Neurotherapeutics (2022) 19:1467–1488
https://doi.org/10.1007/s13311-022-01274-z

CURRENT PERSPECTIVES

# Neuroimaging Assessment of Pain

**Jing Luo[1,2] · Hui-Qi Zhu[2,3] · Bo Gou[1] · Xue-Qiang Wang[2]**

Accepted: 5 July 2022 / Published online: 28 July 2022


**Abstract**
Pain is an unpleasant sensory and emotional experience. Understanding the neural mechanisms of acute and chronic pain and the brain changes affecting pain factors is important for finding pain treatment methods. The emergence and progress of non-invasive neuroimaging technology can help us better understand pain at the neural level. Recent developments in identifying brain-based biomarkers of pain through advances in advanced imaging can provide some foundations for predicting and detecting pain. For example, a neurologic pain signature (involving brain regions that receive nociceptive afferents) and a stimulus intensity-independent pain signature (involving brain regions that do not show increased activity in proportion to noxious stimulus intensity) were developed based on multivariate modeling to identify processes related to the pain experience. However, an accurate and comprehensive review of common neuroimaging techniques for evaluating pain is lacking. This paper reviews the mechanism, clinical application, reliability, strengths, and limitations of common neuroimaging techniques for assessing pain to promote our further understanding of pain.

**Keywords** Neuroimaging · Pain · Mechanism · Reliability · Review

## Introduction

The current International Association for the Study of Pain definition of pain is "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [1]. Pain has a certain protective effect on the body from excessive nociceptive behavior. However, an increasing number of people suffer from months or years of pain, which can seriously impair their quality of life [2]. Pain is widely thought to emerge from distributed brain networks involving sensory, emotional, and cognitive processes [3]. Acute pain caused by noxious stimuli has been explored in many experimental studies. The general pain pathway of acute pain begins with nociceptive neurons in the periphery, detecting signals from injurious stimuli and transmitting these signals to the spinal cord via primary afferent nerve fibers. These signals are then fed into several ascending spinal pathways, which serve thalamic targets and brainstem nuclei. Finally, the nociceptive impulses project to the cortex, producing pain perception and modulation, which will be sent to the spinal cord via descending pathway to induce pain modulation. Therefore, multiple pathways in the central nervous system are involved in pain processing, and distinguishing distinct brain functions becomes extremely complex [4, 5]. Given the complexity of pain, the research process of pain is long and difficult. To date, piecing together the pain system in the brain has been a question of frustration and debate. Before the advent of neuroimaging technology, our understanding of the role of the brain in pain was limited to autopsies, a series of experiments in neurosurgery, and corresponding animal models [6]. As a result of the brain's key role in generating pain perception, the ability to noninvasively assess brain function in vivo is important. These examples of decoding visual perception by analyzing brain activities via advanced algorithms provide a theoretical basis for decoding pain using functional imaging [7, 8]. Therefore, functional

Bo Gou and Xue-Qiang Wang contributed equally.

✉ Bo Gou
85244025@qq.com

✉ Xue-Qiang Wang
qiang897@163.com

[1] Department of Sport Rehabilitation, Xian Physical Education University, Xian, China

[2] Department of Sport Rehabilitation, Shanghai University of Sport, Shanghai, China

[3] Department of Sport Rehabilitation, Shenyang Sport University, Shenyang, China

neuroimaging can be used to derive brain biomarkers as an objective evaluation of pain to address dependence on assessing pain via verbal reports [9]. However, contextual factors largely influence the subjective pain experience and the report of the pain experience [10], which significantly increases the difficulty of the objective evaluation of pain. The development of modern noninvasive neuroimaging technology allows the study of pain in different directions, such as anatomy, physiology, and psychology. A neuroimaging study of acute pain caused by noxious stimulation is a milestone for understanding the neural basis of pain. The brain areas most commonly activated by acute pain are the primary somatosensory cortex (S1), the secondary somatosensory cortex (S2), anterior cingulate cortex (ACC), insula, prefrontal cortex (PFC), thalamus, and cerebellum. These areas are often referred to as the "pain matrix" [11]. Although this "pain matrix" has been widely used to build models of where and how nociception is processed in the brain, convincing experimental evidence demonstrating that this network is specifically related to nociception is lacking. In addition to these regions, other regions have been shown by neuroimaging to have nociceptive input, including the nucleus accumbens, amygdala [12, 13], and periaqueductal grey (PAG) [14]. In recent years, identifying brain mapping for pain perception has been a hotly debated topic because the inherently subjective quality of pain and the functional multiplicity of the brain largely limit the identification of areas that are only activated by pain [15]. For example, the "pain matrix" is also activated by non-nociceptive stimuli [16], which suggests that the "pain matrix" may involve a large-scale sensory matrix containing pain. Therefore, there is still disagreement about the extent to which neuroimaging assessments of pain-related brain function are related to pain. A novel concept is that pain might emerge from the coordinated activity of an integrated brain network. Over the past decade, the use of better biomarkers based on multivariate modeling to examine information generated from many brain regions has been a hot topic, and some developments have been made, such as the neurological pain signature (NPS; see details in 2) [15].

Changes in pain-related neurons can be assessed through two imaging modalities of these neuroimaging techniques, which measure alterations in metabolism (blood flow, volume, oxygen, and glucose metabolism) and alterations in neurochemistry (neurotransmitter precursor uptake and receptor binding) [11]. These common functional neuroimaging techniques are magnetic resonance imaging (MRI), functional MRI (fMRI), near-infrared spectrum instrument (NIRS), electroencephalogram (EEG), magnetoencephalography (MEG), and positron emission tomography (PET). Among them, fMRI, NIRS, and PET are based on hemodynamic methods, whereas EEG and MEG are based on electrophysiological methods [6]. In the acute and chronic phases of patients with low back pain, using functional neuroimaging to derive brain biomarkers may be an objective evaluation of pain level and guide clinical rehabilitation treatment decisions for pain. However, contextual factors largely influence the subjective pain experience and the report of the pain experience, which can significantly increase the difficulty of the objective evaluation of pain in the clinical context. Therefore, applying and selecting the appropriate assessment tool are particularly important. This paper systematically summarizes the description, reliability, validity, applications, strengths, and limitations of common assessment pain neuroimaging techniques that guide pain neuroimaging assessment. The limitations and strengths of these neuroimaging techniques in pain assessment are compared (Fig. 1).

## MRI and fMRI

### Description

MRI is a noninvasive medical imaging technique based on nuclear magnetic resonance (NMR) and is widely used


**Fig. 1** Common neuroimaging techniques for assessing pain. This chart only represents the high and low rankings of various technologies, not the exact value. Temporal resolution: compared with other technologies, EEG and MEG have higher time resolution. Spatial resolution: fMRI and PET undoubtedly have the highest spatial resolution. Coverage: fMRI and PET provide detection of all regions of the whole brain, whereas other techniques usually cannot detect the prefrontal lobe and cerebellum. Signal detection: EEG and MEG directly provide neuronal activity, whereas other techniques detect it indirectly. Silence: fMRI and PET produce high noise in pain assessment, whereas fNIRS, EEG, and MEG are silent recording techniques. Mobility: the high mobility of fNIRS and EEG can be used for bedside monitoring, whereas other technologies do not do this due to the limitation of mobility. Affordability: compared with fNIRS and EEG, fMRI and PET are costly, followed by MEG

in clinical and research applications [17]. The two main derivative techniques for assessing pain are as follows: [1] diffusion tensor imaging (DTI)—MRI quantifies and images the characteristics of water diffusion, including directivity and anisotropy. On the basis of quantitative information to describe microscopic changes in cerebral white matter in pain, the main principal diffusivity parameters in the assessment of pain are fractional anisotropy (FA) and mean diffusivity (MD), which are used to measure changes in the brain microstructure caused by chronic pain. FA is a measure that describes the direction and degree of water diffusion. FA decreases in the primary somatosensory cortex that represents the lower face in patients with trigeminal neuropathy pain. MD describes the average degree of water movement; MD is low in the globus pallidus but increases in the thalamus and internal capsule in recurrent abdominal pain [18–20]. Breivik et al. [2] Structural MRI (sMRI) is based on voxel-based morphometry (VBM) for clear imaging of white and gray matter information in the brain. For example, VBM analysis found that the grey matter density of the dorsolateral prefrontal cortex (DLPFC), thalamus, and middle cingulate cortex (MCC) increased in patients with chronic low back pain; thus, gray matter structural changes in pain moderation-related areas in chronic pain are important [21]. A detailed assessment mechanism is shown in Fig. 2.

fMRI is a neuroimaging technique for measuring hemodynamic changes after pain, especially the influence of emotion and cognition on pain. fMRI also has two frequently used derivative techniques to assess pain: [1] blood-oxygen-level-dependent (BOLD) imaging is the current standard in pain neuroimaging. When pain stimulation is applied, neural activity increases, causing local cerebral blood flow (CBF) and cerebral metabolic rate of oxygen (CMRO2) to increase. The vasodilatation reaction occurs to reverse deoxygenated hemoglobin (dHb) accumulation and oxygenated hemoglobin (HbO2) reduction. dHb is paramagnetic and causes endogenous gradients. Gradient refocused echo (GRE) methods can be used to acquire BOLD signals [22, 23]. Breivik et al. [2] Arterial spin labeling (ASL) fMRI uses arterial water as an endogenous tracer to acquire the so-called labeled and control images, obtain the difference image (by "control" images– "labeled" image), and convert the difference image to the CBF image. Given that the endogenous tracer is arterial water, ASL fMRI is a noninvasive and repeatable imaging technology [24].

In recent years, MRI and fMRI research on pain has become more extensive and gradually more mature. Recently, in the PubMed database, the keywords "MRI" or "fMRI" and "pain" returned over 53,600 related articles, whereas the keywords "fMRI" and "pain" returned over 46,900 related articles. Both values showed that the number of MRI or fMRI research articles on pain has shown a significant upward trend since the 1980s. In particular, fMRI has been extensively used for the study of pain brain processes. When subjects perform pain tasks or other related neurological events, fMRI can show dynamic brain processing, which is critical for the neural pathway, regulation mechanism, and treatment of pain.

## Clinical Applications

The application of MRI and fMRI to the study of pain focuses on the mechanisms of pain perception and analgesia.

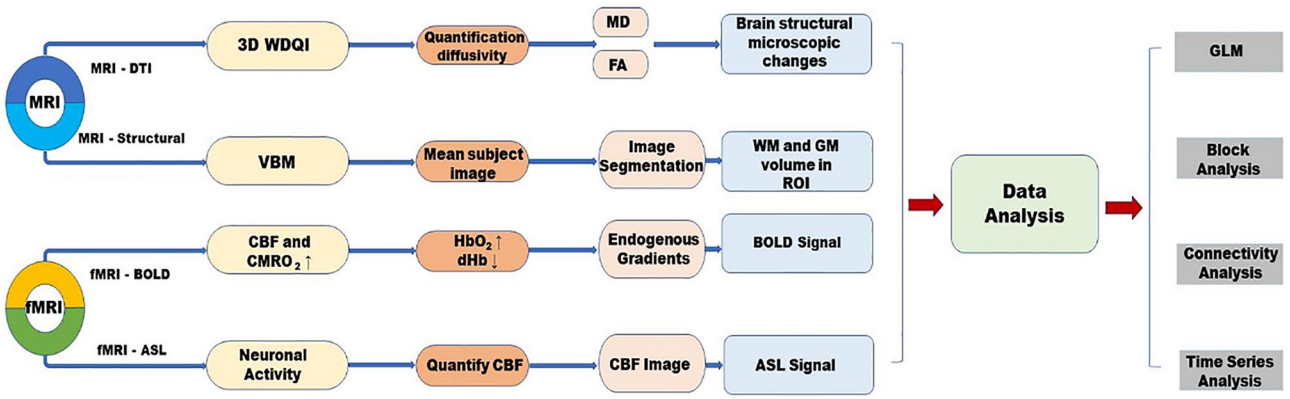


**Fig. 2** Overview of data acquisition and data preprocessing of the main derivative techniques of MRI and fMRI. MRI-DTI obtains the quantification of diffusivity based on 3D water diffusion quantitative information (WDQI) and then measures the microscopic changes in brain structure caused by pain according to the main diffusion rate parameters (MD, mean diffusivity, FA, fractional anisotropy). MRI-structural obtains the mean subject image based on voxel-based morphometry (VBM) and then obtains the white matter (WM) and gray matter (GM) in the region of interest (ROI) after image segmentation. fMRI-BOLD obtains BOLD signal according to the increase in cerebral blood flow (CBF) and cerebral metabolic rate of oxygen ($CMRO_2$) caused by pain, which leads to the increase in deoxyhemoglobin (dHb) and the decrease in oxyhemoglobin ($HbO_2$). fMRI-ASL obtains a CBF image by quantifying CBF and then obtains an ASL signal. The data analysis for these technologies is usually general linear model (GLM), block analysis, connectivity analysis, and time series analysis

Investigating pain-specific and pain-selective brain activity is central to pain perception. For example, for specific brain activity that encodes the intensity of pain stimuli, Zhang et al. used multisensory fMRI and found nociceptive-specific brain regions (the dorsolateral part of superior frontal gyrus, supplementary motor area, and medial part of superior frontal gyrus) and nociceptive-preferential regions (the Rolandic operculum, dorsolateral part of superior frontal gyrus, and opercular part of inferior frontal gyrus). However, confused stimulus intensity processing with pain perception may obscure nociceptive-specific brain regions and nociceptive-preferential regions [25]. In another study investigating different stimulus intensities around the pain threshold to separate brain processing of pain stimulus intensity, they applied noxious stimuli of gaseous carbon dioxide to the nasal mucosa of 24 healthy subjects. They changed the concentrations of gaseous carbon dioxide from below the pain threshold to above the pain threshold. Their results suggest that the brain processing of pain qualitative changes caused by nociceptive stimuli may be restricted to the posterior insular cortex [26]. Similarly, Horing et al. found that insular and peri-insular regions are strongly involved in processing painful stimuli, and an area in the posterior parietal operculum showed pain preference [27]. This result suggested that neurons are selective for pain in this area and exhibit a response preference for pain [8]. Extensive work has been carried out to explore the cerebral cortex of pain perception through pain specificity and sensitivity. Despite some achievements, defining further anatomy is challenging due to heterogeneous microscale neuronal processing units in fMRI [15].

