

UC San Diego

UC San Diego Previously Published Works

Title

Unveiling the phantom: What neuroimaging has taught us about phantom limb pain

Permalink

<https://escholarship.org/uc/item/98n416bk>

Journal

Brain and Behavior, 12(3)

ISSN

2162-3279

Authors

Browne, Jonathan D

Fraiser, Ryan

Cai, Yi

et al.

Publication Date

2022-03-01

DOI

10.1002/brb3.2509

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

REVIEW

Unveiling the phantom: What neuroimaging has taught us about phantom limb pain

Jonathan D. Browne¹  | Ryan Fraiser² | Yi Cai²  | Dillon Leung³ | Albert Leung² | Michael Vaninetti²

¹School of Medicine, California University of Science and Medicine, Colton, California, USA

²Center for Pain Medicine, University of California San Diego, La Jolla, California, USA

³College of Letters and Science, University of California Berkeley, Berkeley, California, USA

Correspondence

Michael Vaninetti, Center for Pain Medicine, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093.
Email: Mvaninetti@ucsd.edu

Phantom limb pain (PLP) is a complicated condition with diverse clinical challenges. It consists of pain perception of a previously amputated limb. The exact pain mechanism is disputed and includes mechanisms involving cerebral, peripheral, and spinal origins. Such controversy limits researchers' and clinicians' ability to develop consistent therapeutics or management. Neuroimaging is an essential tool that can address this problem. This review explores diffusion tensor imaging, functional magnetic resonance imaging, electroencephalography, and magnetoencephalography in the context of PLP. These imaging modalities have distinct mechanisms, implications, applications, and limitations. Diffusion tensor imaging can outline structural changes and has surgical applications. Functional magnetic resonance imaging captures functional changes with spatial resolution and has therapeutic applications. Electroencephalography and magnetoencephalography can identify functional changes with a strong temporal resolution. Each imaging technique provides a unique perspective and they can be used in concert to reveal the true nature of PLP. Furthermore, researchers can utilize the respective strengths of each neuroimaging technique to support the development of innovative therapies. PLP exemplifies how neuroimaging and clinical management are intricately connected. This review can assist clinicians and researchers seeking a foundation for applications and understanding the limitations of neuroimaging techniques in the context of PLP.

KEYWORDS

DTI, EEG, fMRI, MEG, phantom limb pain

1 | INTRODUCTION

Pain is unique to individuals who experience it, and the subjective nature of pain challenges its fundamental understanding. Phantom limb pain (PLP) is one such clinical mystery for researchers, clinicians, and patients. While PLP phenomenon has been well documented in recent history, the underlying pathophysiology was poorly

understood due to limitation in investigational tools. Ambroise Paré described patients feeling absent limbs following amputations he performed during the 16th century, and in the 17th century, philosopher René Descartes concluded that there might be a dissociation between nerve signals and cognitive interpretation in amputees (Finger & Hus-twit, 2003). Later, during the American Civil War, surgeon Silas Weir Mitchell was frustrated by ineffective treatments for PLP and became

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2022 The Authors. *Brain and Behavior* published by Wiley Periodicals LLC

notable for advocating formal scientific investigations (Finger & Hus-twit, 2003). This mystery continues to draw curiosity and interest, and it now leverages modern technology to uncover its truth.

More than merely quenching scientific curiosity, further PLP research is needed to improve the lives of amputees. The amputee population in America is estimated to increase from 1.6 million in 2005 to 3.6 million by 2050 (Ziegler-Graham et al., 2008). PLP, which is the pain of the amputated limb that is variable in timing, is experienced by up to 79.9% of amputees (Ehde et al., 2000; Ephraim et al., 2005). The severity of phantom limb sensations ranges from nonpainful to disabling and, in some instances, can be physically and psychologically debilitating (Ephraim et al., 2005). For surgical amputees, chronic preoperative pain and acute postoperative phantom pain are risk factors for PLP (Hanley et al., 2007; Larbig et al., 2019). Still, correlations for the severity of pain have been inconsistent (Sherman et al., 1984). These variations in the clinical presentation of PLP continue to burden amputees, warranting a deeper understanding of its mechanism to improve diagnosis and efficacious clinical approaches. As the demand for a conclusive understanding grows, so does the controversy among scientists and clinicians.

PLP is a particularly challenging syndrome to diagnose and treat, which may be related to the fact that, by mechanistic nature, it is challenging to understand. Nonspecific and highly varied symptoms can make diagnosing PLP difficult, requiring a comprehensive history, examination, tests, and exclusion of other possible neuropathies (Ferraro et al., 2016). The variety of PLP therapies, including pharmacologic, cranial stimulation, and sensory therapies, have been inconsistent (Aternali & Katz, 2019; Richardson & Kulkarni, 2017) with some potential being demonstrated among integrative approaches (Subedi & Grossberg, 2011). These challenges parallel the equally complex range of mechanistic explanations of PLP, which involve various combinations of cerebral, spinal, and peripheral nervous system pathologies (Flor et al., 2006). These mechanistic, diagnostic, and management inconsistencies underscore the importance of foundational tools for analyzing PLP. Due to the brain's role in interpreting, processing, and modulating pain, neuroimaging may fulfill this need. In addition to aiding understanding of PLP, neuroimaging may assist the development of PLP therapies.

This article will review current noninvasive imaging modalities for PLP research in mechanistic and therapeutic investigations. It will focus on diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG). Researchers and clinicians utilize each imaging modality in distinct ways to complement dynamic research involving diagnosing, characterizing, and treating PLP. By examining how DTI, fMRI, EEG, and MEG have impacted the understanding of PLP, we aim to summarize a baseline of fundamental imaging techniques to foster further research.

1.1 | Background on potential pain mechanisms

In order to understand the impact of the major imaging modalities used in this field, it is helpful to briefly review the prevailing discussed

potential mechanisms behind PLP. In the properly functioning human nervous system, peripheral noxious stimulus generates a sensation of pain via a cascade of neuronal events. The pathway consists of primary afferent pain fibers which carry the afferent signals from the peripheral nociceptors to the spinal cord where they synapse directly or indirectly via interneuron with the secondary neurons at the dorsal horn of the spinal cord. The afferent signals then ascend via the second-order neurons to the brain via either spinothalamic or spinothalamic tracts (Steeds, 2009). Passage of this nociceptive information through the brainstem triggers modulatory signals back through the dorsal horn. These modulatory signals alter primary afferent neuron propagation which can facilitate or inhibit further peripheral nociceptive information (Renn & Dorsey, 2005). Additionally, supraspinal pain signal processing and modulation are important for healthy pain perception. First, the thalamus and pons relate afferent sensory signals to other supraspinal regions. Other supraspinal groups include the somatosensory cortices and inferior parietal lobe, anterior cingulate cortex (ACC) and insula (IN), and dorsolateral prefrontal cortex, which are also important sensory discriminatory, affective, and modulatory regions, respectively (Leung, 2020). Furthermore, supraspinal modulatory functional connectivity deficits have been associated with white matter tract deficits, emphasizing the vital role of supraspinal processing (Leung et al., 2016, 2018). These normal pain mechanisms involve the intricate relationship between peripheral, spinal, and supraspinal regions.

