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Cortical plasticity as a basis of phantom limb pain: Fact or fiction?

J. Andoh,[a]* C. Milde,[a] J. W. Tsao[b,c,d] and H. Flor[a]*

[a] *Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, D-68159 Mannheim, Germany*

[b] *Department of Neurology, University of Tennessee Health Science Center, Memphis, TN, USA*

[c] *Children's Foundation Research Institute, Le Bonheur Children's Hospital, Memphis, TN, USA*

[d] *Department of Neurology, Memphis Veterans Affairs Medical Center, Memphis, TN, USA*

Abstract—Cortical reorganization has been proposed as a major factor involved in phantom pain with prior nociceptive input to the deafferented region and input from the non-deafferented cortex creating neuronal activity that is perceived as phantom pain. There is substantial evidence that these processes play a role in neuropathic pain, although causal evidence is lacking. Recently it has been suggested that a maintenance of the cortical representation of the former hand area is related to phantom pain. Although interesting, evidence for this process is so far scarce. In addition, peripheral factors have been proposed as important for phantom limb pain. Although often introduced as contradictory, we suggest that cortical reorganization, preserved limb function and peripheral factors interact to create the various painful and nonpainful aspects of the phantom limb experience. In addition, the type of task (sensory versus motor), the interaction of injury- and use-dependent plasticity, the type of data analysis, contextual factors such as the body representation and psychological variables determine the outcome and need to be considered in models of phantom limb pain. Longitudinal studies are needed to determine the formation of the phantom pain experience.

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Key words: phantom limb pain, cortical reorganization, preserved limb, context dependency, peripheral input.

INTRODUCTION

There is considerable evidence that phantom limb pain is related to changes in the somatotopic map in primary sensory and motor cortex, although causal evidence is lacking and it has been debated whether maladaptive cortical plasticity or preserved function of the representation of the limb contribute to pain (cf., Flor et al., 2006, 2013; Makin et al., 2013a, 2015). In this review, we present evidence for the central changes related to phantom limb pain and discuss their interaction with peripheral factors. In addition, we evaluate the role of methodological aspects of assessing cortical reorganization, type of experimental task (sensory, motor or both) and the role of body perception and use-dependent plasticity. We also address the role of psychological factors and how they relate to phantom pain. A better understanding of how these factors interact could help to understand differences between studies and could advance the analysis of mechanisms of phantom limb pain. Finally, we review some training interventions for phantom limb pain, aiming at inducing changes in the perception of the phantom limb and we discuss their contribution to our current understanding of phantom pain.

PERSPECTIVES ON THE NEURAL BASIS OF PHANTOM LIMB PAIN

Neural plasticity is generally viewed as an adaptive learning process enabling the cortex to redistribute computational resources to focus on brain regions containing behaviorally relevant information. For example, the cortical representation of the ventral body surface is expanded in nursing rats (Xerri et al., 1994). Map expansions also occur in humans following extensive sensory and sensorimotor training (e.g., Merzenich et al., 1990; Recanzone et al., 1992; Elbert et al., 1995; Molina-Luna et al., 2008; Xerri, 2012). Neural plasticity can, however, also be maladaptive, as shown by significant changes in several cortical regions resulting from injury (e.g., Latremoliere and Woolf, 2009; Lozano, 2011) and various types of chronic pain (e.g., Juottonen et al., 2002; Maihofner et al., 2003; Vartiainen et al., 2008, 2009; Wrigley et al., 2009).

*Corresponding authors. Address: Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, J5, D-68159 Mannheim, Germany. Fax: +49-621-1703-6305.
E-mail addresses: jamila.andoh@zi-mannheim.de (J. Andoh), herta.flor@zi-mannheim.de (H. Flor).
Abbreviation: MEG, magnetoencephalography.

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A previous systematic review summarized studies investigating the relationship between chronic pain and functional reorganization (Jutzeler et al., 2015). The authors focused on functional magnetic resonance imaging studies in support for either maladaptive or preserved cortical function in relation with neuropathic pain or phantom limb pain and highlighted conflicting findings.

