

Electroencephalography and magnetoencephalography in pain research—current state and future perspectives

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1. Introduction

Pain is a highly variable and subjective experience, which results from the flexible integration of sensory and contextual (eg, cognitive, emotional, and motivational) information. In acute pain, this integration usually results in a coherent percept and behavioral adaptations, which serve the protection of the body. By contrast, in chronic pain, these integration processes fail to produce adaptive behavior but result in ongoing pain with devastating effects on quality of life. Understanding how the brain processes and integrates nociceptive and contextual information is, thus, of central importance for understanding the mechanisms of pain in health and disease.

In this article, we will discuss the contribution and perspectives of electroencephalography (EEG)⁵¹ and magnetoencephalography (MEG)⁷² in pain research. EEG and MEG are direct and noninvasive measures of brain function. While EEG measures the small electrical currents resulting from postsynaptic potentials, MEG measures the magnetic fields induced by these currents. The major strength of both methods is their high temporal resolution in the range of milliseconds. EEG and MEG, thus, complement other imaging methods, such as functional magnetic resonance imaging (fMRI), which have an excellent spatial but lower temporal resolution. A particular strength of EEG is that it is affordable, broadly available, and mobile. Limitations of EEG are its low spatial resolution and its insensitivity to processes in deep brain areas. Magnetoencephalography does not need placement of electrodes on the scalp, is mostly sensitive to tangentially oriented currents, has a higher spatial resolution than EEG, and is particularly well suited for source localization procedures. However, MEG is technically more demanding, more expensive, rarely available, and stationary. In the following sections, we use the term “EEG” for convenience, but most parts apply similarly to MEG.

2. Current state

2.1. Experimental pain

The most popular EEG approach to pain is the assessment of evoked potentials in response to brief noxious stimuli such as thermal laser stimuli of milliseconds duration.⁵⁵ This approach yields a typical sequence of responses that, based on their sequence and polarity, are termed N1, N2, and P2^{14,32,55} and mainly originate from somatosensory, insular, and cingulate cortices.^{14,32} The amplitudes of these responses are sensitive to damage to nociceptive pathways and have, thus, been established as a clinically useful measure of the integrity of nociceptive pathways to the brain.^{22,75,76} Moreover, they covary with objective stimulus intensity and the subjective perception of pain under certain conditions^{32,40} and are modulated by contextual factors such as attention^{13,36} or placebo effects.^{74,80} Interestingly, novel paradigms have recently revealed that pain-related evoked potentials are not specific to pain or nociception but mostly reflect the salience^{7,28,47,48,61} of noxious stimuli and defensive actions.⁴⁵

During the past decade, time–frequency analyses have complemented and extended the evoked potential approach. These analyses have revealed that brief noxious stimuli also modulate neuronal oscillations at alpha (8–13 Hz), beta (13–30 Hz), and gamma (40–100 Hz) frequencies,^{21,59,67,84} which partially overlap in time and space with the evoked potentials. These responses at different frequencies have again been shown to be modulated by contextual factors and to reflect complementary steps in the translation of noxious stimuli into pain.^{21,24,43,67,74,84} Consequently, pain is not determined by a single feature of brain activity but rather by complex spatial-temporal-spectral patterns of brain activity.

Finally, novel paradigms of experimental pain have extended the EEG-based assessment of pain from brief noxious stimuli to longer-lasting tonic stimuli as a first step towards the main clinical problem of ongoing pain.^{6,16,19,26,49,50,52,66} The results have shown that tonic pain is associated with decreases and increases of brain activity at alpha and gamma frequencies encoding objective stimulus intensity and subjective pain intensity, respectively.^{6,16,19,26,49,50,52,66} Moreover, the patterns of brain activity during tonic noxious stimulation fundamentally differ from those of brief noxious stimuli with a shift from the encoding of pain intensity by activity in multiple frequency bands in somatosensory cortices to an encoding by gamma oscillations in the prefrontal cortex.^{49,52,66}

Taken together, evoked potentials have been established as the first clinically useful measure of pain-related brain activity, rendering pain and its many modulations into biologically objectifiable phenomena and thereby significantly shaping the

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current understanding of pain. Beyond, it has become clear that not isolated features but complex spatial-temporal-spectral patterns of brain activity eventually determine the subjective experience of pain. These patterns seem to change with the duration of pain, which has recently become accessible using novel experimental pain paradigms.