Moreover, cognitive and emotional factors have a significant influence on pain perception. The medial pain system is involved in the emotional dimension of pain [28], and somatosensory circuits are reciprocally interconnected in pain perception and converge on the same anterior cingulate cortical and subcortical structures [29]. The neural mechanisms of different cognition, emotions, and mood states that impact pain perception and ability are also part of the neuroimaging assessment of pain. For example, Orenius et al. investigated the interaction of negative and positive emotions with pain at the nerve level and found a valence-independent interaction of emotion and pain in SII [30]. By contrast, pain attracts attention to interfere with cognitive functioning via a pain-specific interruptive mechanism that disrupts visual encoding to impaired memory over and above the unpleasantness of a stimulus. At the nerve level, the activity of the right anterior hippocampus and the functional connectivity (FC) of this region with extrastriate regions decrease [31]. These findings indicate the current absence of a specific brain system for pain.

Multi-variate pattern analyses (MVPAs) based on functional neuroimaging allow the integration of information from multiple areas of the brain network [32, 33]. Previous fMRI studies by MVPAs examined all voxels in the brain and used the finite impulse model of task-evoked hemodynamic responses to avoid the limitations of temporal and spatial assumptions. The results showed a supramodal network involved in orienting attention to, detecting, and reacting to salient events, including a sensorimotor response network, salience-mediated attention network, and a default-mode network [34, 35]. Moreover, Mano et al. used the MVPA approach of fMRI and decoded detailed information about subjective visual perception [36]. Wager et al. used machine-learning (ML) analyses for fMRI data of many brain network activities associated with thermal pain, and they called this "decode method" NPS. The NPS, as a multivariate brain pattern tracking nociceptive pain, demonstrates high sensitivity and specificity for distinguishing somatic pain and nonpainful warmth pain, pain anticipation, and pain recall [37]. However, a meta-analysis suggested that NPS is not effective for tracking modulated pain (placebo analgesia) [38]. If NPS predicts pain experience based on above and beyond classic nociceptive pain-related brain regions, then it may provide a more comprehensive pattern of pain prediction. Woo et al. developed a multivariate pattern signature to predict activity patterns involving brain regions that do not show increased activity in proportion to noxious stimulus intensity, including the nucleus accumbens, lateral prefrontal, and other regions. This multivariate pattern signature response mediates psychological manipulations of expectations that NPS cannot mediate. They called this multivariate pattern signature the stimulus intensity-independent pain signature [39]. Recent developments are based on neural signatures to identify brain-based biomarkers of pain. For example, Lee et al. developed an fMRI signature based on the FC of the whole brain that tracks experimental tonic pain. This signature showed high sensitivity and specificity to tonic pain and predicted clinical pain severity [40]. Overall, the use of neuroimaging biomarkers based on multivariate modeling provided some foundation for the prediction, prognosis, and detection of pain.

These interconnections provide the theoretical basis or hypothetical model for analgesics. Expectations and anticipation of pain are considered major contributors to placebo analgesia [41]. Anticipation modulates pain through a top-down mechanism, whether in nonpainful or painful conditions; individual psychophysical pain intensity is positively correlated with the activation of contralateral SI and bilateral ACC, anterior insula, and medial PFC [42]. Schmid et al. conducted a further placebo study on this basis; they applied positive and negative treatment expectations for 36 healthy subjects in visceral pain. Compared with neutral expectations, they found that positive expectations significantly reduce activation of S1 and S2 during anticipation and significantly reduce activation of the insula, somatosensory cortex, and amygdala during pain stimulation, thereby explaining

the central mechanism of placebo analgesia [43]. Thus, the modulatory system associated with placebo analgesia may be similar to the emotional modulation of the pain system. The circuitry involved in placebo analgesia with the attentional modulation of pain appears to be independent [44].

Real-time fMRI (rtfMRI) is a technique that allows simultaneous BOLD fMRI data analysis and image acquisition. Neurofeedback allows subjects to observe their own brain's fMRI signal and modulate it. RtfMRI neurofeedback is a novel technique that combines rtfMRI and neurofeedback techniques, allowing subjects to learn to modulate the brain regions of pain perception and control pain [45]. The use of rtfMRI feedback trained to modulate rACC in healthy controls and patients with chronic pain activity and alter pain perception allows the control of the endogenous pain modulatory system. This may help pain patients directly activate the endogenous pain modulatory system for better pain relief [46, 47].

In addition, the central mechanism of analgesia is the focus of fMRI research on acupuncture. Acupuncture achieves analgesia by inhibiting the activity of pain stimulation activation areas, and optimal intensities of acupuncture will achieve better analgesia effects [48]. Given that acupuncture is not given once in clinical practice but is repeated several times, Li et al. repeated acupuncture stimulation for 40 healthy subjects at acupoint Zusanli (ST36). Their results indicated the cumulative effects of acupuncture analgesia response by bilateral MCC, bilateral paracentral lobule, S2, and right thalamus [49]. Another study indicated a longer duration of acupuncture analgesia effects than the needling period, which may explain the cumulative effects of acupuncture analgesia from the side [50].

Assessment of clinical pain via fMRI focuses on chronic musculoskeletal pain, chronic neuropathic pain, and chronic and chronic visceral pain. Fibromyalgia (FM) is chronic musculoskeletal pain with clinical symptoms such as sleep disturbance, fatigue, and cognitive disturbance; its pathogenesis remains unclear [51]. The central mechanism of common intervention methods for FM pain is to activate the pain regulation areas and inactivate the pain sensory areas. Exercise therapy in FM has been proven to be highly effective in recent years. McLoughlin et al. applied heat pain stimulation and physical activity in 16 patients with FM, and their results found that physical activity is positively correlated with activation of the DLPFC, posterior cingulate cortex (PCC), and posterior insula but negatively correlated with activation of S1 and superior parietal cortices. These results indicate that the central mechanism of exercise therapy is increased activation of pain regulation areas and inhibition of pain sensory areas [52]. Given that patients with FM experience exercise difficulty, cognitive behavioral therapy (CBT) is widely used to treat FM. A randomized controlled trial showed that CBT increases the activation of pain regulation areas and changes the brain process of pain [53].

fMRI is used for the assessment of neuropathic pain to study the central mechanism of pain and intervention methods. Postherpetic neuralgia (PHN) is a complex neuropathic pain that is directly caused by herpes zoster, and it is the most frequent chronic complication of herpes zoster [54, 55]. Compared with healthy subjects, activation in patients with PHN increases in the left striatum, right thalamus, left S1, left insula, left amygdala, and left inferior parietal lobule but decreases in the frontal cortex. The reward circuitry is highly correlated with symptoms of patients with PHN [56]. The use of rtfMRI neurofeedback to self-regulate the activation of the rostral anterior cingulate cortex (rACC) may be an effective treatment for PHN [57].

Irritable bowel syndrome (IBS) is a functional disorder of the gastrointestinal tract with a high prevalence worldwide [58]. Berman et al. applied aversive pelvic visceral distention to 14 patients with IBS and 12 healthy subjects; compared with the control group, they found that patients with IBS exhibit significant inactivation in the right posterior insula and bilateral dorsal brainstem (DBS). Inactivation of DBS appears to interfere with descending corticolimbic inhibition, leading to enhanced pain sensitivity in patients with IBS [59].

## Reliability of fMRI Assessment of Pain

To examine the consistency, stability, and reliability of fMRI assessment of pain, related reliability studies are essential. We included articles about the reliability of fMRI assessment of pain studies in the PubMed database. Test–retest reliability is a measurement theory concept that quantifies the stability of a measure under repeated measurements [60]. Given that the intraclass correlation coefficient (ICC) is widely used to examine the reliability of neuroimaging technology [61, 62], the ICC value may be used as an indicator to assess the test–retest reliability. ICC, based on the analysis of variance, is a widely used reliability index in the medical field [63]. In the studies of neuroimaging assessment of pain, typical ICC is defined as the proportion of total measured variance; the between-subject variance is in the numerator and within-subject variance is included in the total variance in the denominator: $\mathrm{ICC} = \frac{\text{between-subject variance}}{\text{between-subject variance+within-subject measurement variance}}$. Therefore, a decrease in the ICC ratio represents subjects becoming more similar to each other and/or within-subject measurements becoming more distinct [61, 64, 65]. The ICC ratio index ranges from 0 to 1, where 0 means completely unreliable, less than 0.4 means poor reliability, between 0.4 and 0.6 means fair reliability, between 0.61

and 0.8 means good reliability, greater than 0.8 means excellent reliability, and 1 means completely reliable [66]. Information related to these studies is in Table 1.

The analysis of the included studies found that the reliability of fMRI focuses on the reliability of fMRI brain imaging, especially BOLD-fMRI. Most studies show high test–retest reliability, indicating that the results have high reliability and compared with the test–retest reliability of the VAS pain rating. To assess the reliability of fMRI for pain-related regions, Letzen et al. performed three fMRI scans on 22 young healthy subjects (mean age = 22.6, 13 females) during heat pain stimulation, and their results appeared reliable ($0.32 < ICC < 0.88$). However, higher reliability of VAS pain ratings was reported ($0.93 < ICC < 0.96$) [67]. A subsequent study yielded similar results; the test–retest reliability of BOLD-fMRI is also reliable ($0.5 < ICC < 0.859$), and subtle differences may be due to subject differences, such as all subjects being males and the mean age being 31. The reliability of VAS pain ratings showed almost no difference (ICC = 0.938) [68]. Moreover, Letzen et al. reported the test–retest reliability for FC of pain-related brain regions and VAS. FC showed that they varied widely in reliability ($0.174 < ICC < 0.766$) for different regions, and FC between the right nucleus accumbens and medial PFC showed the highest reliability ($0.649 < ICC < 0.766$) [69]. These findings suggest that fMRI provides reliable results of pain brain response, but complex influences may make fMRI a poor substitute for the self-reporting of pain in aspects of the psychological properties of pain.

In a longitudinal fMRI pain study, different brain regions showed various degrees of reliability, namely, high reliability in ACC, MCC, AI, and S2 but low reliability in pregenual ACC, S1, and PI [70]. The reliability of pain stimuli differed between levels, and a higher level of pain stimuli appeared to have more reliable results [68]. Time may also affect the reliability of fMRI assessment of pain. Han et al. found different reliability of fMRI-based NPS in within-day (ICC = 0.84), 5-day (ICC = 0.74), and 1-month (ICC = 0.46) [71].

To improve the feasibility, reliability, and breadth of fMRI assessment of pain, new pain stimulation devices and methods have been proposed. For example, to better assess central nervous system processes following dentoalveolar tactile stimulation using fMRI, Moana-Filho et al. provided a dental chair-side device and obtained reliable results (ICC = 0.89) [72]. In addition, Gay et al. proposed a novel MR-compatible device to apply pressure pain stimulation in the lumbar spine of 8 patients with LBP and 5 healthy subjects (mean age = 42.5); their results found good to excellent reliability for peak-voxel T-score ($0.78 < ICC < 0.89$) and fair reliability for cluster size ($0.43 < ICC < 0.76$) [66].

## Strengths of fMRI for Pain Assessment

### High Spatial Resolution

The millimeter-level high spatial resolution of fMRI provides fine soft-tissue contrast and accurate dynamic physiologic changes to assess pain brain processing [73]. This high spatial resolution of fMRI is useful in multivariate pattern analysis under specific decoding of pain-related brain regions [74].

### Noninvasiveness and Nonionizing Radiation

For fMRI assessment of pain, noninvasiveness is essential. Thus, it can be performed in safe, noninvasive conditions, repeated multiple times, and provide reliable test–retest reliability. Compared with PET, MRI and fMRI do not use radiotracers. Radiotracers will put subjects at a significantly increased risk of exposure to ionizing radiation, especially in children [75].

### Multi-sequence Imaging

Multi-sequence assessments may be valuable for pain, and MRI satisfies this point compared with other neuroimaging techniques. For example, a multi-sequence fusion of fMRI, DTI, and MWI has been used to assess Parkinson's disease [76].

## Limitations of fMRI for Pain Assessment

### Susceptibility Artifacts

Pain itself or the effects of painful stimuli will cause head movement during scanning and generate motion and susceptibility artifacts to confound fMRI data, even though many current studies have proposed various ways to remove this effect [77].

### Acoustic Noise and Indirect Detection of Neuronal Activity

According to related reports, MRI will generate noise in the range of 122–131 dB during scanning. Despite wearing earplugs, cochlear function can be affected [78]. In the fMRI assessment of pain, some ceiling effects on blood flow and deoxyhemoglobin/oxyhemoglobin may influence the detection of neuronal activity and the assessment of pain specificity [79].