PLP draws attention because there is still no consensus on its mechanism. Cerebral, spinal, and peripheral explanations each bear scientific evidence, perpetuating the controversy (Collins et al., 2018). Mechanisms within these groups are not mutually exclusive and PLP may be explained by some combination. Furthermore, researchers speculate if PLP may be a cluster of pain disorders, rather than a single disorder (Griffin & Tsao, 2014). Researchers have prioritized this mechanistic puzzle as it is essential for providing quality care to these patients.

Cerebral mechanisms consist of cortical reorganization, alterations in sensory and motor feedback, and pain memory (Flor et al., 2006). PLP is commonly correlated with reorganization and furthermore related to the self-perception of one's own body (Subedi and Grossberg, 2011). In support of cerebral mechanisms, a 1998 study found hemispheric differences in cortical representation in traumatic amputees absent in subjects with congenital absence of limb (Montoya et al., 1998).

Spinal mechanisms relate to amputation-related nerve injury causing spinal cord hypersensitization and further reorganization of spinal cord areas formerly occupied by functioning afferent nerves (Flor et al., 2006). Connections between the proximal sections of amputated nerves can form disruptive connections with receptive spinal nerves. Additionally, distorted neuronal activity, hyperexcitability, and central nociceptive neuron firing pattern changes may also contribute to PLP (Subedi and Grossberg, 2011).

The peripheral mechanisms involve nerve ending and dorsal root ganglion reorganization following amputations (Flor et al., 2006). Efficacious pre- and postoperative peripheral interventions for PLP support this explanation. Patients receiving peripheral nerve interfaces before surgery have had lower rates of peripheral neuromas and

PLP (Kubiak et al., 2019). Additionally, minimally invasive percutaneous peripheral nerve stimulation programs improved functionality in patients with chronic pain postamputation (Gilmore et al., 2019). Peripheral nervous system treatment has addressed PLP functionality and pain, which validates this mechanism.

Cerebral, spinal, and peripheral PLP mechanisms have each endured scientific evaluation with no distinct victor. These are also not mutually exclusive and PLP may be a product of a combination of these mechanisms. Makin and Flor further expand upon the multifactorial nature through a review of factors beyond remapping that may come together to contribute to PLP (Makin & Flor, 2020). Broad consideration of mechanism and dynamic changes warrants a comprehensive analysis of this complex disease. Investigators continue to explore this scientific question using several specialized neuroimaging techniques.

2 | METHODS

A literature search was conducted using the PubMed database between January 2020 and August 2021. The literature search was organized using the following keywords/keyword combinations: "phantom limb pain and diffusion tensor imaging (DTI)," "phantom limb pain mechanism," "phantom limb pain and electroencephalography (EEG)," "phantom limb pain and functional magnetic resonance imaging (fMRI)," "phantom limb pain and amputation," "phantom pain," "phantom limb pain and mirror therapy," "phantom limb pain and magnetoencephalography (MEG)," "phantom limb pain and therapeutics," "diffusion tensor imaging (DTI)," "electroencephalography (EEG)," "magnetoencephalography (MEG)," "functional magnetic resonance imaging (fMRI)." The articles generated from the search were then screened and additional articles referenced by the searched articles were also utilized. Articles were selected based on the inclusion of amputees with PLP or phantom sensations along with the utilization of DTI, fMRI, EEG, or MEG to investigate mechanism or response to therapy.

3 | RESULTS

3.1 | Diffusion tensor imaging

DTI is a variant of conventional MRI that has become a standard tool in researching PLP. As a general MRI principle, tissue microstructure determines water diffusion, which translates into an image. Anisotropy describes water diffusion that is directionally dependent while isotropy describes unrestricted water diffusion; white matter is more anisotropic than gray matter, while cerebrospinal fluid is isotropic (Hagmann et al., 2006; Pierpaoli et al., 1996). DTI capitalizes on white matter tracts to assess structural integrity and connectivity (Bandettini, 2009). In PLP, DTI has become the most common tool for evaluating anatomical changes.

Important DTI scalars include axial diffusivity (AD), radial diffusivity (RD), mean diffusivity (MD), and fractional anisotropy (FA). AD and RD characterize rates of diffusion in principal and perpendicular directions, respectively, while MD is the net displacement of water molecules (Feldman et al., 2010). FA is a ratio that describes the degree of anisotropic diffusion (Feldman et al., 2010). These scalars allow DTI to interpret structural changes within the brain. A 2019 study employed DTI to determine a connection between PLP and white matter changes. Interestingly, these researchers found symmetrically increased white matter AD bilaterally, but a stronger white matter RD association with visual analog scale (VAS) score in the corpus callosum and hemisphere associated with the amputated limb (Seo et al., 2019). Guo et al. (2019) studied changes in FA following upper-limb amputation using DTI and positively correlated contralateral middle temporal gyrus nodal strength with the magnitude of PLP. In contrast, Jiang et al. studied lower-limb amputees using DTI and described ipsilateral decreased FA in the superior corona radiata, sub-temporal lobe white matter, and inferior fronto-occipital fasciculus. Additionally, they noted contralateral reduced FA in the left premotor cortex. Utilizing tractography in the premotor cortices, they also found altered interhemispheric fibers (Jiang et al., 2015).

Structural analysis is useful for understanding physical changes due to PLP and potentially planning for interventions. The properties of DTI have propelled it to become a standard tool for such structural analysis. Corpus callosum changes identified via DTI provide clues regarding the connection between phantom sensations and sensorimotor cortex inhibition (Simões et al., 2012). Furthermore, Owen et al. (2007) utilized DTI tractography to guide deep brain stimulation in an amputee experiencing stump pain. DTI applications and key findings are summarized in Table 1.