2.2. Clinical pain

Although EEG is available in nearly every neurology office and department, evidence on the EEG correlates of chronic pain is surprisingly limited.⁵⁴ Two different EEG approaches have been pursued so far. The first one uses the evoked potential approach to investigate whether the processing of painful or nonpainful stimuli is abnormal in chronic pain. The results show that damage to nociceptive pathways in neuropathic pain is associated with a reduction of evoked potentials.^{22,75,76} In addition, at least in some chronic pain conditions, other abnormalities can be observed. For instance, in migraine,⁹ fibromyalgia,^{10,46} and chronic back pain,^{11,12,27} a disinhibition or lack of habituation of evoked responses to noxious and nonnoxious stimuli has been shown. However, it remains unclear how these findings relate to the basic pathology of chronic pain and phenomena such as central sensitization.⁸³

The second approach quantifies ongoing brain activity as a function of frequency based on short resting-state EEG recordings of patients with chronic pain. The most noted finding is a widespread increase of brain activity at theta frequencies (3–8 Hz),^{64,71} paralleled by abnormal theta activity in the thalamus of patients with chronic pain.^{29,37} Together, these observations have motivated the thalamocortical dysrhythmia model of chronic pain.^{38,81} In this model, abnormal nociceptive input yields abnormal thalamic bursts at theta frequencies. These theta oscillations are transmitted to the cerebral cortex where they result in disinhibition of neighboring areas, which, in turn, results in abnormal oscillations at gamma frequencies and eventually in ongoing pain. This model is highly appealing, but evidence is still sparse. For instance, some large EEG studies on chronic pain did not find abnormal theta activity.^{65,78}

Other recent studies did not directly address the EEG correlates of chronic pain but investigated whether EEG signals can predict responses to analgesic treatment. The results have revealed that some EEG features such as the amplitude of delta (1–3 Hz) activity during tonic pain can, indeed, predict treatment success, eg, the responsiveness to postsurgical opioid treatment.^{17,18,31} This approach represents an appealing and clinically useful direction for future studies.

Taken together, abnormalities of stimulus processing and resting-state brain activity have been observed in chronic pain. Moreover, EEG signals can be useful to predict analgesic treatment success. However, convincing and clinically useful EEG markers of chronic pain remain to be demonstrated.

3. Future perspectives

3.1. Challenges

A major challenge for EEG in basic pain research is to understand the translation process of sensory and contextual information into pain. In particular, a systematic assessment of the brain mechanisms underlying different contextual modulations of pain is lacking so far.⁵⁶ Moreover, the brain mechanisms subserving different, ie, perceptual, behavioral, and autonomic aspects of pain are largely unknown. Finally, although it has been shown that the brain mechanisms of pain can change over time, the dynamics of these changes remain to

be explored. Understanding these integration and translation processes is an indispensable prerequisite for understanding whether and how they contribute to the pathology of chronic pain and how they can be systematically modulated and harnessed for pain therapy. EEG can elucidate these processes non-invasively with a high temporal resolution.

A major clinical challenge is to define abnormalities of brain function in chronic pain. Such abnormalities might serve as EEG-based markers of chronic pain, which do not have to be pain specific to be clinically helpful.²³ For instance, objective markers could be diagnostically useful when verbal report is not available or reliable. Moreover, they could help to classify chronic pain and to tailor individual treatment. Beyond, EEG-based markers of chronic pain could represent direct targets of pain therapy. For instance, abnormal EEG patterns might be modulated by neurofeedback approaches³⁰ or by recent noninvasive brain stimulation techniques, which can selectively alter neuronal oscillations at certain frequencies.⁷³ The feasibility, limitations, and perspectives of such brain-based biomarkers of pain are currently intensively discussed in the pain research community^{8,23,62} and beyond.^{41,60,82}

The following section highlights how the application of conceptual and methodological progress might open new perspectives for EEG and MEG in pain research and help to meet the outlined challenges.

3.2. Next steps

3.2.1. Standardization and data sharing

A standardization of EEG recordings and analyses would allow for comparing, exchanging, and integrating data, which could result in higher participant/patient numbers and address issues of reproducibility⁴ and generalizability and increase sensitivity. Adaptations of guidelines for EEG⁵³ and MEG²⁰ research as well as the extension of data sharing initiatives in neuroimaging⁵⁸ and pain³⁵ research to EEG data would be helpful.

