used to image chronic pain

The many variations of MRI technology

MRI is one of the most widely used modalities for the study of chronic pain. It combines a strong magnetic field with radiofrequency pulses to display high-spatial-resolution structural images. These images can be used to measure the density and distribution of gray matter (voxel-based morphometry, cortical thickness analysis), and white matter (diffusion tensor imaging, functional anisotropy). Functional MRI (fMRI) allows for an indirect measurement of brain activity by tracking changes in blood oxygenation levels (referred to as the BOLD signal) [27]. Additional techniques include magnetic resonance spectroscopy (MRS), which measures relative concentrations of metabolites in the brain [28,29], and arterial spin labeling fMRI, which uses magnetically labeled protons in the blood as an endogenous tracer to measure changes in global and regional blood flow [30,31].

Neuroimaging allows us to study neural activity in individuals with chronic pain when they are either completely at rest, or while they are subjected to various tasks, interventions and procedures. These can include applying physical stimuli, such as heat pain, pressure or body movement, in a block design and exposing the patient to event-related stimuli, such as emotion-evoking images, working memory tasks and auditory stimuli. Neuroimaging experiments using combinations of imaging modalities and these various techniques are rapidly advancing our knowledge of how chronic pain affects brain structure and activity.

What MRI has taught us about chronic pain

Keeping the CNS in perspective: how pain (as nociceptive information) gets to the brain

Pain processing typically involves transmission and modulation of nociceptive signals along a predictable pathway. Noxious stimuli trigger signals in the peripheral nerves. A-delta nerve fibers transmit the 'first-pain' signals, the pricking, sharp sensations felt immediately after the painful stimulus is applied. C fibers transmit 'second-pain' signals, the dull, aching and throbbing pain felt after a 1–2-s delay [32]. These peripheral nerve fibers synapse in the dorsal horn of the spinal cord, where interneurons cause inhibitory/excitatory modulation. Secondary spinal projection neurons then transmit the information to two areas of the brainstem – the rostral ventral medulla and periaqueductal gray, where they are further modulated and relayed first to the thalamus and then to the somatosensory cortex in the cerebrum, where they are interpreted as pain (for review [33]).

In chronic pain states, inflammatory factors and sensitized receptors in the skin are thought to cause an abnormal increase in the transmission of nociceptive signals from the periphery as well as either a lack of inhibition or increased excitation, or both, at the spinal cord, brainstem or cortical levels, called 'central sensitization' [34,35].

Specific brain & brainstem regions implicated in chronic pain

Neuroimaging provides a means of noninvasively studying altered activity levels in the CNS. Specifically, neuroimaging can be used to study the brain, brainstem and spinal cord, where central sensitization and pain modulation occur and contribute to the ongoing experience of chronic pain and related symptoms [35,36]. Much of neuroimaging research has focused on identifying the brain regions that demonstrate altered structure and activity in chronic pain states. A major goal of this research is to identify specific brain regions as future targets for chronic pain therapy.

Several key brain regions have been identified as potentially playing a role in chronic pain. These regions are primarily implicated in sensory and affective components of pain processing and perception, motor function and higher order brain processing and integration, as reviewed below.

Structural changes

Differences in brain structure have been widely assessed in individuals with chronic pain, typically using voxel-based morphology [37] and cortical thickness analysis [38]. Regional increases and decreases in cortical thickness and gray matter density have been observed across several types of chronic pain, including CRPS [10], fibromyalgia [39,40], migraine [41–43], temporomandibular disorders (TMD) [15] and cLBP [6,44–46] and in visceral pain states, such as irritable bowel syndrome (IBS) [47]. One study demonstrated these changes simultaneously among different chronic pain syndromes, including CRPS, knee osteoarthritis and cLBP [48]. These studies indicate that the key areas of observed gray matter change include regions within the insular, somatosensory, motor and associated cortices; in subcortical structures, including the thalamus and basal ganglia, and parietal

cortices; in regions within the prefrontal cortex; and in structures implicated in memory and emotion regulation, such as the hippocampus and amygdala, respectively.

