

Peripheral and Central Mechanisms of Limb Position Sense and Body Representation

A thesis submitted in fulfilment of the requirements for
the Doctor of Philosophy

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ABSTRACT

Each of us holds a unique and specific view of our own body. This arises from sensations, such as the sense of limb position and interoception (awareness of internal sensations of the body), allowing us to make conscious appraisals about our bodies. For instance, when we feel hungry, where our mouth is relative to our hands, and how to get food from the plate into the mouth with our fingers.

Little is known in regards to how the brain processes sensory information in order to build a coherent central representation of the body. Muscle spindles, considered the main receptor in signalling position and movement sense, are one contributor to the body representation. The aim of the thesis was to explore the mechanisms of position sense and, more broadly, to investigate the sensory information involved in generating the central representation of the body.

The findings in this thesis provided evidence to support the view that the brain is concerned with the signal difference coming from muscle spindles of antagonist muscles. Further, the brain likely compares this difference between limbs when matching the position of two limbs to determine their relative position (Chapter two, three). The studies utilise a history-dependent property of muscle fibres, thixotropy, to produce a directional bias in perceived limb position, referred to as position error.

In Chapters four and five, position sense was examined using a two-arm matching task and a single-arm pointing task. It was found that manipulating muscle spindle signals through thixotropic muscle conditioning and vibration did not elicit the same effect on position sense between tasks. Hence, the existence of two distinct position senses was proposed. One sense was concerned with the position of a body part relative to the other, while the other sense was used to determine the location of a body part in extrapersonal space.

Position sense tasks were also performed by individuals with chronic pain to examine the role of spindle signals in proprioception (Chapter seven) and body representation (Chapter

six, eight). While it was shown that position sense appeared unaltered in chronic pain, the participants, who reported severe body image distortions, were more likely to have poor interoceptive awareness compared to those with no or minor distortions. This suggests that pain-related disturbance in body image was associated with awareness of the internal sensations of the body.

Taken together, this thesis supports the existence of multiple body representations that derive and weigh information from various sensory sources to generate the sense of the body.

GENERAL DECLARATION

Monash University

Declaration for thesis based on conjointly published and unpublished work

In accordance with Monash University Doctorate Regulation 17.2 Doctor of Philosophy and Research Master's regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes six original papers published in peer reviewed journals and one manuscript under review. The core theme of the thesis was the influence of thixotropic muscle conditioning on muscle spindles in signalling position sense, and more broadly, its contribution in generating a central representation of the body. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the School of Public Health and Preventive Medicine, Monash University, under the supervision of Dr Melita Giummarra, Dr Trevor Allen and Prof Uwe Proske.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of chapters 2, 3, 4, 5, 6, 7, and 8 my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status	Nature and extent of candidate's contribution	Co-Author name(s) Nature and extent of author's contribution	Co-Author(s) Monash student Y/N
2	Limb position sense, proprioceptive drift and muscle thixotropy at the human elbow joint	Published	<p>The candidate conducted the experiments, statistical analysis and construction of figures. The candidate was extensively involved in the editing of the manuscript.</p> <p>In terms of intellectual contribution, the candidate developed the protocol used in experiments 5 and 6 – slackening the elbow antagonist muscles by adding a stretch after an initial muscle conditioning contraction. The candidate also made significant contributions in the reply to reviewers. (60%)</p>	<p>Gemma Savage: Conducted initial pilot experiments as part of her honours project. (20%)</p> <p>Trevor Allen: Discussion of literature, experimental design, editing paper.</p> <p>Uwe Proske: Discussion of literature, experimental design, writing the paper.</p>	Y

3	Position sense at the human forearm after conditioning elbow muscles with isometric contractions	Published	The candidate co-designed the experimental protocol, collected and analysed the data, constructed the figures and edited the manuscript. (70%)	Trevor Allen: Discussion of literature, editing paper. Uwe Proske: Discussion of literature, experimental design, writing of paper.	N
4	The sensory origins of human position sense	Published	The candidate co-designed the study, conducted the experiments, collected and analysed the data, and was involved in the construction/editing of the manuscript. (70%)	Melita Giummarra: Editing of manuscript. Trevor Allen: Discussion of literature, experimental design, editing of manuscript. Uwe Proske: Discussion of literature, experimental design, writing of manuscript.	N
5	Position sense at the human elbow joint measured by arm matching or pointing	Published	The candidate co-designed the study, conducted the experiments, collected and analysed the data, and was involved in the construction/editing of the manuscript. (70%)	Trevor Allen: Discussion of literature, experimental design, editing of manuscript. Uwe Proske: Discussion of literature, experimental design, writing of manuscript.	N
6	Sensing the body in	Published	The candidate planned and wrote the review	Trevor Allen: Discussion of literature,	N

	chronic pain: A review of psychophysical studies implicating altered body representation		with feedback and guidance from co-authors. (80%)	editing of paper. Uwe Proske: Discussion of literature, editing of paper. Melita Giummarra: Discussion of literature, editing of paper.	
7	Position sense in chronic pain: Separating peripheral and central mechanisms in proprioception in unilateral limb pain	Published	The candidate generated the experimental question, designed the experiments, collected and analysed the data, and wrote the paper with guidance and feedback from co-authors. (80%)	Melita Giummarra: Co-design of study, discussion of findings, data analysis, editing of paper.	N
8	Are body image and cardiac interoceptive sensitivity disturbed in chronic pain?	Under Review	The candidate planned and executed the study, collected and analysed the data, and wrote the paper with guidance and feedback from the co-author. (75%)	Melita Giummarra: Co-design of study, statistical analysis, discussion of findings, editing of paper.	N

I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Signed:

A handwritten signature in black ink, appearing to read 'Anthony Gray', with a long horizontal stroke extending to the right.

Date: 25th August 2016

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my supervisors Melita Guimmarra, Trevor Allen and Uwe Proske.

I would also like to thank my friends, fellow PhD candidates, and team members from the Georgious-Karistianis lab.

An honourable mentioned should be given to the Department of Physiology, Monash University, where I previously completed my Honours research and conducted some of the initial experiments in my doctoral candidature. However, this thesis could not have been possible without the generosity of Prof Robert Widdop, who granted us lab space in the Department of Pharmacology, Monash University.

In regards to my clinical studies, I would like to thank the staff at Caulfield Pain Management and Research Centre, Caulfield Hospital, in particular Dr Carolyn Arnold, Prof Stephen Gibson, Ms Alison Johnson and Ms Fiona Thomas for their help and support.

Also, my thanks to School of Public Health and Preventive Medicine, Monash University, where I completed the final months of my PhD candidature.

Finally, to my family whom have supported, nurtured and waited, patiently, through my academic journey – I would like to formally acknowledge that this thesis could not have been possible without you.

LIST OF PUBLICATIONS

PEER REVIEWED PAPERS (submitted)	Impact Factor	Number of Times Cited
Tsay, A. J. and M. J. Giummarra (Submitted). "Are body image and cardiac interoceptive sensitivity disturbed in chronic pain?" <u>Euro J Pain</u> .	2.92	-
PEER REVIEWED PAPERS	Impact Factor	Number of Times Cited
Tsay, A., Allen, T. & Proske, U. (2016). "Position sense at the human elbow joint measured by arm matching or pointing." <u>Exp Brain Res</u> . 234(10): 2787-2798.	2.04	0
Tsay, A. J. and M. J. Giummarra (2016). "Position sense in chronic pain: Separating peripheral and central mechanisms in proprioception in unilateral limb pain." <u>J Pain</u> 17(7): 815-823.	4.01	0
Tsay, A., Giummarra, M., Allen, T. J. & Proske, U. (2016). "The sensory origins of human position sense." <u>J Physiol</u> 594(4): 1037-1049.	5.04	3
Tsay, A., Allen, T. J. & Proske, U. (2015) "Position sense at the human forearm after conditioning elbow muscles with isometric contractions" <u>Exp Brain Res</u> 233(9): 2635-2643.	2.04	4
Tsay, A., Allen, T., Proske, U. & Giummarra, M. (2015) "The sense of the physical self in chronic pain: A review of psychophysical studies implicating altered body representation." <u>Neurosci Biobehav Rev</u> 52(0): 221-232.	8.80	13
Proske, U., Tsay, A. & Allen, T. (2014) "Muscle thixotropy as a tool in the study of proprioception." <u>Exp Brain Res</u> 232(11): 3397-3412.	2.04	11

Tsay, A., Savage, G., Allen, T. J. & Proske, U. (2014) "Limb position sense, proprioceptive drift and muscle thixotropy at the human elbow joint." <u>J Physiol</u> 592(Pt 12): 2679-2694.	5.04	12
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CONFERENCE AND POSTER PRESENTATIONS

- Tsay, A., Allen, T., Proske, U. & Giummarra, M. (2015) The influence of muscle conditioning on limb position errors in patients with chronic pain. Australian Pain Society 35th Annual Scientific Meeting, Brisbane.
- Tsay, A., Allen, T. J., Giummarra, M. & Proske, U. (2015) Sensory basis of limb position sense differs between pointing and matching. Sensorimotor Control Meeting. The University of Queensland, Brisbane.
- Tsay, A., Allen, T., Proske, U. & Giummarra, M. (2014) The influence of muscle conditioning on limb position errors in patients with chronic pain. Early Career Research Neuroscience Showcase, Melbourne.
- Proske, U., Allen, T. & Tsay, A. (2014) Using intrafusal thixotropy as a tool to study the role of muscle spindles in proprioception. Something old, something new, something borrowed, something... Else! A mechano-‘reception’ for Bob Banks: celebrating a career in stretching the imagination, Durham.
- Allen, T. J., Jones, T., Morgan, D. L., Tsay, A. & Proske, U. (2014). Factors influencing muscle damage from isometric exercise. 6th Exercise & Sports Science Australia Conference and Sports Dietitians Australia Update - Research to Practice, Adelaide.

AWARDS AND GRANTS

- Australian Postgraduate Award (2013) Department of Industry and Science, Australian Government
- PhD Student Travel Grant (2015) Australian Pain Society

ABBREVIATIONS

CLBP	Chronic Lower Back Pain
CRPS	Complex Regional Pain Syndrome
EC	Extension Conditioning
EMG	Electromyogram
FC	Flexion Conditioning
HBAT	Heartbeat Awareness Task
HRV	Heartrate Variability
IND	Indicator Arm
MVC	Maximum Voluntary Contraction
REF	Reference Arm
RHI	Rubber Hand Illusion
TMS	Transcranial Magnetic Stimulation
TVR	Tonic Vibration Reflex

CHAPTER 1: GENERAL INTRODUCTION AND THESIS OVERVIEW

1.1 Position Sense and Body Representation

To make purposeful movements, the body must distinguish the self from the external environment. The five classical senses – sight, hearing, smell, taste and touch – enable us to perceive the world around us. But other sensory modalities exist to specifically monitor the physiological condition of the body, interoception, as well as actions generated by the body itself, proprioception.

Collectively, proprioception refers to sensations of force, effort, movement and position. Afferent information arising from our muscles, as they are stretched, provides us with information about limb position and movement. The brain uses this information, along with other sensory inputs (i.e. vision, touch, hearing, interoception) to create and maintain a central representation of the body (Proske & Gandevia, 2012).

At the periphery, the muscle spindles are considered the primary receptors responsible for signalling limb position and movement sense. Historically, their role was identified by vibrating a muscle, eliciting an illusion of a lengthening muscle (Goodwin et al., 1972) during a two arm tracking task. Importantly, no illusions were observed when vibration was applied at the joints.

In more recent times, the thixotropic properties of the muscle have also been exploited to investigate the role of muscle spindles in position sense (Gregory et al., 1988; Proske et al., 1993). That is, changing the muscle's history of contraction or stretch subsequently raises or lowers the spindle discharge rate, leading to predictable changes in perceived limb position that is consistent with spindle discharge.

Based on the premise that muscle vibration and thixotropic conditioning influence position sense, the current thesis explores the contribution of limb position sense in generating an up-to-date representation of the body.

1.2 Aims of the Research

The aim of this thesis was to explore the mechanisms of position sense through the use of thixotropic muscle conditioning, and more broadly, to investigate the sensory information involved in generating the central representation of the body.

The aim of this thesis was addressed by investigating three questions:

- Firstly, our initial investigations asked how does the brain use muscle spindle information to determine the alignment of the two arms in a forearm position matching task (Chapter two, three)?
- Secondly, do muscle spindle signals contribute to positional information in the same way when the task is to indicate the position of a single arm that is hidden from view (Chapter four, five)?
- Finally, position sense (Chapter seven) and interoception (Chapter eight) were examined in individuals with chronic pain, to explore how this information contributes to the generation of the central body representation.

1.3 An Overview of the Thesis Format

The present thesis is a thesis by publication, which differs from conventional thesis formatting and narrative. This thesis consists of six published papers, along with one manuscript currently under review. All papers have been researched and written during the course of the PhD candidature, as per Monash University requirements for [Thesis by Publication](#). Since each chapter was essentially a stand-alone publication, there is some unavoidable repetition between chapters; for example, repetition of methods and discussion of the overlapping literature. Each chapter does, however, address unique issues and/or findings from the studies and narrative reviews conducted.

The thesis is divided into three main sections. The first section provided an overview of muscle thixotropy and its influence on position sense (Chapters two, three). In the second part, the thesis moves away from the muscle spindles as the main source of positional

information (Chapters four, five). Finally, the thesis investigated thixotropic muscle conditioning (Chapter seven) and central body representation (Chapters six, eight) in individuals with chronic pain.

Explanatory notes precede all papers for any necessary clarification and to provide a link between chapters. The thesis concludes with an integrative discussion presenting the studies into a broader context. The general discussion also explores the significance of the studies conducted and provides suggestions for future research directions.

SECTION ONE: PERIPHERAL MECHANISMS OF POSITION SENSE

CHAPTER 2: PROPRIOCEPTIVE DRIFT AND RECEPTOR ADAPTATION

Tsay, A., Savage, G., Allen, T. J. & Proske, U. (2014). "Limb position sense, proprioceptive drift and muscle thixotropy at the human elbow joint." *J Physiol* **592**(Pt 12): 2679-2694.

2.1 Explanatory Notes

Most of the observations in this thesis were uncovered by utilising a history-dependent property of skeletal muscles, thixotropy, which is exhibited by both intrafusal and extrafusal muscle fibres. A recent review and synthesis of the literature on the mechanisms involved in thixotropy can be found in [Appendix 1](#), entitled *Muscle thixotropy as a tool in the study of proprioception* (Proske et al., 2014).

For muscle spindles, the background firing rate is dependent on the preceding contraction and length changes of the intrafusal muscle fibres (Proske et al., 1993). Thixotropic behaviour occurs with the formation of stable cross-bridges between actin and myosin when the muscle relaxes after a contraction. Shortening the muscle introduces slack in the sensory ending of spindles, lowering the rate of spindle discharge. Because the length of the muscle is signalled by muscle spindle activity, it was proposed that manipulating spindle sensitivity with a contraction or stretch can lead to reproducible errors in perceived limb position (Proske et al., 2014).

The following published paper investigated the signalling behaviour of muscle spindles in position sense. It was proposed that the decline in muscle spindle discharge due to receptor adaptation influenced the perceived position of a limb over time. This has direct implications for the proprioceptive drift phenomenon, which was thought to be primarily due to central mechanisms (Wann & Ibrahim, 1992; Brown et al., 2003).

2.2 Declaration for Thesis Chapter Two

Declaration by candidate

In the case of Chapter two, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
<p>The candidate conducted the experiments, statistical analysis and construction of figures. The candidate was extensively involved in the editing of the manuscript.</p> <p>In terms of intellectual contribution, the candidate developed the protocol used in experiments five and six – slackening the elbow antagonist muscles by adding a stretch after an initial muscle conditioning contraction. The candidate also made significant contributions in the reply to reviewers when the manuscript was under review.</p>	60%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Gemma Savage	Conducted initial pilot experiments as part of her honours project.	20%
Trevor Allen	Discussion of literature, experimental design, editing paper.	
Uwe Proske	Discussion of literature, experimental design, writing the manuscript.	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

**Candidate's
Signature**



Date
25/08/16

**Main
Supervisor's
Signature**



Date
25/08/16

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

Limb position sense, proprioceptive drift and muscle thixotropy at the human elbow joint

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Key points

- When a blindfolded subject holds his or her arm at a particular angle, its reported position shifts over time; this is known as proprioceptive drift.
- Here, we show that in relation to position sense at the elbow, the direction of perceived shifts is consistent with adaptation in discharge levels of sensory receptors in elbow muscles.
- Raising or lowering receptor discharge levels by similar amounts in opposing muscles at the elbow using muscle conditioning abolishes proprioceptive drift, but large position errors may result.
- The present experiments provide an explanation for proprioceptive drift and indicate that, in a forearm position-matching task, the brain is not concerned with actual discharge levels from arm muscles, but with their difference.

Abstract These experiments on the human forearm are based on the hypothesis that drift in the perceived position of a limb over time can be explained by receptor adaptation. Limb position sense was measured in 39 blindfolded subjects using a forearm-matching task. A property of muscle, its thixotropy, a contraction history-dependent passive stiffness, was exploited to place muscle receptors of elbow muscles in a defined state. After the arm had been held flexed and elbow flexors contracted, we observed time-dependent changes in the perceived position of the reference arm by an average of 2.8° in the direction of elbow flexion over 30 s (Experiment 1). The direction of the drift reversed after the arm had been extended and elbow extensors contracted, with a mean shift of 3.5° over 30 s in the direction of elbow extension (Experiment 2). The time-dependent changes could be abolished by conditioning elbow flexors and extensors in the reference arm at the test angle, although this led to large position errors during matching ($\pm 10^\circ$), depending on how the indicator arm had been conditioned (Experiments 3 and 4). When slack was introduced in the elbow muscles of both arms, by shortening muscles after the conditioning contraction, matching errors became small and there was no drift in position sense (Experiments 5 and 6). These experiments argue for a receptor-based mechanism for proprioceptive drift and suggest that to align the two forearms, the brain monitors the difference between the afferent signals from the two arms.

(Resubmitted 4 December 2013; accepted after revision 19 March 2014; first published online 24 March 2014)

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Abbreviation EMG, electromyography.

Introduction

It is now generally accepted that muscle spindles are the principal proprioceptors concerned with the senses of limb position and movement, and that skin receptors play a minor contributory role (Proske & Gandevia, 2012). With reference to muscle spindles, including both the primary and secondary endings (McCloskey, 1973), it is believed that when a muscle is stretched, the maintained increase in discharge rate is interpreted by the brain as a longer muscle, and thus a more flexed or extended joint. An interesting point made by Matthews (1988) is that for most sensory receptors an increase in discharge rate is perceived as an increase in stimulus intensity; in muscle spindles it implies an increase in muscle length.

It is a common experience that when we touch an object and maintain contact with it for a period of time, the touch sensation gradually fades as a result of adaptation processes, including receptor adaptation. Muscle spindles also exhibit receptor adaptation. The adaptation mechanisms may be both mechanical and ionic in origin (Matthews, 1972, p270). Whereas adaptation in other sensory receptors results in the perception of a weaker stimulus, in muscle spindles, based on the considerations outlined above, it can be interpreted as the muscle becoming shorter. Thus, the adaptation of spindle discharge in elbow flexor muscles would be perceived as indicating a more flexed elbow and that in elbow extensors would be perceived as indicating a more extended elbow. This point is the subject of the present study.

When a limb is held steady in a particular posture for a period, the change in its perceived position over time, in the absence of vision, is referred to as 'proprioceptive drift' (Wann & Ibrahim, 1992; Desmurget *et al.* 2000; Brown *et al.* 2003). In a simple position-matching experiment (Paillard & Brouchon, 1968), subjects were required to move a vertical slide with one hand to match the position of the other hand. If a delay between the placement of the reference hand and the matching of its position by the other hand was introduced, time-dependent errors emerged in the form of proprioceptive drift. Wann & Ibrahim (1992) considered the possibility that proprioceptive drift was a consequence of the slowly adapting properties of limb proprioceptors, but rejected this explanation on the grounds that vision and proprioception were only partially effective in resetting the perceived limb position. Desmurget *et al.* (2000) claimed that in the search for an explanation of proprioceptive drift two factors had been overlooked: the influence of motor outflow, and the ability to memorize position. When the reference hand was moved to its position, at zero delay it had available not only a static proprioceptive signal, but also information related to the magnitude of the performed displacement. This latter cue would be expected to fade, leading to the perceived proprioceptive drift. In support

of their view, Desmurget *et al.* (2000) showed that, in the absence of vision, if one hand was moved to a target position following an indirect, randomly varying movement, the accuracy of the localization of its position by the other hand was unaltered over a measurement period of 20 s. Thus, this study suggested that proprioceptive drift was a consequence of a fading memory of the initial displacement.

More recently, Brown *et al.* (2003) asked subjects to carry out a series of repetitive movements without vision. The starting location was observed to visibly drift with time, but movement distance and direction remained unaffected. These authors concluded that after a prolonged period without vision, proprioceptive information was used differently by separate position and movement controllers. Drift occurred because the two controllers were differentially sensitive to small position errors. The movement controller tracked intrinsic limb posture (from a body map), whereas the position controller tracked extrinsic hand location.

The term 'proprioceptive drift' has also been used in relation to the rubber hand illusion (Botvinick & Cohen, 1998). By using touch in combination with vision, a rubber hand can be successfully incorporated into one's own body representation. The accompanying relocation of the felt position of the unseen hand towards the rubber hand has been referred to as proprioceptive drift (Kammers *et al.* 2009). In the present study, we restrict the meaning of the term to perceived changes in the position of a limb over time which, we propose, result from alterations in afferent activity in muscles acting at the joint under study. An illusory change in the ownership of a body part, generated by a sensory conflict situation, is something quite different and presumably operates entirely centrally.

In summary, none of the studies referred to above suggest that proprioceptive drift is a direct consequence of a declining afferent discharge by muscle proprioceptors. In the present study, we provide evidence that a component of proprioceptive drift can be attributed to receptor adaptation. The supporting evidence is derived from the finding that, at a given limb position, the direction of drift can be manipulated and can be changed according to how the muscles acting at the joint have been conditioned.

The present study is concerned with position sense at the elbow. Position sense is defined here as the ability to perceive the position of a limb in the absence of vision. Position sense at the elbow is signalled predominantly by afferents of muscle spindles in elbow flexors and extensors (Goodwin *et al.* 1972). It is believed that the level of background activity in spindles provides the positional signal (Clark *et al.* 1985). Position sense can be measured in a forearm-matching task, in which the experimenter places one arm of the subject at a predetermined angle and the blindfolded subject is required to match its position with his or her other arm. It is the muscle undergoing

stretch during placement of the reference arm at the test angle that provides the positional information used to match its position (Gilhodes *et al.* 1986; Ribot-Ciscar & Roll, 1998). Because the evidence in this task suggests that afferent activity from both arms contributes to the perceived position of the reference arm (Lackner, 1984; Lackner & Taublieb, 1984; Allen *et al.* 2007; White & Proske, 2009; Izumizaki *et al.* 2010), some experimenters prefer to measure position sense only in one arm and thus require the subject to indicate the position of the hidden arm with a pointer (Walsh *et al.* 2013). Here, we have chosen a two-arm matching task to measure position sense. We have done so because matching and pointing tasks do not measure exactly the same thing and we wanted to relate findings from the present study to previous observations made using a matching task.

In the present work, we used the technique of conditioning forearm muscles with contractions and length changes to systematically alter their afferent activity. The technique relies on a property of muscle called 'thixotropy', a contraction history-dependent, passive stiffness (Lakie *et al.* 1984). Changing the thixotropic state of elbow muscles by conditioning alters the responses of muscle spindles and therefore can alter position sense at the forearm (Gregory *et al.* 1988).

Muscle thixotropy is a consequence of longterm stable cross-bridges (Hill, 1968) between the myofilaments of both extrafusal and intrafusal muscle fibres (Proske *et al.* 1993). When a muscle is conditioned with a voluntary contraction at a particular length, fusimotor neurones are coactivated together with skeletomotor neurones (Vallbo, 1971, 1974), leading intrafusal fibres to contract. At the end of the contraction, stable cross-bridges will form, leaving the intrafusal fibres taut and imposing their resting tension on the spindle sensory ending. As a result, spindle background discharge rises and spindles become stretch-sensitive. If an intrafusal contraction takes place in a stretched muscle and the muscle is then shortened, the stiffness imposed on the intrafusal fibres by their stable cross-bridges prevents them from shortening as well and they fall slack. Slack spindles have low resting discharge rates and low sensitivities to movements (Proske *et al.* 1992; Scott *et al.* 1994). Thus the ability to manipulate spindle responsiveness between two extremes, a sensitized state and a state of low sensitivity, can be used as a tool in the study of position sense. Although the thixotropic behaviour of muscle spindles has been studied largely in animal experiments (Proske *et al.* 1993), there is evidence from human spindles (Jahnke *et al.* 1989; Burke & Gandevia, 1995; Wilson *et al.* 1995) consistent with such behaviour.

In recent experiments concerned with the effects of exercise on forearm position sense (Tsay *et al.* 2012), we observed position errors in control measurements before the exercise had started, despite the fact that both arms

had been conditioned identically. At the time we suspected that the time delay between the placement of the reference arm and the matching of its position was responsible and thus that the errors were caused by receptor adaptation in proprioceptors of the reference arm. In the present study, we put this idea to the test.

We hypothesized that at least one component of proprioceptive drift is caused by adaptation of receptor discharge. By adaptation, we mean the progressive slowing of muscle spindle discharge following a conditioning contraction used to remove any pre-existing slack in muscle and its spindles. Without the contraction, because of the presence of slack, spindle discharge levels are too low for significant adaptation to take place. We propose that these adaptive changes occur at the level of background discharge, signalling limb position, and do not reflect the signal generated by the movement from the conditioning length to the test length. Finally, by combining a conditioning contraction with a stretch, we deliberately introduced slack in spindles to lower their background discharge.

Methods

A total of six experiments were carried out. Experiments 1 and 2 used 12 subjects; the other experiments each used nine subjects. One cohort of subjects participated in both Experiments 1 and 2, and another participated in both Experiments 5 and 6. This made for a total of 39 subjects, of whom 22 were male and 17 were female. The mean \pm S.E.M. age of the subjects was 24.5 ± 1.3 years. Subjects gave informed written consent prior to participating in an experiment. The work was approved by the Monash University Human Research Ethics Committee. The ethical aspects of the experiments conformed to the Declaration of Helsinki.

All position matching was performed in the vertical plane. Blindfolded subjects sat at a table and placed both forearms on the lightweight paddles of a custom-built apparatus for measuring forearm position sense (Allen & Proske, 2006). The forearms were strapped to the paddles by Velcro straps of 5 cm in width placed just below the crease of the wrist with the palms facing upward. The tension of the strapping was verified as equal before the experiment was started in order to minimize potential differences in skin sensation between the two arms. The upper arms rested on horizontal supports, which allowed subjects to relax their shoulder muscles during matching trials. One arm was designated the reference arm (the arm placed at the target angle by the experimenter) and the other was the indicator arm (the arm moved by the subject to match the position of the reference arm).

Forearm angle was measured using potentiometers (25 k Ω ; Spectra Symbol Corp., Salt Lake City, UT,

USA) located at the hinges of each paddle. The hinges were co-linear with the elbow joint. The potentiometers provided a continuous voltage output proportional to the angle of each paddle, in which a reading of 0° referred to the forearm in a horizontal position and a reading of 90° referred to it in a vertical position. The calibration of the potentiometers was checked before each experiment.

Muscle activity in the reference arm was measured using surface electromyography (EMG). A pair of Ag/AgCl electrodes with an adhesive base and solid gel contact points (3M Health Care, London, ON, Canada) were placed approximately 2.5 cm apart over the surface of the biceps brachii and triceps brachii. A grounding electrode was placed on the collar bone. EMG output was connected to an audio amplifier for biofeedback. Position signals were acquired at 20 Hz and EMG signals at 1000 Hz using a MacLab 4/s data acquisition module running Chart software (ADInstruments Pty Ltd, Castle Hill, NSW, Australia) on a Macintosh computer.

Position errors between the two arms were calculated using the formula:

$$\text{position error (}^\circ\text{)} = \text{reference angle (}^\circ\text{)} - \text{indicator angle (}^\circ\text{)}.$$

According to the convention used, when the indicator arm was placed in a more extended position than the reference arm, errors were given a positive value. When the indicator arm was placed in a more flexed position, errors were assigned a negative value.

Of the 39 subjects, 32 were right-handed. Reference and indicator arms were randomly assigned to reduce any biases caused by matching with a dominant or non-dominant arm (Goble *et al.* 2006). The reference arm was the dominant arm in 18 subjects and the non-dominant arm in 21 subjects. During a trial the paddle strapped to the reference arm was moved by the experimenter to the test angle and the blindfolded subject was asked to match its perceived position with his or her indicator arm. The test angle chosen was approximately 45°. The actual angle achieved in each trial depended on placement by the experimenter and ranged from 40° to 50°. The variation in target angle from trial to trial meant that the subject was unable to use timing or movement cues to guess the actual test angle. During the movement of the reference arm to the test angle, subjects were asked to remain relaxed. This was monitored using auditory feedback of EMG in the reference arm. In each experimental trial, conditions were randomized.

Throughout these experiments, once the reference arm had been placed at the test angle, its position was maintained by the subject voluntarily. All matching with the indicator arm was also performed voluntarily by the subject. Subjects were therefore required to generate mild contractions sufficient to support the arms against gravity and to move the indicator arm into the matching position.

These conditions were chosen to keep the matching process close to the type of activity the subjects might carry out in everyday life. During the matching process, subjects were asked not to rush and to move the indicator arm into position carefully and deliberately. Once the reference arm was in position at the test angle, moving the indicator from its starting position into the matching position took about 5 s. At the end of each trial the arms were brought back to their resting positions one at a time in order to make it difficult for subjects to obtain cues about the test angle from the time it took to return the arms to their initial positions.

Muscle conditioning

It was necessary at the start of each position-matching trial to put the elbow muscles of both the reference and indicator arms into a defined thixotropic state. This is called muscle conditioning. Typically the muscle is conditioned with a half-maximum voluntary contraction (Gregory *et al.* 1998). In Experiment 1, elbow flexors in both arms were contracted with the arms held flexed. Flexion conditioning altered the mechanical state of elbow flexors in both arms, leaving them taut and leaving elbow extensors slack during the matches (*flexor taut*, Fig. 1A). In Experiment 2, elbow extensors in both arms were contracted with the arms held extended; this is extension conditioning. Here, during matching the elbow flexors in both arms lay slack and the extensors were taut (*extensor taut*, Fig. 1B).

In Experiments 3 and 4, we wanted to measure position sense under conditions in which the proprioceptive bias imposed on the reference arm by flexion conditioning (Experiment 1) or extension conditioning (Experiment 2) was no longer present. In order to do this, the reference arm was conditioned in a way that left both elbow flexors and extensors in a sensitized state during matching (*both taut*, Fig. 1C). Conditioning used isometric contractions of elbow flexors and extensors at the test angle. Any adaptation in one antagonist would be offset by similar adaptation in the opposite direction in the other and therefore the signal difference from them would not be expected to change with time.

In Experiments 5 and 6, we wanted to measure position sense under conditions in which the sensitivity of muscle receptors in both reference and indicator muscles had been reduced by conditioning (*both slack*, Fig. 1D). To desensitize proprioceptors in a muscle, the muscle must be stretched and held at the stretched length for several seconds to allow stable cross-bridges to reassemble at that length (Morgan *et al.* 1984). If the muscle is then shortened, the muscle fibres, stiffened by the presence of the stable bridges, will fall slack, rather than shorten. A slack intrafusal fibre does not exert any tension on the

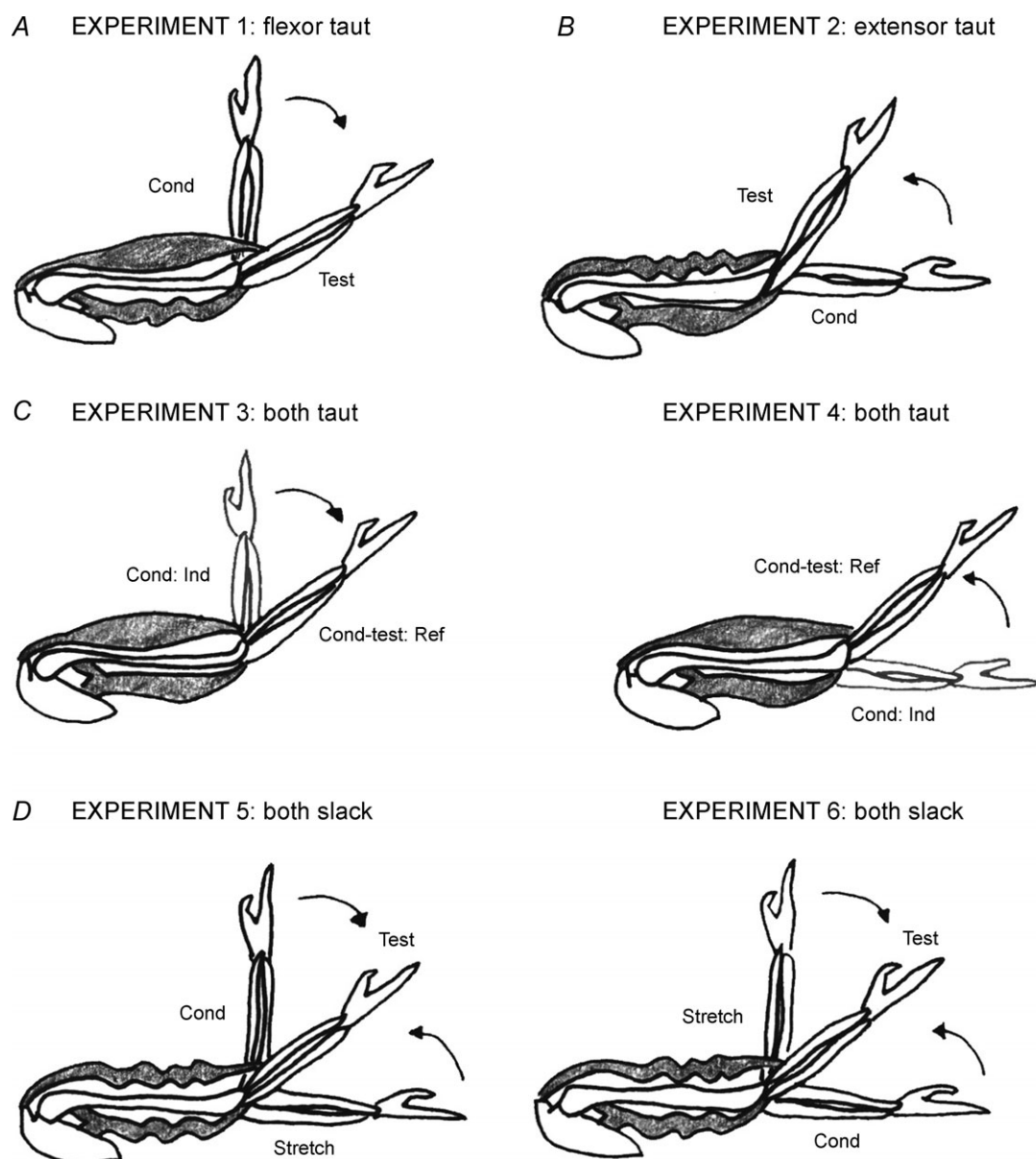


Figure 1. Mechanical state of elbow muscles after conditioning

All conditioning of arm muscles and subsequent position matching was performed in the vertical plane. *A*, in the *flexor taut* condition, elbow flexors were contracted with the arm held at 90°. After the contraction, subjects were asked to relax while the arm was moved by the experimenter into extension to the test angle (40–50°). In the process elbow flexors were stretched, leaving them taut, and elbow extensors were shortened, leaving them slack. The slack state is indicated by the rippling. The direction of movement of the arm to the test angle is indicated by the arrow. *B*, in the *extensor taut* condition, elbow extensors were contracted with the arm held at 0°. After the contraction the relaxed arm was moved by the experimenter into flexion to the test angle. In the process elbow extensors were stretched, leaving them taut, and elbow flexors were shortened, leaving them slack. The direction of movement to the test angle is shown by the arrow. *C*, in the *both taut* condition, the arm was moved to the test angle and held fixed in position while elbow flexors and then elbow extensors underwent conditioning isometric contractions (Experiment 3). The contractions removed any pre-existing slack in both muscle groups. The conditioning was repeated, but beginning with an extension contraction (Experiment 4). The position of the indicator arm during the conditioning contraction is shown in grey. *D*, in the *both slack* condition, for Experiment 5, after contraction of flexors at 90°, the arm was moved into extension (arrow), stretching flexors, shortening and slackening extensor muscles. Once the arm was fully extended, (0°), it was held there for 6 s before being moved into flexion to the test angle (arrow). The movement shortened and therefore slackened flexors so that both flexors and extensors were slack. The same result could be achieved by beginning with an extensor contraction at 0° and moving the arm to 90° for 6 s before placing it at the test angle (Experiment 6).

sensory ending of the spindle and thus both spindle resting activity and stretch responsiveness are reduced.

Experiments 1 and 2: time-dependent changes in position sense after flexion or extension conditioning in both arms

Position sense was measured using four lengths of delay (1 s, 5 s, 10 s and 30 s) between the placement of the reference arm at the test angle and the matching of its position by the indicator. Subjects carried out six trials at each interval of delay. For each subject, the order of the trial conditions (i.e. the delay intervals) was randomized from trial to trial. For trials involving a time delay of 1 s, subjects were asked to begin moving the indicator arm into a matching position as soon as they felt the experimenter starting to move the reference arm from its conditioning position towards the test angle. About 1 s elapsed between the placement of the reference arm at the test angle and the subject's matching of its position with the indicator arm. In the 5 s delay condition, subjects were asked not to move the indicator arm until the reference arm had been placed at the test angle. Moving the indicator arm from its starting position to the matching position and declaring a match took 5 s. In the 10 s delay condition, subjects were asked to wait for 5 s before moving the indicator arm into the matching position. In the 30 s delay condition, subjects were asked to wait for 25 s before moving the indicator arm.

In Experiment 1 flexion conditioning was used. Here, both arms were moved to 90°, the paddles locked in position and the subject was asked to generate a 2 s, approximately half-maximum, isometric contraction with the elbow flexors by attempting to flex the elbows towards the body. The conditioning procedure took about 5 s. Once the arms had relaxed, the metal struts were removed and the reference arm was immediately moved into extension to the test angle (40–50°). The blindfolded subject then matched its position with his or her indicator arm. In Experiment 2, both arms were moved into full extension (0°) and the subject was asked to push the arms down on the supports to generate a half-maximum contraction in the elbow extensors. Once the subject had relaxed, the reference arm was moved in the direction of flexion to the test angle and its position was matched.

Experiments 3 and 4: time-dependent changes in position sense after co-contraction of reference muscles

In Experiment 3, the blindfolded subject's reference arm was moved to the test angle (45° from the horizontal). The subject was asked to generate a half-maximum contraction in extensor muscles by pushing the arm away from the

body. During the contraction the arm was rigidly fixed at the test angle by a pair of metal struts bolted to the frame of the apparatus. The subject was then asked to generate a half-maximum flexion contraction, the arm again being held fixed at the test angle. Thus, the reference arm had now undergone isometric flexion and extension contractions at the test angle, leaving spindles in both muscle groups in a sensitized state. The indicator, by contrast, had only been flexion-conditioned before the subject moved it into a matching position. The nature of the matching procedure did not make it possible to condition indicator muscles at the test angle.

In Experiment 4, the same procedure was repeated, but this time the subject was asked to begin with an isometric flexion contraction of the reference arm, followed by an isometric extension contraction. After arm muscles had relaxed, the extension-conditioned indicator arm was moved into a matching position.

In both Experiments 3 and 4, after the conditioning procedure had been completed, position sense was measured at three intervals of delay (5 s, 10 s and 30 s). It was not possible to include a 1 s delay as the conditioning took several seconds to complete. Subjects carried out a series of six trials at each delay interval.

Experiments 5 and 6: time-dependent changes in position sense after stretching of reference and indicator elbow muscles

To desensitize muscle receptors, in Experiment 5 both arms of the blindfolded subject were initially flexion-conditioned, as before, by holding them at 90° and contracting them isometrically in the direction of flexion using a half-maximum contraction. The contraction removed any pre-existing slack in elbow flexors in both arms. At 90° the elbow extensors were stretched; stable cross-bridges in extensor muscles would be expected to form at that stretched length. After the flexor contraction, both arms were moved into full extension (0°). In the process, the flexors were now stretched to a long length and the extensors were shortened. The arm was held at 0° for 6 s to allow cross-bridges in flexors that had been detached by the stretch to reassemble at the longer length (Morgan *et al.* 1984). We believe there was no comparable reassemblage of cross-bridges in the extensors because their bridges had formed at 90° and the shortening movement to 0° simply meant that they fell slack. The experimenter then moved the reference arm from 0°, in the direction of flexion, to the test angle, and the subject moved the indicator arm into flexion to a matching position. In the process, elbow flexor muscles in both arms were shortened and fell slack. The movement into flexion represented a stretch from 0° to 40–50°, which, we believe, was too small a stretch of extensor muscles to reset their cross-bridges as these had

formed at 90°. All the stretch did was to take up some, but not all, of the slack in the extensors. If there is any slack at all in a muscle, spindle background rates will remain low. Thus, now both flexor and extensor spindle rates in both arms were low because the muscles lay slack.

The conditioning procedure for Experiment 6 was essentially the same, except that it began with the contraction of elbow extensors in both arms while the arms were held extended (0°). Then both arms were flexed to 90° and held there for 6 s before the reference arm was extended to 40–50° and the indicator arm was moved into a matching position.

In both Experiments 5 and 6, after the conditioning procedure had been completed, position sense was measured at three intervals of delay (5 s, 10 s and 30 s). A shortest delay of 5 s rather than of 1 s was chosen to allow for a direct comparison between these data and data from Experiments 3 and 4. Subjects carried out a series of six trials at each delay interval.

