

## Review

# Advances and challenges in neuroimaging-based pain biomarkers

Li-Bo Zhang,<sup>1,2,3,5</sup> Yu-Xin Chen,<sup>1,2,5</sup> Zhen-Jiang Li,<sup>1,2</sup> Xin-Yi Geng,<sup>1,2</sup> Xiang-Yue Zhao,<sup>1,2</sup> Feng-Rui Zhang,<sup>1,4</sup> Yan-Zhi Bi,<sup>1,2</sup> Xue-Jing Lu,<sup>1,2,\*</sup> and Li Hu<sup>1,2,\*</sup>

<sup>1</sup>CAS Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China

<sup>2</sup>Department of Psychology, University of Chinese Academy of Sciences, Beijing 100049, China

<sup>3</sup>Neuroscience and Behaviour Laboratory, Italian Institute of Technology, Rome 00161, Italy

<sup>4</sup>Department of Neuroscience, Washington University School of Medicine, St. Louis, MO 63110, USA

<sup>5</sup>These authors contributed equally

\*Correspondence: luxj@psych.ac.cn (X.-J.L.), huli@psych.ac.cn (L.H.)

<https://doi.org/10.1016/j.xcrm.2024.101784>

## SUMMARY

Identifying neural biomarkers of pain has long been a central theme in pain neuroscience. Here, we review the state-of-the-art candidates for neural biomarkers of acute and chronic pain. We classify these potential neural biomarkers into five categories based on the nature of their target variables, including neural biomarkers of (1) within-individual perception, (2) between-individual sensitivity, and (3) discriminability for acute pain, as well as (4) assessment and (5) prospective neural biomarkers for chronic pain. For each category, we provide a synthesized review of candidate biomarkers developed using neuroimaging techniques including functional magnetic resonance imaging (fMRI), structural magnetic resonance imaging (sMRI), and electroencephalography (EEG). We also discuss the conceptual and practical challenges in developing neural biomarkers of pain. Addressing these challenges, optimal biomarkers of pain can be developed to deepen our understanding of how the brain represents pain and ultimately help alleviate patients' suffering and improve their well-being.

## INTRODUCTION

Pain, especially chronic pain that persists after the usual healing period,<sup>1</sup> is a huge public health issue and imposes substantial socioeconomic burdens worldwide. Chronic pain afflicts approximately 30% of the world's population<sup>2–5</sup> and causes hundreds of billions of dollars of economic costs each year in some countries.<sup>6–8</sup> However, pain is essentially subjective and self-reports are generally regarded as the final arbiter of how much pain one is experiencing.<sup>9</sup> Despite decades of dedicated research, it remains a mystery how the brain generates the pain experience. Driven by theoretical curiosity and clinical necessity, identifying neural biomarkers of pain has long been one of the main themes in pain neuroscience. Such biomarkers not only help reveal the neural underpinnings of pain<sup>10</sup> but also assist in developing effective pain treatments to improve patients' well-being.<sup>11</sup>

By definition, neural biomarkers are neural characteristics “measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions.”<sup>12</sup> An ideal pain neural biomarker should possess at least three key properties: (1) high model sensitivity, accurately indicating the presence or severity of pain when pain is present; (2) high model specificity, correctly indicating the absence of pain when pain is absent; and (3) strong model generalizability, applicable to inde-

pendent groups different from those in which the biomarker was developed.<sup>13</sup> Using noninvasive neuroimaging techniques on the central nervous system like magnetic resonance imaging (MRI) and electroencephalography (EEG), decades of research have developed numerous candidates for neural biomarkers of pain.<sup>14–20</sup> These biomarkers can be classified into two general categories: biomarkers of acute pain and chronic pain (Figure 1). Importantly, acute pain and chronic pain do not necessarily have shared biomarkers. In fact, their biomarkers are often distinct.<sup>21</sup>

Depending on whether they capture the states or traits of pain, acute pain biomarkers can be dichotomized into biomarkers of within-individual pain perception and between-individual pain sensitivity.<sup>22</sup> In this review, biomarkers of within-individual pain perception are defined as those that respond to pain but not to non-pain perception and closely track different levels of pain perception at the within-individual level.<sup>20</sup> Biomarkers of between-individual pain sensitivity are defined as those that predict individual differences in perceiving the same nociceptive stimuli.<sup>16</sup> The distinction between within-individual pain perception and between-individual pain sensitivity is not always recognized in the literature, but has been highlighted recently due to their conceptual and neuropsychological differences.<sup>22</sup> Conceptually, within-individual pain perception reflects momentary pain states, varying on a short timescale and influenced by momentary psychological and physiological factors. In contrast, while not completely unchanging, between-individual pain sensitivity



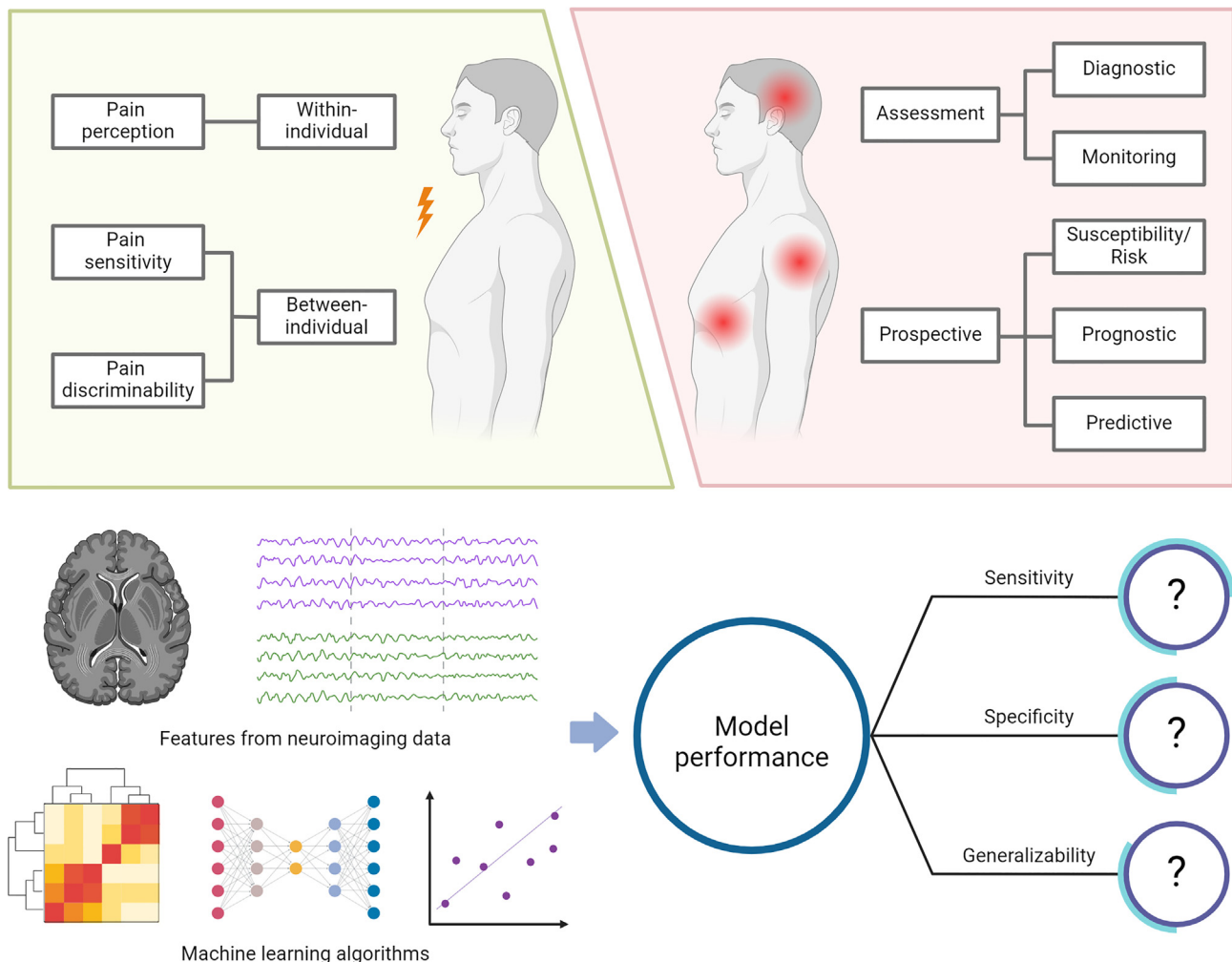


**Figure 1. Typology of biomarkers of pain**

Different types of neuroimaging-based biomarkers can be discerned for acute pain and chronic pain. For acute pain induced by transient noxious stimuli (e.g., radiant thermal laser, contact heat, and electrical stimuli) and tonic noxious stimuli (e.g., cold pressor and capsaicin), biomarkers are developed to distinguish pain from non-pain states and track pain severity (i.e., within-individual pain perception), or predict individual differences in pain sensitivity and discriminability. For chronic pain like chronic back pain and migraine, assessment biomarkers are identified to distinguish patients with chronic pain from healthy individuals or to identify patients with different subtypes of chronic pain (diagnostic), assessing the status of chronic pain like the severity of spontaneous pain or pain attack/free periods (monitoring); prospective biomarkers are developed to predict pain chronification (susceptibility/risk), recovery (prognostic), and responses to treatments (predictive). Using noninvasive neuroimaging techniques like magnetic resonance imaging (MRI) and electroencephalography (EEG) to sample brain activities and analysis methods like machine learning algorithms to build models, numerous potential neural biomarkers of pain have been developed. Any pain neural biomarker can be assessed in terms of model sensitivity, model specificity, and model generalizability.

is more of a characteristic pain trait, remaining relatively stable over time and mainly influenced by disease and other long-lasting conditions.<sup>22,23</sup> Within-individual pain perception and between-individual pain sensitivity can also have different neural correlates. For example, many EEG responses to pain seem to only encode within-individual pain perception but not between-individual pain sensitivity.<sup>16</sup>

Importantly, pain sensitivity can be further categorized into two subtypes: absolute and differential sensitivities, corresponding to the absolute and difference thresholds in classical psychophysics.<sup>24</sup> Absolute pain sensitivity refers to the characteristic of an individual that is reflected by the amount of pain they

feel when exposed to nociceptive stimuli of the same physical intensity.<sup>25</sup> Differential pain sensitivity pertains to individual differences in the ability to discriminate between two or more nociceptive stimuli of different physical intensities.<sup>26</sup> In pain neuroscience, “pain sensitivity” typically denotes absolute pain sensitivity.<sup>27</sup> To follow this convention and highlight the distinction between absolute and differential pain sensitivities, here we define “pain sensitivity” as absolute pain sensitivity and “pain discriminability” as differential pain sensitivity. A biomarker of pain sensitivity should thus be able to distinguish individuals experiencing more pain from those experiencing less pain when they receive the same nociceptive stimuli.<sup>16</sup> A biomarker

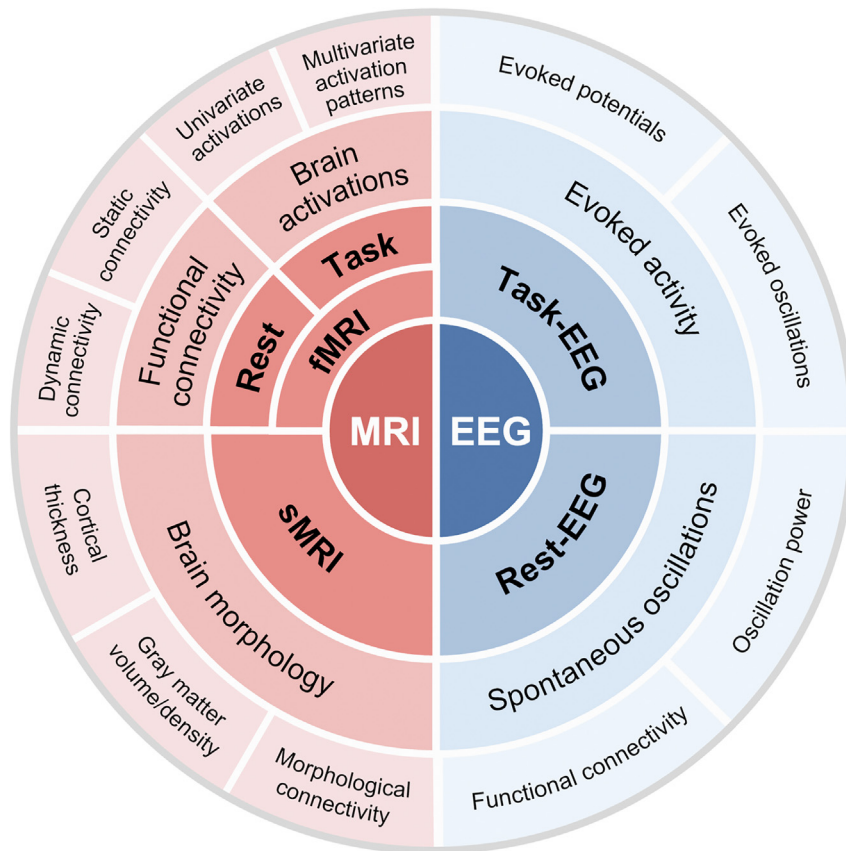


**Figure 2. Neuroimaging features for biomarkers of pain**

Magnetic resonance imaging (MRI) and electroencephalography (EEG) are the primary techniques used to develop neuroimaging-based biomarkers of pain. Different functional MRI (fMRI), structural MRI (sMRI), and EEG features can be extracted to identify biomarkers of pain.

established 2016 FDA-NIH Biomarker Working Group glossary BEST [Biomarkers, EndpointS, and other Tools Resource]), and those assessing the status of chronic pain like the severity of spontaneous pain or pain attack/free periods (i.e., monitoring biomarker in the BEST taxonomy).<sup>17</sup> On the other hand, prospective biomarkers are future oriented, consisting mainly of those indicating whether a certain individual will develop chronic pain (i.e., susceptibility/risk biomarker in the BEST taxonomy)<sup>14</sup> and whether patients with chronic pain will recover or deteriorate (i.e., prognostic biomarker in the BEST taxonomy), or respond to treatments (i.e., predictive biomarker in the BEST taxonomy).<sup>38</sup> Assessment and prospective biomarkers serve distinct clinical purposes, one for the diagnosis of existing chronic pain, the other for the prediction of future clinical events (e.g., development of

of pain discriminability should indicate how well a person can discriminate between two or more nociceptive stimuli of different physical intensities.<sup>26</sup> Previous studies have associated pain sensitivity and discriminability with chronic pain, suggesting clinical relevance of their biomarkers. For example, high pain sensitivity is a risk factor of chronic pain,<sup>27–29</sup> and normal pain sensitivity has been associated with better treatment outcomes.<sup>30</sup> Furthermore, patients with chronic pain have been shown to have lower pain discriminability compared with healthy individuals,<sup>31–34</sup> and higher pain discriminability prior to treatment has been related to better recovery after pain treatment.<sup>35,36</sup> Biomarkers of pain sensitivity and discriminability may thus aid in the early screening of at-risk individuals and prediction of treatment outcomes. Due to the association between pain sensitivity/discriminability and chronic pain, biomarkers of pain sensitivity/discriminability may also inform the development of biomarkers of chronic pain.

Biomarkers of chronic pain are concerned with how chronic pain develops, maintains, is diagnosed or treated. In this context, two broad types of biomarkers, assessment and prospective biomarkers, can be identified depending on whether the focus is the current state or future.<sup>37</sup> Assessment biomarkers are concerned with the current state of chronic pain. They can be further classified into those distinguishing patients with chronic pain from healthy individuals or identifying patients with different subtypes of chronic pain (i.e., diagnostic biomarker in the well-

chronic pain, recovery/progression, or response to treatment). Therefore, assessment biomarkers are not necessarily prospective biomarkers, and vice versa. Note that this classification concerns only the purpose of different biomarkers. Different conditions of chronic pain can have entirely different biomarkers of a certain category. For example, there may be a diagnostic biomarker for low back pain and another diagnostic biomarker for fibromyalgia.

Although clinically applicable pain biomarkers are still rare, decades of research have proposed numerous pain biomarker candidates. In this review, we adhere to the typology introduced earlier (Figure 1) and evaluate available candidates for neural biomarkers of pain in each category according to the three key properties of ideal biomarkers. Our focus is on biomarkers developed using noninvasive neuroimaging techniques, including functional MRI (fMRI), structural MRI (sMRI), and EEG (Figure 2). We first discuss neural biomarkers of acute pain, including phasic pain and tonic pain. We then provide a summary of assessment and prospective biomarkers of chronic pain. Finally, we discuss challenges and future directions in the development of clinically useful neural biomarkers of pain (Figure 3).

## BIOMARKERS FOR ACUTE PAIN

Acute pain arises from actual or potential tissue damage that typically subsides once the underlying cause is resolved. It

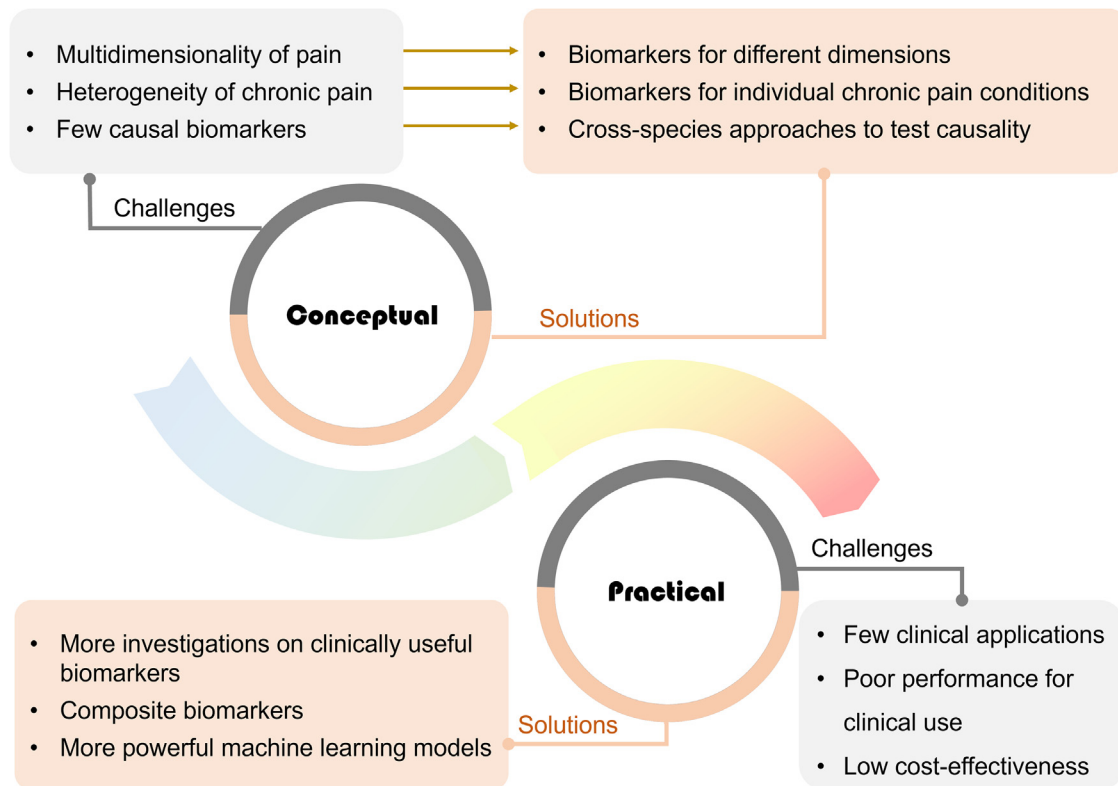


**Figure 3. Challenges of and viable solutions to developing pain biomarkers**

Developing biomarkers of pain faces conceptual and practical challenges. Conceptual challenges include the multidimensional nature of pain, huge heterogeneity of chronic pain, and few causal biomarkers. To address these challenges, future studies can develop different biomarkers for different dimensions of pain and individual chronic pain condition and adopt cross-species approaches to test the causal relationship between potential biomarkers and pain. Practical challenges include that most biomarkers still have few real clinical applications and deficient performance for clinical use, and the other is their low economic cost-effectiveness, which poses constraints on their widespread implementation in clinical settings. Future studies can conduct more direct investigations on clinically useful biomarkers, develop composite biomarkers, and train more powerful machine learning models.

serves as a warning signal for the body, yet it can progress to chronic pain if not properly managed.<sup>39</sup> Based on its duration, acute pain can be categorized into phasic pain and tonic pain. Phasic pain is fast rising and short lived, while tonic pain is more long lasting.<sup>40</sup>

### Phasic pain

Phasic pain can be easily induced in the laboratory using noxious stimuli such as thermal stimuli (e.g., radiant thermal laser and contact heat), electrical stimuli, and mechanical stimuli (e.g., pinprick). These stimuli can be readily applied and removed without causing real tissue damage, making them widely used in pain research.<sup>41</sup>

### MRI-based biomarkers of phasic pain

Phasic pain stimuli activate a wide range of brain areas, including but not limited to the primary somatosensory cortex (S1), secondary somatosensory cortex (S2), insula, anterior cingulate cortex (ACC), prefrontal cortex (PFC), and thalamus.<sup>42–44</sup> Numerous neuroimaging studies have established a close link between activations in these areas and pain perception.<sup>45–48</sup> Activations in these areas increased with stimulus intensity of painful stimuli<sup>49</sup> and perceptual pain ratings.<sup>50–54</sup>

Some studies have also developed multivariate machine learning models to predict pain perception based on brain activation patterns.<sup>20,55,56,57,58</sup> Marquand et al.<sup>55</sup> were the first to illustrate how whole-brain fMRI data could be used to classify pain vs. non-pain states and predict continuous pain ratings with greater accuracy than using any single brain area alone. A notable study by Wager et al.<sup>20</sup> developed a model termed the Neural Pain Signature (NPS) and comprehensively evaluated the model's performance. The NPS primarily includes activation patterns in pain-related areas such as the bilateral dorsal posterior insula, anterior insula, S2, ventrolateral thalamus, medial thalamus, hypothalamus, and dorsal ACC. They found that the NPS could accurately distinguish heat pain from warm stimuli, physical pain from pain anticipation/recall and social rejection, as well as predict perceptual ratings of pain. By controlling for stimulus intensity, Woo et al.<sup>56</sup> identified an activation pattern (stimulus intensity independent pain signature-1, SIIPS1) that includes activations in the nucleus accumbens (NAc), lateral PFC, parahippocampal cortex, and other regions. SIIPS1 not only predicted trial-by-trial pain ratings independent of the physical intensity of pain stimuli but also mediated the modulating effects of expectations and perceived control on pain.