### Low Portability and High Cost

Traditional MRI scanning needs a specially shielded room and bulky, hard-to-move devices [80]. In general, patients

**Table 1** Reliability of fMRI assessment of pain

| Reference | Pain type | Task | Sample | Test–retest reliability | Reliability-related areas | Evaluation |
|---|---|---|---|---|---|---|
| [72] | Dental pain | Intraoral stimulation | *N*1 = 5 healthy; mage = 51<br>*N*2 = 5 atypical odontalgia patients; mage = 53 | Pain threshold: ICC = 0.89 | NA | Feasibility of delivering dentoalveolar dynamic pressure device |
| [70] | Thermal pain | Painful heat stimulation, motor task | *N* = 14 healthy 7 M 7F; mage = 44.3 | BOLD-fMRI: 0.4 < ICC < 0.8 | High: ACC, MCC, AI, S2<br>Low: pregenual ACC, S1, PI | Reliability of brain areas related to pain |
| [67] | Thermal pain | Painful heat stimulation | *N* = 22 healthy 9 M 13F; mage = 22.6 | BOLD-fMRI: 0.32 < ICC < 0.88<br>VAS: 0.93 < ICC < 0.96 | ACC, AI | Reliable fMRI test–retest reliability |
| [66] | Pressure pain | Pressure pain stimulation | *N* = 13 7 M 6F; mage = 42.5<br>(*N*1 = 8 LBP, *N*2 = 5 healthy) | BOLD-fMRI: 0.78 < ICC < 0.89 (peak-voxel T-score), 0.43 < ICC < 0.76 (cluster size) | ACC, insula, S1 | Reliability of delivering pressure pain stimulus to the lumbar spine device |
| [199] | Pressure pain | Pressure pain stimulation | *N* = 23 CLBP 11 M 12F; mage = 25.7 | Pain threshold: ICC = 0.913 | NA | Reliability of delivering pressure pain stimulus to the lumbar spine device |
| [68] | Thermal pain | Thermal pain stimulation | *N* = 12 healthy all M; mage = 31 | BOLD-fMRI: 0.520 < ICC < 0.682 (40 and 44 °C heat pain stimuli); 0.5 < ICC < 0.859 (7/10 heat pain stimuli)<br>VAS: ICC = 0.938 | 40 and 44 °C: superior frontal lobe, thalamus, cerebellum, and AI<br>7/10: frontal lobe, cingulate, SMA, thalamus, cerebellum, and AI | Different reliability in different levels of pain stimuli |
| [69] | Thermal pain | Thermal pain stimulation | *N* = 32 healthy 17 M 15F; mage = 22.5 | BOLD-fMRI: 0.174 < ICC < 0.766<br>VAS: 0.906 < ICC < 0.947 | FC: Nac-mPFC, IC-ACC, thalamus-IC, and thalamus-S1 | Reliability of FC-related pain |
| [200] | Pressure pain | Pressure pain stimulation | *N* = 23 healthy 14 M 9F; mage = 26 | BOLD-fMRI: ICC = 0.46 (brain), ICC = 0.6 (network)<br>VAS: ICC = 0.75 | Thalamus, insula, S1, S2, and inferior frontal regions | Reliable fMRI test–retest reliability |
| [201] | Laser pain | Laser pain stimulation | *N* = 22 healthy | BOLD-fMRI: 0.4 < ICC < 0.8<br>Pain threshold: ICC = 0.56<br>VAS: ICC = 0.657 | ACC, insula, thalamus, S1, and S2 | Importance of baseline mental state changes on the impact of reliability of fMRI |
| [71] | Thermal pain, pressure pain | Thermal and pressure pain stimulation | *N* = 444 | BOLD-fMRI: ICC = 0.84 (within-day), ICC = 0.74 (5-day), ICC = 0.46 (1-month) | Thalamus, PI, MI, S2 | Reliability of the fMRI-based neurologic pain signature |

*Mage*, mean age; *N*, number; *M*, male; *F*, female; *ICC*, intraclass correlation coefficient; *BOLD*, blood oxygen level dependent; *VAS*, visual analog scale; *FC*, functional connectivity; *A/M/PCC*, anterior/middle/posterior cingulate cortex; *S1/S2*, primary/second somatosensory cortex; *A/M/PI*, anterior/middle/posterior insula; *mPFC*, medial prefrontal cortex; *Nac*, nucleus accumbens; *SMA*, supplementary motor area; *CLBP*, chronic low back pain; *NA*, not available

with metal or electronic implants in their bodies and with claustrophobia or are pregnant are restricted [81]. The cost of an MRI is $60, which is generally expensive for nondeveloped areas [82]. The use of fMRI to moderate cancer pain is difficult due to the high cost [83].

## NIRS

### Description

fNIRS is a noninvasive, portable neuroimaging technique for monitoring cerebral hemodynamic changes to assess pain. fNIRS records brain function indirectly in the form of fluctuations in the hemoglobin concentration (Fig. 3). fNIRS uses a light source into emit near-infrared light to the head, and the wavelength is usually 650–1000 nm. When passing through the skin, skull, cerebrospinal fluid, and cerebral cortex, it is banana shaped in spatial distribution and then absorbed and scattered, resulting in attenuation to photodetectors 2–5 cm away from the light source. The distance between the light source and photodetectors is determined depending on the intensity of near-infrared light, experimental design, and the basic situation of the subjects. The changes in dHb and HbO2 are separated and monitored based on the changes in wavelength intensity within the spectral range [84]. The three kinds of commonly used near-infrared instruments are divided based on specific illumination type: [1] continuous-wave instrument (CW) emits continuous and constant intensity light and quantifies the intensity of light attenuated through the head; [2] time domain (TD) produces ultra-short pulses of light and measures the time profile of the transmitted light pulse; and [3] frequency domain instrument (FD), in which light radiations and phases are detected using a light source with adjustable light intensity (see details in [85]). Among the three

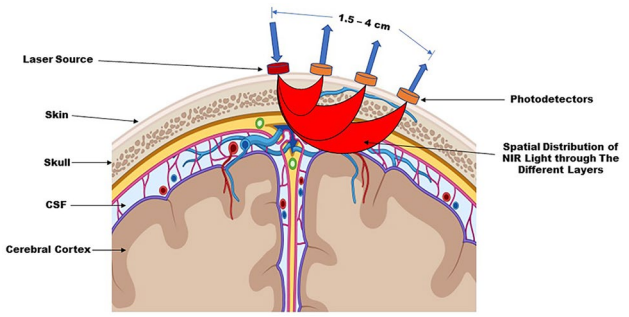


**Fig. 3** Data acquisition of fNIRS. Near-infrared light is emitted by the laser source, and the changes in light intensity are acquired using a photodetector. Many studies use a source-detector separation distance of 1.5–4 cm to assess pain. Changes in oxy- and deoxyhemoglobin concentrations correspond to changes in two wavelength intensities

instruments, the CW instrument is the most commonly used to evaluate pain. Although it cannot measure the oxygen saturation of tissue, it can accurately measure the changes in HbO2, dHb, and total hemoglobin concentration. After using a modified Beer–Lambert law to calculate their concentration changes, functional brain imaging is performed by measuring the hemodynamic response when pain stimulation is applied [86, 87]. Although fNIRS equipment develops rapidly, the standard definitions and tools for data processing and statistical modeling are lacking [84]. The common software and programs processing data, acquisition, image processing, and statistical analysis of fNIRS include HomER [88], fOSA [89], NIRS-SPM [90], and NinPy [91]. Selecting accurate pain biomarker features is equally important for evaluating pain. Gaussian support vector machine (SVM) is a relatively accurate learning model for evaluating pain biomarker features, with an accuracy rate of 94.17% [92].

### Clinical Applications

The application of fNIRS in pain assessment has increased rapidly in the recent two decades, which shows that fNIRS is favored by clinicians and researchers as an objective method of pain assessment. fNIRS records the classic brain dynamic response after pain stimulation, as shown in Fig. 4. This response was reported in a study on pain activation mode. After pain stimulation was applied to the tip of the right index finger, HbO2 increased immediately, peaked at about 20 s, and gradually decreased below the resting state level; dHb decreased slightly, decreased to the peak at about 35 s, and gradually increased to the baseline level [93]. Specific pain-related cortical regions or targets and brain networks are reviewed below.

#### Applications in Normal Subjects

Assessment of the process of pain processing in the brain is particularly important to understand the pain mechanism and search for pain management methods. Experimental pain in healthy subjects is a key point of fNIRS in evaluating pain, such as using fNIRS to study the brain processing mechanism of gingival pain. During pain stimulation, the level of HbO2 in almost the whole frontal cortex decreases, especially in the PFC [94]. This is useful for understanding cortical hemodynamics in toothaches, but it lacks the analysis and results of hemodynamics with time. A subsequent study supplemented this result. HbO2 decreased the most at 20 s after toothache was applied and then gradually recovered, which was consistent with the classic brain response map after pain stimulation recorded by fNIRS; these results indicated a top-down pain regulation pathway in a healthy state [95]. A meta-analysis also pointed out the effects of pain on the PFC and sensory motor cortex during fNIRS [96].

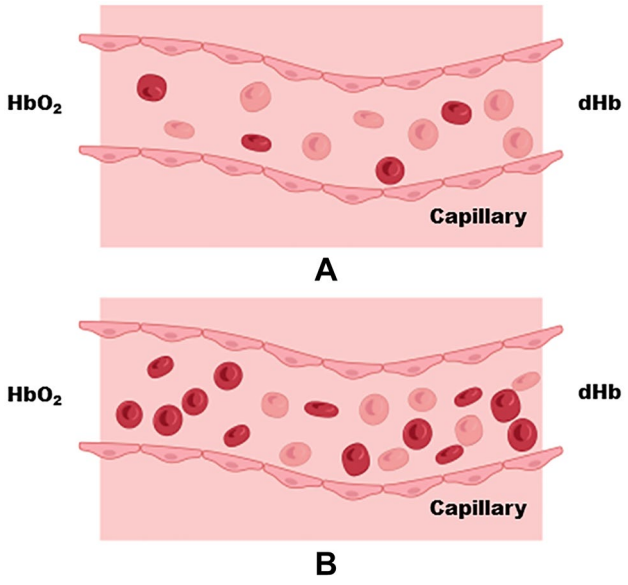


**Fig. 4** Hemodynamic changes during pain in healthy subjects. **A** The concentration of oxy- ($HbO_2$) and deoxyhemoglobin (dHb) in a steady state. **B** The concentration of $HbO_2$ and dHb in the pain state

Interestingly, in another study of dental pain, resting baseline functional connectivity (rSFC) between cognitive, emotional, and somatosensory cortical areas and hemodynamic responses were found to predict pain experience. Specifically, subjects' subjective pain scores at the moderate level were influenced by baseline PFC-S1 rSFC and the sustained hemodynamic response from expectation to pain. This positive effect can predict the patient's nociception, and it persists after the pain has ended [97]. The more widespread activation of these brain regions in response to pain also predicts a decrease in nociception, especially empathy for pain [98, 99]. This phenomenon also offers a way to manage central pain. Notably, asymmetric activation and gender differences have been reported in the "far" and "near" channels when using fNIRS for pain monitoring [100].

### Applications in Patients with Chronic Pain

Compared with healthy individuals, patients with pain-related disorders process painful stimuli differently, perhaps because pain affects brain function and alters brain structure [101]. For example, patients with somatoform pain disorder with persistent chronic pain exhibit cognitive dysfunction and significantly reduced activation of PFC and DLPFC compared with healthy controls [102]. The same conclusion was obtained in the fNIRS pain assessment in patients with FM, where frontal lobe activity was significantly reduced in patients with FM compared with healthy subjects [103]. These results explain the cognitive deficits in patients with chronic pain at a neurological level, suggesting the importance of the frontal lobes and PFC in chronic pain. These findings indicate that fNIRS is a potentially valid tool for assessing brain function in patients with chronic pain. Not all pain is hemodynamically specific, and no hemodynamic differences were found between chronic lower back pain (CLBP) and healthy subjects during sensorimotor stimulation of low back pressure pain [104].

Pain relief is necessary and urgent for patients with chronic pain. Research on the neural mechanisms of pain relief is a focus of fNIRS, which is important for finding treatments and brain region targets for pain. Application of fNIRS to the study of pyramidal thorn patches for the relief of musculoskeletal pain revealed that HbO2 levels are reduced in the left DLPFC, which suggests that the left DLPFC should be further investigated as a target for the treatment of chronic joint pain [105]. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive neuropathic pain treatment with potential for the future [106]. For example, results of the fNIRS study on the analgesic of rTMS stimulation in patients with neuropathic pain showed that the analgesic effect was more significant in the rTMS group than in the control group. The activation of motor-related regions such as the primary motor cortex (M1) and premotor cortex (PMC) was inhibited. These results suggest that the mechanism of high-frequency rTMS analgesia may be related to ameliorated M1 and PMC hypersensitivity [107]. From another perspective on analgesic methods, the combination of multiple analgesic methods for the treatment of pain may be a future field of research for fNIRS.

## Reliability of fNIRS Assessment of Pain

As a neuroimaging technique for assessing pain, fNIRS is essential for the study of the validity and reliability of its assessment results. Peng et al. investigated the remeasurement reliability of the pain response in the anterior prefrontal cortex (aPFC) based on the estimated hemodynamic response functions (HRFs). Their results showed that the left inner channel of fNIRS has reliable results (ICC = 0.660–0.785), and a general linear model (GLM)-based detection model was proposed, which obtained reasonable reliability [108]. At present, there are few studies on the reliability and validity of fNIRS, as well as calibration methods and detection models, and further research on this aspect is needed in the future.

## Strengths of fNIRS for Pain Assessment

### High Portability and Nonionizing Radiation

With the update of the fNIRS device, the current NIRS system requires only a suitcase-sized piece of specialized

hardware and a laptop computer to perform pain assessments [109]. For critically ill patients, pain assessment methods that require a specific environment, such as fMRI and PET, are not feasible. The high portability of fNIRS allows it to be carried directly to the patient's bedside for long-term monitoring and assessment [110]. Nonionizing radiation makes fNIRS strongly suitable for prolonged and repeated assessments in infants and children, and it is useful for understanding changes in brain function and structures in response to pain from infancy to childhood to adulthood [85, 111].

#### High Temporal Resolution and Complete Hemodynamic Response

Compared with fMRI, fNIRS has a higher temporal resolution. The acquisition rate of fMRI is reported to be as low as 1 Hz, whereas fNIRS can provide acquisition rates of up to several hundred hertz, thereby providing a complete temporal image [112]. fNIRS measurements of HbO2 and dHb can obtain a detailed measure of cerebral blood volume [113].

#### Low Cost and Low Use Difficulty

Compared with other neuroimaging techniques, fNIRS is inexpensive because it does not require injectables and specific rooms, and it involves a shorter test period. fNIRS is relatively simple to use and can be performed with only minimal training.

### Limitations of fNIRS for Pain Assessment

#### Low Spatial Resolution

Low spatial resolution has been one of the biggest disadvantages of fNIRS because NIRS signals are influenced by many factors for monitoring cortical hemodynamics. These factors include source-detector distance, attenuation of NIR light in head tissues (skin, bone, and cerebrospinal fluid), and detector sensitivity. Overcoming the attenuation of NIR light by extracerebral tissues is the main difficulty of fNIRS, which leads to the limitation of fNIRS hemodynamic measurements of brain tissue to the outer cortex at a depth of about 1.5 cm. Thus, the fNIRS study of deep brain tissue for pain processing is limited [114]. In addition, separating the hemodynamic responses of extracerebral tissue and cerebral cortex has a significant impact on the assessment of pain because the signals generated by extracerebral tissue can contaminate the NIRS signal in the cerebral cortex, which is a difficult problem for subsequent data processing [115].

#### Susceptibility Artifacts

The movement of the head and torso during painful stimulation causes changes in the distance and contact between the light source and the photodetector. The fiber, which is highly sensitive to these changes, causes changes in head light coupling, resulting in coarse artifacts in the fNIRS signal. Further research on the placement of the fiber and the attachment method is necessary [84, 115].