It was initially thought that changes in gray matter, primarily decreased gray matter density, were associated with increased rates of age-related gray matter atrophy [49,50]. However, this theory is being questioned because several chronic pain studies have shown a mixture of regional increases and decreases in gray matter density [15,51], as well as reversal of gray matter change following effective therapy [52]. The exact nature and cause of these changes are currently unknown. Moreover, we do not know whether the observed changes represent existing differences in brain structure that predispose individuals to chronic pain, whether they occur as a result of the presence of chronic pain (e.g., due to additional stress and pain experience itself), or whether they are functionally linked to the maintenance of chronic pain. In addition, it is unclear whether these detected differences in gray matter structure are specifically due to chronic pain, or whether they are more complex in nature and result from multiple factors linked to chronic pain (such as depression or the medications that the patient is taking for pain). For example, a meta-analysis of several studies of structural brain changes in patients with FM indicated that the depression score accounted for most, if not all, of the changes in gray matter structure in individuals with FM as compared with healthy volunteers [53,54]. However, gray matter changes have also been shown to occur in patients with cLBP with little to no emotional distress [6].

Connections between brain regions are now under study as well. Diffusion tensor imaging and fractional anisotropy have been used to investigate differences in white matter structure seen in various chronic pain states, including TMD [55], and IBS [56,57]. Changes in brain structure have also been observed using combined voxel-based morphology and diffusion tensor imaging to analyze interactions between regions of gray matter change and white matter change in patients with CRPS [58] and FM [59,60].

Functional changes

Alterations in brain function have been demonstrated in multiple chronic pain syndromes, and many of the identified regions of functional change overlap with regions of structural change [61]. Investigations of brain function in the presence of chronic pain typically involve protocols to assess brain function in response to pain evoked by noxious or innocuous stimulation [62–64], in the presence of emotional or cognitive tasks [65,66] or stress [67], or while patients rate their ongoing chronic pain symptoms [68]. Ultimately, no one region within the brain, brainstem or spinal cord is singularly responsible for chronic pain: all neuroimaging studies have shown that chronic pain and its comorbid symptoms cause neurological changes across several brain regions [69]. Moreover, these studies repeatedly demonstrate altered function in several key regions within the CNS, as described below.

Altered activity within the primary somatosensory cortex and posterior insular cortex has been observed when noxious stimuli are applied in individuals with cLBP, FM, CPP and CRPS [70]. These are regions typically associated with intensity coding (which measures how painful a stimulus is), and these functional alterations suggest altered intensity processing of pain in chronic pain states. Similarly, the secondary somatosensory cortex

(SII) is a region of higher order sensory processing and integration, and has shown both structural and functional alterations [66,71].

The primary motor cortex, premotor cortex and supplementary motor areas also play a role in chronic pain. Alterations within these motor regions may be related to the changes seen within the cerebellum, which have been historically reported, yet minimally discussed, in the literature. Currently, however, insights into cerebellar changes in chronic pain are accumulating and may add to the known function of the cerebellum and how it coordinates with altered sensory motor and emotional processing in the presence of chronic pain [72,73].

Several investigators have examined the relationship between cognitive processes and chronic pain [74]. These studies primarily identify functional changes in higher order regions within the prefrontal cortex (PFC), including the ventromedial PFC, dorsolateral PFC and orbitofrontal PFC [75–77]. Regions within the parietal cortex, including the temporo-parietal junction, precuneus and posterior cingulate cortex, also demonstrate functional changes in individuals with chronic pain. These regions are involved in introspection, mind wandering and self-referential thought processes [78], which may be more highly integrated with pain processing and experience in chronic pain states.

Brain regions related to the affective aspects of pain processing (such as the level of unpleasantness, negative context), including the anterior insular cortex [79] and anterior cingulate cortex [80], demonstrate altered function in chronic pain states [81]. Studies investigating the psychological aspects of chronic pain, including altered fear and emotional processing, have identified scale-based correlations of altered emotion processing with altered brain structure and function in emotion and fear-processing regions, including the amygdala [82], and in memory-related processing regions including the hippocampus [83]. While changes in the amygdala have been observed, fear avoidance (of movement) is not indicated as being responsible for these changes [84]. Therefore, these alterations are more likely due to general changes in limbic and memory networks.