However, it is a logical fallacy (i.e., reverse inference) to infer the presence of pain based on the activation of brain areas that can be activated by noxious stimuli.<sup>59,60</sup> Reverse inference can be corrected only if the corresponding brain activity is pain selective, that is, it is absent when there is no pain. Importantly, some studies have questioned the pain selectivity of these pain-related brain areas, suggesting that their activity encodes stimulus salience rather than pain per se.<sup>61,62</sup> For example, Mouraux et al.<sup>63</sup> found substantial overlap between brain activations induced by painful, tactile, auditory, and visual stimuli. Further analyses suggested that activations in the pain-related brain areas could be largely explained by brain responses common to multiple sensory modalities. Nevertheless, these findings do not conclusively rule out the possibility of some brain activity selectively encoding pain. A recent study identified some brain regions exclusively activated by painful stimuli rather than non-painful stimuli, including part of the cingulate gyrus, precuneus, supplementary motor area (SMA), and dorsolateral and medial superior frontal gyri.<sup>64</sup> By manually matching stimulus intensity, Su et al.<sup>65</sup> also found that painful laser stimuli induced stronger activations in the Rolandic operculum, SMA, middle frontal gyrus, and inferior frontal gyrus than non-painful electrical stimuli. Similarly, Horing et al.<sup>66</sup> controlled the salience of thermal pain and auditory stimuli using skin conductance and found that the posterior parietal operculum selectively correlated with perceptual pain ratings. Using machine learning algorithms, some studies have also identified brain patterns seemingly unconfounded by stimulus salience. For example, Liang et al.<sup>67</sup> found that activity patterns composed of certain voxels within the thalamus, insula, ACC, mid-cingulate cortex (MCC), SMA, and brainstem could accurately distinguish between salience-matched painful and non-painful stimuli. Furthermore, Tu et al.<sup>68</sup> found an activation pattern in the medial-dorsal thalamus that selectively responded to painful stimuli rather than non-painful tactile, auditory, and visual stimuli, even after controlling for stimulus salience. Overall, the pain-related areas appear to be functionally heterogeneous, with at least part of them potentially constituting selective biomarkers of pain perception.

Many brain regions related to within-individual pain perception are also involved in between-individual pain sensitivity. A seminal study by Coghill et al.<sup>69</sup> found that the subgroup of healthy participants with high pain sensitivity exhibited stronger activations in the S1, ACC, and PFC compared to the subgroup with low pain sensitivity. However, a recent study with a large sample size ( $n = 101$ ) yielded inconsistent results, showing no significant correlation between pain sensitivity and fMRI responses in any brain area.<sup>70</sup> Furthermore, machine learning models based on brain activations failed to predict pain sensitivity.<sup>70</sup> Unsurprisingly, this study ignited intense debate and inspired other large-scale studies to unveil the seemingly mysterious relationship between brain activations and pain sensitivity.<sup>71,72</sup> Using five large fMRI datasets (total  $n = 1,010$ ), Zhang et al.<sup>72</sup> demonstrated that pain sensitivity was robustly correlated with activations in a wide range of brain regions, including the S1, S2, ACC, insula, thalamus, and cerebellum, but only when the sample size reached nearly 300. They also trained a machine learning model that could predict individual differences in sensitivity to laser heat, contact heat, and mechanical pain.<sup>72</sup> Brain activa-

tions thus may function as biomarkers of pain sensitivity, although they do not seem to be particularly pain selective, since they also correlated with tactile sensitivity.<sup>72</sup>

Apart from brain activations, resting-state functional connectivity (FC) between brain areas during the pain-free period also holds promise for indexing pain sensitivity, although it often lacks pain selectivity. One study developed machine learning models using FC to predict pain sensitivity, with the media-frontal and frontoparietal networks being the most predictive.<sup>73</sup> Another study built a predictive model with contributions from FC between the posterior putamen and parietal operculum/posterior superior temporal gyrus, and between the cerebellum and various cortical areas, and demonstrated this model's generalizability in three independent datasets.<sup>19</sup> In addition to raw FC, pain sensitivity has also been related to other derived measures from FC, such as the local clustering coefficients<sup>74</sup> and spatial gradients of FC<sup>75</sup> in the insula, and the occurrence frequency of a default mode network-dominated state.<sup>76</sup>

Brain morphology has also been related to pain sensitivity. An early study found that the thickness of S1 was positively correlated with cold pain sensitivity, and the thickness of S1, MCC, and orbital frontal cortex (OFC) was positively correlated with heat pain sensitivity.<sup>77</sup> Later studies linked pain sensitivity with morphological features like volume and density of gray matter in other areas such as the insula, rostral ACC, precuneus, thalamus, and parahippocampus.<sup>74,78–81</sup> Although some areas like the precuneus exhibited consistent correlations with pain sensitivity,<sup>79,81</sup> both positive<sup>77,80</sup> and negative correlations<sup>77,78</sup> have been reported between gray matter morphology and pain sensitivity. One explanation for this discrepancy could be the heterogeneity in the relationship between pain sensitivity and gray matter features in different brain areas. Some studies have developed multivariate machine learning models to predict pain sensitivity using morphological brain features.<sup>78,82</sup> A model by Zou et al.<sup>82</sup> leveraged morphological connectivity in addition to gray matter volume and exhibited excellent predictive power. One recent study combined brain morphology with resting-state FC and identified a covarying structural and functional brain pattern associated with cold pain sensitivity,<sup>83</sup> highlighting the potential of incorporating multimodal neuroimaging data in the development of pain biomarkers.

In contrast to within-individual pain perception and between-individual pain sensitivity, neural biomarkers of pain discriminability have received considerably less attention in the literature. One recent study observed that activation differences between high- and low-pain conditions in most pain-related brain regions (e.g., the S1, S2, ACC, insula, and thalamus) selectively correlated with pain discriminability, but not tactile, auditory, or visual discriminability.<sup>26</sup> This study also developed a machine learning model based on brain activations that significantly predicted pain discriminability, but not sensory discriminability in non-pain modalities. In agreement with these findings, the NPS response differences between high- and low-intensity pain stimuli also showed significant correlations with pain discriminability.<sup>84</sup> These consistent findings imply that activity in regions typically related to pain processing could also serve as biomarkers of pain discriminability.

In summary, numerous MRI-based biomarker candidates have been developed for within-individual pain perception,

between-individual pain sensitivity, and pain discriminability. The model sensitivity of these potential biomarkers is generally good. For biomarkers of pain perception, their model specificity remains questionable and needs further testing. Indeed, only a few biomarkers of pain perception have explicitly addressed the confounding effects of stimulus salience and showed good model specificity.<sup>67,68</sup> The model generalizability of pain perception biomarkers appears robust, as evidenced by countless independent studies using different painful stimuli. For biomarkers of pain sensitivity, the model specificity is a critical issue, as nearly all such biomarkers are either not pain selective or have not been tested for pain selectivity. The model generalizability of pain sensitivity biomarkers appears good, at least in some large-scale studies with multiple datasets.<sup>19,72</sup> Biomarkers of pain discriminability remain severely under-investigated. The only available biomarker has shown reasonably good model specificity and generalizability,<sup>26</sup> but further validation from additional studies is needed.

### **EEG-based biomarkers of phasic pain**

Phasic noxious stimuli like nociceptive laser could evoke a plethora of electrophysiological responses, such as event-related potentials (e.g., the N2-P2 complex) and event-related synchronization/desynchronization (ERS/ERD) at different frequencies (e.g.,  $\alpha$ - and  $\gamma$ -band oscillations). These responses have been widely utilized to decode pain perception in both humans<sup>23,85–90</sup> and animals.<sup>91,92</sup> Event-related potentials like N2 and P2 waves have been well documented to be associated with pain perception.<sup>93,94</sup> Based on single-trial N2 and P2 features, machine learning models have also been developed to predict within-individual pain perception,<sup>85</sup> which not only accurately distinguished high and low pain states but also predicted continuous perceptual ratings. However, a crucial problem of using event-related potentials as biomarkers of pain perception is that they are heavily affected by stimulus salience and, therefore, are not pain selective.<sup>95–98</sup> Alpha-band ERD ( $\alpha$ -ERD) has been associated with pain perception,<sup>99–102</sup> but it does not seem to selectively encode pain perception, since it can also be evoked by various non-painful sensory stimuli.<sup>16</sup> In contrast, gamma-band ERS ( $\gamma$ -ERS) appears more pain selective. An early study by Gross et al.<sup>15</sup> demonstrated that  $\gamma$ -ERS correlated with perceived pain ratings and was larger when stimuli at the pain threshold were perceived as painful than when they were perceived as non-painful. Importantly, the correlation between  $\gamma$ -ERS and pain perception has been shown to be unconfounded by stimulus salience.<sup>103</sup> Furthermore, optogenetically induced  $\gamma$ -ERS in the S1 amplified pain-related behaviors in animals, affirming its causal role in pain perception.<sup>104</sup>  $\gamma$ -ERS may thus represent a promising selective biomarker of pain perception with significant translational value.

Unlike within-individual pain perception, fewer studies have investigated the relationship between phasic pain-evoked brain responses and between-individual pain sensitivity. An early study with a small sample size of 18 reported a correlation between laser-evoked potentials (LEPs) and pain sensitivity.<sup>23</sup> However, a larger scale study with 96 participants yielded inconsistent findings, showing no predictive power of LEPs on pain sensitivity.<sup>16</sup> On the other hand, both studies illustrate that  $\gamma$ -ERS contributed to models predictive of pain sensitivity.<sup>16,23</sup>

Animal studies also confirmed the link between  $\gamma$ -ERS and individual differences in pain-related behavior in rodents.<sup>105</sup> Importantly,  $\gamma$ -ERS could not encode individual differences in auditory, visual, and tactile sensitivity, thus showing pain selectivity.<sup>16,106</sup> Apart from pain-evoked responses, some studies have explored biomarkers of pain sensitivity using resting-state EEG features. For example, the power of resting-state  $\gamma$ -band oscillations has been shown to positively correlate with pain sensitivity.<sup>107</sup> Machine learning models using resting-state neural oscillation power and FC also accurately predicted pain sensitivity.<sup>108</sup> Nevertheless, it is unclear whether these findings could be generalized to different populations, and the pain selectivity of these resting-state EEG features has not been tested.

Biomarkers of pain discriminability have been even less investigated. In a rare study directly investigating pain discriminability, Beck et al.<sup>109</sup> found that LEPs could encode individual differences in pain discriminability. A recent study also found that LEPs were robustly correlated with pain discriminability.<sup>26</sup> Furthermore, this study showed that machine learning models based on LEPs accurately predicted pain discriminability in independent datasets. Crucially, EEG responses evoked by non-painful tactile, auditory, and visual stimuli did not show robust correlations with the corresponding sensory discriminability, suggesting that LEPs may serve as selective biomarkers of pain discriminability.<sup>26</sup>

In summary, while EEG biomarkers of within-individual pain perception generally exhibit reasonably good model sensitivity, most of them, except for  $\gamma$ -ERS, lack model specificity and are confounded by stimulus salience.  $\gamma$ -ERS, although pain selective, suffers from a low signal-to-noise ratio due to its small magnitude and susceptibility to muscle artifacts,<sup>110</sup> making it challenging to apply without advanced signal processing. The model generalizability of these EEG biomarkers is rarely directly tested but seems to be fairly good due to the independent replication of their associations with pain perception in numerous studies. Regarding biomarkers of pain sensitivity,  $\gamma$ -ERS stands out as the only reliable biomarker exhibiting good model sensitivity and model specificity. Its model generalizability, however, requires further testing with additional independent datasets. Some resting-state EEG-based biomarkers of pain sensitivity have been developed, but their model specificity and generalizability have not been adequately tested. Biomarkers of pain discriminability are rarely explored. Interestingly, in contrast to within-individual pain perception and between-individual pain sensitivity, biomarkers of pain discriminability based on LEPs seem to have acceptable model sensitivity, specificity, and generalizability. Although further investigation is warranted, the distinct roles of LEPs and  $\gamma$ -ERS in pain perception, pain sensitivity, and pain discriminability suggest that incorporating these EEG features may provide a promising tool to comprehensively assess pain.

### **Tonic pain**

Tonic pain is more long lasting and exhibits different qualities of painful experience compared to phasic pain.<sup>111</sup> It can be produced experimentally by persistent heat, cold pressor, or chemicals, such as bee venom and capsaicin. Tonic pain shares experiential and neural characteristics with chronic pain, thus making

it a valuable experimental model for studying chronic pain. However, neural biomarkers of tonic pain have received less attention than those of phasic pain.

### **MRI-based biomarkers of tonic pain**

Similar to phasic pain, tonic pain induces significant brain activations within pain-related brain areas, including the ACC, thalamus, insula, PFC, and periaqueductal gray (PAG).<sup>112–115</sup> The relationship between activations in these areas and pain perception has also been explored. For instance, La Cesa et al.<sup>115</sup> demonstrated that the magnitude of PAG activations exhibited a negative correlation with perceived pain intensity. Importantly, these brain activations exhibit dynamic fluctuations corresponding to the evolving experience of tonic pain. In the initial stage of tonic pain, brain activations were observed in areas such as the dorsolateral PFC, insula, and dorsal ACC, while in the later stage, brain activations shifted to areas such as the anterior insula, dorsal ACC, and bilateral PFC.<sup>112,113</sup>

Given the inherently prolonged duration of tonic pain, the search for biomarkers predominantly relies on findings derived from FC accompanying tonic pain rather than transient brain activations. Using a capsaicin-heat pain model, Meeker et al.<sup>116</sup> found that FC between the PAG and subgenual ACC positively correlated with experienced pain intensity. In a longitudinal study applying tonic heat pain across four sessions, Deak et al.<sup>117</sup> identified two somatosensory networks with distinct functions: one network, primarily including the bilateral S1, encoded small fluctuations in temperature, while the other, a right-lateralized network involving the S1, S2, posterior cingulate cortex (PCC), and thalamus, encoded the perceived pain induced by tonic heat.

Recently, researchers have also attempted to construct machine learning models using fMRI signals to track tonic pain. Lee et al.<sup>17</sup> developed a model based on whole-brain dynamic FC to track experimentally induced tonic pain intensity. This model, termed the Tonic Pain Signature (ToPS), accurately predicted within-individual dynamic changes in tonic pain intensity over time in three datasets. Notably, the ToPS demonstrated greater responsiveness to tonic pain than to tonic aversive stimuli such as bitter taste or odor, indicating both model sensitivity and specificity. Positive weights in the ToPS were mainly associated with FC among the somatomotor network, frontoparietal network, visual network, and dorsal attention network, whereas negative weights were linked to the limbic and paralimbic cortical areas. In a subsequent study, Lee et al.<sup>118</sup> investigated the temporal dynamics of brain networks during capsaicin-induced tonic orofacial pain. They observed that the somatomotor-dominant network expanded during sustained orofacial pain, incorporating multiple subcortical and frontoparietal regions. As the pain decreased over time, the frontoparietal regions dissociated from this extended somatomotor-dominant network and established connections with several cerebellar areas. A machine learning model based on these network features showed significant predictions of pain intensity changes over time, and importantly, the model could be generalized to an independent tonic pain dataset.

In summary, the search for MRI-based biomarkers of tonic pain is primarily focused on within-individual pain perception, with almost no tonic pain biomarkers developed for between-individual pain sensitivity and pain discriminability. The dynamic

nature of tonic pain, along with its co-occurring cognitive and emotional factors, makes it challenging to identify biomarkers based solely on brain activations, which often lack satisfactory model specificity and generalizability. In contrast, FC, especially dynamic FC, appears to be more suitable for identifying biomarkers of tonic pain, as some models demonstrate good model sensitivity and specificity (e.g., ToPS). Despite the low signal-to-noise ratio of spontaneous neural activity, these analyses could identify patterns of changes associated with tonic pain, elucidating how tonic pain propagates in the brain and how brain networks reconfigure.

### **EEG-based biomarkers of tonic pain**

Like phasic pain, tonic pain perception is also associated with a suppression of  $\alpha$ -band oscillations<sup>18,40,119–124</sup> and an enhancement of  $\gamma$ -band oscillations.<sup>18,122,125</sup>  $\alpha$ -ERD over the somatomotor areas contralateral to the noxious stimulation side is thought to reflect the translation of sustained nociception into pain perception, as  $\alpha$ -ERD mediated the relationship between duration of the nociceptive stimuli and subjective pain experience.<sup>126</sup> In contrast to  $\gamma$ -ERS evoked by phasic pain,  $\gamma$ -ERS evoked by tonic pain occurs at lower frequencies<sup>125</sup> and is primarily observed in the medial PFC.<sup>18,122</sup>  $\gamma$ -ERS was also positively associated with tonic pain perception.<sup>119</sup> A recent intracranial EEG study further demonstrated that  $\gamma$ -ERS in areas such as the ACC, hippocampus, inferior frontal gyrus, medial temporal gyrus, OFC, and striatum predicted pain intensity at the onset of tonic heat pain, whereas  $\gamma$ -ERS in the amygdala and fusiform gyrus predicted pain ratings at stimulus offset.<sup>127</sup> These findings suggest that during a tonic painful experience,  $\gamma$ -band oscillations shift from brain areas encoding the sensory-discriminative aspect of pain to those encoding the emotional-motivational aspect of pain.<sup>40</sup> Notably, the selectivity of neural oscillations during tonic pain has been questioned. Similar changes in neural oscillations can also be observed in response to stimuli of other modalities, such as non-painful cold stimuli<sup>128</sup> and warm stimuli.<sup>119</sup> In addition to neural oscillations, tonic pain induces FC between brain areas. For instance, Modares-Haghighi et al.<sup>129</sup> found that  $\alpha$ -band FC in frontoparietal and frontotemporal networks was crucial for distinguishing different pain levels.

Very little research has explored biomarkers of between-individual tonic pain sensitivity and discriminability, since tonic pain research mostly focuses on the dynamic changes in within-individual pain perception. Nevertheless, Furman et al.<sup>130</sup> found that individuals with high pain sensitivity displayed slower central peak alpha frequency (PAF) at both pain-free and tonic pain states, when compared with individuals with low pain sensitivity. Furman et al.<sup>131</sup> further showed that PAF in pain-free state was a candidate biomarker of pain sensitivity occurring over clinically relevant timescales (i.e., weeks). In a subsequent study, Furman et al.<sup>132</sup> demonstrated that PAF in pain-free state can successfully identify the most pain-sensitive individuals, and this finding was validated on a separate, independent dataset. A recent study further combined somatomotor PAF with corticomotor excitability to distinguish high and low pain-sensitive individuals, with an excellent performance on both training set (100%) and test set (88%).<sup>133</sup>

In summary, EEG-based biomarkers for within-individual tonic pain perception typically show acceptable model sensitivity.

However, the model specificity varies greatly across studies, depending on the features included in the models, and the model generalizability of these biomarkers is rarely directly tested. Crucially, the low signal-to-noise ratio of spontaneous EEG signal can potentially impact model performance. To deal with this issue, future research should employ advanced feature extraction and data integration methods, such as the inter-subject correlation method, which originated from fMRI studies to process neural responses during sustained stimuli, e.g., movies and music.<sup>134</sup> Regarding EEG-based biomarkers of between-individual tonic pain sensitivity, only one research team conducted a series of studies to investigate whether PAF holds promise as a biomarker of tonic pain sensitivity. The model seems to have reasonably good model sensitivity and its generalizability is validated, but its model specificity is not addressed. Even so, the close link between tonic pain and chronic pain suggests that biomarkers identified for tonic pain have a higher potential for generalizing to clinical pain than biomarkers for phasic pain.<sup>17</sup>

## BIOMARKERS FOR CHRONIC PAIN

Chronic pain differs from acute pain in terms of pain duration and neurological bases. Unlike short-lived phasic pain and relatively long-lasting tonic pain, chronic pain can persist for several years or even decades,<sup>1</sup> leading to pathological alterations in the nervous system.<sup>135</sup> Therefore, despite abundant research on acute pain, directly identifying biomarkers of chronic pain is still crucial. Such biomarkers are essential for improving the diagnosis, precision modulation, and personalized treatment of chronic pain.