## PET

### Description

PET is a nuclear medicine imaging method [116]. Using PET to study the functional anatomy of the brain is a recent trend. Upon intravenous injection of "radioactive drugs" or "radioactive tracers" carrying isotopes into the brain, the PET camera directly measures the radioactive distribution of these biomarkers in the brain, and the relevant physiological changes are measured by the carrying positron-emitting isotope [117]. Several common positron-emitting radioisotopes used in PET are O-15, N-13, C-11, and F-18 (from short to long according to half-life) [118]. By measuring the changes in rCBF and glucose metabolism, the response of neurons to pain stimulation is measured indirectly and directly. The rCBF and glucose metabolism values obtained under different conditions are statistically analyzed to obtain the processing information of the brain on noxious stimulation and specific tasks [6, 119]. Given that the brain's response to pain is mainly hemodynamic changes, the main application of radioisotope in PET research on pain is O-15. However, the most commonly used radioisotope in other clinical studies is F-18, because it provides a half-life that allows regional distribution and minimizes patient radiation exposure [118].

### Clinical Applications

#### Applications in Normal Subjects

The application of PET to pain allows an understanding of the general brain processing of acute pain by comparing the brain responses to pain and non-pain stimuli and provides a broad field for research on chronic pain. Pain lacks specificity, and an increasing number of people believe that pain is the integration of distributed neural networks [15]. Thus, cortical regions of interest for different

treatments of pain must be separated. Table 2 summarizes the results of previous studies on the PET evaluation of pain management in healthy subjects.

**Anterior Cingulate Cortex** the anterior cingulate cortex (ACC) is one of the most frequently activated brain regions in which pain stimulation leads to changes in rCBF (only after the insula, see Table 2). Andersson et al. used C-fiber nociceptive stimulation provided by capsaicin to measure the changes in cerebral hemodynamics during pain in different body parts. In the somatotopic contrast of different parts of the body, ACC showed no difference, indicating that ACC was not related to the localization of pain stimulus [120]. In previous studies, ACC was associated with the emotional component of pain experience. For example, Tölle et al. conducted a regulation analysis on the experimental parameters related to thermal pain, and they found that the unpleasant emotion related to pain is encoded in the posterior sector of the ACC and may affect pain intensity, which is encoded in the persistent gray and the PCC [121].

**Insula/Secondary Somatosensory Cortex (S2)** Given the difficulty in distinguishing the regions of some special anatomical structures using the 3D positioning coordinates provided by PET, the regions with increased CBF will overlap on the insular and S2 cortex in some PET studies [122]. Casey et al. found that the activity of bilateral S2 and insula cortex increases with stimulation temperature [123]. This result was consistent with the results of an animal study involving primates [124]. In another study on cerebral hemodynamics of acute muscle pain, the activation of the insula/S2 cortex was always displayed under several pain stimulation conditions [125]. These studies showed that the nociceptive stimulation network contains an insular/S2 cortex and encodes the intensity of pain.

**PFC and Cerebellum** Many studies have reported that the activation of the PFC and cerebellum is related to pain. They are well-known areas involving cognition and movement and have been repeatedly reported in experiments related to pain perception, arousal, and cognition. They usually show the dominant activity of the right cerebral hemisphere, regardless of which side the stimulation is. Thus, the PFC and cerebellum may be involved in the intensity, localization, and cognitive coding of pain stimulation in the experimental pain of healthy people [126, 127].

**Thalamus and PAG** Pain stimulation generally activates the thalamus, especially in the thermal pathway [128]. Thalamus and PAG are also involved in the arousal process of acute traumatic nociceptive pain [126]. In the study of thermal pain stimulation, the activity of the thalamus may reflect pain arousal. In addition, processes involving attention diversion activate the thalamus [129]. Therefore, the hemodynamic response of the thalamus in pain may be part of the brain's processing network for pain discrimination and attention.

### Applications in Patients with Chronic Pain

**Chronic Neuropathic Pain** Spontaneous pain or chronic neuropathic pain is not easy to study in PET. In these reports, the use of anesthetic blocks to relieve chronic neuropathic pain was the most commonly used method. For example, Hsieh et al. found that persistent chronic neuropathic pain activates the part of the classical pain network by comparing the state

**Table 2** Summary of pain assessment of healthy subjects with PET

| Reference | Pain type | *N* | Age | Side | Reported regions | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Tha | ACC | Ins | PFC | Cere | S1 | S2 | LN |
| [128] | Thermal pain | 6 | 28–50 | R | C ↑ | C ↑ | C ↑ | I ↑ | | | | C ↑ |
| [126] | Traumatic nociceptive pain | 4 | 27–46 | R | C ↑ | C ↑ | C ↑ | C ↑ | I ↑ | C ↑ | | |
| [120] | Capsaicin injection pain | 6 | 22–27 | R | | C ↑ | I ↑ | I ↑ | | B ↑ | | |
| [127] | Thermal pain | 12 | 19–47 | R | I ↑ | B ↑ | C ↑ | I ↑ | I ↑ | | | C ↑ |
| [121] | Thermal pain | 12 | 23–75 | R | | B ↑ | C ↑ | | | | | |
| [123] | Thermal pain | 14 | 18–42 | L | B ↑ | C ↑ | B ↑ | | I↑ | C ↑ | B ↑ | |
| [125] | Muscle pain | 16 | 18–40 | L | | | C ↑ | I ↓ | C ↓ | | | |
| [202] | Muscle pain | 10 | 21–25 | R | | B ↑ | B ↑ | B ↑ | I ↑ | | | |
| [203] | Thermal pain | 14 | NA | L | I ↑ | B ↑ | B ↑ | B ↑ | | | | |
| [204] | Thermal pain | 9 | 20–35 | L | C ↑ | C ↑ | C ↑ | C ↑ | | C ↑ | C ↑ | |

*Tha*, thalamus; *ACC*, anterior cingulate cortex; *Ins*, insula; *PFC*, prefrontal cortex; *Cere*, cerebellum; *S1*, primary somatosensory cortex; *S2*, secondary somatosensory cortex; *LN*, lentiform nucleus; *N*, number of subjects; *R*, right side; *L*, left side; *I*, ipsilateral; *B*, bilateral; *C*, contralateral; "↑" increased rCBF; "↓" decreased rCBF; *NA*, not available

of persistent chronic neuropathic pain with that after pain relief with lidocaine. Among them, the right ACC is preferentially and significantly activated regardless of the side of pain, suggesting that ACC participates in the cognition and emotion of pain experience and the right hemisphere is lateralized [130]. A follow-up study also showed that chronic neuropathic pain causes a decrease in rCBF in the contralateral thalamus. These results suggest that the changes in thalamic pain processing circuit may be the focus of modulating chronic neuropathic pain [131]. The method of relieving pain by stimulating the thalamus has a long history. Relevant reports pointed out that somatosensory thalamus stimulation may activate the thalamic cortical pain regulation pathway of thermal pain, suggesting that the thermal pathway is helpful to alleviate persistent chronic neuropathic pain [132]. Davis et al. showed that the continuous activation of ACC during thalamic stimulation may explain this hypothesis [133].

Another method to study chronic neuropathic pain is motor cortex stimulation (MCS). During MCS, the rCBF of the thalamus increases significantly, and a nonsignificant increase occurs in ACC, insula, and brain stem. The thalamus is the key structure to mediating the function of MCS [134]. However, after stopping MCS, the analgesic effect still exists and exceeds the treatment time of MCS [135]. Therefore, the study of PET in this aspect is more inclined to the hemodynamic changes after actual MCS. Peyron et al. found that after MCS of 19 patients with refractory neurological pain, the CBF of contralateral ACC, MCC, and DLPFC increased during MCS compared with baseline. After MCS stopped, the activity of the brainstem and most cortical and subcortical structures (such as PFC and thalamus) increased, and these changes were significantly related to pain relief. Therefore, the analgesic mechanism of MCS may be through the top-down pain modulation pathway, and the clinical effect has a long time window [136]. Another method with a low application is cancer pain followed by cordotomy (see, [137] for details).

Many patients with chronic neuropathic pain have allodynia (abnormal pain triggered by non-noxious stimulation) [119], hyperalgesia (increased pain induced by nociceptive stimuli that provoke pain) [138], and wind-up pain (amplification of nociceptive messages from C-fibers in the spinal cord) [139], which results in abnormal pain. In the studies using PET for abnormal pain, they usually compared allodynia, hyperalgesia, and wind-up pain stimulation with similar stimulation in the mirror area on the non-painful side. For example, Peyron et al. stimulated allodynia in patients with dynamic mechanical allodynia (N = 19; experimental group). Compared with the same stimulation applied to the non-neuropathic pain area (control group), different types of activation were limited to one activation of the contralateral anterior insula, but the contralateral S1, S2, and insula and the ipsilateral cerebellum shared a common response in the experimental group and the control group. Thermal pain stimulation applied to the neuropathic pain area normally activates the insula. Considering the type of stimulation, the insula is improperly activated by abnormal pain [140]. Similarly, upon comparing wind-up pain with non-neuropathic pain regional stimulation, the results showed that wind-up pain has more significant activation in the contralateral S2, insula, ACC, right DLPFC, thalamus, and cerebellum, but wind-up pain has no specific activation compared with pressure pain under the same conditions [141].

**Other Chronic Pain** For other clinical chronic pain, PET showed that ACC is the target of hemodynamic abnormalities. For example, in atypical facial pain, the rCBF of ACC increases significantly and the PFC decreases compared with normal subjects [142]. After inhibiting pain, rCBF of PFC, anti-insula cortices, hypothalamus, and PAG increases significantly, but ACC does not change [143]. These findings not only illustrate the importance of ACC in chronic pain but also suggest that it may be related to the interaction between ACC and PFC. The specific mechanism of action, whether inhibition or promotion, needs further research.

## Reliability of PET Assessment of Pain

As a result of radioactive factors, research on the reliability of PET in evaluating pain is limited to a great extent. However, the reliability of PET in evaluating pain has been studied from the technical accuracy of segmental perfusion parameters. For example, Valentina Berti et al. carried out quantitative cardiac PET imaging to assess the technical accuracy of segmental perfusion parameters in patients with coronary artery disease and stable angina; PET images were analyzed by two observers who were independent and blinded to clinical and instrumental data. The overall consistency of the analysis results was 90%, the accurate recognition rate of patients was 85%, the overall sensitivity was 86%, and the specificity was 84%. These results show that the measurement results of segmental PET are reliable [144].

## Strengths of PET for Pain Assessment

### Measure Brain Metabolism and Hemodynamic Changes

Metabolism and blood circulation are important for the evaluation of pain. PET mainly uses F-18 as a tracer to measure brain metabolism and O-15 as a tracer to measure hemodynamic changes. Under these conditions, PET can accurately measure the response of specific receptor distribution areas to pain [145].

#### High Spatial Resolution

PET 3D imaging technology can provide high energy resolution and robust scattering suppression, so it has a good spatial resolution (millimeter level). For the evaluation of pain, good spatial resolution is the basis for obtaining accurate information [6, 118].

### Limitations of PET for Pain Assessment

#### Low Temporal Resolution and High Cost

The half-life of O-15 is only about 2 min, so the required regional distribution in a short time period causes low temporal resolution, and current PET scanners require a measurement time of at least 90 min to obtain the best signal-to-noise ratio [146]. A long evaluation time will aggravate the burden of patients [118]. According to the cost-effectiveness report of PET, the research cost of PET is US$1800 [147], which is among the highest of all neuroimaging technologies.

#### Radiation and Low Portability

The injection of a radioactive tracer is inevitable in pain assessment with PET, and the potential harm of radioactive tracers to human health and the environment cannot be ignored [148]. Moreover, the repeatability of the measurement is limited due to radioactivity, which may reduce the reliability of the evaluation. The preparation of commonly used radioisotopes requires a cyclotron, and scanning needs to be carried out in a special closed environment. These factors contribute to the fact that PET is not as highly portable as fNIRS [118].

## EEG and MEG

### Description

Unlike fMRI, fNIRS, and PET, which use hemodynamics to evaluate pain, EEG and MEG use electrophysiological methods and have high temporal resolution, but their functions in the spatial domain are worse than fMRI and PET [149].

EEG and MEG are closely related complementary neuroimaging methodologies and should be interpreted together when assessing pain [150]. EEG is a graphical representation of the voltage differences between different brain regions over time [151]. When the pain stimulus acts on the human body, activated neurons generate synchronized synaptic activity in the soma-dendritic membrane and further ionic currents generate at the level of cellular membranes. The ionic currents generate an active sink (region of negative charge) and an active source (region of positive charge) in the extracellular medium. For EEG and MEG, the pyramidal neurons of the cortex are the neurons that generate the electric and magnetic fields, and they are activated synchronously and arranged in a parallel fashion. These pyramidal neurons are called "current dipoles," and their activity can be detected by electrodes placed on the surface of the scalp [152, 153]. EEG can detect two major types of dipoles, which are tangent dipoles perpendicular to the surface of the scalp and radial dipoles parallel to the surface of the scalp [154]. Unlike EEG, MEG is only sensitive to currents perpendicular to cortical fissures; in contrast to EEG, MEG signals are mainly generated by the tangential component of cortical currents [155]. The propagation of the EEG signal is carried out by volume conduction. Volume conduction is the process by which a pool of ions repels nearby ions of the same charge. Given that volume conduction cannot cross to another volume, volume conduction cannot cross the dura layers, the skull layers, the scalp, and to the electrode. Instead of capacitive conduction, a form of capacitance becomes responsible for the signal's propagation [153]. For MEG, the above ionic currents generate a corresponding single magnetic field when passing through the nearby neurons with a similar orientation. The MEG sensor distributed on the scalp records the total magnetic field intensity added by the single magnetic field to generate MEG signals [156].

In pain assessment, the oscillatory activity of neurons between euphoria and low excitability is called neural oscillations, which are commonly used as follows (EEG similar to MEG [150]): [1] Alpha band: 8–13 Hz. Some researchers believe that thalamocortical loop generation is usually related to memory, cognition, and pain sensitivity [2]. Theta band: 4–8 Hz. This band is generally believed to be produced in the hippocampus. Chronic pain usually leads to an increase in θ band activity [3]. Beta band: 13–30 Hz. The presumed mechanism of generation is local pyramidal cells and local interneurons. It is usually related to anticipation, detection of sensory change, and motor planning. (4) Delta band: 0–4 Hz. It is most obvious in deep sleep and may be produced in the thalamocortical loop. (5) Gamma band: 30 + Hz. The gamma band might generate in the local interneuron network and local pyramidal cells, and it may be related to cognition and saliency to pain [157, 158].