3.2.2. Connectivity/network analysis

As pain results from the integration of nociceptive and contextual factors, it essentially depends on the integration of brain activity across different areas, ie, on brain connectivity.⁶⁹ The investigation of brain connectivity is, thus, a very promising direction for pain research.⁵⁷ Because of its high temporal resolution, EEG is particularly suitable for investigating connectivity at different frequencies and time scales. Such connectivity analyses might not only assess static connectivity patterns but also the dynamics of connectivity,¹⁵ which likely contain functionally important information about pain.³³ Moreover, interactions between neural oscillations at different frequencies termed cross-frequency coupling are also known to contain functionally significant information,⁵ but their role in the processing of pain has not been explored so far. However, in EEG-based connectivity analyses, problems of volume conduction have to be taken into account by choosing the right connectivity measures,^{1,63} performing analyses in source space, and/or by comparing conditions or groups with similar volume conduction effects. Moreover, the role of different connectivity measures and their relation to each other in pain-related brain connectivity needs to be clarified. Furthermore, EEG-based connectivity analyses, especially when combined with source reconstruction methods, can yield huge data sets demanding data reduction. Graph theory can meet these demands by assessing the local and global characteristics of

connectivity networks with a few measures.³ Such analyses have successfully been applied to fMRI³ and EEG⁷⁰ data in different neuropsychiatric disorders, and recommendations as how to apply them to EEG and MEG data have been developed.⁷⁷ Recently, first applications of graph theory to fMRI⁴² data of patients with chronic pain have been published. This approach promises to be useful for defining brain connectivity patterns related to chronic pain.

3.2.3. Multivariate pattern analysis

Pain is encoded by complex spatial-temporal-spectral patterns of brain activity, which can be assessed by the multivariate analysis of multiple EEG features at once using machine-learning approaches. Such approaches have been successfully applied to define fMRI-based spatial patterns⁷⁹ and EEG-based spatial-temporal-spectral patterns^{25,44,68} of brain activity related to experimental pain. The application of such EEG approaches to chronic pain could represent an important step towards an EEG-based biomarker of chronic pain. Recent fMRI³⁹ and EEG³⁴ studies represent important first steps in that direction. Considering the important role of connectivity in the processing of pain, such approaches might not only be applied to patterns of brain activity but also to patterns of brain connectivity.

3.2.4. New devices

A major strength of EEG is its broad availability and potential portability. Recently, new devices have been developed, which are portable and can be easily connected to mobile phones. Usage of such devices might offer new perspectives for the widespread and mobile use of EEG, for example, for the diagnosis or the neurofeedback-based therapy of pain. Moreover, new magnetic fields sensors, which operate at room temperature, promise to significantly simplify MEG recordings.²

4. Conclusions

Because of its high temporal resolution, its broad availability, and potential portability, EEG has a high potential for investigating the brain mechanisms of pain. Electroencephalography-based measures have been established as the first pain-unspecific but clinically useful brain-based measures of pain and its modulations and thereby significantly shaped the current understanding of pain (Fig. 1). Moreover, EEG has revealed that complex patterns of brain activity rather than isolated brain activity features determine pain. In the future, the standardization of recordings and analyses, novel analysis approaches as well as new mobile EEG devices might help to exploit the full potential of EEG in pain research (Fig. 2). This will be

