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The Role of Neuroimaging in Analgesic Drug Development

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Abstract

Rapidly developing, non-invasive, neuroimaging methods provide increasingly detailed structural and functional information about the nervous system, helping advance our understanding of pain processing, chronic pain conditions, and the mechanisms of analgesia. However, effective treatment for many chronic pain conditions remains a large, unmet medical need. In this review, we examine how the neuroimaging of pain has enhanced our understanding of the mechanisms of chronic pain, our current understanding of the central neural correlates of pharmacologic modulation of pain, and the role of neuroimaging in analgesic development, discussing both current limitations and future directions

Introduction

Neuroimaging has rapidly changed the field of pain research. Electrophysiological, radiological, and magnetic resonance methods reveal increasingly detailed information about the neural correlates of pain perception and modulation in both animal and human models. These methods have helped identify the central neural structures involved in pain processing termed the “pain matrix” [1], and establish hypotheses related to the central mechanisms responsible for the generation and maintenance of chronic pain conditions. These methods have the potential to objectively diagnose central nervous changes in pain disorders and to identify better neural targets for treating chronic pain.

In previous reviews, investigators have discussed the application of functional magnetic resonance imaging (fMRI) to the research and development of novel drugs [2–4]. In this review, we examine how the neuroimaging of pain has enhanced our understanding of the mechanisms of chronic pain and the neural correlates of pharmacologic modulation of pain. We will discuss the current limitations and future directions of the role of neuroimaging in analgesic development.

Neuroimaging of pain

The use of neuroimaging has enabled the non-invasive study of the central nervous system. Several techniques have been used to investigate pain including electrophysiological methods such as, electroencephalogram (EEG) and magnetoencephalogram (MEG), radiological methods such as positron emission tomography (PET) and single emission computerized tomography (SPECT), and magnetic resonance (MR) techniques such as magnetic resonance spectroscopy (MRS), structural magnetic resonance imaging (MRI), diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI). These neuroimaging techniques can be categorized as structural (revealing anatomical information, e.g., MRI, DTI), biochemical

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(revealing information regarding the local chemical environment, e.g., MRS) or functional (revealing signal changes related to neuronal activity, e.g., EEG, MEG, fMRI).

Investigators have employed structural imaging to associate anatomical changes in the brains of chronic pain patients. Although structural imaging gives no direct information about neural function, it provides indirect information about how chronic pain effects central plasticity and identifies the anatomical differences between pain patients and healthy controls. Structural imaging can be used to track longitudinal changes due to disease severity and progression and may potentially characterize changes following treatment. The regions of interest identified using structural imaging may then be targeted for follow-up investigations into brain function. Structural imaging methods include voxel-based morphometry (VBM) and cortical thickness analysis (CTA). Investigators have used VBM and CTA to identify structural differences in the gray matter densities of subjects with low back pain [5] and fibromyalgia [6]. Decreases in prefrontal gray matter in these patients may help explain some of the cognitive issues noted in patients with chronic pain. Furthermore, white matter tract changes can be characterized using DTI tractography. Hadjipavlou et al. used this technique in healthy subjects to observe the physical connections of the periaqueductal gray (PAG) and nucleus cuneiformis to the amygdala, hypothalamus, prefrontal cortex, rostroventral medial medulla and thalamus [7]. This method could identify associated differences in anatomical connectivity in chronic pain conditions.

Imaging of the biochemical environment of the central nervous system can help reveal abnormalities in chronic pain. Investigators have used magnetic resonance spectroscopy (MRS) to identify biochemical differences in brain regions of healthy individuals and chronic pain patients. Decreases in N-acetylaspartate (NAA) have been observed in the dorsolateral PFC of subjects with chronic low back pain [8] and complex regional pain syndrome type I [9] and in the thalami of neuropathic pain patients [10]. NAA, considered a marker of neuronal activity, is found only in mature neurons [11,12]. Investigators have proposed NAA as a possible biomarker of neuronal health and function that can be assessed non-invasively using MRS [8-10].

Neuroimaging studies of pain have largely used fMRI and PET. Both techniques rely on hemodynamic responses in order to identify areas of metabolic change. Functional MRI uses an endogenous contrast mechanism, changes in the blood oxygenation to identify areas of neuronal activity. This is called Blood Oxygenation Level Dependent (BOLD) imaging [13]. PET imaging requires injection of a labeled tracer, commonly $H_2^{15}O$. SPECT imaging provides unique insight into brain function by providing a snap shot or frozen look at the brain state immediately after perfusion tracer injection. This is advantageous in the diagnosis of neuropathic brain states, as the dynamic nature of signal change in fMRI and PET may in some cases, yield complicated results [14].

These functional imaging methods have been used to characterize the complex network of nociceptive, affective, and cognitive elements that process pain. The thalamus, primary and secondary somatosensory cortex, insula, prefrontal cortex (PFC) and anterior cingulate cortex (ACC) have been identified to be involved with the perception and modulation of pain and are collectively known as the “pain matrix”[1]. In addition, other regions such as the amygdala, caudate, amygdala, and parahippocampal area are known to influence pain perception. Ultimately, these activity maps may some day provide an objective measure of pain and its modulation in comparison to self report. This task, however, is complicated by the multiple cognitive and psychological factors that mediate pain perception. As a result, the neural picture of pain is also complicated.

