A new kind of spatial inattention associated with chronic limb pain?

Running title: Somatospatial inattention in pain

Emily Reid[1] BPhty (Hons), Sarah B Wallwork[1] BPhty (Hons), Daniel Harvie[1] MSc, K. Jane Chalmers[1], BPhty (Hons), Alberto Gallace[2], PhD (Hons), Charles Spence[3], PhD, G. Lorimer Moseley,[1,4] PhD FACP

[1] Sansom Institute for Health Research, University of South Australia, Adelaide, Australia

[2] Department of Psychology, University of Milano-Bicocca, Lombardy, Italy.

[3] Department of Experimental Psychology, University of Oxford, Oxford, UK.

[4] Neuroscience Research Australia, Sydney, Australia.

Author correspondence: G. Lorimer Moseley

Sansom Institute for Health Research, University of South Australia

GPO Box 2471, Adelaide, South Australia 5001 Australia

e: Lorimer.Moseley@gmail.com | p: +61 8 83022454 | fax: +61 8 83022853

Website: www.bodyinmind.org.

Characters including spaces in title: 68. In running head: 33.

Words in abstract: 89. Introduction: 356. Discussion: 479. In body of manuscript: 1642

Abstract

Pathological limb pain patients show decreased attention to some stimuli on the painful limb and increased attention to others, a paradox that has dogged the field for over a decade. We hypothesized that pathological pain involves a spatial inattention confined to bodily representations. Patients showed inattention to the painful side for: visual processing of body parts but not letters; tactile processing but not auditory; body-part bisection tasks but not line bisection tasks. We propose the new term ‘somatospatial inattention’ to describe bodily-specific spatial inattention associated with pathological limb pain.

INTRODUCTION

Pathological pain is associated with a perplexing array of dysfunctions that have bewildered neurologists for decades[1]. For example, complex regional pain syndrome (CRPS)[2] and chronic back pain[3] are associated with sensory processing deficits that can not be explained by problems at the tissue, peripheral or spinothalamic level. Patients also report that the painful limb 'has a mind of its own' or 'requires all their attention to move'[2]. These problems seem consistent with the spatial neglect that can occur after brain damage, where stimuli from the ipsilesional side of space are prioritized over those from the contralesional side[4]. People with CRPS demonstrate a bias in tactile processing according to where *in space*, stimuli occur[5]. Yet they perform normally on visuospatial attention tasks[6] and in body midline judgments, they misplace the midline *towards* the affected side[7]. This evidence of decreased attention to some stimuli and increased attention to others remains to be reconciled – current theories of spatial inattention cannot explain it.

One explanatory mechanism for hemispatial neglect after stroke is an imbalance in the interhemispheric push-pull pattern of influence between the hemispheres[8]. A similar problem might occur with CRPS: the strongest predictor of CRPS is severe pain in the acute phase after injury[9]; pain compels us to protection, limiting movement and increasing visual scanning[10]. We speculate that visuospatial representations of the at-risk space become stronger, which would explain the visuospatial bias *towards* the painful side in midline judgments[7], and functional or applied limb immobilisation and compensatory over-use of the healthy limb (augmenting ipsilateral to contralateral interhemispheric inhibition[11]), would explain the processing biases *away* from the painful side for body-relevant stimuli. This might also explain other perplexing aspects of CRPS: the imbalance between somatosensory representations of the painful and healthy limbs[12] and abnormally large representation of the healthy limb[13]; poor tactile acuity on the painful limb unrelated to stimulus detection or transmission[14]; and disinhibition within the ipsilateral cortex[15]. We hypothesised that CRPS involves a deficit in the integration of bodily representations with spatial processing, not a deficit in spatial processing *per se*. We tested our hypothesis in three separate experiments, each one dissociating spatial processing from its integration with bodily representations.

PATIENTS AND METHODS

Experiment One

147 people with CRPS volunteered between 2004 and 2011. Full data were obtained from 130 (mean ± SD age =44 ± 16 years; duration of symptoms =30 ± 21 months; 101 arm; 29 leg). Patients performed left/right judgments of pictured hands or feet, presented in a range of postures and perspectives ('Is this a left hand or a right hand?')[16], and left/right judgments of two-dimensional line-drawn letters ('Is this a letter or the mirror image of a letter?')[17]. We predicted that patients would show a bias in visuospatial processing towards images presented on the side of the monitor contralateral to the painful limb, for the hand judgment task but not the letter task. RT for accurate responses was compared between stimuli presented on either the side of the monitor. Participants rated their pre-task pain level ('Pain now') and their average pain over the last two days ('Average pain').