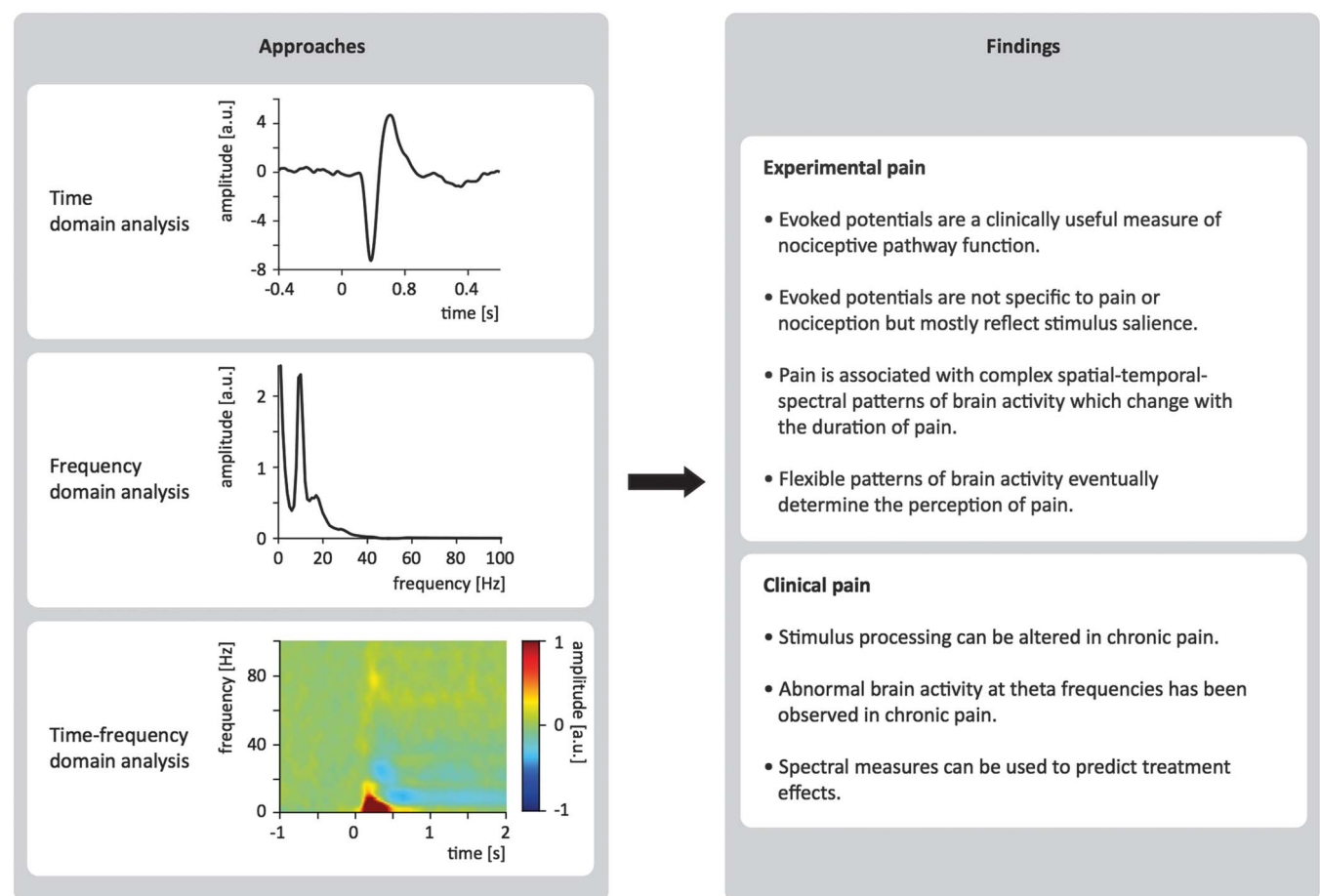


Figure 1. Electroencephalography (EEG) and magnetoencephalography (MEG) in pain research—current state. The left box shows main approaches for the analysis of EEG and MEG data. Time domain analysis quantifies brain activity as a function of time and is particularly well suited for investigating the processing of repeatedly applied brief stimuli, for example, phase locked–evoked brain responses to phasic experimental noxious stimuli. Frequency domain analysis quantifies brain activity as a function of frequency and is well suited for investigating brain activity related to stable states, for example, tonic experimental pain or ongoing clinical pain during the resting state. Finally, time–frequency analysis quantifies brain activity as a function of time and frequency. This approach is well suited to investigate nonphase-locked, induced brain responses to phasic experimental stimuli and the dynamics of tonic experimental and ongoing clinical pain. The right box shows main EEG and MEG findings related to pain obtained by the approaches shown on the left.