Altered function within subcortical, midbrain and brainstem regions suggests that chronic pain modifies brain circuits and modulation. Thalamic lesions have been implicated in central pain [85], and they frequently accompany altered activity and structure in other chronic pain states as well. Functional alterations within the basal ganglia [86,87] suggest altered motor and general connectivity of the brain. Altered activity within midbrain regions, in particular in the ventral tegmental area [88,89], may signal that chronic pain disrupts the mechanisms of reward, punishment and dopamine function.

Altered activity within brainstem regions, especially involving the periaqueductal gray [90–92], may signify disrupted regulatory control of pain [93]. However, further research is needed because the small size and highly complex, multifunctional heterogeneity of the brainstem has thus far limited study within this region.

Although invasive electrophysiology studies of chronic pain and chronic pain models have observed altered activity within the spinal cord, MRI imaging of the cervical spinal cord has to date been conducted only in healthy individuals [94,95]. This technology is evolving and may soon be useful for the study of chronic pain. However, technological advances are

necessary to improve the S/N in cervical spinal cord imaging, which is greatly diminished by local pulsation and physiological noise [96].

Brain network-based approach: resting state fMRI

Recent methods of resting-state fMRI have focused on multiple regions in the brain, targeting inherent and altered measures of connectivity between regions and within brain 'networks' [97]. Resting-state fMRI has the advantage of enabling neuroimaging data to be collected while individuals with chronic pain simply rest in the MRI scanner. Moreover, it provides information about the natural state of brain activity in chronic pain without having to apply any external sensory or cognitive stimulation. Resting-state fMRI methods investigate the degree of functional connectivity, seen as changes in correlation of low-frequency oscillations in neural activity between brain regions. These changes can provide information about altered resting-state brain activity in chronic pain states [98]. Chronic pain has been noted to alter several networks, or groups, of individual brain regions with similar low-frequency oscillatory activity and an increase or decrease in the presence or absence of external stimulation [99]. These primarily include the default-mode networks (DMN) [100], which are more active at rest; salience and executive control networks, which are more active during stimulation of the senses or tasks; and sensory motor networks, which are related to sensory and motor processing. Notably, altered DMN function in chronic pain has also been demonstrated in a study using arterial spin labeling [31].

Decreased DMN connectivity, specifically within the medial PFC, posterior cingulate cortex and amygdala, has been observed in cLBP [101]. Conversely, greater connectivity within the default mode and executive attention networks has been observed in FM [102]. Greater connectivity between the DMN and insular cortex has also been observed, indicating that these regions function together differently in FM as compared with healthy states [102]. Additional studies in FM have noted similar alterations between the insular cortex and other cortical regions [103]. Low-frequency fluctuations within brain regions are also altered in chronic pain, specifically within the primary somatosensory cortex, supplementary motor area, dorsolateral prefrontal cortex and amygdala [104]. Conversely, in CRPS, reduced resting-state functional connectivity has been observed within the DMN, and greater connectivity has been noted in the sensory and motor regions with other pain-processing-related regions [105]. Altered resting state activity within sensory and motor network regions [106] and within the DMN have been demonstrated in CPP [107]. Several studies have shown that altered functional connectivity of the brainstem [108], basal ganglia [109] and other regions within the frontal and temporal cortices [110] may underlie chronic migraine. Diabetic neuropathic pain also shows similar alterations in resting state activity [111].

Longitudinal changes & limitations

The majority of investigations mentioned thus far are nonlongitudinal, and none of these observational studies track individuals before the onset and through the development of chronic pain. This is a major limitation for all neuroimaging studies of chronic pain: the observed functional and structural changes cannot specifically be determined to be caused by the presence of chronic pain. Typically, in order to gain some sense of the longitudinal

progression of structural and functional brain changes in chronic pain, the observed alterations are assessed for correlations with the duration and intensity of pain within the studied population. However, more recently, a growing number of longitudinal investigations have been conducted, in particular for cLBP [112] and IBS [113]. A recent study that tracked patients who transitioned from subacute to cLBP noted changes in the structure of white matter [114]. A few interesting studies have also shown that brain changes reverse when chronic pain is reduced by means of various effective therapies [52,115], including psychological therapy [116]. This indicates that although CNS abnormalities are highly implicated in chronic pain states, they may not have to be permanent – the use of appropriate, effective therapy may be able to restore normal brain function, at least in part.