### MRI-based biomarkers of chronic pain MRI-based assessment biomarkers

MRI-based assessment biomarkers include diagnostic and monitoring biomarkers.<sup>12</sup> Diagnostic biomarkers that distinguish patients from healthy individuals mainly employ abnormal alterations in brain activations, resting-state FC, and brain morphology. Analyzing brain activations in response to painful stimuli, Baliki et al.<sup>136</sup> found that patients with chronic back pain (CBP) showed reduced responses to the offset of painful stimuli in the NAc, and NAc activity-based models distinguished patients from healthy individuals with an accuracy as high as 100%. López-Solà et al.<sup>137</sup> developed two models based on brain activations in response to painful stimuli and non-painful stimuli, respectively, and combined these two models with the NPS to distinguish patients with fibromyalgia from healthy controls, achieving remarkable model sensitivity (92%) and model specificity (94%). The model based on pain activations was characterized by increased activity in patients with fibromyalgia in areas like the S2, middle insula, and dorsomedial PFC, highlighting the association between pathological alterations in these areas and fibromyalgia.

Many studies have also attempted to identify diagnostic biomarkers with resting-state FC. For instance, Tu et al.<sup>138</sup> identified abnormal FC between the medial PFC and brain regions within the default mode network and other brain networks in patients with CBP. They developed an FC-based model that successfully discriminated patients with CBP from healthy controls in two independent datasets. In addition to static FC, Tu et al.<sup>139</sup> further

employed dynamic FC measures and identified abnormal thalamocortical network dynamics in patients with CBP. They found that patients with CBP stayed longer in a state of increased FC between the lateral nucleus of thalamus and somatosensory networks and decreased FC between the medial nucleus of thalamus and insula, compared to healthy controls. Similarly, the ToPS model established by dynamic FCs during tonic pain could classify patients with CBP and healthy controls, achieving accuracies of 71% and 73% in two independent datasets.<sup>17</sup> To diagnose migraine, other studies showed that FC of regions such as the middle frontal gyrus, PFC, OFC, temporal pole, superior and middle temporal gyrus, ACC, MCC, insula, and amygdala contributed significantly to classifiers that differentiate individuals with migraine from healthy controls.<sup>140–142</sup> Notably, Chong et al.<sup>140</sup> showed that patients with a longer duration of migraine (>14 years) could be more accurately distinguished from healthy controls compared to patients with a shorter duration of migraine. This finding suggests that prolonged migraine episodes may lead to more profound reorganization of brain FC patterns, highlighting the importance of considering clinical indices in the search for biomarkers of chronic pain.

Alternations in brain morphology have also been utilized to develop candidate diagnostic biomarkers.<sup>143</sup> Ung et al.<sup>144</sup> distinguished patients with CBP and healthy controls with an accuracy of 76% using a machine learning model, which was based on gray matter density patterns in brain regions such as the S1, S2, motor cortex, PFC, insula, and ACC. Likewise, Labus et al.<sup>145</sup> developed a model to distinguish patients with irritable bowel syndrome from healthy controls using morphological features like cortical thickness in the left S1 and mean curvature in the right primary motor cortex, achieving an overall predictive accuracy of 70%.

In addition to distinguishing patients with chronic pain from healthy controls, identifying diagnostic markers that can distinguish between disease subtypes is also a matter of concern. Patients with migraine without aura (MWOA) and migraine with aura (MWA) were confirmed to be different in blood-oxygen-level-dependent responses to visual stimuli<sup>146</sup> and expression of the visual resting-state FC.<sup>147</sup> In a recent study, Liu et al.<sup>148</sup> integrated clinical measurements and whole-brain FC to identify two migraine subgroups based on a clustering approach. These subgroups differed in headache frequency and self-ratings of depression, and between-group differences in FCs were predominantly related to the amygdala, thalamus, hippocampus, and parahippocampal area.

Candidate monitoring biomarkers have also been developed to predict the severity of spontaneous pain in patients with chronic pain. ToPS, which could distinguish patients with CBP and healthy controls, has also been shown to successfully predict between-individual differences in pain severity among patients with CBP.<sup>17</sup> Brain features, such as elevated regional cerebral blood flow in the thalamus, PFC, and PCC, as well as increased FC between the S1 and the frontoinsula cortex, have also been identified to classify high vs. low pain intensity states in patients with CBP.<sup>149</sup> Notably, monitoring biomarkers for classifying patients with different pain severity are not necessarily the same as diagnostic biomarkers for distinguishing patients from healthy controls. For instance, Zhang et al.<sup>150</sup> found

that the amplitude of low-frequency fluctuations (ALFFs) of paracentral lobule/SMA reliably contributed to discriminate patients with CBP from healthy controls, while pain intensity change induced by pain-exacerbating maneuvers in subjects with CBP was negatively correlated with ALFF change of medial PFC/rostral ACC.

### **MRI-based prospective biomarkers**

Prospective biomarkers of chronic pain include susceptibility/risk, prognostic, and predictive biomarkers.<sup>12</sup> Susceptibility/risk biomarkers of pain chronification can assist in the early screening of patients likely to develop chronic pain. Typically, the identification of these biomarkers is based on longitudinal studies, which track patients over a long period of time to observe the progression from acute to chronic pain. A pioneering study by Baliki et al.<sup>14</sup> observed that the magnitude of FC in frontostriatal circuits, specifically between the NAc and medial PFC, was increased in patients with CBP. This increased FC could predict the transition from subacute to chronic back pain one year later. These findings were further validated in an independent dataset, demonstrating the replicability of the predictive power of the NAc-medial PFC circuit on back pain chronification. Additionally, the volume of NAc shrank only in patients with subacute lower back pain who transitioned to CBP compared to those who did not and to healthy controls. A follow-up research identified a white matter fractional anisotropy difference which could also predict the chronification of subacute back pain groups one year later.<sup>151</sup> Furthermore, higher white matter connectivity and FCs within the dorsal medial PFC-amygdala-accumbens circuit, as well as smaller amygdala volume, together accounted for 60% of the variance for pain persistence.<sup>152</sup> These studies support the notion that neuroanatomical differences predispose individuals with acute pain to pain chronification.<sup>151,152</sup>

Prognostic biomarkers of chronic pain aim to predict which patients with chronic pain would improve or deteriorate over time. At present, few studies have focused on this topic. Kutch et al.<sup>153</sup> reported that the resting-state FC between the left frontal and left parietal lobes significantly predicted improved vs. non-improved patients with urologic chronic pelvic pain syndrome over three months, indicating that it may be a promising prognostic biomarker.

Predictive biomarkers help identify patients who would respond to treatment. Tetreault et al.<sup>154</sup> reported that a classification model developed with right midfrontal gyrus connectivity could differentiate responders and non-responders to the placebo therapy with an area under the curve (AUC) at 95% in patients with knee osteoarthritis (OA), but that model could not identify the responders and non-responders to the duloxetine (AUC = 33%). In contrast, a positive correlation was found between right parahippocampal gyrus connectivity and the placebo-corrected analgesic response to duloxetine.<sup>154</sup> The distinct neural circuits engaged by different treatments suggest that it may be better to develop treatment-specific predictive biomarkers rather than treatment-general predictive biomarkers.

In summary, many biomarker candidates for chronic pain have been developed based on alternations of brain structure, function, and connectivity patterns in patients with chronic pain. The model sensitivity of these biomarkers is typically good. How-

ever, the model specificity of these biomarkers normally needs further testing with datasets encompassing a variety of pain conditions. Biomarkers identified within one specific pain condition or treatment may not fully encapsulate the complexity of other types of chronic pain, limiting their generalizability across different pain conditions. One approach to tackling this challenge is to build specialized models for each chronic pain condition and ensure high model specificity to this specific pain condition.

### **EEG-based biomarkers of chronic pain**

#### **EEG-based assessment biomarkers**

Previous studies have utilized evoked responses, spontaneous oscillations, and spectral FCs to develop EEG-based diagnostic biomarkers.<sup>155</sup> Some EEG responses to exogenous stimuli show potential to function as diagnostic biomarkers. Lenoir et al.<sup>156</sup> summarized 18 studies that recorded neural responses evoked by nociceptive stimuli in patients with various types of chronic pain (e.g., tension-type headache, low back pain, and fibromyalgia). Most studies found no significant difference in the latency and amplitude of pain-evoked brain responses (e.g., N2 and P2 waves in LEPs). Only patients with chronic neuropathic pain<sup>157</sup> and fibromyalgia<sup>158</sup> with small fiber dysfunction showed a decreased amplitude of N2 and P2 waves compared to the healthy population, suggesting that thin fiber dysfunctions contribute to the abnormalities in these brain responses. In addition to noxious stimuli, event-related potentials evoked by cognitive tasks<sup>159</sup> have also been utilized to diagnose chronic pain. For instance, pain-related faces evoked an enhanced P2 amplitude and decreased N2a amplitude in patients with fibromyalgia as compared to healthy controls.<sup>159</sup>

Candidate diagnostic biomarkers have also been developed with spontaneous EEG oscillations. Zebhauser et al.<sup>160</sup> reviewed 30 studies comparing brain oscillations between patients with chronic pain and healthy controls. They reported that 46.67% of the studies indicated higher activity in both  $\theta$ - and  $\beta$ -bands. Importantly, even within a single type of chronic pain, substantial heterogeneity exists across studies. Mussigmann et al.<sup>161</sup> summarized 10 studies exploring changes in  $\beta$ -band oscillations for chronic neuropathic pain, showing that five studies reported no significant change, two reported decreases, and three reported increases in beta activity.

Spectral FCs have been widely used to identify diagnostic biomarkers as well. A study involving 101 patients with chronic pain and 84 healthy controls showed that patients with chronic pain exhibited significantly increased connectivity in  $\theta$  and  $\gamma$ -bands within the PFC,<sup>162</sup> which was involved in the pathophysiology of chronic pain. Besides, patients with painful diabetic polyneuropathy (DPN) exhibited higher cortical FC in  $\theta$ - and  $\beta$ -bands compared to patients with non-painful polyneuropathy.<sup>163</sup> Subtypes of a certain pain condition may also be diagnosed by spectral FCs. For instance, the resting-state FC metrics effectively differentiated between patients with MWA and MWoA, achieving an average classification accuracy of 84.62%.<sup>164</sup> Patients with MWoA exhibited significantly higher  $\theta$ -band FC at rest compared to patients with MWA.<sup>164</sup>

Similar to diagnostic biomarkers, EEG-based monitoring biomarkers also rely on evoked responses, spontaneous

oscillations, and spectral FCs. Evoked EEG responses are often used to monitor pain states, particularly in patients who are sensitive to external stimuli, such as patients with migraine. Zhu et al.<sup>165</sup> trained a model that classified healthy volunteer and patients with migraine during ictal or interictal periods, with key contributions from the parietal N20 component of somatosensory evoked potentials (SSEPs), high-frequency oscillations of SSEPs, and spectral power in 450–750 Hz. Besides, patients with migraine exhibited habituation of visual evoked potentials induced by repetitive stimuli before a migraine attack.<sup>166</sup> This habituation was less pronounced during attack and was replaced by potentiation 2 days following the attack, suggesting that such habituation may act as monitoring biomarkers.<sup>166</sup> Using spectral features, Teixeira et al.<sup>167</sup> demonstrated that the power of  $\delta$ - and  $\theta$ -band oscillations in the central area could positively predict the severity of CBP. Another study showed that an increase in the  $\delta$ -band within the frontocentral region in patients with migraine during the interictal phase correlated with headache intensity.<sup>168</sup> For chronic neuropathic pain,  $\beta$ -band oscillations in widespread areas (i.e., the somatomotor, parietal, and occipital cortices) correlated with pain intensity.<sup>169</sup> Resting-state FC in certain frequencies may also serve as monitoring biomarkers. For example, FC in  $\theta$ - and  $\beta$ -bands positively correlated with reported pain intensity in patients with DPN.<sup>163</sup>

#### **EEG-based prospective biomarkers**

Spontaneous EEG signals and induced responses have both been used to develop EEG-based susceptibility/risk biomarkers. For spontaneous EEG, low-frequency spectral activity in the resting state is particularly important to chronic pain development. Whereas  $\delta$ -band oscillations were consistent in the recovery and chronification processes,  $\theta$ -band and low  $\beta$ -band oscillations were decreased with development of chronic pain, compared to the group becoming pain-free.<sup>170</sup> In addition, node strength in  $\beta$ -band at the right insula, S1, bilateral medial frontal cortex, S2, and ACC was different between episodic migraineur and chronic migraineur.<sup>171</sup> Induced responses were also associated with migraine chronification. Somatosensory gating ratio induced by paired stimuli at stimuli-contralateral S1 increased continually across healthy controls, patients with MWA, and patients with chronic migraine.<sup>172</sup>

There were few studies exploring the prognostic biomarkers for the recovery or deterioration of chronic pain. More studies center on predicting treatment efficacy with EEG. Such predictive biomarkers mainly rely on resting-state oscillations. One study showed that the nerve block procedure caused increased  $\delta$ -band,  $\theta$ -band, and  $\alpha$ -band activity in patients with chronic pain in the upper or lower extremity, but only midfrontal  $\theta$ -band power showed a significant correlation with pain reduction.<sup>173</sup> Similarly, Hunter et al.<sup>174</sup> identified that the occurrence of  $\theta$ -band in the left frontal brain region at the first week after duloxetine treatment significantly predicted pain severity and pain reduction at week 12 for fibromyalgia. In patients suffering from visceral pain due to chronic pancreatitis,  $\theta$ -band activity could also classify the patients receiving pregabalin and those receiving placebo with a maximal accuracy at 85.7%.<sup>175</sup> Additionally, Jensen et al.<sup>176</sup> examined the effects of non-pharmacological treatments, such as hypnosis, meditation, EEG biofeedback, and transcranial direct current stimulation, on patients with spinal cord injury

and chronic pain. They found that  $\theta$ - and  $\alpha$ -band oscillations at baseline strongly predicted pain reduction after hypnosis and meditation treatments, respectively. In another study, enhanced  $\alpha$ -band oscillations in the somatosensory region induced by transcranial alternative current stimulation showed a significant correlation with pain relief in patients with CBP.<sup>177</sup>

In summary, EEG-based biomarkers of chronic pain show high heterogeneity, not only stemming from both the diversity of EEG features examined but also the inherent variability of chronic pain conditions. Moreover, the low signal-to-noise ratio of EEG data in patients with chronic pain poses significant challenges to the development of reliable biomarkers. Patients with chronic pain often experience comorbid emotional disturbances, such as depression and anxiety,<sup>178</sup> and cognitive impairments, such as attention deficits and memory problems.<sup>179</sup> These factors can also considerably affect the model sensitivity, specificity, and generalizability of both assessment and prospective biomarkers. It should be noted that, although these comorbid symptoms and the underlying neural mechanisms may not be directly related to pain (e.g., deficits in learning, memory processes), they may be potential predictors in certain patient subgroups, as chronic pain is not merely a sensory issue but also associated with cognitive impairments.<sup>180</sup> These challenges highlight the need for rigorous validation, and the development of robust methodologies to ensure the reliability and utility of EEG-based biomarkers in the context of chronic pain assessment and treatment.

#### **CHALLENGES AND FUTURE DIRECTIONS**

Over the past decades, numerous candidates for neural biomarkers of acute and chronic pain have been developed using advanced imaging techniques and analytical methods. These biomarker candidates have provided critical insights into how the brain represents acute and chronic pain and have shown the potential to improve neurophysiological pain assessment for guiding personalized treatment and evaluating the effectiveness of interventions. However, many conceptual and practical challenges still need to be addressed in the search for theoretically valuable and clinically applicable pain biomarkers (Figure 3).

##### **Conceptual challenges in developing pain neural biomarkers**

Conceptual challenges in pain biomarker development stem primarily from the multidimensional and heterogeneous nature of pain and the correlational nature of human neuroimaging studies. Although existing neuroimaging-based pain biomarkers serve multiple purposes, they predominantly focus on the sensory-discriminative dimension of pain, especially the perception of pain intensity. This narrow focus echoes the gold standard to assess the presence and severity of pain in practice—asking a person to describe their pain on a rating scale. However, pain is conceptually a complex and subjective experience that encompasses not only sensory-discriminative but also affective and cognitive dimensions.<sup>181,182</sup> Distinct neural mechanisms contribute to the generation and maintenance of this complex, multidimensional, and subjective experience. For instance, the

unpleasantness of pain is mainly encoded in the ACC rather than S1 that is more related to the sensory-discriminative dimension of pain,<sup>183</sup> and the negative affect of pain is encoded in a distinct neural ensemble in the basolateral amygdala.<sup>184</sup> These findings suggest that different pain dimensions are likely to involve distinct biomarkers. A further issue is that the sensory-discriminative and emotional aspects of pain are inherently intertwined, making it difficult to separate them practically.<sup>185</sup> It is thus unclear whether existing pain biomarkers predict a unitary experience of pain comprising multiple components or only the sensory-discriminative dimension of pain. To address this issue, future studies need to separate different dimensions of pain and search for biomarkers that can best capture each dimension.

Developing biomarkers for chronic pain is even more challenging due to its high heterogeneity. Even among patients with similar symptoms, such as inflammation, chronic pain may arise from various underlying mechanisms, resulting in a heterogeneous population with different subtypes of chronic pain.<sup>21</sup> Moreover, patients with chronic pain often exhibit varying degrees of cognitive impairments<sup>180,186,187</sup> and half of them report pain at multiple body sites,<sup>188</sup> which could also reduce the specificity of diagnostic biomarkers. The development of assessment chronic pain biomarkers is thus extremely challenging. A feasible solution would involve identifying biomarkers for individual chronic pain conditions and ensuring their specificity to this particular pain condition. The identification of prospective biomarkers for chronic pain also poses significant challenges, as the underlying mechanisms driving pain chronification and recovery may vary across individuals and disease states. Instead of solely relying on static biomarkers for their predictive value, future studies can explore dynamic assessment strategies to capture the development of chronic pain and pain recovery. In addition, biomarkers for predicting treatment responses are mainly transferred from diagnostic or monitoring biomarkers, which assumes different treatments have shared mechanisms, that is, altering abnormal neural activity associated with the diagnosis or monitoring of chronic pain. However, this assumption is overly simplistic, since different treatments may involve different mechanisms and require specific predictive biomarkers. Future studies may need to develop treatment-specific biomarkers. For instance, neural biomarkers for physical interventions (e.g., transcranial direct current stimulation, transcranial alternating current stimulation, and transcranial magnetic stimulation) could ideally be extracted from responses at the target areas of stimulation. In contrast, when developing neural biomarkers for psychological therapies (e.g., hypnosis, meditation, and cognitive-behavioral therapy), it is advisable to focus on brain regions involved in cognitive or emotional processes, such as the prefrontal cortex, cingulate cortex, and amygdala. Such biomarkers could be sensitive to identify responders and non-responders to a certain treatment.