Statistical analysis

A repeated-measures ANOVA was used to test for the effects of time delay on position errors. If significance was found, a *post hoc* least significant differences (LSD) test was used to determine which of the matching trial types were significantly different from one another. Pooled data from each group of experiments are shown as means \pm S.E.M.

Results

Time-dependent changes in position sense after flexion or extension conditioning of both arms

The aims of these experiments were to confirm the suggestion that when an arm sits at a test angle for a period of time, time-dependent changes in position sense occur (Paillard & Brouchon, 1968; Wann & Ibrahim, 1992) and to test the hypothesis that the direction of these changes is consistent with adaptation of the discharge of muscle spindles.

Experiment 1: conditioning reference elbow flexors.

In the first experiment, time-dependent changes in position sense were studied after both arms were flexion-conditioned with the arms held at 90°. As soon as the subject had relaxed, the reference arm was moved to the test angle (40–50°) by the experimenter and the subject followed the movement with the indicator arm to adopt a matching position as soon as the reference arm had stopped moving. This was the 1 s delay condition. In the 5 s, 10 s and 30 s delays, the movement of the indicator arm was delayed.

Data for a single subject are shown in Fig. 2 (filled circles). With a 1 s delay between the placement of the reference arm and the matching of its position, the single subject made an error of -3.4° . When a delay of 5 s was introduced between the placement of the reference arm and the matching of its position, the subject made an error of -10.8° . This error reduced to -8.5° at 10 s and increased further to -13.0° at 30 s. This trend in the single subject was reflected in pooled data from 12 subjects (Fig. 3). With a 1 s delay, the mean \pm S.E.M. error was $-1.3 \pm 1.5^\circ$. The error into flexion increased to $-2.9 \pm 1.5^\circ$ with a 5 s delay, was $-2.8 \pm 1.7^\circ$ with a 10 s delay and increased to $-4.1 \pm 1.5^\circ$ with a 30 s delay. A repeated-measures ANOVA showed a significant effect of time delay ($F_{(3,33)} = 3.1$, $P < 0.05$). A *post hoc* LSD test showed a significant difference in outcomes between the 1 s and 30 s delays, as well as between the 5 s and 30 s delays. Therefore, systematic changes with time occurred in the perceived position of the reference arm. The errors increased in the direction of elbow flexion, consistent with previous reports (Wann & Ibrahim, 1992). In other words, over time, subjects believed that their reference arm was in a progressively more flexed position than it really was.

Experiment 2: conditioning reference elbow extensors.

The working hypothesis for Experiment 1 was that conditioning of elbow flexors with the arms held flexed (*flexor taut*, Fig. 1A) led to time-dependent changes in matching errors in the direction of flexion as a result of adaptation processes in the discharges of the reference flexor spindles. To test the adaptation hypothesis, we repeated the experiment, but raised discharges in the spindles of extensor muscles (*extensor taut*, Fig. 1B). Adaptation of discharge in elbow extensors should lead to time-dependent changes in matching errors in the direction of extension.

Figure 2 shows data for extension conditioning (open circles) in the same single subject previously tested with flexion conditioning. The trends in position error after the two forms of conditioning clearly lie in opposite directions. In extension conditioning, when the indicator was matched as soon as the reference had reached its test angle (the 1 s delay condition), the single subject matched with a mean error of $+2.6^\circ$. After a 5 s delay between placement and matching, the error increased to $+6.4^\circ$. When the delay was increased to 10 s, the error decreased slightly to $+5.9^\circ$, but then increased further to $+7.3^\circ$ with a delay of 30 s. Similar trends were apparent in the pooled data. With a 1 s delay, the mean error was $-0.5 \pm 1.3^\circ$. The mean error increased to $+2.3 \pm 1.9^\circ$ with a 5 s delay, to $+2.7 \pm 2.1^\circ$ with a 10 s delay and to $3.0 \pm 2.1^\circ$ with a 30 s delay. A repeated-measures ANOVA showed a significant effect of time delay ($F_{(3,33)} = 6.7$, $P < 0.05$). A *post hoc* LSD test showed a significant difference between the 1 s and all other time delays.

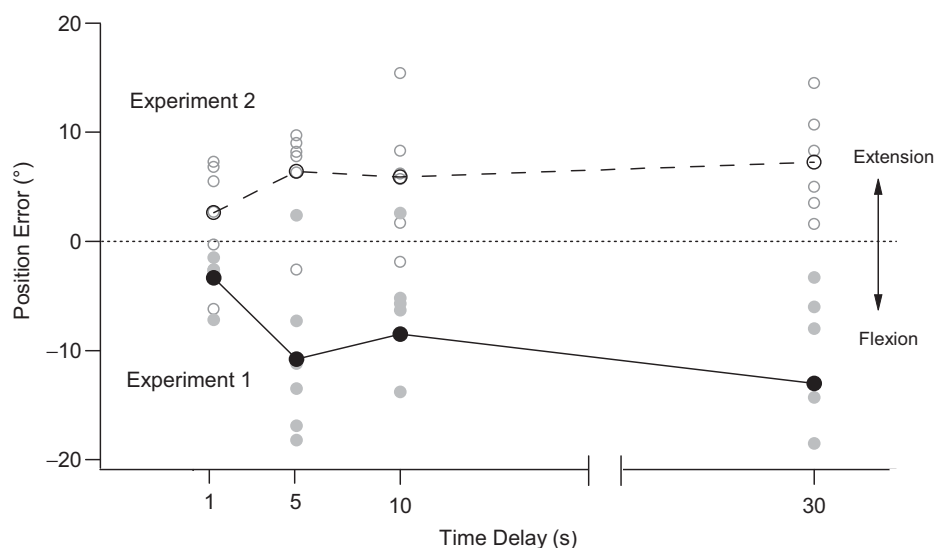


Figure 2. Single-subject data for changes with time in position errors at the elbow joint after flexion or extension conditioning of elbow muscles

The filled circles and continuous line show mean position errors after flexion conditioning. The open circles and dashed line show mean position errors after extension conditioning. Grey symbols show individual matching trials. At the start of each flexion conditioning trial the elbow flexors of both arms were contracted with the arms held flexed (90°). The reference arm was then moved into extension to the test angle and its position matched by the indicator arm, immediately (1 s), and after 5 s, 10 s and 30 s (Experiment 1). In extension conditioning trials, elbow extensors of both arms were contracted with the arm held extended (0°) and the position of the reference arm was then matched at the test angle by the indicator arm at the same four time delays as in flexion conditioning (Experiment 2). Position errors are plotted against time. Errors into flexion are shown as negative and errors into extension as positive. Dotted line indicates zero error.

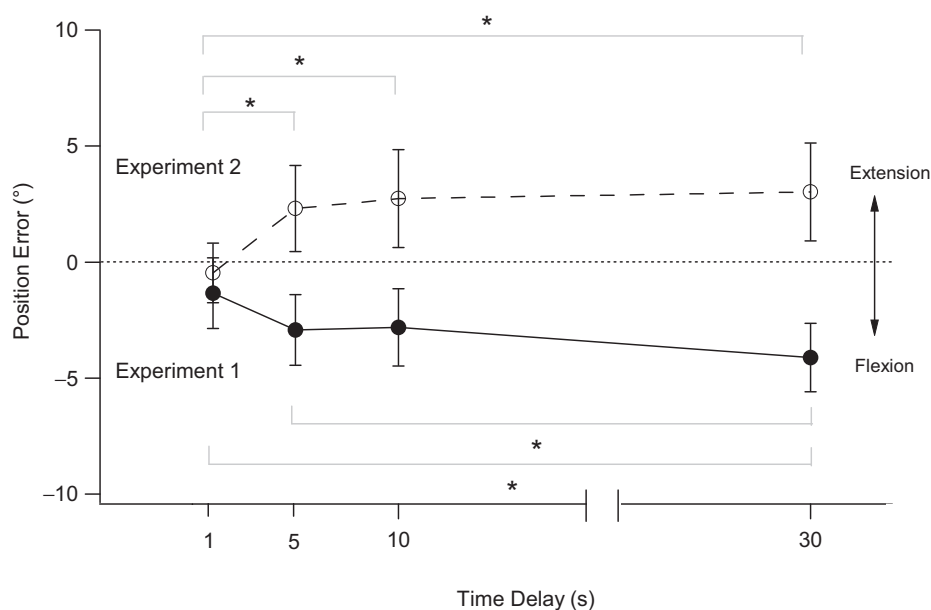


Figure 3. Pooled data for changes with time in position errors at the elbow joint after flexion or extension conditioning of elbow muscles

Data refer to 12 subjects. The filled circles and continuous line show position errors after flexion conditioning. The open circles and dashed line show position errors after extension conditioning. Position errors are plotted against time. Errors into flexion are shown as negative and errors into extension as positive. Data are means \pm S.E.M. *Significant differences between bracketed values ($P < 0.05$). Dotted line indicates zero error.

These two sets of observations provide experimental support for the hypothesis that when conditioning is restricted to a single muscle group, be it elbow flexors or extensors, time-dependent errors in position sense occur in a direction consistent with adaptation of the discharge in the conditioned muscles.

Time-dependent changes in position sense after co-contraction of reference antagonists

In this experiment, the aim was to condition reference muscles in such a way that both flexor and extensor spindles were left in a sensitized state (*both taut*, Fig. 1C). We would expect adaptation to occur over time in spindles of both antagonists. If spindle adaptation followed a similar time course, the fall in reference flexor spindle discharges, leading the arm to be perceived as becoming more flexed, would be offset by the fall in reference extensor discharges, leading the arm to be perceived as more extended. Thus, the hypothesis for this experiment was that there would be no time-dependent changes in position sense.

Experiment 3: flexion conditioning of the indicator arm.

In this experiment, carried out in nine subjects, both flexors and extensors of the reference arm were contracted at the test angle. At the same time, the indicator arm was flexion-conditioned. In these experiments, because the reference arm had to be conditioned before the indicator, it was not possible to have a 1 s delay and the shortest matching interval was 5 s.

Pooled data are shown in the lower panel of Fig. 4. When the delay between the placement of the reference arm and the matching of its position was 5 s, subjects matched the position of the reference arm by placing the indicator arm at $-9.8 \pm 2.3^\circ$. In other words, subjects thought their reference arm was more flexed than it really was by nearly 10° . When a 10 s delay was introduced, the matching error increased slightly to $-10.3 \pm 2.0^\circ$. With a 30 s delay, the error was $-10.8 \pm 2.2^\circ$. These differences in error were small and not significant. The errors at all time delays were significantly different from zero error ($P < 0.05$).

Experiment 4: extension conditioning of the indicator arm.

Here, the conditions of Experiment 3 were repeated, but, following the co-conditioning of reference elbow muscles at the test angle, the indicator arm was extension-conditioned. The pooled data for the nine subjects are shown in the upper panel of Fig. 4. With a 5 s delay between conditioning and matching, the mean error in position was $+9.6 \pm 2.0^\circ$. That is, subjects felt their arm positions were accurately aligned, when in fact the indicator was nearly 10° more extended than the reference arm. The error increased slightly to $9.8 \pm 1.9^\circ$

with a 10 s interval and $10.6 \pm 2.0^\circ$ with a 30 s interval. These differences in error with time were small and not significant. The errors at all time delays were significantly different from zero error ($P < 0.05$).

The results of Experiments 3 and 4 support our working hypothesis in that after co-conditioning of reference muscles there was no longer any evidence for a shift in the perceived position of the arm with time because the influences from the two antagonists impacted in opposite directions and so annulled one another. The presence of large bias errors, in the direction of flexion or extension, was interpreted as attributable to the indicator arm, in which the elbow muscles had been conditioned to generate a strong flexor or extensor signal.

Time-dependent changes in position sense after stretch of elbow muscles

The question of why initial bias errors occurred during a normal matching trial remained. For example, why was there an error of -2.3° with a 1 s delay in Experiment 1? Given that the two arms had been conditioned identically, why did average matching errors not fall to zero? Our proposed explanation is that once the conditioned reference arm had been placed at the test angle, its spindles were likely to maintain a level of background activity proportional to the length of the muscle at that angle. However, during the movement of the indicator arm to the matching position, its spindles would respond to both the length change and the rate of length change, which would raise their discharge rates well above those in the reference muscles. Therefore, the indicator arm was perceived as more extended than the reference arm. As a result, the subject stopped moving the indicator arm before he or she achieved an accurate match. The same argument can be applied to extension conditioning, but here the errors would occur in the opposite direction.

To test this idea, we tried to lower spindle discharge rates in flexors and extensors in both arms using conditioning techniques. If spindle rates could be lowered, any difference between the static signal from the reference arm and the static plus dynamic signal from the indicator arm would be smaller and should therefore lead to smaller bias errors. In order to achieve lower rates, attempts were made to introduce slack into elbow muscles in both arms (*both slack*, Fig. 1D).

Experiment 5: introducing slack after flexion conditioning.

The experiment was begun with flexion conditioning of both arms. After subjects had relaxed, both arms were moved by the experimenter to full extension (0°) and held there for 6 s. Then the reference arm was moved to the test angle (40 – 50°) and its position was matched by the indicator arm.

Data for a group of nine subjects using flexion conditioning are shown in Fig. 5. At 5 s after the reference arm had been placed at the test angle, its position was matched by the indicator arm with a mean error of $+0.5 \pm 1.1^\circ$ in the direction of extension. The error at 10 s was $+0.8 \pm 0.9^\circ$ and that at 30 s was $+0.1 \pm 1.1^\circ$. Mean errors therefore lay close to zero and statistical analysis showed no significant effect of time delay on position error. Therefore, there was no evidence of adaptation over the 30 s of measurement. In addition, the errors at all time delays did not differ significantly from zero error.

Experiment 6: introducing slack after extension conditioning. This time, the experiment began with extension conditioning of both arms at 0° . After subjects had relaxed, both arms were moved to 90° and held there for 6 s before the reference arm was extended to the test angle ($40\text{--}50^\circ$) and its position matched by the indicator arm. Mean values for the nine subjects are shown in Fig. 5.

When the placement of the reference arm was matched by the indicator arm after a delay of 5 s, an error of $0.1 \pm 1.3^\circ$ into extension occurred. This error increased to $+0.4 \pm 1.2^\circ$ at 10 s and $-0.4 \pm 1.5^\circ$ at 30 s. Again, statistical analysis showed no significant effect of time delay on position error and there was no evidence of adaptation

over the 30 s. Furthermore, none of the errors differed significantly from zero error.

In Experiments 5 and 6, although mean errors from the pooled data lay close to zero, individual subjects showed degrees of variability in performance from trial to trial similar to those seen in the other experiments. There was no suggestion that the conditions of these experiments had altered inter-trial variability. Furthermore, conditioning eliminated any directional bias in the placement of the indicator, allowing pooled means to lie close to zero.

Discussion

The findings of this study contribute two new observations to the study of limb position sense in human subjects. They provide evidence in support of the view that receptor adaptation is responsible, at least in part, for time-dependent errors in position sense, referred to previously as proprioceptive drift. Secondly, they confirm reports that position sense derives from a difference in signals from proprioceptors of the two antagonists acting at the elbow joint. We extend this concept to include signals from both arms. Our data are consistent with the view that for position sense at the forearm, the difference in signals from the two arms is computed and that when this reaches a minimum value, the arms are assumed to be aligned.

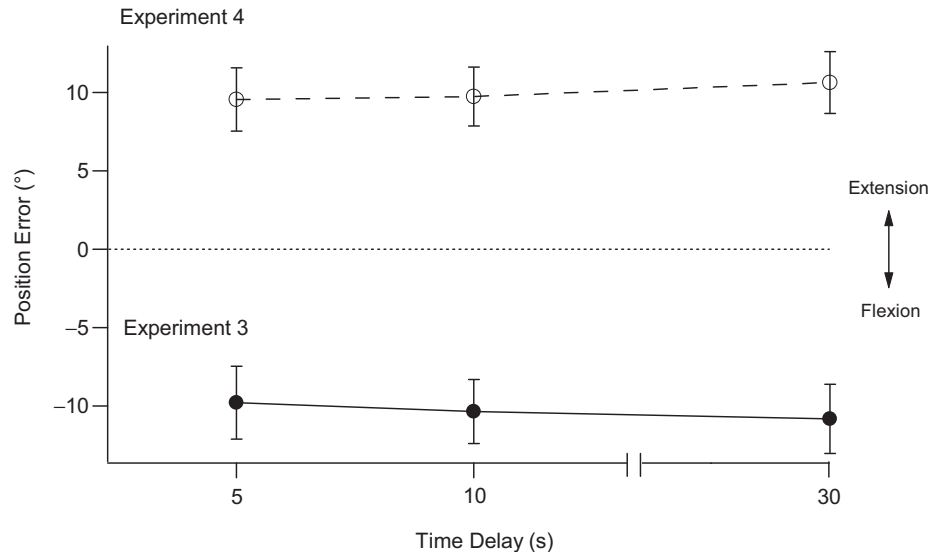


Figure 4. Position errors after isometric contractions of reference flexors and extensors at the test angle

The reference arm was moved to the test angle and held there, fixed in position. The filled circles and continuous line show pooled means \pm s.e.m. of position errors for nine subjects after the reference arm had undergone an isometric extensor contraction followed by an isometric flexor contraction while elbow flexors of the indicator arm were contracted with the arm held flexed (90°). The indicator arm was then moved to match the perceived position of the reference arm at 5 s, 10 s and 30 s after the reference had reached the test position (Experiment 3). The open circles and dashed line show the pooled means \pm s.e.m. of position errors for nine subjects after the reference had undergone an isometric flexor contraction and then an isometric extensor contraction while indicator extensors were contracted with the arm held extended (0°). The indicator arm then matched the perceived position of the reference arm after delays of 5 s, 10 s and 30 s (Experiment 4). The dotted line indicates zero error. Errors into flexion are shown as negative and errors into extension as positive.

In all the present experiments, subjects held their reference arms at the test angle, unsupported. We do not believe that the motor commands and muscle contraction required to hold the arm in place were responsible for any position errors in their own right. Our previous work (Ansems *et al.* 2006; Allen *et al.* 2010; Walsh *et al.* 2013) has shown that position errors measured in a relaxed supported arm do not differ significantly from errors measured when arm muscles contract to support a load. Furthermore, it could be argued that in situations in which the muscle and its spindles were meant to lie slack, the contractions required to hold the reference arm and to move the indicator arm into a matching position risked removing the slack. The elbow flexor torque required to hold an arm at 45° has been estimated at 5% of maximum (Winter *et al.* 2005). Contractions of that strength are insufficient to reset the muscle's conditioned state (Gregory *et al.* 1998).

The present experiments are based on the thixotropic behaviour of muscle spindles. Although our interpretations are consistent with observations made in human spindles (Jahnke *et al.* 1989; Burke & Gandevia, 1995; Wilson *et al.* 1995) and animal spindles (Morgan *et al.* 1984; Gregory *et al.* 1988), the approach is, by necessity, indirect, although the consistency of the findings and their predictability, based on theory, support our view.

Time-dependent changes in position sense after flexion or extension conditioning of both arms (Experiments 1 and 2)

These experiments were based on the hypothesis that the time-dependent changes in position sense previously reported (Paillard & Brouchon, 1968; Wann & Ibrahim, 1992; Brown *et al.* 2003) resulted from adaptation processes at the level of muscle receptors. It was proposed that by conditioning a muscle with a contraction, high levels of resting discharge would be generated in spindles and discharge rates would fall over time as a result of adaptation. Indeed, time-dependent changes in position sense did occur and the direction of the changes depended on which muscle group had been conditioned (Figs 2 and 3). Such a directional change in the distribution of the errors argues in support of a peripheral signal for the origin of proprioceptive drift and makes an explanation based entirely on central mechanisms less likely.

Evidence for adaptation was sought over four periods of delay. It could be argued that in the first condition, of 1 s interval measurements, subjects were carrying out not a position-matching task, but a movement-tracking task. This raises the possibility that the subsequent time-dependent changes in position errors did not reflect

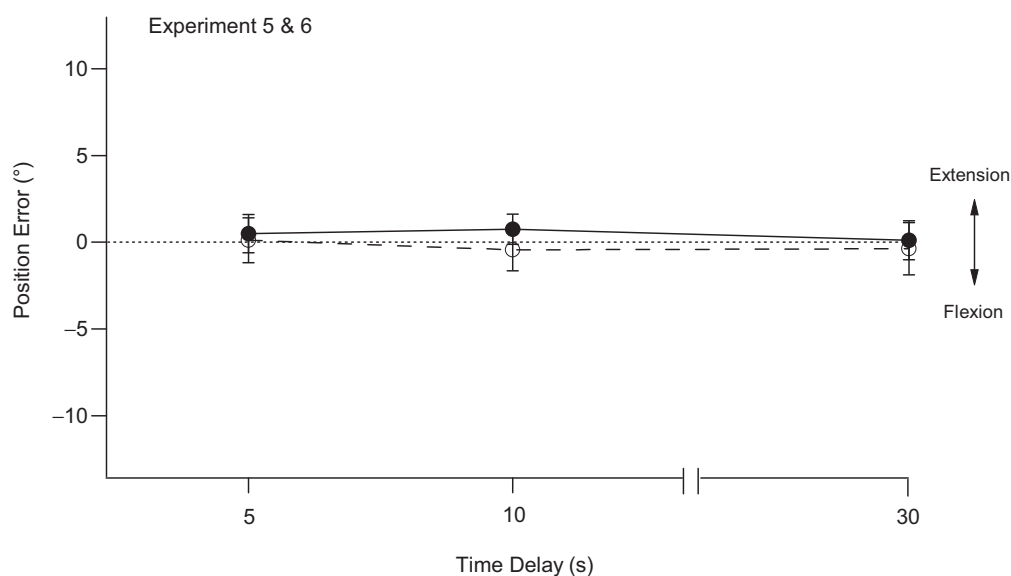


Figure 5. Position errors after conditioning to introduce slack in both reference and indicator muscles

The filled circles and continuous line show pooled means \pm S.E.M. of position errors in nine subjects after elbow flexors of both arms had first undergone contractions with the arms held flexed (90°). Both arms were then moved into full extension (0°) and held there for 6 s before the reference arm was moved to the test position and its position matched by the indicator arm. Matching was performed at 5 s, 10 s and 30 s after the reference arm had reached the test angle (Experiment 5). The open circles and dashed line show pooled means \pm S.E.M. of position errors of nine subjects after elbow extensors of both arms had first undergone contractions with the arms held extended (0°). Both arms were then moved into full flexion (90°) and held there for 6 s before the reference arm was moved to the test angle and its position matched by the indicator arm after delays of 5 s, 10 s and 30 s (Experiment 6). The dotted line indicates zero error. Errors into flexion are shown as negative and errors into extension as positive.

receptor adaptation but the fading effects of a tracking task. The difficulty with such an interpretation is that it is not easy to distinguish between changes caused by adaptation and those of a movement-tracking task. The interval most likely to be influenced by the preceding movement is the 1 s interval. If this is excluded from the analysis of the time-dependent changes in error, the result is no longer significant. Such an outcome is not surprising because during the time course of adaptation of a typical spindle discharge, most of the changes occur within the first second after a stretch [Fig. 5B in Roll & Vedel (1982)].

In Fig. 3, notice that after flexion conditioning errors differ significantly between the 1 s and 30 s delays, as well as between the 5 s and 30 s delays. Significant changes in error beyond the 1 s interval support our case for receptor adaptation. The same is not true in extension conditioning, in which the change in errors between the 5 s and 30 s intervals is not significant. This may be because after extension conditioning subjects were required to hold their arms at the test angle and this may have removed some slack in elbow flexors and thus reduced the difference in signals from flexors and extensors.

Perusal of the literature has not revealed any examples of time-dependent changes in position errors following a limb-tracking task. It has been reported that when movement of one arm is suddenly stopped, the distance it has moved is overestimated in the placement of the other arm (Hollingworth, 1909). However, in the present experiments, errors in the opposite direction occurred. After flexion conditioning, when the movement of the reference arm into extension was stopped, it led to matching errors into flexion (Fig. 2).

In Experiment 1, it was postulated that when the reference arm was moved to the test angle, the conditioned elbow flexors were stretched by the movement, generating a high level of spindle discharge. The same movement would shorten the extensors, which would fall slack. We assumed that the high rate of discharge in flexors would adapt with time, leading to the perception over time of the elbow as being more flexed. In an alternative interpretation, the low level of activity in the slack elbow extensors picks up with time, perhaps as a result of spontaneous uptake of intrafusal slack, leading to the sensation that the extensors are becoming longer (i.e. the elbow is becoming more flexed). The time-dependent changes in position error would remain in the same direction, but the explanation would not be in terms of receptor adaptation. In animal studies of conditioning effects on discharges of identified muscle spindles, we observed that after slack had been introduced, spindles maintained a low and steady level of discharge for long periods, unless the muscle was held at a rather long length, when slack was removed spontaneously as a result of rising passive tension (Gregory *et al.* 1986). At the test angle of 40–50°, passive tension in human elbow muscles is low

and thus the spontaneous removal of slack in spindles is unlikely. Therefore, our preferred explanation for the observations in Experiments 1 and 2 remains receptor adaptation, although we cannot exclude a contribution from changes in the activity of the antagonists. In any case, the principal conclusion from these experiments, that proprioceptive drift is attributable to a peripheral receptor mechanism, remains the same.

Although we have argued in favour of receptor adaptation as the principal mechanism for proprioceptive drift, we do not, of course, exclude an additional contribution from central sources. However, we believe there is now an adequate peripheral mechanism available to account for proprioceptive drift and, in the absence of new evidence, it is unnecessary to invoke a central mechanism as well.

According to current opinion, the brain does not listen to individual spindles but to the population of afferents transmitting from a muscle or group of muscles (Bergenheim *et al.* 2000). In view of this, it is remarkable how closely the drift in time of perceived limb position follows the time course of adaptation estimated from individual spindle discharges. Presumably the population signal changes with a time course that differs little from that of individual afferents. In addition, the process of converting a change in afferent impulse stream into a change in sensation of limb position must be relatively direct, with little loss or distortion of information. Such considerations are of interest within the context of recent efforts to improve acceptance of prosthetic devices by providing amputees with gradable, distally referred sources of touch or movement information (Dhillon & Horsch, 2005).

As far as we know, the notion that proprioceptive drift arises as a result of influences originating in the proprioceptors has not been proposed previously. Here, we have argued that the relevant afferent signal used to align the forearms in a position-matching task is the antagonist difference signal from each arm. The brain compares the two arms and calculates an overall difference. When this difference reaches a minimum value, the arms are assumed to be aligned. It remains uncertain whether any of this involves reference to a central map and it may not do so. Certainly, when position sense is measured using a pointing task rather than a matching task, there is no other arm with which to compare and reference to a central map will be necessary.

It has been proposed that there are at least two distinct body representations in the brain: the body image, and the body schema (De Vignemont, 2010). Their relationship to a third representation, the body model, remains uncertain (Longo & Haggard, 2010). The body schema could conceivably be used as a central reference point for position sense. It is dependent on ongoing proprioceptive input, operates largely unconsciously and is concerned with body

movements. It is known to change rapidly as a result of a change in peripheral afferent input produced by a progressive nerve block (Inui *et al.* 2011). It is therefore conceivable that errors in position sense triggered by muscle conditioning are the result of changes evoked by afferents in the body schema.

Time-dependent changes in position sense after co-contraction of reference muscles (Experiments 3 and 4)

These experiments were designed to provide controls for the time-dependent changes observed in Experiments 1 and 2. In Experiments 1 and 2 only flexors or only extensors of both arms were selectively conditioned by a voluntary contraction. Adaptation of the spindle signal in the reference arm led to shifts in the perceived position of the arm in a direction that depended on which muscle had been conditioned. If this interpretation is correct, raising spindle rates in both antagonists of the reference arm should lead to time-dependent changes which annul one another because they occur in opposite directions. The reference flexors and extensors were therefore both conditioned at the test angle with isometric contractions. This would leave spindles of both muscle groups in a sensitized state. As the reference flexor signal fell from adaptation, this would be accompanied by a similar fall in extensor signal. Therefore, the difference in signals from the reference arm was predicted to be close to zero. Such low signals would not be expected to show time-dependent changes.

This result was achieved and a reduction in time-dependent errors was observed (Fig. 4). Selective conditioning of one or other of the reference antagonists led to time-dependent changes in position errors of 2.4° and 3.4° , whereas conditioning of both groups reduced the error to 1.0° . This small, non-significant change in error with time, in the direction of flexion in Experiment 3 and in the direction of extension in Experiment 4 (Fig. 4), was probably a consequence of the sequence of conditioning used (i.e. flexion first or extension first).

Experiments 3 and 4 revealed important new trends. After flexion conditioning, all errors lay 10° in the direction of flexion; thus, subjects believed their arms to be accurately aligned when in fact they differed by roughly 10° (Fig. 4). This was a very different result from that of Experiment 1. Here, we believe the source of error was the indicator arm. Our working hypothesis was that the brain calculates the difference between the flexor and extensor signals of each arm and compares these two differences to calculate the overall difference. After conditioning, the indicator flexor signal is high, whereas the difference in signals from the reference arm is low. As a result, as the indicator arm moves into the matching position, in an

attempt to match the low reference signal, it stops early, 10° short of the actual position of the reference arm. This means that the stretch of indicator flexors was kept to a minimum. The same argument can be applied to the 10° of error into extension seen after extension conditioning of the indicator (Fig. 4). We therefore suspect that the brain listens to the afferent streams from each arm and during a position-matching task computes their difference. When this difference reaches a minimum value, the arms are assumed to be accurately aligned.

We do not believe the 10° of error in the direction of flexion or extension was some kind of non-specific effect resulting from indicator conditioning. In a new experimental series (Proske *et al.*, 2014), we explored the point further. Experiment 3 was carried out in nine subjects, using the 5 s time delay. The mean \pm S.E.M. position error measured was $-9.3 \pm 2.2^\circ$. This essentially confirms our previous result. The experiment was repeated, but this time, before the match, slack was introduced into indicator flexors by having the subject hold the arm stretched for 6 s after conditioning, as in Experiment 5. The matching error now fell to $-1.4 \pm 2.0^\circ$. The same cohort of subjects then carried out Experiment 4. The observed error was $7.4 \pm 1.7^\circ$, again confirming earlier results. Repeating the experiment after slack had been introduced into extensors led the mean error to fall to $-1.4 \pm 1.5^\circ$. Thus, the introduction of slack in indicator muscles caused the difference between flexor and extensor signals in the indicator to become smaller and this compared with the reference difference signal, which was also small. As a result, errors lay close to zero.

Experiments 3 and 4 led to three important conclusions. Firstly, the brain does not determine position sense from the afferent streams from individual muscles, but computes the difference signal from the antagonists. Experiments using muscle vibration, which is a rather more artificial method of stimulating muscles than conditioning with voluntary contractions, have led to similar conclusions (Gillhodes *et al.* 1986; Ribot-Ciscar & Roll, 1998). Secondly, these experiments highlight the contribution made by the indicator arm in a position-matching task at the forearm. Again, similar conclusions have been reached by others (Lackner & Taublieb, 1984; Allen *et al.* 2007; White & Proske, 2009; Izumizaki *et al.* 2010). Finally, Experiments 3 and 4 demonstrate that proprioceptive drift in the reference arm depends on the adaptation of discharge from one muscle group when its discharge is higher than that of its antagonist. Raising discharge rates in both antagonists reduces the drift because the signal difference is now smaller.

It is interesting that the errors made under the conditions of Experiments 3 and 4 were each of about 10° , although in opposite directions. In previous experiments, in which the arms were conditioned differently, errors of a

similar magnitude were observed (Allen *et al.* 2007; White & Proske, 2009). It is somewhat unexpected that errors larger than 10° have not previously been encountered. Perhaps this represents the limit of a spindle-based system for signalling disparities in forearm position. This makes forearm position matching a short-range system with limits of $\pm 10^\circ$.

Time-dependent changes in position sense after stretching of elbow muscles (Experiments 5 and 6)

The main aim of these experiments was to eliminate the initial offset errors after identical flexion or extension conditioning of both arms (Experiments 1 and 2). We hypothesized that the errors arose from the high spindle signal from the indicator arm during its movement into the matching position. The introduction of slack in the muscles of both arms would lower the discharge rates of muscle spindles and so reduce the error. Slack was introduced by stretching arm muscles and then shortening them (Morgan *et al.* 1984). As a consequence, spindle discharges dropped to low levels (Proske *et al.* 1992; Scott *et al.* 1994).

Lowering spindle discharges in both arms removed the offset errors (Fig. 5). In addition, there was no adaptation of discharge over the period of measurement because of the low rates of discharge. Therefore, by slackening muscles and their spindles, we were able to reduce position errors to lie close to zero. This indicates that if the aim in an arm-matching task is to keep position errors as small as possible, slack must first be introduced in muscles of both arms. In everyday activities, we do not systematically condition our muscles. Presumably the thixotropic status of muscles varies so that sometimes slack is present and sometimes, particularly after a contraction, parts of the muscles become sensitized. This means that over time position errors are likely to be distributed over a considerable range, underlining the inaccuracy of the muscle proprioceptive system and the need for additional inputs from vision and touch (Proske & Gandevia, 2012). In addition, it emphasizes the importance of putting muscle into a defined state for the study of position sense in humans.

Conclusions

These experiments provide evidence for some of the neural processes likely to underlie the process of forearm matching. Firstly, evidence is provided in support of the hypothesis that proprioceptive drift can be accounted for by receptor adaptation. Secondly, the experiments provide evidence that the brain is listening to the difference in the discharges from the two antagonists of each arm. It does not appear to matter whether the actual spindle rates from

each antagonist are high or low because, provided that they are equal, the outcome is the same. It is the difference in rates that matters. Finally, both arms play major and probably equal roles in determining position sense at the forearm and, if the discharges from the indicator are higher than those from the reference, large errors in position matching can result (Fig. 4).

In previous experiments, when large position errors were generated by muscle conditioning, such as in Experiments 3 and 4, when subjects were asked at the end of the match whether they were satisfied with their matches, they assured the investigator that they had aligned their arms accurately (Proske & Gandevia, 2009). This suggests that the brain was unaware of the large mismatch between the two arms. It implies that once a minimum difference in signals between the two arms has been achieved, the brain assumes that the two arms are accurately aligned. When a minimum difference signal is significantly above or below zero, position errors result, errors of which the subject remains unaware. This suggests that the brain assumes similar thixotropic states for the elbow muscles of both arms, which is likely to be correct in most everyday situations. Only by experimentally imposing differences in states in the two arms can the flaws in this system be revealed.

Can these findings be applied to any other joint? For example, are the neural mechanisms for aligning the lower limbs much the same as those for aligning the forearms? While we do not yet know the answer to this question, some limited evidence is available from position matching and pointing experiments at the wrist and forearm (Walsh *et al.* 2013). The data suggest that the level of precision with which an unseen limb can be indicated with a pointer is similar for the elbow and wrist, but at the elbow this is inherently less precise than a comparison of signals in a two-limb matching task. Thus, at the elbow the neural mechanism concerned with comparing signals from the two arms has evolved a high level of accuracy that is higher than at other joints, such as the wrist. We propose that this is a short-range system ($\pm 10^\circ$) in which limits are defined by the range of background discharges of spindles in the two arms.

Our current working hypothesis is that in position matching at the elbow, in the absence of vision, the initial alignment of the arms makes use of a central reference map. When the arms are sufficiently close to one another, within a range of $\pm 10^\circ$, a second mechanism comes into play, which uses the difference signal coming from arm proprioceptors. This second mechanism is more accurate than a mechanism based on reference to a central map. Why do we need such an accurate system? In everyday tasks we commonly use a posture in which the arms are held in front of the body, with the hands facing each other, in order to use the two hands as a single instrument, to make skilled cooperative movements and to fashion tools.

Such skills in our ancestors are likely to have contributed to our present-day dominance over other animals.

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Additional information

Competing interests

None declared.

Author contributions

All authors participated in the conception and execution of the project, and in data processing and the preparation of the material for publication. All experiments were carried out in the Department of Physiology at Monash University.

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CHAPTER 3: POSITION SENSE AND THE DIFFERENCE SIGNAL

Tsay, A., Allen, T. J. & Proske, U. (2015). "Position sense at the human forearm after conditioning elbow muscles with isometric contractions." Exp Brain Res **233**(9): 2635-2643.

3.1 Explanatory Notes

In Chapter two, it was proposed that the brain monitors the afferent signals from the antagonist pairs of the two arms, in order to align the forearms in a limb matching task. This hypothesis arose from the findings of experiment three and four (Tsay et al., 2014), where co-conditioning the elbow flexors and extensors of the reference arm generated large position errors ($\pm 10^\circ$), with the direction of the errors depending on how the indicator arm was conditioned beforehand.

Chapter three (Tsay et al., 2015) provides further evidence that central processing of positional information, in a matching task, is concerned with the afferent signal difference between the antagonist muscles, as well as the difference between limbs. Here we report small position errors (1.4° in the direction of flexion) when antagonist muscles of the reference arm were both contracted at the test angle, leading to a similarly large increase in afferent activity from both muscle groups. In contrast, the indicator antagonist arm muscles were slackened by lengthening the muscles and then stretching them before the position matching trial. The aim of the study was to test if accurate alignment of the forearms would occur despite both arms having undergone two very different methods of conditioning.

3.2 Declaration for Thesis Chapter Three

Declaration by candidate

In the case of Chapter three, the nature and extent of my contribution to the work was the following:


Nature of contribution	Extent of contribution (%)
The candidate co-designed the experimental protocol, collected and analysed the data, constructed the figures and edited the manuscript.	70

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Trevor Allen	Discussion of literature, editing paper.	
Uwe Proske*	Discussion of literature, experimental design, writing of paper.	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's
Signature



Date

25/08/16

Main
Supervisor's
Signature



Date

25/08/16

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

Position sense at the human forearm after conditioning elbow muscles with isometric contractions

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Abstract These experiments were designed to test the idea that, in a forearm position-matching task, it is the difference in afferent signals coming from the antagonist muscles of the forearm that determines the perceived position of the arm. In one experiment, flexor and then extensor muscles of the reference arm were conditioned by isometric voluntary contractions while the arm was held at the test angle, approximately 45° from the horizontal. At the same time, indicator arm flexor muscles were contracted while the arm was flexed, or extensors were contracted while it was extended. After an indicator flexor contraction, during matching, subjects made large errors in the direction of flexion, by 9.3° relative to the reference arm and after an indicator extensor contraction by 7.4° in the direction of extension. In the second experiment, with reference muscles conditioned as before, slack was introduced in indicator muscles by a combination of muscle contraction and stretch. This was expected to lower levels of afferent activity in indicator muscles. The subsequent matching experiment yielded much smaller errors than before, 1.4° in the direction of flexion. In both experiments, signal levels coming from the reference arm remained the same and what changed was the level of indicator signal. The fact that matching errors were small when slack was introduced in indicator muscles supported the view that the signal

coming from reference muscles was also small. It was concluded that the brain is concerned with the signal difference from the antagonist pair of each arm and with the total signal difference between the two arms.

Keywords Muscle spindle · Thixotropy · Position sense · Proprioception · Elbow muscles

Introduction

It has long been known that in a position-matching task at the forearm, signals from muscle spindles provide positional information. The most important piece of supporting evidence is that muscle vibration, a powerful stimulus for muscle spindles, generates illusions of arm movement and displacement (Goodwin et al. 1972). Vibration of elbow flexor muscles generates the illusion of arm extension; vibration of extensors generates the illusion of arm flexion. The generally accepted interpretation is that the increase in spindle discharge rates evoked by vibration is interpreted by the brain as a lengthening of the vibrated muscle, leading to a perception of movement about the elbow joint. Interestingly, vibrating elbow flexors and extensors together at a similar frequency and amplitude generates no illusion, as measured in a two-arm matching task (Gilhodes et al. 1986).

We have been studying position sense using an arm-matching task, but rather than using vibration to manipulate the sense we have exploited a property of passive muscle called thixotropy. This is a history dependence of muscle properties, which can alter passive tension and stiffness depending on what has been done to the muscle beforehand (Proske et al. 2014). Since the intrafusal fibres of muscle spindles exhibit thixotropic behaviour, it has been possible

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to produce systematic changes in spindle discharge levels using this property (Gregory et al. 1988). The level of spindle background activity is believed to be responsible for generating the limb position signal (Clark et al. 1985), and it is likely that most of the positional signals are coming from the secondary endings of spindles (Matthews 1988). Since background activity levels in spindles can be altered, depending on the thixotropic state of the intrafusal fibres, it is possible to generate predictable errors in limb position sense with this method (Gregory et al. 1988; Tsay et al. 2014).

The theory underlying the conditioning method is that after a contraction stable cross-bridges form between actin and myosin of sarcomeres (Hill 1968). After a flexion contraction of elbow muscles, as the arm is extended to the test angle, these cross-bridges in intrafusal fibres of flexor spindles are stressed by the stretch. At the same time, elbow extensors are shortened by the movement and they fall slack (Proske et al. 2014). Flexor conditioning therefore leaves flexor spindles taut, with a high level of background activity and stretch sensitivity, while extensor spindles exhibit a low level of background activity and low stretch sensitivity. The same argument can be applied after an extensor contraction. It leaves extensor spindles in a sensitised state and a low level of activity in flexors.

We recently devised a new method of muscle conditioning, with the aim of avoiding the usual dominance of flexor or extensor signals associated with flexion or extension conditioning, trying to achieve similar levels of activity in both antagonists (Tsay et al. 2014). In the new experiment, the reference arm was moved to the test angle and fixed in position while elbow flexors and then extensors underwent isometric contractions (co-contraction conditioning). Position of the arm was indicated by the indicator arm, which had been either flexion or extension conditioned in the conventional way. Because both antagonists of the reference arm had undergone a contraction at the same length and this was not followed by any movement, both were in a near identical thixotropic state; there was no slack in either muscle and the afferent signals coming from both were likely to be similarly large. It was therefore unexpected that when position of the reference arm was indicated, large matching errors into flexion were observed when the indicator had been flexion conditioned and large errors into extension were observed after extension conditioning of the indicator (Tsay et al. 2014, Figure 4).