Despite its growing prevalence in neuroimaging, DTI maintains technical issues such as subject motion, eddy currents, and low resolution (Bandettini, 2009). A review of DTI imaging by Alexander et al. found that its measure of FA was sensitive for finding microstructure changes, but this alone was less useful for characterizing such changes. They emphasized the importance of utilizing additional DTI scalars in concert for comprehensive cerebral pathology classification (Alexander et al., 2007). Hakulinen et al. caution the acceptance of FA, considering it to be nonspecific to various pathologies. They also note the variation in the DTI technique, potentially compromising different reports' comparability without a validated method. The review concludes that the circular method has better repeatability, while the free-hand method has less variation; these characteristics may be advantageous for studying distinct aspects of the brain (Hakulinen et al., 2012). Furthermore, Soares et al. (2013) address the technical components of DTI interpretation at each stage of data collection and propose conformity that may serve to reduce variability among researchers.

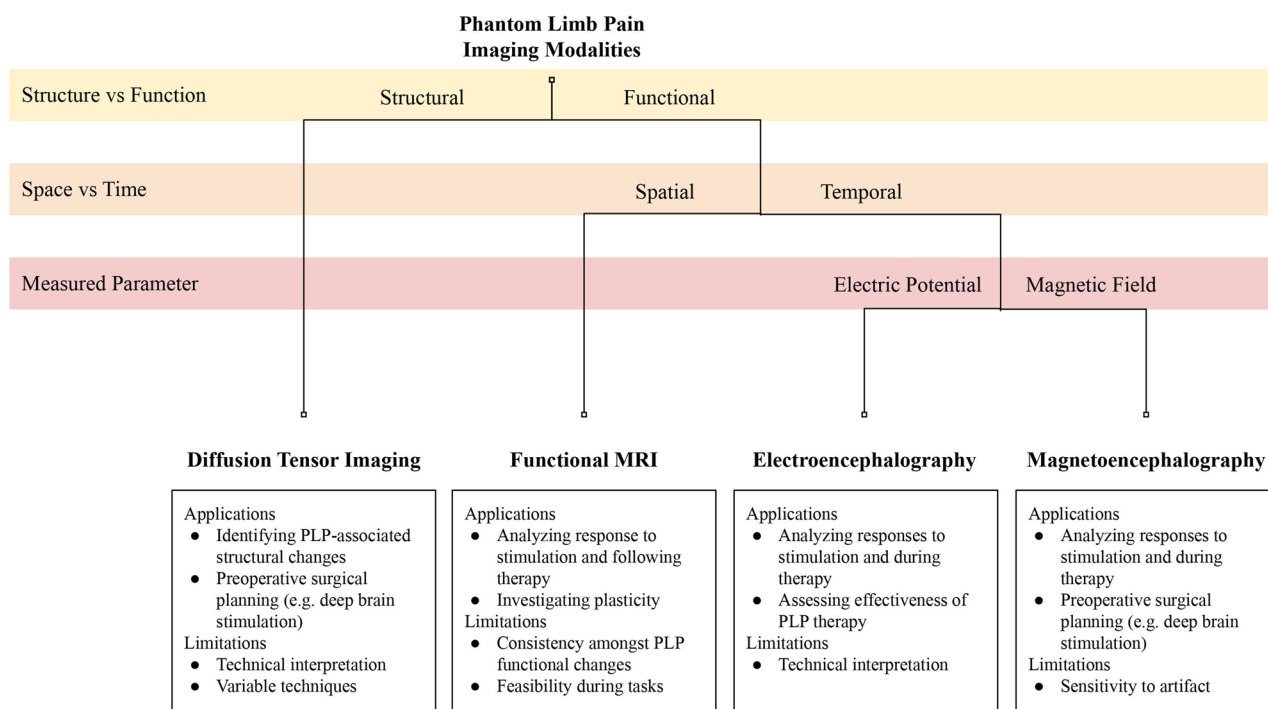
In summary, DTI exploits water diffusion due to tissue microstructures to reveal critical structural changes due to PLP. As depicted in Figure 1, analysis of these structural changes can contribute to studying cerebral mechanisms of PLP. Technical aspects limit this imaging technique and may compromise data collection and interpretation. DTI should continue to be used to characterize how particular structural

TABLE 1 Diffusion tensor imaging (DTI) and phantom limb pain (PLP)

Author	Sample size: Study control	Application	Key findings
Seo et al., 2019	10 16	Identified structural changes	Stronger white matter radial diffusivity in corpus callosum and hemisphere associated with amputated limb
Guo et al., 2019	22 15	Identified structural changes	Positive correlation between contralateral middle temporal gyrus nodal strength and PLP magnitude
Jiang et al., 2015	17 18	Identified structural changes	Decreased ipsilateral fractional anisotropy in superior corona radiata, sub-temporal lobe white matter, and inferior fronto-occipital fasciculus
Simões et al., 2012	9 ^a 9	Identified structural changes	Structural changes in corpus callosum; related “painless” phantom sensations and sensorimotor cortex inhibition
Owen et al., 2007	1 0	Preoperative deep brain stimulation planning	Utility of DTI in assisting planning for PLP interventions

Note: Study sample size reflects amputees with phantom limb pain unless otherwise noted.

^aAmputees with “painless” phantom sensations.

**FIGURE 1** Flowchart of imaging modalities within the context of phantom limb pain.

changes relate to the presence and severity of PLP in correlation with functional changes.

3.2 | Functional magnetic resonance imaging

fMRI employs many of the same concepts as DTI. However, in contrast to DTI structural imaging, fMRI is an essential functional imaging

technique utilized in PLP research. Magnetic forces create particular arrangements of water molecules. Additionally, oxyhemoglobin and deoxyhemoglobin have different magnetic properties (Bunge & Kahn, 2009). Thus, fMRI can measure tissue perfusion and changes in oxygen that are interpreted to create a functional activity map (Logothetis, 2008). It is a commonly used neuroimaging technique due to logistic factors such as availability, low cost, and low risks (Bunge and Kahn, 2009). Compared to the other functional imaging techniques discussed

TABLE 2 Functional magnetic resonance imaging (fMRI) and phantom limb pain (PLP)

Author	Sample size: Study control	Application	Key findings
Simões et al., 2012	9 ^a 9	Response to phantom limb stimulation	Functional remapping of S1 in setting of “painless” phantom sensations
Pasaye et al., 2010	2 6	Response to phantom limb stimulation	Distinct Brodmann areas activated following stump stimulation
Andoh et al., 2017	5 5	Response to phantom limb stimulation	Hemispheric differences in amputees with “painless” phantom sensations; bilateral SI and intraparietal sulcus activation
Andoh et al., 2020	40 ^b 20	During virtual reality therapy	Motor cortex activity positively related to PLP intensity
Foell et al., 2014	11 0	Response to mirror therapy	Decreased inferior parietal cortex activity and reversal of maladaptive cortical reorganization
Roux et al., 2008	1 0	Assisted surgical electrode placement and monitored response to motor cortex stimulation	Detected inhibiting effects on primary sensorimotor cortex and contralateral primary motor and sensitive cortices
MacIver et al., 2008	13 6	Response to mental imagery therapy	Reduced cortical reorganization, which correlated with reduction in pain intensity

Note: Study sample size reflects amputees with phantom limb pain unless otherwise noted.