The maladaptive plasticity model is based on a series of studies by Flor et al. (1995) and others (e.g., Lotze et al., 1999; MacIver et al., 2008; Diers et al., 2010, 2015) that examined cortical map changes related to phantom pain. These studies reported that, after an amputation, the severity of pain in the missing limb (phantom pain) and the degree of topographic reorganization in the somatosensory and motor cortices were positively correlated (e.g., Flor et al., 1995; Karl et al., 2001; Lotze et al., 2001; Raffin et al., 2016). In particular, the authors observed that stimulation of the mouth in upper extremity amputees led to a peak of neuronal activation in the deafferented hand area in primary somatosensory cortex. The larger the shift, the higher the magnitude of phantom limb pain. Such findings have also been shown in the deprived motor cortex (e.g., Karl et al., 2001; Raffin et al., 2016). It was proposed that these plastic brain changes might be a correlate of phantom pain and it was furthermore suggested that this reorganization may be primed by nociceptive input prior to the amputation (cf. Flor et al., 2006). This view is in line with a recent study showing that compared with no pain, application of tonic pain prior to temporary ischemic hand deafferentation (induced by inflation of an arm cuff) increased corticospinal excitability in healthy participants (Mavromatis et al., 2016), which has also been observed after amputation (Kew et al., 1994) and has been related to phantom limb pain (Karl et al., 2001).

A different model for PLP has recently been suggested, stating that a maintained representation of the phantom limb, potentially stabilized by nociceptive input, might be causal for phantom limb pain, and concluded that such results invalidate the previous maladaptive reorganization data (Makin et al., 2013a). While the maladaptive plasticity model was suggested based on previous studies investigating the functional reorganization surrounding the cortical representation of the missing limb, Makin et al. investigated the cortical representation of the missing limb itself. The authors used functional magnetic resonance imaging while the amputees were instructed to perform movements of the phantom or to imagine phantom movements if they were unable to move the phantom. The authors showed that greater activation in the region of the deprived sensorimotor cortex, where the amputated limb was represented, was positively correlated with phantom limb pain. The use of phantom movements as done in Makin et al. is an interesting approach, but may lead to different patterns of activation than the previously used sensory stimulation or movements of adjacent body parts, such as the mouth, since the organization of motor cortex follows other principles than that of somatosensory cortex (Graziano, 2016). In addition, the nature of the neural representation of the phantom limb is of importance since the preserved topography model focused on the current representation of the phantom, which may differ from the original hand representation as a consequence of the amputation whereas the ‘‘maladaptive” model measured changes in the relationship of the representation of the adjacent body site and the former hand representation and relied on sensory input. So far, there is little evidence for preserved topography related to pain chronicity. It is nevertheless possible that both processes – preserved limb function and reorganization – occur and that both differentially contribute to nonpainful and painful phantoms (Flor et al., 2013; Raffin et al., 2016). The idea that deafferentation-induced changes in representation do not necessarily affect the original representation is supported by a previous study showing that an increase in the representation of the biceps as a result of a 40-min ischemic block did not decrease the hand representation in healthy participants (McNulty et al., 2002).

Both, the maladaptive plasticity and the preserved function models are based on the neural representation of primary somatosensory and motor areas, although alterations might extend to other primary or higher level areas, for example, visual or temporo-parietal cortices (Makin et al., 2010; Preissler et al., 2013), underlining the multidimensionality of the pain experience.

CONTEXT MATTERS

It is important to emphasize conceptual differences across studies in assessing cortical reorganization following amputation. While some studies used various types of phantom movements (imagined, executed, or a combination), other studies used innocuous stimulation at body sites represented adjacent to the former hand area, movement of adjacent body parts such as the mouth or illusory movement, such as that related to mirrored movements.

For example, in a functional magnetic resonance imaging study, Diers et al. (2010, 2015) used perceived movement of the phantom based on a mirror illusion where the intact hand was moved in front of a mirror and gave the visual impression of the phantom moving. In this set-up, amputees with phantom pain failed to show activation in the phantom hand cortex and amputees with more activation had less phantom pain, contrary to the Makin et al. (2013a) study. The main difference between the experiments was that there was no active production of phantom movement in the Diers et al. study, but the perceived phantom movement was based on a sensory illusion.

Since sensory and motor maps are structured by their function and dynamics over time, contextual differences may have contributed to the different results. Such differences in task-context involve varying functional somatotopies. For example, different networks underlie motor execution and motor imagery both in healthy subjects (Jeannerod, 2001; Park et al., 2015) and amputees, where motor execution recruited primary motor, somatosensory and dorsal premotor cortices, whereas motor imagery involved the inferior and superior parietal lobules (Raffin et al., 2012b). Such findings argue against

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