Even when accounting for the multidimensionality and heterogeneity of pain, a crucial challenge remains—pain biomarkers are mostly correlational, not causal. Whereas purely correlational biomarkers can be useful in predicting pain,<sup>13</sup> they may lack pain selectivity, behave unpredictably in some cases,<sup>189</sup> and have limited value in revealing the neural bases of pain if the causal

relationship between biomarkers and pain is unclear.<sup>190</sup> Multivariate biomarkers of pain are particularly difficult to interpret causally since they are usually based on a prodigious number of predictors (e.g., tens of thousands of voxels in fMRI biomarkers) and rarely constrained by *a priori* hypotheses.<sup>191</sup> Nevertheless, correlational biomarkers may not necessarily be causally irrelevant to pain. A recent neurofeedback study has showed that downregulating the expression of SIIPS1 was associated with reduced pain intensity,<sup>192</sup> suggesting that SIIPS1 may be causally involved in the perception of pain. Further studies are thus needed to test whether pain biomarkers are causally relevant for pain, rather than assuming that they are. One promising approach to testing the causality of biomarkers is the cross-species approach, which integrates findings from both animal models and human studies.<sup>193</sup> Given the evolutionary conservation of neural circuits and molecular pathways involved in pain processing across species,<sup>194–196</sup> animal studies can complement human studies to examine the causal relationship between biomarkers and pain, reveal the neuronal underpinnings of pain biomarkers, and strengthen the validity, selectivity, and generalizability of pain biomarkers. Some studies have identified pain-evoked  $\gamma$ -ERS as an EEG-based pain biomarker using the cross-species approach<sup>16,105</sup> and revealed the neural origins of this biomarker.<sup>197</sup> Future studies can delve more deeply into exploring neural biomarkers of pain through cross-species approaches, wherein animal models can serve as preclinical platforms for testing hypotheses generated from human neuroimaging studies and uncovering the neuronal mechanisms of human pain biomarkers. Such cross-species studies can facilitate the development of mechanism-based pain biomarkers and ultimately improve the clinical diagnosis and treatment of pain.<sup>11,198,199</sup>

### Practical challenges in applying pain neural biomarkers

Although some promising candidates for pain biomarkers have been proposed, their clinical applications are still far from commonplace. In addition to the conceptual challenges which we discussed earlier, a key practical issue is that most proposed pain biomarkers still lack clinical usefulness. One main reason is that many pain biomarkers, particularly those related to phasic pain, are developed in healthy individuals using simple painful stimuli like transient heat that are detached from real-world clinical pain.<sup>191</sup> Acute pain and chronic pain are so different that their biomarkers are by no means guaranteed to be the same. Another reason is that the performance of existing pain biomarkers is too poor to be clinically useful. The lack of excellent model specificity and generalizability is particularly noteworthy. Model specificity of many biomarkers is undermined by the pervasive and persistent confounding of stimulus salience in both univariate and multivariate biomarkers of pain except for a few studies that explicitly control stimulus salience,<sup>16,6466–68,103</sup> even though the problem was highlighted more than a decade ago.<sup>52</sup> Furthermore, model generalizability is not properly tested. Studies using univariate analysis typically do not test model generalizability. While multivariate decoding studies often use internal cross-validation to assess the generalizability of biomarkers, most only rely on leave-one-out cross-validation,<sup>200</sup> a method prone to overestimating model performance. Independent external validation is

crucial for accurately estimating model generalizability. In its absence, model performance can be still overestimated, even when internal cross-validation is employed.<sup>201</sup> Biomarkers of chronic pain are, by their very nature, clinically useful. Nevertheless, fewer high-performing chronic pain biomarkers are available than needed, and most biomarkers of chronic pain concern only limited types of chronic pain, primarily CBP and fibromyalgia.<sup>200</sup>

Three potential approaches may improve the clinical usefulness of pain biomarkers: (1) to conduct more direct investigations on clinically useful pain biomarkers, (2) develop composite biomarkers, and (3) train more powerful machine learning models, while carefully controlling for key confounding factors like stimulus salience and testing generalizability in diverse and external datasets. First and foremost, the development of pain biomarkers needs to focus more on the clinical value of biomarkers. For biomarkers of acute pain, future studies need to test and increase the transferability of the models. A few potential biomarkers of acute pain have shown some clinical use. For instance, NPS and SIIPS1 seemed to be able to diagnose patients with knee OA,<sup>202</sup> and ToPS could diagnose CBP.<sup>17</sup> Nevertheless, the clinical usefulness of acute pain biomarkers needs extensive testing before they can be applied in real clinical situations. For biomarkers of chronic pain, the focus should be on improving the model performance of available biomarkers (see discussion below) and developing biomarkers for under-investigated chronic pains. Although many potential biomarkers of chronic pain have been developed, the complexity of chronic pain warrants even more investigations into biomarkers of different types of chronic pain, or biomarkers of subtypes of a certain chronic pain, especially those under-studied, and biomarkers for various purposes (e.g., susceptibility/risk, prognostic, and predictive biomarkers).

Developing composite biomarkers integrating various measures is a viable approach to improve the performance of pain biomarkers. Multiple sources of data can be utilized to develop composite biomarkers. First, neural activities not directly related to pain processing (e.g., those reflecting cognitive processing) can be extracted to complement pain-related activities. Biomarkers reflecting neural representations of pain processing itself often fail to capture the complex and multidimensional nature of chronic pain. Indeed, patients with chronic pain frequently report cognitive difficulties, and impairments have been observed in areas such as attention, learning and memory, psychomotor ability, and executive function.<sup>187</sup> Future studies could benefit from an integrative approach that includes both pain-specific biomarkers and those related to other neural processes, allowing for more tailored and accurate models across different patient populations. Second, spontaneous neural activities can be combined with task-evoked activities. Although frequently used in chronic pain studies, spontaneous neural activities typically have a low signal-to-noise ratio and lack pain selectivity. Adopting task-based experimental designs, including both somatosensory-related tasks and cognitive tasks, could also have the potential to enhance both the signal-to-noise ratio of sampled brain responses and estimate the secondary deficit in other functions (e.g., cognition), which improves the selectivity of developed chronic pain biomarkers.<sup>203,204</sup> Third, data from different modalities of neuroimaging can also be inte-

grated. A variety of neuroimaging techniques, including fMRI, sMRI, and EEG, have been applied to explore neuroimaging-based biomarkers of pain.<sup>199</sup> However, a single neuroimaging technique alone is unlikely to provide a complete picture of the source, cause, or experience of pain,<sup>205</sup> since each technique samples only part of the structure and function of the brain, and has its own limitations, such as insufficient temporal (e.g., MRI) or spatial (e.g., EEG) resolution. Integrating data from multiple neuroimaging modalities can help extract complementary information about pain and improve the overall performance of biomarkers. One recent study even suggests that incorporating data from multiple imaging modalities boosts prediction accuracy with an effect equivalent to doubling the sample size.<sup>206</sup> Various strategies can be employed to integrate imaging modalities, such as combining brain imaging with spinal imaging<sup>207</sup> or structural imaging with functional imaging.<sup>83</sup> Fourth, neuroimaging can further be combined with other non-imaging data. A practice issue of neuroimaging is its economic costs. Neuroimaging is typically expensive, and integrating multiple modalities of neuroimaging can be more financially prohibitive. Cost-effective measures such as self-reporting questionnaires and behavioral tests<sup>208,209</sup> may serve as valuable complements to neuroimaging-based biomarkers of pain, as they are easily administered and provide critical information about patients' conditions.<sup>148</sup> In addition, combining neuroimaging biomarkers with other biomarkers like genetic biomarkers<sup>199</sup> and blood-based biomarkers seems more economical and practical. These strategies can help construct more powerful composite pain biomarkers, thus providing a more comprehensive and mechanistic understanding of pain.

In the past decade, machine learning modeling has emerged as a revolutionary tool for identifying and evaluating candidate neural biomarkers of pain.<sup>210,211</sup> However, the majority of available machine-learning-based pain biomarkers are linear models.<sup>13</sup> Admittedly, linear models are interpretable and powerful to decode pain from brain activity in most cases. Nevertheless, it is highly unlikely that the relationship between pain and the brain is only linear. Non-linear models like deep learning may prove more powerful in developing sensitive and selective pain biomarkers than linear models.<sup>212</sup> However, machine learning models, especially deep learning models, require a huge amount of data.<sup>213</sup> Indeed, a large sample size is essential for neuroimaging-based pain biomarkers to capture the complexity and variability of pain processing in the brain, thus improving the reliability of findings and facilitating validation and translation into clinical practice.<sup>72</sup> Paradoxically, neuroimaging studies typically have very small sample sizes, possibly due to the prohibitive cost of collecting huge neuroimaging data. Rarely can a neuroimaging study recruit more than 100 participants, which is only one-tenth or even one-hundredth of the sample size necessary for machine learning models to fully achieve their power to predict behavior measures like pain.<sup>212,213</sup> By mutualizing neuroimaging databases from various pain research groups (e.g., the ENIGMA Chronic Pain Working Group<sup>214</sup>), future studies could make full use of big neuroimaging datasets and more advanced non-linear models to develop more clinically applicable biomarkers of pain.

In conclusion, while various potential neural biomarkers of acute and chronic pain have been identified (Table 1), significant

**Table 1. Summary of neuroimaging-based biomarker candidates for acute and chronic pain**

| Pain types | Biomarker types | Target                                                                                                                                                | Algorithms                                                           | Sample size                                                  | Features                                                                   | Model sensitivity                                                                                                                                                                                                                                    | Model specificity                                                 | Model generalizability   | Reference                     |
|------------|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|--------------------------------------------------------------|----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|--------------------------|-------------------------------|
| Phasic     | pain perception | continuous pain rating                                                                                                                                | LASSO-PCR                                                            | (1) training set: 20, (2) test set 1: 33, (3) test set 2: 40 | fMRI: brain activation from pain-related areas                             | (1) training set: $r = 0.74$ , (2) test set 1: $r = 0.73$ , (3) test set 2: $r = 0.44$                                                                                                                                                               | pain vs. pain recall, pain anticipation, warmth, social rejection | three different datasets | Wager et al. <sup>20</sup>    |
| Phasic     | pain perception | (1) classification: pain tolerance vs. pain threshold, thermal threshold; (2) regression: continuous pain rating at pain tolerance and pain threshold | (1) Gaussian process classification, (2) Gaussian process regression | 16                                                           | fMRI: whole brain activation                                               | (1) classification: pain tolerance vs. pain threshold: Acc = 71.67%; pain tolerance vs. thermal threshold: Acc = 91.67%; pain threshold vs. thermal threshold: Acc = 71.11%; (2) regression: pain tolerance: $r = 0.87$ ; pain threshold: $r = 0.73$ | –                                                                 | –                        | Marquand et al. <sup>55</sup> |
| Phasic     | pain perception | continuous pain rating                                                                                                                                | PCR                                                                  | (1) training set: 137, (2) test set: 46                      | fMRI: brain activation independent of stimulus intensity and NPS responses | (1) training set: $r = 0.68$ , explained variance = 9.71%; (2) test set: explained variance = 6.73%                                                                                                                                                  | –                                                                 | two different datasets   | Woo et al. <sup>56</sup>      |

(Continued on next page)

| Table 1. Continued |                  |                                  |                        |                                                              |                                                |                                                                                                                                                                                                                                                                                          |                                                             |                          |                             |
|--------------------|------------------|----------------------------------|------------------------|--------------------------------------------------------------|------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|--------------------------|-----------------------------|
| Pain types         | Biomarker types  | Target                           | Algorithms             | Sample size                                                  | Features                                       | Model sensitivity                                                                                                                                                                                                                                                                        | Model specificity                                           | Model generalizability   | Reference                   |
| Phasic             | pain perception  | pain vs. touch, audition, vision | SVC                    | (1) Dataset 1: 14; (2) Dataset 2: 51                         | fMRI: brain activation from pain-related areas | (1) Dataset 1: pain vs. touch: Acc = 85%; pain vs. audition: Acc = 90%; pain vs. vision: Acc = 94%; (2) Dataset 2: pain vs. touch: 75%; (3) Datasets 1&2 (Dataset 2 as training set): pain vs. touch: Acc = 80%; (4) Datasets 1&2 (Dataset 1 as training set): pain vs. touch: Acc = 69% | pain vs. salience/intensity-matched touch, audition, vision | –                        | Liang et al. <sup>67</sup>  |
| Phasic             | pain perception  | pain vs. touch, audition, vision | SVC                    | 399                                                          | fMRI: brain activation from thalamus           | (1) pain vs. touch: Acc = 58.3%; (2) pain vs. audition: Acc = 70.5%; (3) pain vs. vision: Acc = 68.5%                                                                                                                                                                                    | pain vs. touch, audition, vision                            | –                        | Tu et al. <sup>68</sup>     |
| Phasic             | pain sensitivity | continuous pain sensitivity      | elastic net regression | (1) training set: 35; (2) test set 1: 37; (3) test set 2: 19 | fMRI: whole-brain FC in resting state          | (1) training set: $r = 0.63$ ; (2) test set 1: $r = 0.43$ ; (3) test set 2: $r = 0.47$                                                                                                                                                                                                   | –                                                           | three different datasets | Spisak et al. <sup>19</sup> |
| Phasic             | pain sensitivity | continuous pain sensitivity      | LASSO-PCR              | 124                                                          | fMRI: whole brain activation                   | $r = 0.252$                                                                                                                                                                                                                                                                              | –                                                           | –                        | Gim et al. <sup>71</sup>    |

(Continued on next page)

**Table 1. Continued**

| Pain types | Biomarker types  | Target                      | Algorithms                       | Sample size                                                                                                  | Features                                                          | Model sensitivity                                                                                                                                                                                                                                                                                                          | Model specificity | Model generalizability  | Reference                         |
|------------|------------------|-----------------------------|----------------------------------|--------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-------------------------|-----------------------------------|
| Phasic     | pain sensitivity | continuous pain sensitivity | LASSO-PCR                        | (1) training set: 199; (2) holdout test set: 200; (3) external test set 1: 369; (4) external test set 2: 124 | fMRI: whole brain activation                                      | (1) training set: $r = 0.531$ ; (2) holdout test set: $r = 0.496$ ; (3) external test set 1: high pain: $r = 0.274$ ; medium pain: $r = 0.217$ ; low pain: $r = 0.292$ ; (4) external test set 2: $r = 0.323$                                                                                                              | –                 | four different datasets | Zhang et al. <sup>72</sup>        |
| Phasic     | pain sensitivity | continuous pain sensitivity | SVR                              | 24                                                                                                           | fMRI: whole-brain FC in resting state                             | (1) within-session: heat pain on leg: $r = 0.60$ ; heat pain on arm: $r = 0.56$ ; pressure pain on leg: $r = 0.57$ ; pressure pain on thumbnail: $r = 0.53$ ; (2) between-session: heat pain on leg: $r = 0.56$ ; heat pain on arm: $r = 0.55$ ; pressure pain on leg: $r = 0.55$ ; pressure pain on thumbnail: $r = 0.50$ | –                 | –                       | Tu et al. <sup>73</sup>           |
| Phasic     | pain sensitivity | continuous pain sensitivity | LASSO regression                 | 133                                                                                                          | sMRI: whole-brain cortical thickness                              | $r = 0.36$                                                                                                                                                                                                                                                                                                                 | –                 | –                       | Kotikalapudi et al. <sup>78</sup> |
| Phasic     | pain sensitivity | continuous pain sensitivity | partial least-squares regression | 221                                                                                                          | sMRI: whole-brain gray matter connectivity and gray matter volume | (1) laser pain threshold: $r = 0.75$ ; (2) cold pain sensitivity: $r = 0.80$ ; (3) pain sensitivity score: $r = 0.77$                                                                                                                                                                                                      | –                 | –                       | Zou et al. <sup>82</sup>          |

(Continued on next page)

Table 1. Continued

| Pain types | Biomarker types       | Target                                                              | Algorithms                                                 | Sample size                                                                     | Features                                       | Model sensitivity                                                                                                                                                             | Model specificity                | Model generalizability | Reference                        |
|------------|-----------------------|---------------------------------------------------------------------|------------------------------------------------------------|---------------------------------------------------------------------------------|------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|------------------------|----------------------------------|
| Phasic     | pain discriminability | continuous pain discriminability                                    | LASSO-PCR                                                  | (1) training set: 212; (2) test set: 187                                        | fMRI: brain activation from pain-related areas | (1) training set: $r = 0.348$ ; (2) test set: $r = 0.227$                                                                                                                     | pain vs. touch, audition, vision | two different datasets | Zhang et al. <sup>26</sup>       |
| Phasic     | pain perception       | continuous pain rating                                              | simple correlation                                         | 96 samples for nociceptive stimuli; 107 samples for stimuli of other modalities | EEG: ERP and TFR                               | (1) N1 amplitude: $r = -0.11$ ; (2) N2 amplitude: $r = -0.49$ ; (3) P2: $r = 0.43$ ; (4) TFR-LEP: $r = 0.61$ ; (5) $\alpha$ -ERD: $r = -0.06$ ; (6) $\gamma$ -ERS: $r = 0.16$ | –                                | two different species  | Hu and Iannetti <sup>16</sup>    |
| Phasic     | pain perception       | continuous pain rating                                              | linear mixed model                                         | 18                                                                              | EEG: TFR                                       | (1) $\theta$ oscillations: $t = 9.4$ ; (2) $\gamma$ oscillations: $t = 6.8$                                                                                                   | –                                | –                      | Schulz et al. <sup>23</sup>      |
| Phasic     | pain perception       | (1) low pain vs. high pain; (2) continuous pain rating              | (1) naive Bayes classifier; (2) multiple linear regression | 29                                                                              | EEG: LEP                                       | (1) within-subject: Acc = 86.3%; cross-subject: Acc = 80.3%; (2) within-subject: MAE = 1.031; cross-subject: MAE = 1.821                                                      | –                                | –                      | Huang et al. <sup>85</sup>       |
| Phasic     | pain perception       | mild pain vs. maximum pain                                          | multilayer perceptron                                      | 14                                                                              | EEG: Granger causality between different TFR   | mean Acc = 99.35%                                                                                                                                                             | –                                | –                      | Tripanpitak et al. <sup>86</sup> |
| Phasic     | pain perception       | no feeling, non-pain sensation, minimal painful, and pain tolerance | neural network                                             | 13                                                                              | EEG: nonlinear features of ERP                 | mean Acc = 87.5% for four-level classification                                                                                                                                | –                                | –                      | Tripanpitak et al. <sup>87</sup> |
| Phasic     | pain perception       | low pain vs. high pain                                              | SVC                                                        | 96                                                                              | EEG: prestimulus TFR                           | mean Acc = 58%                                                                                                                                                                | –                                | –                      | Tu et al. <sup>88</sup>          |

(Continued on next page)

**Table 1. Continued**

| Pain types | Biomarker types       | Target                                                 | Algorithms         | Sample size                                                  | Features                                                                                                   | Model sensitivity                                                                                     | Model specificity                          | Model generalizability   | Reference                     |
|------------|-----------------------|--------------------------------------------------------|--------------------|--------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|--------------------------------------------|--------------------------|-------------------------------|
| Phasic     | pain perception       | (1) low pain vs. high pain; (2) continuous pain rating | (1) SVC; (2) SVR   | 96                                                           | EEG: LEP and TFR                                                                                           | (1) classification: highest Acc = 83.5%; (2) regression: lowest MAE = 1.15                            | –                                          | –                        | Tu et al. <sup>89</sup>       |
| Phasic     | pain sensitivity      | continuous pain rating                                 | random forest      | 96                                                           | EEG: $\gamma$ -ERS                                                                                         | $r = 0.931$                                                                                           | pain vs. touch, audition, vision           | –                        | Hu and Iannetti <sup>16</sup> |
| Phasic     | pain sensitivity      | continuous pain rating                                 | linear mixed model | 18                                                           | EEG: TFR                                                                                                   | $\theta$ oscillations: $r = 0.48$                                                                     | –                                          | –                        | Schulz et al. <sup>18</sup>   |
| Phasic     | pain sensitivity      | low pain sensitivity vs. high pain sensitivity         | SVC                | 23                                                           | EEG: TFR                                                                                                   | Acc = 83%                                                                                             | –                                          | –                        | Schulz et al. <sup>90</sup>   |
| Phasic     | pain sensitivity      | continuous pain threshold                              | simple correlation | 27                                                           | MEG: (1) resting-state $\gamma$ oscillations; (2) resting-state connectivity at $\alpha$ and $\beta$ -band | (1) $r > 0.49$ ; (2) $r > 0.51$                                                                       | –                                          | –                        | Hsiao et al. <sup>107</sup>   |
| Phasic     | pain sensitivity      | low pain sensitivity vs. high pain sensitivity         | SVC                | (1) training set: 65; (2) test set: 20                       | EEG: resting-state PSD and FC                                                                              | (1) Acc >85%; (2) Acc = 90%                                                                           | –                                          | –                        | Hsiao et al. <sup>108</sup>   |
| Phasic     | pain discriminability | continuous pain discriminability                       | LASSO-PCR          | (1) training set: 114; (2) test set: 111                     | EEG: LEPs                                                                                                  | (1) training set: $r = 0.536$ ; (2) test set: $r = 0.423$                                             | pain vs. touch, audition, vision           | one new dataset          | Zhang et al. <sup>26</sup>    |
| Tonic      | pain perception       | ongoing pain ratings                                   | PCR                | (1) training set: 19; (2) test set 1: 42; (3) test set 2: 48 | fMRI: whole-brain dynamic FC patterns                                                                      | (1) training set: $r = 0.64$ ; (2) test set 1: $r = 0.47$ ; (3) test set 2: $r = 0.51$                | tonic pain vs. bitter taste, aversive odor | three different datasets | Lee et al. <sup>17</sup>      |
| Tonic      | pain perception       | (1) pain vs. rest; (2) continuous pain rating          | (1) SVC; (2) PCR   | training set: 48; test set: 74                               | fMRI: reconfiguration of whole-brain functional networks over time                                         | (1) training set: Acc = 98%; test set: Acc = 81%; (2) training set: $r = 0.29$ ; test set: $r = 0.32$ | tonic pain vs. bitter taste, aversive odor | two different datasets   | Lee et al. <sup>118</sup>     |

(Continued on next page)