^aAmputees with “painless” phantom sensations.

^bCompared 20 PLP amputees, 20 non-PLP amputees, and 20 controls.

in this review (EEG and MEG), fMRI has more substantial spatial resolution but lower temporal resolution (Meyer-Lindenberg, 2010).

Simoes et al. (2012) combined fMRI and DTI to study cortical and colossal plasticity and found that neuroplastic modifications were present in subjects who reported PLP and those who reported only phantom limb sensations. Pasaye et al. (2010) also utilized fMRI to show activation of distinct areas within the brain upon stump stimulation. Andoh et al. (2017) identified inter- and intrahemispheric differences in amputees via fMRI in addition to bilateral SI and intraparietal sulcus activation upon phantom sensation evocation. In a later study, Andoh et al. (2020) also utilized fMRI during a virtual reality (VR) task to demonstrate that motor cortex activity was positively related to PLP intensity.

When characterizing the efficacy of PLP rehabilitative techniques, researchers often utilize fMRI. Foell et al. focused on fMRI to identify physical changes in response to mirror therapy, which involved movement of the intact limb in front of a mirror to create the perception of movement in the amputated limb. They report decreased inferior parietal cortex activity and the reversal of maladaptive cortical reorganization (Foell et al., 2014). In a case report about using chronic motor cortex stimulation to treat PLP, researchers used fMRI for precise surgical electrode placement and monitored the patient's response to therapy (Roux et al., 2008). A study of 13 upper limb amputees utilized fMRI that showed reduced cortical reorganization in PLP patients following mental imagery therapy by contrasting pretraining diffuse cortical activation upon motor tasks, such as a lip purse, with post-training isolated lip area activation. This 6-week training additionally correlated reductions in pain intensity with a decrease in cortical reorganization (MacIver et al., 2008). fMRI applications and key findings are summarized in Table 2.

Logothetis explains that fMRI interpretation requires caution as this neuroimaging technique may not make key distinctions, such as top-down versus bottom-up, excitation versus inhibition, or regional differences (Logothetis, 2008). Another recent review of 10 fMRI investigations from 2001 to 2015 found that this imaging technique did not comprehensively support maladaptive brain plasticity, including the relationship between pain intensity and reorganization (Jutzeler et al., 2015). In studying fMRI during a VR movement task, Andoh et al. (2020) found that fMRI findings for PLP may vary based on methodology. These findings suggest that fMRI is inconsistent in evaluating changes due to PLP, or perhaps there are gaps in understanding of plasticity in PLP. This principle reiterates the importance of the link between PLP and neurologic adaptation and the need for collaborative techniques.

fMRI measures functional changes with strong spatial resolution but is prone to certain ambiguities in interpretation. The lack of critical distinctions may be why fMRI studies have shown mixed results in PLP research. fMRI has utility in supplementing studies of PLP therapies and interventions (Figure 1).

3.3 | Electroencephalography

EEG is a temporal-functional imaging technique that is useful in PLP research. EEG interprets electrical flow across membranes as neurons depolarize. It is distinct from the other imaging techniques discussed in this review by recording real-time measurements in varying cognitive states (Bunge and Kahn, 2009). By measuring perpendicular electrical flow, EEG can analyze gyri and deep sulci pyramidal cells (Bunge and Kahn, 2009). EEG has been further touted, along with MEG, as a

TABLE 3 Electroencephalography (EEG) and phantom limb pain (PLP)

Author	Sample size: Study control	Application	Key findings
Walsh et al., 2015	1 0	During attempted movement of phantom limb	Left frontal EEG pattern similar to a healthy cohort of a previous report
Lyu et al., 2016	22 24	Assessed reorganization following amputation	Distinct global and local network changes in alpha and beta bands
Vase et al., 2012	18 0	Response to phantom limb stimulation	Increased response at the N/P135 dipole of the affected side; attention to stimuli may be associated with PLP
Osumi et al., 2020	2 0	During virtual reality rehabilitation with vibrotactile stimulation	PLP alleviation and increased alpha wave coherence

Note: Study sample size reflects amputees with phantom limb pain unless otherwise noted.

method of analyzing cortical reorganization due to advantageous temporal and spatial resolution (Wiech et al., 2004). Other researchers have challenged EEG and MEG for truly assessing signal sources, and suggest employing fMRI as a tertiary, complementary component for signal localization (Bunge and Kahn, 2009; Cottureau et al., 2015). EEG, along with MEG, has higher temporal resolution but lower spatial resolution than fMRI (Meyer-Lindenberg, 2010). The unique ability to perform EEG simultaneously with fMRI further distinguishes this tool as a select method for capturing nonrepeatable events (Bandettini, 2009).

A case report of a subject with a congenitally absent limb found EEG signatures during attempted movements of the phantom limb to be similar to a cohort of healthy volunteers (Walsh et al., 2015). Another study analyzed a cohort of 22 right-hand amputees via EEG showed distinct global and local network changes in alpha and beta bands (Lyu et al., 2016). An investigation of the connection between pain catastrophizing and PLP using EEG showed that these patients had an increased response at the N/P135 dipole of the affected side, suggesting that attention to stimuli may be associated with PLP (Vase et al., 2012).

Mirror therapy has been studied as a potential PLP treatment, but recent developments in VR have enabled inventive therapeutic techniques. One such VR investigation utilized EEG and observed PLP alleviation and alpha wave coherence during stimulation of referred sensation areas (Osumi et al., 2020). EEG presents a safe and practical way to monitor the forefront of therapeutic techniques for PLP. It allows researchers to gather robust functional change data during therapies. EEG applications and key findings are summarized in Table 3.

While it has many applications and strengths, EEG is limited by lower spatial resolution than fMRI (Meyer-Lindenberg, 2010). The spatial resolution has important utility in the investigation of cerebral PLP mechanisms. If only certain superficial regions are reliably captured, deeper cortical reorganization may be missed. Additionally, a review of the EEG technique concluded that EEG deflections are challenging to interpret, and this tool should be one of many used in conjunction (Jackson & Bolger, 2014). EEG alone therefore may not provide adequate information about functional changes due to PLP.

