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A review on the ongoing quest for a pain signature in the human brain

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KEYWORDS

pain signature, neuroimaging, machine learning, saliency, MVPA, specificity

ABSTRACT

Developing an objective biomarker for pain assessment is crucial for understanding neural coding mechanisms of pain in the human brain as well as for effective treatment of pain disorders. Neuroimaging techniques have been proven to be powerful tools in the ongoing quest for a pain signature in the human brain. Although there is still a long way to go before achieving a truly successful pain signature based on neuroimaging techniques, important progresses have been made through great efforts in the last two decades by the Pain Society. Here, we focus on neural responses to transient painful stimuli in healthy people, and review the relevant studies on the identification of a neuroimaging signature for pain.

1 Introduction

Pain is a complex and subjective experience that consists of sensory, emotional, cognitive and social components [1]. When a noxious stimulus was detected by primary sensory neurons such as A δ - and C-fiber nociceptors in the skin, the signal will

be transmitted by specific transduction machinery from primary afferents to the spinal cord, then relayed to the brain stem, subcortical nuclei and cerebral cortex where pain emerges as a perception [2–5]. People who are born insensitive to pain cannot behave timely against dangerous conditions and are often caught in life-threatening

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situations [6–8]. Therefore, pain is crucial for survival as it alarms people of danger in the environment, injury or presence of disease. Nevertheless, pain produces unpleasant and aversive emotions, and it often plays an unfavorable role in modern society especially when it becomes chronic. It is well known that pain is one of the most common symptoms of many clinical diseases, demonstrating the importance of understanding how pain is generated for developing effective treatments for pain disorders. However, the underlying neural mechanisms of pain perception remain unclear, especially in the brain.

Understanding the neural mechanisms of pain perception is also the foundation of objective pain assessment. Indeed, in both scientific research and medical interventions, the detection and measurement of pain mainly rely on one's oral report of pain [9, 10]. Such oral report is highly subjective, prone to response biases, and is thus often considered as "inadequate", "misleading" and "unreliable" [11–13]. This could be one reason contributing to the current crisis of opioid addiction related to clinical pain management in the United States [13]. In addition, it is difficult or practically impossible to collect oral reports of pain in some populations such as young children or patients with language disorders, dementia or minimally conscious state. For these reasons, the availability of an objective means for pain assessment that bypasses the subjective report would be of paramount importance, as highlighted in the guidelines on neuropathic pain assessment of European Federation of Neurological Societies [9]. To achieve this goal, in the past decade or so, researchers have suggested various techniques which may help identify potential objective measures of pain (i.e., pain biomarkers), such as skin biopsy, microneurography, quantitative sensory testing, indirect physiology and neuroimaging [3, 4, 12, 14–18]. In particular, neuroimaging, as a non-invasive technique

that can explore pain-induced neural activity in the human brain, has received a lot of attention and become a popular and promising tool in the search for pain biomarkers. An array of neuroimaging techniques have been used to study brain mechanisms of acute and chronic pain, including electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET), and also magnetic resonance imaging (MRI)-related methods such as blood-oxygen-level-dependent (BOLD) functional MRI (fMRI), structural MRI, diffusion MRI, arterial spin labeling (ASL) and MR spectroscopy (MRS). All these methods allow for a system-level investigation of neural representations of pain, and can be used to develop predictive biomarkers for components related to pain [3, 4, 12, 19–23].

Therefore, in the present review, we focus on neuroimaging studies, and provide a review on the efforts of identifying a pain signature in the following sections. First, we elaborate on the specificity issue in most previous studies and highlight the necessity of including saliency/intensity matched non-painful stimuli as a control condition when identifying pain-specific brain activities. Second, we review on the studies in which stimulus saliency/intensity were matched between painful and non-painful conditions when identifying brain regions or EEG components preferentially responding to pain. Third, we highlight the machine learning techniques as a promising tool for the identification of neural representations specific to pain. Last, we summarize the main messages from the reviewed studies in the closing remarks.