**Table 1. Continued**

| Pain types | Biomarker types  | Target                                                             | Algorithms                      | Sample size                                                                                        | Features                                                                                                                                                                                               | Model sensitivity                                                | Model specificity                                                                                                  | Model generalizability | Reference                              |
|------------|------------------|--------------------------------------------------------------------|---------------------------------|----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|------------------------|----------------------------------------|
| Tonic      | pain perception  | continuous pain rating                                             | simple correlation              | 38                                                                                                 | EEG: (1) noxious-attended condition vs. innocuous-distracted condition, noxious-distracted condition: $\alpha$ -band power; (2) noxious-attended condition vs. resting condition: $\gamma$ -band power | (1) $r < -0.32$ ; (2) $r > 0.33$                                 | noxious-attended condition vs. resting condition, innocuous-distracted condition, and noxious-distracted condition | –                      | Peng et al. <sup>119</sup>             |
| Tonic      | pain perception  | no pain, low pain, medium pain, high pain, and intolerable pain    | multilayer SVC                  | 23                                                                                                 | EEG: $\alpha$ coherence                                                                                                                                                                                | five-level classification: Acc = 86.84%                          | –                                                                                                                  | –                      | Modares-Haghighi et al. <sup>129</sup> |
| Tonic      | pain sensitivity | continuous pain rating                                             | multiple linear regression      | 21                                                                                                 | EEG: PAF                                                                                                                                                                                               | $r = 0.55$                                                       | –                                                                                                                  | –                      | Furman et al. <sup>130</sup>           |
| Tonic      | pain sensitivity | (1) continuous pain rating; (2) least sensitive vs. most sensitive | (1) simple correlation; (2) SVC | (1) visit 1: 61, visit 2: 46; (2) training set: 61, test set: 21                                   | EEG: PAF                                                                                                                                                                                               | (1) $p < -0.34$ ; (2) training set: F1 > 0.6; test set: F1 > 0.6 | –                                                                                                                  | two different datasets | Furman et al. <sup>132</sup>           |
| Tonic      | pain sensitivity | high vs. low pain-sensitive individuals                            | logistic regression             | (1) training set: 100; (2) test set: 50                                                            | EEG: PAF and corticomotor excitability                                                                                                                                                                 | (1) training set: AUC = 1; (2) test set: AUC = 0.88              | –                                                                                                                  | two different datasets | Chowdhury et al. <sup>133</sup>        |
| Chronic    | diagnostic       | patients with chronic back pain vs. healthy controls               | PCR                             | (1) test set 1: 24 patients, 39 healthy controls; (2) test set 2: 17 patients, 17 healthy controls | fMRI: whole-brain dynamic FC patterns                                                                                                                                                                  | (1) test set 1: Acc = 73%; (2) test set 2: Acc = 71%             | –                                                                                                                  | two different datasets | Lee et al. <sup>17</sup>               |

(Continued on next page)

**Table 1. Continued**

| Pain types | Biomarker types | Target                                               | Algorithms                               | Sample size                                                                                                                                             | Features                                                                         | Model sensitivity                                                                                                                        | Model specificity | Model generalizability   | Reference                        |
|------------|-----------------|------------------------------------------------------|------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|-------------------|--------------------------|----------------------------------|
| Chronic    | diagnostic      | patients with chronic back pain vs. healthy controls | /                                        | 16 patients, 16 healthy controls                                                                                                                        | fMRI: (1) brain activation from nucleus accumbens; (2) FC with nucleus accumbens | (1) sensitivity: 50%–100%; (2) /                                                                                                         | –                 | –                        | Baliki et al. <sup>136</sup>     |
| Chronic    | diagnostic      | patients with fibromyalgia vs. healthy controls      | (1) SVC; (2) logistic regression         | 37 patients; 35 healthy controls                                                                                                                        | fMRI: whole-brain activation patterns                                            | (1) Acc = 70%; (2) Acc = 93%                                                                                                             | –                 | –                        | López-Solà et al. <sup>137</sup> |
| Chronic    | diagnostic      | patients with chronic back pain vs. healthy controls | SVC                                      | (1) Dataset 1: 50 patients, 44 healthy controls<br>(2) Dataset 2: 30 patients, 30 healthy controls                                                      | fMRI: whole-brain FC in resting state                                            | (1) Dataset 1: Acc = 91%; (2) Dataset 2: Acc = 78%                                                                                       | –                 | two different datasets   | Tu et al. <sup>138</sup>         |
| Chronic    | diagnostic      | patients with chronic back pain vs. healthy controls | /                                        | (1) Dataset 1: 90 patients, 74 healthy controls;<br>(2) Dataset 2: 30 patients, 30 healthy controls;<br>(3) Dataset 3: 25 patients, 25 healthy controls | fMRI: dynamic FC                                                                 | /                                                                                                                                        | –                 | three different datasets | Tu et al. <sup>139</sup>         |
| Chronic    | diagnostic      | patients with migraine vs. healthy controls          | diagonal quadratic discriminate analysis | 58 patients, 50 healthy controls                                                                                                                        | fMRI: FC of 33 seeded pain-related regions                                       | (1) overall Acc = 86.1%; (2) Acc for patients with migraine (>14 years) = 96.7%; (3) Acc for patients with migraine (≤ 14 years) = 82.1% | –                 | –                        | Chong et al. <sup>140</sup>      |
| Chronic    | diagnostic      | patients with chronic back pain vs. healthy controls | PCA-SVC                                  | 47 patients; 47 healthy controls                                                                                                                        | sMRI: gray matter density                                                        | Acc = 76%                                                                                                                                | –                 | –                        | Ung et al. <sup>144</sup>        |

(Continued on next page)

Table 1. Continued

| Pain types | Biomarker types     | Target                                                                                                                                      | Algorithms                                             | Sample size                                                                                                                                        | Features                                                                                                                                  | Model sensitivity                                    | Model specificity | Model generalizability | Reference                   |
|------------|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|-------------------|------------------------|-----------------------------|
| Chronic    | diagnostic          | patients with irritable bowel syndrome vs. healthy controls                                                                                 | sparse partial least squares for discriminant analysis | (1) training set: 80 patients, 80 healthy controls; (2) test set: 26 patients, 26 healthy controls                                                 | sMRI: gray matter morphology                                                                                                              | Acc = 70%                                            | –                 | –                      | Labus et al. <sup>145</sup> |
| Chronic    | monitoring          | continuous pain severity score                                                                                                              | PCR                                                    | 17                                                                                                                                                 | fMRI: whole-brain dynamic FC patterns                                                                                                     | r = 0.56                                             | –                 | –                      | Lee et al. <sup>17</sup>    |
| Chronic    | monitoring          | (1) high vs. low spontaneous pain in patients with chronic back pain; (2) between-subject pain intensity in patients with chronic back pain | (1) SVC; (2) SVR                                       | 53 patients                                                                                                                                        | fMRI: (1) resting-state FC of the back representation in the S1; (2) whole-brain regional cerebral blood flow; (3) heart rate variability | (1) Acc = 92.45%; (2) r = 0.63                       | –                 | –                      | Lee et al. <sup>149</sup>   |
| Chronic    | susceptibility/Risk | patients with persistent subacute pain vs. patients recovering from subacute pain 1 year after baseline                                     | /                                                      | (1) Dataset 1: 19 patients with persistent subacute pain, 20 patients recovering from subacute pain; (2) Dataset 2: 13 patients with subacute pain | fMRI: FC between nucleus accumbens and medial prefrontal cortex                                                                           | (1) Dataset 1: AUC = 0.83; (2) Dataset 2: AUC = 0.81 | –                 | two different datasets | Baliki et al. <sup>14</sup> |

(Continued on next page)

**Table 1. Continued**

| Pain types | Biomarker types         | Target                                                                             | Algorithms                             | Sample size                                                                                                                                                       | Features                                                                                                                                                                                                                                  | Model sensitivity                                  | Model specificity | Model generalizability | Reference                                    |
|------------|-------------------------|------------------------------------------------------------------------------------|----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|-------------------|------------------------|----------------------------------------------|
| Chronic    | susceptibility/<br>Risk | patients with subacute back pain recovering from vs. transitioning to chronic pain | path analysis with logistic regression | 39 patients with persistent subacute back pain at year 1, 30 patients recovering from subacute back pain at year 1, 39 patients with subacute back pain at year 3 | fMRI+sMRI: (1) white matter network: dorsomedial prefrontal cortex-amygdala-nucleus accumbens; (2) gray matter volume: amygdala; (3) functional network: dorsomedial prefrontal cortex-amygdala-nucleus accumbens; (4) gene: rs678849 SNP | explained variance = 60%                           | –                 | –                      | Vachon-<br>Presseau<br>et al. <sup>152</sup> |
| Chronic    | prognostic              | improvers vs. non-improvers of patients with urologic chronic pelvic pain syndrome | SVC                                    | 52 patients                                                                                                                                                       | fMRI: whole-brain FC in resting state                                                                                                                                                                                                     | improvers vs. non-improvers at 3 months: Acc = 73% | –                 | –                      | Kutch et al. <sup>153</sup>                  |
| Chronic    | predictive              | pain relief induced by placebo in patients with knee osteoarthritis                | linear regression equations            | (1) training set: 17; (2) test set: 20                                                                                                                            | fMRI: whole-brain FC in resting state                                                                                                                                                                                                     | (1) training set: R = 0.60; (2) test set: R = 0.64 | –                 | one different dataset  | Tétreault<br>et al. <sup>154</sup>           |
| Chronic    | diagnostic              | patients with complex regional pain syndrome vs. healthy controls                  | /                                      | 25 patients, 25 healthy controls                                                                                                                                  | EEG: nociceptive stimuli evoked N2 latency, P2 latency, and N2-P2 amplitude                                                                                                                                                               | /                                                  | –                 | –                      | Caty et al. <sup>157</sup>                   |

(Continued on next page)

| Table 1. Continued |                         |                                                                                                                       |                                 |                                                                              |                                                                                  |                                                                                                                               |                   |                        |                                           |
|--------------------|-------------------------|-----------------------------------------------------------------------------------------------------------------------|---------------------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-------------------|------------------------|-------------------------------------------|
| Pain types         | Biomarker types         | Target                                                                                                                | Algorithms                      | Sample size                                                                  | Features                                                                         | Model sensitivity                                                                                                             | Model specificity | Model generalizability | Reference                                 |
| Chronic            | diagnostic              | patients with fibromyalgia vs. healthy controls                                                                       | /                               | 199 patients, 109 healthy controls                                           | EEG: N2-P2 amplitude and N2-P2 habituation index                                 | /                                                                                                                             | –                 | –                      | de Tommaso et al. <sup>158</sup>          |
| Chronic            | diagnostic              | patients with fibromyalgia vs. healthy controls                                                                       | /                               | 25 patients, 25 healthy controls                                             | EEG: facial expression evoked P2 amplitude and latency, as well as N2a amplitude | /                                                                                                                             | –                 | –                      | Fernandes-Magalhaes et al. <sup>159</sup> |
| Chronic            | monitoring & diagnostic | (1) between-subject pain intensity in patients with chronic pain; (2) patients with chronic pain vs. healthy controls | (1) simple correlation; (2) SVC | (1) Dataset 1: 101 patients; (2) Dataset 2: 84 patients, 84 healthy controls | EEG: all frequency band power and FC                                             | (1) $\theta$ PLV: $r = -0.18$ ; $\alpha$ PLV: $r = -0.19$ ; (2) Mean Acc = 57%                                                | –                 | –                      | Ta Dinh et al. <sup>162</sup>             |
| Chronic            | diagnostic              | painful vs. non-painful polyneuropathy participants                                                                   | SVC                             | 133 painful patients, 47 non-painful patients                                | EEG: resting-state FC                                                            | (1) $\theta$ -band: AUC = 0.93; (2) $\alpha$ -band: AUC = 0.83; (3) $\beta$ -band: AUC = 0.89; (4) $\gamma$ -band: AUC = 0.87 | –                 | –                      | Topaz et al. <sup>163</sup>               |
| Chronic            | diagnostic              | patients with migraine with aura vs. without aura                                                                     | SVC                             | 30 patients with migraine with aura, 22 patients with migraine without aura  | EEG: resting-state FC                                                            | mean Acc = 84.62%; AUC = 0.88                                                                                                 | –                 | –                      | Frid et al. <sup>164</sup>                |
| Chronic            | monitoring              | patients with migraine under ictal phase, interictal phase vs. healthy controls                                       | XGB                             | 13 patients under ictal, 29 patients under interictal, 15 healthy controls   | EEG: SSEPs                                                                       | Acc = 72.4%                                                                                                                   | –                 | –                      | Zhu et al. <sup>165</sup>                 |

(Continued on next page)

**Table 1. Continued**

| Pain types | Biomarker types     | Target                                                                             | Algorithms                 | Sample size                                                                                                                       | Features                                                                                                          | Model sensitivity                     | Model specificity | Model generalizability | Reference                       |
|------------|---------------------|------------------------------------------------------------------------------------|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|---------------------------------------|-------------------|------------------------|---------------------------------|
| Chronic    | monitoring          | before, during, one day following, vs. two days following migraine attack          | /                          | 11 patients before attack, 24 patients during attack, 28 patients one day following attack, 14 patients two days following attack | EEG: visual evoked potentials                                                                                     | /                                     | –                 | –                      | Judit et al. <sup>166</sup>     |
| Chronic    | monitoring          | between-subject pain intensity in patients with non-specific chronic low back pain | multiple linear regression | 30 patients                                                                                                                       | EEG: (1) $\delta$ -band power; (2) $\theta$ -band power                                                           | (1) $R^2 = 0.20$ ; (2) $R^2 = 0.21$   | –                 | –                      | Teixeira et al. <sup>167</sup>  |
| Chronic    | monitoring          | between-subject pain intensity in patients with migraine                           | simple correlation         | 33 patients                                                                                                                       | EEG: (1) $\delta$ -band power; (2) $\alpha$ -band asymmetry                                                       | (1) $\rho > 0.46$ ; (2) $\rho > 0.34$ | –                 | –                      | Bjork et al. <sup>168</sup>     |
| Chronic    | monitoring          | between-subject pain intensity in patients with orofacial neuropathic pain         | simple correlation         | 20 patients                                                                                                                       | EEG: (1) $\alpha$ -band power at T4 electrode; (2) $\beta$ power at somatomotor, parietal, and occipital cortices | (1) $r = 0.60$ ; (2) $r > 0.53$       | –                 | –                      | Di Pietro et al. <sup>169</sup> |
| Chronic    | susceptibility/risk | developing chronic pain vs. becoming pain-free                                     | /                          | 8 for development pain group, 15 for becoming pain-free group                                                                     | EEG: $\theta$ - and $\beta$ -band power                                                                           | /                                     | –                 | –                      | Schuurman et al. <sup>170</sup> |

(Continued on next page)

Table 1. Continued

| Pain types | Biomarker types         | Target                                                             | Algorithms                 | Sample size                                                                                                 | Features                                                                                                                                             | Model sensitivity                                                                                                                          | Model specificity | Model generalizability | Reference                       |
|------------|-------------------------|--------------------------------------------------------------------|----------------------------|-------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|-------------------|------------------------|---------------------------------|
| Chronic    | susceptibility/<br>risk | patients with episodic migraine vs. patients with chronic migraine | /                          | 70 patients with episodic migraine, 80 patients with chronic migraine                                       | MEG: the sum of the FC values connected to the right insula, S1, bilateral medial frontal cortex, S2, and anterior cingulate cortex in $\beta$ -band | /                                                                                                                                          | –                 | –                      | Hsiao et al. <sup>171</sup>     |
| Chronic    | predictive              | pain relief in response to duloxetine injection at 12 weeks        | multiple linear regression | 5 patients with fibromyalgia                                                                                | quantitative EEG: left frontal cordance at week 1                                                                                                    | $R^2 = 0.93$                                                                                                                               | –                 | –                      | Hunter et al. <sup>174</sup>    |
| Chronic    | predictive              | receiving pregabalin vs. receiving placebo                         | SVC                        | 14 patients with chronic pain for receiving pregabalin, 14 patients with chronic pain receiving placebo     | EEG: $\theta$ -band power                                                                                                                            | Acc = 85.7%                                                                                                                                | –                 | –                      | Graversen et al. <sup>175</sup> |
| Chronic    | predictive              | pain relief induced by hypnosis or meditation treatments           | simple correlation         | patients with spinal cord injury and chronic pain: (1) hypnosis treatment: 29; (2) meditation treatment: 30 | EEG: pre-treatment spectral power                                                                                                                    | (1) $\theta$ -band power predicts response to hypnosis: $r = 0.46$ ; (2) $\alpha$ -band power predicts response to meditation: $r = -0.45$ | –                 | –                      | Jensen et al. <sup>176</sup>    |
| Chronic    | predictive              | pain relief induced by $\alpha$ -tACS                              | simple correlation         | 20 patients with chronic low back pain                                                                      | EEG: $\alpha$ -band power                                                                                                                            | $\rho > 0.3$                                                                                                                               | –                 | –                      | Ahn et al. <sup>177</sup>       |

Note: Acc, accuracy; AUC, area under the receiver operating characteristic curve; EEG, electroencephalography; ERD, event-related desynchronization; ERP, event-related potential; ERS, event-related synchronization; F1, F1 score; FC, functional connectivity; fMRI, functional magnetic resonance imaging; LASSO, least absolute shrinkage and selection operator; LEP, laser-evoked potential; MAE, mean absolute error; MEG, magnetoencephalography; NPS, Neurological Pain Signature; PAF, peak  $\alpha$  frequency; PCA, principal component analysis; PCR, principal component regression; PLV, phase-locking value; PSD, power spectral density;  $r$ , Pearson correlation coefficient;  $R^2$ , coefficient of determination;  $\rho$ , Spearman correlation coefficient; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SSEPs, somatosensory evoked potentials; SVC, support vector classifier; SVR, support vector regression; sMRI, structural magnetic resonance imaging; t, t value in t tests; tACS, transcranial alternating current stimulation; TFR, time frequency representation; XGB, extreme gradient-boosting trees. Slash (“/”) means the paper did not specify a particular algorithm or sensitivity score. Minus sign (“–”) means the paper did not test the model specificity or generalizability of the biomarker.

conceptual and practical challenges persist. Despite these obstacles, the search for neuroimaging-based pain biomarkers remains of great value, holding profound implications for both basic science and clinical applications. Focusing more on clinical usefulness and leveraging multimodal neuroimaging techniques and cutting-edge machine learning algorithms, we anticipate the forthcoming emergence of increasingly precise and reliable pain biomarkers. These advancements hold the potential not only to deepen our understanding of how the brain processes pain but also to alleviate patients' suffering and improve their well-being.

### ACKNOWLEDGMENTS

L.H. is supported by the National Key Research and Development Program of China (2023YFC2508702), the National Natural Science Foundation of China (32071061), and Beijing Natural Science Foundation (JQ22018). X.-J.L. is supported by the National Natural Science Foundation of China (32171077) and a grant from the Youth Innovation Promotion Association, CAS.

### AUTHOR CONTRIBUTIONS

Conceptualization, L.-B.Z. and L.H.; writing – original draft, L.-B.Z., Y.-X.C., Z.-J.L., X.-Y.G., X.-Y.Z., Y.-Z.B., and X.-J.L.; writing – review and editing, L.-B.Z., Y.-X.C., X.-Y.G., X.-J.L., and L.H.; visualization, L.-B.Z., F.-R.Z., X.-J.L., and L.H.; funding acquisition, X.-J.L. and L.H.; project administration, L.H.; supervision, L.H.

### DECLARATION OF INTERESTS

The authors declare no competing interests.