Greatest future potential for neuroimaging in the study of chronic pain

The use of neuroimaging technology to study chronic pain continues to gain interest and momentum. Noninvasive imaging techniques, including MRI, EEG, MEG and others, are being used with increasing frequency; this may largely be a function of the fact that neuroimaging can gather large amounts of data without requiring study subjects to engage in activity that could aggravate their pain – they are allowed to simply rest while the images are passively obtained.

In future, developments in three main areas hold the most promise to add to our understanding of CNS involvement in chronic pain, which will spur the subsequent development of novel therapies: combining imaging technologies to obtain simultaneous high-spatial and high-temporal resolution scans; identifying neurological signature patterns and prediction potential; and continuing to develop clinical neuroimaging-based interventions.

Good qualities: noninvasive & high-spatial & high-temporal resolution

Researchers have begun to combine functional imaging technologies for use in some medical research, but few studies have used this technique to study chronic pain. For example, MRI can be combined with EEG or MEG, which achieves measures of both high spatial resolution from the MRI/fMRI scans and high temporal resolution from the EEG/MEG scans [117]. The technology for simultaneous acquisition of MRI and EEG scans and for combining the images still needs to be developed. However, future studies using combined neuroimaging may provide invaluable insight into the brain changes in chronic pain states.

Multivariate pattern analysis: machine learning technology

New advances in the technology for neuroimaging data analysis are gaining momentum and showing promise, specifically in the case of multivariate pattern analysis (MVPA) (for review: [118]). MVPA is a machine-learning technology that can be applied as an algorithm to analyze large data sets and identify signature patterns that represent subgroups. Moreover, MVPA can function as a predictive tool; once a signature pattern has been identified in individuals with chronic pain versus healthy controls, data from a single individual can be classified as belonging to one of the groups, based on that individual's pattern of brain

structure or activity and its similarity to the signature patterns of the group [119,120]. MVPA technology has already been applied to identify acute pain related changes in healthy human volunteers [17,121], and has been extended to differentiate patients with chronic pain from healthy volunteers based on brain structure [6]. Ultimately, it is anticipated that MVPA technology will advance neuroimaging to the next level, allowing it to be useful as a diagnostic tool to predict an individual's prognosis and define the appropriate therapies based on an individual's brain structure and activity patterns. In the future, this technology could also be combined with big data, such as phenotype and genetic information, to create a more personalized approach for diagnosing and treating the each patient. Longitudinal studies using MVPA may also provide scientific grounds for assessing the transition from acute to chronic pain. Overall, MVPA technology is a powerful tool that is expected to improve the clinical utility of neuroimaging for chronic pain and to advance neuroimaging analyses from the current standard of group comparisons to an individualized approach.

Brain-based therapies: real-time fMRI neurofeedback & neurostimulation

Neuroimaging continues to advance our understanding of how the CNS is affected by and involved in chronic pain, and neuroimaging interventions are being and gaining momentum as an alternative or supplement to pharmaceutical therapy, or both [122,123]. Several studies of real-time neurofeedback for chronic pain have been conducted [124,125], but further research and additional clinical trials are still needed. The efficacy and benefits of real-time neurofeedback for an individual may be better harnessed in the future by the combining real-time neurofeedback fMRI and machine-learning classifiers (MVPA) to identify spatiotemporal brain maps ideal for individualized, real-time manipulation for each patient [126].

Although neurostimulation is invasive and is only implicated for use in the most severe, intractable cases of chronic pain, novel tools are being developed to better select patients who are most likely to benefit from this intervention [127]. Implantation of neurostimulators is still an option for targeted manipulation of brain activity within specific brain regions, and there have been great advances in this technology since its inception [128]. Current techniques use adaptive models [129] and target brain regions, such as the motor cortex, that have the potential to activate multiple downstream effects [130].