### Clinical Application

#### Electrophysiology Signature of Tonic Pain in Healthy Condition

The traditional recording of neurophysiological responses to pain stimuli is based on event-related potentials (ERPs), but the nociceptive stimuli that induce ERPs are transient and do

not truly reflect clinical pain. Continuous EEG has been used in many studies to evaluate the perception of tension pain because tonic pain is closer to clinical pain compared with ERPs [159]. We summarize the research on EEG assessment of tonic pain in healthy subjects in the past few decades and summarize several common band change areas of EEG in the frontal lobe, parietal lobe, and temporal lobe. The more specific cortical areas for pain perception will be reviewed in the next paragraph, and the details of the research are summarized in Table 3.

In most EEG changes caused by tonic experimental pain, alpha and beta bands decreased in a wide range of the head, whereas delta and gamma bands increased, especially in the front and middle of the head. For example, Tiemann et al. used EEG to evaluate the EEG data of acute tonic pain in healthy conditions. Compared with the painless state, the theta band in the left medical front and left superior front cortices, the alpha band in ACC, and the beta band in PCC decreased in tonic pain [160]. The different results of similar studies are due to many factors, such as the depth of tonic pain. Although the EEG patterns at different depths are not exactly the same, they are roughly similar [161]. Understanding the contribution of specific neural oscillations in pain perception is also important for assessing pain. For example, studies on dissociative intensity and pain intensity showed that alpha band and beta band frequencies in sensorimotor areas decrease to encode stimulus intensity, whereas the gamma band in the medial PFC encodes pain intensity [162]. Another study investigated the properties of peak alpha frequency in pain, and the results showed a stable correlation between numerical pain scores and peak alpha frequency in tonic pain; thus, peak alpha frequency is critical in the subjective perception of pain [159].

Pain is not the expression of a single hurtful sensation but a multidimensional experience involving emotion, cognition, and attention. EEG patterns for the different dimensions of pain are one of the focuses of these studies. A study on ERP found that unpleasant emotions lead to a decrease in event-related synchronization in the theta band but an increase in event-related desynchronization in the alpha band. These results suggest that the alpha band and the theta band are involved in the expression of painful emotions [163]. The mechanism by which peripheral pain affects central pain has been repeatedly mentioned in many studies, such as the imposition of tonic pain in subjects with empathic pain, which was found to alter the delta band in the central region, thereby affecting pain attention and the degree of cognition associated with empathic pain [164]. Interestingly, to avoid the effect of attention on pain perception, Giehl et al. investigated EEG patterns in tonic pain under controlled attention conditions and reported lower central alpha-band activity and higher delta in tonic pain band activity in the parietal and occipital cortex compared with painless thermal stimulation, but confounding pain intensity largely influenced EEG results [165].

MEG has higher spatial resolution compared with EEG, so MEG is more accurate in locating the brain processing area after pain than the latter. The combination of EEG and MEG compensates for their respective defects. For example, in the evaluation of burning pain ascending through C fibers,

**Table 3** Summary of tonic pain assessment of healthy subjects with EEG

| Reference | Year | Stimulus type | *N* | Mage ± SD | Reported regions | | |
|---|---|---|---|---|---|---|---|
| | | | | | Frontal cortex | Parietal cortex | Temporal cortex |
| [162] | 2017 | Thermal stimulation | 39 | 24.3 ± 5.6 | α↓ β↓ γ↑ | α↓ β↓ | |
| [159] | 2010 | Thermal stimulation | 18 | 26 ± 2.1 | | α↓ | α↓ |
| [205] | 2012 | Thermal stimulation | 18 | 26 ± 2.1 | | | α↓ |
| [206] | 2006 | Thermal stimulation | 16 | 18–40 | α↓ δ↑ θ↓ | δ↑ | α↓ δ↑ θ↓β↑ |
| [165] | | Thermal stimulation | 20 | 23.3 ± 3.3 | α↓ δ↑ | α↓ δ↑ | |
| [207] | 1994 | Cold stimulation | 19 | 22.6 ± 3.3 | α↓ θ↓β↑ | α↓ θ↓ β↑ | |
| [208] | 2008 | Cold stimulation | 15 | 20.1 ± 2.9 | γ↑ | | α↓ |
| [209] | 2021 | Cold stimulation | NA | 18–70 | α↓ θ↓ γ↑ | α↓ θ↓ | |
| [160] | 2012 | Cold stimulation | 26 | 25.1 ± 3.3 | α↓ β↑ θ↓ | α↓ β↑ | β↑ |
| [210] | 2001 | Capsaicin injection | 15 | 25.6 | | α↓ θ↓ | |
| [161] | 2004 | Capsaicin injection | 15 | 25.6 ± 3.2 | α↓ β↓ δ↑ | α↓ β↓ | θ↓ |
| [211] | 2016 | Hypertonic saline injection | 43 | 22 ± 3 | γ↑ | | |
| [212] | 2000 | Hypertonic saline injection | 12 | 26.6 ± 5.8 | | α↑ β↑ δ↑ | |
| [213] | 2003 | Hypertonic saline injection | 13 | 25.9 ± 2.7 | β↑ | α↓ | β↑ |
| [214] | 2016 | Electrical stimulation | 20 | 26.9 ± 6.9 | γ↑ | | θ↓ |

*N*, number of subjects; *Mage* ± *SD*, mean age ± standard deviation; *α*, alpha band; *β*, beta band; *δ*, delta band; *θ*, theta band; *γ*, gamma band; "↑" increased band; "↓" decreased band; *NA*, not available

the most contralateral S1 and S2 in MEG are activated simultaneously after pain stimulation, and the ipsilateral S2 is then activated. Finally, the structures of limbic systems, such as the insula and cingulate cortex, are activated in EEG [166].

#### Electrophysiology Signature of Chronic Pain

One focus of using EEG to assess chronic pain is FM. Previous studies of other neuroimaging techniques have found that the degree of connectivity between brain regions moderating pain in patients with FM is reduced, whereas the degree of connectivity between regions responding to pain is increased [167]. The abnormal brain function of FM in the source localization analysis of EEG oscillation is helpful to understand its pain mechanism. Compared with the painless group, the resting delta band power density and alpha band power density of the right insula, right superior and middle temporary gyri, central, temporoparietal, and local brain areas in patients with FM decreased, whereas the beta band in the right middle frontal lobe, midcingulate gyrus, and theta band in PFC increased [168–170]. Choe et al. used MEG to image the pain network connectivity of patients with FM in a resting state and found that patients with FM were in reduced connectivity within the default mode network, between the middle/infection temporary gyrus and visual cortex [171]. In the nonresting state, patients with FM showed similar EEG patterns to healthy patients but had earlier pain perception in time [172]. An MEG study showed that the healthy control group had stronger alpha desynchronization for empathic pain during empathic pain stimulation, whereas FM patients did not, suggesting that patients with FM may have insufficient sensorimotor cortex moderation [173]. The effective treatment for FM analgesia is EEG biofeedback [174]. This treatment changes the attention and pain perception abnormalities of patients with FM by enhancing sensorimotor rhythm, reducing the high beta band and theta band, and increasing the sensorimotor rhythm/theta wave ratio [175].

### Reliability of EEG and MEG Assessment of Pain

As with other imaging techniques, the reliability of pain assessment is equally important for the application of EEG. Gram et al. discussed the reliability of EEG in evaluating resting and tonic pain (cold compression test) and obtained excellent reliability in resting state (α wave average ICC = 0.945, β wave average ICC = 0 0.763). In tonic pain, the results obtain excellent reliability (α wave average ICC = 0.895, β wave average ICC = 0.713). These results prove that the EEG frequency band analysis of the EEG response induced by tension pain is reliable [176]. The reliability of EEG on the spatial information of cortical areas activated by tension pain has also been studied. Hansen et al. analyzed the cortical source generators via experimental tonic pain and found that all frequency bands of EEG showed high reliability, whether in resting state or tonic pain (ICC = 0.47–0.83) [177]. These results suggest that tonic pain via EEG induced by experimental pain is a reliable model for the evaluation of pain, and source localization of EEG is a reliable method for the objective evaluation of the response of the cerebral cortex to pain.

### Strengths of EEG and MEG for Pain Assessment

#### High Temporal Resolution and Silence

The time resolution of EEG and MEG is the highest among all neuroimaging techniques (up to the millisecond level), which is advantageous for assessing the time component of pain and measuring the rapid changes in brain activity. Compared with fMRI, EEG and MEG have lower noise during measurement, which can prevent the interference of noise to subjects [156].

#### Direct Measurement of Neuronal Activity

In pain assessment, EEG directly records the changes in the electric field generated by the activity of pyramidal cortical neurons, rather than indirectly recording pain signals through hemodynamic changes, such as other imaging techniques [178]. MEG is a direct recording of the magnetic field generated by the activity of potential neurons. This directness indicates that the recording process is not affected by other problems, such as neurovascular coupling [156].

#### High Coverage and Measurement Period

EEG can detect two major types of dipoles, which are tangent dipoles perpendicular to the surface of the scalp and radial dipoles parallel to the surface of the scalp. By contrast, MEG usually detects the tangential component of cortical currents. Therefore, compared with the MEG signal, the EEG signal may be more sensitive to wider brain structures and deeper brain structures [150, 153, 179]. In terms of measurement time, EEG can measure subjects for a long time, leading to its wide application. Unlike MEG, EEG can be measured during sleep and long-term activity [180].

#### High Mobility and Affordability

The latest generation of portable digital video 128-channel EEG equipment only needs the size of a mobile trolley, and subjects can move during evaluation. By contrast, MEG has

low mobility during evaluation. In addition, the cost of EEG assessment is low at only about $20, whereas cost is a limitation for MEG [178, 181].

### Limitations of EEG and MEG for Pain Assessment

#### Low Spatial Resolution

The spatial resolution of EEG is lower than that of fMRI. Therefore, the combination of EEG and fMRI can overcome this limitation. The advantage of this method is that it studies the temporal components of pain by using the good temporal resolution of EEG and the spatial components of pain by using fMRI. The combination of EEG and MEG allows the spatial resolution to reach 10 mm [11].

#### Susceptibility Artifacts

Pain stimulus artifacts often interfere with the use of EEG and MEG to assess the electrophysiological activity of the brain, because pain stimuli are easily confused with electrophysiological activities caused by other factors. Although many analysis pipelines to reduce artifacts have been developed, the limitation of application remains a difficulty to overcome. For example, when performing spiritual cord stimulation in patients with neuropathic pain, spatial filters are used to eliminate artifacts and enhance activity [182].

#### Limited Detection of Oscillation Amplitude and Area of Cortex

The attenuation of electrophysiological signals by scalp, bone, and cerebrospinal fluid and the uncertainty of the number and spacing of electrodes lead to poor detection of low amplitude oscillations, such as gamma [183] and theta oscillations [184]. The response area of the brain region to pain is also a factor limiting detection, which is usually caused by a small pain activation area and extremely low pain intensity [185].

## Application of Artificial Intelligence/ Machine Learning in Neuroimaging

Given that each neuroimaging technique involves multiple layers of data sets and analysis of this complex and multivariate brain imaging data is challenging, artificial intelligence (AI)/ML provides an automated approach to distinguish brain imaging data [186]. Some studies report that neuroimaging combining machine learning can diagnose, predict, and prognosticate pain biomarkers to further research pain [187–190]. In addition, some ML algorithms have developed models to assess pain [191, 192], like SVM, the most widely applied and high-accuracy rate ML classifier [92, 193]. Therefore, advanced analytical approaches have significantly extended our understanding of brain imaging of pain. Moreover, a developing synergy between emerging analysis techniques and data-sharing initiatives has the potential to close the gap between basic neuroscience and pain neuroimaging [194]. Future studies can target performing cross-validation within the same cohort to identify clinical biomarkers for pain further.

## Conclusion

Neuroimaging techniques used to assess pain are usually divided into two categories. One is hemodynamic methods with good spatial resolution, including fMRI, PET, and fNIRS; these methods broadly identify the brain processing areas of pain, including medial and lateral pain systems, for affective-motivational and sensory-discriminative processing. Given that MEG and EEG have unparalleled time resolution, they are often used to analyze the time components of pain. For example, S2 activity does not change in the time dynamics of expectation of pain, whereas the activity of MCC increases with time [195].

These neuroimaging techniques are relatively mature in the application of pain assessment, but only fMRI has a large number of studies to detect the test–retest reliability of the assessment and has good reliability. However, there is a lack of research on the reliability and validity of pain assessment in the literature related to other neuroimaging techniques. Limitations of these neuroimaging technologies (e.g., acoustic noise and high cost) may have affected pain research. For example, such techniques involve low replicability and low sample sizes; given the constraints on the participants that can be recruited for an imaging study, a convenience sample may be used, which usually comprises healthy young adults from the university environment. However, such a low sample size may not represent those disproportionately affected by chronic pain [196]. Neurofeedback training through neuroimaging technology to modulate pain has recently become popular, such as rtfMRI feedback to modulate ACC and posterior insula cortex [197]. EEG feedback strengthens either alpha or sensorimotor rhythms and suppresses theta and beta bands in brain regions [198]. Although this method has a good analgesic effect, large-sample size randomized trials are still needed to provide reliable evidence. In summary, the development and validation of imaging and electrophysiological signatures may help infer pathophysiological mechanisms in individual patients, thereby supporting the use of a personalized medicine approach in the treatment of patients with chronic pain and identifying clinically useful biomarkers for chronic pain.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s13311-022-01274-z.

**Required Author Forms** Disclosure forms provided by the authors are available with the online version of this article.

**Author Contributions** X-QW and BG: draft conception, project administration, and funding acquisition. JL, H-QZ, BG, and X-QW: writing, reviewing, and editing. All authors contributed to the article and approved the submitted version.

**Funding** This study received funding from the scientific and technological research program of the Shanghai Science and Technology Committee (Fund number: 19080503100; 21S31902400), Shanghai Key Lab of Human Performance (Shanghai University of Sport) (11DZ2261100), Talent Development Fund of Shanghai Municipal (2021081), and Shanghai Clinical Research Center for Rehabilitation Medicine (21MC1930200).