EEG is one of the two main techniques for identifying functional changes with temporal resolution. It measures changes in electrical potential perpendicular to the direction of neuronal signal propagation. While EEG is limited by a lack of spatial resolution, its inherent design

allows it to be easily used alongside other tools to provide comprehensive results. EEG is a practical way to monitor functional changes while developing PLP therapies (Figure 1).

3.4 | Magnetoencephalography

MEG is another temporal-functional imaging technique used in PLP research. It functions by measuring the small magnetic fields created by electrical currents involved in neuronal signaling. The measured magnetic dipole is 90° off phase with the electrical one. The electrical and magnetic fields detected by EEG and MEG are generated by extracellular and intracellular currents, respectively (Singh, 2014). Both of these measured phenomena occur at directions perpendicular to that of neuronal signal propagation. Because it assesses magnetic activity at and parallel to the brain's surface, MEG is limited to the analysis of superficial sulci pyramidal cells (Bunge & Kahn, 2009). As mentioned before, EEG and MEG share a common caveat as they both have difficulty localizing signal sources (Bunge & Kahn, 2009). MEG also has a higher temporal resolution but lower spatial resolution compared to fMRI (Meyer-Lindenberg, 2010).

In a 2001 study, researchers induced acute left thenar pain in healthy non-PLP patients through capsaicin injections. MEG analysis revealed increased proximity between hand and lip representation, suggesting an acute reorganization in response to the stimulus (Sörös et al., 2001). Blume et al. later utilized MEG and identified lip and hand cortical reorganization following an amputated limb replantation. In contrast to other reports, they also found a negative correlation between pain and cortical reorganization (Blume et al., 2014).

Kringelbach et al. employed MEG to investigate the effect of deep brain stimulation on a PLP patient. The researchers found changes in mid-anterior orbitofrontal and subgenual cingulate activity after stimulation was stopped and associated these regions of the brain with pain relief. Their results demonstrate that MEG is useful for identifying response to therapy and potential surgical targets for pain relief (Kringelbach et al., 2007). Another investigation of brain-machine interface training integrated MEG reading with a robotic hand. Interestingly, they found this training to intensify pain when used with the

TABLE 4 Magnetoencephalography (MEG) and phantom limb pain (PLP)

Author	Sample size: Study control	Application	Key findings
Blume et al., 2014	13 0	Assessed reorganization following amputation	Negative correlation between pain and cortical reorganization
Kringelbach et al., 2007	1 0	Response to deep brain stimulation and identified surgical targets	Return of pain associated with changes in mid-anterior orbitofrontal and subgenual cingulate activity after stopping stimulation
Yanagisawa et al., 2018	10 ^a 0	During brain-machine interface training	MEG-based therapy can induce cortical plasticity to help treat PLP

Note: Study sample size reflects amputees with phantom limb pain unless otherwise noted.

^aAssessed one amputee and nine brachial plexus avulsion patients with phantom pain.

phantom limb. At the same time, it reduced pain during dissociative prosthetic-phantom hand training, further suggesting a link between plasticity and pain (Yanagisawa et al., 2016). MEG applications and key findings are summarized in Table 4.

Despite its usefulness and safety, MEG has sensitivity to artifacts. Ray et al. addressed the challenge of deep brain stimulation artifact when using MEG by focusing on the occipital lobe following a visual stimulus (Ray et al., 2009). The study shows that this tool can provide relevant information if researchers account for its limitations.

MEG is another primary technique for identifying functional changes with temporal resolution. In contrast to EEG, MEG detects magnetic activity parallel to the brain surface. This imaging modality is mostly limited by potential artifacts, which an adapted approach may control. MEG has promising future use for studying robotic and interventional therapy in PLP research (Figure 1).

4 | DISCUSSION

Neuroimaging has proven paramount in the study of PLP (Figure 1). DTI readily outlines structural changes and has potential for surgical applications but is frequently cited for technical limitations, such as subject motion and resolution. Additionally, DTI has often been criticized for variation in measuring technique and data interpretation. fMRI captures functional changes with spatial resolution in various PLP therapies, but cannot make critical neurologic distinctions, which limits data interpretation without behavioral or structural correlation. EEG and MEG are notable for identifying functional changes with a strong temporal resolution and are differentiated by perpendicular electric and parallel magnetic activity, respectively. EEG is significant for spatial limitations, while both EEG and MEG are limited by artifact. Overall, all four imaging techniques provide unique perspectives that have shaped the modern understanding of PLP.

Accessibility and practicality are common barriers that limit PLP neuroimaging. The study scale is often resource dependent, which has restricted how much imaging data can be collected. Limited reproducibility of neuroimaging findings may also hinder the analysis of PLP in certain cases. Consistent techniques and collaboration may alleviate the burden on groups studying PLP. Additionally, the automation of

imaging analysis using artificial intelligence and machine learning algorithms may generate uniformity among data interpretation (Hu et al., 2019; Vieira et al., 2017). These advancements enable the synthesis of data sets to help map neural changes. Robust data collection illustrates the key intersection of imaging and analytical technology, especially in the context of clinical disease. As this field evolves, researchers will continue to utilize neuroimaging aiming to provide fundamental insight into PLP's pathogenesis and treatment.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1002/brb3.2509>

ORCID

Jonathan D. Browne  <https://orcid.org/0000-0002-6233-2997>

Yi Cai  <https://orcid.org/0000-0003-2714-5384>

REFERENCES

- Alexander, A. L., Lee, J. E., Lazar, M., & Field, A. S. (2007). Diffusion tensor imaging of the brain. *Neurotherapeutics*, 4(3), 316–329. <https://doi.org/10.1016/j.nurt.2007.05.011>
- Andoh, J., Diers, M., Milde, C., Frobél, C., Kleinböhl, D., & Flor, H. (2017). Neural correlates of evoked phantom limb sensations. *Biological Psychology*, 126, 89–97. <https://doi.org/10.1016/j.biopsycho.2017.04.009>
- Andoh, J., Milde, C., Diers, M., Bekrater-Bodmann, R., Trojan, J., Fuchs, X., Becker, S., Desch, S., & Flor, H. (2020). Assessment of cortical reorganization and preserved function in phantom limb pain: A methodological perspective. *Scientific Reports*, 10(1), 11504. <https://doi.org/10.1038/s41598-020-68206-9>
- Aternali, A., & Katz, J. (2019). Recent advances in understanding and managing phantom limb pain. [version 1; peer review: 2 approved]. *F1000Research*, 8, 1167. <https://doi.org/10.12688/f1000research.19355.1>
- Bandettini, P. A. (2009). What's new in neuroimaging methods? *Annals of the New York Academy of Sciences*, 1156, 260–293. <https://doi.org/10.1111/j.1749-6632.2009.04420.x>