To explain this result, our working hypothesis was that in determining the position of the forearm, the brain calculated a difference signal between inputs from elbow flexor and extensor spindles. When both inputs were of similar size, be it large or small, it meant the difference signal was always small, indicating that the arm had not moved in either the direction of flexion or extension. We saw the

situation as similar to that during simultaneous vibration of the antagonists which abolished any kinaesthetic illusions (Gilhodes et al. 1986). If this interpretation was correct, then in the experiments of Tsay et al. (2014) subjects were trying to match a low reference signal with a high indicator flexor or extensor signal, leading to large matching errors.

In order to obtain supporting evidence for our proposal, we used a method to introduce slack in both antagonists of both arms by means of a conditioning contraction followed by stretch. This led matching errors to lie close to zero (Tsay et al. 2014, Figure 5). However, since in that experiment slack had been introduced in muscles of both the reference and indicator arms, it remained uncertain whether the resulting errors close to zero were due to the conditioned state of the reference arm or the indicator arm. What was required was an experiment in which the reference arm was always kept co-contraction conditioned while the conditioned state was altered only for the indicator arm. The question was posed, with the reference arm co-contraction conditioned and therefore spindles of both reference antagonists sensitised, did the introduction of slack in indicator muscles, lowering their afferent discharge levels, reduce matching errors to zero? In the present report, we describe the outcome of such an experiment. It was concluded that isometric contractions of both reference antagonists lead the brain to interpret the difference signal coming from the arm as being low.

Methods

The experiment used nine subjects. The average age of subjects was 24.1 (± 1.2) years. Subjects gave informed, written consent prior to undertaking an experiment. The work was approved by the Monash University Human Research Ethics Committee, and the ethical aspects of the experiments conformed to the Declaration of Helsinki.

The apparatus

All position matching was done in the vertical plane. Blind-folded subjects sat at a table and placed both forearms on lightweight paddles of a custom-built apparatus for measuring forearm position sense (Allen and Proske 2006). The forearms were strapped to the paddles by Velcro straps placed just below the crease of the wrist and 5 cm in width, palms facing upward. Equal tension from the strapping was checked before proceeding with the experiment, to minimise potential differences in skin sensation between the two arms. The upper arms rested on horizontal supports, allowing subjects to relax their shoulder muscles during matching trials. One arm was designated the reference arm (the arm placed at the target angle by the experimenter),

while the other arm was the indicator arm (the arm moved by the subject to match the position of the reference arm).

Forearm angle was measured using potentiometers (25 K Ω Spectra Symbol, Salt Lake City, USA) located at the hinges of each paddle. The hinges were co-linear with the elbow joint. The potentiometers provided a continuous voltage output proportional to the angle of each paddle, where 0° was when the forearm was horizontal and 90° when it was vertical. Calibration of the potentiometers was checked before each experiment.

Muscle activity of reference arm flexors and extensors was measured using surface electromyogram (EMG). A pair of Ag–AgCl electrodes with an adhesive base and solid gel contact points (3M Health Care, London, Ontario, Canada) were placed approximately 2.5 cm apart over the surface of the biceps brachii and triceps brachii. A grounding electrode was placed on the collar bone. EMG output was connected to an audio amplifier for biofeedback. Position signals were acquired at 20 Hz, EMG signals at 1000 Hz using MacLab 4/s data acquisition module running Chart software (AD Instruments, Castle Hill, NSW, Australia) on an Apple computer.

Measuring position sense

During each trial, the paddle strapped to the reference arm was moved by the experimenter to the test angle and the blindfolded subject was asked to match its perceived position with their indicator arm. The test angle chosen was approximately 45° to the horizontal. The actual angle achieved in each trial depended on placement by the experimenter and angles lay in the range 40°–50°. The variation in target angle from trial to trial meant that the subject was unable to use timing or movement cues to guess the actual test angle. During movement of the reference arm to the test angle, subjects were asked to remain relaxed. This was monitored with auditory feedback of EMG in the reference arm.

Throughout these experiments, once the reference arm had been placed at the test angle, the subject maintained its position voluntarily. All of the matching by the indicator arm was done voluntarily by the subject. Subjects were therefore required to generate mild contractions sufficient to support the arms against gravity and for movement of the indicator into the matching position. These conditions were chosen to keep the matching process close to what subjects might do in everyday tasks. During the matching process, subjects were asked not to rush but to move their indicator arm into position, carefully but deliberately. Once the reference arm was in position at the test angle, moving the indicator from its starting position into the matching position took about 5 s. At the end of each trial, the arms were brought back to their resting position, one at a time,

making it difficult for subjects to guess the test position of the reference arm from the time it took to move there.

Position errors between the two arms were calculated from the difference in angle between the reference arm and the indicator arm. The convention was used that when the indicator matched in a more extended position, relative to the reference, errors were given a positive value. When the indicator was placed in a more flexed position, errors were assigned a negative value.

Muscle conditioning

It was necessary at the start of each position-matching trial to put elbow muscles of both the reference and indicator arms into a defined thixotropic state. This is called muscle conditioning. Gregory et al. (1998) showed that it required a 10 % MVC contraction to fully reset the thixotropic state of a muscle using a voluntary contraction. To ensure subjects exceeded this level of contraction, we instructed them to carry out a half-maximum flexion or extension effort, lasting 2–3 s. Audio biofeedback of the EMG signal during the contraction was also provided.

The aim of the present experiment was to measure position sense under conditions where the proprioceptive bias imposed on muscles of the reference arm was always the same. To do that, the reference arm was conditioned in such a way that it left both elbow flexors and extensors in a sensitised state during matching (Fig. 1A–D, reference, co-contract). This conditioned state for the reference arm was used in both experiments 1 and 2. Conditioning used isometric contractions of elbow flexors and extensors at the test angle. To do that, the blindfolded subject's reference arm was moved to the test angle (40°–50°). They were asked to generate a half-maximum contraction in extensor muscles by pushing the arm away from the body. During the contraction, the arm was rigidly fixed at the test angle by a pair of metal struts bolted to the frame of the apparatus. Subjects were then asked to generate a half-maximum flexion contraction, the arm again being held fixed at the test angle. So now the reference arm had undergone isometric flexion and extension contractions at the test angle, leaving both muscle groups in a sensitised state. For such conditioning, the symmetries of the contractions in the antagonist pair did not matter, provided that each muscle had been fully reset.

Experiment 1

While the reference arm was being isometrically conditioned at the test angle, the indicator arm was either flexion conditioned (in a flexed position) or extension conditioned (in an extended position). In the first series of five trials, the elbow flexors of the indicator arm were contracted with the arms

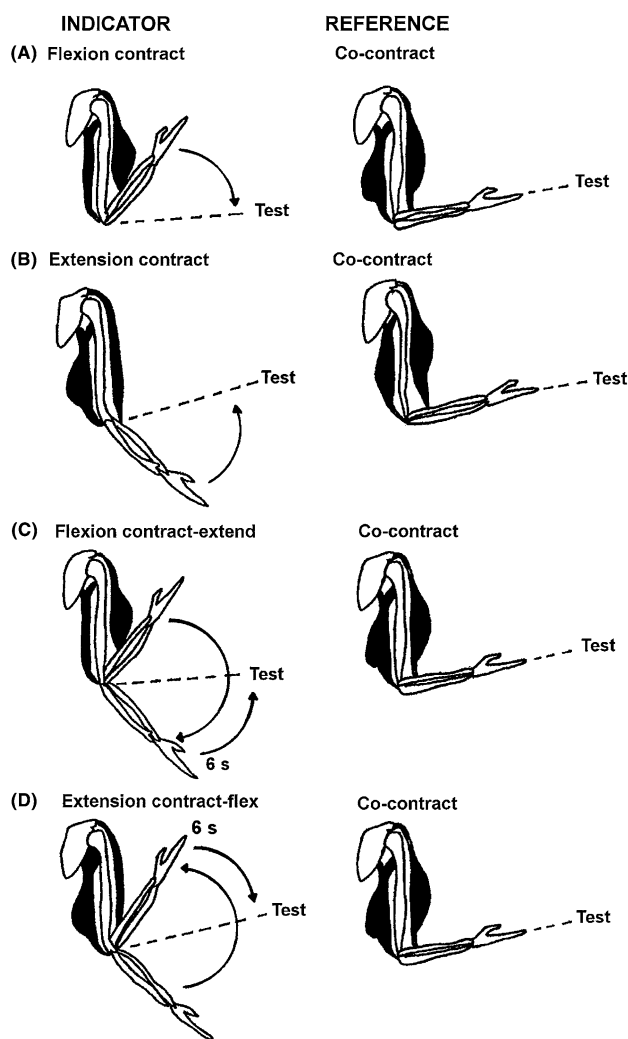


Fig. 1 Diagrammatic representations of mechanical state of arm muscles during conditioning. All matching of arm positions was done by blindfolded subjects, matching in the vertical plane, while supporting their arms themselves. Conditioning procedures for the reference arm were the same for all four panels **A**, **B**, **C** and **D**. Here, the arm was moved by the experimenter to the test angle and held fixed in position while elbow flexors and then extensors underwent isometric contractions. In **A** the indicator arm was flexion conditioned (flexion contract). To do that, its position started at 90° at the elbow, that is, with the forearm in a vertical position. The subject contracted elbow flexors by trying to pull the arm towards their body. Once they had relaxed from the contraction, they moved the arm to a matching position with the reference arm (*dashed line*). In **B**, the reference arm was conditioned, as above, the indicator arm extension conditioned (extension contract). Here, the arm was moved into full extension (0°), and the subject pressed it down on the supporting surface, in the process contracting their elbow extensors. Once they had relaxed, they were asked to move their arm to a matching position. In **C**, the reference arm was again conditioned as before. Conditioning of the indicator arm (flexion contract-extend) began with a flexion contraction at 90° . After the subject had relaxed, the arm was moved into full extension (0°) and left there for 6 s (*large arrow*). This resets flexor cross-bridges to the longer length. The subject then moved the arm to a matching position with the reference arm (*small arrow*). In **D**, the sequence of conditioning of the indicator was reversed. It began with a contraction of elbow extensors with the arm held extended (0°). Then, the arm was moved into full flexion (90° large arrow), held there for 6 s and finally moved into a matching position with the reference arm (*small arrow*)

held flexed at 90° (Fig. 1A, indicator, flexion contract). After the blindfolded subject had relaxed from the conditioning contraction, they moved their indicator into a position matching the perceived position of the reference arm. When they declared they had achieved a satisfactory match, a marker was placed on the angle trace, which was recorded continuously during the matching procedure. Flexion conditioning altered the mechanical state of elbow flexors leaving them taut and leaving elbow extensors slack during the matches.

In the second series of five trials, elbow extensors of the indicator arm were contracted with the arm held extended to 0° (Fig. 1B, indicator, extension contract). Again, after the subject had relaxed, they moved their indicator arm to a matching position with the reference arm. Here, during matching, the elbow flexors lay slack and the extensors were taut.

Experiment 2

In the first series of five trials of this experiment, muscles of the indicator arm of the blindfolded subject were initially

flexion conditioned (in flexed position), as before. At 90° , the elbow extensors lay stretched and stable cross-bridges in extensor muscles would be expected to form at that stretched length. After the flexor contraction, the arm was moved into full extension (0°). In the process, the flexors were now stretched to a long length and the extensors were shortened. The arm was held at 0° for 6 s to allow cross-bridges in flexors that had been detached by the stretch to reassemble at the longer length (Morgan et al. 1984). There was no comparable reassemblage of cross-bridges in the extensors because their bridges had formed at 90° and the shortening movement to 0° would expect them to fall slack. The subject then moved their indicator into flexion to a matching position (Fig. 1C, indicator, flexion contract-extend). In the process, elbow flexor muscles were shortened and fell slack. The movement into flexion was from 0° to 40° – 50° , which, we believe, was too small a stretch of extensor muscles to reset their cross-bridges, since these had formed at 90° . All the stretch did was to take up some of the slack in the extensors, but not all of it. If there is any slack at all in a muscle, spindle background rates will continue to remain low. So now both flexor and extensor spindle rates of the indicator arm were expectedly low because both antagonists lay slack while reference muscles lay taut.

In the second series of five trials, elbow muscles of the indicator arm were again slackened, but this time the process began with elbow extensors being contracted while the arm was held extended (0°). Then, the arm was flexed to

90°, held there for 6 s and finally moved into a matching position with the reference arm (Fig. 1D, indicator, extension contract-flex).

In both experiments 1 and 2, after the conditioning procedures had been completed, position sense was measured. Subjects carried out a series of five trials under each of the four conditions.

Statistical analysis

A repeated-measures ANOVA was used to test for the effects of different conditioning trials on position errors. If significance was found, a post hoc (Bonferroni) test was used to determine which of the matching trial types were significantly different from each other. Pooled data from each group of experiments were shown as means \pm standard errors of the mean (S.E.M.).

Results

Experiment 1

Data for a single subject for this experiment are shown in Fig. 2A, B. For both sets of trials, the right arm (reference) had been conditioned with a co-contraction. At the same time, for the trials in (A) elbow flexors of the indicator arm were flexion conditioned. The indicator arm was then moved by the subject into a matching position. Diagrams illustrating the conditioning sequences for reference and indicator arms are shown in Fig. 1A. The resulting position errors for the five trials all lay in the direction of flexion relative to the true position of the reference. For this subject, errors were scattered about a mean of $-9.2^\circ (\pm 6.2^\circ)$. That is, the subject considered that they had achieved a satisfactory match with the indicator arm lying too flexed by an average of 9.2° , relative to the position of the reference. The pooled data for the nine subjects (Fig. 3A) gave a mean error of $-9.3^\circ (\pm 2.2^\circ \text{ SEM})$.

For the trials in (B), the reference arm had again been co-conditioned at the test angle, while the indicator arm was extension conditioned, rather than flexion conditioned (diagram in Fig. 1B). Here, all five matching errors lay in the direction of extension (Fig. 2B). That is, the subject believed that they had achieved a satisfactory match with the indicator arm held by an average of $8.2^\circ (\pm 2.6^\circ)$ more extended than the actual position of the reference. The pooled data (Fig. 3B) yielded a mean of $+7.4^\circ (\pm 1.7^\circ)$.

The conclusion from this experiment was that position-matching errors could be seen to shift over a range of nearly 17° simply by changing conditioning of the indicator arm from flexion conditioning to extension conditioning (Tsay et al. 2014). Asking subjects about their matching

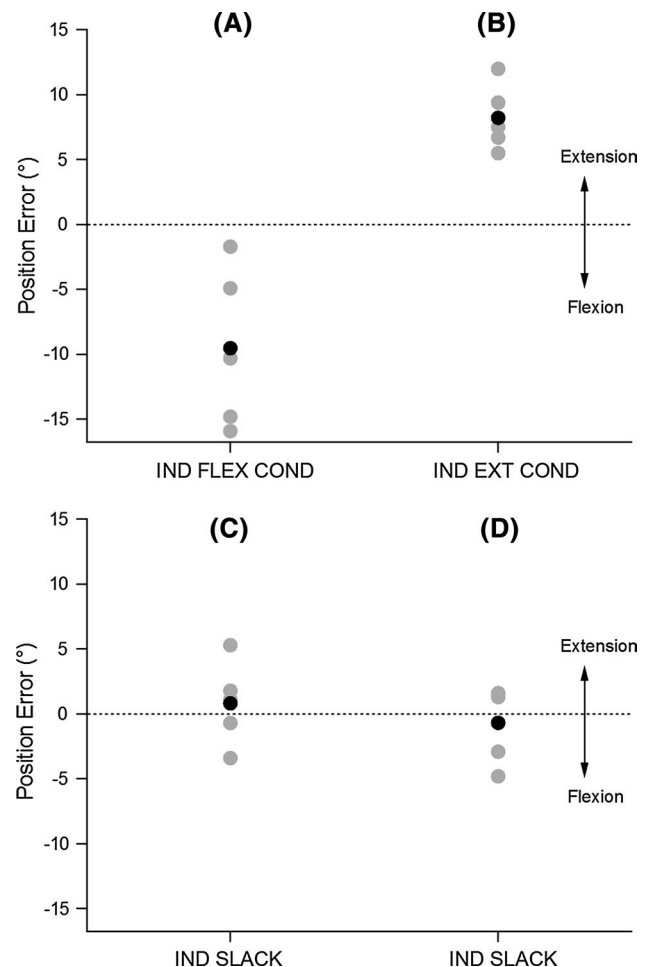


Fig. 2 Position-matching errors by an individual subject. The diagrammatic representation of the conditioned state of muscles in both arms for these trials is shown in Fig. 1, where A, B, C and D correspond to panels A, B, C and D in this figure. For all four panels, the muscles of the reference arm had both undergone isometric co-contractions. In A, the indicator arm had been flexion conditioned (IND FLEX COND), while in B it had been extension conditioned (IND EXT COND). In C and D, the indicator arm was conditioned to introduce slack (IND SLACK). The difference between C and D was that in C, the slackening process began with a flexor contraction, while in D, it began with an extensor contraction. Greyscale points, individual values for matches, point in bold, mean value. The convention has been used that overestimates by the indicator arm, in the direction of extension, have been assigned a positive value, underestimates, in the direction of flexion, a negative value. Dotted line indicates zero error

accuracy during these trials, they assured the experimenter that on each occasion they had been able to achieve what they believed was a satisfactory match.

Experiment 2

In this experiment, conditioning of the reference arm was done in exactly the same way as in Experiment 1. Here, however, rather than simply flexion or extension

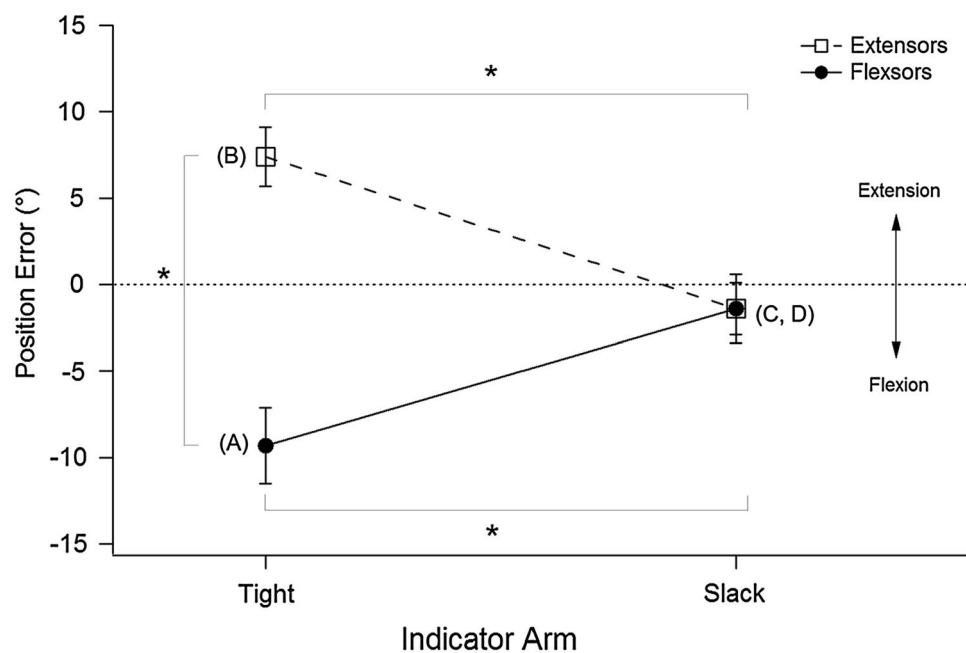


Fig. 3 Position errors for nine subjects after four forms of conditioning. Point A is a plot of matching errors (mean \pm SEM) after the conditioning sequence shown in Fig. 1A. Position errors were measured after both elbow muscles of the reference arm had been conditioned isometrically at the test angle and the indicator arm flexion conditioned (indicator arm tight, *filled circle A*). In Fig. 1B, the reference arm was again co-contrast conditioned, and the indicator arm was extension conditioned (indicator arm tight, *open square B*). For point C and shown diagrammatically in Fig. 1C, the reference arm

was again co-contrast conditioned while the indicator had been flexion conditioned and then moved into full extension before matching (indicator slack, *filled circle C*). For point D, the reference had again been co-contrast conditioned, with the indicator extension conditioned and then moved into full flexion before matching (indicator slack, *open square D*). Trends in the data were indicated by a *solid line* where the conditioning procedure began with flexion conditioning and by a *dashed line* where it began with extension conditioning. *Dotted line* zero error. Asterisks significant differences between points

conditioning the indicator, a method of conditioning was employed that generated slack in both indicator elbow flexor and extensor muscles (Tsay et al. 2014). The method is shown diagrammatically in Fig. 1C, D. For (C), conditioning began with a flexor contraction with the arm held at flexed. The experimenter then fully extended the arm, held it in that position for 6 s before asking the subject to bring it back into a matching position with the reference arm.

The data for a single subject are shown in Fig. 2C. Matching errors lay scattered approximately uniformly about zero, with a mean error of $+0.8^\circ (\pm 3.2^\circ)$. The pooled values for the nine subjects (Fig. 3C) yielded a mean of $-1.4^\circ (\pm 2.0^\circ)$.

The experiment was repeated, but this time conditioning of the indicator was begun with an extensor contraction with the arm held extended (Fig. 1D). The arm was then moved into full flexion, held there for 6 s before being moved by the subject into a matching position with the reference arm. After conditioning, matching errors again lay scattered about zero, giving a mean value of $-0.7^\circ (\pm 3.0^\circ)$ for the five trials (Fig. 2D). The mean value for the nine subjects (Fig. 3D) was -1.4°

($\pm 1.5^\circ$). The conclusion from this experiment was that introducing slack in indicator muscles and thereby lowering levels of proprioceptor discharges in both indicator antagonists led to much smaller matching errors when the reference muscles had been conditioned with a co-contraction.

The pooled data from both experiments are shown together in Fig. 3. The condition of the indicator arm, shown as either 'slack' or 'tight,' relates to whether its arm muscles had been either flexion or extension conditioned, or slack had been introduced by flexion/extension conditioning followed by stretch. Analysis using repeated-measures ANOVA confirmed that these errors were significantly different, $F(2.9, 23.1) = 19.0, p = 0.000$. Further Bonferroni post hoc testing showed that when indicator muscles had been flexion conditioned, matching errors lay significantly more into flexion when compared with extension conditioning of the indicator arm ($p < 0.05$). Introducing slack in indicator muscles led to significant falls in matching errors from both the flexion conditioned value and the extension conditioned value ($p < 0.05$), errors which were no longer significantly different from zero.

Discussion

The original experiments that provided evidence for a role for muscle spindles in position sense used a forearm matching task and vibration of elbow muscles (Goodwin et al. 1972). The technique brought by our group to the study of the role of muscle spindles in human position sense makes use of a property of passive muscle called thixotropy (Gregory et al. 1988). Based on observations in animal experiments, we were able to use thixotropic conditioning of muscles to selectively alter levels of spindle background activity (Gregory et al. 1991). In this way, we could generate consistent, predictable position errors in a limb-matching task (Gregory et al. 1988; Allen et al. 2007; Tsay et al. 2014).

In the past, we have conditioned both arms with voluntary flexor or extensor contractions while the arms were held either flexed or extended. Such conditioning always left each arm with one muscle taut and its spindles sensitive and the antagonist slack, with spindles insensitive. More recently, we devised forms of conditioning that left both antagonists in a similar thixotropic state (Tsay et al. 2014). We have done that in two ways, co-contracting both muscles (Reference arm, Fig. 1) or, alternatively, contraction followed by stretch to introduce slack (Indicator arm, Fig. 1C, D). For conditioning the reference arm, it was placed at the test angle, held fixed in position, and one muscle group was contracted isometrically, then the other. Because there was no subsequent movement of the arm, both antagonists were in a similar, sensitised state. In the experiment where the reference arm had been conditioned in this way, when its position was indicated by the other arm, which had been flexion or extension conditioned in the conventional way (Indicator arm, Fig. 1A, B) large matching errors resulted. The errors were in the direction of flexion after flexion conditioning and into extension after extension conditioning (Figs. 2, 3; see also Tsay et al. 2014).

It had previously been shown that simultaneous vibration of forearm antagonists led to abolition of the illusion of movement and position experienced when only one of the muscle groups was vibrated (Gilhodes et al. 1986). The authors concluded that the illusory movement from vibration was 'related to the difference in vibration frequency applied to the two muscles'. The implication was that the brain was not listening to the streams of afferent signals coming from any one muscle group at a time, but to the antagonist difference signal. When both antagonists generated similar rates of discharge, be they low or high, the difference signal would be low and this was what the brain used to compare with the signals coming from the other arm. By co-contraction of reference arm muscles without any movement, both were in a similar, sensitised

state, leading both to generate high levels of afferent discharge. However, the difference signal was low. If now the other arm was flexion or extension conditioned, with afferent activity coming predominantly from only one of the antagonist pair, in order to align the positions of the two arms the subject had to move their indicator in a direction which best matched the low activity coming from the reference arm. They did so by moving their indicator very little, keeping stretch of the conditioned muscle to a minimum. As a consequence, large matching errors resulted in the present experiments, 9.3° in the direction of flexion after flexion conditioning of the indicator and 7.4° into extension after extension conditioning (Fig. 3).

The first point to emerge from this result is that signals from both arms contribute to the matching process (Allen et al. 2007; White and Proske 2009; Izumizaki et al. 2010). The large matching errors resulted from disparate levels of signal coming from the two arms. It suggests that the brain is listening to signals coming from muscles of both arms to determine the degree of their alignment. Our working hypothesis is that the brain not only calculates the difference signal from the antagonist pair of each arm, but, in addition, the overall difference in signal coming from the two arms. In Experiment 1, the small difference signal coming from the reference arm was compared with a large difference signal coming from the indicator, and in their attempt to align their forearms, subjects made large matching errors.

In the circumstances where large matching errors were made because of the state of the indicator arm (Figs. 2A, B, 3A, B), it is interesting that subjects appeared to be unaware of the errors. They were sometimes asked by the experimenter whether they were satisfied with the matching position they had adopted with their indicator arm and they invariably declared they felt that they had made a reasonable match. It suggests that they remained unaware of the large matching errors they had made.

The second conditioning method, described in Experiment 2 (indicator arm, Fig. 1C, D), deliberately introduced slack in elbow antagonists of the indicator arm, so that the signals from both muscle groups would be low, as would be their difference. To use the sequence illustrated for the indicator in Fig. 1C as an example, the initial flexion conditioning left elbow flexors short and taut, the contraction removing any slack. At the same time, elbow extensors lay stretched and their stable cross-bridges reassembled at this stretched length. Moving the arm into extension stretched the elbow flexors and shortened the extensors. The 6-s waiting period in the extended position allowed stable cross-bridges in the flexors to reassemble at the longer length (Morgan et al. 1984). Finally, moving the arm into a matching position shortened the flexors and they fell slack, while stretching the extensors a little, but not sufficiently for

all of their slack to be taken up. So now, at the test angle, signals coming from both flexors and extensors were low because of slack in both muscle groups. A similar situation applied to the conditioning shown in Fig. 1D, except that here the conditioning sequence was reversed, beginning with an extensor contraction with the arm held extended.

In the original experiment (Tsay et al. 2014), this conditioning had been applied to both reference and indicator arms. Therefore, since slack was present in muscles of both arms, both generated low levels of proprioceptive signals and that led to the expected result of a low matching error. The point that remained uncertain was whether the same result of low matching errors could be achieved if reference muscles were left co-contraction conditioned and slack was introduced only in indicator muscles. This would leave reference muscles with high levels of afferent activity and indicator muscles with low levels. However, the signal difference hypothesis dictated that absolute discharge rates of muscle receptors were not what mattered, it was the difference signal from the antagonist pair that was used by the brain to align the two arms. This point was tested in the present experiments. The hypothesis was that the high rates of afferent activity in reference antagonists, as a difference signal, were comparable to the low rates coming from indicator antagonists when these had slack introduced in them. That, indeed, was what was observed. Position errors lay close to zero when the position of a reference arm with co-contraction conditioned elbow muscles was matched by an arm with slack introduced in its muscles (Fig. 3C, D). Similar conclusions were drawn by Gilhodes et al. (1986) who showed that simultaneous vibration of both antagonists of an arm prevented generation of a vibration illusion and it did not matter whether muscles were vibrated at 20 or at 40 Hz, provided the frequency was the same for each antagonist.

In saying that the difference signal coming from an arm is close to zero, we do not mean to imply that at this point the arm is deprived of all proprioceptive afference. We are simply proposing that such a calculated difference is what is used by the brain to compare with the signal coming from the other arm to achieve arm alignment. The ‘null point’ mechanism (Proske et al. 2014) then aligns the two arms, based on achieving a minimum signal difference between them. If the nett signal coming from the other arm is larger, for example, as a result of it having been flexion or extension conditioned, the arm-matching error will be larger. If it has a similarly small signal coming from it, the matching error will be smaller. For large separations, of the arm, beyond an angular difference of 20°, we believe that another mechanism comes into play, one that involves a central map of the body. We hypothesise that there are two mechanisms for generating position sense. One is the mechanism we have been discussing, which compares

differences in spindle signals from the two arms and another which does not necessarily involve muscle spindles (Proske 2015). Here, sensory information from the arm is referred to a central map of the body, the postural schema (Longo and Haggard 2010) to determine its position. This mechanism does not depend on a comparison between the arms, and each arm generates a position signal in its own right.

Concluding comments

We are beginning to learn some of the rules by which accurate alignment of the forearms is achieved in a position-matching task. First, both arms probably contribute equally to the task (Allen et al. 2007; White and Proske 2009; Izumizaki et al. 2010; Hakuta et al. 2014). Secondly, the brain calculates a difference signal from the afferent activity coming from the antagonist pair of each arm. It is interesting that when the signals from the two arms are made deliberately different, as in the present study, by co-contraction of the reference and flexion or extension conditioning of the indicator, large errors result (Fig. 3A, B). In similar experiments of this kind (Allen et al. 2007; White and Proske 2009; Tsay et al. 2014), the observed errors were never more than about 10°. It suggests that the limits of the angular range for the matching process are $\pm 10^\circ$, that is, a total of 20°, which represents about a quarter of the movement range available to subjects (Allen et al. 2007). In the future, it would be interesting to explore matching performance beyond the limits of this range and, at that point, to look for evidence of a change in the underlying mechanism.

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SECTION TWO: INVESTIGATING THE CENTRAL BODY REPRESENTATION

CHAPTER 4: SENSORY ORIGINS OF HUMAN POSITION SENSE

Tsay, A., Giummarra, M., Allen, T. J. & Proske, U. (2016). "The sensory origins of human position sense." J Physiol **594**(4): 1037-1049.

4.1 Explanatory Notes

Section two of the thesis included a new task for assessing position sense: the pointing task. This task required subjects to declare the position of their arm by manoeuvring a pointer paddle to the perceived position of their reference arm, which was hidden behind a partition.

The experiments presented in Chapter four came about after discrepancies were noticed when position sense was measured between the wrist and elbow joint, after contraction of the muscles (Gandevia et al., 2006; Smith et al., 2009; Walsh et al., 2013). In the earlier experiments, wrist position sense was measured using a pointing task, whereas matching tasks were conducted at the elbow. Walsh et al. (2013) subsequently confirmed that motor command signals play a role at the wrist but not at the elbow, by measuring elbow and wrist position sense using both matching and pointing tasks.

Our interpretation of this result was that peripheral signals were the dominant source of positional information at the elbow joint. This raised the question: how can a mechanism dependent on muscle spindle signals from both arms generate positional information in a single-limb pointing task?

The findings presented in this chapter were perhaps the most important publication in this thesis (Tsay et al., 2016) and generated its own *Perspectives* commentary in the *Journal of Physiology* by Rasman and Blouin (2016).

4.2 Declaration for Thesis Chapter Four

Declaration by candidate

In the case of Chapter four, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
The candidate co-designed the study, conducted the experiments, collected and analysed the data, and was involved in the construction/editing of the manuscript.	70

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Melita Giummarra	Editing of manuscript.	
Trevor Allen	Discussion of literature, experimental design, editing of manuscript.	
Uwe Proske	Discussion of literature, experimental design, writing of manuscript.	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work.

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The sensory origins of human position sense

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Key points

- Position sense at the human forearm can be measured in blindfolded subjects by matching positions of the arms or by a subject pointing to the perceived position of an unseen arm.
- Effects on position sense tested were: elbow muscle conditioning with a voluntary contraction, muscle vibration, loading the arm and elbow skin stretch.
- Conditioning contractions and vibration produced errors in a matching task, consistent with the action of muscle spindles as position sensors. Position errors in a pointing task were not consistent with the action of muscle spindles. Loading the arm or skin stretch had no effect in either matching or pointing tasks.
- It is proposed that there are two kinds of position sense: (i) indicating positions of different body parts relative to one another, using signals from muscle spindles; and (ii) indicating position of the body in extrapersonal space, using signals from exteroceptors, vision, touch and hearing.

Abstract Human limb position sense can be measured in two ways: in a blindfolded matching task, position of one limb is indicated with the other limb. Alternatively, position of a limb, hidden from view, is indicated with a pointer, moved by pressing a lever. These experiments examined the sensory basis of position sense measured in these two ways. Position errors were measured in 14 subjects after elbow flexors or extensors had been conditioned with a half-maximum voluntary contraction. In agreement with previous studies, in the matching trials, position errors were distributed according to a pattern consistent with the action of muscle spindles as the position sensors. In the pointing trials, all errors lay in the direction of extension of the true position of the hidden arm and their distribution was inconsistent with influences arising in muscle spindles. Vibration of elbow muscles produced an illusion of muscle lengthening during a matching task, while during the pointing task no illusion was present. Finally, the matching–pointing error difference was preserved, even when one arm was loaded with a weight or skin over the elbow was stretched. It is proposed that there are two kinds of position sense. One is signalled by muscle spindles, indicating position of one part of the body relative to another. A second provides information about the position of the body in extrapersonal space and here we hypothesise that exteroceptors, including vision, touch and hearing, acting via a central map of the body, provide the spatial information.

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Abbreviations EC, extension conditioning; FC, flexion conditioning; MVC, maximum voluntary contraction; TVR, tonic vibration reflex.

Introduction

Proprioception is the group of sensations generated by the body's own actions. It includes the senses of limb position and movement, the senses of force and heaviness, the sense of effort and the sense of balance. The present account concerns the sense of limb position. For a recent review, see Proske & Gandevia (2012).

Up to the 1970s it was believed that joint receptors provided the afferent signals for position sense. The experiments of Goodwin *et al.* (1972) changed that view, providing evidence for muscle spindles as the principal kinaesthetic sensors. At the time of those experiments it was already known from animal experiments that in a passive muscle the muscle spindles were selectively sensitive to vibration (Brown *et al.* 1967). Goodwin *et al.* showed that vibration of human elbow muscles produced illusions of movement and changed position of the forearm. The interpretation was that the increase in spindle activity produced by the vibration generated a sensation of lengthening of the muscle, leading to an illusion of movement about the elbow. The conditions for this experiment required the subject to track with one arm the perceived sensation generated in the other. So to demonstrate the illusion it was necessary to carry out an arm matching task. Since that time this experiment has been repeated many times at a number of different joints with essentially similar results (see recent review by Proske, 2015).

For a number of years the observations of Goodwin *et al.* (1972) remained the principal evidence in support of muscle spindles as proprioceptors. Subsequently additional evidence was provided from a rather different quarter. Passive muscle has a property, thixotropy, which gives it a history-dependent, passive tension and stiffness (see Proske *et al.* 2014). The intrafusal fibres of muscle spindles exhibit thixotropy and the effects of thixotropic changes in a muscle on the responses of muscle spindles have been studied in animal preparations (Proske *et al.* 1993). Effects of thixotropic conditioning on muscle spindle discharges were shown by Gregory *et al.* (1988) in an animal preparation, and in a parallel series of experiments they demonstrated that similar sequences of conditioning of human elbow muscles generated predictable errors in a forearm matching task.

The importance of thixotropy is that only skeletal muscle and muscle spindles exhibit this property. So effects on position sense from thixotropic conditioning must be attributed to changes in discharges of muscle spindles and not to skin or joint receptors. It is known that conditioning can change the level of background discharge in muscle spindles (Gregory *et al.* 1991). Background activity is believed to provide the afferent

signal for limb position sense (Clark *et al.* 1985). Input from primary endings of spindles contributes to both position and movement sense, while secondary endings contribute predominantly to position sense (Matthews, 1988).

The experiments on position sense by Gregory *et al.* (1988) and many other experiments since then all have in common that they use a limb matching task to demonstrate position errors, in much the same way as Goodwin *et al.* (1972) had done. The underlying idea is that a blindfolded subject locates the position of one arm by moving the other arm until the sensations of position generated by the two arms feel the same. It is a sensation matching task.

Intuitively, the obvious method of measuring the position of an unseen body part is not by aligning it with another body part, but by pointing to where we think it is. So position sense could be measured by pointing rather than by matching. Velay *et al.* (1989) were the first to recognise the distinction between the two methods of measurement. In order to explore possible differences between them, they exposed subjects to 11 deg wedge prisms and found that the shift in gaze produced by repeated exposure to the prisms led to subsequent errors only in blindfolded pointing tasks, not in matching tasks. The authors proposed that pointing measured orientation in space so that wearing the prisms led to displacement of objects along the axis of gaze, producing an adaptive shift that was responsible for the subsequent errors. Position matching measured the relative angular positions of limb segments in intrapersonal space that were left unaffected by prism exposure.

We have been studying position sense for a number of years (Proske *et al.* 2014). Up until now we have mostly determined position sense using a limb matching task. In recent matching experiments at the forearm, using the muscle conditioning method, we concluded that central processing of the positional information was concerned with the afferent signal difference coming from the antagonist muscle pair at the elbow of each arm and with the total signal difference between the two arms (Tsay *et al.* 2014, 2015).

The limb position matching method requires information provided by afferent input from both arms (Allen *et al.* 2007; White & Proske, 2009; Izumizaki *et al.* 2010; Hakuta *et al.* 2014). Since the evidence points to muscle spindles as playing a dominant role in such tasks, it raises the question, how can a mechanism dependent on impulses in muscle spindles from both arms generate positional information in a one-limb pointing task? This question was addressed in the present experiments. The hypothesis was tested that limb position, when measured by moving a pointer, would not use the signals from muscle spindles in the same way as in matching.

Methods

Three experiments were carried out. In the first 14 subjects were recruited, in the second 10 subjects and in the third nine subjects, making for a total of 33 subjects, 12 male and 21 female. The average age of subjects was 23.9 ± 0.7 years. Subjects gave informed, written consent prior to participating in the study, which was approved by the Monash University Human Research Ethics Committee. The ethical aspects of the experiments conformed to the *Declaration of Helsinki*.

The apparatus

Position sense was measured in two ways (Fig. 1). For the matching task the blindfolded subject sat at a table and placed both forearms on the lightweight paddles of a custom-built piece of apparatus like that used previously for measuring forearm position sense (Allen & Proske, 2006). The forearms, palms facing upward, were strapped to the paddles by Velcro straps 5 cm in width, placed just below the crease of the wrist. In order to minimise potential differences in skin sensation between the two arms, equal tension from the strapping was checked before proceeding with the experiment. One arm was designated the reference arm (the arm placed at the target angle by the experimenter), while the other arm was the indicator arm (the arm moved by the subject to match the position of the reference arm.)

In the pointing task the two arms were separated by a screen, in such a way that the subject was unable to see the reference arm. The reference arm was strapped in, as before, and its position set by the experimenter. In a pointing trial the subject moved a lever at the base of the pointer paddle, pushing it downwards to move the pointer upwards until it was perceived to be aligned with the hidden reference paddle (Fig. 1).

Forearm and pointer angles were measured using potentiometers located at the hinges of each paddle. The hinges were co-linear with the elbow joint. The potentiometers provided a continuous voltage output proportional to the angle of each paddle, where 0 deg indicated that the forearm was horizontal and 90 deg indicated that it was vertical. Calibration of the potentiometers was checked before commencement of an experimental series with each subject.

Muscle activity of the reference arm was measured using surface electromyogram (EMG). Here we did not analyse the EMG signal as such, but simply used it as an indication of whether or not the subject had remained relaxed as the experimenter moved the reference arm to the test angle. A pair of Ag–AgCl electrodes with an adhesive base and solid gel contact points (3M Health Care, London, Ontario, Canada) were placed approximately 2.5 cm apart over the surface of the biceps brachii and triceps brachii. A

grounding electrode was placed on the collar bone. The EMG signal was band-pass filtered (high pass, 1 kHz; low pass, 0.3 Hz) and the output was connected to an audio amplifier for biofeedback. Position, force and EMG signals were acquired at 40 Hz using a MacLab 4/s data acquisition module running Chart software (ADInstruments, Castle Hill, NSW, Australia) on an Apple Macintosh computer.

The two paddles could be locked in position at 90 deg by metal struts to which force transducers had been attached. The force signal was amplified and displayed on the screen of a computer. Real-time force levels could be displayed to help subjects generate maximum voluntary contractions

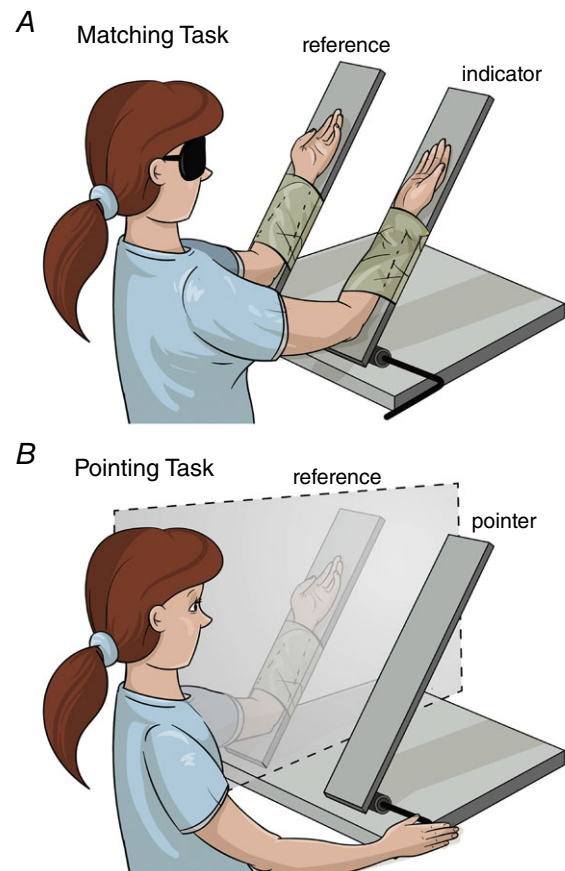


Figure 1. The position sense tasks

Position sense was measured in two ways. *A*, in the matching task, blindfolded subjects' arms were strapped to paddles, one arm designated the reference, the other the indicator. Forearm position was measured by potentiometers located at the hinges of the paddles, which were co-linear with the elbow joint. The experimenter placed the reference arm at a test angle and the subject held it there while moving the indicator arm into a matching position. *B*, in the pointing task the two arms were separated by a screen (dashed line) which blocked the subject's view of the reference arm. The reference arm was strapped to a paddle, as before, and was placed at the test angle by the experimenter. Once the reference arm was in position, the subject pressed a lever with the other hand to move the pointer paddle to align it with the perceived position of the hidden reference arm.