FMRI, in particular, has revolutionized our understanding of the brain's role in the perception and maintenance of pain and the neural correlates of factors modulating it including: attention [15], anticipation [16], fear/anxiety [17], and direct control [18]. Functional MRI has been employed to investigate differences in how healthy individuals process pain during normal and sensitized conditions [19], and its use has advanced our knowledge of the central neural correlates associated with a number of chronic pain conditions [20].

PET imaging is another functional neuroimaging method used extensively to characterize the neural correlates of pain processing and modulation. PET requires the use of radio-labeled ligands which restrict the duration of scanning and the quantity of scans that can be performed. PET can be used to investigate changes in metabolic activity related to a disease condition or to an evoked response. For example, Witting et al., has recently used PET imaging to identify the neural correlates of pain processing in chronic neuropathic pain conditions and shown it to differ from that observed during evoked pain in healthy subjects [21]. Additionally, PET can be used to investigate the role and function of specific drugs and neurotransmitters. In these studies, investigators use sub-therapeutic doses of radio-labeled agents to investigate the functioning of the targeted systems. For example, Zubieta et al., has used PET to reveal opioid binding in brain regions associated with the perception of pain and has characterized specific binding sites related to the sensory and affective dimensions of pain [22]. This group has also used PET imaging to characterize genetic and gender variability in opioids system activation [23,24]. Additionally, PET imaging has identified decreases in opioid receptor binding in central and peripheral neuropathic pain [25,26] and central poststroke pain [27]. More recently, combined opioid and dopamine systems have been imaged, providing opportunities to investigate multiple neurotransmitters and their interactions [28]. These studies shed light on the functioning of specific neurotransmitter systems in both healthy and in chronic pain conditions. While important in identifying potential targets for analgesia, these studies do not use therapeutic doses of PET ligands to investigate pharmacologic manipulation of the pain processing and modulation systems. Such studies are important in identifying the central mechanisms of effective and ineffective analgesia.

Neuroimaging the pharmacologic modulation of pain

Although the integration of neuroimaging and drug administration has helped elucidate the neural correlates of pain and analgesia, neuroimaging techniques can further characterize the pharmacodynamics and pharmacokinetics of analgesics by identifying the sites, actions and time course of modulation. Whereas current analgesia methods include diverse drugs that act on a range of targets, if we can characterize the brain regions each drug acts upon, then we can more fully understand the neural mechanisms of analgesia. Table 1 lists the existing neuroimaging studies in which pharmacologic modulation of pain has been investigated.

Investigators have primarily used two methods, PET and fMRI, to investigate the pharmacological modulation of pain. To date, PET studies that have integrated analgesia and pain have used ¹⁵O-water to identify areas in which changes in regional cerebral blood flow (rCBF) occur [29-31]. Remifentanyl administration during painful heat stimulation has led to increased rCBF in the PAG and perigenual ACC, and decreased rCBF in the thalamus and somatosensory cortex [31]. These results have important implications for our understanding of the pharmacologic modulation of pain and the central opioidergic system as it demonstrates regions that may be involved in the control of pain (PAG and perigenual ACC) and those that may be involved in perception of decreased pain (somatosensory cortex) [31]. Casey et al. observed fentanyl induced rCBF changes in the mid-anterior region of the cingulate cortex during modulation of painful cold, but not during non-painful cold [30]. Interestingly, an earlier study by Adler et al., found that the fentanyl induced modulation of painful heat, but not non-painful heat, resulted in rCBF increases in the supplementary motor area and frontal cortex

[29]. The variability amongst these two studies warrants further investigation to determine the influence of the type of pain and other variables which may contribute to the differences in the responses observed. As ^{15}O -water labeled PET indirectly is sensitive to regional cerebral blood flow, interpretation of results must be performed carefully as any effect of the analgesic on the relaxation properties of the central vasculature may affect the hemodynamic response. A global relaxation in the responsiveness of the vasculature would result in a decrease in the ability to obtain further changes in signal. The use of fluorodeoxyglucose may more specifically identify areas of pharmacologic modulation by relying on glucose metabolism rather than hemodynamics for the source of the signal.

PET imaging has also been used to observe drug distribution. Otte et al. investigated the distribution of $[^{11}\text{C}]$ labeled eletriptan, an anti-migraine medication to observe the location and amount of medication that crosses the blood brain barrier [32].