### REFERENCES

- Merskey, H., and Bogduk, N. (1994). *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*, 2nd ed. (IASP Press), p. xi.
- Chen, B., Li, L., Donovan, C., Gao, Y., Ali, G., Jiang, Y., Xu, T., Shan, G., and Sun, W. (2016). Prevalence and characteristics of chronic body pain in China: a national study. *SpringerPlus* 5, 938. <https://doi.org/10.1186/s40064-016-2581-y>.
- Dahlhamer, J., Lucas, J., Zelaya, C., Nahin, R., Mackey, S., DeBar, L., Kerns, R., Von Korff, M., Porter, L., and Helmick, C. (2018). Prevalence of chronic pain and high-impact chronic pain among adults - United States, 2016. *MMWR Morb. Mortal. Wkly. Rep.* 67, 1001–1006. <https://doi.org/10.15585/mmwr.mm6736a2>.
- Fayaz, A., Croft, P., Langford, R.M., Donaldson, L.J., and Jones, G.T. (2016). Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. *BMJ Open* 6, e010364. <https://doi.org/10.1136/bmjopen-2015-010364>.
- Yu, S., Liu, R., Zhao, G., Yang, X., Qiao, X., Feng, J., Fang, Y., Cao, X., He, M., and Steiner, T. (2012). The prevalence and burden of primary headaches in China: a population-based door-to-door survey. *Headache* 52, 582–591. <https://doi.org/10.1111/j.1526-4610.2011.02061.x>.
- Gaskin, D.J., and Richard, P. (2012). The economic costs of pain in the United States. *J. Pain* 13, 715–724. <https://doi.org/10.1016/j.jpain.2012.03.009>.
- Phillips, C.J. (2009). The cost and burden of chronic pain. *Rev. Pain* 3, 2–5. <https://doi.org/10.1177/204946370900300102>.
- Zhang, F., Xiang, W., Li, C.Y., and Li, S.C. (2016). Economic burden of irritable bowel syndrome in China. *World J. Gastroenterol.* 22, 10450–10460. <https://doi.org/10.3748/wjg.v22.i47.10450>.
- Raja, S.N., Carr, D.B., Cohen, M., Finnerup, N.B., Flor, H., Gibson, S., Keefe, F.J., Mogil, J.S., Ringkamp, M., Sluka, K.A., et al. (2020). The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain* 161, 1976–1982. <https://doi.org/10.1097/j.pain.0000000000001939>.
- Woo, C.W., Chang, L.J., Lindquist, M.A., and Wager, T.D. (2017). Building better biomarkers: brain models in translational neuroimaging. *Nat. Neurosci.* 20, 365–377. <https://doi.org/10.1038/nn.4478>.
- Davis, K.D., Aghaepour, N., Ahn, A.H., Angst, M.S., Borsook, D., Brenton, A., Burczynski, M.E., Crean, C., Edwards, R., Gaudilliere, B., et al. (2020). Discovery and validation of biomarkers to aid the development of safe and effective pain therapeutics: challenges and opportunities. *Nat. Rev. Neurol.* 16, 381–400. <https://doi.org/10.1038/s41582-020-0362-2>.
- BEST (Biomarkers, EndpointS, and other Tools) Resource (2016). <http://www.ncbi.nlm.nih.gov/books/NBK326791/>.
- van der Miesen, M.M., Lindquist, M.A., and Wager, T.D. (2019). Neuroimaging-based biomarkers for pain: state of the field and current directions. *Pain Rep.* 4, e751. <https://doi.org/10.1097/PR9.0000000000000751>.
- Baliki, M.N., Petre, B., Torbey, S., Herrmann, K.M., Huang, L., Schnitzer, T.J., Fields, H.L., and Apkarian, A.V. (2012). Corticostriatal functional connectivity predicts transition to chronic back pain. *Nat. Neurosci.* 15, 1117–1119. <https://doi.org/10.1038/nn.3153>.
- Gross, J., Schnitzler, A., Timmermann, L., and Ploner, M. (2007). Gamma oscillations in human primary somatosensory cortex reflect pain perception. *PLoS Biol.* 5, e133. <https://doi.org/10.1371/journal.pbio.0050133>.
- Hu, L., and Iannetti, G.D. (2019). Neural indicators of perceptual variability of pain across species. *Proc. Natl. Acad. Sci. USA* 116, 1782–1791. <https://doi.org/10.1073/pnas.1812499116>.
- Lee, J.J., Kim, H.J., Čeko, M., Park, B.Y., Lee, S.A., Park, H., Roy, M., Kim, S.G., Wager, T.D., and Woo, C.W. (2021). A neuroimaging biomarker for sustained experimental and clinical pain. *Nat. Med.* 27, 174–182. <https://doi.org/10.1038/s41591-020-1142-7>.
- Schulz, E., May, E.S., Postorino, M., Tiemann, L., Nickel, M.M., Witkovsky, V., Schmidt, P., Gross, J., and Ploner, M. (2015). Prefrontal gamma oscillations encode tonic pain in humans. *Cereb. Cortex* 25, 4407–4414. <https://doi.org/10.1093/cercor/bhv043>.
- Spisak, T., Kincses, B., Schlitt, F., Zunhammer, M., Schmidt-Wilcke, T., Kincses, Z.T., and Bingel, U. (2020). Pain-free resting-state functional brain connectivity predicts individual pain sensitivity. *Nat. Commun.* 11, 187. <https://doi.org/10.1038/s41467-019-13785-z>.
- Wager, T.D., Atlas, L.Y., Lindquist, M.A., Roy, M., Woo, C.W., and Kross, E. (2013). An fMRI-based neurologic signature of physical pain. *N. Engl. J. Med.* 368, 1388–1397. <https://doi.org/10.1056/NEJMoa1204471>.
- Reckziegel, D., Vachon-Presseau, E., Petre, B., Schnitzer, T.J., Baliki, M.N., and Apkarian, A.V. (2019). Deconstructing biomarkers for chronic pain: context- and hypothesis-dependent biomarker types in relation to chronic pain. *Pain* 160, S37–S48. <https://doi.org/10.1097/j.pain.0000000000001529>.
- Davis, K.D., and Cheng, J.C. (2019). Differentiating trait pain from state pain: a window into brain mechanisms underlying how we experience and cope with pain. *Pain Rep.* 4, e735. <https://doi.org/10.1097/PR9.0000000000000735>.
- Schulz, E., Tiemann, L., Schuster, T., Gross, J., and Ploner, M. (2011). Neurophysiological coding of traits and states in the perception of pain. *Cereb. Cortex* 21, 2408–2414. <https://doi.org/10.1093/cercor/bhr027>.
- Kantowitz, B.H., Roediger, I.H.L., and Elmes, D.G. (2014). *Experimental Psychology*, 10th edition (Cengage Learning), pp. 159–160.
- Mogil, J.S. (2021). Sources of individual differences in pain. In *Annual Review of Neuroscience*, 44, B. Roska and H.Y. Zoghbi, eds. (Annual Reviews), pp. 1–25. <https://doi.org/10.1146/annurev-neuro-092820-105941>.
- Zhang, L.B., Lu, X.J., Huang, G., Zhang, H.J., Tu, Y.H., Kong, Y.Z., and Hu, L. (2022). Selective and replicable neuroimaging-based indicators

- of pain discriminability. *Cell Rep. Med.* 3, 100846. <https://doi.org/10.1016/j.xcrm.2022.100846>.
27. Nielsen, C.S., Staud, R., and Price, D.D. (2009). Individual differences in pain sensitivity: measurement, causation, and consequences. *J. Pain* 10, 231–237. <https://doi.org/10.1016/j.jpain.2008.09.010>.
28. Werner, M.U., Mjöbo, H.N., Nielsen, P.R., and Rudin, Å. (2010). Prediction of postoperative pain: a systematic review of predictive experimental pain studies. *Anesthesiology* 112, 1494–1502. <https://doi.org/10.1097/ALN.0b013e3181dcd5a0>.
29. Campbell, P., Foster, N.E., Thomas, E., and Dunn, K.M. (2013). Prognostic indicators of low back pain in primary care: five-year prospective study. *J. Pain* 14, 873–883. <https://doi.org/10.1016/j.jpain.2013.03.013>.
30. Pan, L.L.H., Wang, Y.F., Ling, Y.H., Lai, K.L., Chen, S.P., Chen, W.T., Treede, R.D., and Wang, S.J. (2022). Pain sensitivities predict prophylactic treatment outcomes of flunarizine in chronic migraine patients: a prospective study. *Cephalalgia* 42, 899–909. <https://doi.org/10.1177/03331024221080572>.
31. Cohen, M.J., Naliboff, B.D., Schandler, S.L., and Heinrich, R.L. (1983). Signal-detection and threshold measures to loud tones and radiant-heat in chronic low-back-pain patients and cohort controls. *Pain* 16, 245–252. [https://doi.org/10.1016/0304-3959\(83\)90112-4](https://doi.org/10.1016/0304-3959(83)90112-4).
32. Malow, R.M., Grimm, L., and Olson, R.E. (1980). Differences in pain perception between myofascial pain dysfunction patients and normal subjects - a signal-detection analysis. *J. Psychosom. Res.* 24, 303–309. [https://doi.org/10.1016/0022-3999\(80\)90021-5](https://doi.org/10.1016/0022-3999(80)90021-5).
33. Naliboff, B.D., Cohen, M.J., Schandler, S.L., and Heinrich, R.L. (1981). Signal detection and threshold measures for chronic back pain patients, chronic illness patients, and cohort controls to radiant heat stimuli. *J. Abnorm. Psychol.* 90, 271–274. <https://doi.org/10.1037/0021-843x.90.3.271>.
34. Yang, J.C., Richlin, D., Brand, L., Wagner, J., and Clark, W.C. (1985). Thermal sensory decision-theory indexes and pain threshold in chronic pain patients and healthy-volunteers. *Psychosom. Med.* 47, 461–468. <https://doi.org/10.1097/00006842-198509000-00006>.
35. Malow, R.M., and Olson, R.E. (1981). Changes in pain perception after treatment for chronic pain. *Pain* 11, 65–72. [https://doi.org/10.1016/0304-3959\(81\)90139-1](https://doi.org/10.1016/0304-3959(81)90139-1).
36. Yang, J.C., Clark, W.C., and Janal, M.N. (1991). Sensory decision-theory and visual analog scale indexes predict status of chronic pain patients 6 months later. *J. Pain Symptom Manage.* 6, 58–64. [https://doi.org/10.1016/0885-3924\(91\)90519-a](https://doi.org/10.1016/0885-3924(91)90519-a).
37. Tu, Y., Cao, J., Bi, Y., and Hu, L. (2021). Magnetic resonance imaging for chronic pain: diagnosis, manipulation, and biomarkers. *Sci. China Life Sci.* 64, 879–896. <https://doi.org/10.1007/s11427-020-1822-4>.
38. Bosma, R.L., Cheng, J.C., Rogachov, A., Kim, J.A., Hemington, K.S., Osborne, N.R., Venkat Raghavan, L., Bhatia, A., and Davis, K.D. (2018). Brain dynamics and temporal summation of pain predicts neuropathic pain relief from ketamine infusion. *Anesthesiology* 129, 1015–1024. <https://doi.org/10.1097/ain.0000000000002417>.
39. Glare, P., Aubrey, K.R., and Myles, P.S. (2019). Postoperative pain management and opioids 1 Transition from acute to chronic pain after surgery. *Lancet* 393, 1537–1546. [https://doi.org/10.1016/s0140-6736\(19\)30352-6](https://doi.org/10.1016/s0140-6736(19)30352-6).
40. Ploner, M., Sorg, C., and Gross, J. (2017). Brain rhythms of pain. *Trends Cogn. Sci.* 21, 100–110. <https://doi.org/10.1016/j.tics.2016.12.001>.
41. Arendt-Nielsen, L., Curatolo, M., and Drewes, A. (2007). Human experimental pain models in drug development: translational pain research. *Curr. Opin. Investig. Drugs* 8, 41–53.
42. Apkarian, A.V., Bushnell, M.C., Treede, R.D., and Zubieta, J.K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *Eur. J. Pain* 9, 463–484. <https://doi.org/10.1016/j.ejpain.2004.11.001>.
43. Tracey, I., and Mantyh, P.W. (2007). The cerebral signature and its modulation for pain perception. *Neuron* 55, 377–391. <https://doi.org/10.1016/j.neuron.2007.07.012>.
44. Xu, A., Larsen, B., Baller, E.B., Scott, J.C., Sharma, V., Adebimpe, A., Basbaum, A.I., Dworkin, R.H., Edwards, R.R., Woolf, C.J., et al. (2020). Convergent neural representations of experimentally-induced acute pain in healthy volunteers: a large-scale fMRI meta-analysis. *Neurosci. Biobehav. Rev.* 112, 300–323. <https://doi.org/10.1016/j.neubiorev.2020.01.004>.
45. Coghill, R.C., Talbot, J.D., Evans, A.C., Meyer, E., Gjedde, A., Bushnell, M.C., and Duncan, G.H. (1994). Distributed-processing of pain and vibration by the human brain. *J. Neurosci.* 14, 4095–4108. <https://doi.org/10.1523/JNEUROSCI.14-07-04095.1994>.
46. Davis, K.D., Wood, M.L., Crawley, A.P., and Mikulis, D.J. (1995). fMRI of human somatosensory and cingulate cortex during painful electrical nerve stimulation. *Neuroreport* 7, 321–325. <https://doi.org/10.1097/00001756-199512290-00077>.
47. Jones, A.K., Brown, W.D., Friston, K.J., Qi, L.Y., and Frackowiak, R.S. (1991). Cortical and subcortical localization of response to pain in man using positron emission tomography. *Proc. Biol. Sci.* 244, 39–44. <https://doi.org/10.1098/rspb.1991.0048>.
48. Talbot, J.D., Marrett, S., Evans, A.C., Meyer, E., Bushnell, M.C., and Duncan, G.H. (1991). Multiple representations of pain in human cerebral-cortex. *Science* 251, 1355–1358. <https://doi.org/10.1126/science.2003220>.
49. Derbyshire, S.W.G., Jones, A.K.P., Gyulai, F., Clark, S., Townsend, D., and Firestone, L.L. (1997). Pain processing during three levels of noxious stimulation produces differential patterns of central activity. *Pain* 73, 431–445. [https://doi.org/10.1016/s0304-3959\(97\)00138-3](https://doi.org/10.1016/s0304-3959(97)00138-3).
50. Bornhövd, K., Quante, M., Glauche, V., Bromm, B., Weiller, C., and Büchel, C. (2002). Painful stimuli evoke different stimulus-response functions in the amygdala, prefrontal, insula and somatosensory cortex: a single-trial fMRI study. *Brain* 125, 1326–1336. <https://doi.org/10.1093/brain/awf137>.
51. Büchel, C., Bornhövd, K., Quante, M., Glauche, V., Bromm, B., and Weiller, C. (2002). Dissociable neural responses related to pain intensity, stimulus intensity, and stimulus awareness within the anterior cingulate cortex: a parametric single-trial laser functional magnetic resonance imaging study. *J. Neurosci.* 22, 970–976. <https://doi.org/10.1523/jneurosci.22-03-00970.2002>.
52. Coghill, R.C., Sang, C.N., Maisog, J.M., and Iadarola, M.J. (1999). Pain intensity processing within the human brain: a bilateral, distributed mechanism. *J. Neurophysiol.* 82, 1934–1943. <https://doi.org/10.1152/jn.1999.82.4.1934>.
53. Favilla, S., Huber, A., Pagnoni, G., Lui, F., Facchin, P., Cocchi, M., Baraldi, P., and Porro, C.A. (2014). Ranking brain areas encoding the perceived level of pain from fMRI data. *Neuroimage* 90, 153–162. <https://doi.org/10.1016/j.neuroimage.2014.01.001>.
54. Porro, C.A., Cettolo, V., Francescato, M.P., and Baraldi, P. (1998). Temporal and intensity coding of pain in human cortex. *J. Neurophysiol.* 80, 3312–3320. <https://doi.org/10.1152/jn.1998.80.6.3312>.
55. Marquand, A., Howard, M., Brammer, M., Chu, C., Coen, S., and Mourão-Miranda, J. (2010). Quantitative prediction of subjective pain intensity from whole-brain fMRI data using Gaussian processes. *Neuroimage* 49, 2178–2189. <https://doi.org/10.1016/j.neuroimage.2009.10.072>.
56. Woo, C.W., Schmidt, L., Krishnan, A., Jepma, M., Roy, M., Lindquist, M.A., Atlas, L.Y., and Wager, T.D. (2017). Quantifying cerebral contributions to pain beyond nociception. *Nat. Commun.* 8, 14211. <https://doi.org/10.1038/ncomms14211>.
57. Brown, J.E., Chatterjee, N., Younger, J., and Mackey, S. (2011). Towards a physiology-based measure of pain: patterns of human brain activity distinguish painful from non-painful thermal stimulation. *PLoS One* 6, e24124. <https://doi.org/10.1371/journal.pone.0024124>.
58. Tu, Y.H., Fu, Z.N., Tan, A., Huang, G., Hu, L., Hung, Y.S., and Zhang, Z.G. (2018). A novel and effective fMRI decoding approach based on sliced

- inverse regression and its application to pain prediction. *Neurocomputing* 273, 373–384. <https://doi.org/10.1016/j.neucom.2017.07.045>.
59. Hu, L., and Iannetti, G.D. (2016). Painful issues in pain prediction. *Trends Neurosci.* 39, 212–220. <https://doi.org/10.1016/j.tins.2016.01.004>.
60. Poldrack, R.A. (2006). Can cognitive processes be inferred from neuroimaging data? *Trends Cogn. Sci.* 10, 59–63. <https://doi.org/10.1016/j.tics.2005.12.004>.
61. Iannetti, G.D., and Mouraux, A. (2010). From the neuromatrix to the pain matrix (and back). *Exp. Brain Res.* 205, 1–12. <https://doi.org/10.1007/s00221-010-2340-1>.
62. Salomons, T.V., Iannetti, G.D., Liang, M., and Wood, J.N. (2016). The "pain matrix" in pain-free individuals. *JAMA Neurol.* 73, 755–756. <https://doi.org/10.1001/jamaneurol.2016.0653>.
63. Mouraux, A., Diukova, A., Lee, M.C., Wise, R.G., and Iannetti, G.D. (2011). A multisensory investigation of the functional significance of the "pain matrix. *Neuroimage* 54, 2237–2249. <https://doi.org/10.1016/j.neuroimage.2010.09.084>.
64. Zhang, X., Li, L., Huang, G., Zhang, L., Liang, Z., Shi, L., and Zhang, Z. (2021). A multisensory fMRI investigation of nociceptive-preferential cortical regions and responses. *Front. Neurosci.* 15, 635733. <https://doi.org/10.3389/fnins.2021.635733>.
65. Su, Q., Qin, W., Yang, Q.Q., Yu, C.S., Qian, T.Y., Mouraux, A., Iannetti, G.D., and Liang, M. (2019). Brain regions preferentially responding to transient and iso-intense painful or tactile stimuli. *Neuroimage* 192, 52–65. <https://doi.org/10.1016/j.neuroimage.2019.01.039>.
66. Horing, B., Sprenger, C., and Büchel, C. (2019). The parietal operculum preferentially encodes heat pain and not salience. *PLoS Biol.* 17, e3000205. <https://doi.org/10.1371/journal.pbio.3000205>.
67. Liang, M., Su, Q., Mouraux, A., and Iannetti, G.D. (2019). Spatial patterns of brain activity preferentially reflecting transient pain and stimulus intensity. *Cereb. Cortex* 29, 2211–2227. <https://doi.org/10.1093/cercor/bhz026>.
68. Tu, Y., Li, Z., Zhang, L., Zhang, H., Bi, Y., Yue, L., and Hu, L. (2024). Pain-preferential thalamocortical neural dynamics across species. *Nat. Hum. Behav.* 8, 149–163. <https://doi.org/10.1038/s41562-023-01714-6>.
69. Coghill, R.C., McHaffie, J.G., and Yen, Y.F. (2003). Neural correlates of interindividual differences in the subjective experience of pain. *Proc. Natl. Acad. Sci. USA* 100, 8538–8542. <https://doi.org/10.1073/pnas.1430684100>.
70. Hoeppli, M.E., Nahman-Averbuch, H., Hinkle, W.A., Leon, E., Peugh, J., Lopez-Sola, M., King, C.D., Goldschneider, K.R., and Coghill, R.C. (2022). Dissociation between individual differences in self-reported pain intensity and underlying fMRI brain activation. *Nat. Commun.* 13, 3569. <https://doi.org/10.1038/s41467-022-31039-3>.
71. Gim, S., Lee, D.H., Lee, S., and Woo, C.W. (2023). Interindividual differences in pain can be explained by fMRI, sociodemographic, and psychological factors. *bioRxiv*. <https://doi.org/10.1101/2023.07.06.547919>.
72. Zhang, L.B., Lu, X.J., Zhang, H.J., Wei, Z.X., Kong, Y.Z., Tu, Y.H., Iannetti, G.D., and Hu, L. (2024). A replicable and generalizable neuroimaging-based indicator of pain sensitivity across individuals. *bioRxiv*. <https://doi.org/10.1101/2024.06.08.597884>.
73. Tu, Y., Zhang, B., Cao, J., Wilson, G., Zhang, Z., and Kong, J. (2019). Identifying inter-individual differences in pain threshold using brain connectome: a test-retest reproducible study. *Neuroimage* 202, 116049. <https://doi.org/10.1016/j.neuroimage.2019.116049>.
74. Neumann, L., Wulms, N., Witte, V., Spisak, T., Zunhammer, M., Bingel, U., and Schmidt-Wilcke, T. (2021). Network properties and regional brain morphology of the insular cortex correlate with individual pain thresholds. *Hum. Brain Mapp.* 42, 4896–4908. <https://doi.org/10.1002/hbm.25588>.
75. Grouper, H., Löffler, M., Flor, H., Eisenberg, E., and Pud, D. (2022). Increased functional connectivity between limbic brain areas in healthy individuals with high versus low sensitivity to cold pain: a resting state fMRI study. *PLoS One* 17, e0267170. <https://doi.org/10.1371/journal.pone.0267170>.
76. Yuan, Y., Zhang, L., Li, L., Huang, G., Anter, A., Liang, Z., and Zhang, Z. (2019). Distinct dynamic functional connectivity patterns of pain and touch thresholds: a resting-state fMRI study. *Behav. Brain Res.* 375, 112142. <https://doi.org/10.1016/j.bbr.2019.112142>.
77. Erpelding, N., Moayedi, M., and Davis, K.D. (2012). Cortical thickness correlates of pain and temperature sensitivity. *Pain* 153, 1602–1609. <https://doi.org/10.1016/j.pain.2012.03.012>.
78. Kotikalapudi, R., Kincses, B., Zunhammer, M., Schlitt, F., Asan, L., Schmidt-Wilcke, T., Kincses, Z.T., Bingel, U., and Spisak, T. (2023). Brain morphology predicts individual sensitivity to pain: a multicenter machine learning approach. *Pain* 164, 2516–2527. <https://doi.org/10.1097/j.pain.0000000000002958>.
79. Emerson, N.M., Zeidan, F., Lobanov, O.V., Hadsel, M.S., Martucci, K.T., Quevedo, A.S., Starr, C.J., Nahman-Averbuch, H., Weissman-Fogel, I., Granovsky, Y., et al. (2014). Pain sensitivity is inversely related to regional grey matter density in the brain. *Pain* 155, 566–573. <https://doi.org/10.1016/j.pain.2013.12.004>.
80. Ruscheweyh, R., Wersching, H., Kugel, H., Sundermann, B., and Teuber, A. (2018). Gray matter correlates of pressure pain thresholds and self-rated pain sensitivity: a voxel-based morphometry study. *Pain* 159, 1359–1365. <https://doi.org/10.1097/j.pain.0000000000001219>.
81. Zhang, X., Chen, Q., Su, Y., Meng, J., Qiu, J., and Zheng, W. (2020). Pain in the default mode network: a voxel-based morphometry study on thermal pain sensitivity. *Neuroreport* 31, 1030–1035. <https://doi.org/10.1097/wnr.0000000000001512>.
82. Zou, R., Li, L., Zhang, L., Huang, G., Liang, Z., and Zhang, Z. (2021). Predicting individual pain thresholds from morphological connectivity using structural MRI: a multivariate analysis study. *Front. Neurosci.* 15, 615944. <https://doi.org/10.3389/fnins.2021.615944>.
83. Zhang, H., Zhao, L., Lu, X., Peng, W., Zhang, L., Zhang, Z., Hu, L., Cao, J., and Tu, Y. (2024). Multimodal covarying brain patterns mediate genetic and psychological contributions to individual differences in pain sensitivity. *Pain* 165, 1074–1085. <https://doi.org/10.1097/j.pain.0000000000003103>.
84. Golttermann, O., and Büchel, C. (2023). Improving fMRI-based prediction of individual pain ratings by accounting for interindividual variance. *bioRxiv*. <https://doi.org/10.1101/2023.07.06.548050>.
85. Huang, G., Xiao, P., Hung, Y.S., Iannetti, G.D., Zhang, Z.G., and Hu, L. (2013). A novel approach to predict subjective pain perception from single-trial laser-evoked potentials. *Neuroimage* 81, 283–293. <https://doi.org/10.1016/j.neuroimage.2013.05.017>.
86. Tripanpitak, K., He, S., Sonmezisik, I., Morant, T., Huang, S.Y., and Yu, W. (2021). Granger causality-based pain classification using EEG evoked by electrical stimulation targeting nociceptive A $\delta$  and C fibers. *IEEE Access* 9, 10089–10106. <https://doi.org/10.1109/access.2021.3050302>.
87. Tripanpitak, K., Viriyavit, W., Huang, S.Y., and Yu, W. (2020). Classification of pain event related potential for evaluation of pain perception induced by electrical stimulation. *Sensors* 20, 1491. <https://doi.org/10.3390/s20051491>.
88. Tu, Y., Zhang, Z., Tan, A., Peng, W., Hung, Y.S., Moayedi, M., Iannetti, G.D., and Hu, L. (2016). Alpha and gamma oscillation amplitudes synergistically predict the perception of forthcoming nociceptive stimuli. *Hum. Brain Mapp.* 37, 501–514. <https://doi.org/10.1002/hbm.23048>.
89. Tu, Y., Tan, A., Bai, Y., Hung, Y.S., and Zhang, Z. (2016). Decoding subjective intensity of nociceptive pain from pre-stimulus and post-stimulus brain activities. *Front. Comput. Neurosci.* 10, 32. <https://doi.org/10.3389/fncom.2016.00032>.
90. Schulz, E., Zherdin, A., Tiemann, L., Plant, C., and Ploner, M. (2012). Decoding an individual's sensitivity to pain from the multivariate analysis of EEG data. *Cereb. Cortex* 22, 1118–1123. <https://doi.org/10.1093/cercor/bhr186>.
91. Zhang, Q., Hu, S., Talay, R., Xiao, Z., Rosenberg, D., Liu, Y., Sun, G., Li, A., Caravan, B., Singh, A., et al. (2023). A prototype closed-loop brain-