(MVCs). At the beginning of an experiment, subjects were asked to generate an MVC of their elbow flexors by flexing both arms towards the body while the supporting paddles were locked in position at 90 deg. The value of MVC was used as a guide for generating approximately half-maximal MVCs for the muscle conditioning and for calculation of 10% MVC values for the extra load in Experiment 3.

Measuring position errors

Position errors between the two paddles were calculated using the formula: position error = reference angle – indicator angle, where all three are measured in degrees. The convention was used that a positive error was an error in the direction of extension relative to the position where the two arms were accurately aligned. A negative error was an error in the direction of flexion.

Reference and indicator arms were randomly assigned for each set of trials to reduce any biases from matching with a dominant or non-dominant arm (Goble *et al.* 2006). During a matching trial the reference arm was placed by the experimenter at an angle of 40–50 deg and the blindfolded subject was asked to match its perceived position with their indicator arm. In a pointing trial the reference arm was positioned in the same way, but the subject indicated its position by moving the pointer paddle to align it with the hidden arm.

During movement of the reference arm subjects were asked to remain relaxed. This was monitored with auditory feedback of EMG. Throughout these experiments, once the reference arm had been placed at the test angle, the subject maintained its position voluntarily. All of the matching by the indicator arm was also done voluntarily by the blindfolded subject. In both matching and pointing trials subjects were therefore required to generate mild contractions sufficient to support the reference arm against gravity and in the matching task for movement of the indicator into the matching position. These conditions were chosen to keep both matching and pointing processes close to what subjects might do in everyday life.

Experiment 1: muscle conditioning

The thixotropic state of a muscle can significantly alter the responses of muscle spindles and therefore exerts a strong influence on the measurement of position sense (Proske *et al.* 2014). In order to avoid thixotropy-related misinterpretations it is necessary at the start of each position matching trial to put elbow muscles of both the reference and indicator arms into a defined state. This is called muscle conditioning. In the pointing trial it was, of course, only necessary to condition the reference arm. In Experiment 1 two different forms of conditioning were used. In the matching task, for flexion conditioning (FC),

both arms were moved to 90 deg and the blindfolded subject was asked to generate a 2 s, approximately half-maximum, isometric contraction with elbow flexors of both arms by flexing the forearms towards the body. Once the arms had relaxed, the reference was moved by the experimenter into extension to the test angle and the blindfolded subject attempted to match its position by moving the indicator arm. For extension conditioning (EC) the arms were moved into full extension (0 deg) and subjects were asked to push down onto the paddles to generate a half-maximum contraction in elbow extensors. Once the subject had relaxed, the reference arm was moved in the direction of flexion to the test angle and its position was matched.

In the pointing task the conditioning procedures were the same except that only the reference arm was flexion or extension conditioned.

In an experimental trial one or both arms had been either flexion or extension conditioned. For flexion conditioning it left elbow flexors taut after the conditioning contraction and when the reference arm was moved from 90 deg to the test angle, the flexors were stretched by the movement and therefore their spindles were kept in a sensitised state. The same movement slackened the extensors whose spindle activity therefore fell to low levels. This meant that after flexion conditioning the proprioceptive signal coming from the reference arm was biased in favour of elbow flexors. After extension conditioning the reverse was true, the signal predominantly coming from elbow extensors.

Subjects carried out a series of five trials using each conditioning sequence, making for a total of 10 trials. The same sequence of trials was used in the pointing task, but conditioning was applied only to the reference arm.

Experiment 2: muscle vibration

This experiment was carried out on an additional cohort of 10 subjects. Muscle vibration elicits an illusion of muscle stretch, producing a sensation of elbow extension when biceps brachii is vibrated and elbow flexion when triceps brachii is vibrated (Goodwin *et al.* 1972). Here the question was posed, is there was any difference in size of the vibration illusion if it was measured in a matching or a pointing task? For these trials muscle conditioning was again used, flexion or extension conditioning of both arms in the matching task and of the reference arm in the pointing task. Inspection of the earlier data indicated that three trials for each condition, rather than five, were sufficient to achieve a statistically reliable result. Therefore in this experiment a total of 12 trials was carried out in the matching task and 12 trials in the pointing task, three trials for each of four conditions: flexion conditioning only, flexion conditioning plus vibration,

extension conditioning only and extension conditioning plus vibration.

Past experiments have shown that conditioning sensitises a muscles to vibration and this enhances the vibration illusion (Gooney *et al.* 2000). So after matching trials with both muscles flexion conditioned, matching was repeated during vibration of elbow flexors. After matching trials with muscles extension conditioned, vibration was applied to elbow extensors. Similarly in the pointing task, vibration was always applied to the muscle that had been contraction conditioned.

A vibrator was strapped to the belly of biceps or triceps brachii of the reference arm using elastic straps. The vibrator consisted of a custom-built plastic cylinder which housed a weight mounted eccentrically on the shaft of a small electric motor. The vibrator was 3 cm in diameter and 8 cm long. Vibration amplitude was approximately 1 mm and the frequency could be adjusted to lie near 70 Hz, close to the optimum for generating the illusion (Tidoni *et al.* 2015). Because of the small size of the vibrator, its stimulus was relatively localised, acting predominantly on biceps or triceps, depending on its placement. It is not possible to be certain whether there was some spread of the vibration, but the consistency of the illusions it generated and, when present, the direction of any reflex contraction supported the view that the stimulus was largely limited to the muscle to which the vibrator had been attached. In each trial the vibrator was turned on after muscles had been conditioned and the reference arm had been placed at the test angle. After 10 s of vibration subjects carried out a match or pointed to the position of the hidden arm, while vibration continued. The vibrator was turned off as soon as the subject declared that a satisfactory match had been achieved. In some subjects a tonic vibration reflex (TVR) developed during the vibration. Subjects were asked to focus their attention on the illusion of arm movement into extension produced by the vibration and to try to ignore any reflex contraction. They readily did this and unless it was a strong contraction they were happy to ignore it. If they developed a strong TVR they were excluded from further measurements.

Experiment 3: loading the arm and skin stretch at the elbow

The experiment, carried out on a cohort of nine subjects, explored possible factors responsible for the difference in the distribution of errors in forearm pointing and matching tasks. In this experiment we first considered the possibility that a signal of central origin associated with the effort required to support the weight of the arm provided positional information. To test that idea, the reference arm was loaded with a weight corresponding to 10% MVC attached to the end of the paddle. Matching and pointing tasks were then carried out as in Experiment 1. The

subject had to maintain position of the arm at the test angle while generating the extra force required to support the load. For the sake of simplicity, in this experiment position sense was measured only after flexion conditioning.

In a second task, for both matching and pointing, the role of cutaneous input to position sense was tested. The hypothesis was tested that afferent activity generated by skin stretch during elbow flexion provided positional information (Collins & Prochazka, 1996). To do that, skin over the elbow joint of the reference arm was stretched in a distal direction by means of a thread taped to skin of the forearm with 3.5 cm wide sports tape. The thread was attached at a point just distal to the elbow joint. After muscle conditioning, the reference arm was placed at the test angle and its position maintained by the subject. A force transducer (Attonic, Toyohashi, Aichi, Japan) attached to the end of the thread monitored the force of the stretch which was set at between 10 and 15 N. Subjects were instructed to wait until they were told by the experimenter to make a match. This ensured that in the reference arm the required force of skin stretch had been reached by the experimenter before each pointing or matching attempt.

Each subject carried out the loading and skin stretch trials in blocks of five repetitions. The order of the blocks was presented at random to each subject.

Statistical analysis

In each experiment trial conditions were randomised.

For Experiments 1 and 2, Student's paired *t* test was used to test for the effect of task and vibration, respectively, on position errors. In Experiment 3, the effect of load and skin stretch on matching and pointing errors was tested using a repeated measures ANOVA. All group data are shown as means \pm standard error of the mean (SEM).

Results

In the first experiment we compared position errors in matching and pointing tasks after altering muscle afferent activity in elbow muscles using muscle conditioning techniques. In the second experiment we compared the size of the illusion of muscle lengthening during muscle vibration as measured in matching and pointing tasks. In the third experiment the effects of loading the arm and of stretch of skin over the elbow joint were tested in matching and pointing tasks.

Experiment 1: muscle conditioning

Position errors measured in a matching task. Typical results for a single subject in a forearm matching task after flexion and after extension conditioning are shown in Fig. 2A. In the five trials with flexion conditioning,

the subject consistently matched with small errors in the direction of flexion, with a mean error of -3.9 deg. After extension conditioning the subject matched with errors consistently in the direction of extension, with a mean error of $+6.7$ deg. These trends were confirmed by the group data for the 14 subjects (Fig. 2B). Mean matching error after flexion conditioning was -0.3 ± 1.2 deg and after extension conditioning it was $+2.4 \pm 1.7$ deg. The directions and sizes of the errors were similar to those reported previously for matching tasks, using similar

muscle conditioning (Tsay *et al.* 2014). The difference between values observed here and obtained previously after flexion conditioning was 2.6 deg and after extension conditioning the difference was 0.1 deg. So the results in the matching trials of the present study were in line with expectations, based on previous observations.

Position errors measured in a pointing task. The experiment described above was repeated, but conditioning was restricted to only one arm, the unseen reference arm. Its position was indicated by the subject moving the pointer paddle (Fig. 1B). For the single subject, with five trials after flexion conditioning, the mean error between the position of the reference arm and the position of the pointer was $+6.1$ deg. After extension conditioning the error was $+4.9$ deg (Fig. 3A). These trends were reflected in the group data (Fig. 3B). The

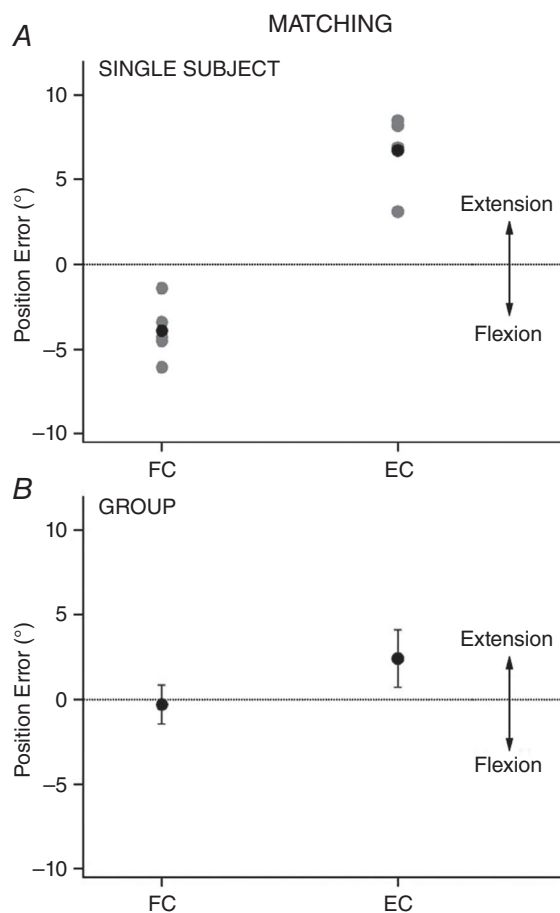


Figure 2. Position errors in a forearm matching task

Position errors are shown for a single subject (A) and the group of 14 subjects (B). Matching errors were measured after flexion conditioning (FC) or extension conditioning (EC). Conditioning consisted of a half-maximum voluntary contraction of both arms with the arms held flexed or extended. The reference arm was then moved to the test angle by the experimenter and the subject matched its position with the other arm. For the single subject (A), matching errors for each of the 5 trials are shown as grey circles, and the mean is shown as a black circle. The group data (B) show mean errors for the group (filled circles \pm SEM) after the two forms of conditioning. In this and subsequent figures the convention is used that errors by the indicator arm in the direction of extension relative to the position of the reference arm have been assigned a positive value, errors in the direction of flexion a negative value. Dotted line denotes zero error.

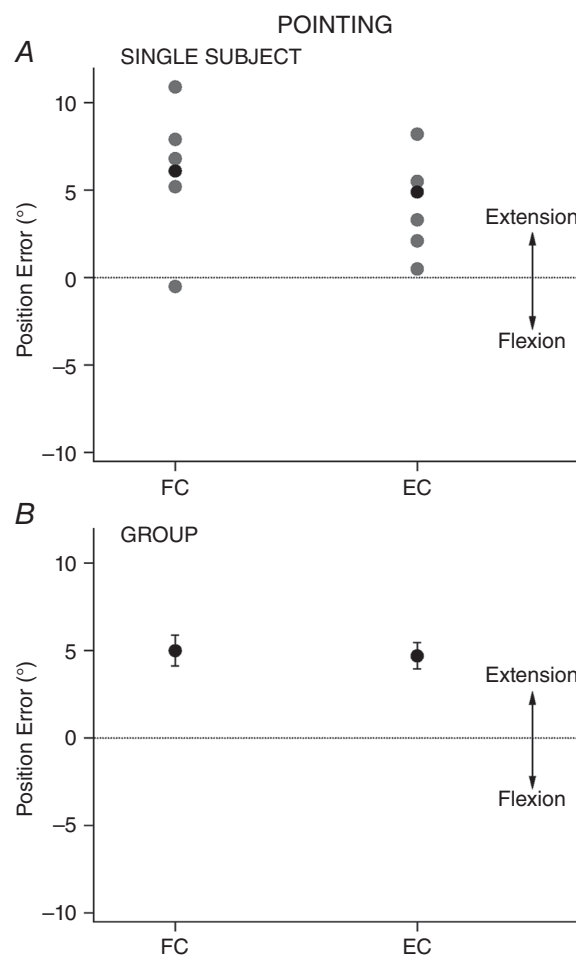


Figure 3. Position errors in a forearm pointing task

Position errors are shown for a single subject (A) and for the group (B). For the single subject pointing errors in individual trials are shown as grey circles, and the mean is shown as a black circle. For the group, means (\pm SEM) are shown as filled circles. Error display as for Fig. 2.

mean error after flexion conditioning was $+5.0 \pm 0.9$ deg, and after extension conditioning $+4.7 \pm 0.8$ deg. The effect of task, matching versus pointing, was examined using a paired t test, which was significant ($t(27) = -3.1$, $P = 0.005$).

The important difference in outcomes between the pointing and matching trials was the difference in the pointing trials between the observed and predicted errors, based on previous matching experiments (Tsay *et al.* 2014). For the pointing trials the observed errors differed from expectation by 4.8 deg for flexion conditioning and 14.3 deg for extension conditioning. Such large differences indicated that during pointing the errors did not conform to predictions based on postulated changes in afferent activity produced by muscle conditioning.

Experimenter-move versus self-move. As the results unfolded, it became clear that muscle conditioning had different effects on forearm position errors measured in pointing and matching tasks. While errors measured in the matching task were roughly in line with observations made in the past, there was no obvious explanation for the distribution of errors in the pointing tasks. It is known that in forearm matching, signals from both arms make a contribution (White & Proske, 2009; Hakuta *et al.* 2014; Tsay *et al.* 2014; Tsuge *et al.* 2012). In the search for an explanation of the pointing results, the possibility was considered that the movement carried out by the arm pressing the lever to align the indicator paddle (Fig. 1B) influenced, in some way, the measured values.

To put this idea to the test, for 8 of the 14 subjects pointing errors were measured both with the subjects aligning the pointer themselves and with the alignment carried out by the experimenter. Here the experimenter adjusted the position of the pointer until the subject declared accurate alignment with the unseen arm. Throughout the trial the subjects' other arm rested on their lap, unmoving.

Results for the eight subjects are shown in Fig. 4, for both forms of conditioning. Notice that the general trends of the data are in the same direction as for pointing errors in Fig. 3, but they remain different from the distribution of matching errors (Fig. 2). It can be seen that when the pointer paddle was moved by the experimenter, position errors lay further in the direction of extension. For flexion conditioning mean values were $+4.3 \pm 0.9$ deg for self-moved versus $+8.6 \pm 1.4$ deg for experimenter-moved. For extension conditioning, values were $+5.0 \pm 1.0$ deg for self-moved versus $+8.2 \pm 1.4$ deg for experimenter-moved. A paired t test showed a significant difference between self- and experimenter-moved errors ($t(15) = -3.3$, $P = 0.005$). It was concluded that there was a difference in pointing errors when the pointer was moved by the experimenter,

compared with when it was moved by the subject. The more general trend previously seen in pointing trials that the errors all lay in the direction of extension remained unchanged.

In the present experiments, the pooled matching trials generated mean errors 1.4 deg different from errors observed in previous matching experiments, while for pointing trials the mean difference was 9.6 deg. It was clear that position errors in a pointing task did not conform to predictions based on previous observations.

There was an obvious trend that for pooled means all of the pointing errors lay in the direction of extension relative to the true position of the reference arm; none lay in the direction of flexion. Secondly, the size of the errors was roughly similar, about 5 deg. This implied that conditioning was not having the expected effect and similar errors were produced no matter what form of conditioning was used. That is, it was possible that in a forearm pointing task the central processes involved in generating the sensation of limb position were relatively insensitive to changes in spindle afferent input generated by muscle conditioning. In order to test this idea, a more powerful stimulus for muscle spindles than muscle conditioning was necessary. To do that, elbow flexors and extensors were vibrated and the sizes of the vibration illusions were compared in matching and pointing tasks.

Experiment 2: muscle vibration

Muscle vibration at 70 Hz was applied to elbow flexors after flexion conditioning and elbow extensors after extension conditioning (Gooley *et al.* 2000). In the matching task

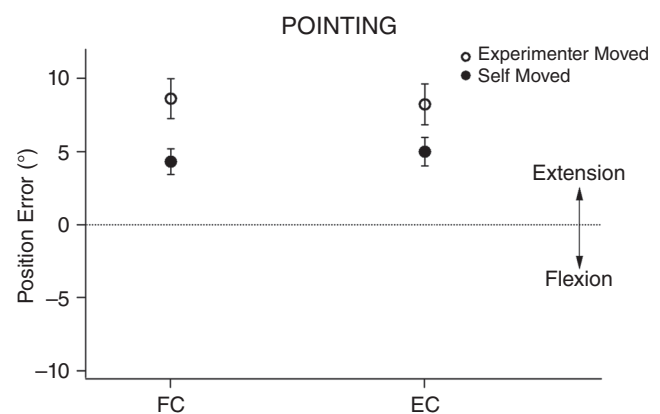


Figure 4. Errors in a pointing task when the pointer is moved by the subject or the experimenter

Mean pointing errors (\pm SEM) for a group of 8 subjects, using flexion conditioning (FC) and extension conditioning (EC). Filled circles, pointing errors when the subject moved the pointer themselves, open circles, when the pointer was moved by the experimenter. Analysis using a paired t test showed a significant difference between self- and experimenter-moved pointing trials ($P < 0.05$).

subjects were instructed to follow any perceived movement of the vibrated reference arm with their indicator arm. In the pointing task they were asked to point to where the vibrated arm had appeared to move. The results are shown in Fig. 5.

In the matching trials, after flexion conditioning of both arms, without vibration, errors were -4.9 ± 1.1 deg. When matching was done while the reference arm was vibrated, errors fell to -0.6 ± 1.1 deg. That is, the expected illusion of arm extension by 4.3 deg had been induced by the vibration. When the experiment was repeated, but this time only the reference arm was conditioned and its position determined with the pointer, the error after flexion conditioning, before vibration, was $+5.0 \pm 1.3$ deg. In the presence of vibration of the reference arm the error fell slightly to $+3.7 \pm 1.4$ deg. This was a trend in a direction opposite to that predicted since vibration should have produced errors into extension, not flexion.

After extension conditioning, the mean matching error before vibration was $+1.0 \pm 1.6$ deg and during vibration of elbow extensors it fell, in the expected direction of flexion, to -5.3 ± 1.0 deg. That is, an illusion of 6.3 deg in the direction of flexion had been generated. During pointing trials, the mean error in the absence of vibration was $+3.9 \pm 1.4$ deg, which changed only slightly during vibration to $+3.6 \pm 2.4$ deg. To summarise, in the matching tasks elbow flexor vibration produced the expected illusion of arm extension and elbow extensor vibration produced the expected illusion of arm flexion. These vibration-evoked errors were not present when position sense was measured in a pointing task.

A paired *t* test was used to examine the effect of vibration on flexion and extension conditioning for both matching and pointing trials. A significant effect was found in the matching trials (FC vs. FC + Vib, $t(9) = -3.2$, $P = 0.011$; EC vs. EC + Vib, $t(9) = 4.8$, $P = 0.001$). However, no effect of vibration was found in either pointing conditions (FC vs. FC + Vib, $t(9) = 0.75$, $P = 0.47$; EC vs. EC + Vib, $t(9) = 0.12$, $P = 0.91$). It was

concluded that in an experiment specifically designed to powerfully stimulate muscle spindles to evoke the expected kinaesthetic illusions, those illusions were present only in the forearm position matching task but not the pointing task.

Experiment 3: loading the arm and skin stretch at the elbow

The question was posed, if muscle spindles are not responsible for providing the position signal in pointing tasks, how is position signalled? One possible source of signal was the motor command generated by the subjects to support their arm at the test angle. Another was input from stretch-sensitive cutaneous receptors around the elbow joint. These possibilities were explored in the next experiment. For simplicity, this experiment used only flexion conditioning of the arms.

The working hypothesis for the loading experiment was that in the pointing task the effort required to support the arm provided positional information and this accounted for the difference in errors between matching and pointing. We hypothesised that if the arm was loaded, the extra effort required to maintain its position at the test angle would lead to perception of a more flexed arm than was really the case (Walsh *et al.* 2013). To test that idea, the reference arm was loaded with a weight corresponding to a muscle force of 10% MVC. We predicted pointing errors after arm loading that would lie further in the direction of flexion.

In the search for additional sources of sensory input that might account for the difference in position errors during pointing and matching, we considered the afferent signals generated by stretch of skin over the elbow joint. To alter this signal a thread was attached by tape to a point just distal to the joint and pulled distally with a stretch force of 10–15 N. Here the working hypothesis was that skin stretch would raise the cutaneous afferent signal about the elbow joint, leading to perception of a more flexed arm.

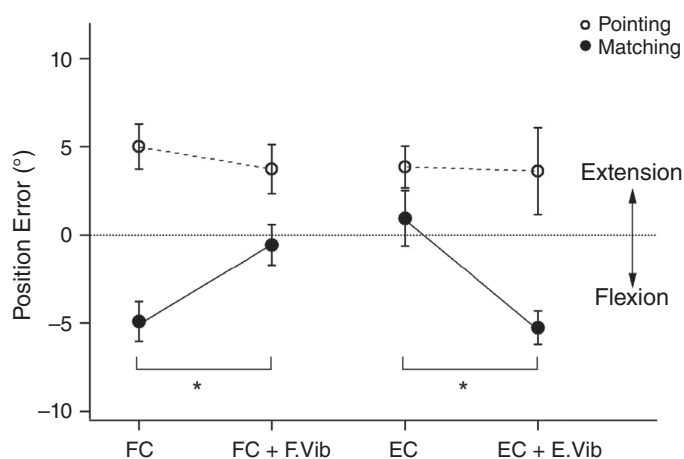


Figure 5. Errors in matching and pointing tasks during muscle vibration

Subjects carried out matching trials (filled circles \pm SEM) or pointing trials (open circles \pm SEM) after flexion conditioning (FC), or extension conditioning (EC) and then repeated them in the presence of muscle vibration at 70 Hz. After FC the elbow flexors were vibrated (FC + F.Vib), after EC the extensors were vibrated (EC + E.Vib). Asterisk indicates significant difference between conditions ($P < 0.05$).

The results are shown in Fig. 6. For this cohort, in the control matching task after flexion conditioning, subjects matched quite accurately, with a mean error of $+0.9 \pm 2.0$ deg. The matching errors shifted further into extension under 10% MVC load (1.4 ± 1.6 deg and skin stretch (1.3 ± 1.7 deg. However, analysis using a repeated measures ANOVA found no significant differences between matching conditions ($F(2, 16) = 0.71$, $P = 0.507$).

In the pointing task, position errors following flexion conditioning were $+12.8 \pm 2.4$ deg. Pointing errors under 10% MVC load were 10.9 ± 2.5 deg and 11.6 ± 1.9 deg with skin stretch. Similar to the matching errors, a repeated measures ANOVA found no significant effect between conditions ($F(2, 16) = 0.60$, $P = 0.560$).

Discussion

We have presented evidence in support of the view that for two simple, psychophysical tests of human limb position sense, the afferent signals are different. More specifically, we propose that the contribution from muscle spindles is not the same in matching and pointing tasks.

Experiment 1: muscle conditioning

We used two techniques to test for a role for muscle spindles in position sense. The first was muscle conditioning. The present matching experiments generated position errors after conditioning that conformed to predictions based on known properties

of muscle spindles and on the findings in previous experiments (Proske *et al.* 2014). However, in the pointing task all errors lay in the direction of extension, regardless of the form of conditioning, a result that goes against predictions. Flexion conditioning is predicted to raise flexor spindle activity and lower extensor activity. The stronger flexor signal would be interpreted by the brain as a longer, more stretched flexor muscle, leading to perception of a more extended forearm. Conversely, extension conditioning would be expected to raise extensor spindle activity and lower flexor activity, leading to perception of a more flexed forearm. If spindles were involved in pointing, position errors after flexion conditioning should have been in the direction of extension; after extension conditioning they should have been in the direction of flexion. That was not the case, and the simplest explanation of the pointing results is that the position signal generated in the hidden limb is insensitive to changes in spindle activity produced by muscle conditioning. Why the position errors measured in pointing all lay in the direction of arm extension and why they became larger when the experimenter moved the pointer (Fig. 4) remain unclear. The error bias into extension is reminiscent of a positional bias observed when subjects are asked to point to the position of their unseen hand. They tend to perceive their left hand as shifted to the left and their right hand shifted to the right, independent of hand position (Bellan *et al.* 2015).

There has been one other recent study in which matching and pointing tasks were compared at the wrist and elbow (Walsh *et al.* 2013). In experiments using essentially the same procedures as the present study, it was found at the elbow that errors in the matching task lay near zero, as they did in our experiments (Fig. 2B) and in the pointing task they were all distributed in the direction of elbow extension, as also seen in the present study. At the wrist, while matching errors remained close to zero, pointing errors all lay in the direction of flexion. These observations raise the possibility that the direction of the pointing errors seen in the present study may be unique to the elbow joint and that at other joints, including the wrist, the bias of errors may be different. This is a point for future experiments.

Experiment 2: muscle vibration

The conclusion from the muscle conditioning experiments that spindle activity was not directly involved in generating the pointing errors was reinforced by the results of Experiment 2. Vibration is a powerful stimulus for muscle spindles (Brown *et al.* 1967; Roll *et al.* 1989). The rates of increase in spindle firing during vibration of a passive muscle are likely to be much higher than would normally be encountered in everyday life. Despite this, the vibration illusion, measured as perceived arm extension during

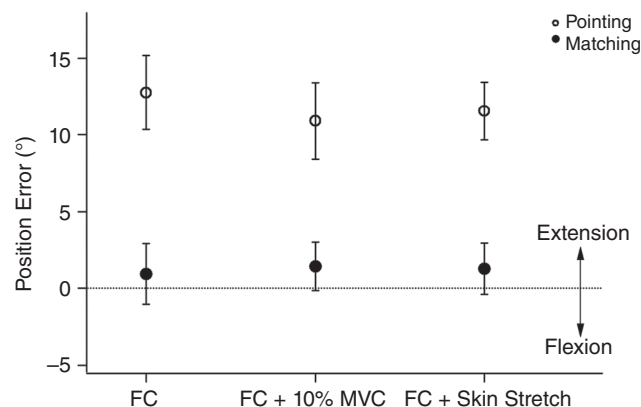


Figure 6. Errors in matching and pointing task during loading and skin stretch

Matching errors (filled circles) and pointing errors (open circles) after flexion conditioning of arm muscles (FC), after flexion conditioning when the reference arm was loaded with a 10% MVC weight (FC + 10% MVC) and after flexion conditioning, while skin over the elbow was stretched in a distal direction (FC + Skin Stretch). No effect of load or skin stretch was detected with either the pointing or matching tasks ($P < 0.05$). Dotted line, zero error.

vibration of elbow flexors and as arm flexion during vibration of elbow extensors (Goodwin *et al.* 1972), was only present in the matching task. It was not present when subjects pointed to the hidden arm during vibration (Fig. 5).

The present results do not entirely agree with the observations of others. Izumizaki *et al.* (2010) measured position sense in blindfolded subjects during vibration of the reference elbow flexors and compared the size of the vibration illusion, in a matching task, with the illusion measured in a pointing task by moving a dummy arm. In the pointing task with the dummy, the vibration illusion was still present, but reduced by 30%. Kammers *et al.* (2006) reported that during vibration of elbow flexors, the size of the illusory displacement of the arm was three times larger in a matching task, compared with a reaching task. Both of these reports suggest that the vibration illusion may not always be completely suppressed during pointing. What does emerge is that changing from a matching to a pointing task alters the central expression of the spindle signal evoked by vibration. Presumably, under the specific conditions of our experiment, 70 Hz vibration applied for 10 s, the illusion was fully suppressed during the pointing task. By comparison, Kammers *et al.* (2006) used 75 Hz vibration for 10 s and Izumizaki *et al.* (2010) used 70–80 Hz for the duration of the matching process. So the parameters of stimulation in the three studies were comparable.

If the central processes underlying the generation of position sense signals in matching and pointing tasks are indeed different, it is still possible that both may be able to coexist at any one time. In the pointing experiments of Kammers *et al.* (2006) and Izumizaki *et al.* (2010) the arms were relatively closely placed, raising the possibility that here position signals for pointing and matching tasks could have been present at the same time. Evidence for a participating matching signal during the pointing task would be the presence of vibration responses. In the present study, for the pointing tasks, positions of the arms were too different for any matching signal to be able to be generated (Fig. 1B).

Experiment 3: loading the arm and skin stretch at the elbow

If, during pointing, muscle spindles no longer provided the principal position signal, what might be the neural basis for position sense in this task? In all of the present experiments the reference arm was strapped to a paddle and the subject held the arm at the test angle after it had been placed there by the experimenter. It raises the possibility that motor activity associated with holding the arm in place is involved in generating a position signal. In addition there would be some skin stimulation from contact between arm and paddle, as well as input

from joint receptors, all of which could provide cues for position of the arm in space. These considerations led to Experiment 3, which tested whether position errors could be altered by increasing the load on the arm or by stretching the skin over the elbow joint.

Loading the arm. When the load on the arm was increased by 10% MVC there was no change in position errors in either the matching or pointing tasks (Fig. 6). Here the underlying hypothesis was that the additional motor command signals required to support the increase in load would contribute to the positional signal. It has been calculated that the torque required from elbow flexors to support the arm at 45 deg represents about 5% MVC (Winter *et al.* 2005). So a 10% MVC load represents an approximate tripling of the weight of the arm. It was therefore expected that after flexion conditioning, pointing errors with a loaded arm would lie further in the direction of flexion (Walsh *et al.* 2013). That was not the case.

The idea of an effort-related signal contributing to kinaesthesia is well established in the literature. It has been shown in paralysed, anaesthetised wrist muscles that a 30% MVC isometric effort leads to sensations of movement and displacement of the hand about the wrist in the direction of the applied effort (Gandevia *et al.* 2006; Smith *et al.* 2009). However, similar evidence from loading the arm is lacking for the elbow (Ansems *et al.* 2006; Allen *et al.* 2007, 2010). This difference in outcomes was recently addressed by Walsh *et al.* (2013) who confirmed all of the earlier observations on the wrist and forearm and concluded that for both matching and pointing tasks the contribution of motor commands to position sense differed between the elbow and wrist. At the forearm there was no evidence of an effort-related position signal.

Stretch of skin over the elbow. There is evidence that skin receptors, most probably the slowly adapting Type II receptors served by Ruffini endings, are able to act as proprioceptors (Proske & Gandevia, 2012). This has been shown by applying stretch to skin over a joint (Collins & Prochazka, 1996; Collins *et al.* 2005). However, the applied stretches were pulsatile and all of the sensations reported were of movement, not of displaced position. In Experiment 3 we attempted to increase skin afferent input at the elbow by applying a strong static stretch to elbow skin in the direction of the hand. This would be expected to tighten the skin over the elbow joint, as would occur from flexing the elbow. We therefore expected skin stretch to lead to position errors in the direction of flexion. In the event, skin stretch did not produce any new position errors in either the matching or pointing tasks (Fig. 6). We consider this an inconclusive result, which was perhaps to be expected, in view of the lack of available evidence for

an effect of skin stretch on static position sense. In future experiments attempts should be made to try to increase the intensity of skin stimulation using stretch in combination with vibration (Collins *et al.* 2005) and perhaps also skin cooling (Hunt & McIntyre, 1960) in order to try to get to a point where there is an effect on position sense.

Afferent projection pathways for matching and pointing.

In their report of differences in outcomes for position sense measurements using pointing and matching tasks, Velay *et al.* (1989) postulated a central transformation process, converting postural space coordinates into extrapersonal space coordinates. They supported this proposal with cited clinical evidence of patients with parietal cortical lesions having difficulty in locating one of their hands in space, yet still being able to reproduce with one arm the posture passively imposed on the other. They did not, however, discuss in any detail what kinds of sensory receptors might be involved in signalling the two kinds of position sense.

Velay *et al.* (1989) mentioned the observations of McCloskey (1973) who showed for two split-brain patients that section of the corpus callosum did not interfere with the subjects' ability to carry out simple forearm matching tasks, including responding to the vibration illusion. McCloskey concluded that there must be a bilateral central projection of muscle afferents and that commissural connections below the neocortical commissures must be responsible for the matching mechanism. These observations raise the possibility that the centrally projecting pathways relaying positional information generated by matching and pointing tasks are anatomically distinct.

Wider considerations. Based on the present findings, we propose that there are two kinds of position sense. One is concerned with the position of one body part relative to another. So, for example, the observations of Lackner (1988) on vibration would all fall under the heading of matching tasks. The principal source of afferent signal in this kind of task is postulated to be the muscle spindle. For the forearms, accurate alignment by means of a spindle signal mechanism is important for the cooperative use of the hands, such as in the fashioning of objects and tools (Izumizaki *et al.* 2010). The second position sense determines the locations of parts of the body in extrapersonal space. This is measured in a pointing task. Knowledge of the location of the arms in extrapersonal space allows them to act as 'antennae' of the body, as we move about in our surroundings.

Our present working hypothesis is that for the sense of position measured by pointing, the principal receptors are exteroceptors, vision, touch and hearing. We use the term exteroceptor to include receptors providing information about objects in peripersonal space as well

as at a distance (teloreceptors). We propose that muscle spindles do not contribute to forearm position sense measured in pointing, at least not under the conditions of our experiments.

For position sense by pointing, an additional requirement is access to a postural schema. This is necessary for converting the exteroceptor signals into spatial information. For example, a stimulus to the skin triggers a peripheral afferent signal that is projected to the topographically organised, primary somatosensory cortex. There information is generated about which part of the skin has been touched. For accurate localisation when that body part is moving, knowledge is required about its position at the time of stimulation. It is assumed that proprioceptive inputs acting through the body schema (Longo & Haggard, 2010) contribute to generating those location signals. Integration of somatosensory and spatial inputs ('tactile remapping', Canzoneri *et al.* 2014) allows location of the stimulus to be mapped in external space. It remains for future experiments to determine the composition of this proprioceptive signal. We would predict that it does not involve muscle spindles.

It is somewhat ironic that the experiments of Goodwin *et al.* (1972), which established muscle spindles as the principal proprioceptors, used the highly specific task of matching elbow angles. For this kind of task the evidence from muscle conditioning (Proske *et al.* 2014; Tsay *et al.* 2014) points to a comparison mechanism between spindle afferent signals from the two arms. Here spatial information about the position of one arm relative to the other is inherent in the difference signal from antagonist elbow muscles of each arm and from the calculated difference signal between the two arms, that is, here there is no need for reference to a body schema. When the difference signal from the arms is at a minimum the arms are considered aligned. The evidence suggests that this matching mechanism operates over only a relatively narrow range of elbow angles, with a maximum difference of 20 deg (Proske *et al.* 2014). The limits of the range are probably determined by the range of firing of muscle spindle afferents. Outside this range another mechanism must come into play, since when blindfolded we know where our arms are even when they are at very different angles. We postulate that for larger angular differences the mechanism for position sense, as measured by pointing, comes into play. Such a proposition could be tested by experiment.

How does the proposal that spatial location during pointing is signalled predominantly by exteroceptors stand up against the present body of knowledge on the subject? A well-known illusion is the rubber hand illusion (Botvinick & Cohen, 1998). Vision of a rubber hand and synchronous tactile stimulation of the rubber hand and the hidden, real hand leads to adoption of the rubber hand as part of the body. This is essentially a pointing task that involves both

vision and touch. However, proprioception, which would be expected to include input from muscle receptors, has been considered to be involved as well. There is a perceived displacement of the real hand in the direction of the rubber hand (Botvinick & Cohen, 1998) and this has been referred to as proprioceptive drift (Kammers *et al.* 2009; see also Tsay *et al.* 2014). In terms of the present proposal it might be worthwhile to reassess the origin of this drift. Could it be generated by influences arising from the central changes triggered by vision and touch?

An illusion of movement is generated in a hidden, stationary arm by watching a mirror image of the other, moving arm (Metral *et al.* 2015). The subject falsely interprets the mirror image as being their hidden arm. Here there is evidence for a mechanism whose action is not consistent with input from muscle spindles. When the angular difference in the starting positions between the moving and stationary arms was increased, there was a longer delay in onset of the illusion and the speed of the illusion slowed. Such behaviour would not be expected from influences arising in muscle spindles.

Concerning the contribution of cutaneous receptors to matching and pointing tasks, they are able to act both as proprioceptors and as exteroceptors. Stretch of skin over the elbow joint can lead to sensation of movement of the elbow, a proprioceptive sensation (Collins *et al.* 2005). As we move about in our surroundings, the elbows may come in contact with external objects. Here cutaneous receptors are acting as exteroceptors by providing information about spatial relationships between ourselves and our immediate surroundings. The contribution of joint receptors to signalling spatial information remains more problematical. The present-day view is that they are principally movement detectors, but may provide positional information towards the extremes of the range of joint movements (Ferrell & Smith, 1988; Fuentes & Bastian, 2010), so they are potentially able to contribute in both pointing and matching tasks.

How might auditory signals contribute spatial information? While it is intuitively obvious that our facility of sound localisation provides us with spatial information about our surroundings, there is also some recent, more specific information available. In a timed finger tapping task, altering the timing of the auditory feedback associated with the tapping sounds can lead to perception of an altered arm length (Tajadura-Jiménez *et al.* 2012). So auditory information can provide input to the postural schema to determine the size and location of the body and its limbs.

Conclusion

Traditionally it has been assumed that the term 'proprioceptors' refers to a collection of sensory receptors of

different kinds all of which contribute in some form or other to sensations of body movement and position. It has been tacitly assumed that muscle spindles play a role in all of these sensations. On the basis of the present experiments we propose that the afferent origins of position sense should be reassessed in terms of how it is measured, whether by pointing or matching. The present report provides evidence that in position sense measured by pointing, muscle spindles do not play a prominent role. If our proposal stands up to further tests by experiment, it will represent an important step forward in our understanding of the central processing of spatial information.

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Additional information

Competing interests

The authors have no competing interests.

Author contributions

A.T.: provision of study materials; recruitment of subjects; collection and assembly of data; data analysis and statistics; manuscript writing. M.G.: manuscript writing; final approval of manuscript. TA: Data analysis and interpretation; manuscript writing. U.P.: Conception and design of experiments; manuscript writing. The experiments were carried out in the Department of Physiology at Monash University. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

CHAPTER 5: POINTING AND MATCHING AT THE ELBOW JOINT

Tsay, A., T. Allen and U. Proske (2016). "Position sense at the human elbow joint measured by arm matching or pointing." Exp Brain Res. **234**(10): 2787-2798.

5.1 Explanatory Notes

Following the observation that muscle vibration and muscle conditioning did not influence position errors during a pointing task (Chapter four; Tsay et al., 2016), further experiments were carried out to test for other possible contributing factors (i.e. placement of the indicator by the subject vs experimenter, and the introduction of visual control in the pointing task). These investigations formed the basis for Chapter five (Tsay et al., 2016).

In this chapter, co-contracting the antagonist muscles at the test angle, as described in Chapters two and three (Tsay et al., 2014; Tsay et al., 2015), was used to lower the spindle activity difference between antagonist muscles of the reference arm. It was hypothesised that if spindle information was used in a single-limb pointing task, position errors would lie close to zero following co-conditioning. The results did not support this hypothesis, as all pointing errors after co-conditioning lay in a more extended direction. Hence, this study supports the view presented in Chapter four (Tsay et al., 2016), that muscle spindles do not appear to play a major role in limb pointing tasks, compared to limb matching.