One of the advantages of neuroimaging methods is the ability to identify the dose-dependent actions on specific neural systems, rather than on self-reports. Recently, Wagner et al. used PET to investigate the neural correlates of dose-dependent modulation of evoked pain by remifentanyl in healthy subjects [31]. They demonstrated dose-dependent reductions in the thalamus, basal ganglia, prefrontal, secondary somatosensory (S2), insular, temporal, parahippocampal, and occipital cortices and increases in the cingulo-frontal cortex and PAG. They compared only two dosage levels of remifentanyl due to the limitations imposed by the administration of radio-labeled tracers that restrict the time in which imaging can be performed and number of times a subject can be scanned. Functional MRI would be advantageous in such studies as it would allow greater flexibility in the number of times scans could be repeated in the same individuals, and it would enable the same study to be performed with smaller steps of increasing dosage. Similarly, repeated scans can be obtained in SPECT perfusion imaging if split doses are used [43]. Functional MRI has been integrated with the pharmacologic modulation of brain activity using two approaches: one in which alterations in brain activity are observed following drug administration and a second in which the neural correlates of a task are observed under basal conditions and following drug administration. The utilization of these two methods have been previously discussed [3]. Wise et al. used the latter method in a study in which they integrated a pharmacokinetic model into fMRI analysis (Figure 1) [34]. In their paper, they estimated the effect site concentration of remifentanyl to identify pharmacologic modulation of evoked pain. They extended this study to use fMRI to monitor the time course of actions of remifentanyl in the insula of healthy volunteers during evoked pain [35]. Using the insular cortical time course together with a simple pharmacokinetic model, they predicted the half-life of activity of remifentanyl. They demonstrated reductions in BOLD activity in the right insula during remifentanyl administration as compared to saline [34,35]. Their work provided important insights and support the concept that pharmacologic fMRI (phfMRI) can be used to investigate both the central neural systems correlates of analgesia and its time course.

The integration of pharmacologic modulation in fMRI studies can also be used to characterize different qualities of pain perception. Wise et al. have investigated the anxiolytic action of midazolam during pain-related anxiety [44]. They hypothesized that fMRI would reveal changes related to the modulation of anxiety related to a conditioned painful stimulus, however, pain related fMRI activity would remain unchanged. Percentage signal changes during pain were not significantly different between midazolam and saline infusions in the ACC, contralateral primary sensory cortex, bilateral anterior and posterior insula, or bilateral thalami. During anticipation of pain, significantly different percentage signal changes were observed in the contralateral anterior insula. Additionally, differences were observed in the ACC and ipsilateral S2. Studies such as this help characterize specific dimensions of pain.

In addition to PET and fMRI, MEG has also been used to observe the pharmacologic modulation of pain [42]. The greatest advantage of this technique may be that the source of the signal arises from magnetic dipoles due to neuronal activity and therefore is independent of any hemodynamic response. This method also offers advantages in terms of cost and temporal resolution. However, there are significant limitations of this technique in that imaging is restricted to cortical areas. Therefore, imaging of deep brain structures of interest such as PAG, thalamus, and ACC are not possible.

The role of neuroimaging in analgesic development

Despite the variety of available analgesics, many chronic pain patients receive inadequate relief. Physicians treating these challenging patients face daunting obstacles. To optimize compliance, minimize side-effects, and maximize analgesia, each one of these anti-neuropathic medications needs to be started at a low dose and titrated to effect over many weeks in a manner well-described as “labor-intensive” [45]. Frustratingly, each anti-neuropathic medication produces pain relief for only a minority of patients with neuropathic pain [46]. Not surprisingly, few physicians have the patience required to persist in a strategy involving months of frustrating, side-effect-laden medication trials. Therefore, novel methods to optimize the matching of a particular drug to a particular patient are needed.

These challenges not only affect the physician taking care of patients but also the pharmaceutical companies developing novel drugs. Drug development is an expensive process in terms of time and money and neuroimaging may improve the efficiency of that process. It is unknown why some chronic patients do not respond to some treatments. Neuroimaging could play an important role in discerning the neural differences between responsive and unresponsive patients that may lead to less expensive and more revealing clinical trials. Neuroimaging may also reveal potential targets that have yet to be explored. These techniques can also help identify more accurate dose response curves, thereby minimizing required dosages. The inclusion of neuroimaging may increase confidence in drug trial results by verifying that the desired targets are met.

The use of neuroimaging techniques in drug development may alter the way in which drug trials are designed and implemented [47,48]. Drug trials are a lengthy and costly process. By identifying if drugs are successfully modulating target regions early on, neuroimaging techniques may decrease the time of drugs trials and may allow the earlier termination of ineffective drugs. Non-invasive imaging techniques enable repeated scans within individual subjects. As a result this can decrease the number of subjects that are required. Further longitudinal studies may provide insight into the central mechanisms of drug sensitivity.

Remaining issues

Several remaining issues must be addressed to enable functional neuroimaging to be utilized successfully as a research and clinical tool to characterize the effects of analgesic agents in the human central nervous system. These issues include better characterization of the neural correlates underlying the inter-subject variability of pain perception, the heterogeneity of different pain conditions, appropriate experimental design including the selection of evoked pain stimuli and the value of applying our knowledge of acute pain processing in the context of chronic pain conditions. Additionally, appropriate controls must be defined in order to address placebo, expectancy and variables that may affect the neural-hemodynamic coupling. Finally the pharmacodynamics of a pharmacological agent must be considered in order to determine the most appropriate experimental method in which to study its actions.

Establishing the appropriate experimental conditions in which to study chronic pain can also be difficult. The nature of examining pain relief in chronic pain patients may include confounds

due to placebo and expectancy. These can be reduced by appropriate blinding, cross-over studies and other sophisticated study design and statistical methods [49]]. It remains unclear as to whether placebo responders should or should not be included in studies. To confound the discussion, it may be that the placebo responders are also the pharmacologic responders. Appropriate application of neuroimaging may distinguish the true pharmacologic response from the placebo response.