2 A true signature for pain should be specific to pain processing

Pain, as a conscious sensation like any other unique percept, is a product of neural activities in the brain [24]. Therefore, to be distinguished

from non-painful sensations, painful percepts must have a specific neurophysiological representation in the brain [20]. In fact, understanding how pain is specifically encoded in the human brain is not only important for developing reliable and objective measures for pain evaluation but also for developing effective treatments for pain. However, it still remains a fundamental challenge in the Pain Society. A large number of neuroimaging studies have attempted to image brain activities elicited by noxious stimuli, hoping to identify the neural representations of pain in the human brain, and have made important progress [25]. All these studies can be largely summarized in two types—one type of studies utilized the high spatial resolution of fMRI or PET to study the spatial pattern of pain-elicited brain activations, whereas the other type of studies utilized the high temporal resolution of EEG to study the temporal characteristics of pain-elicited brain activity.

In the spatial domain, extensive fMRI and PET studies have confirmed that painful stimuli robustly elicit responses in a large brain network composed of several spatially distributed areas considered to be involved in sensory, affective and cognitive processing [2, 26–40]. Melzack first described this set of brain regions as the “neuromatrix” [41], which is later more commonly referred to as the “pain matrix”, mainly including the thalamus, the primary and secondary somatosensory cortices (S1 and S2), the anterior/mid cingulate cortex (ACC/MCC) and the insula. It has been suggested that these brain areas can be divided into the medial pain system and the lateral pain system [42]. The lateral pain system is thought to be predominantly involved in sensory discriminative aspect of pain, mainly including the S1 and S2 that receive input from the lateral thalamic nuclei [2]. The medial pain system is considered to be predominantly involved in the emotional-cognitive aspect of pain, mainly

including the ACC/MCC which receives its major afference from the medial thalamic nuclei. The insula has been implicated in the sensory as well as in the emotional-cognitive aspects of pain processing and is thus considered to be part of both the medial and the lateral pain systems [40].

In the temporal domain, by activating cutaneous A δ and C nociceptors, a number of temporal components can be detected by event-related potentials (ERPs) extracted from EEG signals [43]. Notably, laser stimuli are considered to be the optimal nociceptive stimuli, because laser stimuli can selectively elicit painful pinprick sensation mediated by the activation of A δ nociceptors, without the contamination by activations of A β mechanoreceptors [44, 45], they are commonly used to elicit painful sensations. Many studies have characterized the temporal aspects of pain-elicited brain activities using the transient brain responses (i.e., ERPs) evoked by laser stimuli, named laser-evoked potentials (LEPs). The earliest response detected by LEPs is a small negative component (N1) wave, peaking at ~160 ms and maximal over the temporal region contralateral to the stimulated side [46]. The largest part of LEPs is a negative-positive biphasic wave (N2-P2), peaking at ~200–350 ms after stimulus onset and maximal at the scalp vertex [47]. Source analyses showed that these LEP components could be modeled by a combination of brain areas composing the “pain matrix” [48], which were further confirmed by consistent results obtained using subdural [49–51] and intracerebral recordings [52–54]. It has also been shown that features of LEPs can be used to successfully predict pain perception [18]. It should be noted that the aforementioned LEPs are mostly related to A δ input (A δ -LEPs) rather than C-fiber input (C-LEPs). Comparing with A δ -LEPs, temporal components related to the activation of C-fibers are much more difficult to detect. However, two studies have showed that, although much weaker,

the C-LEPs can also be reliably detected when using optimal stimulus parameters such as sufficient number of stimuli (e.g., ≥ 80 stimuli) and restricted stimulated area [55, 56]. Although it has been confirmed that the C-LEPs also show a somatotopic representation in S1 [56], the relationship of the stimulus intensity with the C-LEPs seems more complex than with the A δ -LEPs (that is, the correlation between the amplitude of C-LEPs and stimulus intensity changes from positive when the stimulus intensity is relatively low to negative when the stimulus intensity is relatively high) [55].