5.2 Declaration for Thesis Chapter Five

Declaration by candidate

In the case of Chapter five, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
The candidate co-designed the study, conducted the experiments, collected and analysed the data, and was involved in the construction/editing of the manuscript.	70

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Trevor Allen	Discussion of literature, experimental design, editing of manuscript.	
Uwe Proske	Discussion of literature, experimental design, writing of manuscript.	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's
Signature



Date

25/08/16

Main
Supervisor's
Signature



Date

25/08/16

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

Position sense at the human elbow joint measured by arm matching or pointing

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Abstract Position sense at the human elbow joint has traditionally been measured in blindfolded subjects using a forearm matching task. Here we compare position errors in a matching task with errors generated when the subject uses a pointer to indicate the position of a hidden arm. Evidence from muscle vibration during forearm matching supports a role for muscle spindles in position sense. We have recently shown using vibration, as well as muscle conditioning, which takes advantage of muscle's thixotropic property, that position errors generated in a forearm pointing task were not consistent with a role by muscle spindles. In the present study we have used a form of muscle conditioning, where elbow muscles are co-contracted at the test angle, to further explore differences in position sense measured by matching and pointing. For fourteen subjects, in a matching task where the reference arm had elbow flexor and extensor muscles contracted at the test angle and the indicator arm had its flexors conditioned at 90°, matching errors lay in the direction of flexion by 6.2°. After the same conditioning of the reference arm and extension conditioning of the indicator at 0°, matching errors lay in the direction of extension (5.7°). These errors were consistent with predictions based on a role by muscle spindles in determining forearm matching outcomes. In the pointing task subjects moved a

pointer to align it with the perceived position of the hidden arm. After conditioning of the reference arm as before, pointing errors all lay in a more extended direction than the actual position of the arm by 2.9°–7.3°, a distribution not consistent with a role by muscle spindles. We propose that in pointing muscle spindles do not play the major role in signalling limb position that they do in matching, but that other sources of sensory input should be given consideration, including afferents from skin and joint.

Keywords Spatial sense · Muscle spindle · Proprioception · Muscle conditioning · Body schema

Introduction

The proprioceptive senses, the senses signalling the body's own actions, are sometimes referred to collectively as the sixth sense. This is a mysterious sense because it acts largely unconsciously. It includes the sense of limb position and movement, the sense of force or of effort and the sense of balance. The subject of the present study is the sense of limb position. Where is my arm? I know where it is, but there is no identifiable sensation that I can attribute to its adopted position.

We have been studying the sensory neural basis of position sense for a number of years (Proske and Gandevia 2012). The work has been based on the landmark observations by Goodwin et al. (1972), who showed that vibration of elbow flexor muscles of one arm led to sensations of movement and displaced position of the arm in the direction of elbow extension as indicated in tracking movements by the other arm. As a result, the final position the arm appeared to adopt was more extended than its actual position. Similarly, vibration of elbow extensors led

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to sensations of movement into flexion. At the time it was known from animal experiments that in a passive muscle the muscle spindles were exquisitely sensitive to vibration (Brown et al. 1967). By implication it was assumed that muscle spindles were responsible for the movement illusions generated by vibration. This assumption was subsequently proved correct when direct recordings were made from human spindles during muscle vibration (Roll et al. 1989). It is now generally accepted that muscle spindles are responsible for the vibration illusion, the primary endings contributing to both the senses of limb movement and position, while the secondary endings signal limb position (Matthews 1988).

Our own past experiments sought additional supporting evidence for a role for muscle spindles in position sense. We brought a new technique to bear on the problem. Both the ordinary muscle fibres of a muscle and the intrafusal muscle fibres of muscle spindles exhibit a contraction history-dependent property called thixotropy which influences the passive tension and stiffness in resting muscle fibres. It has been shown in animal experiments that spindle discharge rates can be raised or lowered as a consequence of thixotropic conditioning and in parallel experiments on human subjects, similar conditioning produced reproducible errors in limb position sense (Gregory et al. 1988). For reviews, see Proske et al. (1993, 2014).

The original observations of Goodwin et al. (1972) were all made using a forearm matching task. One elbow muscle was vibrated, and the blindfolded subject was required to track the perceived movement of the forearm with their other arm. Similar matching experiments, with or without vibration, have now been carried out on the fingers (Ferrell and Smith 1988), hands (Walsh et al. 2013), knee (Givoni et al. 2007) and ankle (Boisgontier and Nougier 2013), and the results are generally supportive of the findings of Goodwin et al.

When a blindfolded subject carries out a forearm position matching task, the experimenter moves one arm, the reference arm, to the test angle and the subject moves their other arm, the indicator arm, into a matching position. That is, the subject moves their indicator arm until the sensations generated by the two arms feel the same. It is a sensation matching task.

When we ask ourselves “where is my arm?” we typically do not locate it by moving our other arm into a matching position. Yet we know where our arm is and we are able to point to its position. That conclusion has recently led us to revisit the question of position sense at the elbow, but this time we have used two different methods of measurement of position sense: a conventional forearm matching task and a position pointing task (Tsay et al. 2016). In the pointing task the reference arm is hidden behind a screen and the

subject is required to move a pointer until this aligns with the perceived position of the hidden arm.

We posed the question: do muscle spindles contribute to position sense in the same way in matching and pointing tasks? In a matching task spindle signals from both arms contribute to achieve accurate alignment of the forearms (White and Proske 2009; Izumizaki et al. 2010; Tsuge et al. 2012). In a pointing task the relevant afferent information is coming from only one arm, so here the role of spindles was likely to be different. We recently explored this possibility using both thixotropic conditioning and muscle vibration (Tsay et al. 2016). It was concluded that for position sense measured by pointing, muscle spindles did not play the prominent role that they did in matching. Such a conclusion departs from the conventional view of the sensory origins of proprioception and deserves to be tested further by experiment.

The idea that the origin of afferent signals might be different in matching and pointing tasks is not new. Velay et al. (1989) concluded that matching and pointing did not test the same position sense. They proposed that basic position sense was coded by proprioceptors in terms of angular position in intrapersonal space, but that another form of coding was required to provide continuous knowledge of limb location in extrapersonal space. They speculated about a central transformation process which converted one sense to the other.

We have recently introduced a new method of thixotropic muscle conditioning, which we have called test angle co-conditioning (Tsay et al. 2014, 2015). Here the reference arm is brought to the test angle, elbow flexors and elbow extensors are both contracted isometrically, and the subject is then asked to match position of the arm with the indicator arm which has been either flexion or extension conditioned. In trials with such a conditioning procedure large matching errors were observed (Tsay et al. 2014).

In the present study we have resorted to the same method of test angle conditioning in an attempt to further explore the recently observed differences in the sensory afferent basis of position sense measured in pointing and matching tasks. Given that test angle conditioning produces large errors in a matching task, it was hoped that the same method applied to a pointing task would reveal new differences in position sense measured in this way.

Methods

A total of 23 subjects were recruited for this study. They included 9 males and 14 females with an average age of 24.5 (± 0.6) years. Subjects gave informed, written consent prior to participating in the study, which was approved by the Monash University Human Research Ethics Committee.

The ethical aspects of the experiments conformed to the Declaration of Helsinki.

The apparatus

Position sense was measured in two ways. For the matching task the blindfolded subject sat at a table and placed both forearms on lightweight paddles attached to a custom-built piece of apparatus for measuring forearm position sense (Allen and Proske 2006). The forearms, palms facing upward, were strapped to the paddles by Velcro straps placed just below the crease of the wrist and 5 cm in width. In order to minimise potential differences in skin sensation between the two arms, equal tension from the strapping was checked before proceeding with the experiment. One arm was designated the reference arm (the arm placed at the target angle by the experimenter), while the other arm was the indicator arm (the arm moved by the subject to match the perceived position of the reference arm).

In the pointing task the two arms were separated by a screen. The screen consisted of a large, removable board that obscured subjects' vision of their reference arm, including the shoulder. The reference arm was strapped in, as before, its position set by the experimenter. In a pointing trial the subject was required to push or pull a lever at the base of the pointer paddle to move the pointer upwards or downwards until it was perceived to be aligned with the hidden reference arm (Tsay et al. 2016, Fig. 1).

Forearm and pointer paddle angles were measured using potentiometers located at the hinges of each paddle. When an arm was strapped to a paddle, the paddle hinges were co-linear with the elbow joint (Allen and Proske 2006, Fig. 1). The potentiometers provided a continuous voltage output proportional to the angle of each paddle, where 0° indicated that the forearm was horizontal and 90° indicated that it was vertical. Calibration of the potentiometers was checked before commencement of an experimental series with each subject.

Muscle activity of the reference arm was measured using surface electromyogram (EMG). Here we did not analyse the EMG signal as such, but used it to provide feedback, indicating whether or not the subject had remained relaxed as the experimenter moved the reference arm to the test angle. A pair of Ag–AgCl electrodes with an adhesive base and solid gel contact points (3 M Health Care, London, Ontario, Canada) were placed approximately 2.5 cm apart over the surface of the biceps brachii and triceps brachii. A reference electrode was placed on the collar bone. EMG output was connected to an audio amplifier for biofeedback. Position, force and EMG signals were acquired using a MacLab 4/s data acquisition module running Chart software (AD Instruments, Castle Hill, NSW, Australia) on a Macintosh computer.

Measuring position errors

Position errors between the two paddles were calculated using the formula:

$$\text{Position error}(^{\circ}) = \text{Reference angle}(^{\circ}) - \text{Indicator angle}(^{\circ})$$

The convention was used that 0° represented a fully extended arm with the forearm horizontal, 90° a flexed arm with the forearm in the vertical position. A positive error was an error in the direction of extension relative to the position of the reference arm, and a negative error, an error in the direction of flexion.

Reference and indicator arms were randomly assigned for each set of trials to reduce any biases from matching with a dominant or non-dominant arm (Goble et al. 2006). During a matching trial the reference arm was placed by the experimenter at an angle of 45° and the blindfolded subject was asked to match its perceived position with their indicator arm. In a pointing trial the reference arm was positioned in the same way, but the subject indicated its perceived position by moving the pointer paddle to align it with the hidden arm.

During movement of the reference arm to the test angle by the experimenter subjects were asked to remain relaxed. This was monitored with auditory feedback of EMG. Throughout these experiments, once the reference arm had been placed at the test angle, the subject maintained its position voluntarily. All of the matching by the indicator arm was also done voluntarily by the blindfolded subject. In both matching and pointing trials subjects were therefore required to generate mild contractions sufficient to support the reference arm against gravity and in the matching task for movement of the indicator into the matching position. These conditions were chosen to keep both matching and pointing processes close to what subjects might do in everyday life.

Muscle conditioning

Muscle thixotropy is a property of resting skeletal muscle, a contraction history-dependent change in passive tension and stiffness dependent on the presence of long-term stable cross-bridges between actin and myosin in sarcomeres. The thixotropic state of a muscle can significantly alter the responses of muscle spindles and therefore exerts a strong influence on the measurement of position sense (Proske et al. 2014). In order to control for thixotropy-related position errors it is necessary at the start of each matching trial to put elbow muscles of both arms into a defined state. This is called muscle conditioning. In the pointing trial it was only necessary to condition the reference arm.

We have previously applied two forms of conditioning to both arms, called flexion conditioning and extension

conditioning (Allen et al. 2007). In the present study such conditioning was applied only to the indicator arm in the matching trials. For flexion conditioning (FC) the forearm was moved into a vertical position (90°) and the blind-folded subject was asked to generate a 2 s, approximately half-maximum contraction, flexing the arm towards the body. Once arm muscles had relaxed, the subject moved the arm in the direction of extension into a matching position with the reference arm which had been isometrically conditioned at the test angle. For extension conditioning (EC) the indicator arm was moved into full extension (0°) and the subject was asked to push down onto the supporting table to generate a half-maximum contraction in elbow extensors. Again, once arm muscles had relaxed, the subject moved the indicator arm in the direction of flexion to adopt a matching position with the isometrically conditioned reference arm.

Therefore, in a matching trial muscles of the reference arm had been co-conditioned, while muscles of the indicator arm had been either flexion or extension conditioned. For flexion conditioning it left indicator flexor muscles taut after the conditioning contraction, and when the indicator arm was extended from 90° to the test angle (45°), they were stretched by the movement and therefore kept in a taut state. The same movement slackened the extensors whose passive tension therefore fell to low levels. This meant that after flexion conditioning flexor spindles were sensitised, while extensor spindles were de-sensitised. As a consequence, the proprioceptive signal coming from the indicator arm was biased in favour of elbow flexors. Similarly, after extension conditioning the signal was biased in favour of elbow extensors.

Experiment 1: Co-conditioning at the test angle

We wanted to measure position sense under conditions where such a bias in the origin of the proprioceptive signal from flexion or extension conditioning was not present. An additional form of conditioning was therefore used with the reference arm that left its elbow flexors and extensors in the same sensitised state (Tsay et al. 2014). To do that, isometric contractions of both antagonists were carried out at the test angle (co-conditioning).

Two conditioning sequences were used: in one the arm was placed at the test angle (45°) by the experimenter and the subject was asked to generate a half-maximum contraction of elbow extensors, followed by a half-maximum contraction of elbow flexors (Ref: EC + FC, Fig. 1). Alternatively, the reverse sequence was used, beginning with a flexor contraction followed by an extensor contraction (Ref: FC + EC, Fig. 1). During the contractions the paddle supporting the arm was held fixed in position at the test angle, so there was no accompanying movement.

In the matching trials, for the reference conditioning sequence EC + FC, at the same time as performing the flexor contraction of the reference arm, the subject also carried out flexion conditioning of their indicator arm while it was held at 90° . The conditioning was done in this way, finishing up with flexion conditioning of both arms, to minimise any differences between the arms in adaptation effects of afferent responses. For the reference sequence FC + EC the same procedure was carried out, but the indicator arm was extension conditioned by holding it at 0° and carrying out an extensor contraction. Once it had relaxed, the indicator arm was moved by the subject into a matching position. So the elbow of the reference arm had undergone both extension and flexion contractions at the test angle, while the indicator had been either flexion conditioned (filled circle, Matching, Fig. 1) or extension conditioned (open circle, Matching, Fig. 1).

In the pointing task, only the reference arm was conditioned, using the same two sequences of test angle extensor and flexor contractions: EC + FC (filled circle, pointing, Fig. 1) and FC + EC (open circle, pointing, Fig. 1). When the reference conditioning had finished with a flexor contraction, the subject moved the pointer paddle downwards from a starting angle of 90° , into a position where they considered it to be aligned with the hidden reference arm. When reference conditioning had finished with an extensor contraction, they moved the pointer upwards from an initial position of 0° . The pointing was done in this way to make the direction of movement of the pointer similar to that for the indicator arm in the matching task.

Experiment 2: Experimenter-move versus self-move

A question that arose during the pointing experiments was whether signals coming from the arm moving the pointer to indicate location of the reference arm contributed in some way to the position errors. It was therefore decided to do a series of control experiments where in addition to trials in which the subject moved the pointer themselves, a further set was carried out where the pointer was moved into alignment by the experimenter, under instructions from the subject. During these trials the subject was asked to place the pointing arm in their lap, unmoving.

Experiment 3: Matching with the indicator under visual control

In the pointing trials the subject could see the pointer as they moved it into the perceived position of the hidden reference arm, so the pointing was done under visual control, even though it was non-informative vision. In contrast, the matching trials had all been done with the subject

blindfolded. It was therefore felt necessary to do an additional series of control matching trials where the subject could see their indicator arm (experiment 3). Here the reference arm was always co-conditioned, and in the matching trials the indicator arm was flexion or extension conditioned, as before. However, in addition to the blindfolded matching trials, a second set of matching trials was done where the subject moved their indicator arm into a matching position with the arm in full view. The reference arm remained hidden.

Statistical analysis

In experiment 1 subjects carried out a series of 5 trials with each conditioning sequence. For matching there were 10 trials: 5 where the reference arm was isometrically conditioned and the indicator flexion conditioned and 5 where the reference was isometrically conditioned and the indicator extension conditioned. For pointing there were also 10 trials: 5 trials where the reference arm was isometrically conditioned, beginning with an extension contraction (EC + FC) and 5 trials where the isometric contraction began with a flexor contraction (FC + EC). This made for a total of 20 trials. For 8 subjects an additional 10 trials were carried out where the experimenter rather than the subject moved the pointer. The results from these trials were compared with 10 trials where the subject moved the pointer themselves (experiment 2). A new cohort of 9 subjects did two series of matching trials: one under visual control, the other blindfolded, as well as the pointing trials, making for a total of 30 trials (experiment 3).

In each experimental trial conditions were randomised.

The effect of conditioning on position errors for each task, matching and pointing, was analysed using a two-tailed paired *t*-test. Further, separate, repeated-measures ANOVA were used to test for the effects on arm position errors of self-moved versus experimenter-moved placement of the indicator, as well as for the effects of vision on pointing and matching trials. If significance was found, a Bonferroni post hoc test was used to determine which pointing trials were significantly different.

Pooled data from each experiment were shown as mean \pm standard error of the mean (SEM).

Results

In previous experiments we had shown that distributions for position errors measured in matching trials were significantly different from the distributions in pointing trials under conditions where the arms had been either flexion or extension conditioned (Tsay et al. 2016). In the present

experiments the aim was to further explore this difference, using co-conditioning at the test angle (Tsay et al. 2014). This additional method of conditioning was selected because it was predicted to produce rather large differences in outcomes for matching and pointing trials.

Experiment 1: Co-conditioning at the test angle

Matching

For the co-conditioning sequence EC + FC of the reference arm and with flexion conditioning of the indicator arm, in the matching trials (filled circle, left-hand panel, Fig. 1), the pooled data for the 14 subjects gave a mean error of -6.2° ($\pm 1.3^\circ$). That is, the blindfolded subject tended to indicate the position of their reference arm as more flexed than its actual position. Here the error was somewhat smaller than expected, based on similar recent experiments (Tsay et al. 2015).

The conditioning order was now reversed. Instead of the isometric conditioning starting with a contraction of extensors, it began with a contraction of flexors to give the sequence for the reference arm, FC + EC. Here the indicator arm was always extension conditioned. The reason for choosing such a reversal of the conditioning sequence was that in previous matching experiments it had led to a reversal of the direction of the errors. The pooled data for the 14 subjects (open circle, left-hand panel, Fig. 1) gave a mean error of $+5.8^\circ$ ($\pm 1.7^\circ$); that is, subjects perceived their reference arm to be more extended than its true position. The errors into extension were as had been predicted, in a direction opposite to that following flexion conditioning of the indicator, although their size was smaller than had been anticipated from previous experiments (Tsay et al. 2015).

Pointing

The experiment was repeated, but this time only the reference arm was conditioned. Position of the hidden arm was indicated by the subject moving the pointer paddle to a position where the subject felt it was in alignment with the reference arm. So this was measuring position sense by pointing. Data for pointing trials are shown in the right-hand panel in Fig. 1. For the conditioning sequence EC + FC of the reference arm (filled circle, right-hand panel, Fig. 1) the mean error for the 14 subjects was $+7.2^\circ$ ($\pm 1.1^\circ$). That is, subjects felt that the pointer paddle was accurately aligned with the hidden reference arm when in fact its position was more extended than the reference arm by an average of 7.2° . Therefore, using the same conditioning of the reference arm as in matching (EC + FC), the pointing trials produced errors differing from the matching errors by 13.4° ($6.2^\circ + 7.2^\circ$).

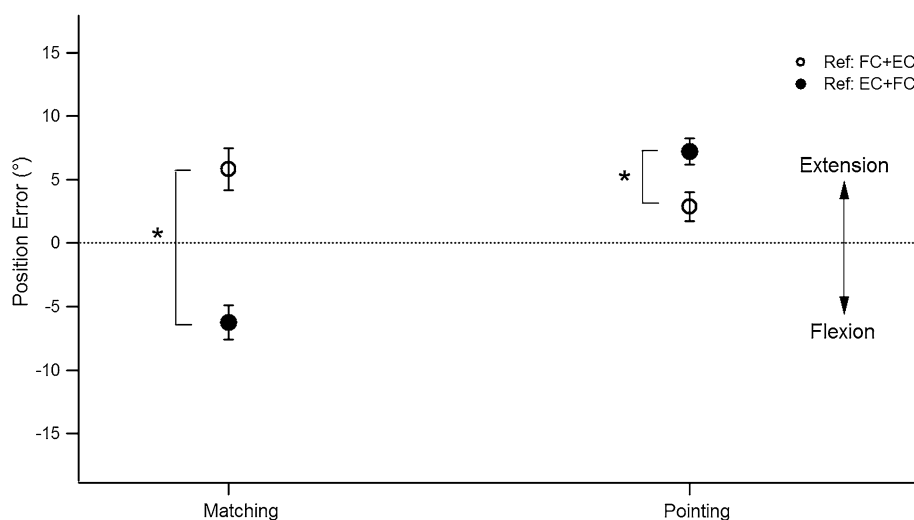


Fig. 1 Position errors measured in matching and pointing tasks after co-conditioning of the reference arm. Mean matching errors (*left-hand panel*) and pointing errors (*right-hand panel*) after co-conditioning the reference arm at 45° with the sequence EC + FC (*filled circles*) and FC + EC (*open circles*). In the matching trials the indicator arm was either flexion conditioned at 90° (*filled circle*) or extension conditioned at 0° (*open circle*).

In the pointing task the position of the hidden arm was indicated with a pointer. In this and subsequent figures the convention is used that errors by the indicator arm, or the pointer, in the direction of extension are given a positive value. Errors in the direction of flexion are given a negative value. Dotted line zero error. Asterisk indicates significant difference

In interpreting this result it should be kept in mind that matching trials involve proprioceptive signals coming from both arms while in pointing trials presumably only a signal from the reference arm was involved. We have previously provided evidence that co-conditioning of elbow antagonists at the test angle led to a difference signal coming from the conditioned arm that lay close to zero relative to the signal coming from the indicator arm (Tsay et al. 2015). We therefore predicted that in the present experiments conditioning the reference arm in this way would similarly generate a difference signal close to zero. So in the pointing trials the observed errors were in the opposite direction from the errors in the matching trials and, in addition, they did not lie close to zero, as had been predicted.

The experiment was then repeated but using pointing trials, with the reference arm conditioned with the reverse sequence, FC + EC (open circle, right-hand panel, Fig. 1). The pooled data for the 14 subjects yielded a mean error of +2.9° (±1.0°). This compared with an expected error of 0° (Tsay et al. 2015). So again the outcome of the pointing trials differed from expectations.

When the distributions of errors using the two forms of conditioning shown in Fig. 1 were compared, statistical analysis, using paired *t*-tests, showed that they were significantly different ($p < 0.05$) for both pointing ($t(13) = 2.709$, $p < 0.01$) and matching tasks ($t(13) = -6.341$, $p < 0.05$). A significant difference was expected for the errors in the matching tasks, given that two forms of conditioning were used, but they were unexpected for the pointing tasks since here the hypothesis was

that the distribution of errors was independent of the form of conditioning (see “Discussion”).

Experiment 2: Experimenter-move versus self-move

The data presented so far suggested that muscle conditioning had different effects on forearm position errors measured in pointing and matching trials. This conclusion was in line with other recent observations (Tsay et al. 2016). It is known that in forearm matching trials signals from both arms make a contribution (White and Proske 2009; Hakuta et al. 2014; Tsay et al. 2014). In the search for an explanation of the pointing results, the possibility was considered that proprioceptive activity associated with the arm moving the indicator paddle to align it with the perceived position of the hidden reference arm influenced, in some way, the measured values.

To put this idea to the test, for 8 of the 14 subjects pointing errors were measured both with the subject aligning the pointer themselves and with the alignment carried out by the experimenter. Here the experimenter adjusted the position of the pointer until the subject declared accurate alignment with the unseen arm. Throughout the trial the subject's other arm rested on their lap, unmoving.

Results for the 8 subjects are shown in Fig. 2 for the same forms of conditioning of the reference arm as had been used in the previous trials (EC + FC and FC + EC). Notice that the general trend of the data with errors lying in the direction of extension was the same as for pointing errors observed in the earlier trials (Fig. 1). When the pointer paddle was moved by the experimenter, position

Fig. 2 Errors in a pointing task when the pointer is moved by the subject or the experimenter. Mean pointing errors (\pm SEM) for a group of 8 subjects with the reference arm co-conditioned at the test angle with two forms of conditioning (FC + EC and EC + FC). *Filled circles*, values when the subject moved the pointer themselves; *open circles*, when the pointer was moved by the experimenter. Error displays as in Fig. 1. Asterisk indicates significant difference

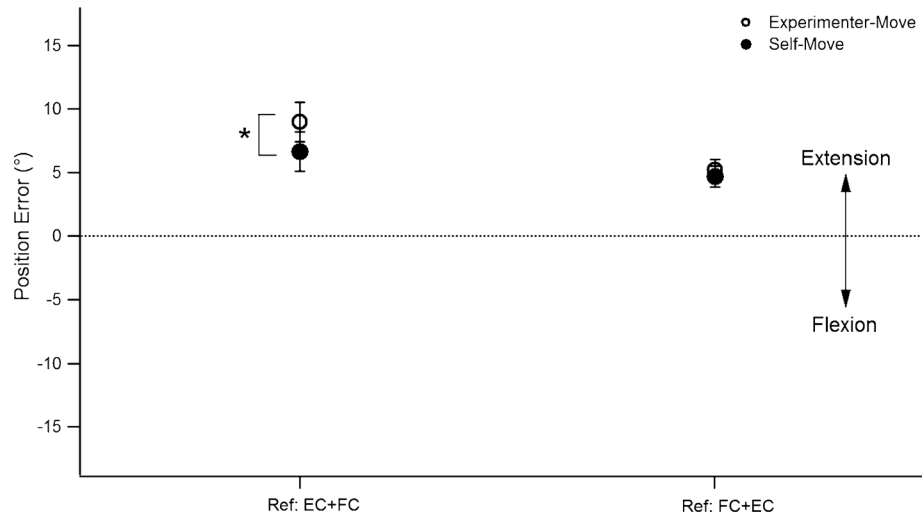
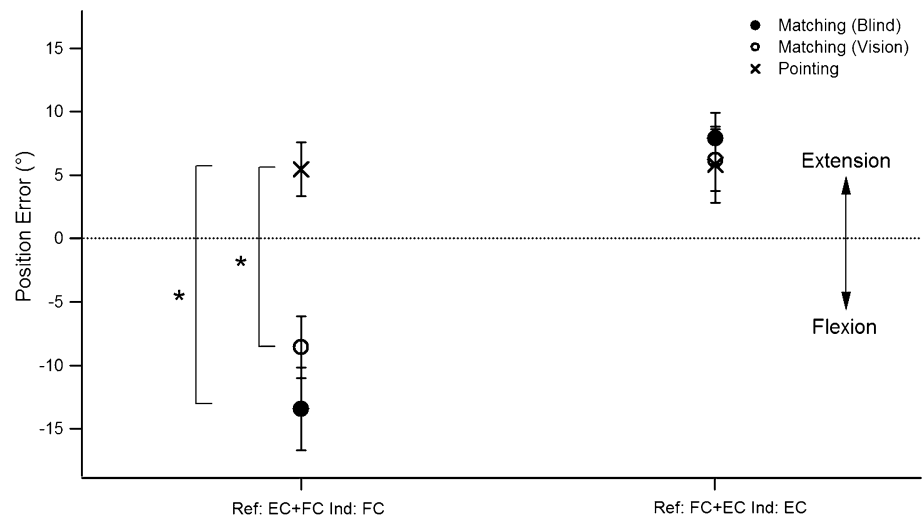


Fig. 3 Position errors in matching and pointing tasks where the matching was done with or without visual control. Mean matching and pointing errors (\pm SEM) for a group of 9 subjects where pointing (*crosses*) was done as before, but matching was done blindfolded (*filled circles*) or under visual control (*open circles*). Error displays as in Fig. 1. Asterisks indicate significant differences



errors lay a little further in the direction of extension than when the subject moved the pointer themselves. For co-contraction conditioning of the reference arm, EC + FC, self-moved pointing produced an error of $+6.7^\circ$ ($\pm 1.6^\circ$), while for experimenter-moved pointing the error was $+9.0^\circ$ ($\pm 1.3^\circ$). Reversing the isometric conditioning to FC + EC yielded a self-moved pointing error of $+4.7^\circ$ ($\pm 0.8^\circ$), while experimenter-moved error gave $+5.2^\circ$ ($\pm 2.3^\circ$).

A repeated-measures ANOVA between subjects showed that these differences were significant $F(7, 49) = 2.384$, $p = 0.04$. Bonferroni post hoc tests showed significant differences ($p < 0.05$) in values for experimenter-moved versus self-moved pointing for EC + FC.

Experiment 3: Matching with the indicator under visual control

In this experiment two sets of matching trials were carried out: in one the subject remained blindfolded, as before, and

in the other they could see their indicator arm. The reference arm always remained hidden from view. The matching with vision was done as a control since in the pointing trials the subject could always see the pointer. The experiment was carried out with a new cohort of 9 subjects. The results are shown in Fig. 3.

For blindfolded matching with the reference arm conditioned EC + FC and the indicator FC, the mean error was -13.4° ($\pm 3.2^\circ$). In the trials where the subject could see their indicator arm the mean error was -8.6° ($\pm 2.5^\circ$). So matching under visual control reduced the errors by 4.8° . In the pointing trials where the reference arm was conditioned EC + FC, position errors were $+5.4^\circ$ ($\pm 2.1^\circ$). The pointing result was therefore similar to previous values (Fig. 1, 2).

The experiment was now repeated using the reverse conditioning sequence FC + EC for the reference arm and EC for the indicator arm. Blindfolded matching gave a mean error of $+7.9^\circ$ ($\pm 2.0^\circ$). When matching was repeated with the indicator arm visible, the error was $+6.2^\circ$ ($\pm 2.4^\circ$). So

here the difference in errors with and without the indicator arm visible was rather smaller, 1.7° . For pointing, using the conditioning sequence FC + EC, the mean error was 5.8° ($\pm 3.0^\circ$). The result was approximately in line with the earlier finding (Fig. 1, 2).

Statistical analysis using a repeated-measures ANOVA showed a significant difference between values: $F(5, 40) = 15.5$, $p = 0.0$. Post hoc analysis (Bonferroni test), with the reference arm conditioned EC + FC, revealed a significant difference between pointing and blindfolded matching ($p = 0.01$) and between pointing and matching under visual control ($p = 0.04$). There was no significant difference between the matching values, with and without vision. For conditioning of the reference arm, FC + EC, there were no significant differences between the errors in the matching and pointing tasks, with and without vision.

Discussion

These experiments are submitted in support of the view that there is a task dependency in the afferent origins of proprioceptive signals responsible for generating human position sense. In a forearm position matching task muscle spindles play a prominent role, while in a pointing task spindles are relegated to play only a minor role, if any, in providing the position signal.

Experiment 1: Co-conditioning at the test angle

For the matching trials in experiment 1 the observed distribution of position errors compared favourably with findings from a similar experiment carried out previously (Tsay et al. 2015). In that study we had observed that when the reference arm had elbow muscles conditioned at the test angle and the indicator arm was flexion conditioned, errors lay 9.2° in the direction of flexion. This was rather more than the errors seen in the present study (6.2°), although their direction was the same. When the indicator had been extension conditioned, errors were 7.5° in the direction of extension which again was consistent with observations in the present study (5.8°). We then showed that if slack was introduced in indicator flexor and extensor muscles to effectively lower their levels of spindle afferent activity (Tsay et al. 2015; Fig. 1c, d), matching errors lay close to zero. The result implied that the net spindle discharge rate and therefore the position signal coming from the co-conditioned reference arm was low.

For the pointing trials the most important consideration is that here the afferent information is coming largely from one arm, while in matching trials afferent input from both arms contributes (White and Proske 2009; Izumizaki et al. 2010; Tsuge et al. 2012). We predicted errors for the

pointing trials to be lying close to zero. We have explained above that the output from a co-conditioned reference arm is predicted to be close to zero. In the event errors in the pointing trials all lay in the direction of extension.

While the general trend observed in the pointing trials was errors in the direction of extension, there were significant differences in size between the pooled values for conditioning FC + EC and its reverse, EC + FC (Fig. 1). There is no obvious explanation for this result given that two near-identical forms of conditioning had been used. Further, pointing errors for the same two conditioning sequences in the experimenter-move versus self-move experiment (Fig. 2) yielded values that were not significantly different from one another for this cohort of subjects (paired sample *t*-test, $p < 0.05$). Hence, we retain the view that in a pointing task all errors are approximately the same no matter what form of conditioning is used.

Experiment 2: Experimenter-move versus self-move

Here we assessed the possibility that one source of the error distribution in the pointing task was the arm moving the pointer. Indeed, it was found that there was a significant difference when the pointer was moved by the experimenter, compared with when it was moved by the subject (Fig. 2). It implied some, if small, influence on the measured errors coming from the pointing arm. However, more importantly, the general trend seen in pointing trials that the distribution of errors was insensitive to the form of muscle conditioning of the reference arm and always lay in the direction of extension remained unchanged (see also Tsay et al. 2015).

Experiment 3: Matching with the indicator under visual control

The differences in errors in the forearm matching task obtained with the subject blindfolded and with the indicator arm in view were relatively small (Fig. 3). They were only significant for the conditioning sequence of the reference arm EC + FC, not for the reverse, FC + EC. More importantly, whether the indicator arm was visible or not did not alter the overall pattern of matching errors, with values lying in the direction of flexion or extension, depending on the form of conditioning of the reference arm. It suggests that vision of the indicator arm exerts only a limited influence on the error distribution. The finding is consistent with our earlier observation that vision of the indicator arm altered only slightly, non-significantly, the angular difference in an arm matching task, even when measured during vibration of the reference arm (Izumizaki et al. 2010). Similarly, Longo (2014) found that hand shape distortions seen in implicit maps drawn by pointing to the unseen hand

persisted, but were significantly altered by non-informative vision of the pointing arm. We conclude that in a pointing task vision can influence the position error distribution, but does not alter the general trend of errors lying in the direction of arm extension.

Mechanism

Our interpretations are based on the assumption that spindle resting discharge levels determine limb position (Clark et al. 1985) and that changes in limb position produced by muscle conditioning are a result of alterations in spindle resting discharge (Gregory et al. 1988). We have previously proposed that it is the difference in afferent signal coming from the two antagonists at the elbow that determines the perceived position of the forearm (Proske et al. 2014). When these muscles are conditioned with a voluntary contraction at the test angle, thixotropic considerations dictate that any pre-existing slack is removed in extrafusal and intrafusal muscle fibres of both muscle groups. As a consequence, resting discharge rates in spindles of both muscle groups rise to similarly high levels. When this is the case, the difference signal is low. This leads to generation of a low position signal.

There is evidence from other quarters that supports such an interpretation. Gilhodes et al. (1986) showed that raising spindle discharge rates by similar amounts in both antagonists at the elbow, using vibration, led to abolition of the vibration illusion seen when only one muscle was vibrated. More recently, the technique of co-vibration of antagonists has been used as a method for degrading or masking proprioceptive feedback from an arm (Bock et al. 2007; Brun and Guerraz 2015). Our interpretation of these results is that the similarly high levels of spindle signal in both antagonists during co-vibration lead to a low difference signal which is interpreted centrally as reduced proprioceptive input from the arm. We are therefore proposing that co-conditioning of the antagonists with voluntary contractions at a given test angle leads to a similar outcome as co-vibration. However, there is one distinction. While the vibration can potentially engage a range of receptor types, including muscle, tendon, joint and skin receptors, only striated muscle, including the intrafusal fibres of spindles, exhibits thixotropic properties (Proske et al. 2014). So the effects of a conditioning contraction can be attributed specifically to afferents of muscle spindles.

It is currently believed that both primary and secondary endings of muscle spindles contribute to limb position sense (McCloskey 1973). The question arises: do all afferents of muscle spindles exhibit thixotropic behaviour? In an animal study, the responses of single, identified afferents of muscle spindles, including primary and secondary endings, were tested for thixotropic properties (Proske et al. 1992).

It was found that all primary endings exhibited such behaviour, but 16 of 35 secondary endings did not. These afferents had characteristically low conduction velocities, and it was speculated that the lack of a history dependence related to the location of the sensory terminals on the intrafusal fibres. The result means that thixotropic conditioning of human muscle may not engage all spindle afferents in the muscle. It raises the possibility, although unlikely, that in a pointing task there is a contribution to the position signal from spindle secondary endings which are unresponsive to the conditioning.

Accepting that a reference arm with antagonists co-conditioned at the test angle generated a net low proprioceptive signal, why were the errors so large after flexion or extension conditioning of the indicator? We propose that flexion conditioning of the indicator arm at 90°, followed by movement of the arm to the matching position generated in the arm a signal strongly biased in favour of flexor spindles, so the subject was trying to match a weak reference signal with a strong indicator flexor signal. It led the subject to match with the indicator elbow flexed, trying to keep elbow flexor muscles short and therefore their spindle discharge rates low. So position errors lay in the direction of flexion (-6.2° , filled circle, left-hand panel, Fig. 1). The same kind of explanation can be applied to extension conditioning of the indicator where the proprioceptive signal was biased in favour of extensors, so matching errors were predicted to lie in the direction of extension ($+5.8^\circ$, open circle, left-hand panel, Fig. 1).

The trend in the pointing trials that all of the errors lay in the direction of extension was similar to that seen previously (Tsay et al. 2016). The result suggested that the central processes involved in generating the sensation of limb position in a pointing task were relatively insensitive to changes in spindle afferent input produced by muscle conditioning. In that report we provided additional evidence for our view by showing that the illusions of limb position generated by muscle vibration in matching tasks (Goodwin et al. 1972) were not present in pointing tasks. Since muscle vibration is a powerful stimulus for muscle spindles (Roll et al. 1989), it was concluded that spindle signals played a lesser role in position sense measured in a pointing task compared with a matching task. As a consequence, in a pointing task position errors generated by muscle conditioning no longer conformed to predictions.

The finding of no vibration response in a pointing task (Tsay et al. 2016) remains controversial. Izumizaki et al. (2010) observed a 30 % reduction of the vibration illusion in a pointing task compared with a matching task, while Kammers et al. (2006) found the illusion three times larger in a matching task compared with a reaching task. So it may be that the vibration illusion is not always fully suppressed in a pointing task.

Recently, Kigawa et al. (2015) showed that the size of the vibration illusion generated in one arm could be reduced by vibrating the other arm. Such an outcome is presumably due to a signal difference mechanism operating during forearm matching (Proske et al. 2014). Kigawa et al. showed further that if the second arm was vibrated in an abducted position, the crossed effect on the other arm was no longer present. Yet it was possible to demonstrate a healthy vibration response in the abducted arm itself. Some years ago it was shown that when position sense was measured in a matching task, with both arms abducted, the standard deviation of matching errors was double that seen in a matching task with the arms in front (Gooney et al. 2000). The result suggested that subjects were less sure of the positions of their abducted arms. All of this emphasises the importance of arm posture for the position matching mechanism. When we carry out skilled manipulations with our hands, the hands are in front, forearms aligned. It is under these conditions that high alignment accuracy is required.

What might be the reason for the distribution of errors in the direction of extension in the pointing tasks? We have previously proposed that in a matching task it is the difference in afferent signals coming from the two arms that is used to indicate their degree of alignment (Proske et al. 2014). Obviously, in a task such as arm pointing the sense of limb position cannot be generated using such a difference mechanism since afferent signals from only one arm are available. We have postulated that in a pointing task the afferent signals from the reference arm access a central map of the body, the postural schema (Longo et al. 2010) to generate the positional information. One possible factor contributing to the distribution of position errors in a pointing task is a distortion of central somatosensory maps, reflecting regional differences in sensory innervation (Miller et al. 2016). It is conceivable that map distortions of forearm length and its angular location are responsible for errors lying in the direction of extension.

Wider implications

The original experiments establishing a role for muscle spindles in proprioception were by Goodwin et al. (1972). Their findings have been very influential; whenever the subject of proprioceptors is brought up and their role in human position sense is considered, it is tacitly assumed that muscle spindles comprise a major source of the afferent input (see, for example, Goble et al. 2009). The present report is submitted in support of the view that the role of muscle spindles in position sense depends on how position sense is measured. If it is measured in a pointing task, evidence from thixotropic conditioning of muscle, including the present study, and from the effects of muscle vibration

(Tsay et al. 2016), does not support a prominent role for muscle spindles. On the other hand, where position sense is measured in a matching task, by placing one limb to align it with the perceived position of the other, the evidence for spindle involvement is strong.

If our conclusion is accepted and muscle spindles do not contribute significant proprioceptive signals in a position pointing task, what source of afferent signal might be responsible for providing the positional information? In the pointing trials the errors all lay 3° – 7° in the direction of extension. So subjects were aware of the position of their reference arm, if less precisely than in a two-arm matching task. In an arm movement task concerned with interlimb coupling, Brun and Guerraz (2015) reported that when elbow antagonists of the moving arm were vibrated, a “condition of proprioceptive masking”, subjects reported that they could still feel the passive displacement of the arm. It was concluded that the effect of the vibration was not sufficient to fully suppress conscious movement perception. The authors speculated that other muscle, skin or joint receptors were responsible for the remnant sensation.

These considerations lead to the suggestion that we have two senses of limb position. When both arms are involved in determining limb position and they are relatively closely aligned ($\pm 10^{\circ}$, Proske et al. 2014), the spindle mechanism plays a prominent role and it ensures an alignment accuracy of $\pm 2^{\circ}$. If this mechanism is unable to be engaged because the two arms are too far apart, or if the task involves afferent input predominantly from only one arm (pointing), an additional underlying source of position signal is accessed.

Given that subjects were blindfolded in the main experiment, senses such as vision and hearing, which are able to provide spatial information, were not involved. Apart from spindles, other sensory receptors which have been considered to contribute to position sense include skin and joint receptors (Proske and Gandevia 2012). Potential candidates for position sensors in the skin are the slowly adapting Type II, Ruffini endings that respond to skin stretch. We have recently attempted to bias limb position sense at the forearm by stretching skin over the elbow joint (Tsay et al. 2016). This did not produce any detectable effect on position sense measured in either a position matching or pointing task. Such a negative result does not mean, of course, that cutaneous input plays no role, but simply that position sense cannot be significantly modified with the method used. There is, however, evidence that movement sense can be altered by skin stretch (Collins and Prochazka 1996; Collins et al. 2005). Similarly for joint receptors, they are considered principally to be movement detectors, but the presence in many joints of Ruffini endings means they are potentially capable of providing positional information, especially towards the extremes of the range of joint movement (Ferrell and Smith 1988; Fuentes and Bastian 2010).