Transcranial magnetic stimulation is also gaining popularity as an interventional and alternative method for reducing the symptoms of chronic pain (for review, see [131,132]). Preliminary clinical trials of transcranial magnetic stimulation have demonstrated effective pain reduction that persists days to weeks after treatment [133–136]. However, current investigations continue to search for ideal brain region targets and delivery specifications (such as parameters and treatment frequency).

Additional exciting advancements for the future use of neuroimaging in chronic pain-related therapy include the development of brain–computer interfaces using electrocorticography and visual feedback, which has been tested as a potential therapy for phantom limb pain [137]. Advancements in the use of PET imaging are making it possible to use this technique to predict the efficacy of motor cortex stimulation, in particular using opioid binding and receptor density to predict the efficacy of motor cortex stimulation [138]. Advances in

present technology and combinations of old and new neuroimaging modalities will continue to help pain researchers decode the mysteries of the brain's response to chronic pain, which will enable the development of new and improved therapies for this complex and often disabling condition.

Conclusion

Neuroimaging has provided evidence of structural and functional brain changes in the majority of chronic pain syndromes. To date, cLBP, FM, neuropathic pain and TMD have been the most widely studied pain syndromes using this technology. The expression that 'pain is in a patient's head' no longer reflects the idea that chronic pain is a largely psychological problem. Rather, it can now be taken more literally, because neuroimaging studies have repeatedly demonstrated extensive alterations in brain structure and function in chronic pain states. To date, we have accumulated a large amount of somewhat variable, yet overlapping, evidence indicating that altered brain mechanisms may, in many cases, greatly contribute to, if not wholly underlie, real pain sensations. Moreover, neuroimaging has shown that multiple regions of the brain are involved in a range of pain, sensory, motor, cognitive, motivational, memory, emotion and fear processes. Individual variability in the pain experience remains a challenge in the clinical care of chronic pain. Continued research and advances in neuroimaging technology are needed to further clarify brain mechanisms involved in chronic pain and to further develop novel brain-based treatment approaches for patients with chronic pain.

Future perspective

Neuroimaging of chronic pain has largely focused on identifying individual regions of the brain implicated in chronic pain, and determining what these regions contribute to the development and persistence of chronic pain and its comorbid symptoms. Neuroimaging has demonstrated that we need a more network-based approach to the study of chronic pain, with a particular focus on how the various regions in the brain interact with each other and with other regions of the CNS, such as the cervical spinal cord. Neuroimaging has shown us that no specific pain center exists in the brain, and the quest to find this conceptual single pain center responsible for chronic pain may have ended. However, all of the regions that have been found to play specific roles in chronic pain will continue to be useful targets for brain-based therapies. Eventually, neuroimaging of chronic pain will evolve into a therapy-driven field. We are building a large knowledge-base about regional alterations seen in chronic pain states, and we are redirecting research efforts to examine networks and combinations of regions that are altered in the presence of chronic pain (Figure 1).

Additional integration of pain medicine with other fields, such as psychology, physical and occupational therapy, immunology and other chronic pain-related fields will continue to increase the potential for us to develop interventions that modulate response of the CNS to chronic pain. The ultimate goal is to prevent and reverse the maladaptive processes that take place in the CNS in the presence of chronic pain.

Acknowledgments

Special thanks to Maureen Donohue, Editor for the Department of Anesthesiology, Pain and Perioperative Medicine at Stanford, for editing the manuscript.

Financial disclosure

Writing of this review article was supported by the Chris Redlich Pain Research Endowment (to S Mackey), NIH K24 DA029262 (to S Mackey), NIH P01 AT006651 (to S Mackey) and NIH T32 GM89626 (KT Martucci).

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EXECUTIVE SUMMARY

- Pain-related changes in brain structure and activity have been observed across several regions of the brain. These most notably include the anterior cingulate cortex, insular cortex, prefrontal cortex, primary and secondary somatosensory cortices (S1 and S2), motor cortex (M1) and supplementary motor area, thalamus, basal ganglia, amygdala, hippocampus and cerebellum.
- Ultimately, no one region within the brain, brainstem or spinal cord is singularly responsible for chronic pain; across all neuroimaging studies of chronic pain, the general consensus is that neurological changes across several brain regions are implicated in the presence of chronic pain and its comorbid symptoms.
- Resting-state functional MRI allows researchers to focus on network-based changes and has revealed changes within the default mode network salience network, executive control network and sensory motor network in chronic pain.
- Multivariate pattern analysis, which focuses on a whole-brain approach to identify differences in brain structure and activity, is gaining momentum as a new method of analysis for MRI studies of chronic pain.
- Advancements in real-time functional MRI, transcranial magnetic stimulation and other neuroimaging-based therapies continue to promise novel and more effective treatments for chronic pain.