The method in which to study pain in a chronic pain group is also difficult. Some of this difficulty is related to the heterogeneity of chronic pain conditions. This contributes to a significant variance between subjects with different pain conditions. There is a need for larger number of studies in homogeneous patient populations that have been carefully phenotyped. Additionally, the manner in which pain is elicited in chronic pain patients can be a significant confounder. Commonly, an evoked stimulus is used. The central changes that take place in chronic pain conditions may result in differences in the processing of evoked pain as compared to unaffected individuals. Additionally, it is not clear how an experimentally evoked stimulus relates to a patient's spontaneous or dynamic pain. One recent option is to directly measure the patient's own endogenous or dynamic pain while simultaneously measuring the resulting brain activity. Apkarian et al., has performed this in low back pain patients and was able to use a patient's changing pain measurement as a regressor to identify specific brain regions involved with the perception of their spontaneous back pain [50]. Ultimately, this may find utility in combining this dynamic pain measurement with an analgesic. Even this method, however, has limitations as the very process of cognitively evaluating one's pain involves specialized brain regions that may confound interpretation of the specific analgesic activity.

An alternative to studying heterogeneous chronic pain conditions is to attempt to mimic chronic pain in healthy individuals. Topical capsaicin has been used to establish a sensitized state in healthy individuals [19]. Iannetti et al. used this experimental model to compare pain processing in healthy subjects under normal conditions and following capsaicin-induced secondary hyperalgesia as well as analgesia by gabapentin (Figure 2) [19]. These experimentally induced pain conditions clearly do not reproduce the true altered neural processing present in a chronic pain condition however, it may provide a model in which aspects of chronic pain can be studied under more controlled conditions.

There are technical limitations to consider in the application of neuroimaging to study pharmacologic analgesia. The main issue is the physiological source of the signal that many techniques depend on. Methods such as PET and fMRI are dependent on activity related neural-metabolic changes (e.g. glucose or oxygenation) and hemodynamic responses. Uncoupling of this relationship by pharmacologic actions will therefore adversely affect the observed signal. Changes in signal observed in fMRI and PET can then be the result of not only changes in neuronal activity, but global changes in cerebral blood flow or cerebral blood volume. Therefore, it is important to consider other sources of signal and verify that other factors are not major contributors. A recent review has identified key problem areas that should be considered in order to improve phfMRI [51]. Study designs must include controls to verify that the effects of the drugs are not on the hemodynamics, and are not global. One method of identifying the effects of pharmacologic agents on the properties of vasodilation is a breath holding task. Pattinson et al. [52] employed a breath holding task to demonstrate that the hemodynamic response observed was not a global effect and was in fact localized to target regions and were related to neural activity.

Some studies have included additional functional tasks that target regions that are known not to be modulated by the drug of interest. This delineates any global effects of the agent. A third control is to employ a crossover study that observes a task during analgesic and placebo administration such as that used by Iannetti et al. [19]. This design can control confounding

effects due to expectancy and placebo and allows each subject to be used as their own control. However, often same day scanning is impossible due to the latency of drug action.

There are some experimental limitations to be aware of that are governed by the properties of the analgesic of interest. The method of administration, drug action, latency, and period of effectiveness are all factors that need to be considered. The administration and latency of the drug may determine if studies are longitudinal or done over a single session or day. Medications administered intravenously have an advantage in that they have shorter latencies and so baseline scans can be acquired minutes before analgesia is achieved. There can also be variation in metabolism rates of medications across individuals. One approach taken to address this issue is the sampling of serum levels to identify the circulating level of analgesic.

Future Directions

Neuroimaging can aid the identification of the neural correlates of analgesia, the identification of new targets, and quicker and more accurate assessment of novel analgesics. The use of neuroimaging can help supplement the experimental design used to study the treatment of poorly understood chronic pain conditions such as central neuropathic pain. The central mechanisms underlying neuropathic pain are believed to include hyperexcitability of neurons [53]. Neuroimaging may first play a role in enhancing elegantly designed studies of pharmacological pain management. Siddall et al. recently observed several clinical measures of reduced neuronal hyperexcitability in spinal cord injury patients with neuropathic pain treated with pregabalin in comparison to placebo [54]. The use of neuroimaging would be helpful in elucidating the mechanisms and sites of modulation.

New techniques in neuroimaging could also be applied. An emerging field in fMRI is the use of resting state fMRI, or investigation of the default mode. Such experiments examine fluctuations in the signal changes during a task-free state and identify regions of neural activity by data driven analysis such as independent component analysis. To date this work has identified possible circuitry that is active when the brain is “resting” or not focused on a particular task. Differences in default mode networks have recently been observed in disorders such as depression [55] and anxiety [56] in comparison to healthy individuals. The technique could potentially identify differences in the general neural networking in chronic pain conditions.

A natural progression of phfMRI research is to look beyond individual regions of modulation and examine the networking between them. Connectivity analyses are used to establish the temporal relationship between areas of fMRI signal change observed and provide estimations of causality. To date, one animal study has measured cerebral blood volume (CBV) changes following administration of D-amphetamine and fluoxetine in order to delineate the functional connectivity of the dopamine and serotonin neurotransmitter systems [57]. The application of connectivity analyses in pain models may aid in identifying the network changes that lead to chronic pain conditions.