In summary, the jury is still out over the afferent origins of position sense measured in a pointing task. Our evidence suggests spindles do not play a major role, but that other sources of position signals including skin and joint should be given further consideration (Tsay et al. 2016).

One other possibility is that the positional information in a pointing task is generated centrally, perhaps the result of an effort-related signal generated by the subject as they support the weight of their arm. We have tested this possibility, and the evidence does not support a role for a motor command signal in position sense at the elbow (Tsay et al. 2016).

To conclude, we present the observations in this report in support of the view that in tasks measuring position sense by pointing to the hidden limb, the afferents of muscle spindles do not play a prominent role. By contrast, spindles make a major contribution to position sense measured in a forearm matching task. The realisation that the sensory origins of position sense measured by matching and pointing are different offers new insight into the underlying mechanisms. If this view is confirmed, it represents an important advance in our understanding of the processing of spatial information.

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SECTION THREE: BODY REPRESENTATION IN CHRONIC PAIN

CHAPTER 6: BODY REPRESENTATION IN CHRONIC PAIN REVIEW

Tsay, A., Allen, T. J., Proske, U. & Giummarra, M. J. (2015). "Sensing the body in chronic pain: A review of psychophysical studies implicating altered body representation." Neurosci Biobehav Rev **52**(0): 221-232.

6.1 Explanatory Notes

In this final section of the thesis, position sense and body representation was examined in individuals with chronic pain. Chronic pain is defined as pain that has persisted for more than three months or beyond the expected time for healing (Merskey et al., 2011). While the aetiology is frequently unclear, both peripheral (tissue damage) and central (cortical reorganization) components are thought to be major contributors in the development of chronic pain (Lund et al., 1991; May, 2008; Wand et al., 2011; Melzack & Katz, 2013).

The first chapter in this section is a review paper (Chapter six; Tsay et al., 2015), published in *Neuroscience and Biobehavioral Reviews* that discussed the representation of the body in individuals with chronic pain. The review adopted the classification system described by Sherrington (1906), where the sense of one's physical-self comprises of three inter-related physiological systems: proprioception, exteroception and interoception. Within a year of publication this review had been cited 11 times (Akbari et al., 2015; Clayton et al., 2015; Schirmer-Mokwa et al., 2015; Adamczyk et al., 2016; Blickenstaff & Pearson, 2016; Bordoni et al., 2016; Martini, 2016; Ricciardi et al., 2016; Sano et al., 2016; Scheper et al., 2016; Senkowski & Heinz, 2016; Tsay & Giummarra, 2016) making it one of the most highly cited papers in this thesis.

6.2 Declaration for Thesis Chapter Six

Declaration by candidate

In the case of Chapter six, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
The candidate planned and wrote the review with feedback and guidance from co-authors.	80

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Trevor Allen	Discussion of literature, editing of paper.	
Uwe Proske	Discussion of literature, editing of paper.	
Melita Giummarra	Discussion of literature, editing of paper.	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work.

Candidate's
Signature



Date

25/08/16

Main
Supervisor's
Signature



Date

25/08/16



Review

Sensing the body in chronic pain: A review of psychophysical studies implicating altered body representation

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ABSTRACT

There is growing evidence that chronic pain conditions can have an associated central pathology, involving both cortical reorganisation and an incongruence between expected and actual sensory–motor feedback. While such findings are primarily driven by the recent proliferation of neuroimaging studies, the psychophysical tasks that complement those investigations have received little attention. In this review, we discuss the literature that involves the subjective appraisal of body representation in patients with chronic pain. We do so by examining three broad sensory systems that form the foundations of the sense of physical self in patients with common chronic pain disorders: (i) reweighting of proprioceptive information; (ii) altered sensitivity to exteroceptive stimuli; and, (iii) disturbed interoceptive awareness of the state of the body. Such findings present compelling evidence for a multisensory and multimodal approach to therapies for chronic pain disorders.

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Abbreviations: CLBP, chronic low back pain; CRPS, complex regional pain syndrome; EMG, electromyography; HRV, heart rate variability.

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1. Introduction

In health, we possess a certain affinity with our limbs, whose posture we can easily discern, even without looking at them. Indeed we take the spatial perception of our body for granted, as it operates largely in the absence of any apparent awareness. However,

this may not be the case for the 1 in 5 adults living with chronic pain-related disorders (Breivik et al., 2006), many reporting that the mental representation of their affected body part is somehow distorted—either in size, posture or even absent entirely (Melzack, 1990; Lewis et al., 2010; Wand et al., 2011).

Chronic pain is defined as pain that has persisted for more than 3 months or beyond the expected time for healing (Merskey et al., 2011). This encompasses conditions such as complex regional pain syndrome (CRPS), phantom limb pain, chronic low back pain (CLBP) and fibromyalgia syndrome. It is unlike acute pain, which plays a protective role by eliciting motivation to minimise harm. Rather, chronic pain is considered a disease in itself (Niv and Devor, 2004). Due primarily to the recent proliferation of neuroimaging studies, there is growing evidence of a central pathology associated with chronic pain (Wiech et al., 2000; Lima and Fregni, 2008), as distinct from acute pain profiles (Apkarian et al., 2005). While such evidence has been reviewed previously, particularly the associated cortical changes (Flor et al., 2006; Lotze and Moseley, 2007; May, 2008; Apkarian et al., 2011; Wand et al., 2011), the psychophysical tasks that are used clinically and in research to assess these disturbances have received little attention.

In this review, we discuss the literature that involves the subjective appraisal of body representation in patients with chronic pain by exploring the possible mechanisms by which a distortion of body representation might occur. Psychophysical tasks are of particular importance because they possess considerable potential for translational outcomes in clinical practice. In addition, these tasks provide a non-invasive and clinically-viable method of assessing cortical reorganisation—without the complexities and expense associated with neuroimaging. We have adopted the classification system described by Sherrington (1906), where the sense of one's physical-self comprises three inter-related physiological systems. We begin by discussing sensory inputs generated by the body itself (proprioception), and from the surrounding environment (the exteroceptive senses). Finally we discuss awareness of sensations within the body (interoception) and changes in autonomic regulation in common chronic pain disorders. Distinctions between these sensations have been made for the purposes of the review. In reality, however, there is probably considerable overlap between the interoceptive, exteroceptive and proprioceptive systems in generating the central representation of the body.

2. Proprioception

Proprioception refers to sensations generated by the body's own actions (Proske and Gandevia, 2012). By convention, these include four senses: (i) the sense of movement and limb position (kinaesthesia); (ii) the sense of tension or force; (iii) the sense of effort; and (iv) the sense of balance.

It is now widely accepted that information from proprioceptors project to the cerebral cortex of the brain (Oscarsson and Rosen, 1963; Landgren and Silfvenius, 1969; McIntyre, 1974; McIntyre et al., 1984), contributing to and maintaining a mental map of the body (Head and Holmes, 1911). While there is evidence for multiple body maps (Schwoebel and Coslett, 2005; Kammers et al., 2006), their role and function has historically remained ambiguous (de Vignemont, 2010). In this review, we refer to them collectively as *body representations*. One such map is the body schema (Head and Holmes, 1911) – or postural schema (Longo and Haggard, 2010) – an internal representation of the body's posture, which appears to be constantly updated based on current experiences (Matthews, 1988; Berlucchi and Aglioti, 2010). Hence, the role of the body schema is to guide motor actions as distinct from the conscious perception, belief and attitude of the body by its owner—i.e. body image (Gallagher and Cole, 1995; de Vignemont, 2010). It is known that

the experimental manipulation of afferent signals can lead to false impressions of limb position (Lackner, 1988) that temporarily disrupts the body schema (Melzack and Bromage, 1973; de Vignemont et al., 2005; Inui et al., 2011). The idea that changes in afferent signalling may cause distorted body representation in chronic pain has been raised before (Melzack, 1990). Indeed, there is evidence that large-diameter afferents are responsible for the pain commonly experienced after exercise, implicating access to the pain pathway by spindle afferents (Weerakkody et al., 2001, 2003b). However, recordings of afferents in healthy human subjects during stimulation of group III and IV afferents, via hypertonic saline, does not alter fusimotor excitability or muscle spindle discharge (Birznieks et al., 2008; Fazalbhoy et al., 2013). In light of such observations, the associated changes in chronic pain patients regarding proprioception more likely involves upstream disturbances, such as the neural processing of proprioceptive signals (Brumagne et al., 2004; Popa et al., 2007; McCabe and Blake, 2008). Conversely, higher-order alterations in body representation (Bultitude and Rafal, 2010) through cortical reorganisation have also been implicated (Moseley and Gandevia, 2005).

2.1. Kinaesthetic awareness

Historically, the sensations of limb position and movement were considered a single sense, termed kinaesthesia (Bastian, 1880). This is because both senses share inputs from the same mechanoreceptors within the muscle, i.e. the muscle spindles, which project to the cerebral cortex to provide information regarding the posture of the body and whether or not it is moving (Proske and Gandevia, 2009; Proske and Gandevia, 2012). However, it is now generally regarded that kinaesthesia consists of two distinct senses, comprising both position and movement sense (McCloskey, 1973). Of these two senses, position sense is the most widely tested sense in people with chronic pain, often involving the reproduction of a remembered posture or limb position (generally, in the absence of visual feedback). While there is evidence of reduced acuity during joint position sense tasks in those with chronic pain (Gill and Callaghan, 1998; Brumagne et al., 2000; Newcomer et al., 2000b; O'Sullivan et al., 2003; Pözl et al., 2004; Cuomo et al., 2005; Knox et al., 2006; Paulus and Brumagne, 2008; Lewis et al., 2010; Ha et al., 2011; Sheeran et al., 2012), there are also a number of studies that have found no significant differences in limb repositioning acuity between patient and control groups (Lam et al., 1999; Newcomer et al., 2000a; Descarreaux et al., 2005; Asell et al., 2006; Lee et al., 2010; Mörl et al., 2011).

Such contrasting views may be explained by differences in posture during the experimental protocols, such as whether participants were standing, sitting or lying down during the task. This is based on the premise that the latter postures would minimise the proprioceptive information available to the participant (Gill and Callaghan, 1998; Gooley et al., 2000; Lee et al., 2010). However, the available literature suggests that kinaesthetic acuity is not influenced by the posture adopted at the time of testing in these groups (Gill and Callaghan, 1998; Lee et al., 2010). That is, repositioning errors were no greater when patients with CLBP were seated, lying on their side or supine (Lee et al., 2010); likewise, the reproduction of trunk position was not significantly different when standing compared to kneeling (Gill and Callaghan, 1998).

A possible explanation for the lack of an effect between postural conditions comes indirectly, through studies that elicit muscle lengthening illusions. One method of examining the effects of altering afferent signals is to apply a vibration stimulus to the muscle, which leads to a dramatic increase in spindle afferent firing rates (Goodwin et al., 1972; Lackner, 1988). For example, Brumagne et al. (2000) assessed lumbosacral position sense in seated CLBP patients by vibrating the lumbar multifidus muscle. Given that spindle

discharge is proportional to muscle length (Proske and Gandevia, 2012), a lengthening illusion in the vibrated muscle would be expected. This was observed for the asymptomatic control group; however, the low back pain group produced errors in line with a muscle-shortening illusion. In other words, the direction of the illusion was reversed in the pain group. This cannot be explained by a contraction of the painful muscle during vibration, as this would suppress the lengthen illusion. These results were partially replicated in a later study using posturography (Brumagne et al., 2004), with CLBP patients showing a reduced centre of pressure displacement during paraspinal muscle vibration, as well as an increased centre of pressure displacement under vibration of triceps surae muscles, compared to healthy controls, during quiet standing. The authors proposed that such changes in centre of pressure reflect an altered sensitivity to proprioceptive input. However, interpreting such studies is complicated by co-activation of the fusimotor system during voluntary contractions (Vallbo, 1971), which attenuates vibration illusions (McCloskey, 1973; Capaday and Cooke, 1983; Inglis and Frank, 1990; Ansems et al., 2006). The implication is that when a muscle is contracting, the increase in spindle firing rate due to fusimotor activity does not contribute to the signalling of positional information. Such considerations were not accounted for in the aforementioned studies (Gill and Callaghan, 1998; Brumagne et al., 2000, 2004; Lee et al., 2010) and may be responsible for their observations.

One further explanation for the conflicting findings across position sense studies in patients with chronic pain is the failure to account for the thixotropic properties of muscle (Proske et al., 1993). To elaborate, the amount of stiffness and tension in a relaxed muscle is dependent on the immediate preceding contraction and length changes. This property is due to the formation of stable cross-bridges between actin and myosin, which form when the muscle relaxes after a contraction. This influences the kinaesthetic senses by altering the background discharge rates of the muscle spindles, leading to errors in perceived limb position during blind-folded matching tasks (Allen et al., 2008; Walsh et al., 2009; Tsay et al., 2012; Walsh et al., 2013; Proske et al., 2014). Failure to control for background spindle discharge rates, prior to a position sense judgement, may lead to uncertainties in the interpretation of data (for a detailed review, see Proske et al., 2014). At present, this crucial factor has not been considered in studies investigating position sense in chronic pain disorders and may account for the contrasting findings across studies.

With this in mind, evaluation from the kinaesthetic literature seems to suggest sensory re-weighting of afferent information in the presence of chronic pain (Brumagne et al., 2004). That is, patients with chronic pain appear to rely less on proprioceptive signals coming from the painful region (Brumagne et al., 2000, 2004, 2008; Claeys et al., 2011; Willigenburg et al., 2013). While few prospective studies have been carried out in this area, there is evidence of improvements in both position and movement sense when joint function is restored (Cuomo et al., 2005), hinting at a possible gating mechanism between proprioceptive and nociceptive afferents. Unfortunately, no attempts were made to quantify pain in this cohort; hence, the relation between pain and kinaesthesia requires further clarification.

Impairments in precise trunk movement under visual feedback have also been demonstrated (Willigenburg et al., 2013). This is further supported by findings concerning movement sense. The minimum threshold needed to detect movement is a commonly used protocol for the assessment of movement sense (Proske and Gandevia, 2012), with chronic pain populations being less sensitive to movement detection when compared to both the unaffected limb and control groups (Cuomo et al., 2005; Lee et al., 2010). One possible explanation may be due to the neglect-like symptoms associated with chronic pain (Frettlöh et al., 2006; Moseley et al.,

2012c). Alternatively, altered sensitivity to movement detection may be influenced by the increased stiffness and altered activation of the painful muscle (Lund et al., 1991; Hodges and Tucker, 2011; Jacobs et al., 2011). Similarly to the position sense literature, uncontrolled muscular contractions may influence movement detection threshold (Wise et al., 1998) by the muscles thixotropic properties. The importance of EMG or other measures to verify the state of the muscle during assessment is therefore critical.

2.2. Force discrimination and production

While the kinaesthetic senses enable us to determine the location of a limb even when the muscles are completely relaxed, the perception of heaviness, force and effort are generated – at least in part – by a central motor command (McCloskey et al., 1983). As a result, these sensations are generally accompanied by a muscular contraction. During such contractions, the perception of the associated descending motor command form a sensation of effort. At the periphery, it is likely that muscle spindle and Golgi tendon organs, well as cutaneous receptors, act as the principle receptors that signal the amount of tension at the muscle (Roland and Ladegaard-Pedersen, 1977; Proske and Gandevia, 2012). These receptors provide afferent feedback, which is compared to the efference copy—an internally generated signal of the motor outflow associated with the motor command (Wolpert et al., 1995). It is believed that a mismatch between the afferent information and the predicted sensory feedback is responsible for the perceived sensations of tension or force. However, additional receptors may be involved in the estimation of force (refer to Walsh et al., 2011), including muscle spindles (Luu et al., 2011).

Impaired perception and regulation of muscle tension has been implicated in chronic pain (Flor et al., 1992, 1999), particularly in individuals experiencing chronic tension headaches (Appelbaum et al., 1984), as well as pain in the neck, shoulder (Fowler and Kraft, 1974) and jaw regions (Flor et al., 1992). Hence, interest in this area is fuelled by the notion that relief can be brought about by relaxing the muscle. Indeed, studies have confirmed increased activity of the affected muscle using EMG (Lund et al., 1991; Jacobs et al., 2011), which can be resolved with biofeedback and training (Fowler and Kraft, 1974). When assessing tension and/or force awareness during both acute pain states (e.g., induced with hypertonic saline injections (Weerakkody et al., 2003a)) or chronic pain states (Flor et al., 1992, 1999), there is a consistent underestimation of the force generated by the painful muscle. An underestimation of tension by the affected muscle is consistent with the kinaesthetic data, suggesting a blunted awareness of feedback from the painful muscle, and may be involved in the long-term stiffening of muscles in the affected body part (Hodges and Tucker, 2011).

Inadequate regulation of muscle tension may not only contribute to the maintenance of chronic pain, but also influences force production (Lund et al., 1991). Descarreaux et al. (2004) examined isometric force production parameters in patients with chronic low back pain. Whilst the CLBP group performed similarly to controls overall, in terms of maximum voluntary contraction strength and variability, a subgroup within the pain group was identified as having a longer time to peak force production. Interestingly, this subgroup reported less pain during the time of testing, suggesting that the differences in motor strategy were adopted as a way of reducing the anticipated pain that may be elicited during the task. Hence, a psychological element, mediated by fear-avoidant behaviour (Vlaeyen and Linton, 2000), cannot be entirely excluded in these experiments.

It is believed that our sense of heaviness shares similar mechanisms to the sense of force, with the added component of dynamic muscle spindle signals (Luu et al., 2011; Proske and Gandevia, 2012). Interestingly, changes in limb weight as well as pain have

been reported by McCabe et al. (2005) during movements that conflicted with visual information. In this study, healthy participants were asked to report their sensory experience when performing a series of bilateral upper and lower limb movements. A sensory–motor conflict was imposed by obstructing the view of one limb using a whiteboard or mirror, whilst the seen limb performed asynchronous movements. It is conceivable that afferent signals may be involved in these experiences. However, an alternate hypothesis proposed by the authors is that the efferent copies, rather than a peripheral signal, may be responsible for these sensory anomalies. When similar experiments were performed with right brain-damaged individuals (Zampini et al., 2004), illusory movements of the paralysed left hand were only observed in patients with bodily disorders (i.e. neglect, anosognosia, disownership) upon viewing the mirror reflection of the moving right hand. Indeed, these findings suggest that illusory experiences occur in higher order, multimodal areas involved with the integration of sensory information, which may be prioritised depending on the task (Guerraz et al., 2012), to form a coherent body representation.

Other investigations relating to the perception of heaviness involve the size-weight illusion, in which the larger of two objects of equal weight is perceived as heavier. It has been proposed that the illusion is driven by the expectation of how something of a certain size should weigh (Buckingham and Goodale, 2013). This expectation presumably leads to a greater descending motor command when one attempts to lift the object (Jones, 1986). Other factors such as muscle stiffness (Koike et al., 2006) and perceived size (Linkenauger et al., 2011) of the limb involved in the task also play a role in the illusion. Future investigations into the size-weight illusion in chronic pain groups may prove fruitful, as both increases in muscle stiffness and alterations in perceived limb size have been reported in patients with chronic pain, and shed light on the role between motor commands and sensory feedback in the generation of pain.

2.3. Balance and postural assessments

The balance organs of the vestibular system, found in the inner ear, signal rotation and acceleration movements of the head. While it is believed to provide sensory input to body representations, particularly the body schema (Schwoebel and Coslett, 2005), it is also responsible for separating self-motion from non-self-motion, oculomotor control and automatic postural adjustments during tasks such as standing (Day and Fitzpatrick, 2005). The influence of pain, particularly chronic back pain, on postural stability has been studied extensively (for reviews see: Ruhe et al., 2011; Mazaheri et al., 2013). Ruhe et al. (2011) systematically reviewed the literature to determine whether patients with CLBP exhibit poorer balance compared to healthy controls. Of the 16 eligible studies, 14 showed that patients exhibited greater postural instability than healthy controls. More recently, however, Mazaheri et al. (2013) found great inconsistencies between studies, and were therefore unable to provide a definitive answer. They attributed these differences to the methodological approach employed by Ruhe et al. (2011), in which all experimental conditions were considered in determining an overall significant effect thereby increasing the likelihood of a type one error. Nevertheless, both reviews seem to agree that during quiet standing, without any experimental perturbation, patients with CLBP generally exhibit greater postural sway.

One explanation for an increased body sway in CLBP populations is that damage to sensory tissue in the lumbar spine, trunk or lower extremities leads to disturbed sensory feedback. However, there is growing evidence of a central origin in chronic back pain (Flor et al., 1997; Sipko and Kuczyński, 2013), relating to altered postural adjustment strategies (Moseley and Hodges, 2005; Popa et al., 2007; Tsao et al., 2008) and not to the descending

motor drive (Hodges, 2001). Recently, it was proposed that sensory feedback from the painful muscle is re-weighted, whereby more reliable signals coming from non-painful regions are given preference (Brumagne et al., 2000, 2004, 2008; Popa et al., 2007; Claeys et al., 2011). Similar findings have been reported in patients with muscle weakness who show an increased reliance on other sensory modalities, particularly vision, during quiet standing (Butler et al., 2008).

Another possible mechanism for postural instability in patients with chronic pain relates to the changes in motor planning and/or postural strategies in the presence of pain. It is known that EMG activation of the transverse abdominals (Hodges and Richardson, 1996) and external oblique muscles (Hodges, 2001) is delayed in the presence of low back pain during arm movements. Activation of these muscles is generated through feed-forward control, to counter perturbations and stabilise the spine prior to arm movements. A delayed transmission of a descending motor command (Hodges, 2001), or a disruption of normal postural control in the CNS (Moseley and Hodges, 2005), cannot adequately explain such changes in activation time. Rather it was thought that pain, or fear of pain, influences postural adjustments because the processing of pain information is given priority over other sensory inputs, termed “pain interference” (Crombez et al., 1996; Moseley and Hodges, 2005). For this to be true, the effect of pain on postural adjustments should be greatest at the onset of pain, habituate with repeated exposure, and be resolved immediately upon cessation of the painful stimulus. However, more recent investigations, involving noxious cutaneous electric stimulation in healthy individuals (Moseley and Hodges, 2005) and chronic low back pain (della Volpe et al., 2006), did not support such predictions. Instead, the authors concluded that the changes in postural adjustments are likely to reflect the adaptation of an alternate postural strategy. Whether such changes are a protective adaptation (Lund et al., 1991) or a dysfunction relating to the processing of proprioceptive information is still unclear.

3. Exteroception

Sherrington (1906) initially classified the special senses under three broad categories: tactile sensation, teleoreception (vision and audition) and chemoreception (olfaction and gustation). These senses are considered exteroceptive as they confer sensations arising from outside of the body, such as the valence of odours or the intensity of auditory stimuli. Their role in constructing the representation of the body is to define the boundaries of the organism with respect to its external environment. Hence, the implication is that a breakdown of these sensory systems compromises the integrity of the self.

3.1. Tactile sensation

The role of touch in the modulation of pain has long been recognised (Melzack and Wall, 1965). With respect to experimentally-induced pain, both external stimulation – applied via von Frey hair filaments (Mancini et al., 2014) – and self-touch (Kammers et al., 2010) have demonstrated analgesic effects in healthy subjects. Of particular interest are the results of the latter study by Kammers et al. (2010), who found that bringing together the hands under the thermal grill illusion weakened the heat sensation in the cool finger. In the traditional thermal grill illusion, a cool middle finger surrounded by warm outer fingers (index and ring fingers) feels painfully hot. Analgesia through self-touch may drive the anecdotal behaviour of clutching the painful hand with the other hand, thereby increasing a coherent cognitive body representation. The reinstatement of body representation through

self-touch has also been demonstrated in a case report involving a stroke patient with somatoparaphrenia, the denial of ownership of a limb (van Stralen et al., 2011). Interestingly, patients with chronic pain report a weakened heat sensation by the cool finger during the thermal grill illusion compared with pain-free controls (Sumracki et al., 2014). An altered central integration of ascending pain and temperature signals was concluded by the investigators, given that no significant difference was observed in thermal thresholds amongst the pain and pain-free groups.

Tactile responses are often assessed, in both the clinic and laboratory, by examining two-point discrimination threshold (Lotze and Moseley, 2007; Catley et al., 2013), with chronic pain populations showing impairments in discrimination (Moseley, 2008; Stanton et al., 2013). In such tasks, the jaws of a mechanical calliper are placed on the surface of the skin and spread apart gradually until the patient is able to discern two points, instead of one. Further, when asked to identify the location of the unseen tactile stimulus, patients with CPRS and CLBP commonly report the wrong location (Moseley et al., 2008c; Wand et al., 2013). Reduced tactile discrimination and mislocalisation have also been reported in the amputated limb in people suffering from phantom limb pain (Ramachandran et al., 1995; Flor et al., 2001; Ramachandran and Altschuler, 2009). Taken together, these studies demonstrate that increases in two-point detection discrimination are consistent with perceiving the painful limb to be larger (Moseley, 2005a, 2008). Such changes in body representation and tactile acuity have been linked with reorganisation of the primary somatosensory cortex (Ramachandran and Altschuler, 2009; Vartiainen et al., 2009; Haggard et al., 2013), and may be improved with training (Flor et al., 2001; Moseley et al., 2008c; Moseley and Wiech, 2009; Wand et al., 2011).

Further biases have been found by adjusting the relative time in tactile stimulus delivery. Such tasks, called temporal order judgements, examine perceptual latency by identifying a speeding-up (prioritisation) or slowing down (neglect) of neural processing. In those who experience chronic pain, for paired vibrotactile stimuli to be perceived as synchronous the stimulus needs to be delivered earlier at the site of pain—as if the stimulus is processed more slowly in the affected area (Moseley et al., 2012c). Emerging evidence from patients with CRPS and CLBP suggest that this effect is derived from a spatially-defined reference frame. That is, when the unaffected arm was placed over the body midline so that it was positioned in the space normally occupied by the affected arm and vice versa, a prioritisation of the affected arm was observed. The opposite response was seen when both limbs were uncrossed. Thus the effect appears to be related to the space in which the affected limb normally resides, not by the affected limb itself (Moseley et al., 2009). Comparisons have been drawn with observations in brain-damaged patients with spatial neglect (Moseley et al., 2012c), who display similar temporal biases (Rorden et al., 1997).

3.2. *Teleroception: Visual and auditory illusions, recognition and sensitivity*

Vision plays an important role in body representation. When we detect a noxious stimulus we cannot help but to look at where it hurts. Perhaps this is because seeing the painful body part reduces the intensity of acute pain (Longo et al., 2009) and allows us to more accurately localise pain. Indeed, visual analgesia may be mediated by somatosensory bodily representation (for a review, see Haggard et al., 2013). This effect can be enhanced by viewing an enlarged image of the limb experiencing heat pain (Mancini et al., 2011). Yet for patients with CRPS, pain is exacerbated when performing movements of the affected limb under magnification (Moseley et al., 2008b). As will be discussed, such discrepancies from visual

information may relate to differences in body representation between healthy and chronic pain groups.

Distortions in perceived limb size (Moseley, 2005a; Bultitude and Rafal, 2010), as well as changes to subjective body midline have also been observed in patients with chronic pain (Sumitani et al., 2007), supporting a role for higher order regulation of visual information when experiencing pain (Mancini et al., 2011). Indeed, Preston and Newport (2011) have demonstrated that visual manipulation of the perceived size of the affected limb can modulate the pain experience in osteoarthritis. Significant reductions in pain were reported when participants watched real-time video feedback of the arthritic hand being stretched or shrunk. This was done by producing virtual illusions, via a computer generated system called MIRAGE, which retains the same position and perspective of the hand as if viewed directly from the real hand. Light pulling and squeezing of the finger was also coupled with the visual illusion, which suggests involvement of the sensory–motor focused body schema, which receives information from visual, proprioceptive, auditory and vestibular sources.

Another method for investigating the body schema involves the recognition of body parts, which requires actively mapping visual sensations onto stored mental representations (Parsons, 2001; Longo et al., 2010). In chronic pain, the spatial recognition of the affected body part has received considerable attention. This is because the time to identify the orientation of a body part correlates with the time taken to position their own body part into that same posture (Parsons, 1987). Hence, limb laterality judgement tasks provide a measure of integration between visual information processing, working body schema and premotor processes (Hudson et al., 2006). In these tasks, participants make judgements as quickly as they can of whether images of hands or feet belong to the left or right side of the body. Consistent with neglect-like symptoms reported elsewhere (Frettloh et al., 2006; Lewis et al., 2010), patients with unilateral pain often take longer (Schwoebel et al., 2001) and are less accurate (Coslett et al., 2010) in performing the task when the pictured limb corresponds to their affected side. Likewise, the identification of left/right trunk rotation movements is also impaired in people with chronic back pain (Bray and Moseley, 2011; De Lussanet et al., 2012; Bowering et al., 2014). Lower-limb paraplegics, as a result of complete spinal section, also exhibit difficulty in recognising lower-limb movements (Pernigo et al., 2012). In contrast, when asymptomatic participants experience experimentally-induced acute pain, via hypertonic saline injections, they exhibit a longer response time to the *unaffected* hand (Hudson et al., 2006). This has been interpreted as either an attentional bias, in which the CNS has difficulty in allocating attentional resources away from the painful body part during acute pain, or that the working body schema of the painful limb becomes more accessible than the non-painful limb. This is yet another point of divergence between chronic and acute pain profiles.

Recent interventions involving the manipulation of visual-motor information have yielded analgesic effects for both phantom limb pain and CRPS patients (Ramachandran and Altschuler, 2009). Collectively, the use of mirror box therapy and prism adaptation have shown improvements in range of motion and function (Moseley, 2005b; Bultitude and Rafal, 2010), temporary relief from pain (McCabe et al., 2003; MacLachlan et al., 2004; Sumitani et al., 2008; Ramachandran and Altschuler, 2009; Bultitude and Rafal, 2010; Foell et al., 2014), reduction in swelling (Bultitude and Rafal, 2010), reversal of maladaptive brain changes (Foell et al., 2014), and restoration of subjective body mid-line (Bultitude and Rafal, 2010). Part of the success of these therapies is purportedly due to the re-establishment of sensory and motor feedback (Harris, 1999; Moseley and Gandevia, 2005; Flor et al., 2006; Swart et al., 2009), by coupling limb movements with visual feedback. As briefly

described earlier, movements that conflict with sensory information may result in pain (McCabe et al., 2005). Hence, pathological pain in parts of the body from which visual and proprioceptive feedback of movement are limited – for example, chronic back pain, cramping foot pain and phantom pain, each of which cannot be directly seen – may share similar origins (Harris, 1999). This idea is further supported by recent evidence of pain relief by providing site-specific visual feedback of the painful region (Wand et al., 2012; Diers et al., 2013).

The apparent weighting of visual information over proprioception and touch can also be utilised to generate illusions of ownership and embodiment (Holmes and Spence, 2005). When synchronous tactile stimulation is applied to an obscured hand and an adjacent rubber hand (which is in-view), the illusion of ownership over the rubber hand arises. Vision alone, however, is not the primary driver of this illusion, as Ehrsson et al. (2004) have shown using fMRI, that there is a shift in self-attribution in the premotor cortex and its associated areas. While the rubber hand illusion does not seem to affect pain threshold or intensity (Mohan et al., 2012), a full body version of the rubber hand illusion does generate increased pressure pain thresholds in healthy individuals (Hänsell et al., 2011). Hence a breakdown in self-attribution, mediated by visual input, may be associated with ongoing pain.

In regards to those who experience chronic pain, the rubber hand illusion has been successfully performed to reduce phantom limb pain in amputees (Ramachandran et al., 1995; Ehrsson et al., 2008; Giummarra et al., 2010) and patients with CRPS (Reinersmann et al., 2013). The strength of the illusion does not appear to be influenced by pain or motor impairment; nor does the illusion necessarily require synchronous tactile stimulation (Giummarra et al., 2010). Further, higher order multisensory integration appears to be unaffected (Reinersmann et al., 2013), but may help to reinforce the strength of the illusion when the motor system is engaged – through the voluntary or involuntary execution of motor schemata – when the rubber hand is threatened (Giummarra et al., 2010).

Finally, there is evidence that patients with chronic pain have a lower noise tolerance and prefer lower levels of external stimulation (McDermid et al., 1996; Wilbarger and Cook, 2011). This is not surprising considering the degree of overlap between nociceptive, somatosensory, visual and auditory brain regions (Mouraux et al., 2011; Haggard et al., 2013). An auditory-evoked potential study in fibromyalgia patients found significant differences in N1 and P2 latencies, particularly at louder intensities, suggesting that deficits in an inhibitory system protecting against overstimulation may be a crucial factor in fibromyalgia (Carrillo-de-la-Pena et al., 2006). A significant correlation between sound and pressure sensitivity has also been demonstrated in both control and patient groups (Geisser et al., 2008). These findings have two key implications. First, the underlying mechanism may be due to a global disturbance in sensory processing. Second, improvement in one sensory modality, such as touch sensitivity may influence another. However, at present, experimental and psychophysical findings are largely restricted to patients with fibromyalgia. A broader scope that is inclusive of other chronic pain disorders may aid in the understanding of the mechanisms that lead to increased sensitivity in relation to chronic pain. Moreover, whilst some have attributed such characteristics to hypervigilance (McDermid et al., 1996), aversions to loud noises and sensory-rich environments is reminiscent of Dunn's model of sensory processing (Dunn, 1997), in which sensory thresholds influence behaviour. Such ideas are only speculative at this stage, as this model has not been applied to patients with chronic pain, but may have the potential of identifying populations of people who are "at-risk" of developing chronic pain disorders (Alterio, 2008).

3.3. Chemoreception: Gustatory and olfactory stimulation

The systems of nociception, gustation and olfaction share a fundamental evolutionary role in alerting an individual to threatening, noxious or toxic stimuli. There is, consequently, considerable overlap in brain regions involved in processing pain, taste and smell; namely, the insula cortex, anterior cingulate cortex, amygdala and orbitofrontal cortex (Small and Apkarian, 2006; Villemure et al., 2006). Despite these overlaps, few studies have explored multi-sensory interactions between these systems and their implications for understanding and treating pain.

Whilst somewhat intuitive, empirical evidence is only now emerging in support of gustation in the modulation of pain (Bastian et al., 2014). It is known that increased bitter taste sensitivity is correlated with increased intensity pain during propofol injections (Erden et al., 2007), while sweet oral solutions have shown analgesic efficacy in neonates (Johnston et al., 2011). In relation to chronic pain, there is a higher prevalence of self-reported taste disturbances in patients with temporomandibular disorder (Nixdorf et al., 2009), such as a reduced impression of flavour. For individuals with CLBP, studies have reported an increased sensitivity to bitter tastes (Small and Apkarian, 2006) and a blunting of hedonic sensation to highly palatable foods (Geha et al., 2014). Interestingly, it may be that this effect is reciprocal. In other words, pain does not only influence taste, but certain tastes may evoke pain, at least for some neuropathic pain patients (Scrivani et al., 1998). Recently, Bastian et al. (2014) demonstrated that the removal of acute painful stimuli, involving a modified version of the cold-pressor task, may serve to enhance the capacity for gustatory pleasure. Whilst they do not exclude the possible role of the opioid system and/or associative learning, it is argued that the body remains vigilant after exposure to pain—thereby maintaining increased arousal. Collectively, these studies concerning pain and gustation demonstrate that one system is able to modulate the sensory experience of the other.

Similar to taste, researchers have explored the role of hedonic states in olfaction and pain perception by specifically examining the associated mood changes brought on by the valence of certain odours. However, this is complicated by the fact that any change to pain perception from mood could, in fact, originate from alterations in attention (Villemure et al., 2003), or even attention to pain (Keogh et al., 2001). Indeed, attending to pain not only increased pain unpleasantness and intensity (Villemure et al., 2003), but also influenced sensitivity in other domains, such as touch (Vanden Bulcke et al., 2013). Nevertheless, it has been shown that patients with fibromyalgia present with greater sensitivity to unpleasant odours (Schweinhart et al., 2008), whilst the smell of certain foods may also trigger pain in patients with gustatory neuralgia (Scrivani et al., 1998). Further, a fMRI study has shown increased activation following unpleasant odours in several pain-related brain regions in a patient with neuropathic pain who reported that odours exacerbated his pain (Villemure et al., 2006). Whilst the literature surrounding body representation and olfaction remains scarce, there is emerging evidence that humans have the ability to distinguish their own major histocompatibility complex peptides from those of others based on body odour (Milinski et al., 2013). Such findings have been implicated in the selection of potential mating partners (Wedekind et al., 1995), as well as recognition of kin (Blaustein, 1983), supporting a role for olfaction in establishing identity. Considering the shared neurocircuitry between processing odours, taste, emotion and pain, there are considerable therapeutic implications for pain treatment by targeting the gustatory or olfactory systems (Scrivani et al., 1998; Nixdorf et al., 2009; Bastian et al., 2014). However for this to occur, the mechanisms of how taste, smell and mood may influence body representation need to be elucidated.

4. Interoception

This review has so far focused on the sensory systems involved in detecting where the body is and what it is doing (proprioception and exteroception), rather than how it is *feeling*. Interoception, the sense of the physiological condition of the body, has broadened substantially from how Sherrington (1906) initially envisioned it, which was restricted to visceral sensations. This broadening is based on emerging evidence that small diameter afferents project to autonomic and homeostatic centres of the spinal cord and brainstem, which are then relayed to the ACC and dorsal posterior insula (Craig, 2002–2004). This relaying of information is due to the thalamo-cortical extension that provides a direct pathway to the insular cortex. As the afferents include both Aδ and C fibres, the implication is that feelings of pain, temperature and itchiness are distinct from the exteroceptive sense of touch. Since the discovery of a cortical representation of homeostatic afferent activity, researchers have only recently begun exploring the role of interoceptive awareness – the discrimination of perceived changes in physiological sensations – in pain disorders.

4.1. Autonomic awareness and regulation

Quantification of interoceptive sensitivity has predominantly focused on sensitivity to cardiac activity; largely on the basis that heart rate is a non-invasive measure of autonomic arousal and assessment of internal bodily sensations. During assessment with validated techniques such as the Schandry mental tracking method (Schandry, 1981), participants are instructed to count the number of heartbeats under different length intervals, without feeling their pulse. A sensitivity score, which is calculated from the actual and reported number of heartbeats, is expressed as either a percentage error or dichotomous score of high versus low perceivers (Domschke et al., 2010). Recent work by Tsakiris et al. (2011) have provided the first direct evidence that interoceptive awareness can modulate the exteroceptive representation of the body. When factors such as proprioceptive awareness, autonomic body-state and body image satisfaction were controlled for, individuals with low interoceptive sensitivity were found to be more susceptible to the rubber hand illusion. This is perhaps because those with low interoceptive awareness may rely more on exteroceptive signals for the monitoring of bodily state. In other words, it may be that visual and tactile information is weighted above internal bodily sensations in individuals with low interoceptive sensitivity. At present, there is a distinct lack of studies investigating heartbeat awareness in people with chronic pain. However, evidence from experimentally-induced acute pain show both an enhanced sensitivity and decrease tolerance to pain in those with high interoceptive sensitivity (Pollatos et al., 2012). Given that interoception is associated with both the tolerability of pain and the modulation of exteroceptive representations, there is considerable scope and value for future research in this area.

Recording the patient's resting heart rate also allows for the examination of heart rate variability (HRV), by calculating the time variations between consecutive heartbeats. HRV can provide insight into the adaptability of the autonomic nervous system to stress (Appelhans and Luecken, 2008). Whilst HRV may not directly require the participant to attend to their bodily state, the autonomic nervous system is responsible for maintaining a range of vital and involuntary physiological parameters – such as blood pressure, temperature and heart rate – which may be implicated in the pathogenesis of some chronic pain disorders (Meeus et al., 2013). In addition, HRV provides a measure of sympathetic and parasympathetic activity, as well as a potential marker for deficits in self-regulation. HRV has been extensively investigated in a range

of chronic pain disorders, such as CLBP (Gockel et al., 2008), chronic neck–shoulder pain (Hallman et al., 2011, 2014), fibromyalgia (Mostoufi et al., 2012), CRPS (Terkelsen et al., 2012), and phantom limb pain (Sarabia Cachadiña et al., 2013). Collectively, these studies unanimously support autonomic dysregulation in pain populations, reflected by increased resting heart rate and reduced HRV. In addition, HRV has been linked with perceived physical impairment (Gockel et al., 2008; Mostoufi et al., 2012) and lower physical activity during leisure time (Hallman et al., 2014) in patients with chronic pain. Because low HRV is associated with a plethora of other poor health outcomes (for a review, see Appelhans and Luecken, 2006), characterising its role in chronic pain, particularly whether these changes in autonomic function are a cause or consequence of chronic pain and whether they are amenable to change with successful analgesic intervention, is of great benefit in improving health outcomes and quality of life.

4.2. Spatiality influences ownership and thermoregulation

Other autonomic changes have been observed in chronic pain disorders. In unilateral CRPS, patients exhibit disturbances in temperature, colour, swelling and even abnormal hair and nail growth, between the painful and non-painful limbs (McCabe and Blake, 2008). The work by Moseley et al. (2008a) have demonstrated that temperature regulation can be altered by disrupting the sense of ownership in healthy individuals. Inducing ownership over an artificial hand, via the rubber hand illusion, caused a specific cooling in the experimental hand compared to the control hand. Importantly, the cooling occurs once the illusion takes effect in healthy individuals (Moseley et al., 2012b), implying that as the ownership of one's own limb decreases, so too does the homeostatic control and sensory processing of the relevant areas. Such results demonstrate striking similarities in CRPS patients, who often feel that their painful limb does not belong to them (Galer and Jensen, 1999; Lewis et al., 2010) and that the painful hand is cooler than the non-affected hand (Moseley et al., 2012a). However, more recent investigations by the same group found that spatial perception was responsible for the modulation of ownership and other neglect-like symptoms in patients with unilateral upper limb CRPS (Moseley et al., 2012a). Infrared thermal imaging was employed in a series of experiments to show that crossing the hands over the body's midline led to temperature changes. That is, when both hands were crossed, the affected hand became $0.4 \pm 0.3^\circ\text{C}$ warmer while the healthy hand became $0.3 \pm 0.3^\circ\text{C}$ cooler. In addition, significant improvements in tactile processing, increased sense of ownership and reduced pain were observed in the affected hand when it was placed in the body space of the unaffected hand. The analgesic effects of 'hand crossing' have also been confirmed by Torta et al. (2013) using fMRI of healthy individuals, who rated perceived pain intensity of mechanical pain applied to their hands. Significant reductions in pain intensity and greater activation of the anterior cingulate cortex, insular and prefrontal cortices were observed during the crossed-hands condition, and greater activation in the superior parietal lobe when both hands were uncrossed. Remarkably, such effects may be mediated by the *perceived* location of the limb, rather than its actual location (Moseley et al., 2013), as similar temperature changes were demonstrated when patients with CRPS wore prism glasses that laterally shifted the visual field by 20° and gave the impression that the affected limb was on the healthy side of the body midline. Such findings highlight the role of spatial processing, and more broadly the contribution of body-centred reference frames, as a mediator for several symptoms exhibited in CRPS. Perhaps these findings could be extended to unilateral CLBP patients, who also demonstrate neglect-like symptoms (Moseley et al., 2012c)?