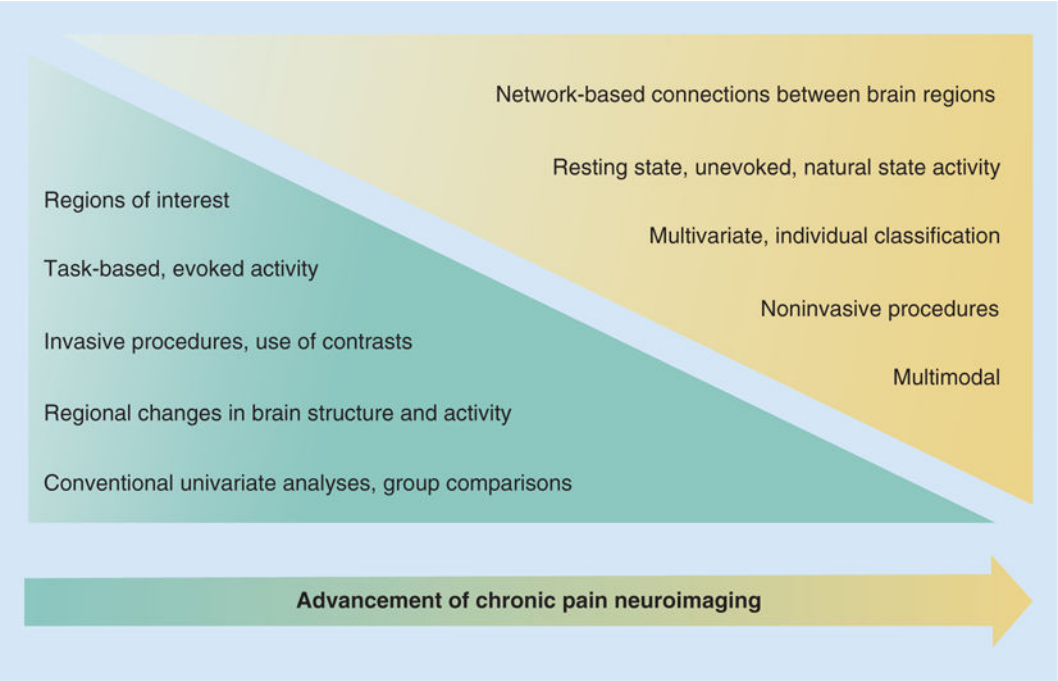

Figure 1. Illustration of the advancement of chronic pain neuroimaging technology and methods

Over the next several years, it is expected that neuroimaging methods will shift from predominantly conventional analyses (blue triangle) toward newer methods (yellow triangle) offering multiple benefits for analysis and interpretative power. Analyses of localized regions of interest will shift toward network-based assessments involving multiple brain regions. Task-based imaging of evoked activity (typical block design and event-related designs) will give way to more natural, resting state imaging of the individual patient in their unprovoked condition of chronic pain. Invasive procedures and contrasts are expected to continue to decline in popularity in favor of more comfortable and noninvasive techniques. Traditional group analyses will eventually be replaced with individual assessment through the continued development of classification and other technology that will enhance the level of power from an individual's brain scan. Multivariate analyses will replace univariate analyses, and these multivariate analyses will also be able to incorporate genetic and biomarker data into their models. Analyses of single modality (e.g., morphometry, functional MRI) will eventually be improved through the ability to combine across data modalities (e.g., combined morphometry, resting state and diffusion tensor imaging; combined functional MRI, EEG, PET) to enhance and validate findings across data types and signals. Ultimately, improved methods and technology will be used to assess a broader scope of data types and modalities, and together these will provide enhance statistical power for understanding CNS alterations in the individual.