Structural imaging techniques may also aid in identifying new targets for analgesia. These methods could aid in identifying longitudinal structural changes following treatment, without susceptibility to hemodynamic signals that functional methods are reliant upon.

Neuroimaging may play an important role in the pain clinic in providing a tool for directing personalized medicine. The combination of neuroimaging and genetic biomarkers may indicate which analgesics a patient is most likely to respond to. Furthermore, these techniques may also identify patients who are likely to suffer side effects. A recent study used cerebral blood flow effects to investigate genotype-based differences in the response to remifentanyl [58].

To this point, we have focused the applications of brain imaging. It is also important to consider applications at the level of the brainstem and spinal cord. The periaqueductal gray, for example, is known to be an important structure in the descending modulation of pain. It is therefore of interest to not only examine regions of the brain involved in chronic pain and pharmacologic modulation, but also the spinal cord. PET has been employed to investigate morphine-induced cholinergic activity in the monkey spinal cord [59]. The development of fMRI for assessment of spinal cord function is relatively new. While it has been used to investigate sensory processing in subjects with spinal cord injury [60], the investigation of spinal cord activity in chronic pain patients has yet to be performed. These potential applications for spinal fMRI in chronic pain conditions and pharmacological interventions have been discussed in a recent review [61]. Investigation of this and other pain conditions and analgesia at the level of the spinal cord remains uncharted territory.

Finally, the use of multi-modal imaging combines the advantages of several techniques in order to gain more comprehensive information. For example, one may utilize the temporal resolution of EEG and the spatial resolution of fMRI. These techniques have been combined to observe the responses to noxious electrical stimulation [62] and laser-evoked responses [63]. Such studies used to investigate chronic pain and the modulation by analgesics pain help elucidate the time course of pharmacologic actions.

Conclusions

Neuroimaging can play an important role in directing the development of novel analgesics. Structural imaging techniques can identify regions of the brain in which anatomical differences exist in chronic pain conditions. Functional techniques such as fMRI and PET can identify the regions of interest in which there are metabolic differences. Techniques such as MRS may identify biomarkers that can be used to identify biochemical changes in these regions of interest. Neuroimaging methods can aid in identifying the brain regions in which modulation is required to achieve analgesia and which areas remain unaffected during inadequate pain relief in order to identify new targets for novel analgesics. In future, fMRI shows promise as a clinical tool for identifying specific analgesic needs of chronic pain patients, as well as in research as a method of assessment of analgesic action. In order for neuroimaging techniques to be utilized to their full potential, further development of proper controls is required to accurately interpret the obtained results. With established protocols in place, neuroimaging methods may lead to quicker and more efficient analgesic development strategies.

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Literature Cited

1. Melzack R. Phantom limbs and the concept of a neuromatrix. *Trends Neurosci* Mar;1990 13(3):88–92. [PubMed: 1691874]
2. Schweinhardt P, Bountra C, Tracey I. Pharmacological FMRI in the development of new analgesic compounds. *NMR Biomed* Oct;2006 19(6):702–11. [PubMed: 16986120]
3. Wise RG, Tracey I. The role of fMRI in drug discovery. *J Magn Reson Imaging* Jun;2006 23(6):862–76. [PubMed: 16649197]
4. Paulus MP, Stein MB. Role of functional magnetic resonance imaging in drug discovery. *Neuropsychol Rev* Jun;2007 17(2):179–88. [PubMed: 17436113]
5. Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *J Neurosci* Nov 17;2004 24(46):10410–5. [PubMed: 15548656]