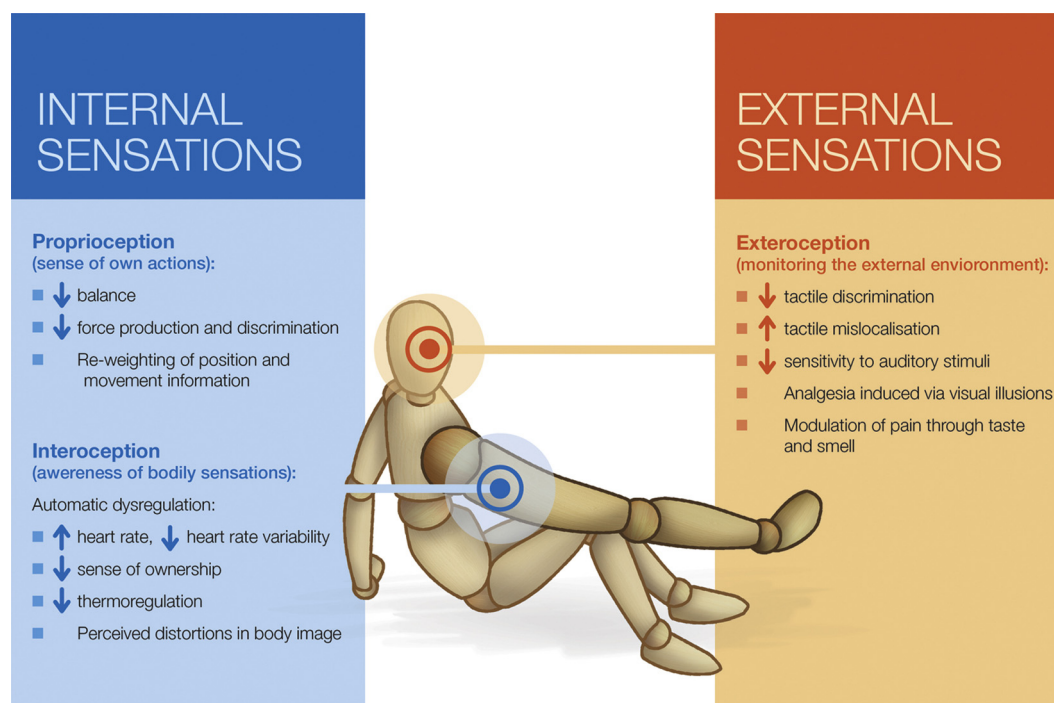


Fig. 1. Summary of the disturbances to the proprioceptive, exteroceptive and interoceptive systems in chronic pain conditions. While these systems are discussed separately, for the purposes of this review, it is emphasised that there exists considerable overlap between these systems. Here, the *painful* right arm is drawn abnormally large compared to the rest of the body figure, as commonly reported by people with chronic pain.

4.3. Pain and body drawings

Clinicians and researchers alike have long since acknowledged the need for a method whereby the state of pain is captured in such a way that accurately conveys pain as experienced by the patient. Attempts at devising such methods have largely taken the form of pain drawings and, more recently, drawings of the mental representation of the body. Pain drawings have been in clinical use since the 1940s (Keele, 1948; Palmer, 1949) and were later incorporated in notable self-reporting pain questionnaires, such as the Brief Pain Inventory (Cleeland and Ryan, 1994) and McGill Pain Questionnaire (Melzack, 1975). When completing these questionnaires, patients are provided with an outline of a human figure and instructed to shade and/or mark the painful area. Perhaps the biggest advantage of pain drawings are their ability to highlight differences in pain location across different pain conditions for comparison (Almay, 1987; Mannion et al., 2007), as well as exploring the lateralising effects of chronic pain (Margolis et al., 1985; Löfvander et al., 2007). Whilst the technique has demonstrated high test–retest reliability (Margolis et al., 1988; Ohnmeiss, 2000), the qualitative nature of such tasks ultimately leads to the question of what is actually being measured (Margolis et al., 1986; Parker et al., 1995). Depending on the scoring method, pain drawings have been used as a measure of psychological distress (Ginzburg et al., 1988; Parker et al., 1995; Ektor-Andersen et al., 1999), a differentiator between organic and non-organic pain (Ransford et al., 1976), and as a measure of disability (Toomey et al., 1991) in patients with chronic pain.

In more recent times, pain drawings have been modified by instructing the patient to draw the mental representation of their body as it feels to them. This may be done with a partially filled outline (Moseley, 2008) or even a blank sheet of paper (Gandevia and Phegan, 1999; Lewis et al., 2010). Hence, these drawings differ from those described earlier, as they are used to depict the body image, the way a person's body feels to them (Lotze and Moseley, 2007), rather than providing a topographic map of pain location. In

patients with CLBP, decreased tactile acuity, assessed by two-point discrimination, coincided with gaps left in the outline of the body drawings (Moseley, 2008). Whilst distorted body drawings – such as missing segments, changes in size, and telescoping of the limb – have also been reported in patients with CRPS (Lewis et al., 2007, 2010) and phantom limb pain (Melzack, 1990), the likelihood of identifying a distortion will ultimately depend on how this data is analysed. Several approaches have been implemented for both types of drawings, ranging from grading the degree of distortion in the body figure (Lewis et al., 2010) to more sophisticated methods involving computation of total number of marks, length of longest mark, symmetry and total area (Margolis et al., 1986; Wenngren and Stålnacke, 2009; Egloff et al., 2012). Because of such analytical differences, it is difficult to draw comparative conclusions until a more standardised scoring method is introduced.

It should be acknowledged that body drawing tasks are limited by the individuals' ability to adequately capture and draw the distortion in body image. However, the advent of new digital 3D modelling tools may lead to a shift from traditional paper-form drawings. Recently, Turton et al. (2013) developed software that allowed users to digitally manipulate bodily segments on a virtual body figure. Consistent with the literature, distortions in size, position, surface texture and the absence of body segments were demonstrated when this technique was applied to a sample of patients with CRPS. Importantly, all patients reported a high level of satisfaction of the program as a method for communicating the perception of their body to clinicians. As one patient describes "it [digital modelling tool] makes you see how distorted your vision of your body is..." (Turton et al., 2013, pp. 5).

A quantitative alternative for the investigation of body image involves the use of templates, in which participants select the image or photograph of a body part that best represented their own corresponding body part (Gandevia and Phegan, 1999; Longo and Haggard, 2012; Fuentes et al., 2013). When applied to CRPS, the results are consistent with a perceived enlargement of the painful limb (Moseley, 2005a). Indeed the template method is better suited

when changes in the apparent size of the limb is being investigated and have limited applications during the study of more subjective disruptions to the body image. While the variations in the scoring of body drawings remain a hurdle, such psychophysical tasks are encouraged in future investigations as they provide a rare insight into distorted body representation as felt by the patient.

5. Conclusion

In summary, we have given an overview of the literature that implicates distorted mental body representation in the presence of chronic and persistent pain (Fig. 1). As body representations are largely derived and generated from sensory information, one possibility is that altered sensory signalling – relating to the sensory organ for instance – may be the cause for the distortion. However, a peripheral mechanism seems unlikely given that multiple sensory modalities are potentially affected in chronic pain disorders. Given what is already known in regards to pathological cortical reorganisation (Moseley et al., 2012b) and reweighting of sensory information (Claeys et al., 2011; Willigenburg et al., 2013) in these patients, a disruption of the body map may influence each sensory modality, albeit perhaps not equally. The body schema is the most likely candidate, as it has been shown to be affected by pain (Schwoebel et al., 2001); however, this is not at the exclusion of other body representations. While neuroimaging techniques have spearheaded the recent advances in neuroscience, how central disturbances affect the day to day functioning of individual patients can only be assessed through psychophysical methods. This approach should be utilised in the future for investigating the interaction between the proprioceptive, exteroceptive and interoceptive systems, as it still remains unclear how these systems work together to form a coherent and integrated body map. Finally, definitive conclusions cannot be reached with respect to the causal relationship between pain and distorted body representation, as prospective studies are scarce. However, the work by Bultitude and Rafal (2010) suggest that pain is a consequence of distorted body representation. Such findings are promising and present an avenue for future research, that takes into account a multisensory and multimodal approach to therapeutic treatment of chronic pain disorders.

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CHAPTER 7: POSITION SENSE IN CHRONIC PAIN

Tsay, A.J. and M.J. Giummarra (2016). "Position sense in chronic pain: Separating peripheral and central mechanisms in proprioception in unilateral limb pain." J Pain. **17**(7): 815-823.

7.1 Explanatory Notes

As highlighted in Chapter six (Tsay et al., 2015), it is possible that persons with chronic pain experience disturbances in proprioception. Hence, Chapter seven (Tsay & Giummarra, 2016) was undertaken to examine whether position errors were altered in persons with chronic pain.

This was the first study to use thixotropic muscle conditioning to manipulate muscle spindle activity in individuals with chronic pain. Previous investigations on limb position sense in chronic pain did not control for the thixotropic behaviour of the muscle spindle receptor possibly leading to conflicting results and interpretations (Brumagne et al., 2000; Asell et al., 2006; Paulus & Brumagne, 2008; Lewis et al., 2010; Tsay et al., 2015). Therefore, it was unclear whether disturbances to position sense in chronic pain occurred at the level of the muscle spindles, or in higher-order brain regions.

The study found similar matching errors when the painful arm was the reference (being matched to) or the indicator arm (positioned to match the reference arm). Further, no group differences were found amongst pain and non-pain groups in either matching or pointing tasks, under various conditioning methods. This suggests that the proprioceptive signals from the painful and non-painful arm contribute equally in limb matching.

A lay summary of the paper was also published on BodyinMind.org, a clinical pain science blog developed by Prof Lorimer Moseley. The article received considerable attention on social media websites, receiving 92 likes and 49 shares on Facebook within the first 48 hours of publication. The manuscript is attached in [Appendix 2](#).

7.2 Declaration for Thesis Chapter Seven

Declaration by candidate

In the case of Chapter seven, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
The candidate generated the experimental question, designed the experiments, collected and analysed the data, and wrote the paper with guidance and feedback from the co-author.	80

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Melita Giummarra	Co-design of study, discussion of findings, data analysis, editing of paper.	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work.

**Candidate's
Signature**



Date

25/08/16

**Main
Supervisor's
Signature**



Date

25/08/16



Position Sense in Chronic Pain: Separating Peripheral and Central Mechanisms in Proprioception in Unilateral Limb Pain

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Abstract: Awareness of limb position is derived primarily from muscle spindles and higher-order body representations. Although chronic pain appears to be associated with motor and proprioceptive disturbances, it is not clear if this is due to disturbances in position sense, muscle spindle function, or central representations of the body. This study examined position sense errors, as an indicator of spindle function, in participants with unilateral chronic limb pain. The sample included 15 individuals with upper limb pain, 15 with lower limb pain, and 15 sex- and age-matched pain-free control participants. A 2-limb forearm matching task in blindfolded participants, and a single-limb pointer task, with the reference limb hidden from view, was used to assess forearm position sense. Position sense was determined after muscle contraction or stretch, intended to induce a high or low spindle activity in the painful and nonpainful limbs, respectively. Unilateral upper and lower limb chronic pain groups produced position errors comparable with healthy control participants for position matching and pointer tasks. The results indicate that the painful and nonpainful limb are involved in limb-matching. Lateralized pain, whether in the arm or leg, does not influence forearm position sense.

Perspective: Painful and nonpainful limbs are involved in bilateral limb-matching. Muscle spindle function appears to be preserved in the presence of chronic pain.

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Key words: Position sense, chronic pain, muscle spindles, proprioception, thixotropy.

The sense of limb position allows us to determine where our limbs are in space when we are not looking at them. This information is primarily derived from muscle spindles, which are stretch receptors that signal length changes imposed on the muscle. Spindles also play a role in motor control, reflexively regulating muscle tension and providing input to body representations in the brain, especially body schemata.⁵² These factors, collectively, appear to be disturbed in patients with chronic pain (for a review, see Tsay et al.⁵⁹).^{2,21,34}

However, the role of muscle spindles in proprioceptive disturbances associated with chronic pain remains unclear.

Although there is evidence of reduced position sense acuity in persons with chronic pain,^{4,7,13,18,26,31,45,46,49,50,56} others have reported no such differences between persons with chronic pain and pain-free control participants.^{1,8,9,28,29,39,44} The aforementioned studies used a repositioning task, in which participants reproduce a previously remembered postural position. In contrast, the present study examined the role of simultaneous afferent information to make positional judgements by manipulating the thixotropic properties of the muscle.^{53,54,59}

The background firing rate in spindles is dependent on the preceding contraction and length changes of the muscle fiber.⁵³ Thixotropic behavior occurs with the formation of stable cross-bridges between actin and myosin when the muscle relaxes after a contraction. Shortening the muscle introduces slack into the sensory ending of spindles, decreasing the spindle discharge. Because the

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length of the muscle is signaled by muscle spindle activity, manipulating its sensitivity to stretch can lead to reproducible errors in perceived limb position.⁵⁴ Previous studies investigating proprioception in chronic pain have not controlled for the thixotropic properties of muscles. Therefore, it is unclear whether disturbances to position sense in persons with chronic pain occur at the level of the muscle spindles,^{2,25} or in higher-order brain regions involved in motor control or body representation.^{19,40}

Our group has developed a simple, noninvasive method of conditioning a muscle, on the basis of recordings of spindle discharges¹⁵ and on measurements of position sense.^{52-54,61} In the present study, we assessed position sense after thixotropic muscle conditioning, to determine whether this led to position errors consistent with an alteration in spindle function in the presence of chronic unilateral limb pain. If proprioceptive disturbance in chronic pain is due to altered activity in, or processing of, spindle discharge, participants with unilateral upper limb pain would be expected to show forearm matching errors that could not be explained by spindle discharge. Because spindles seem to play less of a role in pointing tasks,⁶⁰ differences in pointing errors between pain and control groups would suggest altered reference maps from body schemata or exteroceptive cues in position sense.⁵¹ Finally, disruptions to body schemata seem to generalize to the affected side of the body,⁵⁷ reflecting higher-order neuroplastic changes across the body midline.⁴¹⁻⁴³ Therefore, we expected participants with lower limb pain would show deficits in pointing to the forearm on the affected side of the body, however, the role of spindle signals would remain unaffected. These findings may shed light on the source of motor dysfunctions observed in chronic pain disorders.

Methods

Participants

Forty-five volunteers participated in the study, including 15 with unilateral upper limb pain, 15 with unilateral lower limb pain, and 15 pain-free control participants. Participants were recruited from Caulfield Pain Management and Research Centre, and the general community. Inclusion criteria for the patient groups included: 18 to 65 years of age, having experienced pain more days than not for at least 3 months, experiencing pain that was localized to 1 arm or leg, and having no history of diabetes. Although a wide range of chronic pain etiologies were accepted, we excluded those with pain caused by inflammation, such as arthritis, or fibromyalgia, which is generally experienced as a diffuse pain affecting multiple body regions. Table 1 lists the demographic and clinical characteristics for each group. The pain groups were matched for sex, age, duration of pain, average pain intensity, pain interference, and kinesiophobia (Tampa Scale of Kinesiophobia) scores. However, the upper limb pain group reported higher pain severity (on the Brief Pain Inventory) on average than the lower-limb pain group. All Depression, Anxiety, and Stress Scale (DASS) subscale scores were significantly higher in the pain

groups compared with healthy control participants, confirmed using the Bonferroni post hoc test ($P < .01$). The study was approved by the Alfred Health and Monash University Human Research Ethics Committees. All participants gave written informed consent and were financially reimbursed for their time.

Materials and Procedure

Forearm position sense was assessed in the vertical plane using 2 tasks, which have been described in detail elsewhere.⁶⁰ For the matching task, the blindfolded participant sat at a table with the upper arms on horizontal supports (allowing shoulder muscles to be relaxed), and both forearms placed on lightweight paddles in a custom-built apparatus. Velcro straps (5 cm in width) were wrapped just below the crease of the wrist with the palms supinated. Participants were asked if the tension in the 2 wrist straps felt the same, and adjusted as instructed by the participant to minimize potential differences in skin sensations between the 2 arms. One arm was designated the reference arm (the arm placed at the test angle by the experimenter) and the other was the indicator arm (the arm moved by the participant to match the position of the reference arm). The reference arm was passively moved by the experimenter to the test angle, which ranged from 40° to 50° to the horizon. In all conditions, unless stated otherwise, the painful limb or side was assigned as the reference. For the control group, the reference arm was randomly assigned to minimize biases arising from arm dominance.¹⁴

For the pointer task, only the reference arm remained strapped to the paddle, which was hidden from view by a screen. Unlike the matching task, participants had full view of the contralateral paddle, designated the indicator. Participants could maneuver the indicator paddle to the perceived angle of the reference arm by pushing a lever downward, which was attached to the indicator paddle. They were given the instruction to "show me where your arm is with the paddle."

Potentiometers (25 k Ω ; Spectra Symbol Corp, Salt Lake City, UT) located at the hinges of each paddle were used to measure the angle at the elbow joint. The potentiometers provided a continuous voltage output proportional to the angle of each paddle, a reading of 0° indicated the forearm lay horizontal, and 90° referred to a forearm in the vertical position. Correct calibration of the potentiometers was checked before each experiment.

Position error was calculated between the 2 paddles using the formula:

$$\text{Position error (}^\circ\text{)} = \text{reference angle (}^\circ\text{)} - \text{indicator angle (}^\circ\text{)}$$

Hence, a positive value meant that the indicator was placed in a more extended position than the reference arm. Conversely, where the indicator was placed in a more flexed position, relative to the reference arm, a negative value was assigned.

Muscle Conditioning

Before each trial, the elbow muscles were conditioned to place them into a defined thixotropic state, using

Table 1. Demographic Characteristics and Pain Profile of Participants

	UPPER LIMB PAIN	LOWER LIMB PAIN	CONTROL PARTICIPANTS	P
Sex, male:female	8:7	6:9	5:10	
Mean age \pm SD, y	38.4 \pm 16.5	34.0 \pm 14.3	36.3 \pm 10.9	
Affected side, left:right	6:9	9:6		
Etiology, %				
Fracture	27	27		
CRPS	6	7		
Muscular/tendon	20	26		
Unknown/other	47	40		
Mean pain duration \pm SD, y	6.1 \pm 4.9	4.6 \pm 3.6		
Mean average pain score \pm SD (scale of 0–10)	7.1 \pm 2.4	5.6 \pm 1.5		
Mean BPI severity \pm SD	6.4 \pm 2.2	4.9 \pm 1.7*		.04
Mean BPI interference \pm SD	3.9 \pm 2.7	3.8 \pm 2.3		
Mean TSK \pm SD	34.4 \pm 5.3	37.1 \pm 6.4		
Mean DASS: depression score \pm SD	10.4 \pm 9.7	11.7 \pm 9.0*	1.1 \pm 2.6*	.00
Mean DASS: anxiety score \pm SD	9.7 \pm 7.0	10.9 \pm 10.4*	1.7 \pm 2.4*	.00
Mean DASS: stress score \pm SD	16.0 \pm 8.6	18.9 \pm 8.0*	3.2 \pm 3.3*	.00

Abbreviations: CRPS, chronic regional pain syndrome; BPI, Brief Pain Inventory; TSK, Tampa Scale of Kinesiophobia.

*Indicates significant differences tested using 1-way ANOVA, Bonferroni post hoc, compared with the upper limb pain group.

either a muscle contraction with or without a subsequent stretch. The thixotropic properties arise in a muscle when stable cross-bridges form between actin and myosin filaments in a passive muscle.⁵⁴ This produces tension in the muscle fibers, when contracted at a short muscle length. When the fiber is stretched to a longer length, this raises passive tension further leading to an increase in the background activity. Spindle discharge rates can also be decreased by allowing cross-bridges to be formed when the muscle is held at a long length and later the muscle is brought to a shorter length introducing slack in the muscle fibers.^{15,16}

Two muscle conditioning techniques were performed in this study. The first, flexion conditioning, involved a contraction of the elbow flexors with both arms locked in the vertical position (90°). Participants were instructed to contract with half of their maximal strength. This procedure altered the mechanical state of the elbow flexors in the arms, leaving them taut while slackening the elbow extensors during the matching task.^{54,58} This increases the resting spindle discharge of the elbow flexors.

The second type of muscle conditioning, flexion conditioning and stretch, similarly, involved flexion conditioning of both arms in the vertical position. However, the indicator arm was then passively moved, by the experimenter, to the horizontal position (approximately 0°), thereby stretching the elbow flexors in that arm only to induce asymmetrical spindle signals in each arm. The participant was instructed to rest in that position for 6 seconds, allowing for sufficient time for the formation of stable cross-bridges.³⁸ The reference arm was then moved, by the experimenter, to the test angle, before participants were asked to match the position of the arms. Because the cross-bridges in the indicator arm had formed at a long length, the movement to the test angle by the subject slackened the muscles in the elbow flexors, producing a low resting discharge rate in the muscle spindles. For the single-limb pointer task, only

the reference arm was conditioned. Participants performed 3 trials in each condition, to limit the number of conditioning contractions performed by the painful limb.

To prevent inadvertent muscular contractions, muscle activity of the reference arm was continuously measured and monitored by the experimenter using surface electromyogram (EMG). A pair of Ag-AgCl electrodes with an adhesive base and solid gel contact points (AD Instruments, Castle Hill, New South Wales, Australia) were placed approximately 2.5 cm apart over the surface of the biceps brachii and triceps brachii. A grounding electrode was placed on the collar bone. EMG output was connected to an audio amplifier for biofeedback, producing noise during a muscular contraction. The conditioning contraction was repeated where inadvertent muscle contractions were performed. Position, force, and EMG signals were acquired at 40 Hz using MacLab 4/s data acquisition module running Chart software (AD Instruments) on a Macintosh computer.

Questionnaires

Pain was evaluated using the short-form Brief Pain Inventory,⁵ which profiles a measure of pain severity and interference of pain on daily functions (Table 1). Beliefs, attitudes, and fear of exacerbating pain through movement were measured using the Tampa Scale of Kinesiophobia.³⁷ The short form, 21-item DASS was used to assess mood profiles.³⁵

Statistical Analysis

Statistical tests were performed using SPSS 23 (SPSS, Chicago, IL) with significance at $\alpha = .05$, and all data are reported as mean \pm standard error of the mean. One-way analysis of variance (ANOVA) was used to compare group characteristics, including age, sex, and DASS scores. For the primary outcome of position error, differences between pain groups (upper limb pain/lower

limb pain) were examined with mixed model repeated measures ANOVA with the within subjects factor of limb-side (ie, reference limb: painful side/pain-free side), with a separate ANOVA testing each conditioning method (flexion/flexion and stretch). Because position error did not differ with respect to limb-side, separate univariate ANOVAs then tested differences between groups (upper limb pain/lower limb pain/pain-free control) for position errors in each conditioning method, with the dependent variable collapsed across limb side. One-sample t-tests were used to confirm that position errors for each conditioning method differed significantly from 0. The same analytic approach was applied to the pointing task. Finally, a comparison of position errors between the pointing and matching tasks (flexion conditioning task only) was done using an ANOVA between groups (upper limb pain/lower limb pain) and across limbs (ie, reference limb: painful side/pain-free side). For all ANOVAs the assumption of sphericity was not violated and no corrections were applied to the degrees of freedom. Bonferroni test was used for post hoc analyses.

Results

Matching Trials After Bilateral Flexion Conditioning

Participants performed a flexion contraction in both arms before matching the position of their forearms. Typically, when conditioned in this way, the indicator arm is matched in a slightly more flexed posture relative to the reference arm.^{54,61} That is, errors fall below the 0 line (Fig 1). A mixed model ANOVA comprising the pain group (upper limb pain/lower limb pain) and limb side (ie, when the painful limb or side acted as the refer-

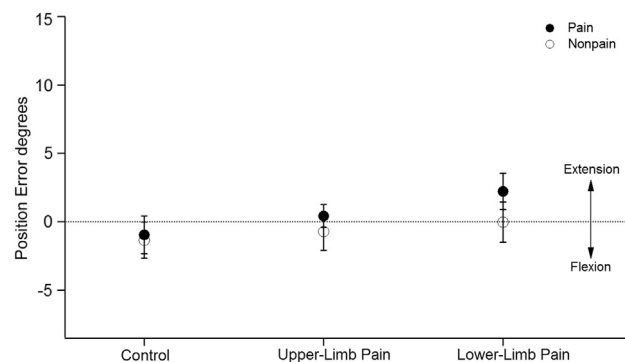


Figure 1. Matching errors after bilateral flexion conditioning. Errors (mean \pm standard error of the mean) are shown for 45 participants. Blindfolded participants performed approximately 50% maximum voluntary contractions in both elbow flexor muscles before declaring a match. The filled circles show matching errors when the painful arm, or side (as was the case for the lower-limb group), acted as the reference arm. In another trial, the nonpainful arm acted as the reference arm, which was matched with the contralateral, painful indicator arm, shown in the open circles. For the control group, the reference arm was randomly assigned. The zero line indicates a perfect match. In repeated measures ANOVA no significant differences across groups in both trials were found ($P > .05$).

ence or indicator arm), did not show a main effect for limb side on matching errors ($F_{1,28} = .81$, $P = .38$, partial eta squared (η_p^2) = .03), nor was there a difference between those with upper limb pain or lower limb pain ($F_{1,28} = .29$, $P = .59$, $\eta_p^2 = .01$, Table 2). The univariate ANOVA showed that there was also no difference in matching errors between participants with upper limb pain ($.43^\circ \pm .84^\circ$), lower limb pain ($2.22^\circ \pm 1.33^\circ$), or pain-free control participants ($-.95^\circ \pm 1.39^\circ$) when indicating perceived forearm location ($F_{2,42} = 1.73$, $P = .19$, $\eta_p^2 = .08$). Thus, participants with chronic unilateral pain did not show significant differences in position error, compared with pain-free control participants, when both arms were flexion conditioned.

Matching Trials After Asymmetrical Muscle Conditioning

Conditioning the indicator arm with a flexion contraction followed by a stretch was then conducted with the intention of decreasing the resting spindle discharge in elbow flexors in 1 of the arms. In these experiments, the reference was always the painful limb or side in the pain group.

Analysis with mixed model ANOVA found no interaction between muscle conditioning (reference limb: flexion conditioned/flexion and stretch conditioned) between groups (upper limb pain/lower limb pain/pain-free control participants; $F_{2,42} = .23$, $P = .80$, $\eta_p^2 = .08$), suggesting the effect of conditioning was not significantly different between control and pain groups. However, there was a significant main effect of muscle conditioning on position error ($F_{1,42} = 57.03$, $P < .01$, $\eta_p^2 = .58$). That is, flexion conditioning without stretch brought about matching errors in the direction of extension for each group (ie, upper limb pain group: $8.7^\circ \pm 2.0^\circ$; lower limb pain group: $8.0^\circ \pm 1.8^\circ$, or pain-free control subjects: $10.8^\circ \pm 1.8^\circ$; Fig 2, filled circles)—which differed significantly from 0 ($t_{44} = 8.48$, $P < .01$). Reversing the conditioning sequence (ie, when the reference arm was flexion conditioned and stretched, and the indicator arm was flexion conditioned only) caused a shift of approximately 13° in the direction of flexion in all groups (control group: $-3.7^\circ \pm 1.7^\circ$; upper limb pain: $-4.5^\circ \pm 1.8^\circ$; lower limb pain: $-4.0^\circ \pm 1.9^\circ$; Fig 2, open circles), which also differed significantly from 0 ($t_{44} = -3.82$, $P < .01$).

The fact that the direction of matching errors were reversed when the conditioning sequence was alternated from the indicator to the reference limb supports the role for muscle spindles in position sense measured using arm-matching. Further, persons with chronic unilateral limb pain seem to generate spindle signals for limb position sense in the same way as persons who are pain-free.

Pointer Trials After Flexion Conditioning

In this task, participants moved the indicator paddle to match the position of the reference arm, which was flexion conditioned and hidden from view.

Table 2. Result of ANOVAs on Position Errors

	ANALYSIS	OUTCOME	EFFECT	F VALUE	SIG	η_p^2	OBSERVED POWER
Matching bilateral FC	Mixed model ANOVA (ULP/LLP)	Position Error	Limb Side	$F_{1,28} = .81$.38	.03	.14
			Limb Side \times Group	$F_{1,28} = .29$.59	.01	.08
Asymmetrical conditioning	Univariate ANOVA (ULP/LLP/CON)	Position Error	Group	$F_{2,42} = 1.73$.19	.08	.34
	Mixed model ANOVA (ULP/LLP/CON)	Position Error	Cond	$F_{1,42} = 57.03$.00*	.58	1.00
			Cond \times Group	$F_{2,42} = .23$.80	.80	.08
Pointing FC	Mixed model ANOVA (ULP/LLP)	Position Error	Limb Side	$F_{1,28} = .28$.60	.01	.08
			Limb Side \times Group	$F_{1,28} = .27$.61	.01	.08
	Repeated measures ANOVA (ULP/LLP/CON)	Position Error	Limb Side \times Group	$F_{2,42} = .15$.87	.01	.07
Matching versus pointing	Repeated measures ANOVA (ULP/LLP/CON)	Position Error	Task	$F_{1,42} = 6.60$.01*	.14	.71
			Task \times Group	$F_{2,42} = .26$.77	.01	.09
			Limb Side	$F_{1,42} = .92$.34	.02	.16

Abbreviations: Sig, significance *P*-value; FC, flexion contraction; ULP, upper limb pain; LLP, lower limb pain; CON, control; Cond, muscle conditioning.

*Indicates $P < .05$; significant main effects. Interaction effects were indicated by \times . The between factor was group (ULP, LLP, CON), and within-subject factors were limb side (painful/nonpainful), cond (muscle conditioning: flexion conditioning vs flexion conditioning with stretch), and task (matching vs pointing).

A mixed model ANOVA was used to examine whether position errors, during pointing, differed for the painful limb or side in participants with upper or lower limb pain. There was no main effect of limb side (ie, whether the reference limb was the painful or pain-free side of the body for pain groups) on position errors ($F_{1,28} = .28$, $P = .60$, $\eta_p^2 = .01$), nor was there a difference between those with upper or lower limb pain ($F_{1,28} = .27$, $P = .61$, $\eta_p^2 = .01$). When the painful limb or side acted as the reference arm, all participants made pointing errors toward extension (control: $3.1^\circ \pm 1.8^\circ$; upper limb pain: $1.3^\circ \pm 3.3^\circ$; lower limb pain: $6.0^\circ \pm 2.7^\circ$), which were significantly different from 0 ($t_{44} = 2.41$, $P < .05$; Fig 3,

filled circles). Similar errors were observed when the pain-free arm acted as the reference, shown in the open circles (control: $2.3^\circ \pm 2.0^\circ$; upper limb pain: $1.9^\circ \pm 1.8^\circ$; lower limb pain: $4.1^\circ \pm 2.3^\circ$), which were also significantly different from 0 ($t_{44} = 2.42$, $P < .05$).

A repeated measures ANOVA, including reference limb side as a within subjects factor, found no significant difference in pointing errors between pain-free control, upper limb pain, and lower limb pain groups on position errors in the pointing task ($F_{2,42} = .15$, $P = .87$, $\eta_p^2 = .01$).

Comparison Between Pointer and Matching Trials After Flexion Conditioning

Finally, a repeated measures ANOVA was used to examine position errors between the pointer and matching tasks, across limbs (reference limb: painful side/pain-free side) and the pain groups (upper limb pain/lower limb pain/pain-free) for the flexion condition task only.

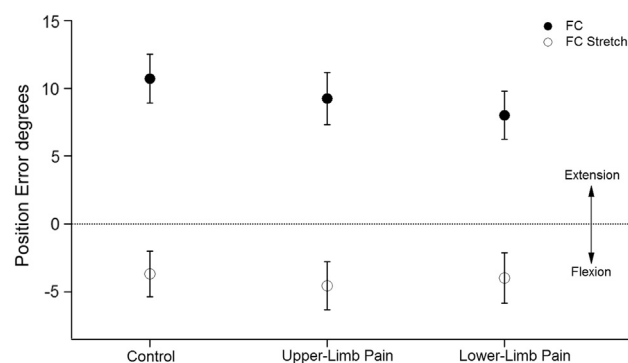


Figure 2. Matching errors after asymmetrical conditioning: flexion contraction (FC) and stretch (FC+Stretch). In these trials, the painful side acted as the reference arm. For the filled circles, the reference arm was flexion conditioned as described previously. The indicator arm also performed the flexion contraction, but was subsequently moved by the experimenter from the vertical position into elbow extension. From the extended position, the subject moved their arm to match the position of the reference. This resulted in matching errors of $\geq 8^\circ$ into extension. In another trial, represented by the open circles, the conditionings of the arms were reversed. The painful reference arm performed a contraction and stretch, while the indicator arm performed the flexion contraction only. There was a significant effect of conditioning on matching errors ($P < .01$), with no difference between groups. Position errors are expressed as mean \pm standard error of the mean for 45 participants. Dotted line indicates zero error.

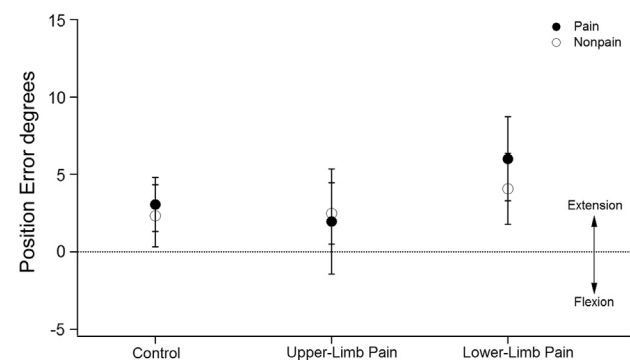


Figure 3. Pointing errors after flexion conditioning. The filled circles show pointing errors after flexion conditioning of the painful arm. Position errors when the nonpainful arm was pointed to (acting as the reference) are shown by the open circles. Participants were asked to indicate the position of the reference arm, which was hidden from view, by maneuvering the angle of the contralateral paddle. In repeated measures ANOVA no difference in pointing errors were found ($P > .05$). Dotted line represents the zero line.

There was a significant effect of task ($F_{1,42} = 6.60$, $P < .05$, $\eta_p^2 = .14$), with the matching task producing errors in the direction of flexion ($3.30^\circ \pm 1.19^\circ$) whereas the pointing task did not generate significant errors ($.06^\circ \pm .52^\circ$). However, these effects were not enhanced as a function of limb side ($P = .92$), nor did they interact with group membership ($P = .77$). The statistical analyses performed are summarized in Table 2.

Discussion

Awareness of limb position is derived from peripheral inputs that signal information about length changes in the muscle, and higher-order body representations, that provide a point of reference and recognition of ownership of the muscle itself.⁵² At the periphery, previous studies on limb position sense in chronic pain did not control for the thixotropic behavior of the muscle spindle receptors leading to conflicting results and interpretations.^{1,4,31,49,59} Therefore, it was unclear whether disturbances to position sense in persons with chronic pain occurred at the level of the muscle spindles, or in higher-order brain regions. This is the first study to use thixotropic muscle conditioning in 2 distinct position sense tasks aimed at testing the peripheral and central components of position sense in chronic pain. The results have shown that in several conditioning protocols and position sense tasks, position errors were comparable between persons who are pain-free and those who report unilateral upper and lower limb pain.

Afferent signals from both arms are thought to be involved in an arm-matching task.^{24,61,63} If chronic pain leads to disruption to the generation or transmission of afferent signals from the painful limb(s), then this would be expected to bring about systematic matching errors compared with persons who are pain-free. The direction of errors should be reversed when the painful arm alternates from acting as the reference arm to the indicator arm. Overall, matching errors were no different when the painful limb was used to indicate the position of the nonpainful arm. Our findings are consistent with previous studies that reported that muscle spindle discharge is not affected by acute painful stimulation, induced via hypertonic saline injections, of group III and IV afferents.^{3,10}

Moreover, we examined position sense after conditioning 1 arm with a flexion contraction followed by a stretch and the other arm with a flexion contraction only, which results in asymmetrical spindle activity between the 2 arms. As a result, participants match the arm positions by 'listening' to very different spindle firing rates. However, there were no differences in position sense between groups. In fact all participants made matching errors of approximately 8° toward extension when the indicator arm was flexion conditioned and stretched. These errors were presumably driven by the high flexor spindle signal in the reference arm. When the reference arm was flexion conditioned and stretched, there was an approximate 13° shift toward flexion. This is consistent with a lower spindle signal in the reference arm, being matched by a higher flexor

spindle signal in the indicator arm. Because the matching errors did not differ across groups it appears that both arms contribute equally to the matching process and this is not disrupted by the presence of chronic limb pain. In other words, it appears that muscle spindle function is relatively undisturbed in the presence of chronic pain.

It has been shown that there are considerable changes in the sensory¹¹ and motor cortices³⁰ associated with chronic pain.^{12,36} Moreover, disturbances in the motor representation of a painful limb have been inferred from reduced accuracy⁶ or slower response time⁵⁵ in laterality judgement tasks when the depicted limb represents the affected limb. In these tasks, the participant must decide as quickly as possible whether an image of a body part (eg, a hand or foot) belongs to the left or right side of the body, requiring them to mentally rotate their own limb.^{47,48} However, this does not involve reference to afferent input from those body parts. In fact, when doing these tasks participants must inhibit any actual movements in the limbs and perform the task using mental rotation only.

It seems plausible that disturbances to body representations may manifest in disturbances to perceived position sense. Because matching errors were comparable across all groups, we used a pointer task, which is believed to derive input from the body schema and other exteroceptive sources.⁵¹ However, we found that regardless of whether participants pointed to the painful or nonpainful arm, the errors always lay into extension, which is consistent with previous experiments on pointing in healthy individuals.⁶⁰ In other words, participants consistently perceive the forearm to be more extended than it really was regardless of whether or not it was the painful arm. This supports the idea that the mental representation of the body parts at rest is naturally distorted,^{32,33} and that this does not appear to change when the limb is chronically painful.

The present findings conflict somewhat with previous research investigating proprioception in chronic pain.^{4,31} For instance, Brumagne et al⁴ vibrated the multifidus muscles in patients with chronic lower back pain and found a shortening illusion in participants with chronic pain, compared with control participants. This is the opposite effect expected from muscle vibration, which typically induces lengthening illusions by increasing the spindle discharge rate. However, the differences between the present findings and those of Brumagne et al may be explained by the position sense tasks used. Brumagne et al used a lumbosacral repositioning task, which requires the participant to reproduce a previously remembered afferent state (ie, postural position). Similarly, Lewis et al³¹ reported bilateral position sense disturbances in individuals with unilateral chronic regional pain syndrome when asked to position their arm in accordance to hours of a clock face. In contrast, participants in our study presumably used concurrent afferent signals to make a positional judgement, during the matching trials. It appears that even in the context of chronic unilateral pain, the spindle afferent signals from both arms are 'listened to' equally, because the

magnitude of the errors was comparable across groups, and when the type of conditioning was alternated between the 2 arms. The implications of these findings are that: 1) spindle function is preserved in the presence of chronic pain; and 2) the retrieval of body schema information is also intact.

Although we accept that motor, sensory, and regulatory dysfunctions are associated with many chronic pain conditions, it may be possible that they do not specifically rely on afferent proprioceptive inputs and instead involve multiple inputs and/or frames of reference. Longo³² has argued for the existence of multiple body representations. One of these operates largely outside of consciousness (ie, the body schema), and another implicit representation forms the way we consciously perceive our bodies (ie, the body image). Indeed several studies have highlighted the distortions in the way the body feels to the pain patient as related to the body image.^{31,34,62} In instances where conflicting proprioceptive and visual sensory feedback is present, vision often overrides the former.^{17,23,24,27} Indeed, in the case of chronic neck pain, when visual feedback is manipulated to overstate neck rotation, pain occurs earlier during the neck rotation movement.²⁰ Future investigations should disentangle the inputs that build and maintain the body representation, with a focus on the associated threat cues, particularly vision, that evoke pain symptoms.

Several limitations of this study should be considered. First, the pain etiology was heterogeneous within and across upper limb and lower limb pain participants. Patients presented with pain arising from a range of conditions such clinically diagnosed chronic regional pain syndrome to pain associated with varicose veins. Our study endeavored to examine disturbances in position sense in relation to unilateral chronic pain regardless of pain condition or mechanism (excluding those with inflammation, diabetes, or widespread pain); however, this should be tested more thoroughly in the future. We attempted to reduce other variabilities such as pain duration,

average pain intensity, sex, and age by matching these factors across the groups. Nevertheless, there was a significant difference of pain severity, as reported by the Brief Pain Inventory, between groups, with the upper limb pain cohort reporting slightly higher pain severity than the lower limb pain group. However, the groups did not differ in their fear of exacerbating their pain through movement. Finally, it should be emphasized that the study was probably underpowered and the findings should be treated carefully.