- p>machine interface for the study and treatment of pain.
- Nat. Biomed. Eng.*
- 7, 533–545.
- <https://doi.org/10.1038/s41551-021-00736-7>
- .
92. Zhang, Q., Xiao, Z., Huang, C., Hu, S., Kulkarni, P., Martinez, E., Tong, A.P., Garg, A., Zhou, H., Chen, Z., and Wang, J. (2018). Local field potential decoding of the onset and intensity of acute pain in rats. *Sci. Rep.* 8, 8299. <https://doi.org/10.1038/s41598-018-26527-w>.
  93. Iannetti, G.D., Zambreanu, L., Cruccu, G., and Tracey, I. (2005). Operculo-insular cortex encodes pain intensity at the earliest stages of cortical processing as indicated by amplitude of laser-evoked potentials in humans. *Neuroscience* 131, 199–208. <https://doi.org/10.1016/j.neuroscience.2004.10.035>.
  94. Iannetti, G.D., Zambreanu, L., and Tracey, I. (2006). Similar nociceptive afferents mediate psychophysical and electrophysiological responses to heat stimulation of glabrous and hairy skin in humans. *J. Physiol.* 577, 235–248. <https://doi.org/10.1113/jphysiol.2006.115675>.
  95. Iannetti, G.D., Hughes, N.P., Lee, M.C., and Mouraux, A. (2008). Determinants of laser-evoked EEG responses: pain perception or stimulus saliency? *J. Neurophysiol.* 100, 815–828. <https://doi.org/10.1152/jn.00097.2008>.
  96. Liberati, G., Klöcker, A., Safronova, M.M., Ferrão Santos, S., Ribeiro Vaz, J.G., Raftopoulos, C., and Mouraux, A. (2016). Nociceptive local field potentials recorded from the human insula are not specific for nociception. *PLoS Biol.* 14, e1002345. <https://doi.org/10.1371/journal.pbio.1002345>.
  97. Mouraux, A., and Iannetti, G.D. (2009). Nociceptive laser-evoked brain potentials do not reflect nociceptive-specific neural activity. *J. Neurophysiol.* 101, 3258–3269. <https://doi.org/10.1152/jn.91181.2008>.
  98. Liberati, G., Algoet, M., Klöcker, A., Ferrao Santos, S., Ribeiro-Vaz, J.G., Raftopoulos, C., and Mouraux, A. (2018). Habituation of phase-locked local field potentials and gamma-band oscillations recorded from the human insula. *Sci. Rep.* 8, 8265. <https://doi.org/10.1038/s41598-018-26604-0>.
  99. Hu, L., Peng, W., Valentini, E., Zhang, Z., and Hu, Y. (2013). Functional features of nociceptive-induced suppression of alpha band electroencephalographic oscillations. *J. Pain* 14, 89–99. <https://doi.org/10.1016/j.jpain.2012.10.008>.
  100. Mouraux, A., Guérit, J.M., and Plaghki, L. (2003). Non-phase locked electroencephalogram (EEG) responses to CO<sub>2</sub> laser skin stimulations may reflect central interactions between A $\delta$ - and C-fibre afferent volleys. *Clin. Neurophysiol.* 114, 710–722. [https://doi.org/10.1016/s1388-2457\(03\)00027-0](https://doi.org/10.1016/s1388-2457(03)00027-0).
  101. Ploner, M., Gross, J., Timmermann, L., Pollok, B., and Schnitzler, A. (2006). Oscillatory activity reflects the excitability of the human somatosensory system. *Neuroimage* 32, 1231–1236. <https://doi.org/10.1016/j.neuroimage.2006.06.004>.
  102. Ploner, M., Gross, J., Timmermann, L., Pollok, B., and Schnitzler, A. (2006). Pain suppresses spontaneous brain rhythms. *Cereb. Cortex* 16, 537–540. <https://doi.org/10.1093/cercor/bhj001>.
  103. Zhang, Z.G., Hu, L., Hung, Y.S., Mouraux, A., and Iannetti, G.D. (2012). Gamma-band oscillations in the primary somatosensory cortex—a direct and obligatory correlate of subjective pain intensity. *J. Neurosci.* 32, 7429–7438. <https://doi.org/10.1523/JNEUROSCI.5877-11.2012>.
  104. Tan, L.L., Oswald, M.J., Heini, C., Retana Romero, O.A., Kaushalya, S.K., Monyer, H., and Kuner, R. (2019). Gamma oscillations in somatosensory cortex recruit prefrontal and descending serotonergic pathways in aversion and nociception. *Nat. Commun.* 10, 983. <https://doi.org/10.1038/s41467-019-08873-z>.
  105. Peng, W., Xia, X., Yi, M., Huang, G., Zhang, Z., Iannetti, G., and Hu, L. (2018). Brain oscillations reflecting pain-related behavior in freely-moving rats. *Pain* 159, 106–118. <https://doi.org/10.1097/j.pain.0000000000001069>.
  106. Liu, X., Wei, S., Zhao, X., Bi, Y., and Hu, L. (2024). Establishing the relationship between subjective perception and neural responses: insights from correlation analysis and representational similarity analysis. *Neuroimage* 295, 120650. <https://doi.org/10.1016/j.neuroimage.2024.120650>.
  107. Hsiao, F.J., Chen, W.T., Liu, H.Y., Wang, Y.F., Chen, S.P., Lai, K.L., Pan, L.L.H., and Wang, S.J. (2020). Individual pain sensitivity is associated with resting-state cortical activities in healthy individuals but not in patients with migraine: a magnetoencephalography study. *J. Headache Pain* 21, 133. <https://doi.org/10.1186/s10194-020-01200-8>.
  108. Hsiao, F.J., Chen, W.T., Pan, L.L.H., Liu, H.Y., Wang, Y.F., Chen, S.P., Lai, K.L., and Wang, S.J. (2021). Machine learning-based prediction of heat pain sensitivity by using resting-state EEG. *Front. Biosci.* 26, 1537–1547. <https://doi.org/10.52586/5047>.
  109. Beck, B., Cook, S., Iannetti, G., and Haggard, P. (2019). Neural markers of nociceptive input and pain intensity coding: a signal detection approach. *psyArxiv*. <https://doi.org/10.31234/osf.io/dxeyn>.
  110. Ray, S., and Maunsell, J.H.R. (2015). Do gamma oscillations play a role in cerebral cortex? *Trends Cogn. Sci.* 19, 78–85. <https://doi.org/10.1016/j.tics.2014.12.002>.
  111. Chen, A.C.N., and Treede, R.D. (1985). The McGill Pain Questionnaire in the assessment of phasic and tonic experimental pain: behavioral evaluation of the 'pain inhibiting pain' effect. *Pain* 22, 67–79. [https://doi.org/10.1016/0304-3959\(85\)90149-6](https://doi.org/10.1016/0304-3959(85)90149-6).
  112. Freund, W., Klug, R., Weber, F., Stuber, G., Schmitz, B., and Wunderlich, A.P. (2009). Perception and suppression of thermally induced pain: a fMRI study. *Somatosens. Mot. Res.* 26, 1–10. <https://doi.org/10.1080/08990220902738243>.
  113. Thunberg, J., Lyskov, E., Korotkov, A., Ljubisavljevic, M., Pakhomov, S., Katayeva, G., Radovanovic, S., Medvedev, S., and Johansson, H. (2005). Brain processing of tonic muscle pain induced by infusion of hypertonic saline. *Eur. J. Pain* 9, 185–194. <https://doi.org/10.1016/j.ejpain.2004.05.003>.
  114. Owen, D.G., Clarke, C.F., Ganapathy, S., Prato, F.S., and St Lawrence, K.S. (2010). Using perfusion MRI to measure the dynamic changes in neural activation associated with tonic muscular pain. *Pain* 148, 375–386. <https://doi.org/10.1016/j.pain.2009.10.003>.
  115. La Cesa, S., Tinelli, E., Toschi, N., Di Stefano, G., Collorone, S., Aceti, A., Francia, A., Cruccu, G., Truini, A., and Caramia, F. (2014). fMRI pain activation in the periaqueductal gray in healthy volunteers during cold pressor test. *Magn. Reson. Imaging* 32, 236–240. <https://doi.org/10.1016/j.mri.2013.12.003>.
  116. Meeker, T.J., Schmid, A.C., Keaser, M.L., Khan, S.A., Gullapalli, R.P., Dorsey, S.G., Greenspan, J.D., and Seminowicz, D.A. (2022). Tonic pain alters functional connectivity of the descending pain modulatory network involving amygdala, periaqueductal gray, parabrachial nucleus and anterior cingulate cortex. *Neuroimage* 256, 119278. <https://doi.org/10.1016/j.neuroimage.2022.119278>.
  117. Deak, B., Eggert, T., Mayr, A., Stankewitz, A., Filippopoulos, F., Jahn, P., Witkovsky, V., Straube, A., and Schulz, E. (2022). Intrinsic network activity reflects the fluctuating experience of tonic pain. *Cereb. Cortex* 32, 4098–4109. <https://doi.org/10.1093/cercor/bhab468>.
  118. Lee, J.J., Lee, S., Lee, D.H., and Woo, C.W. (2022). Functional brain reconfiguration during sustained pain. *Elife* 11, e74463. <https://doi.org/10.7554/eLife.74463>.
  119. Peng, W., Hu, L., Zhang, Z., and Hu, Y. (2014). Changes of spontaneous oscillatory activity to tonic heat pain. *PLoS One* 9, e91052. <https://doi.org/10.1371/journal.pone.0091052>.
  120. Chang, P.F., Arendt-Nielsen, L., Graven-Nielsen, T., Svensson, P., and Chen, A.C.N. (2004). Comparative EEG activation to skin pain and muscle pain induced by capsaicin injection. *Int. J. Psychophysiol.* 51, 117–126. <https://doi.org/10.1016/j.ijpsycho.2003.01.001>.
  121. Dowman, R., Rissacher, D., and Schuckers, S. (2008). EEG indices of tonic pain-related activity in the somatosensory cortices. *Clin. Neurophysiol.* 119, 1201–1212. <https://doi.org/10.1016/j.clinph.2008.01.019>.
  122. Li, L., Liu, X., Cai, C., Yang, Y., Li, D., Xiao, L., Xiong, D., Hu, L., and Qiu, Y. (2016). Changes of gamma-band oscillatory activity to tonic muscle pain. *Neurosci. Lett.* 627, 126–131. <https://doi.org/10.1016/j.neulet.2016.05.067>.

123. Nir, R.R., Sinai, A., Moont, R., Harari, E., and Yarnitsky, D. (2012). Tonic pain and continuous EEG: prediction of subjective pain perception by alpha-1 power during stimulation and at rest. *Clin. Neurophysiol.* **123**, 605–612. <https://doi.org/10.1016/j.clinph.2011.08.006>.
124. Tan, L.L., Oswald, M.J., and Kuner, R. (2021). Neurobiology of brain oscillations in acute and chronic pain. *Trends Neurosci.* **44**, 629–642. <https://doi.org/10.1016/j.tins.2021.05.003>.
125. Li, Z., Zhang, L., Zeng, Y., Zhao, Q., and Hu, L. (2023). Gamma-band oscillations of pain and nociception: a systematic review and meta-analysis of human and rodent studies. *Neurosci. Biobehav. Rev.* **146**, 105062. <https://doi.org/10.1016/j.neubiorev.2023.105062>.
126. Wang, H., Guo, Y., Tu, Y., Peng, W., Lu, X., Bi, Y., Iannetti, G.D., and Hu, L. (2023). Neural processes responsible for the translation of sustained nociceptive inputs into subjective pain experience. *Cereb. Cortex* **33**, 634–650. <https://doi.org/10.1093/cercor/bhac090>.
127. Caston, R.M., Smith, E.H., Davis, T.S., Singh, H., Rahimpour, S., and Rolston, J.D. (2023). Characterization of spatiotemporal dynamics of binary and graded tonic pain in humans using intracranial recordings. *bioRxiv*. <https://doi.org/10.1101/2023.03.08.531576>.
128. Mulders, D., de Bodt, C., Lejeune, N., Courtin, A., Liberati, G., Verleysen, M., and Mouraux, A. (2020). Dynamics of the perception and EEG signals triggered by tonic warm and cool stimulation. *PLoS One* **15**, e0231698. <https://doi.org/10.1371/journal.pone.0231698>.
129. Modares-Haghighi, P., Boostani, R., Nami, M., and Sanei, S. (2021). Quantification of pain severity using EEG-based functional connectivity. *Biomed. Signal Process Control* **69**, 102840. <https://doi.org/10.1016/j.bspc.2021.102840>.
130. Furman, A.J., Meeker, T.J., Rietschel, J.C., Yoo, S., Muthulingam, J., Prokhorenko, M., Keaser, M.L., Goodman, R.N., Mazaheri, A., and Seminowicz, D.A. (2018). Cerebral peak alpha frequency predicts individual differences in pain sensitivity. *Neuroimage* **167**, 203–210. <https://doi.org/10.1016/j.neuroimage.2017.11.042>.
131. Furman, A.J., Thapa, T., Summers, S.J., Cavaleri, R., Fogarty, J.S., Steiner, G.Z., Schabrun, S.M., and Seminowicz, D.A. (2019). Cerebral peak alpha frequency reflects average pain severity in a human model of sustained, musculoskeletal pain. *J. Neurophysiol.* **122**, 1784–1793. <https://doi.org/10.1152/jn.00279.2019>.
132. Furman, A.J., Prokhorenko, M., Keaser, M.L., Zhang, J., Chen, S., Mazaheri, A., and Seminowicz, D.A. (2020). Sensorimotor peak alpha frequency is a reliable biomarker of prolonged pain sensitivity. *Cereb. Cortex* **30**, 6069–6082. <https://doi.org/10.1093/cercor/bhaa124>.
133. Chowdhury, N.S., Bi, C., Furman, A.J., Chiang, A.K., Skippen, P., Si, E., Millard, S.K., Margerison, S.M., Spies, D., Keaser, M.L., et al. (2024). A novel cortical biomarker signature accurately and reliably predicts individual pain sensitivity: the PREDICT longitudinal analytical validation study. *medRxiv*. <https://doi.org/10.1101/2024.06.16.24309005>.
134. Kaneshiro, B., Nguyen, D.T., Norcia, A.M., Dmochowski, J.P., and Berger, J. (2024). Inter-subject correlation of electroencephalographic and behavioural responses reflects time-varying engagement with natural music. *Eur. J. Neurosci.* **59**, 3162–3183. <https://doi.org/10.1111/ejn.16324>.
135. Cauda, F., Palermo, S., Costa, T., Torta, R., Duca, S., Vercelli, U., Geminiani, G., and Torta, D.M.E. (2014). Gray matter alterations in chronic pain: a network-oriented meta-analytic approach. *Neuroimage. Clin.* **4**, 676–686. <https://doi.org/10.1016/j.nicl.2014.04.007>.
136. Baliki, M.N., Geha, P.Y., Fields, H.L., and Apkarian, A.V. (2010). Predicting value of pain and analgesia: nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. *Neuron* **66**, 149–160. <https://doi.org/10.1016/j.neuron.2010.03.002>.
137. López-Solà, M., Woo, C.W., Pujol, J., Deus, J., Harrison, B.J., Monfort, J., and Wager, T.D. (2017). Towards a neurophysiological signature for fibromyalgia. *Pain* **158**, 34–47. <https://doi.org/10.1097/j.pain.0000000000000707>.
138. Tu, Y., Jung, M., Gollub, R.L., Napadow, V., Gerber, J., Ortiz, A., Lang, C., Mawla, I., Shen, W., Chan, S.T., et al. (2019). Abnormal medial prefrontal cortex functional connectivity and its association with clinical symptoms in chronic low back. *Pain* **160**, 1308–1318. <https://doi.org/10.1097/j.pain.0000000000001507>.
139. Tu, Y., Fu, Z., Mao, C., Falahpour, M., Gollub, R.L., Park, J., Wilson, G., Napadow, V., Gerber, J., Chan, S.T., et al. (2020). Distinct thalamocortical network dynamics are associated with the pathophysiology of chronic low back pain. *Nat. Commun.* **11**, 3948. <https://doi.org/10.1038/s41467-020-17788-z>.
140. Chong, C.D., Gaw, N., Fu, Y., Li, J., Wu, T., and Schwedt, T.J. (2017). Migraine classification using magnetic resonance imaging resting-state functional connectivity data. *Cephalalgia* **37**, 828–844. <https://doi.org/10.1177/0333102416652091>.
141. Schwedt, T.J., Chong, C.D., Wu, T., Gaw, N., Fu, Y., and Li, J. (2015). Accurate classification of chronic migraine via brain magnetic resonance imaging. *Headache* **55**, 762–777. <https://doi.org/10.1111/head.12584>.
142. Zhang, Q., Wu, Q., Zhang, J., He, L., Huang, J., Zhang, J., Huang, H., and Gong, Q. (2016). Discriminative analysis of migraine without aura: using functional and structural MRI with a multi-feature classification approach. *PLoS One* **11**, e0163875. <https://doi.org/10.1371/journal.pone.0163875>.
143. Apkarian, A.V., Sosa, Y., Sonty, S., Levy, R.M., Harden, R.N., Parrish, T.B., and Gitelman, D.R. (2004). Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *J. Neurosci.* **24**, 10410–10415. <https://doi.org/10.1523/JNEUROSCI.2541-04.2004>.
144. Ung, H., Brown, J.E., Johnson, K.A., Younger, J., Hush, J., and Mackey, S. (2014). Multivariate classification of structural MRI data detects chronic low back pain. *Cereb. Cortex* **24**, 1037–1044. <https://doi.org/10.1093/cercor/bhs378>.
145. Labus, J.S., Van Horn, J.D., Gupta, A., Alaverdyan, M., Torgerson, C., Ashe-McNalley, C., Irimia, A., Hong, J.Y., Naliboff, B., Tillisch, K., and Mayer, E.A. (2015). Multivariate morphological brain signatures predict patients with chronic abdominal pain from healthy control subjects. *Pain* **156**, 1545–1554. <https://doi.org/10.1097/j.pain.0000000000000196>.
146. Datta, R., Aguirre, G.K., Hu, S., Detre, J.A., and Cucchiara, B. (2013). Interictal cortical hyperresponsiveness in migraine is directly related to the presence of aura. *Cephalalgia* **33**, 365–374. <https://doi.org/10.1177/0333102412474503>.
147. Tedeschi, G., Russo, A., Conte, F., Corbo, D., Caiazzo, G., Giordano, A., Conforti, R., Esposito, F., and Tessitore, A. (2016). Increased interictal visual network connectivity in patients with migraine with aura. *Cephalalgia* **36**, 139–147. <https://doi.org/10.1177/0333102415584360>.
148. Liu, J., Quan, S., Zhao, L., Yuan, K., Wang, Y., Zhang, Y., Wang, Z., Sun, M., and Hu, L. (2023). Evaluation of a clustering approach to define distinct subgroups of patients with migraine to select electroacupuncture treatments. *Neurology* **101**, e699–e709. <https://doi.org/10.1212/WNL.0000000000207484>.
149. Lee, J., Mawla, I., Kim, J., Loggia, M.L., Ortiz, A., Jung, C., Chan, S.T., Gerber, J., Schmithorst, V.J., Edwards, R.R., et al. (2019). Machine learning based prediction of clinical pain using multimodal neuroimaging and autonomic metrics. *Pain* **160**, 550–560. <https://doi.org/10.1097/j.pain.0000000000001417>.
150. Zhang, B., Jung, M., Tu, Y., Gollub, R., Lang, C., Ortiz, A., Park, J., Wilson, G., Gerber, J., Mawla, I., et al. (2019). Identifying brain regions associated with the neuropathology of chronic low back pain: a resting-state amplitude of low-frequency fluctuation study. *Br. J. Anaesth.* **123**, E303–E311. <https://doi.org/10.1016/j.bja.2019.02.021>.
151. Mansour, A.R., Baliki, M.N., Huang, L., Torbey, S., Herrmann, K.M., Schnitzer, T.J., and Apkarian, V.A. (2013). Brain white matter structural properties predict transition to chronic pain. *Pain* **154**, 2160–2168. <https://doi.org/10.1016/j.pain.2013.06.044>.
152. Vachon-Preseu, E., Tetreault, P., Petre, B., Huang, L., Berger, S.E., Torbey, S., Baria, A.T., Mansour, A.R., Hashmi, J.A., Griffith, J.W., et al. (2016).