- Blume, K. R., Dietrich, C., Huonker, R., Götz, T., Sens, E., Friedel, R., Hofmann, G. O., Miltner, W. H. R., & Weiss, T. (2014). Cortical reorganization after macroreplantation at the upper extremity: A magnetoencephalographic study. *Brain: A Journal of Neurology*, 137(Pt 3), 757–769. <https://doi.org/10.1093/brain/awt366>
- Bunge, S. A., & Kahn, I. (2009). Cognition: An overview of neuroimaging techniques. In *Encyclopedia of neuroscience* (pp. 1063–1067). Elsevier. <https://doi.org/10.1016/B978-008045046-9.00298-9>
- Collins, K. L., Russell, H. G., Schumacher, P. J., Robinson-Freeman, K. E., O'conor, E. C., Gibney, K. D., Yambem, O., Dykes, R. W., Waters, R. S., & Tsao, J. W. (2018). A review of current theories and treatments for phantom limb pain. *The Journal of Clinical Investigation*, 128(6), 2168–2176. <https://doi.org/10.1172/JCI94003>
- Cottreau, B. R., Ales, J. M., & Norcia, A. M. (2015). How to use fMRI functional localizers to improve EEG/MEG source estimation. *Journal of Neuroscience Methods*, 250, 64–73. <https://doi.org/10.1016/j.jneumeth.2014.07.015>
- Ehde, D. M., Czerniecki, J. M., Smith, D. G., Campbell, K. M., Edwards, W. T., Jensen, M. P., & Robinson, L. R. (2000). Chronic phantom sensations, phantom pain, residual limb pain, and other regional pain after lower limb amputation. *Archives of Physical Medicine and Rehabilitation*, 81(8), 1039–1044. <https://doi.org/10.1053/apmr.2000.7583>
- Ephraim, P. L., Wegener, S. T., Mackenzie, E. J., Dillingham, T. R., & Pezzin, L. E. (2005). Phantom pain, residual limb pain, and back pain in amputees: Results of a national survey. *Archives of Physical Medicine and Rehabilitation*, 86(10), 1910–1919. <https://doi.org/10.1016/j.apmr.2005.03.031>
- Feldman, H. M., Yeatman, J. D., Lee, E. S., Barde, L. H. F., & Gaman-Bean, S. (2010). Diffusion tensor imaging: A review for pediatric researchers and clinicians. *Journal of Developmental and Behavioral Pediatrics*, 31(4), 346–356. <https://doi.org/10.1097/DBP.0b013e3181dcaa8b>
- Ferraro, F., Jacopetti, M., Spallone, V., Padua, L., Traballesi, M., & Brunelli, S., Cantarella, C., Ciotti, C., Coraci, D., Toffola, E. D., Mandrini, S., Morone, G., Pazzaglia, C., Romano, M., Schenone, A., Togni, R., Tamburin, S., & Italian Consensus Conference on Pain in Neurorehabilitation (ICCPN). (2016). Diagnosis and treatment of pain in plexopathy, radiculopathy, peripheral neuropathy and phantom limb pain. Evidence and recommendations from the Italian Consensus Conference on pain on neurorehabilitation. *European Journal of Physical and Rehabilitation Medicine*, 52(6), 855–866.
- Finger, S., & Hustwit, M. P. (2003). Five early accounts of phantom limb in context: Paré, Descartes, Lemos, Bell, and Mitchell. *Neurosurgery*, 52(3), 675–686; discussion 685. <https://doi.org/10.1227/01.neu.0000048478.42020.97>
- Flor, H., Nikolajsen, L., & Staehelin Jensen, T. (2006). Phantom limb pain: A case of maladaptive CNS plasticity? *Nature Reviews. Neuroscience*, 7(11), 873–881. <https://doi.org/10.1038/nrn1991>
- Foell, J., Bekrater-Bodmann, R., Diers, M., & Flor, H. (2014). Mirror therapy for phantom limb pain: Brain changes and the role of body representation. *European Journal of Pain*, 18(5), 729–739.
- Gilmore, C. A., Ilfeld, B. M., Rosenow, J. M., Li, S., Desai, M. J., Hunter, C. W., Rauck, R. L., Nader, A., Mak, J., Cohen, S. P., Crosby, N. D., & Boggs, J. W. (2019). Percutaneous 60-day peripheral nerve stimulation implant provides sustained relief of chronic pain following amputation: 12-month follow-up of a randomized, double-blind, placebo-controlled trial. *Regional Anesthesia and Pain Medicine*, 45, 44–51. <https://doi.org/10.1136/rapm-2019-100937>
- Griffin, S. C., & Tsao, J. W. (2014). A mechanism-based classification of phantom limb pain. *Pain*, 155(11), 2236–2242. <https://doi.org/10.1016/j.pain.2014.05.016>
- Guo, X., Liu, R., Lu, J., Wu, C., Lyu, Y., Wang, Z., Xiang, J., Pan, C., & Tong, S. (2019). Alterations in brain structural connectivity after unilateral upper-limb amputation. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 27(10), 2196–2204. <https://doi.org/10.1109/TNSRE.2019.2936615>