Experiments 2 and 3

Thirteen patients with CRPS of one hand or wrist (age =41 ± 13 years; duration = 38 ± 20 months; eight females; 11 right-handers; seven dominant-hand affected) were examined clinically and gave written informed consent. In Experiment 2, we predicted that patients would show a bias in tactile processing towards stimuli presented to the healthy limb over perceptually identical stimuli to the painful limb, but no such bias for auditory processing. Using methods described in detail elsewhere,[5, 18] patients made temporal order judgments (TOJ - 'Which stimulus occurred first?') of stimuli delivered at corresponding locations on either side of the body, at various interstimulus intervals (ISI). The ISI at which the stimuli are equally likely to be judged as occurring first is called the Point of Subjective Simultaneity (PSS). A PSS significantly greater than zero reflects a bias in stimulus processing toward the opposite side.[5, 18] We compared PSS between the two TOJ tasks.

Experiment 3 consisted of two bisection tasks: (i) standard line bisections undertaken according to the established method[4], and (ii) bisecting the following: (i) A line along the dorsal surface of the forearm, between the elbow crease and the webspace between the thumb and index finger with the forearm perpendicular to the sagittal plane; measures were taken for the affected and healthy arms on both the affected and healthy side of the body midline; (ii) A line on the back of the hand, from the tip of the middle finger to the wrist, measured on either hand held on either side of the body midline; (iii) A line on the back of the hand from the medial to the lateral edge of the palm, with the hand either perpendicular or parallel to the sagittal plane.

Full methods and *a priori* statistical analysis protocol were locked and published online at www.bodyinmind.org/protocols/Reidetal_somatospatial. Informed consent was obtained. Institutional ethics committees approved all procedures.

RESULTS

Our predictions were upheld. In Experiment 1, RT was longer when the hand or foot image was presented on the side of the monitor ipsilateral to the painful limb (2965 ± 84ms) than when it was presented on the other side (2700 ± 82 ms; main effect of Screen - $F(1, 129) = 270$, $p < 0.001$), but there was no such difference for the letter orientation task (RT between 811 ± 215 ms and 818 ± 201 ms for all; n.s.). A bias in visuospatial processing towards the healthy side also occurred for ipsilateral foot pictures for people with arm pain and vice versa: RT =2058 ± 44ms (painful side); 2025 ± 44 ms (healthy side; $F(1,129) = 48.5$, $p < 0.001$). Accuracy was unaffected (range = 75% - 100%; mean =87% - 90% for all). There was no speed-accuracy trade off ($p > 0.33$ for all). The magnitude of the bias in processing for body images was related to Duration of symptoms, Average pain and Current pain ($R \sim 0.5$, $p < 0.01$ for all).

In Experiment 2, there was a bias in tactile processing towards the healthy side (PSS = 27 ms ± 6.9 ms), but no bias in auditory processing (PSS = 4 ms ± 12.1 ms; Fig. 1). PSS did not relate to

Average pain (p =0.08), nor to Duration of symptoms (p =0.09). There was no difference in PSS between those with left-sided pain and those with right-sided pain (p >0.05).

Insert Figure 1 about here

In Experiment 3, patients were accurate on the conventional line-bisection tasks. However, when patients bisected lines on body parts, the tests were clearly positive for spatial neglect (Fig. 2). For the affected forearm bisection task, the judgment was 14 ± 2 mm from the true midline, towards the healthy side. The magnitude of the error was related to Duration of CRPS (standardized beta = -0.40, p <0.05) and to Average pain (standardized beta = 0.88, p <0.001; R > 0.85 for both). The hand-length and hand-width task results corroborated the forearm findings (Fig. 3).

Insert Figure 2 about here

Insert Figure 3 about here.

DISCUSSION

Here we report the first evidence that pathological limb pain involves a spatial inattention that is confined to bodily representations, a deficit we term 'somatospatial inattention'. The current experiments show that a spatial processing bias is present for categorizing body parts but not letters, for tactile processing but not auditory processing and for the body-part bisection but not line bisection. Experiment 3 perhaps paints the most compelling picture that spatial inattention in pathological pain involves the processing of body-relevant, but not body-irrelevant, stimuli – the problem does not involve spatial processing deficits *per se*, but problems integrating spatial processing with bodily representations. This discovery reconciles two lines of research that have perplexed neurologists, split the field and fostered extensive debate for over a decade[6, 19]. That is, a spatially defined bias in tactile processing *away from* the affected side[5], but that a visuospatial processing bias during midline judgment *towards* the affected side[7] could not be explained by available theories of spatial inattention and processing.

