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Harvie, D; Moseley, G L

*Published in:*  
European Journal of Pain

*DOI:*  
[10.1002/j.1532-2149.2014.00458.x](https://doi.org/10.1002/j.1532-2149.2014.00458.x)

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*Recommended citation(APA):*  
Harvie, D., & Moseley, G. L. (2014). Exploring changes in the brain associated with recovery from phantom limb pain - the potential importance of telescoping. *European Journal of Pain*, 18(5), 601-2.  
<https://doi.org/10.1002/j.1532-2149.2014.00458.x>

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Exploring changes in the brain associated with recovery from phantom limb pain – the potential importance of telescoping.

Daniel Harvie & G Lorimer Moseley

*Sansom Institute for Health Research, University of South Australia & PainAdelaide Research Network, Adelaide, Australia.*

In this issue you will find a paper entitled 'Mirror therapy for phantom limb pain: Brain changes and the role of body representation' (Foell et al. 2013). Thirteen amputees with chronic phantom limb pain (PLP) participated in a four-week mirror therapy programme. Functional brain imaging measures taken before and after the programme were related to change in PLP over the same period.

Phantom limbs have long fascinated psychologists, neuroscientists and neurologists. That the phantom can be distorted, speaks to the plasticity of the brain's representation of the body and flags the potential opportunity for treatments that directly target these representations (see (Moseley, Gallace et al. 2012) for review). Mirror therapy is one such treatment. Foel et al suggest that mirror therapy aims to re-establish normal cortical representations by using visual input of an intact limb as a substitute for the now-missing proprioceptive feedback from the amputated limb. Systematic review suggests that mirror therapy probably reduces PLP, at least for some patients (Bowering, O'Connell et al. 2012). The study by Foel et al. raises two particularly intriguing results that have the potential to shift our thinking with regard to PLP and cortical representations.

First, eight participants had a telescoping phantom and their PLP did not change over the treatment period. In contrast, five patients had a non-telescoping phantom and their PLP halved? Think of how remarkable this is – 16 years after amputation, just 15 minutes a day for a month. Is such a fabulous result attributable to the mirror therapy? There was no control condition, nor group (which the authors acknowledge), and timeline was not jittered, so non-treatment factors - time, regression to the mean and 'non-specific' components - could all have contributed. This is important and we would contend that to conclude on the basis of this study that mirror therapy is effective, is conjecture. Is the fabulous result attributable to having a non-telescoping phantom? It would seem highly unlikely that this alone would bring pain relief – if so, people with an intact phantom should not have PLP, which they clearly do.

We think the two most likely explanations for the difference between groups are: (i) that non-treatment factors introduced by researchers and clinicians not being blinded to phantom type, and (ii) that treatment based on mirror therapy is effective for amputees with an intact phantom, but not for amputees with a telescoping phantom. The latter explanation is clearly more seductive but the former should not, and cannot, be discounted on the basis of this study. Blinding the research/clinical team to the type of phantom, or at least assessing the expectations of the team and patients about the relationship between a telescoping phantom and response to mirror therapy, would greatly strengthen the case for the latter. That said, the remarkable contrast between the telescopers and the non-telescopers begs a second look and we think the authors have every reason to now test this hypothesis in an *a priori* design. If such a study supports the current result, then it would imply that PLP patients with telescoping phantoms not be referred to mirror therapy-based treatment, which would in turn greatly elevate our expectations of a positive response. But why would mirror therapy be ineffective in

the case of telescoping phantoms? The authors suggest that the mismatch between what the limb feels like, and how it looks during mirror therapy, is the likely reason and their data seem supportive of this idea and suggest that first enhancing the congruence between what one sees and what one feels, perhaps via virtual reality, might improve mirror therapy effects on PLP.

The second intriguing result relates to the brain imaging data. Across the whole cohort, there was no change in cortical activation during lip or hand movement tasks between pre and post treatment. Yet the five patients with an intact, non-telescoping phantom showed normalisation of primary sensory cortex activation during lip pursing, a normalisation that was very strongly related to reduction in PLP ( $r=0.75$ ). Such a relationship clearly suggests that reduction in PLP and normalisation of S1 activation during lip pursing, are related, which contrasts with a recent study in which normal (rather than abnormal) S1 activation was positively related to phantom limb pain (Makin, Scholz et al. 2013). That is, phantom limb pain was associated with preserved, or normal, S1 activation during hand movements, not abnormal activation. Foell et al., (2013) however, correctly note that the Makin et al., data relate to the magnitude of activation rather than the spatial representation of activation. Nonetheless, both studies are limited by small samples and the potential contrast between them would suggest that further work is required before we are able to interpret with confidence altered S1 activation in phantom limb pain. Finally, whether or not reduction of PLP is a cause or consequence of altered S1 activation remains to be determined.

Bowering, K. J., N. E. O'Connell, A. Tabor, M. J. Catley, H. B. Leake, G. L. Moseley and T. R. Stanton (2012). "The Effects of Graded Motor Imagery and Its Components on Chronic Pain: A Systematic Review and Meta-Analysis." The journal of pain **14**(1): 3-13.

Makin, T. R., J. Scholz, N. Filippini, D. Henderson Slater, I. Tracey and H. Johansen-Berg (2013). "Phantom pain is associated with preserved structure and function in the former hand area." Nature communications **4**: 1570.

Moseley, G. L., A. Gallace and C. Spence (2012). "Bodily illusions in health and disease: physiological and clinical perspectives and the concept of a cortical 'body matrix'." Neuroscience and Biobehavioral Reviews **36**(1): 34-46.