6. Kuchinad A, Schweinhardt P, Seminowicz DA, Wood PB, Chizh BA, Bushnell MC. Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain? *J Neurosci* Apr 11;2007 27 (15):4004–7. [PubMed: 17428976]
7. Hadjipavlou G, Dunckley P, Behrens TE, Tracey I. Determining anatomical connectivities between cortical and brainstem pain processing regions in humans: a diffusion tensor imaging study in healthy controls. *Pain* Jul;2006 123(12):169–78. [PubMed: 16616418]
8. Grachev ID, Fredrickson BE, Apkarian AV. Abnormal brain chemistry in chronic back pain: an in vivo proton magnetic resonance spectroscopy study. *Pain* Dec 15;2000 89(1):7–18. [PubMed: 11113288]
9. Grachev ID, Thomas PS, Ramachandran TS. Decreased levels of N-acetylaspartate in dorsolateral prefrontal cortex in a case of intractable severe sympathetically mediated chronic pain (complex regional pain syndrome, type I). *Brain Cogn* Jun;2002 49(1):102–13. [PubMed: 12027396]
10. Fukui S, Matsuno M, Inubushi T, Nosaka S. N-Acetylaspartate concentrations in the thalami of neuropathic pain patients and healthy comparison subjects measured with (1)H-MRS. *Magn Reson Imaging* Jan;2006 24(1):75–9. [PubMed: 16410181]
11. Tallan HH, Moore S, Stein WH. N-Acetyl-L-aspartic acid in brain. *J Biol Chem* Mar;1956 219(1):257–64. [PubMed: 13295277]
12. Miller BL. A review of chemical issues in 1H NMR spectroscopy: N-acetyl-L-aspartate, creatine and choline. *NMR Biomed* Apr;1991 4(2):47–52. [PubMed: 1650241]
13. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A* Dec;1990 87(24):9868–72. [PubMed: 2124706]
14. Otte A, Halsband U. Brain imaging tools in neurosciences. *Journal of physiology, Paris* Jun;2006 99 (46):281–92.
15. Petrovic PP K, Ghatan PH, Stone-Elander S, Ingvar M. Pain-related cerebral activation is altered by a distracting cognitive task. *Pain* Apr;2000 4(2):47–52.
16. Koyama TM JG, Laurienti PJ, Coghill RC. The subjective experience of pain: where expectations become reality. *Proceedings of the National Academy of Sciences of the United States of America* Sept 6;2005 102(36):12950–5. [PubMed: 16150703]
17. Ochsner KL DH, Knierim K, Hanelin J, Ramachandran T, Glover GC, et al. Neural correlates of individual differences in pain-related fear and anxiety. 2006 Jan;2006 120(12):69–77.
18. deCharms RC, Maeda F, Glover GH, Ludlow D, Pauly JM, Soneji D, et al. Control over brain activation and pain learned by using real-time functional MRI. *Proc Natl Acad Sci U S A* Dec 20;2005 102(51):18626–31. [PubMed: 16352728]
19. Iannetti GD, Zambreanu L, Wise RG, Buchanan TJ, Huggins JP, Smart TS, et al. Pharmacological modulation of pain-related brain activity during normal and central sensitization states in humans. *Proc Natl Acad Sci U S A* Dec 13;2005 102(50):18195–200. [PubMed: 16330766]
20. Mackey SC, Maeda F. Functional imaging and the neural systems of chronic pain. *Neurosurg Clin N Am* Jul;2004 15(3):269–88. [PubMed: 15246336]
21. Witting N, Kupers RC, Svensson P, Jensen TS. A PET activation study of brush-evoked allodynia in patients with nerve injury pain. *Pain* Jan;2006 120(12):145–54. [PubMed: 16368192]
22. Zubieta JK, Smith YR, Bueller JA, Xu Y, Kilbourn MR, Jewett DM, et al. Regional mu opioid receptor regulation of sensory and affective dimensions of pain. *Science* Jul 13;2001 293(5528):311–5. [PubMed: 11452128]
23. Zubieta JK, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu Y, et al. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science* Feb 21;2003 299(5610):1240–3. [PubMed: 12595695]
24. Zubieta JK, Smith YR, Bueller JA, Xu Y, Kilbourn MR, Jewett DM, et al. mu-opioid receptor-mediated antinociceptive responses differ in men and women. *J Neurosci* Jun 15;2002 22(12):5100–7. [PubMed: 12077205]
25. Jones AK, Watabe H, Cunningham VJ, Jones T. Cerebral decreases in opioid receptor binding in patients with central neuropathic pain measured by [11C]diprenorphine binding and PET. *Eur J Pain* Oct;2004 8(5):479–85. [PubMed: 15324779]