A range of different types of neglect can occur after brain damage, varying according to the area of space affected, for example personal, peripersonal or extrapersonal[20] and according to what is in fact 'neglected', for example faces - prosopagnosia (eg[21]) or words – neglect dyslexia[22]. Aspects of our results might seem to resemble 'material neglect', where the 'material' is the body. However, it is generally held that neglect after brain damage should be classified as a function of the damaged frame(s) of reference, rather than of the neglected material (see[23] for extensive review). In those terms, we might refer to the 'somaspatial inattention' we have discovered in CRPS patients as a deficit relating to personal space, where the spatial frame of reference involved in the deficit is centered on the affected limb.

There are important implications for neurology research and practice. First, we need to discover whether or not somatospatial neglect *contributes* to the signs and symptoms of pathological pain. If it does, simple strategies that involve the personal space and bodily representations, for example imagined and bimanual tasks, would be indicated, but visual or auditory processing tasks in that space would not. Second, the tests of spatial inattention that have been recommended[24] for pathological pain patients need to interrogate bodily representations or they will show false negative findings. Finally, the underlying neurology of somatospatial inattention is unknown and carefully designed experimental lesion and functional imaging studies are indicated.

There are limitations. In Experiment 1, pictures of objects might have been better than letters because objects are arguably more similar to body parts. The inclusion of a visual TOJ would have added confidence but were omitted to minimise patient burden. We based the line bisection task on pilot testing and published literature[4] and to ensure lines of similar lengths for both tasks, but longer lines for the conventional task may have added confidence to the null result.

Acknowledgements:

GLM is supported by a fellowship from the NHMRC ID 1061279. This work is supported by NHMRC grants ID 630431; 1008017.

Author contributions:

ER, SW, KJC and DH contributed to data collection, analysis, interpretation and write-up. CS and AG contributed to conceptual development, interpretation and write-up. GLM contributed to conceptual development, data collection, analysis, interpretation and write-up.

Potential conflicts of interest

The authors report no conflicts of interest.

References

1. Mitchell S. Gunshot wounds, and other injuries of nerves. Philadelphia: Lippincott; 1864.
2. Marinus J, Moseley GL, Birklein F, et al. Clinical features and pathophysiology of complex regional pain syndrome. Lancet Neurol. 2011 Jul;10(7):637-48.
3. Moseley G, Gallace A, Iannetti GD. Neglect-like tactile dysfunction in chronic back pain. Neurology. 2012;79:327-32.
4. Bisiach E, Luzzatti C. Unilateral neglect of representational space. Cortex. 1978 Mar;14(1):129-33.
5. Moseley GL, Gallace A, Spence C. Space-based, but not arm-based, shift in tactile processing in complex regional pain syndrome and its relationship to cooling of the affected limb. Brain : a journal of neurology. 2009 Nov;132(Pt 11):3142-51.

6. Forderreuther S, Sailer U, Straube A. Impaired self-perception of the hand in complex regional pain syndrome (CRPS). Pain. 2004 Aug;110(3):756-61.

7. Sumitani M, Rossetti Y, Shibata M, et al. Prism adaptation to optical deviation alleviates pathologic pain. Neurology. 2007 January 9, 2007;68(2):128-33.

8. Szczepanski SM, Kastner S. Shifting attentional priorities: control of spatial attention through hemispheric competition. J Neurosci. 2013 Mar 20;33(12):5411-21.

9. Moseley GL, Herbert RD, Parsons T, Lucas S, Van Hilten JJ, Marinus J. Intense pain soon after wrist fracture strongly predicts who will develop complex regional pain syndrome: prospective cohort study. J Pain. 2014 Jan;15(1):16-23.

10. Corbetta M, Kincade MJ, Lewis C, Snyder AZ, Sapir A. Neural basis and recovery of spatial attention deficits in spatial neglect. Nat Neurosci. 2005 Nov;8(11):1603-10.

11. Cincotta M, Ziemann U. Neurophysiology of unimanual motor control and mirror movements. Clin Neurophysiol. 2008 Apr;119(4):744-62.