- Corticolimbic anatomical characteristics predetermine risk for chronic pain. *Brain* 139, 1958–1970. <https://doi.org/10.1093/brain/aww100>.
153. Kutch, J.J., Labus, J.S., Harris, R.E., Martucci, K.T., Farmer, M.A., Fenske, S., Fling, C., Ichesco, E., Peltier, S., Petre, B., et al. (2017). Resting-state functional connectivity predicts longitudinal pain symptom change in urologic chronic pelvic pain syndrome: a MAPP network study. *Pain* 158, 1069–1082. <https://doi.org/10.1097/j.pain.0000000000000886>.
154. Tétreault, P., Mansour, A., Vachon-Pressseau, E., Schnitzer, T.J., Apkarian, A.V., and Baliki, M.N. (2016). Brain connectivity predicts placebo response across chronic pain clinical trials. *PLoS Biol.* 14, e1002570. <https://doi.org/10.1371/journal.pbio.1002570>.
155. Ploner, M., and May, E.S. (2018). Electroencephalography and magnetoencephalography in pain research—current state and future perspectives. *Pain* 159, 206–211. <https://doi.org/10.1097/j.pain.0000000000001087>.
156. Lenoir, D., Willaert, W., Coppieters, I., Malfliet, A., Ickmans, K., Nijs, J., Vonck, K., Meeus, M., and Cagnie, B. (2020). Electroencephalography during nociceptive stimulation in chronic pain patients: a systematic review. *Pain Med.* 21, 3413–3427. <https://doi.org/10.1093/pm/pnaa131>.
157. Caty, G., Hu, L., Legrain, V., Plaghki, L., and Mouraux, A. (2013). Psychophysical and electrophysiological evidence for nociceptive dysfunction in complex regional pain syndrome. *Pain* 154, 2521–2528. <https://doi.org/10.1016/j.pain.2013.07.038>.
158. de Tommaso, M., Nolano, M., Iannone, F., Vecchio, E., Ricci, K., Lorenzo, M., Delussi, M., Girolamo, F., Lavolpe, V., Provitera, V., et al. (2014). Update on laser-evoked potential findings in fibromyalgia patients in light of clinical and skin biopsy features. *J. Neurol.* 261, 461–472. <https://doi.org/10.1007/s00415-013-7211-9>.
159. Fernandes-Magalhaes, R., Ferrera, D., Peláez, I., Martín-Buro, M.C., Capiro, A., De Lahoz, M.E., Barjola, P., and Mercado, F. (2022). Neural correlates of the attentional bias towards pain-related faces in fibromyalgia patients: an ERP study using a dot-probe task. *Neuropsychologia* 166, 108141. <https://doi.org/10.1016/j.neuropsychologia.2021.108141>.
160. Zebhauser, P.T., Hohn, V.D., and Ploner, M. (2023). Resting-state electroencephalography and magnetoencephalography as biomarkers of chronic pain: a systematic review. *Pain* 164, 1200–1221. <https://doi.org/10.1097/j.pain.0000000000002825>.
161. Mussigmann, T., Bardel, B., and Lefaucheur, J.P. (2022). Resting-state electroencephalography (EEG) biomarkers of chronic neuropathic pain. A systematic review. *Neuroimage* 258, 119351. <https://doi.org/10.1016/j.neuroimage.2022.119351>.
162. Ta Dinh, S., Nickel, M.M., Tiemann, L., May, E.S., Heitmann, H., Hohn, V.D., Edenharter, G., Utpadel-Fischler, D., Tölle, T.R., Sauseng, P., et al. (2019). Brain dysfunction in chronic pain patients assessed by resting-state electroencephalography. *Pain* 160, 2751–2765. <https://doi.org/10.1097/j.pain.0000000000001666>.
163. Topaz, L.S., Frid, A., Granovsky, Y., Zubidat, R., Crystal, S., Buxbaum, C., Bosak, N., Hadad, R., Domany, E., Alon, T., et al. (2023). Electroencephalography functional connectivity—a biomarker for painful polyneuropathy. *Eur. J. Neurol.* 30, 204–214. <https://doi.org/10.1111/ene.15575>.
164. Frid, A., Shor, M., Shifrin, A., Yarnitsky, D., and Granovsky, Y. (2020). A biomarker for discriminating between migraine with and without aura: machine learning on functional connectivity on resting-state EEGs. *Ann. Biomed. Eng.* 48, 403–412. <https://doi.org/10.1007/s10439-019-02357-3>.
165. Zhu, B., Coppola, G., and Shoaran, M. (2019). Migraine classification using somatosensory evoked potentials. *Cephalalgia* 39, 1143–1155. <https://doi.org/10.1177/0333102419839975>.
166. Judit, A., Sándor, P.S., and Schoenen, J. (2000). Habituation of visual and intensity dependence of auditory evoked cortical potentials tends to normalize just before and during the migraine attack. *Cephalalgia* 20, 714–719. <https://doi.org/10.1046/j.1468-2982.2000.00122.x>.
167. Teixeira, P.E.P., Pacheco-Barrios, K., Uygur-Kucukseymen, E., Machado, R.M., Balbuena-Pareja, A., Giannoni-Luza, S., Luna-Cuadros, M.A., Cardenas-Rojas, A., Gonzalez-Mego, P., Mejia-Pando, P.F., et al. (2022). Electroencephalography signatures for conditioned pain modulation and pain perception in nonspecific chronic low back pain—an exploratory study. *Pain Med.* 23, 558–570. <https://doi.org/10.1093/pm/pnab293>.
168. Bjork, M.H., Stovner, L.J., Engstrom, M., Stjern, M., Hagen, K., and Sand, T. (2009). Interictal quantitative EEG in migraine: a blinded controlled study. *J. Headache Pain* 10, 331–339. <https://doi.org/10.1007/s10194-009-0140-4>.
169. Di Pietro, F., Macey, P.M., Rae, C.D., Alshelhi, Z., Macefield, V.G., Vickers, E.R., and Henderson, L.A. (2018). The relationship between thalamic GABA content and resting cortical rhythm in neuropathic pain. *Hum. Brain Mapp.* 39, 1945–1956. <https://doi.org/10.1002/hbm.23973>.
170. Schuurman, B.B., Vossen, C.J., van Amelsvoort, T.A.M.J., and Lousberg, R.L. (2023). Does baseline EEG activity differ in the transition to or from a chronic pain state? A longitudinal study. *Pain Pract.* 23, 479–492. <https://doi.org/10.1111/papr.13204>.
171. Hsiao, F.J., Chen, W.T., Liu, H.Y., Wang, Y.F., Chen, S.P., Lai, K.L., Hope Pan, L.L., Coppola, G., and Wang, S.J. (2021). Migraine chronification is associated with beta-band connectivity within the pain-related cortical regions: a magnetoencephalographic study. *Pain* 162, 2590–2598. <https://doi.org/10.1097/j.pain.0000000000002255>.
172. Hsiao, F.J., Wang, S.J., Lin, Y.Y., Fuh, J.L., Ko, Y.C., Wang, P.N., and Chen, W.T. (2018). Somatosensory gating is altered and associated with migraine chronification: a magnetoencephalographic study. *Cephalalgia* 38, 744–753. <https://doi.org/10.1177/0333102417712718>.
173. Rustamov, N., Wilson, E.A., Fogarty, A.E., Crock, L.W., Leuthardt, E.C., and Haroutounian, S. (2022). Relief of chronic pain associated with increase in midline frontal theta power. *Pain Rep.* 7, e1040. <https://doi.org/10.1097/pr9.0000000000001040>.
174. Hunter, A.M., Leuchter, A.F., Cook, I.A., Abrams, M., Siegman, B.E., Furst, D.E., and Chappell, A.S. (2009). Brain functional changes and duloxetine treatment response in fibromyalgia: a pilot study. *Pain Med.* 10, 730–738. <https://doi.org/10.1111/j.1526-4637.2009.00614.x>.
175. Graversen, C., Olesen, S.S., Olesen, A.E., Steimle, K., Farina, D., Wilder-Smith, O.H.G., Bouwense, S.A.W., van Gooor, H., and Drewes, A.M. (2012). The analgesic effect of pregabalin in patients with chronic pain is reflected by changes in pharmacoelectroencephalographic indices. *Br. J. Clin. Pharmacol.* 73, 363–372. <https://doi.org/10.1111/j.1365-2125.2011.04104.x>.
176. Jensen, M.P., Sherlin, L.H., Fregni, F., Gianas, A., Howe, J.D., and Hakimian, S. (2014). Baseline brain activity predicts response to neuromodulatory pain treatment. *Pain Med.* 15, 2055–2063. <https://doi.org/10.1111/pme.12546>.
177. Ahn, S., Prim, J.H., Alexander, M.L., McCulloch, K.L., and Fröhlich, F. (2019). Identifying and engaging neuronal oscillations by transcranial alternating current stimulation in patients with chronic low back pain: a randomized, crossover, double-blind, sham-controlled pilot study. *J. Pain* 20, 277.e1–277.e11. <https://doi.org/10.1016/j.jpain.2018.09.004>.
178. Tang, B., Meng, W., Hägg, S., Burgess, S., and Jiang, X. (2022). Reciprocal interaction between depression and pain: results from a comprehensive bidirectional Mendelian randomization study and functional annotation analysis. *Pain* 163, E40–E48. <https://doi.org/10.1097/j.pain.0000000000002305>.
179. Higgins, D.M., Martin, A.M., Baker, D.G., Vasterling, J.J., and Risbrough, V. (2018). The relationship between chronic pain and neurocognitive function—a systematic review. *Clin. J. Pain* 34, 262–275. <https://doi.org/10.1097/ajp.0000000000000536>.
180. Phelps, C.E., Navratilova, E., and Porreca, F. (2021). Cognition in the chronic pain experience: preclinical insights. *Trends Cogn. Sci.* 25, 365–376. <https://doi.org/10.1016/j.tics.2021.01.001>.
181. Price, D.D. (2000). Psychological and neural mechanisms of the affective dimension of pain. *Science* 288, 1769–1772. <https://doi.org/10.1126/science.288.5472.1769>.
182. Koyama, T., McHaffie, J.G., Laurienti, P.J., and Coghill, R.C. (2005). The subjective experience of pain: where expectations become reality. *Proc.*

- Natl. Acad. Sci. USA 102, 12950–12955. <https://doi.org/10.1073/pnas.0408576102>.
183. Rainville, P., Duncan, G.H., Price, D.D., Carrier, B., and Bushnell, M.C. (1997). Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* 277, 968–971.
184. Corder, G., Ahanonu, B., Grewe, B.F., Wang, D., Schnitzer, M.J., and Scherrer, G. (2019). An amygdalar neural ensemble that encodes the unpleasantness of pain. *Science* 363, 276–281. <https://doi.org/10.1126/science.aap8586>.
185. Talbot, K., Madden, V.J., Jones, S.L., and Moseley, G.L. (2019). The sensory and affective components of pain: are they differentially modifiable dimensions or inseparable aspects of a unitary experience? A systematic review. *Br. J. Anaesth.* 123, e263–e272. <https://doi.org/10.1016/j.bja.2019.03.033>.
186. Apkarian, A.V., Sosa, Y., Krauss, B.R., Thomas, P.S., Fredrickson, B.E., Levy, R.E., Harden, R.N., and Chialvo, D.R. (2004). Chronic pain patients are impaired on an emotional decision-making task. *Pain* 108, 129–136. <https://doi.org/10.1016/j.pain.2003.12.015>.
187. Moriarty, O., McGuire, B.E., and Finn, D.P. (2011). The effect of pain on cognitive function: a review of clinical and preclinical research. *Prog. Neurobiol.* 93, 385–404. <https://doi.org/10.1016/j.pneurobio.2011.01.002>.
188. Zhao, W., Zhao, L., Chang, X., Lu, X., and Tu, Y. (2023). Elevated dementia risk, cognitive decline, and hippocampal atrophy in multisite chronic pain. *Proc. Natl. Acad. Sci. USA* 120, e2215192120. <https://doi.org/10.1073/pnas.2215192120>.
189. Kohoutova, L., Heo, J., Cha, S., Lee, S., Moon, T., Wager, T.D., and Woo, C.W. (2020). Toward a unified framework for interpreting machine-learning models in neuroimaging. *Nat. Protoc.* 15, 1399–1435. <https://doi.org/10.1038/s41596-019-0289-5>.
190. Mouraux, A., and Iannetti, G.D. (2018). The search for pain biomarkers in the human brain. *Brain* 141, 3290–3307. <https://doi.org/10.1093/brain/awy281>.
191. Vigotsky, A.D., Iannetti, G.D., and Apkarian, A.V. (2024). Mental state decoders: game-changers or wishful thinking? *Trends Cogn. Sci.* 28, 884–895. <https://doi.org/10.1016/j.tics.2024.06.004>.
192. Berman, T., Cushing, C., Manuel, S., Vachon-Preseu, É., Cortese, A., Kawato, M., Woo, C.-W., Wager, T.D., Lau, H., Roy, M., and Tascheriau-Dumouchel, V. (2023). Modulating subjective pain perception with decoded MNI-space neurofeedback. *bioRxiv*. <https://doi.org/10.1101/2023.10.25.563972>.
193. Paul-Murphy, J., Ludders, J.W., Robertson, S.A., Gaynor, J.S., Hellyer, P.W., and Wong, P.L. (2004). The need for a cross-species approach to the study of pain in animals. *J. Am. Vet. Med. Assoc.* 224, 692–697. <https://doi.org/10.2460/javma.2004.224.692>.
194. Mogil, J.S., Davis, K.D., and Derbyshire, S.W. (2010). The necessity of animal models in pain research. *Pain* 151, 12–17. <https://doi.org/10.1016/j.pain.2010.07.015>.
195. Da Silva, J.T., and Seminowicz, D.A. (2019). Neuroimaging of pain in animal models: a review of recent literature. *Pain Rep.* 4, e732. <https://doi.org/10.1097/PR9.0000000000000732>.
196. Buzsaki, G., Logothetis, N., and Singer, W. (2013). Scaling brain size, keeping timing: evolutionary preservation of brain rhythms. *Neuron* 80, 751–764. <https://doi.org/10.1016/j.neuron.2013.10.002>.
197. Yue, L., Iannetti, G.D., and Hu, L. (2020). The neural origin of nociceptive-induced gamma-band oscillations. *J. Neurosci.* 40, 3478–3490. <https://doi.org/10.1523/jneurosci.0255-20.2020>.
198. Li, Z., Zhang, L., Zhang, F., Yue, L., and Hu, L. (2024). Deciphering Authentic Nociceptive Thalamic Responses in Rats. *Research* 7, 0348. <https://doi.org/10.34133/research.0348>.
199. Tracey, I., Woolf, C.J., and Andrews, N.A. (2019). Composite pain biomarker signatures for objective assessment and effective treatment. *Neuron* 101, 783–800. <https://doi.org/10.1016/j.neuron.2019.02.019>.
200. Lee, D.H., Lee, S., and Woo, C.W. (2023). Decoding pain: uncovering the factors that affect performance of neuroimaging-based pain models. *bioRxiv*. <https://doi.org/10.1101/2023.12.22.573021>.
201. Ho, S.Y., Phua, K., Wong, L., and Bin Goh, W.W. (2020). Extensions of the external validation for checking learned model interpretability and generalizability. *Patterns (N Y)* 1, 100129. <https://doi.org/10.1016/j.patter.2020.100129>.
202. Lopez-Sola, M., Pujol, J., Monfort, J., Deus, J., Blanco-Hinojo, L., Harrison, B.J., and Wager, T.D. (2022). The neurologic pain signature responds to nonsteroidal anti-inflammatory treatment vs placebo in knee osteoarthritis. *Pain Rep* 7, e986. <https://doi.org/10.1097/PR9.0000000000000986>.
203. Greene, A.S., Gao, S., Scheinost, D., and Constable, R.T. (2018). Task-induced brain state manipulation improves prediction of individual traits. *Nat. Commun.* 9, 2807. <https://doi.org/10.1038/s41467-018-04920-3>.
204. Finn, E.S. (2021). Is it time to put rest to rest? *Trends Cogn. Sci.* 25, 1021–1032. <https://doi.org/10.1016/j.tics.2021.09.005>.
205. Mackey, S., Greeley, H.T., and Martucci, K.T. (2019). Neuroimaging-based pain biomarkers: definitions, clinical and research applications, and evaluation frameworks to achieve personalized pain medicine. *Pain Rep.* 4, e762. <https://doi.org/10.1097/PR9.0000000000000762>.
206. Schulz, M.A., Bzdok, D., Haufe, S., Haynes, J.D., and Ritter, K. (2024). Performance reserves in brain-imaging-based phenotype prediction. *Cell Rep.* 43, 113597. <https://doi.org/10.1016/j.celrep.2023.113597>.
207. Khan, H.S., and Stroman, P.W. (2015). Inter-individual differences in pain processing investigated by functional magnetic resonance imaging of the brainstem and spinal cord. *Neuroscience* 307, 231–241. <https://doi.org/10.1016/j.neuroscience.2015.08.059>.
208. Rolke, R., Baron, R., Maier, C., Tölle, T.R., Treede, D.R., Beyer, A., Binder, A., Birbaumer, N., Birklein, F., Bötefür, I.C., et al. (2006). Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values (vol 123, pg 231, 2006). *Pain* 125, 197. <https://doi.org/10.1016/j.pain.2006.09.025>.
209. Becker, S., Löffler, M., and Seymour, B. (2020). Reward enhances pain discrimination in humans. *Psychol. Sci.* 31, 1191–1199. <https://doi.org/10.1177/0956797620939588>.
210. Lotsch, J., Ultsch, A., Mayer, B., and Krings, D. (2022). Artificial intelligence and machine learning in pain research: a data scientometric analysis. *Pain Rep* 7, e1044. <https://doi.org/10.1097/PR9.0000000000001044>.
211. El-Tallawy, S.N., Pergolizzi, J.V., Vasiliu-Feltes, I., Ahmed, R.S., Le-Quang, J.K., El-Tallawy, H.N., Varrassi, G., and Naguib, M.S. (2024). Incorporation of "artificial intelligence" for objective pain assessment: a comprehensive review. *Pain Ther.* 13, 293–317. <https://doi.org/10.1007/s40122-024-00584-8>.
212. Abrol, A., Fu, Z., Salman, M., Silva, R., Du, Y., Plis, S., and Calhoun, V. (2021). Deep learning encodes robust discriminative neuroimaging representations to outperform standard machine learning. *Nat. Commun.* 12, 353. <https://doi.org/10.1038/s41467-020-20655-6>.
213. Schulz, M.A., Yeo, B.T.T., Vogelstein, J.T., Mourao-Miranada, J., Kather, J.N., Kording, K., Richards, B., and Bzdok, D. (2020). Different scaling of linear models and deep learning in UKBiobank brain images versus machine-learning datasets. *Nat. Commun.* 11, 4238. <https://doi.org/10.1038/s41467-020-18037-z>.
214. Quidé, Y., Jahanshad, N., Andoh, J., Antoniou, G., Apkarian, A.V., Ashar, Y.K., Badran, B.W., Baird, C.L., Baxter, L., Bell, T.R., et al. (2024). ENIGMA-Chronic Pain: a worldwide initiative to identify brain correlates of chronic pain. *Pain*. <https://doi.org/10.1097/j.pain.0000000000003317>.