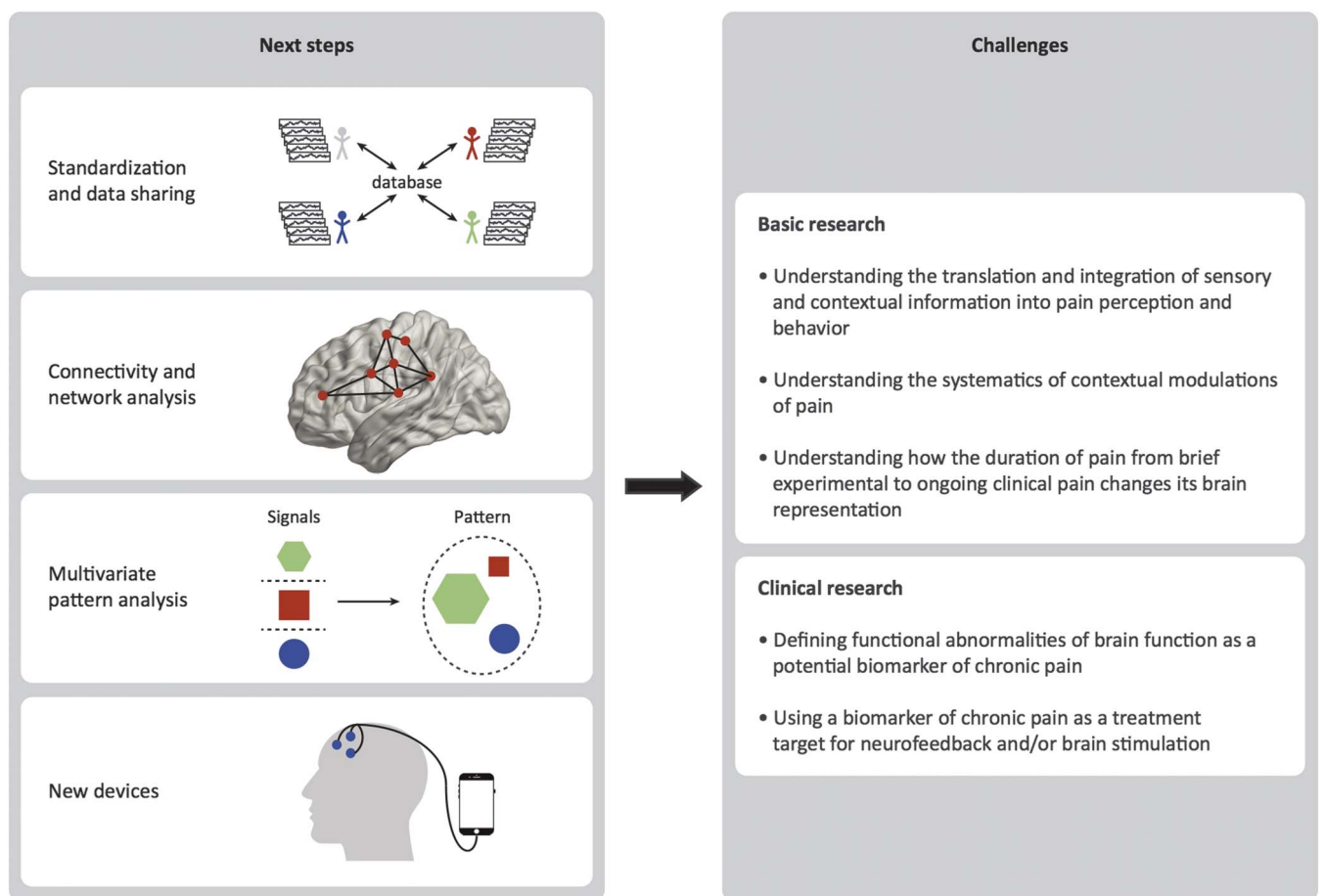


Figure 2. Electroencephalography (EEG) and magnetoencephalography (MEG) in pain research—future perspectives. The left box shows possible next steps in pain research using EEG and MEG, which might help to meet important challenges for basic and clinical pain research shown in the right box. Next steps include data sharing and standardization of recordings and analyses as well as connectivity and network analyses, which quantify frequency-specific connections and interactions between brain areas in source space. In multivariate pattern analysis, multiple brain activity and/or connectivity measures are jointly analyzed rather than investigated in isolation. New devices might include mobile EEG devices and new magnetic field sensors.

particularly important with respect to the establishment of EEG-based markers of chronic pain which could be immensely helpful for the diagnosis, classification, and therapy of chronic pain.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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