## Declarations

**Competing Interests** The authors declare no competing interests.

## References

1. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976–82.
2. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. European Journal of Pain (London, England). 2006;10(4):287–333.
3. Melzack R. From the gate to the neuromatrix. Pain. 1999;Suppl 6:S121-s6.
4. Das V. An introduction to pain pathways and pain "targets." Prog Mol Biol Transl Sci. 2015;131:1–30.
5. Treede RD, Kenshalo DR, Gracely RH, Jones AK. The cortical representation of pain. Pain. 1999;79(2–3):105–11.
6. Morton DL, Sandhu JS, Jones AK. Brain imaging of pain: state of the art. J Pain Res. 2016;9:613–24.
7. Horikawa T, Tamaki M, Miyawaki Y, Kamitani Y. Neural decoding of visual imagery during sleep. Science (New York, NY). 2013;340(6132):639–42.
8. Mouraux A, Iannetti GD. The search for pain biomarkers in the human brain. Brain: a Journal of Neurology. 2018;141(12):3290–307.
9. Kumbhare DA, Elzibak AH, Noseworthy MD. Evaluation of chronic pain using magnetic resonance (MR) neuroimaging approaches: what the clinician needs to know. Clin J Pain. 2017;33(4):281–90.
10. Hoffman KM, Trawalter S, Axt JR, Oliver MN. Racial bias in pain assessment and treatment recommendations, and false beliefs about biological differences between blacks and whites. Proc Natl Acad Sci USA. 2016;113(16):4296–301.
11. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. European Journal of Pain (London, England). 2005;9(4):463–84.
12. Baliki MN, Geha PY, Fields HL, Apkarian AV. Predicting value of pain and analgesia: nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. Neuron. 2010;66(1):149–60.
13. Becerra L, Breiter HC, Wise R, Gonzalez RG, Borsook D. Reward circuitry activation by noxious thermal stimuli. Neuron. 2001;32(5):927–46.
14. Dunckley P, Wise RG, Fairhurst M, Hobden P, Aziz Q, Chang L, et al. A comparison of visceral and somatic pain processing in the human brainstem using functional magnetic resonance imaging. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2005;25(32):7333–41.
15. Mano H, Seymour B. Pain: a distributed brain information network? PLoS Biol. 2015;13(1): e1002037.
16. Baliki MN, Geha PY, Apkarian AV. Parsing pain perception between nociceptive representation and magnitude estimation. J Neurophysiol. 2009;101(2):875–87.
17. Liu TT. MRI in systems medicine. Wiley Interdisciplinary Reviews Systems Biology and Medicine. 2020;12(1): e1463.
18. Neeb L, Bastian K, Villringer K, Gits HC, Israel H, Reuter U, et al. No microstructural white matter alterations in chronic and episodic migraineurs: a case-control diffusion tensor magnetic resonance imaging study. Headache. 2015;55(2):241–51.
19. Gustin SM, Peck CC, Cheney LB, Macey PM, Murray GM, Henderson LA. Pain and plasticity: is chronic pain always associated with somatosensory cortex activity and reorganization? The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2012;32(43):14874–84.
20. Ellingson BM, Mayer E, Harris RJ, Ashe-McNally C, Naliboff BD, Labus JS, et al. Diffusion tensor imaging detects microstructural reorganization in the brain associated with chronic irritable bowel syndrome. Pain. 2013;154(9):1528–41.
21. Ivo R, Nicklas A, Dargel J, Sobottke R, Delank KS, Eysel P, et al. Brain structural and psychometric alterations in chronic low back pain. European Spine Journal: Official Publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society. 2013;22(9):1958–64.
22. Simon AB, Buxton RB. Understanding the dynamic relationship between cerebral blood flow and the BOLD signal: implications for quantitative functional MRI. Neuroimage. 2015;116:158–67.
23. Glover GH. Overview of functional magnetic resonance imaging. Neurosurgery Clinics of North America. 2011;22(2):133–9, vii.
24. Borogovac A, Asllani I. Arterial Spin Labeling (ASL) fMRI: advantages, theoretical constrains, and experimental challenges in neurosciences. Int J Biomed Imaging. 2012;2012: 818456.
25. Zhang X, Li L, Huang G, Zhang L, Liang Z, Shi L, et al. A multisensory fMRI investigation of nociceptive-preferential cortical regions and responses. Front Neurosci. 2021;15: 635733.
26. Oertel BG, Preibisch C, Martin T, Walter C, Gamer M, Deichmann R, et al. Separating brain processing of pain from that of stimulus intensity. Hum Brain Mapp. 2012;33(4):883–94.
27. Horing B, Sprenger C, Büchel C. The parietal operculum preferentially encodes heat pain and not salience. PLoS Biol. 2019;17(8): e3000205.
28. Kulkarni B, Bentley DE, Elliott R, Youell P, Watson A, Derbyshire SW, et al. Attention to pain localization and unpleasantness discriminates the functions of the medial and lateral pain systems. Eur J Neurosci. 2005;21(11):3133–42.
29. Price DD. Psychological and neural mechanisms of the affective dimension of pain. Science (New York, NY). 2000;288 (5472):1769–72.
30. Orenius TI, Raij TT, Nuortimo A, Näätänen P, Lipsanen J, Karlsson H. The interaction of emotion and pain in the insula and secondary somatosensory cortex. Neuroscience. 2017;349:185–94.
31. Forkmann K, Wiech K, Ritter C, Sommer T, Rose M, Bingel U. Pain-specific modulation of hippocampal activity and functional connectivity during visual encoding. The Journal of

Neuroscience: the Official Journal of the Society for Neuroscience. 2013;33(6):2571–81.
32. Marquand A, Howard M, Brammer M, Chu C, Coen S, Mourão-Miranda J. Quantitative prediction of subjective pain intensity from whole-brain fMRI data using Gaussian processes. Neuroimage. 2010;49(3):2178–89.
33. Haynes JD, Rees G. Decoding mental states from brain activity in humans. Nat Rev Neurosci. 2006;7(7):523–34.
34. Damascelli M, Woodward TS, Sanford N, Zahid HB, Lim R, Scott A, et al. Multiple functional brain networks related to pain perception revealed by fMRI. Neuroinformatics. 2021.
35. Kucyi A, Salomons TV, Davis KD. Mind wandering away from pain dynamically engages antinociceptive and default mode brain networks. Proc Natl Acad Sci USA. 2013;110(46):18692–7.
36. Kamitani Y, Tong F. Decoding the visual and subjective contents of the human brain. Nat Neurosci. 2005;8(5):679–85.
37. Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-based neurologic signature of physical pain. N Engl J Med. 2013;368(15):1388–97.
38. Zunhammer M, Bingel U, Wager TD. Placebo effects on the neurologic pain signature: a meta-analysis of individual participant functional magnetic resonance imaging data. JAMA Neurol. 2018;75(11):1321–30.
39. Woo CW, Schmidt L, Krishnan A, Jepma M, Roy M, Lindquist MA, et al. Quantifying cerebral contributions to pain beyond nociception. Nat Commun. 2017;8:14211.
40. Lee JJ, Kim HJ, Čeko M, Park BY, Lee SA, Park H, et al. A neuroimaging biomarker for sustained experimental and clinical pain. Nat Med. 2021;27(1):174–82.
41. Fields HLJTPEAIE. The contribution of desire and expectation to placebo analgesia: implications for new research strategies. 1999;8:117.
42. Porro CA, Baraldi P, Pagnoni G, Serafini M, Facchin P, Maieron M, et al. Does anticipation of pain affect cortical nociceptive systems? The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2002;22(8):3206–14.
43. Schmid J, Theysohn N, Ga F, Benson S, Gramsch C, Forsting M, et al. Neural mechanisms mediating positive and negative treatment expectations in visceral pain: a functional magnetic resonance imaging study on placebo and nocebo effects in healthy volunteers. Pain. 2013;154(11):2372–80.
44. Bushnell MC, Ceko M, Low LA. Cognitive and emotional control of pain and its disruption in chronic pain. Nat Rev Neurosci. 2013;14(7):502–11.
45. deCharms RC. Applications of real-time fMRI. Nat Rev Neurosci. 2008;9(9):720–9.
46. 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 USA. 2005;102(51):18626–31.
47. deCharms RC. Reading and controlling human brain activation using real-time functional magnetic resonance imaging. Trends Cogn Sci. 2007;11(11):473–81.
48. Shukla S, Torossian A, Duann JR, Leung A. The analgesic effect of electroacupuncture on acute thermal pain perception–a central neural correlate study with fMRI. Mol Pain. 2011;7:45.
49. Li C, Yang J, Park K, Wu H, Hu S, Zhang W, et al. Prolonged repeated acupuncture stimulation induces habituation effects in pain-related brain areas: an FMRI study. PLoS ONE. 2014;9(5): e97502.
50. Theysohn N, Choi KE, Gizewski ER, Wen M, Rampp T, Gasser T, et al. Acupuncture-related modulation of pain-associated brain networks during electrical pain stimulation: a functional magnetic resonance imaging study. Journal of Alternative and Complementary Medicine (New York, NY). 2014;20(12):893–900.
51. Bair MJ, Krebs EE. Fibromyalgia. Ann Intern Med. 2020;172(5):Itc33-itc48.
52. McLoughlin MJ, Stegner AJ, Cook DB. The relationship between physical activity and brain responses to pain in fibromyalgia. J Pain. 2011;12(6):640–51.
53. Jensen KB, Kosek E, Wicksell R, Kemani M, Olsson G, Merle JV, et al. Cognitive Behavioral Therapy increases pain-evoked activation of the prefrontal cortex in patients with fibromyalgia. Pain. 2012;153(7):1495–503.
54. Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice ASC, et al. A new definition of neuropathic pain. Pain. 2011;152(10):2204–5.
55. Johnson RW, Rice AS. Clinical practice. Postherpetic neuralgia. N Engl J Med. 2014;371(16):1526–33.
56. Liu J, Hao Y, Du M, Wang X, Zhang J, Manor B, et al. Quantitative cerebral blood flow mapping and functional connectivity of postherpetic neuralgia pain: a perfusion fMRI study. Pain. 2013;154(1):110–8.
57. Guan M, Ma L, Li L, Yan B, Zhao L, Tong L, et al. Self-regulation of brain activity in patients with postherpetic neuralgia: a double-blind randomized study using real-time FMRI neurofeedback. PLoS ONE. 2015;10(4): e0123675.
58. Enck P, Aziz Q, Barbara G, Farmer AD, Fukudo S, Mayer EA, et al. Irritable bowel syndrome. Nat Rev Dis Primers. 2016;2:16014.
59. Berman SM, Naliboff BD, Suyenobu B, Labus JS, Stains J, Ohning G, et al. Reduced brainstem inhibition during anticipated pelvic visceral pain correlates with enhanced brain response to the visceral stimulus in women with irritable bowel syndrome. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2008;28(2):349–59.
60. Battaglia M, Sampling N, Lavrakas PJPd. Encyclopedia of survey research methods. 2008.
61. Xue C, Yuan J, Lo GG, Chang ATY, Poon DMC, Wong OL, et al. Radiomics feature reliability assessed by intraclass correlation coefficient: a systematic review. Quant Imaging Med Surg. 2021;11(10):4431–60.
62. Brandt DJ, Sommer J, Krach S, Bedenbender J, Kircher T, Paulus FM, et al. Test-retest reliability of fMRI brain activity during memory encoding. Front Psych. 2013;4:163.
63. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull. 1979;86(2):420–8.
64. Noble S, Scheinost D, Constable RT. A guide to the measurement and interpretation of fMRI test-retest reliability. Curr Opin Behav Sci. 2021;40:27–32.
65. McGraw KO, Wong SPJPm. Forming inferences about some intraclass correlation coefficients. 1996;1(1):30.
66. Gay CW, Papuga MO, Bishop MD, Dougherty P. The frequency and reliability of cortical activity using a novel strategy to present pressure pain stimulus over the lumbar spine. J Neurosci Methods. 2015;239:108–13.
67. Letzen JE, Sevel LS, Gay CW, O'Shea AM, Craggs JG, Price DD, et al. Test-retest reliability of pain-related brain activity in healthy controls undergoing experimental thermal pain. The Journal of Pain [Internet]. 2014 Oct PMC4182117]; 15(10):[1008–14 pp.].
68. Upadhyay J, Lemme J, Anderson J, Bleakman D, Large T, Evelhoch JL, et al. Test-retest reliability of evoked heat stimulation BOLD fMRI. J Neurosci Methods. 2015;253:38–46.
69. Letzen JE, Boissoneault J, Sevel LS, Robinson ME. Test-retest reliability of pain-related functional brain connectivity compared with pain self-report. Pain. 2016;157(3):546–51.
70. Quiton RL, Keaser ML, Zhuo J, Gullapalli RP, Greenspan JD. Intersession reliability of fMRI activation for heat pain and motor tasks. NeuroImage Clinical. 2014;5:309–21.

