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Topical review

A mechanism-based classification of phantom limb pain

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1. A mechanism-based classification of pain

Despite the abundance of literature on phantom limb pain, there remains no clear consensus on the mechanisms of the disorder: phantom limb pain has been attributed to genetic make-up [11,25], memories [3,21], neuromata [28], spinal plasticity [15], and cortical re-mapping [17,18]. A standard treatment for the disorder remains equally elusive. Treatments range from acupuncture to deep brain stimulation [16] and include mirror/virtual reality therapies [13,26], mental imagery [24], transcutaneous nerve stimulation [22], deep brain, motor cortex, and spinal cord stimulation [2,8,23], and the pharmaceutical agents morphine [39], gabapentin [9], amitriptyline [31], calcitonin [19], ketamine [15], and memantine [27], among others.

The divergence in theories on phantom limb pain stems in part from the heterogeneity of the disorder itself. Although phantom limb pain occurs in up to 85% of patients after amputation [32], the characteristics of this pain vary drastically. The onset of phantom limb pain ranges from hours to decades [12,29], and the frequency of episodes vary from every few days to several times each day [30]. The length of episodes can range from less than 1 minute to continuous [30], and pain descriptors include shooting, squeezing, tingling, throbbing, stabbing, burning, and cramping [32].

The heterogeneity of phantom limb pain is widely acknowledged, and it is recognized that the disorder likely arises from multiple mechanisms [18]. Some authors have argued for mechanism-based management of pain [16,33,36], although others have attempted to classify amputation pain according to severity [20] and etiology [14,34]. However, phantom limb pain remains a blanket term for pain in absent tissue, regardless of the qualities and theorized mechanisms of this pain.

We believe that a paradigm shift in the conceptualization of phantom limb pain from a single disorder to a cluster of pain conditions holds enormous potential. A mechanism-based classification of phantom limb pain promises to resolve major failures in clinical research thus far, leading to more directed research and effective treatment of pain in a missing limb. Further support for the development of a mechanism-based classification of pain comes from parallel work in other lines of pain research.

2. Current phantom limb pain research

The literature abounds with case studies that present novel and promising treatments for phantom limb pain. Less common, yet still prevalent, are randomized, controlled trials (RCTs) that rigorously assess these treatments. These trials tend to present less promising results: Although a few RCTs in the last decade have shown sustained relief for phantom limb pain, the majority of RCTs for phantom limb pain fail to show a statistically significant reduction of pain in the group receiving the treatment of interest [37]. Taking into account the publication bias toward successful RCTs, the treatment prognosis for phantom limb pain seems particularly bleak [35].

However, it is possible that this trend—in which a promising treatment for phantom limb pain fails to prove effective in a RCT—is due to the treatment's specificity rather than its efficacy. That is to say, it is possible that a given treatment effectively reduces pain but only for a subset of patients. When this subset is part of a larger group, the outcomes of the group may dilute these positive outcomes, leading to the false conclusion that the treatment is not an effective therapy. In fact, a review of the literature (Table 1) confirms that inclusion/exclusion criteria for studies tend to be limited to basic characteristics such as intensity of pain (ie, pain must be above a certain threshold), time since injury, and type of injury as well as characteristics that are relevant not to the condition but, rather, to the practicality of the study itself, such as pregnancy, history of allergy to the drug in question, and plans to undergo major surgery in the near future. This tendency is particularly troublesome in light of the fact that the majority of treatments for phantom limb pain are predicated on a theory as to the mechanism of the pain, and it is widely recognized that there are multiple mechanisms for phantom limb pain [18].

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3. Research utility of classification of phantom limb pain

A mechanism-based classification system for phantom limb pain would allow researchers to target a specific patient population according to the theorized mechanism of action of the treatment in question. This approach could reveal, in a subset of patients, therapeutic effects that may be obscured with a more diverse patient population.

Furthermore, a mechanism-based classification would provide valuable direction and structure to the study of phantom limb pain. This approach would direct research toward the elucidation of the mechanisms behind phantom limb pain and the mechanisms of action of pharmaceuticals and other treatments to reduce pain. More importantly, this approach would generate testable hypotheses. A mechanism-based classification of pain creates a clear trajectory for a theory or treatment of phantom limb pain. For each theory of phantom limb pain, it will be necessary to do the following: define the clinical symptom and the mechanism involved; select the affected population with that particular presentation of phantom limb pain; select or develop a treatment targeting this mechanism; test this treatment in the selected population; and re-evaluate the theory based upon these results. For each treatment of phantom limb pain, besides testing the treatment, it will be necessary to characterize this population for factors that contribute to treatment response, determine the factor(s) for treatment response, use this information to determine the subpopulation of patients sensitive to this treatment, and seek to determine the mechanism of pain for this population based upon the mechanism of action of the treatment.