The “pain matrix” detected by fMRI/PET and the temporal components detected by LEPs have long been assumed to reflect the neural representation of transient pain (for a review see [57]), because (1) the activation of the “pain matrix” or the LEP components seem to encode pain intensity as their amplitudes were found to be strongly correlated with the intensity of painful stimuli in most experimental paradigms [58–65]; (2) direct stimulation of particular “pain matrix” regions such as the S2 or insula with intracerebral electrodes could elicit painful sensation in epileptic patients [66, 67]; and (3) the activity of particular regions of the “pain matrix” can be modulated by adjusting different aspects of pain experience (such as pain intensity and pain unpleasantness), for example, it was shown that hypnotic modulation of pain intensity could modulate the pain-elicited activity in S1, whereas hypnotic modulation of pain unpleasantness could modulate the pain-elicited activity in ACC [68, 69]. Based on these findings, some researchers started to use the activation of the “pain matrix” as a “pain signature” to detect whether a person is in pain. For example, it has been suggested that patients in minimally conscious state were able to feel pain because the “pain matrix” was activated by nociceptive stimuli in these patients [32], or social rejection (or social pain) might hurt

similarly as physical pain because some key regions in the “pain matrix” such as ACC or even S2 were activated by social rejection [70, 71]. However, as highlighted in several studies and review papers [12, 57, 72, 73], the above conclusions (e.g., patients in minimally conscious state were found to be able to feel pain because the “pain matrix” was activated in their brain) were made based on reverse inference which, although commonly used in neuroimaging studies, is logically flawed. Indeed, it would be safe to conclude whether a person is in pain based on whether the “pain matrix” is activated if and only if the activation of the “pain matrix” is specific to pain. However, the specificity issue was largely ignored in most previous studies but has been brought into attention in recent years.

It has been hotly debated whether or not neuroimaging-recorded brain responses elicited by transient painful stimuli is specific to pain processing in recent years. This is caused by increasing evidence showing that non-painful stimuli could also elicit very similar brain responses. For example, in the spatial domain with fMRI recordings, Mouraux et al. reported that both painful and non-painful (tactile, auditory, and visual) stimuli activated key regions of the “pain matrix”, especially for painful and tactile stimuli which activated identical brain areas [72]. This finding was later confirmed by another study with a larger sample size and a more rigorous design [64]. Moreover, Salomons et al. recorded fMRI responses to nociceptive stimuli in two patients congenitally insensitive to pain, and found that, although lack of pain perception, the “pain matrix” was also activated in their brain by nociceptive stimuli [74]. These findings indicate that the activation of the “pain matrix” can also be observed when pain is absent. In the temporal domain with EEG recordings, Mouraux et al. applied probabilistic independent component analysis to ERPs elicited by transient nociceptive

(laser), non-nociceptive somatosensory, auditory and visual stimuli, and found that the LEPs could be entirely explained by a combination of multimodal neural activities and somatosensory-specific, but not nociceptive-specific, neural activities [73]. Using depth intracerebral EEG recordings performed in epileptic patients, Liberati et al. reported that both nociceptive stimuli and non-nociceptive vibrotactile, auditory, and visual stimuli elicited consistent local field potentials (LFPs) in the posterior and anterior insular, indicating that nociceptive LFPs recorded from the human insula are not specific to nociception [75]. Furthermore, a series of studies by Iannetti and his colleagues showed that the correlation between the LEP amplitudes and pain intensity can be disrupted by stimulus repetition [76–80]. They showed that, when a train of identical laser stimuli was delivered with a fixed short interval (e.g., 1 Hz), the amplitudes of LEPs (both the vertex and lateral components) elicited by the first stimulus were much larger than those elicited by the subsequent stimuli, although the perceived pain intensity remained roughly the same [80, 81]. This finding, together with the observation from an fMRI study showing that the strength of the activation of most key regions in the “pain matrix” was also correlated with the subjective ratings of stimulus saliency [72], has led to the proposal of a hypothesis that brain responses elicited by transient painful stimuli captured by the “pain matrix” activation or the LEPs reflect multimodal responses such as stimulus saliency rather than pain per se. Indeed, as the saliency of a sensory stimulus is commonly defined as its ability to stand out relative to the background, regardless of its sensory modality [82–85], when a stimulus is repeated and its occurrence is predictable, its novelty reduces and consequently its saliency reduces, which may explain the decreased amplitudes of LEPs. This “saliency hypothesis” may also explain the observation that