26. Maarrawi J, Peyron R, Mertens P, Costes N, Magnin M, Sindou M, et al. Differential brain opioid receptor availability in central and peripheral neuropathic pain. *Pain* Jan;2007 127(12):183–94. [PubMed: 17137714]
27. Willoch F, Schindler F, Wester HJ, Empl M, Straube A, Schwaiger M, et al. Central poststroke pain and reduced opioid receptor binding within pain processing circuitries: a [¹¹C]diprenorphine PET study. *Pain* Apr;2004 108(3):213–20. [PubMed: 15030940]
28. Scott DJ, Domino EF, Heitzeg MM, Koeppe RA, Ni L, Guthrie S, et al. Smoking modulation of mu-opioid and dopamine D2 receptor-mediated neurotransmission in humans. *Neuropsychopharmacology* Feb;2007 32(2):450–7. [PubMed: 17091130]
29. Adler LJ, Gyulai FE, Diehl DJ, Mintun MA, Winter PM, Firestone LL. Regional brain activity changes associated with fentanyl analgesia elucidated by positron emission tomography. *Anesth Analg* Jan; 1997 84(1):120–6. [PubMed: 8989012]
30. Casey KL, Svensson P, Morrow TJ, Raz J, Jone C, Minoshima S. Selective opiate modulation of nociceptive processing in the human brain. *J Neurophysiol* Jul;2000 84(1):525–33. [PubMed: 10899224]
31. Wagner KJ, Sprenger T, Kochs EF, Tolle TR, Valet M, Willoch F. Imaging human cerebral pain modulation by dose-dependent opioid analgesia: a positron emission tomography activation study using remifentanyl. *Anesthesiology* Mar;2007 106(3):548–56. [PubMed: 17325514]
32. Otte AH B, Taylor K, Rubens R. The intracranial distribution of eletriptan: a combined [¹¹C]-eletriptan/[¹⁵O]CO/[¹⁵O]H₂O positron emission tomography (PET) study. *Eur J Nucl Med Mol Imaging* 2003;30(Suppl 2):S292.
33. Maihofner C, Ringler R, Herrndobler F, Koppert W. Brain imaging of analgesic and antihyperalgesic effects of cyclooxygenase inhibition in an experimental human pain model: a functional MRI study. *Eur J Neurosci* Sep;2007 26(5):1344–56. [PubMed: 17767511]
34. Wise RG, Rogers R, Painter D, Bantick S, Ploghaus A, Williams P, et al. Combining fMRI with a pharmacokinetic model to determine which brain areas activated by painful stimulation are specifically modulated by remifentanyl. *Neuroimage* Aug;2002 16(4):999–1014. [PubMed: 12202088]
35. Wise RG, Williams P, Tracey I. Using fMRI to quantify the time dependence of remifentanyl analgesia in the human brain. *Neuropsychopharmacology* Mar;2004 29(3):626–35. [PubMed: 14679387]
36. Rogers R, Wise RG, Painter DJ, Longe SE, Tracey I. An investigation to dissociate the analgesic and anesthetic properties of ketamine using functional magnetic resonance imaging. *Anesthesiology* Feb; 2004 100(2):292–301. [PubMed: 14739803]
37. Baliki M, Katz J, Chialvo DR, Apkarian AV. Single subject pharmacological-MRI (phMRI) study: modulation of brain activity of psoriatic arthritis pain by cyclooxygenase-2 inhibitor. *Mol Pain* Nov 2;2005 1:32. [PubMed: 16266429]
38. Morgan V, Pickens D, Gautam S, Kessler R, Mertz H. Amitriptyline reduces rectal pain related activation of the anterior cingulate cortex in patients with irritable bowel syndrome. *Gut* May;2005 54(5):601–7. [PubMed: 15831901]
39. Becerra L, Harter K, Gonzalez RG, Borsook D. Functional magnetic resonance imaging measures of the effects of morphine on central nervous system circuitry in opioid-naïve healthy volunteers. *Anesth Analg* Jul;2006 103(1):208–16. [PubMed: 16790655]table of contents
40. Sprenger T, Valet M, Woltmann R, Zimmer C, Freynhagen R, Kochs EF, et al. Imaging pain modulation by subanesthetic S-(+)-ketamine. *Anesth Analg* Sep;2006 103(3):729–37. [PubMed: 16931688]
41. Geha PY, Baliki MN, Chialvo DR, Harden RN, Paice JA, Apkarian AV. Brain activity for spontaneous pain of postherpetic neuralgia and its modulation by lidocaine patch therapy. *Pain* Mar;2007 128(12): 88–100. [PubMed: 17067740]
42. Hauck M, Bischoff P, Schmidt G, Zimmermann R, Lorenz J, Morrow TJ, et al. Clonidine effects on pain evoked SII activity in humans. *Eur J Pain* Nov;2006 10(8):757–65. [PubMed: 16439173]
43. Audenaert K, Brans B, Van Laere K, Lahorte P, Versijpt J, van Heeringen K, et al. Verbal fluency as a prefrontal activation probe: a validation study using 99mTc-ECD brain SPET. *European journal of nuclear medicine* Dec;2000 27(12):1800–8. [PubMed: 11189943]