12. Di Pietro F, McAuley JH, Parkitny L, et al. Primary somatosensory cortex function in complex regional pain syndrome: a systematic review and meta-analysis. J Pain. 2013 Oct;14(10):1001-18.

13. Di Pietro F, Stanton TR, Moseley GL, Lotze M, McAuley JH. Interhemispheric somatosensory differences in chronic pain reflect abnormality of the Healthy side. Hum Brain Mapp. 2015 Feb;36(2):508-18.

14. Catley MJ, O'Connell NE, Berryman C, Ayhan FF, Moseley GL. Is tactile acuity altered in people with chronic pain? a systematic review and meta-analysis. J Pain. 2014 Oct;15(10):985-1000.

15. Di Pietro F, McAuley JH, Parkitny L, et al. Primary motor cortex function in complex regional pain syndrome: a systematic review and meta-analysis. J Pain. 2013 Nov;14(11):1270-88.

16. Moseley GL. Why do people with complex regional pain syndrome take longer to recognize their affected hand? Neurology. 2004 Jun;62(12):2182-6.

17. Cooper LA, Shepard RN. Mental Transformations in Identification of Left and Right Hands. J Exp Psychol Human. 1975;104(1):48-56.

18. Axelrod S, Thompson LW, Cohen LD. Effects of senescence on the temporal resolution of somesthetic stimuli presented to one hand or both. J Gerontol. 1968 Apr;23(2):191-5.

19. Kolb L, Lang C, Seifert F, Maihoefner C. Cognitive correlates of neglect-like syndrome in patients with complex regional pain syndrome. Pain. 2012;153(5):1063-73.

20. Bisiach E, Perani D, Vallar G, Berti A. Unilateral neglect: personal and extra-personal. Neuropsychologia. 1986;24(6):759-67.

21. Jacome DE. Subcortical prosopagnosia and anosognosia. Am J Med Sci. 1986 Dec;292(6):386-8.

22. Costello AD, Warrington EK. The dissociation of visuospatial neglect and neglect dyslexia. J Neurol Neurosurg Psychiatry. 1987 Sep;50(9):1110-6.

23. Vallar G. Spatial hemineglect in humans. Trends Cogn Sci. 1998 Mar 1;2(3):87-97.

24. Frettloh J, Huppe M, Maier C. Severity and specificity of neglect-like symptoms in patients with complex regional pain syndrome (CRPS) compared to chronic limb pain of other origins. Pain. 2006 Sep;124(1-2):184-9.

Figure captions

Fig 1. Experiment 2. Tactile and auditory temporal order judgments (TOJs). A) TOJs of paired tactile stimuli. B) TOJs of paired auditory stimuli. Participants judge which of two perceptually identical stimuli, delivered at a range of stimulus onset asynchronies (SOA) from -120 ms to +120 ms, occurred first. Vertical axes denote the proportion of trials to which the participant responded with 'Affected side first', at each SOA. Group mean (circles) and standard deviation (error bars), and line of best fit, are shown. Note that, for tactile stimuli, the SOA at which participants have a 50% chance of making a correct response, the point of subjective simultaneity (PSS), is shifted to the right, demonstrating a spatially-defined bias of tactile processing towards stimuli presented to the healthy hand, confirming the established pattern. In contrast however, for auditory stimuli, the PSS occured at a SOA of approximately zero, indicating no spatially defined bias in auditory processing.

Fig. 2. Experiment 3: Conventional and bodily-relevant line bisection tasks. Vertical axis denotes body midline; displacement to the right denotes that the perceived midpoint of the line was displaced towards the healthy side of space. Group means (circles) and standard deviation (error bars) in mm for line bisections performed on the affected side of the body midline (open circle), centered on the body midline (conventional task only; grey circle), and on the healthy side of the body midline (filled circle) are shown. Asterisk denotes that the 95% confidence interval of the group data did not cross the true midpoint of the line, indicating a positive test for spatially-defined bias. Note that the conventional line bisection task is performed normally (a 'negative' finding) but the same task performed on a body part is abnormal (a 'positive' finding for spatial inattention).

Fig. 3. Experiment 3: task. Line bisection task on hands. Group means (circles) and standard deviation (error bars) for Hand-width line bisections performed in a horizontal orientation or a

vertical orientation on the affected or the healthy hand. Note normal performance in the veridical line but abnormal performance for the bisection of the affected hand held parallel to the body midline. Asterisk denotes that the 95% confidence interval did not cross the body midline. These results corroborate those presented in Figure 2.