- Hagmann, P., Jonasson, L., Maeder, P., Thiran, J.-P., Wedeen, V. J., & Meuli, R. (2006). Understanding diffusion MR imaging techniques: From scalar diffusion-weighted imaging to diffusion tensor imaging and beyond. *Radiographics*, 26(Suppl 1), S205–S223. <https://doi.org/10.1148/rg.26si065510>
- Hakulinen, U., Brander, A., Ryymin, P., Öhman, J., Soimakallio, S., Helminen, M., Dastidar, P., & Eskola, H. (2012). Repeatability and variation of region-of-interest methods using quantitative diffusion tensor MR imaging of the brain. *BMC Medical Imaging*, 12, 30. <https://doi.org/10.1186/1471-2342-12-30>
- Hanley, M. A., Jensen, M. P., Smith, D. G., Ehde, D. M., Edwards, W. T., & Robinson, L. R. (2007). Pre-amputation pain and acute pain predict chronic pain after lower extremity amputation. *The Journal of Pain*, 8(2), 102–109. <https://doi.org/10.1016/j.jpain.2006.06.004>
- Hu, X.-S., Nascimento, T. D., Bender, M. C., Hall, T., Petty, S., O'malley, S., Ellwood, R. P., Kaciroti, N., Maslowski, E., & Dasilva, A. F. (2019). Feasibility of a real-time clinical augmented reality and artificial intelligence framework for pain detection and localization from the brain. *Journal of Medical Internet Research*, 21(6), e13594. <https://doi.org/10.2196/13594>
- Jackson, A. F., & Bolger, D. J. (2014). The neurophysiological bases of EEG and EEG measurement: A review for the rest of us. *Psychophysiology*, 51(11), 1061–1071. <https://doi.org/10.1111/psyp.12283>
- Jiang, G., Yin, X., Li, C., Li, L., Zhao, L., Evans, A. C., Jiang, T., Wu, J., & Wang, J. (2015). The Plasticity of brain gray matter and white matter following lower limb amputation. *Neural Plasticity*, 2015. <https://doi.org/10.1155/2015/823185>
- Jutzeler, C. R., Curt, A., & Kramer, J. L. K. (2015). Relationship between chronic pain and brain reorganization after deafferentation: A systematic review of functional MRI findings. *NeuroImage: Clinical*, 9, 599–606. <https://doi.org/10.1016/j.nicl.2015.09.018>
- Kringelbach, M. L., Jenkinson, N., Green, A. L., Owen, S. L. F., Hansen, P. C., Cornelissen, P. L., Holliday, I. E., Stein, J., & Aziz, T. Z. (2007). Deep brain stimulation for chronic pain investigated with magnetoencephalography. *Neuroreport*, 18(3), 223–228. <https://doi.org/10.1097/WNR.0b013e328010dc3d>
- Kubiak, C. A., Kemp, S. W. P., Cederna, P. S., & Kung, T. A. (2019). Prophylactic regenerative peripheral nerve interfaces to prevent postamputation pain. *Plastic and Reconstructive Surgery*, 144(3), 421e–430e. <https://doi.org/10.1097/PRS.00000000000005922>
- Larbig, W., Andoh, J., Huse, E., Stahl-Corino, D., Montoya, P., Seltzer, Z. E., & Flor, H. (2019). Pre- and postoperative predictors of phantom limb pain. *Neuroscience Letters*, 702, 44–50. <https://doi.org/10.1016/j.neulet.2018.11.044>
- Leung, A., Shukla, S., Yang, E., Canlas, B., Kadokana, M., Heald, J., Davani, A., Song, D., Lin, L., Polston, G., Tsai, A., & Lee, R. (2016). Diminished supraspinal pain modulation in patients with mild traumatic brain injury. *Molecular Pain*, 12. <https://doi.org/10.1177/1744806916662661>
- Leung, A., Yang, E., Lim, M., Metzger-Smith, V., Theilmann, R., Song, D., Lin, L., Tsai, A., & Lee, R. (2018). Pain-related white matter tract abnormalities in mild traumatic brain injury patients with persistent headache. *Molecular Pain*, 14, 174480691881029. <https://doi.org/10.1177/1744806918810297>
- Leung, A. (2020). Addressing chronic persistent headaches after MTBI as a neuropathic pain state. *The Journal of Headache and Pain*, 21(1), 77. <https://doi.org/10.1186/s10194-020-01133-2>
- Logothetis, N. K. (2008). What we can do and what we cannot do with fMRI. *Nature*, 453(7197), 869–878. <https://doi.org/10.1038/nature06976>
- Lyu, Y., Guo, X., Wang, Z., Tong, S., Lyu, Y., Guo, X., ..., & Tong, S. (2016). Resting-state EEG network change in alpha and beta bands after upper limb amputation. *Conference Proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2016, 49–52. <https://doi.org/10.1109/EMBC.2016.7590637>
- Maciver, K., Lloyd, D. M., Kelly, S., Roberts, N., & Nurmikko, T. (2008). Phantom limb pain, cortical reorganization and the therapeutic effect of mental imagery. *Brain: A Journal of Neurology*, 131(Pt 8), 2181–2191. <https://doi.org/10.1093/brain/awn124>