71. Han X, Ashar YK, Kragel P, Petre B, Schelkun V, Atlas LY, et al. Effect sizes and test-retest reliability of the fMRI-based neurologic pain signature. Neuroimage. 2021;247: 118844.
72. Moana-Filho EJ, Nixdorf DR, Bereiter DA, John MT, Harel N. Evaluation of a magnetic resonance-compatible dentoalveolar tactile stimulus device. BMC Neurosci. 2010;11:142.
73. Plewes DB, Kucharczyk W. Physics of MRI: a primer. Journal of Magnetic Resonance Imaging: JMRI. 2012;35(5):1038–54.
74. Gardumi A, Ivanov D, Hausfeld L, Valente G, Formisano E, Uludağ K. The effect of spatial resolution on decoding accuracy in fMRI multivariate pattern analysis. Neuroimage. 2016;132:32–42.
75. Alkhorayef M. Effective radiation doses in pediatric PET/CT examinations: pilot study. Applied Radiation and Isotopes: Including Data, Instrumentation and Methods for use in Agriculture, Industry and Medicine. 2021;168: 109412.
76. Cai J, Kim JL, Baumeister TR, Zhu M, Wang Y, Liu A, et al. A multi-sequence MRI study in Parkinson's disease: association between rigidity and myelin. Journal of Magnetic Resonance Imaging: JMRI. 2021.
77. Yang L, Wu B, Fan L, Huang S, Vigotsky AD, Baliki MN, et al. Dissimilarity of functional connectivity uncovers the influence of participant's motion in functional magnetic resonance imaging studies. Hum Brain Mapp. 2021;42(3):713–23.
78. Radomskij P, Schmidt MA, Heron CW, Prasher D. Effect of MRI noise on cochlear function. Lancet (London, England). 2002;359(9316):1485.
79. Davis KD. Legal and ethical issues of using brain imaging to diagnose pain. Pain Reports. 2016;1(4): e577.
80. Friebe M, Sanchez J, Balakrishnan S, Illanes A, Nagaraj Y, Odenbach R, et al. In-room ultrasound fusion combined with fully compatible 3D-printed holding arm - rethinking interventional MRI. Medical Devices (Auckland, NZ). 2018;11:77–85.
81. Aihara T, Shimokawa T, Ogawa T, Okada Y, Ishikawa A, Inoue Y, et al. Resting-state functional connectivity estimated with hierarchical bayesian diffuse optical tomography. Front Neurosci. 2020;14:32.
82. Watari T, Hlaing TM, Kanda H. The choosing wisely initiative and MRIs: over- and under-diagnosis in Japan and Myanmar. Cureus. 2021;13(4): e14342.
83. Bhaskar AK. Interventional management of cancer pain. Curr Opin Support Palliat Care. 2012;6(1):1–9.
84. Quaresima V, Bisconti S, Ferrari M. A brief review on the use of functional near-infrared spectroscopy (fNIRS) for language imaging studies in human newborns and adults. Brain Lang. 2012;121(2):79–89.
85. Wallois F, Patil A, Héberlé C, Grebe R. EEG-NIRS in epilepsy in children and neonates. Neurophysiologie Clinique = Clinical Neurophysiology. 2010;40(5–6):281–92.
86. Ferrari M, Mottola L, Quaresima V. Principles, techniques, and limitations of near infrared spectroscopy. Canadian Journal of Applied Physiology = Revue canadienne de physiologie appliquee. 2004;29(4):463–87.
87. Liao LD, Tsytsarev V, Delgado-Martínez I, Li ML, Erzurumlu R, Vipin A, et al. Neurovascular coupling: in vivo optical techniques for functional brain imaging. Biomed Eng Online. 2013;12:38.
88. Huppert TJ, Diamond SG, Franceschini MA, Boas DA. HomER: a review of time-series analysis methods for near-infrared spectroscopy of the brain. Appl Opt. 2009;48(10):D280–98.
89. Koh PH, Glaser DE, Flandin G, Kiebel S, Butterworth B, Maki A, et al. Functional optical signal analysis: a software tool for near-infrared spectroscopy data processing incorporating statistical parametric mapping. J Biomed Opt. 2007;12(6): 064010.
90. Ye JC, Tak S, Jang KE, Jung J, Jang J. NIRS-SPM: statistical parametric mapping for near-infrared spectroscopy. Neuroimage. 2009;44(2):428–47.
91. Strangman GE, Zhang Q, Zeffiro T. Near-infrared neuroimaging with NinPy. Front Neuroinform. 2009;3:12.
92. Fernandez Rojas R, Huang X, Ou KL. A machine learning approach for the identification of a biomarker of human pain using fNIRS. Sci Rep. 2019;9(1):5645.
93. Lee CH, Sugiyama T, Kataoka A, Kudo A, Fujino F, Chen YW, et al. Analysis for distinctive activation patterns of pain and itchy in the human brain cortex measured using near infrared spectroscopy (NIRS). PLoS ONE. 2013;8(10): e75360.
94. Sakuma S, Inamoto K, Higuchi N, Ariji Y, Nakayama M, Izumi M. Experimental pain in the gingiva and its impact on prefrontal cortical hemodynamics: a functional near-infrared spectroscopy study. Neurosci Lett. 2014;575:74–9.
95. Sakuma S, Inamoto K, Yamaguchi Y, Takagi S, Higuchi N. Changes in prefrontal cerebral hemodynamics during intermittent pain stimulation to gingiva: preliminary study using functional near infrared spectroscopy. Journal of Dental Sciences. 2021;16(3):980–6.
96. Hall M, Kidgell D, Perraton L, Morrissey J, Jaberzadeh S. Pain induced changes in brain oxyhemoglobin: a systematic review and meta-analysis of functional NIRS studies. Pain Medicine (Malden, Mass). 2021;22(6):1399–410.
97. Hu X, Racek AJ, Bellile E, Nascimento TD, Bender MC, Toback RL, et al. Brain functional changes before, during, and after clinical pain. J Dent Res. 2018;97(5):523–9.
98. Balconi M, Kopis N, Angioletti L. Does aesthetic judgment on face attractiveness affect neural correlates of empathy for pain? A fNIRS study Experimental Brain Research. 2020;238(9):2067–76.
99. Xie J, Yang H, Xia X, Yu S. The influence of medical professional knowledge on empathy for pain: evidence from fNIRS. Front Psychol. 2018;9:1089.
100. Barati Z, Zakeri I, Pourrezaei K. Functional near-infrared spectroscopy study on tonic pain activation by cold pressor test. Neurophotonics. 2017;4(1): 015004.
101. Tracey I, Johns E. The pain matrix: reloaded or reborn as we image tonic pain using arterial spin labelling. Pain. 2010;148(3):359–60.
102. Ren X, Lu J, Liu X, Shen C, Zhang X, Ma X, et al. Decreased prefrontal brain activation during verbal fluency task in patients with somatoform pain disorder: an exploratory multi-channel near-infrared spectroscopy study. Prog Neuropsychopharmacol Biol Psychiatry. 2017;78:153–60.
103. Chou PH, Tang KT, Chen YH, Sun CW, Huang CM, Chen DY. Reduced frontal activity during a verbal fluency test in fibromyalgia: a near-infrared spectroscopy study. Journal of Clinical Neuroscience: Official Journal of the Neurosurgical Society of Australasia. 2018;50:35–40.
104. Vrana A, Meier ML, Hotz-Boendermaker S, Humphreys BK, Scholkmann F. Cortical sensorimotor processing of painful pressure in patients with chronic lower back pain-an optical neuroimaging study using fNIRS. Front Hum Neurosci. 2016; 10:578.
105. Miyashiro S, Yamada Y, Nagaoka M, Shima R, Muta T, Ishikawa H, et al. Pain relief associated with decreased oxyhemoglobin level in left dorsolateral prefrontal cortex. PLoS ONE. 2021;16(8): e0256626.
106. Nardone R, Höller Y, Leis S, Höller P, Thon N, Thomschewski A, et al. Invasive and non-invasive brain stimulation for treatment of neuropathic pain in patients with spinal cord injury: a review. J Spinal Cord Med. 2014;37(1):19–31.
107. Sun X, Long H, Zhao C, Duan Q, Zhu H, Chen C, et al. Analgesia-enhancing effects of repetitive transcranial magnetic stimulation on neuropathic pain after spinal cord injury: an fNIRS study. Restor Neurol Neurosci. 2019;37(5):497–507.

108. Peng K, Yücel MA, Aasted CM, Steele SC, Boas DA, Borsook D, et al. Using prerecorded hemodynamic response functions in detecting prefrontal pain response: a functional near-infrared spectroscopy study. Neurophotonics. 2018;5(1): 011018.
109. McKendrick R, Parasuraman R, Murtza R, Formwalt A, Baccus W, Paczynski M, et al. Into the wild: neuroergonomic differentiation of hand-held and augmented reality wearable displays during outdoor navigation with functional near infrared spectroscopy. Front Hum Neurosci. 2016;10:216.
110. Ranger M, Gélinas C. Innovating in pain assessment of the critically ill: exploring cerebral near-infrared spectroscopy as a bedside approach. Pain Management Nursing: Official Journal of the American Society of Pain Management Nurses. 2014;15(2):519–29.
111. Ranger M, Johnston CC, Limperopoulos C, Rennick JE, du Plessis AJ. Cerebral near-infrared spectroscopy as a measure of nociceptive evoked activity in critically ill infants. Pain Res Manage. 2011;16(5):331–6.
112. Lloyd-Fox S, Blasi A, Elwell CE. Illuminating the developing brain: the past, present and future of functional near infrared spectroscopy. Neurosci Biobehav Rev. 2010;34(3):269–84.
113. Boas DA, Dale AM, Franceschini MA. Diffuse optical imaging of brain activation: approaches to optimizing image sensitivity, resolution, and accuracy. Neuroimage. 2004;23(Suppl 1):S275–88.
114. Strangman G, Boas DA, Sutton JP. Non-invasive neuroimaging using near-infrared light. Biol Psychiat. 2002;52(7):679–93.
115. Perrey S. Non-invasive NIR spectroscopy of human brain function during exercise. Methods (San Diego, Calif). 2008;45 (4):289–99.
116. Verger A, Langen KJ. PET Imaging in glioblastoma: use in clinical practice. In: De Vleeschouwer S, editor. Glioblastoma. Brisbane (AU): Codon Publications Copyright: The Authors.; 2017.
117. Gründer G, Vernaleken I, Bartenstein P. [Use of PET and SPECT in psychiatry]. Der Nervenarzt. 2010;81(1):97–107; quiz 8.
118. Muehllehner G, Karp JS. Positron emission tomography. Phys Med Biol. 2006;51(13):R117–37.
119. Peyron R, Laurent B, García-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis (2000). Neurophysiologie Clinique = Clinical Neurophysiology. 2000;30(5):263–88.
120. Andersson JL, Lilja A, Hartvig P, Långström B, Gordh T, Handwerker H, et al. Somatotopic organization along the central sulcus, for pain localization in humans, as revealed by positron emission tomography. Exp Brain Res. 1997;117(2):192–9.
121. Tölle TR, Kaufmann T, Siessmeier T, Lautenbacher S, Berthele A, Munz F, et al. Region-specific encoding of sensory and affective components of pain in the human brain: a positron emission tomography correlation analysis. Ann Neurol. 1999;45(1):40–7.
122. Casey KL, Minoshima S, Morrow TJ, Koeppe RA. Comparison of human cerebral activation pattern during cutaneous warmth, heat pain, and deep cold pain. J Neurophysiol. 1996;76(1):571–81.
123. Casey KL, Morrow TJ, Lorenz J, Minoshima S. Temporal and spatial dynamics of human forebrain activity during heat pain: analysis by positron emission tomography. J Neurophysiol. 2001;85(2):951–9.
124. Zhang ZH, Dougherty PM, Oppenheimer SM. Monkey insular cortex neurons respond to baroreceptive and somatosensory convergent inputs. Neuroscience. 1999;94(2):351–60.
125. Korotkov A, Ljubisavljevic M, Thunberg J, Kataeva G, Roudas M, Pakhomov S, et al. Changes in human regional cerebral blood flow following hypertonic saline induced experimental muscle pain: a positron emission tomography study. Neurosci Lett. 2002;335(2):119–23.
126. Hsieh JC, Ståhle-Bäckdahl M, Hägermark Ö, Stone-Elander S, Rosenquist G, Ingvar M. Traumatic nociceptive pain activates the hypothalamus and the periaqueductal gray: a positron emission tomography study. Pain. 1996;64(2):303–14.
127. Derbyshire SW, Jones AK. Cerebral responses to a continual tonic pain stimulus measured using positron emission tomography. Pain. 1998;76(1–2):127–35.
128. Jones AK, Brown WD, Friston KJ, Qi LY, Frackowiak RS. Cortical and subcortical localization of response to pain in man using positron emission tomography. Proceedings Biological Sciences. 1991;244(1309):39–44.
129. Fredrikson M, Wik G, Fischer H, Andersson J. Affective and attentive neural networks in humans: a PET study of Pavlovian conditioning. NeuroReport. 1995;7(1):97–101.
130. Hsieh JC, Belfrage M, Stone-Elander S, Hansson P, Ingvar M. Central representation of chronic ongoing neuropathic pain studied by positron emission tomography. Pain. 1995;63(2):225–36.
131. Iadarola MJ, Max MB, Berman KF, Byas-Smith MG, Coghill RC, Gracely RH, et al. Unilateral decrease in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain. Pain. 1995;63(1):55–64.
132. Duncan GH, Kupers RC, Marchand S, Villemure JG, Gybels JM, Bushnell MC. Stimulation of human thalamus for pain relief: possible modulatory circuits revealed by positron emission tomography. J Neurophysiol. 1998;80(6):3326–30.
133. Davis KD, Taub E, Duffner F, Lozano AM, Tasker RR, Houle S, et al. Activation of the anterior cingulate cortex by thalamic stimulation in patients with chronic pain: a positron emission tomography study. J Neurosurg. 2000;92(1):64–9.
134. García-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, Le Bars D, et al. Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. Pain. 1999;83(2):259–73.
135. Nuti C, Peyron R, Garcia-Larrea L, Brunon J, Laurent B, Sindou M, et al. Motor cortex stimulation for refractory neuropathic pain: four year outcome and predictors of efficacy. Pain. 2005;118(1–2):43–52.
136. Peyron R, Faillenot I, Mertens P, Laurent B, Garcia-Larrea L. Motor cortex stimulation in neuropathic pain. Correlations between analgesic effect and hemodynamic changes in the brain. A PET study. NeuroImage. 2007;34(1):310–21.
137. Di Piero V, Jones AKP, Iannotti F, Powell M, Perani D, Lenzi GL, et al. Chronic pain: a PET study of the central effects of percutaneous high cervical cordotomy. Pain. 1991;46(1):9–12.
138. Jensen TS, Finnerup NB. Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. The Lancet Neurology. 2014;13(9):924–35.
139. Herrero JF, Laird JM, López-García JA. Wind-up of spinal cord neurones and pain sensation: much ado about something? Prog Neurobiol. 2000;61(2):169–203.
140. Peyron R, Faillenot I, Pomares FB, Le Bars D, Garcia-Larrea L, Laurent B. Mechanical allodynia in neuropathic pain. Where are the brain representations located? A positron emission tomography (PET) study. European Journal of Pain (London, England). 2013;17(9):1327–37.
141. Kupers R, Lonsdale MN, Aasvang E, Kehlet H. A positron emission tomography study of wind-up pain in chronic posth-erniotomy pain. European Journal of Pain (London, England). 2011;15(7):698.e1-16.
142. Derbyshire SW, Jones AK, Devani P, Friston KJ, Feinmann C, Harris M, et al. Cerebral responses to pain in patients with atypical facial pain measured by positron emission tomography. J Neurol Neurosurg Psychiatry. 1994;57(10):1166–72.
143. Kupers RC, Gybels JM, Gjedde A. Positron emission tomography study of a chronic pain patient successfully treated with somatosensory thalamic stimulation. Pain. 2000;87(3):295–302.