44. Wise RG, Lujan BJ, Schweinhardt P, Peskett GD, Rogers R, Tracey I. The anxiolytic effects of midazolam during anticipation to pain revealed using fMRI. *Magn Reson Imaging*. Apr 24;2007
45. Collins SM RA, McQuay HJ, Wiffen P. Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systemic review. *J Pain Symptom Manage* 2000;20(6): 449–58. [PubMed: 11131263]
46. Katz JFNB, Dworkin RH. Clinical trial outcome in neuropathic pain. Relation to study characteristics. *Neurology*. Oct 3;2007
47. Otte A, Rose C, Zahringer A, Maier-Lenz H. New clinical technologies in drug development. *Der Internist* Feb;2008 49(2):232–7. [PubMed: 18210017]
48. Otte A, Audenaert K, Peremans K, Dierckx RA. Functional neuroimaging endpoints in drug development. *Nuclear medicine communications* Sep;2005 26(9):755–6. [PubMed: 16096577]
49. Dworkin RK J, Gitlin MJ. Placebo response in clinical trials of depression and its implications for research on chronic neuropathic pain. *Neurology* Feb 16;2005 65(12 Suppl 4):57–60.
50. Apkarian AV, Krauss BR, Fredrickson BE, Szevenyi NM. Imaging the pain of low back pain: functional magnetic resonance imaging in combination with monitoring subjective pain perception allows the study of clinical pain states. *Neurosci Lett* Feb 16;2001 299(12):57–60. [PubMed: 11166937]
51. Iannetti GD, Wise RG. BOLD functional MRI in disease and pharmacological studies: room for improvement? *Magn Reson Imaging*. May 11;2007
52. Pattinson KT, Rogers R, Mayhew SD, Tracey I, Wise RG. Pharmacological fMRI: measuring opioid effects on the BOLD response to hypercapnia. *J Cereb Blood Flow Metab* Feb;2007 27(2):414–23. [PubMed: 16736039]
53. Finnerup NB, Jensen TS. Spinal cord injury pain--mechanisms and treatment. *Eur J Neurol* Feb;2004 11(2):73–82. [PubMed: 14748766]
54. Siddall PJ, Cousins MJ, Otte A, Griesing T, Chambers R, Murphy TK. Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. *Neurology* Nov 28;2006 67(10):1792–800. [PubMed: 17130411]
55. Greicius MD, Flores BH, Menon V, Glover GH, Solvason HB, Kenna H, et al. Resting-State Functional Connectivity in Major Depression: Abnormally Increased Contributions from Subgenual Cingulate Cortex and Thalamus. *Biol Psychiatry*. Jan 8;2007
56. Zhao XH, Wang PJ, Li CB, Hu ZH, Xi Q, Wu WY, et al. Altered default mode network activity in patient with anxiety disorders: An fMRI study. *Eur J Radiol*. Mar 30;2007
57. Schwarz AJ, Gozzi A, Reese T, Bifone A. In vivo mapping of functional connectivity in neurotransmitter systems using pharmacological MRI. *Neuroimage* Feb 15;2007 34(4):1627–36. [PubMed: 17188903]
58. Kofke WA, Blissitt PA, Rao H, Wang J, Addya K, Detre J. Remifentanyl-induced cerebral blood flow effects in normal humans: dose and ApoE genotype. *Anesth Analg* Jul;2007 105(1):167–75. [PubMed: 17578972]
59. Gage HD, Gage JC, Tobin JR, Chiari A, Tong C, Xu Z, et al. Morphine-induced spinal cholinergic activation: in vivo imaging with positron emission tomography. *Pain* Mar;2001 91(12):139–45. [PubMed: 11240086]
60. Stroman PW, Kornelsen J, Bergman A, Krause V, Ethans K, Malisza KL, et al. Noninvasive assessment of the injured human spinal cord by means of functional magnetic resonance imaging. *Spinal Cord* Feb;2004 42(2):59–66. [PubMed: 14765137]
61. Kornelsen J, Mackey S. Potential clinical applications for spinal functional MRI. *Curr Pain Headache Rep* Jun;2007 11(3):165–70. [PubMed: 17504642]
62. Christmann C, Koeppe C, Braus DF, Ruf M, Flor H. A simultaneous EEG-fMRI study of painful electric stimulation. *Neuroimage* Feb 15;2007 34(4):1428–37. [PubMed: 17178235]
63. Iannetti GD, Niazy RK, Wise RG, Jezzard P, Brooks JC, Zambreau L, et al. Simultaneous recording of laser-evoked brain potentials and continuous, high-field functional magnetic resonance imaging in humans. *Neuroimage* Nov 15;2005 28(3):708–19. [PubMed: 16112589]

FIG. 2. fMRI signal time courses spatially averaged over the right insular cortex and then averaged over nine subjects in each infusion group: saline (a) and remifentanyl (b). Vertical dashed lines indicate the time of onset of the noxious thermal stimuli of 3-s duration. The background gray scale indicates the estimated remifentanyl effect site concentration through the imaging session.

Figure 1.

Reductions in the fMRI signal response to an evoked noxious thermal stimulus (dashed line) observed in the right anterior cortex following remifentanyl infusion (b) compared to saline (a). Reproduced with permission from [34].

Figure 2.

Modulation of evoked pain under normal and capsaicin induced sensitized states by placebo and gabapentin. Graphs demonstrate percentage signal change observed following an ROI analysis during 1) Normal placebo 2) Normal gabapentin 2) Sensitized placebo 3) Sensitized Gabapentin. Reproduced with permission from [19].

Table 1

Neuroimaging studies that have investigated the pharmacological modulation of pain

PET			
Citation	Subject	Analgesic	Noxious condition
[29]	healthy humans	Fentanyl	Heat pain (47°C - 48°C)
[30]	healthy humans	Fentanyl	Cold pain (1°C)
[31]	healthy humans	Remifentanyl	Heat pain (43.98°C - 46.2°C)
[32]	Humans with migraine	Eletriptan	Migraine headache
Functional MRI			
[33]	healthy humans	1) Parecoxib 2) acetylsalicylic acid	1) Acute mechanical pain 2) Mechanical impact hyperalgesia (induced by UV-B irradiation)
[34]	healthy humans	Remifentanyl	Heat pain (53.5°C - 58.5°C)
[35]	healthy humans	Remifentanyl	Heat pain (60°C)
[36]	healthy humans	Ketamine	Heat pain (55°C - 57.5°C)
[19]	healthy humans	Gabapentin	1) Heat pain (45°C), 2) Heat pain (45°C) during capsaicin induced hyperalgesia
[37]	humans with psoriatic arthritis	Selective cyclooxygenase-2 inhibitor	mechanical stimulation of joint
[38]	humans with irritable bowel syndrome	Amitriptyline	Rectal distention
[39]	healthy humans	Morphine	Heat pain (46°C)
[40]	healthy humans	S-(+)-Ketamine	Heat pain (1°C above individual pain threshold)
[41]	humans with postherpetic neuralgia	Lidocaine patch	Spontaneous pain
MEG			
[42]	healthy humans	Clonidine	Intracutaneous electrical stimulation (Intensity 2-3x individual threshold, 5ms)