4. Clinical utility of classification of phantom limb pain

Currently, treatment of phantom limb pain is through trial and error. This method is inadequate not only in terms of providing pain relief to patients, but also in protecting patients from side effects and adverse reactions to treatments that may not even relieve pain. Many treatments for phantom limb pain and pain in general are associated with a number of side effects, ranging from mild to severe. For example, gabapentin, a commonly used first-line treatment for amputation pain, can be associated with side effects such as involuntary eye movement, lack of coordination, blurred vision, dizziness, decreased energy, drowsiness, and extremity edema [1]. Distinguishing between different types of phantom limb pain would enable clinicians to offer stratified or personalized therapy by selecting the most effective treatment(s) among the many available, allowing safer and more effective reduction of pain. The consequences of this approach could be particularly powerful if accompanied by efforts to characterize the patient population not only in terms of likelihood to respond to treatment but also likelihood to experience noxious effects.

5. Development of a mechanism-based classification system of pain

The effort to develop a mechanism-based classification would not be isolated but, rather, would parallel work in other lines of pain research. Although still in the preliminary stages, this work lends credence to the potential utility of reclassifying phantom limb pain. Furthermore, this work could indicate potentially useful distinctions within phantom limb pain patients.

In 1998, Woolf et al. argued that the development of a taxonomy of pain would allow the development of drugs that target specific mechanisms, the creation of new guidelines for experimental design, and the eventual development of more reliable, validated diagnostic tools for treatment [38]. However, despite the appeal of this approach, it is not yet attainable, as the pathophysiological mechanisms for pain identified in animal research have not yet been translated into clinical practice [5].

Research has therefore emerged seeking to characterize patients according to observable pathophysiology. The most obvious detectable manifestation of pain is the symptom—ie, the qualitative aspects [4,5,10]. Although it remains unclear whether symptoms truly correspond to the pathophysiology of pain, current research using this approach is promising. A study examining neuropathic pain across etiologies used factor analysis to show that pain qualities could be categorized into 5 independent dimensions [6]. The various symptoms that formed these dimensions were rarely associated with a specific etiology, questioning the importance of etiology in the clinical expression of neuropathic pain [6]. A second apparent manifestation of pain is sensory characteristics as measured by quantitative sensory testing (QST). A recent study by Baron et al., which examined patients with diabetic neuropathy and postherpetic neuralgia, used hierarchical cluster analysis to identify 5 distinct subgroups of patients with a characteristic sensory profile [7]. Although more research is necessary to link the pain in each of these dimensions or subgroups of patients to a shared pathophysiological mechanism, it is possible that these studies will generate clinically significant distinctions across patients that can be applied to phantom limb pain research.

6. Challenges for a mechanism-based classification of phantom limb pain

Accepting the utility of a mechanism-based classification of phantom limb pain begets the larger challenge of developing such a classification system. The critical component of this system is validity, defined as how closely the system corresponds to the underlying biology of the disorder. Woolf et al. list 2 approaches for establishing validity in their 1998 article. The first approach is to define validity in terms of a gold standard; the second approach is to "use an iterative, fallible process of searching for and identifying symptom clusters, biological markers, history and treatment response" [38]. Phantom limb pain lacks a gold standard, requiring the second approach.

The key to initiating this fallible search is exploratory work to identify distinctions that can be used to profile patients. These profiles can then be scrutinized to determine whether they are scientifically (ie, link to basic mechanisms identified in animal research) or clinically (ie, predict treatment response or disease progression) meaningful. This approach is inherently inefficient, as it is likely that many distinctions across patients will fail to correspond to underlying pathophysiology or clinical outcomes. However, until a gold standard is established, this imperfect process is necessary to build the classification system that may ultimately streamline phantom limb pain research.

A mechanism-based classification of phantom limb pain will not solve many of the problems intrinsic to the study of a condition that lies at the intersection of experience, psychology, and biology. However, carefully picking apart the mechanisms of phantom limb pain on a given platform can only help to elucidate the factors contributing to pain on another.

7. Conclusion

This article seeks to redefine phantom limb pain as a spectrum of disorders. Discarding the conception of phantom limb pain as a single disorder would allow the identification of distinct conditions of phantom limb pain with clear mechanisms and treatment. Although this article calls for a classification system of these con-

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