144. Berti V, Sciagrà R, Neglia D, Pietilä M, Scholte AJ, Nekolla S, et al. Segmental quantitative myocardial perfusion with PET for the detection of significant coronary artery disease in patients with stable angina. Eur J Nucl Med Mol Imaging. 2016;43(8):1522–9.
145. Sprenger T, Henriksen G, Valet M, Platzer S, Berthele A, Tölle TR. [Positron emission tomography in pain research. From the structure to the activity of the opiate receptor system]. Schmerz (Berlin, Germany). 2007;21(6):503–13.
146. Boecker H, Sprenger T, Henriksen G, Toelle TR, Spilker ME. Optimal duration of PET studies with 18F-fluoroethyl-diprenorphine. Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine. 2005;46(12):2092–6.
147. Valk PE, Pounds TR, Tesar RD, Hopkins DM, Haseman MK. Cost-effectiveness of PET imaging in clinical oncology. Nucl Med Biol. 1996;23(6):737–43.
148. MacKenzie AB. Environmental radioactivity: experience from the 20th century–trends and issues for the 21st century. The Science of the Total Environment. 2000;249(1–3):313–29.
149. Jones AK, Huneke NT, Lloyd DM, Brown CA, Watson A. Role of functional brain imaging in understanding rheumatic pain. Curr Rheumatol Rep. 2012;14(6):557–67.
150. Hari R, Baillet S, Barnes G, Burgess R, Forss N, Gross J, et al. IFCN-endorsed practical guidelines for clinical magnetoencephalography (MEG). Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology. 2018;129(8):1720–47.
151. Olejniczak P. Neurophysiologic basis of EEG. Journal of Clinical Neurophysiology: Official Publication of the American Electroencephalographic Society. 2006;23(3):186–9.
152. Silva FLd. EEG: origin and measurement. EEg-fMRI: Springer; 2009. p. 19–38.
153. Jackson AF, Bolger DJ. The neurophysiological bases of EEG and EEG measurement: a review for the rest of us. Psychophysiology. 2014;51(11):1061–71.
154. Ahlfors SP, Han J, Belliveau JW, Hämäläinen MS. Sensitivity of MEG and EEG to source orientation. Brain Topogr. 2010;23(3):227–32.
155. Hillebrand A, Barnes GR. A quantitative assessment of the sensitivity of whole-head MEG to activity in the adult human cortex. Neuroimage. 2002;16(3 Pt 1):638–50.
156. Gross J. Magnetoencephalography in cognitive neuroscience: a primer. Neuron. 2019;104(2):189–204.
157. Gallinat J, Mulert C, Leicht G. [Significance of clinical electroencephalogram in psychiatry]. Der Nervenarzt. 2016;87(3):323–37; quiz 38–9.
158. Kim JA, Davis KD. Neural oscillations: understanding a neural code of pain. The Neuroscientist: a Review Journal Bringing Neurobiology, Neurology and Psychiatry. 2021;27(5):544–70.
159. Nir RR, Sinai A, Raz E, Sprecher E, Yarnitsky D. Pain assessment by continuous EEG: association between subjective perception of tonic pain and peak frequency of alpha oscillations during stimulation and at rest. Brain Res. 2010;1344:77–86.
160. Shao S, Shen K, Yu K, Wilder-Smith EP, Li X. Frequency-domain EEG source analysis for acute tonic cold pain perception. Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology. 2012;123(10):2042–9.
161. Chang PF, Arendt-Nielsen L, Graven-Nielsen T, Svensson P, Chen AC. Comparative EEG activation to skin pain and muscle pain induced by capsaicin injection. International Journal of psychophysiology: Official Journal of the International Organization of Psychophysiology. 2004;51(2):117–26.
162. Nickel MM, May ES, Tiemann L, Schmidt P, Postorino M, Ta Dinh S, et al. Brain oscillations differentially encode noxious stimulus intensity and pain intensity. Neuroimage. 2017;148:141–7.
163. Mu Y, Fan Y, Mao L, Han S. Event-related theta and alpha oscillations mediate empathy for pain. Brain Res. 2008;1234:128–36.
164. Alba G, Vila J, Miranda JGV, Montoya P, Muñoz MA. Tonic pain reduces autonomic responses and EEG functional connectivity elicited by affective stimuli. Psychophysiology. 2022:e14018.
165. Giehl J, Meyer-Brandis G, Kunz M, Lautenbacher S. Responses to tonic heat pain in the ongoing EEG under conditions of controlled attention. Somatosens Mot Res. 2014;31(1):40–8.
166. Kakigi R, Tran TD, Qiu Y, Wang X, Nguyen TB, Inui K, et al. Cerebral responses following stimulation of unmyelinated C-fibers in humans: electro- and magneto-encephalographic study. Neurosci Res. 2003;45(3):255–75.
167. Cifre I, Sitges C, Fraiman D, Muñoz M, Balenzuela P, González-Roldán A, et al. Disrupted functional connectivity of the pain network in fibromyalgia. Psychosom Med. 2012;74(1):55–62.
168. González-Roldán AM, Cifre I, Sitges C, Montoya P. Altered dynamic of EEG oscillations in fibromyalgia patients at rest. Pain Medicine (Malden, Mass). 2016;17(6):1058–68.
169. Villafaina S, Collado-Mateo D, Fuentes-García JP, Cano-Plasencia R, Gusi N. Impact of fibromyalgia on alpha-2 EEG power spectrum in the resting condition: a descriptive correlational study. Biomed Res Int. 2019;2019:7851047.
170. Fallon N, Chiu Y, Nurmikko T, Stancak A. Altered theta oscillations in resting EEG of fibromyalgia syndrome patients. European Journal of Pain (London, England). 2018;22(1):49–57.
171. Choe MK, Lim M, Kim JS, Lee DS, Chung CK. Disrupted resting state network of fibromyalgia in theta frequency. Sci Rep. 2018;8(1):2064.
172. Stevens A, Batra A, Kötter I, Bartels M, Schwarz J. Both pain and EEG response to cold pressor stimulation occurs faster in fibromyalgia patients than in control subjects. Psychiatry Res. 2000;97(2–3):237–47.
173. Goldstein A, Zeev-Wolf M, Herz N, Ablin JN. Brain responses to other people's pain in fibromyalgia: a magnetoencephalography study. Clin Exp Rheumatol. 2019;37 Suppl 116(1):70–4.
174. Kayiran S, Dursun E, Ermutlu N, Dursun N, Karamürsel S. Neurofeedback in fibromyalgia syndrome. Agri: Agri (Algoloji) Dernegi'nin Yayin organidir = The Journal of the Turkish Society of Algology. 2007;19(3):47–53.
175. Caro XJ, Winter EF. EEG biofeedback treatment improves certain attention and somatic symptoms in fibromyalgia: a pilot study. Appl Psychophysiol Biofeedback. 2011;36(3):193–200.
176. Gram M, Graversen C, Olesen SS, Drewes AM. Dynamic spectral indices of the electroencephalogram provide new insights into tonic pain. Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology. 2015;126(4):763–71.
177. Hansen TM, Mark EB, Olesen SS, Gram M, Frøkjær JB, Drewes AM. Characterization of cortical source generators based on electroencephalography during tonic pain. J Pain Res. 2017;10:1401–9.
178. Lau-Zhu A, Lau MPH, McLoughlin G. Mobile EEG in research on neurodevelopmental disorders: opportunities and challenges. Dev Cogn Neurosci. 2019;36: 100635.
179. Hari R, Puce A. MEG-EEG primer: Oxford University Press; 2017.
180. Baumgartner C. Controversies in Clinical Neurophysiology. MEG is superior to EEG in the localization of interictal epileptiform activity: Con. Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology. 2004;115(5):1010–20.
181. Barkley GL, Baumgartner C. MEG and EEG in epilepsy. Journal of Clinical Neurophysiology: Official Publication of the American Electroencephalographic Society. 2003;20(3):163–78.
182. Buentjen L, Vicheva P, Chander BS, Beccard SA, Coutts C, Azañón E, et al. Spatial filtering of electroencephalography

reduces artifacts and enhances signals related to spinal cord stimulation (SCS). Neuromodulation: Journal of the International Neuromodulation Society. 2021;24(8):1317–26.
183. Raghavachari S, Lisman JE, Tully M, Madsen JR, Bromfield EB, Kahana MJ. Theta oscillations in human cortex during a working-memory task: evidence for local generators. J Neurophysiol. 2006;95(3):1630–8.
184. Kahana MJ, Seelig D, Madsen JR. Theta returns. Curr Opin Neurobiol. 2001;11(6):739–44.
185. Sarco DP, Burke JF, Madsen JR. Electroencephalography in epilepsy surgery planning. Child's Nervous System: ChNS: Official Journal of the International Society for Pediatric Neurosurgery. 2006;22(8):760–5.
186. Boissoneault J, Sevel L, Letzen J, Robinson M, Staud R. Biomarkers for musculoskeletal pain conditions: use of brain imaging and machine learning. Curr Rheumatol Rep. 2017;19(1):5.
187. Chen T, Mu J, Xue Q, Yang L, Dun W, Zhang M, et al. Whole-brain structural magnetic resonance imaging-based classification of primary dysmenorrhea in pain-free phase: a machine learning study. Pain. 2019;160(3):734–41.
188. Chong CD, Gaw N, Fu Y, Li J, Wu T, Schwedt TJ. Migraine classification using magnetic resonance imaging resting-state functional connectivity data. Cephalalgia: an International Journal of Headache. 2017;37(9):828–44.
189. Tan WK, Hassanpour S, Heagerty PJ, Rundell SD, Suri P, Huhdanpaa HT, et al. Comparison of natural language processing rules-based and machine-learning systems to identify lumbar spine imaging findings related to low back pain. Acad Radiol. 2018;25(11):1422–32.
190. van der Miesen MM, Lindquist MA, Wager TD. Neuroimaging-based biomarkers for pain: state of the field and current directions. Pain Reports. 2019;4(4): e751.
191. Ung H, Brown JE, Johnson KA, Younger J, Hush J, Mackey S. Multivariate classification of structural MRI data detects chronic low back pain. Cerebral Cortex (New York, NY: 1991). 2014;24(4):1037–44.
192. Bagarinao E, Johnson KA, Martucci KT, Ichesco E, Farmer MA, Labus J, et al. Preliminary structural MRI based brain classification of chronic pelvic pain: a MAPP network study. Pain. 2014;155(12):2502–9.
193. Tu Y, Cao J, Bi Y, Hu L. Magnetic resonance imaging for chronic pain: diagnosis, manipulation, and biomarkers. Science China Life sciences. 2021;64(6):879–96.
194. Woo CW, Chang LJ, Lindquist MA, Wager TD. Building better biomarkers: brain models in translational neuroimaging. Nat Neurosci. 2017;20(3):365–77.
195. González-Roldan AM, Martínez-Jauand M, Muñoz-García MA, Sitges C, Cifre I, Montoya P. Temporal dissociation in the brain processing of pain and anger faces with different intensities of emotional expression. Pain. 2011;152(4):853–9.
196. Davis KD, Flor H, Greely HT, Iannetti GD, Mackey S, Ploner M, et al. Brain imaging tests for chronic pain: medical, legal and ethical issues and recommendations. Nat Rev Neurol. 2017;13(10):624–38.
197. Rance M, Ruttorf M, Nees F, Schad LR, Flor H. Real time fMRI feedback of the anterior cingulate and posterior insular cortex in the processing of pain. Hum Brain Mapp. 2014;35(12):5784–98.
198. Hesam-Shariati N, Chang WJ, Wewege MA, McAuley JH, Booth A, Trost Z, et al. The analgesic effect of electroencephalographic neurofeedback for people with chronic pain: a systematic review and meta-analysis. Eur J Neurol. 2022;29 (3):921–36.
199. Papuga MO, Burke JR, Dougherty PE. The reliability of a novel magnetic resonance compatible electro-pneumatic device for delivering a painful pressure stimulus over the lumbar spine. Somatosens Mot Res. 2015;32(1):51–60.
200. Jackson JB, O'Daly O, Makovac E, Medina S, Rubio AL, McMahon SB, et al. Noxious pressure stimulation demonstrates robust, reliable estimates of brain activity and self-reported pain. Neuroimage. 2020;221: 117178.
201. Bi Y, Hou X, Zhong J, Hu L. Test-retest reliability of laser evoked pain perception and fMRI BOLD responses. Sci Rep. 2021;11(1):1322.
202. Kupers RC, Svensson P, Jensen TS. Central representation of muscle pain and mechanical hyperesthesia in the orofacial region: a positron emission tomography study. Pain. 2004;108(3):284–93.
203. Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. Brain: a Journal of Neurology. 2003;126(Pt 5):1079–91.
204. Coghill RC, Talbot JD, Evans AC, Meyer E, Gjedde A, Bushnell MC, et al. Distributed processing of pain and vibration by the human brain. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 1994;14(7):4095–108.
205. Nir RR, Sinai A, Moont R, Harari E, Yarnitsky D. Tonic pain and continuous EEG: prediction of subjective pain perception by alpha-1 power during stimulation and at rest. Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology. 2012;123(3):605–12.
206. Huber MT, Bartling J, Pachur D, Woikowsky-Biedau S, Lautenbacher S. EEG responses to tonic heat pain. Exp Brain Res. 2006;173(1):14–24.
207. Chen AC, Rappelsberger P. Brain and human pain: topographic EEG amplitude and coherence mapping. Brain Topogr. 1994;7(2):129–40.
208. Dowman R, Rissacher D, Schuckers S. EEG indices of tonic pain-related activity in the somatosensory cortices. Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology. 2008;119(5):1201–12.
209. Rustamov N, Sharma L, Chiang SN, Burk C, Haroutounian S, Leuthardt EC. Spatial and frequency-specific electrophysiological signatures of tonic pain recovery in humans. Neuroscience. 2021;465:23–37.
210. Chang PF, Arendt-Nielsen L, Graven-Nielsen T, Svensson P, Chen AC. Topographic effects of tonic cutaneous nociceptive stimulation on human electroencephalograph. Neurosci Lett. 2001;305(1):49–52.
211. Li L, Liu X, Cai C, Yang Y, Li D, Xiao L, et al. Changes of gamma-band oscillatory activity to tonic muscle pain. Neurosci Lett. 2016;627:126–31.
212. Le Pera D, Svensson P, Valeriani M, Watanabe I, Arendt-Nielsen L, Chen AC. Long-lasting effect evoked by tonic muscle pain on parietal EEG activity in humans. Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology. 2000;111(12):2130–7.
213. Chang PF, Arendt-Nielsen L, Graven-Nielsen T, Chen AC. Psychophysical and EEG responses to repeated experimental muscle pain in humans: pain intensity encodes EEG activity. Brain Res Bull. 2003;59(6):533–43.
214. Taesler P, Rose M. Prestimulus theta oscillations and connectivity modulate pain perception. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2016;36(18):5026–33.