the amplitudes of the “pain matrix” activation or the LEPs correlated with stimulus intensity because in most experimental settings, stimulus saliency covaries with stimulus intensity—a more intense stimulus is usually more salient (see Fig. S6 in [86]), and they can only be dissociated in some specific paradigms (e.g., [80]).

Although all these findings question the specificity of the neuroimaging-recorded brain responses analyzed with conventional methods, they by no means imply that pain-specific information cannot be captured by neuroimaging techniques. Instead, they highlight the importance of including saliency-matched non-painful stimuli as a necessary control when identifying neuroimaging markers specific to pain. Non-nociceptive somatosensory stimuli are considered to be the best non-painful control stimuli as they also belong to the somatosensory modality and thus the closest stimuli to pain. Moreover, matching the saliency between painful and non-painful stimuli is particularly important considering that painful stimuli are often more salient than non-painful stimuli [12].

3 Univariate comparisons of brain responses between painful and non-painful stimuli with matched stimulus saliency

Realizing the necessity of the inclusion of saliency-matched non-painful stimuli as a control condition, several attempts have been made to search for pain specific neural activities in both the spatial and temporal domain. In the spatial domain, two recent fMRI studies have compared the brain responses elicited by painful and non-painful stimuli using different saliency-matched strategies. In one study, Horing et al. used skin conductance responses (SCRs) as a measure of stimulus saliency, and compared the fMRI responses to painful heat with saliency-unmatched non-painful heat and with saliency-matched unpleasant sound

[87]. In their study, a brain area would be considered to be preferentially responding to pain if it meets the following four criteria: (1) the effect of painful stimulation should be larger than that of nonpainful heat; (2) the effect of painful stimulation should be larger than that of salience-matched unpleasant sound; (3) the relationship of ratings and fMRI response should be stronger for painful heat than for nonpainful heat; and (4) the positive relationship of pain ratings and fMRI responses should be stronger for painful heat than for salience-matched unpleasant sound. They found that an area in the posterior parietal operculum satisfied all four criteria and thus showed a preference for pain processing [87]. This study made an important progress in identifying brain regions having a preferential role in pain processing by matching saliency between painful and non-painful stimuli. However, as mentioned before, the selected saliency-matching control stimuli were auditory stimuli which do not belong to the somatosensory domain, and thus this study has limited evidence to ascertain whether the identified brain area truly has a preference to pain processing or to general somatosensory processing. Indeed, if a brain area responds more strongly to somatosensory stimuli than to auditory stimuli, but does not have preference to pain processing over tactile processing, such a brain area would still meet these four criteria. Therefore, tactile stimuli, also belonging to somatosensory domain, would be more favorable to serve as control stimuli.