- Makin, T. R., & Flor, H. (2020). Brain (re)organisation following amputation: Implications for phantom limb pain. *Neuroimage*, 218, 116943. <https://doi.org/10.1016/j.neuroimage.2020.116943>
- Meyer-Lindenberg, A. (2010). From maps to mechanisms through neuroimaging of schizophrenia. *Nature*, 468(7321), 194–202. <https://doi.org/10.1038/nature09569>
- Montoya, P., Ritter, K., Huse, E., Larbig, W., Braun, C., Töpfner, S., Lutzenberger, W., Grodd, W., Flor, H., & Birbaumer, N. (1998). The cortical somatotopic map and phantom phenomena in subjects with congenital limb atrophy and traumatic amputees with phantom limb pain. *The European Journal of Neuroscience*, 10(3), 1095–1102. <https://doi.org/10.1046/j.1460-9568.1998.00122.x>
- Osumi, M., Sano, Y., Ichinose, A., Wake, N., Yozu, A., Kumagaya, S.-I., Kuniyoshi, Y., Morioka, S., & Sumitani, M. (2020). Direct evidence of EEG coherence in alleviating phantom limb pain by virtual referred sensation: Case report. *Neurocase: Case Studies in Neuropsychology, Neuropsychiatry, and Behavioural Neurology*, 26(1), 55–59. <https://doi.org/10.1080/13554794.2019.1696368>
- Owen, S. L. F., Heath, J., Kringelbach, M. L., Stein, J. F., & Aziz, T. Z. (2007). Pre-operative DTI and probabilistic tractography in an amputee with deep brain stimulation for lower limb stump pain. *British Journal of Neurosurgery*, 21(5), 485–490. <https://doi.org/10.1080/02688690701558358>
- Pasaye, E. H., Gutiérrez, R. A., Alcauter, S., Mercadillo, R. E., Aguilar-Castañeda, E., De Iturbe, M., Romero-Romo, J., & Barrios, F. A. (2010). Event-related functional magnetic resonance images during the perception of phantom limb. A brushing task. *The Neuroradiology Journal*, 23(6), 665–670. <https://doi.org/10.1177/197140091002300604>
- Pierpaoli, C., Jezzard, P., Basser, P. J., Barnett, A., & Di Chiro, G. (1996). Diffusion tensor MR imaging of the human brain. *Radiology*, 201(3), 637–648. <https://doi.org/10.1148/radiology.201.3.8939209>
- Ray, N. J., Jenkinson, N., Kringelbach, M. L., Hansen, P. C., Pereira, E. A., Brittain, J. S., Holland, P., Holliday, I. E., Owen, S., Stein, J., & Aziz, T. (2009). Abnormal thalamocortical dynamics may be altered by deep brain stimulation: Using magnetoencephalography to study phantom limb pain. *Journal of Clinical Neuroscience*, 16(1), 32–36. <https://doi.org/10.1016/j.jocn.2008.03.004>
- Renn, C. L., & Dorsey, S. G. (2005). The physiology and processing of pain: A review. *AACN Advanced Critical Care*.
- Richardson, C., & Kulkarni, J. (2017). A review of the management of phantom limb pain: Challenges and solutions. *Journal of Pain Research*, 10, 1861–1870. <https://doi.org/10.2147/JPR.S124664>
- Roux, F.-E., Ibarrola, D., Lazorthes, Y., & Berry, I. (2008). Chronic motor cortex stimulation for phantom limb pain: A functional magnetic resonance imaging study: Technical case report. *Neurosurgery*, 62(6 Suppl 3), 681–688. <https://doi.org/10.1227/01.neu.0000333765.28198.18>
- Seo, C. H., Park, C.-H., Jung, M. H., Baek, S., Song, J., Cha, E., & Ohn, S. H. (2019). Increased white matter diffusivity associated with phantom limb pain. *The Korean Journal of Pain*, 32(4), 271–279. <https://doi.org/10.3344/kjp.2019.32.4.271>
- Sherman, R. A., Sherman, C. J., & Parker, L. (1984). Chronic phantom and stump pain among American veterans: Results of a survey. *Pain*, 18(1), 83–95. [https://doi.org/10.1016/0304-3959\(84\)90128-3](https://doi.org/10.1016/0304-3959(84)90128-3)
- Simoës, E. L., Bramati, I., Rodrigues, E., Franzoi, A., Moll, J., Lent, R., & Tovar-Moll, F. (2012). Functional expansion of sensorimotor representation and structural reorganization of callosal connections in lower limb amputees. *The Journal of Neuroscience*, 32(9), 3211–3220. <https://doi.org/10.1523/JNEUROSCI.4592-11.2012>
- Singh, S. (2014). Magnetoencephalography: Basic principles. *Annals of Indian Academy of Neurology*, 17(Suppl 1), S107–S112. <https://doi.org/10.4103/0972-2327.128676>
- Soares, J. M., Marques, P., Alves, V., & Sousa, N. (2013). A hitchhiker's guide to diffusion tensor imaging. *Frontiers in Neuroscience*, 7, 31. <https://doi.org/10.3389/fnins.2013.00031>
- Sörös, P., Knecht, S., Bantel, C., Imai, T., Wüsten, R., Pantev, C., Lütkenhöner, B., Bürkle, H., & Henningsen, H. (2001). Functional reorganization of the human primary somatosensory cortex after acute pain demonstrated by magnetoencephalography. *Neuroscience Letters*, 298(3), 195–198. [https://doi.org/10.1016/S0304-3940\(00\)01752-3](https://doi.org/10.1016/S0304-3940(00)01752-3)
- Steeds, C. E. (2009). The anatomy and physiology of pain. *Surgery (Oxford)*, 27(12), 507–511. <https://doi.org/10.1016/j.mpsur.2009.10.013>
- Subedi, B., & Grossberg, G. T. (2011). Phantom limb pain: Mechanisms and treatment approaches. *Pain Research and Treatment*, 2011. <https://doi.org/10.1155/2011/864605>
- Vase, L., Egsgaard, L. L., Nikolajsen, L., Svensson, P., Jensen, T. S., & Arendt-Nielsen, L. (2012). Pain catastrophizing and cortical responses in amputees with varying levels of phantom limb pain: A high-density EEG brain-mapping study. *Experimental Brain Research*, 218(3), 407–417. <https://doi.org/10.1007/s00221-012-3027-6>
- Vieira, S., Pinaya, W. H. L., & Mechelli, A. (2017). Using deep learning to investigate the neuroimaging correlates of psychiatric and neurological disorders: Methods and applications. *Neuroscience and Biobehavioral Reviews*, 74(Pt A), 58–75. <https://doi.org/10.1016/j.neubiorev.2017.01.002>
- Walsh, E., Long, C., & Haggard, P. (2015). Voluntary control of a phantom limb. *Neuropsychologia*, 75, 341–348. <https://doi.org/10.1016/j.neuropsychologia.2015.06.032>
- Wiech, K., Kiefer, R.-T., Töpfner, S., Preissl, H., Braun, C., Unertl, K., Flor, H., & Birbaumer, N. (2004). A placebo-controlled randomized crossover trial of the N-methyl-D-aspartic acid receptor antagonist, memantine, in patients with chronic phantom limb pain. *Anesthesia and Analgesia*, 98(2), 408–413. <https://doi.org/10.1213/01.ane.0000096002.53818.bd>
- Yanagisawa, T., Fukuma, R., Seymour, B., Hosomi, K., Kishima, H., Shimizu, T., Yokoi, H., Hirata, M., Yoshimine, T., Kamitani, Y., & Saitoh, Y. (2016). Induced sensorimotor brain plasticity controls pain in phantom limb patients. *Nature Communications*, 7, 13209. <https://doi.org/10.1038/ncomms13209>
- Yanagisawa, T., Fukuma, R., Seymour, B., Hosomi, K., Kishima, H., Shimizu, T., Yokoi, H., Hirata, M., Yoshimine, T., Kamitani, Y., & Saitoh, Y. (2018). MEG-BMI to control phantom limb pain. *Neurologia Medico-Chirurgica*, 58(8), 327–333. <https://doi.org/10.2176/nmc.st.2018-0099>
- Ziegler-Graham, K., Mackenzie, E. J., Ephraim, P. L., Travison, T. G., & Brookmeyer, R. (2008). Estimating the prevalence of limb loss in the United States: 2005 to 2050. *Archives of Physical Medicine and Rehabilitation*, 89(3), 422–429. <https://doi.org/10.1016/j.apmr.2007.11.005>

How to cite this article: Browne, J. D., Fraiser, R., Cai, Y., Leung, D., Leung, A., & Vaninetti, M. (2022). Unveiling the phantom: What neuroimaging has taught us about phantom limb pain. *Brain and Behavior*, 12, e2509. <https://doi.org/10.1002/brb3.2509>