In another fMRI study published at the same time, nociceptive laser heat was chosen as painful stimuli and non-nociceptive electrical stimuli as non-painful control stimuli [64]. Electrical stimuli below the pain threshold are excellent as saliency-matching control stimuli because (1) they activate the A β fibers and thus belong to somatosensory domain like pain, and (2) they are unnatural stimuli and thus are often very salient even

though they are not painful. In this study, stimulus saliency was matched through matching perceived stimulus intensity. More specifically, participants were asked to rate the perceived stimulus intensity after each stimulus and used the recorded perceived intensity as a measure of stimulus saliency because it was experimentally confirmed that stimulus saliency and perceived stimulus intensity are highly correlated and matching one equals matching the other in such paradigm we used (see more details in [86]). To ensure the saliency was rigorously matched between the painful laser and non-painful electrical stimuli, only a subset of stimuli with very similar perceived intensity ratings was selected, and brain responses were compared between them. Both voxel-wise general linear model (GLM) analysis and region-wise model-free analysis were performed to characterize the differences in the brain responses elicited by transient painful and tactile stimuli. Although the results showed that all brain areas activated by painful stimuli were also activated by tactile stimuli, further confirming that the activation of the "pain matrix" is not specific to pain, a set of brain regions showed stronger responses to painful stimuli than to tactile stimuli with strictly matched perceived intensity. These brain regions exhibiting preferential responses to pain include the bilateral opercular cortex, the left supplementary motor area and the right frontal middle and inferior areas. Even when painful stimuli were less intense than tactile stimuli, the right frontal middle area still responded more strongly to painful stimuli, indicating that its responses have strong preference to pain processing and are less dependent on stimulus saliency/intensity [64].

It is worth noting that information flow between different brain regions (i.e., functional or effective connectivity) could be another target for the identification of neural encoding mechanisms of pain. It is possible that specific representation of pain processing in the human brain exists in the

way how nociceptive information is transferred from subcortical to cortical areas. Indeed, it has been suggested that, in higher primates, nociceptive somatosensory information is processed in parallel in the primary (S1) and secondary (S2) somatosensory cortices, whereas non-nociceptive somatosensory input is processed serially from S1 to S2, although inconsistent evidence also exist. To test whether processing pathways differ between nociceptive and non-nociceptive information, we applied dynamic causal modelling and Bayesian model selection to fMRI responses to nociceptive and non-nociceptive stimuli [88]. However, we observed the same processing hierarchy for the two modalities—parallel processing from the thalamus to S1 and from the thalamus to S2 for both nociceptive and non-nociceptive processing, and thus failed to find evidence for different processing pathways for pain compared to touch. As the estimation of effective connectivity is sensitive to signal temporal resolution, future studies with higher temporal resolution may be needed to confirm this result.

As to the temporal domain, although evidence has shown that the LEPs mainly reflect stimulus saliency rather than pain per se, gamma-band oscillations (GBOs) seem a promising candidate for an EEG marker for pain. A study by Zhang et al. reported that the GBOs probably originated from the S1 recorded by scalp EEG elicited by nociceptive stimuli were an obligatory correlate of subjective pain intensity as its amplitude correlated with perceive pain intensity and at the same time did not habituate with stimulus repetition [89]. Liberati et al. later investigated the nociceptive GBOs recorded in the human insula using depth intracranial electrodes implanted in epileptic patients [90]. Using brief thermonociceptive stimuli and similarly arousing non-nociceptive vibrotactile, auditory, and visual stimuli, they found that nociceptive stimuli elicited a markedly stronger enhancement of GBOs at

all insular sites compared with non-nociceptive control stimuli [90]. Although they further showed that the nociceptive GBOs recorded in the insula showed marked habituation for repeated stimuli, suggesting that they cannot be considered as a correlate of perceived pain [91], the observation of much stronger enhancement of GBOs for nociception than other modalities seems to suggest that the GBOs in insula has some preferential role in pain processing. Furthermore, by recording the GBOs in humans and rodents, a recent study by Hu et al. reported that the GBOs [more specifically the gamma-band event-related synchronization (γ -ERS)] can not only distinguish subjective ratings within the same individual but also code pain sensitivity across different individuals. Interestingly, the ability of GBOs in coding pain sensitivity across subjects seemed to be selective for pain since it did not code the between-subject reported intensity of non-painful but equally salient auditory, visual, and non-nociceptive somatosensory stimuli [92].

4 Machine learning techniques help the identification of pain-specific neural responses

With the rapid hardware and software development related to artificial intelligence, machine learning techniques are becoming increasingly popular in neuroimaging studies due to its high sensitivity in detecting differences in neuroimaging signals between different conditions. In particular, the multivariate pattern analysis (MVPA; sometimes also called “multi-voxel pattern analysis”) is the most typically used machine learning technique in neuroimaging data mining and has been proven to be very powerful in detecting information from neuroimaging signals [93] and for developing neuroimaging biomarkers [94]. MVPA uses a pattern classifier to identify the representational content of the neural responses

elicited by different stimuli [95, 96]. Taking the typical application of MVPA in fMRI data analysis as an example, in contrast with the univariate analyses [such as mass-univariate GLM analysis or regions of interest (ROI) analysis] which detect regional averaged activations and consider a single voxel or a single ROI at a time, MVPA analyzes the spatial pattern of fMRI signals across all voxels within a pre-defined area. That is, MVPA detects condition-specific patterns of activity across many voxels at once. Whereas GLM directly compares differences in signal amplitude on a voxel-by-voxel basis, MVPA projects samples composed by multiple voxels of each condition of interest into a high dimensional space, and searches for the boundary between the samples of two or more conditions [97]. MVPA is usually more sensitive than conventional univariate analysis (e.g., GLM) in disclosing differences in brain activities between experimental conditions not only because it offers a powerful solution to the problem of multiple comparisons, but also because it performs a joint analysis of patterns of activity distributed across multiple voxels.

Therefore, MVPA is also a powerful tool that has been exploited to decode pain-specific neural representations recorded by neuroimaging signals from the human brain. Important progresses have been made in this field. In particular, one of the seminal works by Wager and colleagues showed that the spatial pattern of fMRI responses in the “pain matrix” elicited by nociceptive stimuli can be used to predict successfully the intensity of physical pain, but not social pain, across individuals [97]. They called this fMRI response pattern an “fMRI-based neurologic signature of physical pain”, and showed that this “neurological pain signature” (NPS) could discriminate painful heat from nonpainful warmth, pain anticipation and pain recall, and between physical pain and social pain, and that the strength of the NPS response was substantially reduced when

remifentanyl was administered. Based on this NPS, several follow-up studies were performed and further showed that the NPS was found to be able to distinguish thermal pain from social rejection [98], aversive images [99] and observed pain [100], and it can be generalized to mechanical and electrical pain [100]. However, the same problem of lacking proper saliency-matched non-painful control stimuli exists in these studies. Indeed, in these studies, the salience and aversiveness of non-painful conditions were either not matched with the painful condition (e.g., warmth *vs.* pain), or the non-painful conditions were not in the somatic domain (e.g., social rejection or aversive images *vs.* pain). As discussed in detail in a previous review [101], the data processing protocol in MVPA should be dependent on the desired study objectives. More specifically, when the objective is to identify pain-specific neural activities, signal normalization should be adopted to remove the overall signal amplitude that is unlikely to be unspecific to pain, and consequently to avoid false classification accuracies due to exploiting unspecific signal features. To properly control for stimulus saliency/intensity in the somatic domain, we performed pattern classification to distinguish spatial patterns of fMRI responses after signal normalization in the “pain matrix” between saliency-matched nociceptive and non-nociceptive somatosensory conditions [86]. We found that spatial patterns of fMRI signal allowed distinguishing the responses elicited by a transient painful nociceptive stimulus from those elicited by “equally-intense” and “equally-salient” non-painful stimuli. This result was replicated in two independent datasets collected from different MRI scanners. Importantly, the identified spatial patterns were also generalizable from one dataset to the other. It should be noted that spatial patterns of fMRI signals were also able to distinguish the res-

ponses to high- vs. low-intensity/saliency stimuli, regardless of their sensory modality. These results indicate that the features distinguishing the responses triggered by saliency-matched painful versus non-painful stimuli, and the features distinguishing the responses elicited by high-versus low-saliency stimuli, can both be isolated in the “pain matrix”. Therefore, neural responses within the “pain matrix” are functionally heterogeneous and encode both painfulness and intensity/saliency information. Most of the above studies focused on the neural responses within the “pain matrix”. In another study, we applied the same MVPA analysis using fMRI signals sampled in the primary sensory cortices [93]. Although the primary sensory cortices are traditionally regarded as unisensory areas, strikingly, we found that the spatial patterns of neural activities not only within the S1 but also within other primary sensory cortices (i.e., A1 and V1) are distinguishable between painful and non-painful conditions [93]. This finding not only prompted a reconsideration of how sensory information is coded in the human brain but also suggests that unique representations of pain may exist in much wider brain areas beyond the “pain matrix”. It is worth noting that the main focus in the search of pain-specific neural activities has been on the nociceptive aspect of pain. However, cerebral processes contributing to pain not only include the part of nociceptive inputs but also psychological and behavioural influences. To characterize the cerebral contributions beyond nociception, Woo et al. developed a multivariate pattern signature based on fMRI responses to pain, termed the stimulus intensity independent pain signature-1 (SIIPS1), that predicts pain above and beyond nociceptive input [102]. The SIIPS1 mainly includes patterns of activity in nucleus accumbens, lateral prefrontal and parahippocampal cortices. They found that SIIPS1 responses explained variation in trial-by-trial pain ratings

not captured by the previously developed NPS, and also mediated the pain-modulating effects of three psychological manipulations of expectations and perceived control [102].

In the temporal domain, MVPA has also been used to decode pain-related information based on EEG responses to painful stimuli. Schulz et al. applied MVPA based on the time–frequency transformed single-trial EEG responses to identical painful stimuli and revealed that a classifier trained on a group of participants can be used to successfully predict another individual’s pain sensitivity, indicating that the temporal-spectral information acquired from pain induced EEG signals may contain information about how a person perceives pain [103]. However, the specificity of this temporal-spectral pattern of EEG responses to painful stimuli remains to be tested.

All these machine learning studies on identification of pain-specific neural activities, especially based on fMRI, suggest that spatial patterns of neural activities across multiple brain regions, within and beyond the “pain matrix”, may be important in the neural coding mechanisms of pain. This is compatible with the view of “dynamic pain connectome” which proposes that pain experience emerges from the synchronized or coordinated activity of multiple brain areas which, if considered in isolation, are not specific for pain [20, 104]. The “dynamic pain connectome” hypothesis emphasizes that the pain specific information exists not only in the spatial distribution of brain networks but also the dynamic interflow within and between certain brain networks.

5 Closing remarks

Pain is a complex experience, likely generated from multiple neural networks that responsible for sensory, emotional and cognitive processing.

Extensive evidence suggests that features of brain responses to painful stimuli recorded by neuroimaging techniques and identified by univariate comparisons are largely unspecific to pain, although some of them show preferential responses to pain. Machine learning techniques, utilizing subtle information embedded in the fine-grained spatial and/or temporal pattern of neuroimaging signals, should be exploited in the task of identifying pain-specific neural representations in the human brain. Current efforts based on the combination of neuroimaging and machine learning techniques have shown that unique representations of pain processing may exist in spatial patterns of distributed brain areas across the brain and cannot be ascribed to specific brain regions.

Conflict of interests

The authors declare no conflict of interests.

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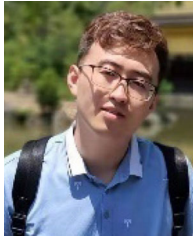
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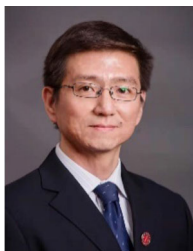
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