Conclusions

To our knowledge, this is the first study to examine position sense in persons with chronic pain while controlling for muscle spindle discharge rates using thixotropic muscle conditioning. This technique is thought to manipulate background spindle afferent discharge, leading to illusions of limb displacement in the absence of vision. We have shown that position errors in persons with chronic pain were comparable to those in healthy control participants. Further, it appears that the affected and pain-free limbs are involved equally when matching the relative position of one arm with the other. These findings indicate that people with chronic pain respond to thixotropic muscle conditioning, leading to reproducible and predictable errors in position sense consistent with their pain-free counterparts. Thixotropic conditioning could be extended to test reflexes and muscle stiffness, often disturbed in chronic pain disorders,²² to further elucidate the signaling behavior of spindles in chronic pain.

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CHAPTER 8: BODY IMAGE AND INTEROCEPTION IN CHRONIC PAIN

Tsay, A. J. and M. J. Giummarra (Submitted). "Body image distortion and cardiac interoceptive sensitivity in chronic pain." The European Journal of Pain.

8.1 Explanatory Notes

Given that muscle spindle signalling appeared to be unaltered in chronic pain (Chapter seven; Tsay & Giummarra, 2016), the role of other aspects of body representation and perception was examined.

This chapter focused on the way people feel about their bodies, termed *body image* (Lotze & Moseley, 2007). While it has been mentioned before that chronic pain is often associated with perceived distortions of the painful limb, be it in size, shape or posture (Melzack, 1990; Lewis et al., 2007; Lotze & Moseley, 2007; Lewis et al., 2010; Tsay et al., 2015), it was unclear where these sensations were derived from.

Given that proprioceptive information appeared similar in those with and without pain, our attention was drawn to the role of interoception, awareness of the internal sensations of the body, in forming the body image. It was hypothesised that greater interoceptive sensitivity would be associated with more severe pain, longer duration of pain, and greater body image distortion.

The manuscript was submitted to *The European Journal of Pain* for review.

8.2 Declaration for Thesis Chapter Eight

Declaration by candidate

In the case of Chapter eight, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
The candidate planned and executed the study, collected and analysed the data, and wrote the paper with guidance and feedback from the co-author.	75

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Melita Giummarra	Co-design of study, statistical analysis, discussion of findings, editing of paper.	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work.

**Candidate's
Signature**



Date

25/08/16

**Main
Supervisor's
Signature**



Date

25/08/16

Body Image Distortion and Cardiac Interoceptive Sensitivity in Chronic Pain

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Running Title: Body image and interoception in chronic pain

Abstract

BACKGROUND: The mental representation of the body is often distorted in chronic pain, both at the level of representation in sensorimotor homunculi and as a phenomenological experience of the body form. It is possible that interoception, awareness of the *internal* sensations of the body, may play a role in the perception that the body form is distorted. This study investigated whether interoception is associated with altered body image in chronic pain.

METHODS: Body image was assessed using a body drawing task, in 30 participants with chronic pain, and interoception was measured using the Schandry heartbeat awareness task. These differences were tested using the Mann Whittney U test and the association between pain severity, duration and interoceptive awareness was explored with Spearman's rank ordered correlations.

RESULTS: Participants with severe body distortions ($n = 14$) had significantly poorer interoceptive awareness, and reported longer duration of pain, than participants with no or minor body image distortions ($n = 16$), with moderate effect sizes ($r = .39$ to $.43$). However, interoceptive awareness and pain duration were not correlated, and there was no association between interoceptive awareness and pain severity.

CONCLUSIONS: These results suggest that over time, body image distortions become more severe and are associated with greater difficulty in unifying bodily sensations with the body representation.

Keywords: Chronic pain; body image; interoception; body awareness; body drawings

Significance

What's already known about this topic?

- Persons with chronic pain frequently describe their painful limb as being disturbed, be it in size, shape or posture.

What does this study add?

- Interoceptive sensitivity is poorer in those with severe body image distortions, and high in those with minor distortions.
- We speculate that as the body image becomes more disturbed over time, neural representations of the affected body part become remapped with the reorganisation of cortical areas.
- As body image becomes more disturbed, one may become poorer at accurately detecting internal bodily sensations.

Introduction

When pain becomes chronic, patients frequently describe that the painful limb has begun to *feel* like it is distorted, be it in shape, size or posture (Tsay et al., 2015). Such experiences reflect a disturbance in the way we perceive our bodies, termed *body image* (Lotze & Moseley, 2007), which is believed to be derived from proprioceptive signals (Proske & Gandevia, 2012), as well as visual and interoceptive information. As described by Craig (2003), interoception is the awareness of the physiological condition arising from within the body, sensations such as hunger, thirst, pain and cardiovascular activity. While the neural networks of interoception have been described in detail (Craig, 2002; Craig, 2009), little is known about how or whether awareness of internal bodily sensations (i.e., interoception) is associated with the subjective experience of complex experiences like chronic pain. Given that nociception, and pain experience, share many overlapping neural networks with other interoceptive mechanisms (May, 2008; Craig, 2009), especially the insular cortex and the anterior cingulate cortex, it is likely that interoceptive acuity and pain experience may be linked.

When anticipating pain, we typically become more aware of innocuous tactile sensations (Vanden Bulcke et al., 2013); however, those who score highly in a heartbeat awareness task (HBAT) have been found to have lower tolerance for acute experimental pain (Pollatos et al., 2012). In the HBAT, one's accuracy in detecting the number of heart beats across several short time periods is ascertained, and is considered a proxy measure of interoceptive awareness (Schandry, 1981). Interestingly, persons with chronic pain tend to exhibit greater preoccupation and hypervigilance towards the painful body part (McDermid et al., 1996; Vlaeyen & Linton, 2000), and hypervigilance to pain and other interoceptive cues (De Peuter et al., 2011).

It is not known whether chronic pain is also associated with increased sensitivity to interoceptive activity, such as cardiovascular events, that is not directly related to the painful body part. In particular, it is not clear whether interoceptive sensitivity in people with chronic pain is associated with aspects of pain experience (i.e., pain severity or duration) or altered body image. The present study aimed to determine whether cardiac

interoceptive awareness is associated with self-reported body image distortions in a heterogeneous sample of individuals with chronic pain. Interoceptive awareness was measured with the Schandry heart beat awareness task. Body image was determined through completion of a modified body drawing task (Moseley, 2008). We hypothesised that greater interoceptive sensitivity would be associated with more severe pain, longer duration of pain, and greater body image distortion.

Methods

Participants

Thirty individuals with unilateral upper or lower limb chronic pain ($M=13$, $age=36.2 \pm 2.8$) participated in this study. Participants were recruited from Caulfield Pain Management and Research Centre, and the general community. Inclusion criteria for the pain group included: being aged 18 to 65 years old and having experienced pain more days than not for at least 3 months. Table 1 presents the demographic and clinical characteristics of the cohort. The study was approved by the Alfred Hospital and Monash University Human Research Ethics Committees. All participants gave written informed consent and were financially reimbursed for their time.

Materials and Procedure

Pain severity

Participants reported how many years they had experience pain, and the intensity of their pain using the short-form Brief Pain Inventory (BPI). Pain severity was calculated as the average across ratings of pain right now, on average, at its worst and least in the past week, according to the scale instructions (Cleeland & Ryan, 1994). The severity score had high internal consistency in this sample with Cronbach's $\alpha = .91$.

Body drawing task

A modification of the task by Moseley (2008) was used to assess body image distortions. Participants were instructed to draw over a template image of the posterior surface of the back (see Figure 1). In the instructions, emphasis was placed on depicting what their body 'feels' like to them, rather than on the quality of their drawing abilities. Unlike the original

study which examined the perception of the back in persons with back pain (Moseley, 2008), our participants were instructed to draw their full body, including head, hands and feet. These drawings were captured on an A4-sized notebook with a smart pen (Livescribe, Oakland, California, USA), which recorded the drawings electronically, enabling the drawing to be reviewed online. Audio feedback and clarification from the participant about their drawings were also recorded in synchrony with the drawing during the task.

==> Insert Figure 1 here.

Quantitative assessment of the drawings was based on the method used by Lewis et al. (2010), who assessed free-hand body drawings in individuals with complex region pain syndrome (CRPS). Each drawing was graded on a three-tier system from 0 = '*no distortion*', 1 = '*minor distortion*', and 2 = '*severe distortion*'. If a distortion in size or shape was depicted within the drawing and/or the accompanying participant descriptions, i.e. that it was not anatomically consistent with the actual shape of the limb, the rating "distortion" was given. If two or more segments of the body were missing or not anatomically consistent, this was rated as a "severe distortion."

Heartbeat Awareness Task (HBAT)

Assessment of interoceptive sensitivity of cardiac activity was based on the Schandry method (Schandry, 1981). Participants sat quietly with their hands resting on their lap and were instructed to count the number of heartbeats in three time periods (25s, 35s, 45s) without taking their pulse. Participants were not aware of the length of each trial, and trial order was randomised. A sensitivity score, based on the average accuracy across trials, was calculated using the following formula:

$$\frac{1}{3} \sum 1 - \frac{(|\text{recorded heartbeats} - \text{counted heartbeats}|)}{\text{recorded heartbeats}}$$

This produced values ranging from 0 to 1, with higher scores indicating higher accuracy or sensitivity to detect ones heartbeat. Heartbeats were measured using three-lead electrocardiography (ECG). Ag-AgCl electrodes with an adhesive base and solid gel contact

points (AD Instruments, Castle Hill, NSW, Australia) were placed on both sides of the chest and a third at the base of the ribcage on the left-side. An ECG trace was acquired at 40 Hz using MacLab 4/s data acquisition module running Chart software (AD Instruments, Castle Hill, NSW, Australia) on a Macintosh computer.

Statistical Analysis

Statistical tests were performed using SPSS 21 (SPSS, Chicago, IL, USA) with significance at $\alpha = 0.05$. Participant characteristics were summarised using descriptive statistics. Pain severity was normally distributed, so group differences were examined with Independent samples t-test. Interoceptive awareness (HBAT) and pain duration data were skewed, and transforming the data did not improve normality. Therefore, nonparametric analyses were conducted to examine whether participants with severe distortions had more severe pain, longer duration of pain and worse interoceptive awareness compared with participants who depicted no/minor distortions. Mann Whitney U tests and effect sizes (r) were calculated, and the associated between pain severity, duration and HBAT were explored with Spearman's rank ordered correlations.

Results

Table 1 details the demographic characteristics of the participants. As a cohort they experienced a 6.27 (SD = ± 1.72) pain on average, as scored by the numerical rating scale, and had median duration of pain for 0.60 years (IQR = 5.50).

==> Insert Table 1 here.

In the drawing task, only a minority of participants were classified as having *no distortions* ($n=4$, 13%), and 87% ($n=26$) depicted the presence of one or more distortions, including enlargement of the body part, shading, additional markings and/or arrows. Almost half ($n=14$, 47%) displayed *severe distortions* – that is, distortions at more than one site of the body. And 12 (40%) participants presented with *minor* distortions located on one body part. In Figure 2, Person A was one of four participants who showed no body distortions, his primary complaint was intermittent pain in his left wrist that began about four months ago.

Person B is an example of a participant with a *minor distortion* in body representation. Here the participant wanted to emphasise that her right shoulder was in pain by bolding the lines around this region. She also felt that there was a slight tilt in her neck, caused by the pain, depicted as a shift in the cervical vertebrae to the left. Her pain began about two years ago and resulted from a muscular overuse injury. Person C was also classified as displaying minor body distortion. He reported persistent pain in his right scapula, which had been present for the past eighteen months. In the drawing, the right shoulder was deliberately offset and drawn higher with an enlarged scapula, compared to the left-hand side. Person D attempted to convey similar distortions by drawing a horizontal line to emphasise that his painful left scapula was also offset, as if it were “bulging out” and sitting higher than his right scapula. Further, additional bolding and line markings were used to show tension and stiffening through the shoulder and neck regions.

Examples of individuals who displayed *severe distortions* are shown by person E and F in Figure 3. Shading was used by person E in regions he considered to feel “inflamed” and “swollen” from a skateboarding accident 6 years prior, in which he injured his left lower back, leading to referred pain in his left leg, elbow and shoulder. Others explained that the additional shading indicated that the area felt “hot,” associated with the swollen limb. Person F had spondylolisthesis in her spine, specifically at L5/S1, causing wide-spread referred pain across her left-hand side, and complex region pain syndrome in her left leg. Notably, she reported that she could feel the presence of her toes in her right foot, but not on the affected left foot. She also reported a head tilt towards the right, as illustrated by the arrow. Others used additional markings such as crosses or circles indicating a “trigger point” or muscular knot and tension at the site.

==> Insert Figure 2 here.

Group differences in pain and interoceptive awareness

Participants with severe distortions had significantly poorer interoceptive awareness [median±IQR = 0.66±0.45 vs 0.85±0.13, $z (N = 30) = -2.33$, $p = .019$, $r = -.43$; see Figure 3] and reported longer duration of pain [median±IQR = 7±8 vs 2±2 yrs, $z (N = 30) = -2.82$, $p = .004$, r

= -.51; see Figure 4] than participants with no/minor distortions. Although body image disturbance was associated with worse interoceptive awareness and longer duration of pain, interoceptive awareness and pain duration were not correlated; $r_s(30) = .14$, $p = .44$. There were no significant group differences in pain severity [$t(28) = -.91$, $p = .37$].

==> Insert Figures 3 and 4 here.

Discussion

This study tested the idea that body image distortion in the presence of chronic pain may be associated with enhanced interoceptive awareness (i.e., cardiac interoceptive awareness), perhaps reflecting increased somatic focus in chronic pain. Our primary hypothesis was that, considering persons with chronic pain tend to be hypervigilant to pain (McDermid et al., 1996) and somatically focussed (Vanden Bulcke et al., 2013), they may have greater sensitivity to other interoceptive signals (i.e., cardiovascular). While we found that pain severity was not associated with body image distortions, persons with more severe distortions actually had *lower* interoceptive awareness compared with participants with minor/no distortions.

Perceived distortions of the image of the painful body part has been reported in numerous chronic pain conditions, especially complex regional pain syndrome (Moseley, 2005; Lewis et al., 2007; Lewis et al., 2010; Turton et al., 2013), chronic back pain (Moseley, 2008), and phantom limb pain (Melzack, 1990; Giummarra et al., 2010). Our pain cohort varied considerably in pain aetiology and the specific location of their pain, although they all reported pain that predominantly affected one limb. Hence, this study is one of the first to characterise significant body image distortions in a heterogeneous cohort of individuals with chronic pain. Similar to previous studies (Moseley, 2008; Lewis et al., 2010; Egloff et al., 2012), distortions were depicted through purposeful bolding of the body outline, or shading and enlargement of the painful area.

A large proportion of the cohort depicted an enlargement of the painful body part. After acute alteration in sensory input, from a peripheral anaesthetic block, cold stimulation of C-

afferent fibres induces a perception of increased size of specific body parts (Gandevia & Phegan, 1999). These perceptual effects have been interpreted as an enlargement of the size of the receptive fields of cortical cells which represent skin areas adjacent to the site from which input was removed (Calford & Tweedale, 1991; Gandevia & Phegan, 1999). Importantly, C and A δ fibres project to cortical and homeostatic centres of the brain (for detailed afferent pathways, see Craig, 2003), contributing to an overall cortical image of afferent activity. In persons with chronic pain, similar effects have been observed whereby the representation of the painful limb (Lotze & Moseley, 2007), or the contralateral limb (Di Pietro et al., 2013), begins to overlap with neighbouring body parts along the somatosensory homunculus (e.g., touch to the face and shoulder may activate regions corresponding to a missing painful hand perceived as a phantom; Flor et al., 2006). Cortical reorganisation may play a central role in body image distortions in chronic pain, perhaps due to enlargement of the receptive fields corresponding to the painful limb. As body image becomes more distorted — perhaps with more widespread pain, given the present coding process reflected the number of minor distortions — one may actually become poorer at accurately detecting internal bodily sensations (Duschek et al., 2015).

Previous studies (Tsakiris et al., 2011; Pollatos et al., 2012) have considered the threshold for high interoceptive sensitivity to be approximately 0.80 in the HBAT, which is consistent with the median score for the minor/no distortion group (0.85 ± 0.13). Hence, those who exhibited minor/no body image distortions would be considered to have high interoceptive awareness. Conversely, we found that participants with severe body image distortions had significantly lower interoceptive awareness than those with minor/no distortions of the body image. Pollatos et al. (2012) also found that heightened sensitivity to cardiovascular signals was associated with lower pain tolerance, which likewise suggests that being *more* aware of interoceptive signals may somehow reduce the capacity to cope with or tolerate acute pain. Interestingly, our groups did not differ in pain severity, suggesting that greater interoceptive awareness may not be associated with decreased pain tolerance when pain becomes chronic.

Significant differences in HBAT or body awareness, measured by the Body Awareness

Questionnaire, have not been found between chronic pain and healthy controls (Ribera d'Alcalà et al., 2015). In contrast, we found that interoceptive awareness was associated with aspects of body image and pain duration. Since our cohort showed no significant group differences in pain severity, it suggests that severe disturbances to the body image may not be due to chronic pain, per se, but perhaps involve difficulty in perceiving and/or integrating bodily sensations with the body representation (Duschek et al., 2015). Further evidence comes from individuals recovering from bulimia nervosa who showed distortions of body image as depicted using body drawings (Guez et al., 2010) and impaired heartbeat awareness (Klabunde et al., 2013), which highlights that disturbances in body image and interoceptive awareness is not exclusive to chronic pain.

Limitations

Ultimately, assessing body awareness through drawing self-images comes with inherent limitations. Whilst the participants with chronic pain reported enlarged painful limbs, we did not specifically assess whether the painful body part/s themselves were actually physically enlarged. No quantifiable measures were made due to the variety of pain location sites and aetiologies in this cohort, although certain participants did present with some noticeable abnormalities, such as altered posture and rigidity of the affected body part.

Attempts to qualitatively capture the perceived body, through body drawings, relied heavily on the participants drawing ability and unintended strokes were often made. Error strokes were later verified by listening back to the simultaneous audio recording of participant comments during the task. Therefore the researcher, whilst blind to individual interoceptive scores when coding the drawings, was not blinded to the participants' pain. Moreover, this observation highlights that assessment of body distortion through drawings should not be undertaken in isolation of the participants qualitative description of their body parts.

The scoring method by Lewis et al. (2010) also has some limitations. Differences between *minor distortion* and *severe distortions* were based on the number of sites in the drawing that were shown to be affected, and the scoring therefore reflected the quantity of distortions rather than the quality or intensity of those distortions. Severe distortions may

simply have indicated that those participants also had more widespread pain. An alternate method was recently devised by Turton et al. (2013), who used computer generated avatars for the depiction of body image distortions in chronic pain. Their approach should be considered in future investigations as they were able to demonstrate high patient satisfaction in capturing the qualitative experience of distortions in body image from chronic pain.

Conclusions

Each of us maintain a specific mental image of how our body looks and feels. In the case of chronic pain, perception of the body is often distorted. Our findings suggest that interoceptive sensitivity is poor in those with severe body image distortions, and high in those with minor distortions. From these findings we speculate that as the body image becomes more disturbed over time and possibly resulting in more widespread pain, neural representations of the affected body part become remapped with an expansion of body maps (Flor et al., 1997; Flor et al., 2006; Lotze & Moseley, 2007). As body representations become disturbed, the capacity to *accurately* perceive internal bodily events that are not associated with the painful body part (i.e., cardiac events) also becomes more disturbed. Further investigation is needed to determine whether training interoceptive sensitivity might attenuate the impact of severe body image distortions due to pain.

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Table 1.

Demographic characteristics and pain profile of participants.

		Participants
Sex	M:F	13:17
Age	Mean \pm SD	36.20 \pm 15.31
Pain Duration (yrs)	Median \pm IQR	0.60 \pm 5.50
Aetiology		
Fracture	N (%)	27%
CRPS	N (%)	7%
Muscular/Tendon	N (%)	23%
Unknown/Other	N (%)	43%
Average Pain	Mean \pm SD	6.27 \pm 1.72
BPI Severity	Mean \pm SD	5.64 \pm 2.11
BPI Interference	Mean \pm SD	3.88 \pm 2.47
HBAT Score	Median \pm IQR	0.75 \pm 0.23

Note: Complex Regional Pain Syndrome (CRPS); Brief Pain Inventory (BPI); Heart Beat Awareness Task (HBAT).

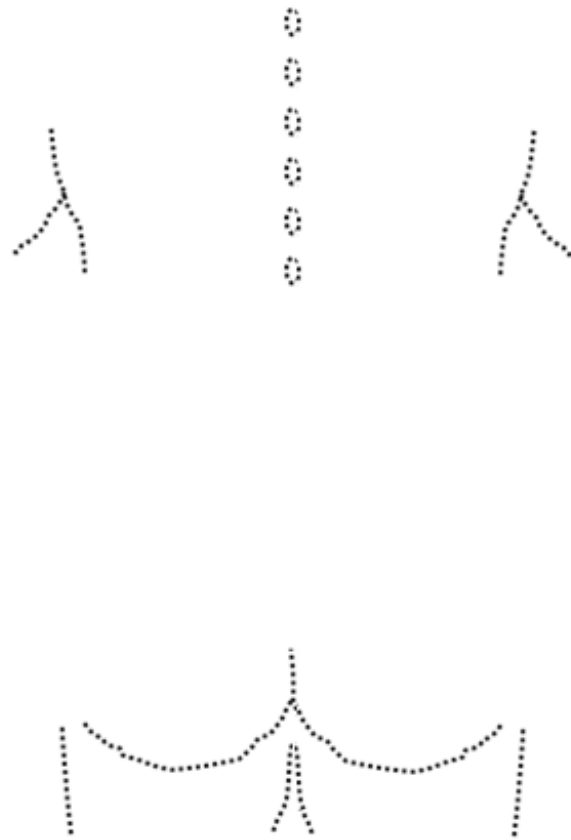


Figure 1. Body drawing template taken from Moseley, 2008. Participants were instructed to complete the rest of the drawing according to how they perceived their own bodies to feel like.

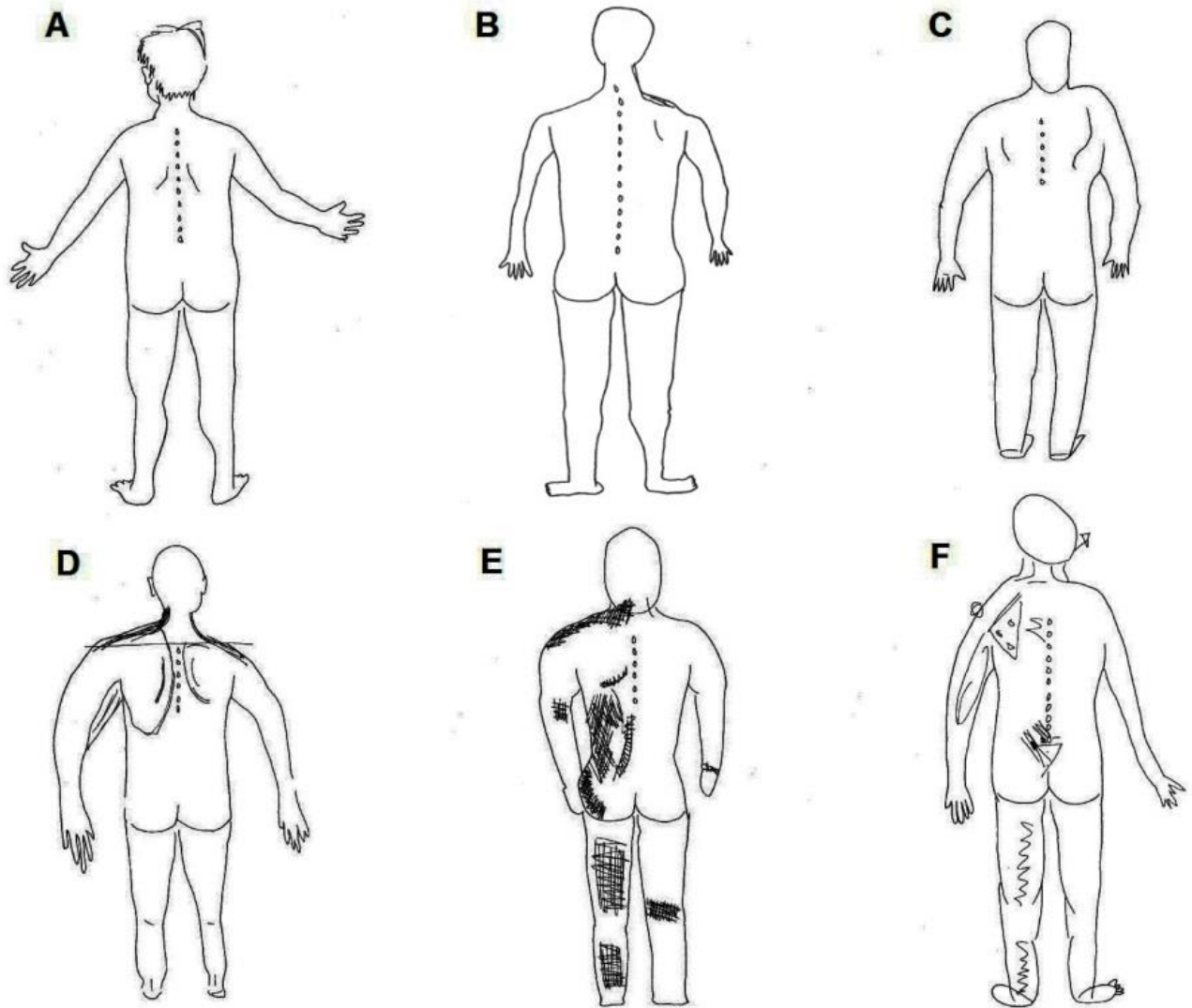


Figure 2. Examples of body drawings from a selection of participants. Person A showed no body distortions, unlike person B and C whom exhibited *minor distortions* limited to one specific site. Examples of more widespread, *severe distortions* are in persons D, E and F, with noticeable distortions impacting multiple body regions.

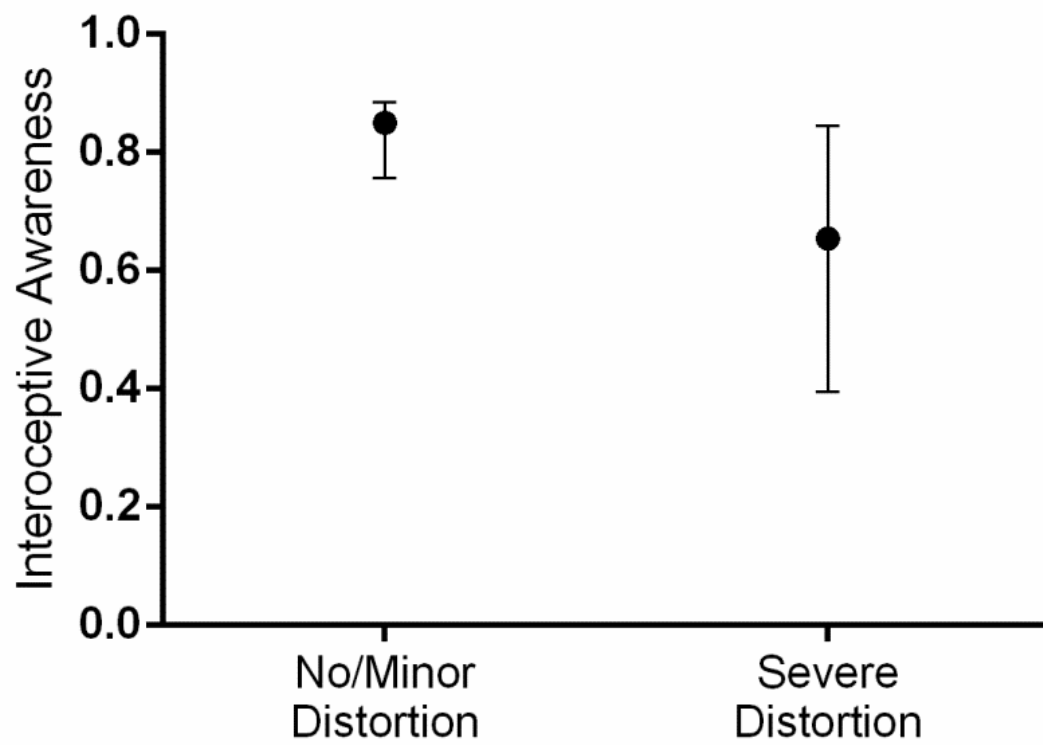


Figure 3. Median (interquartile range) of interoceptive awareness scores for each group (no/minor body image distortion and severe body image distortion).

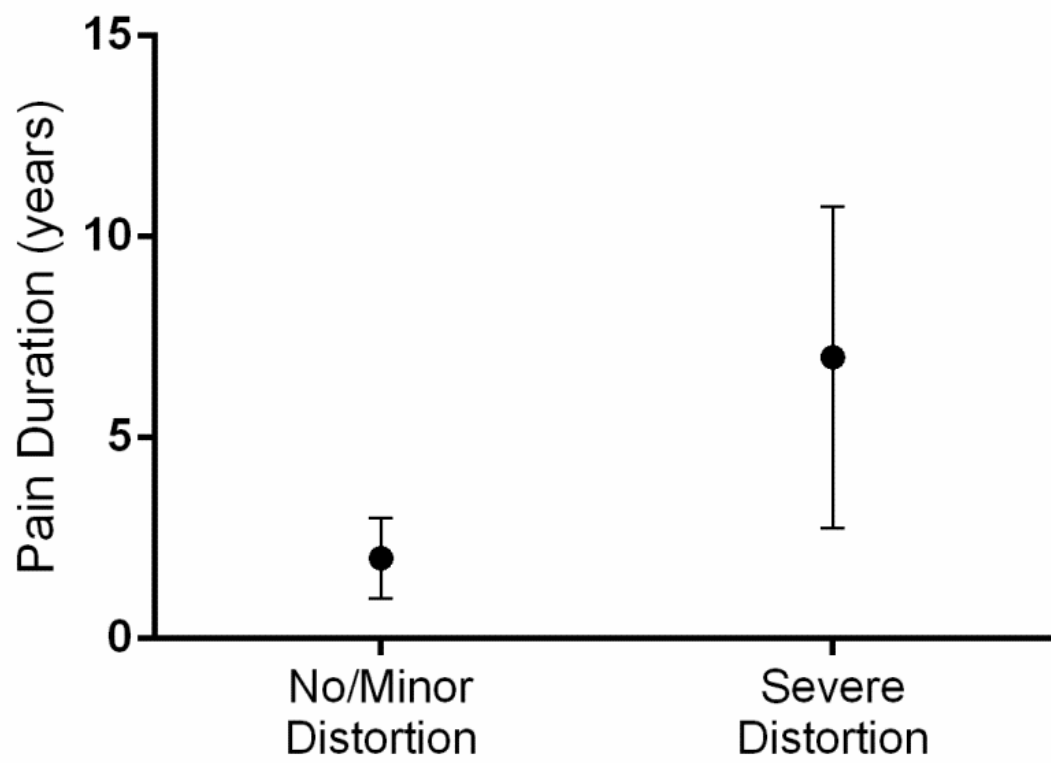


Figure 4. Median (interquartile range) of pain duration in years for each group (no/minor body image distortion and severe body image distortion).

CHAPTER 9: GENERAL DISCUSSION

When our eyes are closed, we intuitively know the location of our arms and legs. The sensation of limb position is one that is often taken for granted. Perhaps this is because it is a sensation that largely operates outside of conscious awareness and requires our focussed attention in order to become apparent. Unlike the other senses, such as vision and hearing, position sense is often overlooked in sensory perception research perhaps because its principal receptors lie hidden, buried within our muscles.

While it is known that muscle spindles contribute to position sense (Goodwin et al., 1972), many aspects of proprioception, particularly how spindle information is converted into percepts of limb position and movement are still poorly understood (Proske & Gandevia, 2012). The aim of this thesis was to explore the mechanisms of position sense through the use of thixotropic muscle conditioning, and more broadly to investigate how muscle spindles are involved in the central representation of the body. The following general discussion provides an overview of the main findings from each section of this thesis. This research began with studies investigating mechanisms of position sense in healthy young adults and proceeded into examining whether such mechanisms are disturbed in individuals with chronic pain. The implications of the findings are then discussed, followed by acknowledgement of the limitations of the research and suggestions for future directions.

9.1 Peripheral Mechanisms of Position Sense: An Overview

The first section of the thesis investigated the signalling of position sense in healthy young adults using a matching task only, whereby the position of one arm was indicated by placement of the other arm. In Chapter two, *Limb position sense, proprioceptive drift and muscle thixotropy at the human elbow joint (Tsay et al., 2014)*, it was observed that time-dependent, directional shifts in perceived arm position could be abolished by introducing slack in the muscle. As muscle spindles are the only known afferent receptor to exhibit thixotropic behaviour (Proske et al., 1993), this study provided evidence for the role of receptor adaptation in the phenomenon known as proprioceptive drift. Secondly, large matching errors (on the order of 10°) were found when the limbs were conditioned

differently to each other – i.e. co-conditioning of the reference arm with either flexion or extension conditioning of the indicator arm. As co-conditioning presumably produced a low nett difference in afferent signals between antagonist muscles in the reference arm, the source of the matching errors is assumed to have predominately originated from the indicator arm. The assumption of a low nett difference signal following conditioning was later supported by introducing slack in both arms that resulted in accurate alignment of the arms (Chapter two, experiments 5 & 6; Tsay et al., 2014), as well as the abolition of proprioceptive drift. Hence, we concluded that in a forearm matching task, the brain monitors the difference signal from the antagonist pairs of the two arms.

Chapter three, *Position sense at the human forearm after conditioning muscles with isometric contractions (Tsay et al., 2015)*, provided further evidence that the brain is concerned with the difference signal coming from antagonist muscles. Here small position errors (1.4° in the direction of flexion) were reported when antagonist muscles in the reference arm were presumably made taut by conditioning them with a co-contraction, and the indicator antagonist arm muscles slackened by stretching and then shortening the muscle. Hence, accurate alignment of the forearms was achieved despite inducing two very different thixotropic states in the reference and indicator arms.

9.2 Investigating the Central Body Representation: An Overview

Section two of the thesis saw the introduction of a new position sense task, the pointing task, to examine how limb position was determined when afferent signals from only one arm were available. These experiments came about after it was recognised that in normal circumstances we do not typically carry out matching tasks with our limbs, to determine their exact position. For instance, we can intuitively locate our right arm when we are not looking at it, and this is done without a conscious comparison with the left arm. Hence, in this section of the thesis the hypothesis tested was that pointing to the position of an arm, which is hidden from view, is derived primarily from central processes. In contrast, *matching* the position of the arms is proposed to rely on computation of the relative difference in peripheral signals from muscle spindles.

Chapter four, *Sensory origins of human position sense* (Tsay et al., 2016), was arguably the most important paper in this thesis and generated its own *Perspectives* commentary in the *Journal of Physiology* by Rasman and Blouin (2016). The main finding of the study was that position errors in the direction of lengthening were not observed in the pointing task when the flexors of the reference arm muscle was vibrated. Further manipulations which were found to shift position errors during matching tasks, including extension muscle conditioning and stretching the skin around the elbow joint had no effect on position errors when indicated with the pointer. Pointing errors were also found to be biased in the direction of extension regardless of the intervention used. These findings could not be explained by a peripheral receptor mechanism. Furthermore, the contribution of motor commands did not change this pattern, as tested through self- vs experimenter-moved placement of the pointer and loading the reference arm with additional weight. This led us to propose the existence of two distinct position senses that draw positional information from different sources.

Additional experiments were reported in Chapter five, *Position sense at the human elbow joint measured by arm matching or pointing* (Tsay et al., 2016), in an attempt to explain the pattern of pointing errors. Co-conditioning of the reference antagonists, intended to induce a low net spindle signal difference, was reintroduced as well as placement of the pointer by the experimenter. However, extension errors were still observed for all conditions suggesting that the arm manoeuvring the pointer had minimal involvement in the pointing task. In addition, matching with the indicator arm under visual control did not significantly alter the overall pattern of matching errors when compared to matching while blindfolded. Hence, the inclusion of vision of the indicator arm during pointing could not explain the apparent absence of effect produced by muscle conditioning in pointing tasks.

9.3 Position Sense and Body Representation in Chronic Pain: An Overview

The findings from the first two sections supported the hypothesis that position sense derives information from both peripheral and central sources, in a task dependent manner. In the final section of the thesis, position sense and body representation were assessed in individuals with chronic pain. Chronic pain is an interesting model because the aetiology is

relatively unknown, with both central and peripheral components likely to play a role in the presence of somatic symptoms — particularly the anecdotal reports of disturbed body image and proprioception — associated with the pain experience (Melzack, 1990; Lotze & Moseley, 2007).

A review entitled *Sensing the body in chronic pain: A review of psychophysical studies implicating altered body representation* (Chapter six; Tsay et al., 2015) detailed evidence for bodily disturbances, which was not limited to proprioception, but also included other classical senses of vision, touch, hearing, taste, and smell. This was in addition to disturbances to autonomic regulation, and possibly interoceptive awareness, which encompasses internal sensations of hunger, thirst and cardiac activity. Given the broad scope of sensory systems affected by chronic pain, it seems unlikely that these disturbances arise at the periphery. Rather, a disruption in the way sensory information is processed is more likely to account for the multiple sensory modalities affected in chronic pain.

In Chapter seven, *Position sense in chronic pain: Separating peripheral and central mechanisms in proprioception in unilateral limb pain* (Tsay & Giummarra, 2016), position sense was assessed using both the matching and pointing tasks, used previously in healthy subjects in Section one and two of this thesis. Position sense was evaluated in persons with unilateral upper- and lower-limb chronic pain. It was found that the pain groups produced position errors comparable to healthy controls in both pointing and matching tasks. These results suggest that the signalling of spindle information by the painful and non-painful limbs were weighted similarly in limb matching. Moreover, it was found that lateralised pain, whether in the arm or leg, did not influence forearm position sense acuity.

As the contribution of muscle spindles appeared to remain unaltered in the presence of chronic pain, we wanted to explore other aspects of body image and awareness that might contribute to body perception in chronic pain. In the final chapter (Chapter eight), *Are body image and cardiac interoceptive sensitivity disturbed in chronic pain?*, qualitative data was gathered about the subjective image of the body as felt by persons with chronic pain to examine the association between body image disturbances and interoceptive cardiac

sensitivity. It was found that those with greater body image distortions had poorer interoceptive sensitivity, compared to those with no/minor body image distortions. This suggests that as the body image becomes more disturbed, in line with the remapping and expansion of body maps (Flor et al., 1997; Flor et al., 2006; Lotze & Moseley, 2007), the capacity to accurately perceive bodily events may also become more disturbed. As these disturbances were not observed in regards to position sense, it perhaps suggests that body image may derive sensory information from other sources.

9.4 Implications

The ability to manipulate spindle activity at a pre-determined length simply by using a voluntary contraction and stretch represents a powerful tool for exploring position sense. The findings from this series of studies holds significant implications for our understanding of the neural processes involved in the interpretation of afferent positional information, and more broadly, on how we detect and perceive our own bodies. This section discusses the implications of a receptor-based mechanism for proprioceptive drift, the possible existence of two distinct position senses, and the sensory information involved in generating a coherent central representation of the body.

9.4.1 Muscle Spindle Signalling

Until recently, the steady change in perceived position or posture over time in the absence of vision, described as proprioceptive drift, was believed to arise from central positional and movement controllers (Wann & Ibrahim, 1992; Brown et al., 2003). Our own observation that proprioceptive drift likely includes a component from spindle adaptation is an important finding. However, it should be noted that muscle spindle afferents were not directly measured in this thesis. Rather the role of muscle spindle afferents was inferred from the existing understanding of their thixotropic properties derived from observations using microneurography recordings from afferent fibres (Hagbarth et al., 1985; Burke et al., 1988; Macefield et al., 1990; Burke & Gandevia, 1995; Fallon & Macefield, 2007). Such methods, however, are confined to measurements of single afferent endings, whereas much of the findings presented in this thesis suggest that activity of the whole population of spindles in a given muscle is monitored by the brain in order to determine limb position.

Direct, single fibre recordings would provide important confirmation, but only a limited view of the signalling activity of the whole muscle in much of the experiments conducted in this thesis.

Proprioceptive drift has been encountered in a variety of psychophysical tasks (Paillard & Brouchon, 1968; Wann & Ibrahim, 1992; Desmurget et al., 2000; Brown et al., 2003). One of the more surprising examples is perhaps its emergence during the rubber hand illusion (Kammers et al., 2009). In such illusions, a sense of ownership is induced over a rubber hand when both the rubber hand and the participant's own hand are synchronously stroked. Importantly, only the rubber hand can be seen by the participant, with their own hand being obscured from view. Aside from the attribution of ownership over the rubber hand, the obscured arm feels as though it is located closer to the fake hand during synchronous stroking, compared with asynchronous stroking. While evidence was provided in Chapter two for a receptor-based mechanism for proprioceptive drift, we do not want to exclude the possibility of contributions from central mechanisms (Wann & Ibrahim, 1992). In the case of the rubber hand illusion, there is likely to be a central component, particularly with the attribution of ownership to the rubber hand (Botvinick & Cohen, 1998; Kilteni et al., 2015) as well as the vividness of the rubber hand illusion experience. It has been shown that muscle spindles can establish their own body ownership illusions, as Walsh et al. (2011) demonstrated with synchronous movement of a finger while cutaneous and joint afferents were blocked by local anaesthesia. However, our findings of a separate mechanism underlying pointing (discussed in detail in the next section: [10.4.2 Two Distinct Position Senses](#)), would suggest that spindle adaptation is unlikely to contribute to the perceived drift of the limb towards the fake finger given that the location of the hidden finger was determined by pointing in the former study.

Another important observation was that proprioceptive drift depends on the adaptation of discharge from one muscle group when its discharge is higher than that of its antagonist. Raising discharge rates in both antagonists reduces the drift presumably because the signal difference is now smaller. Hence, the nett difference signal between antagonists can explain the bias in limb matching errors. During a voluntary contraction, however,

fusimotor co-activation would be expected to increase spindle discharge (Vallbo, 1971; Vallbo, 1974). It has been proposed that a central subtraction of the fusimotor-evoked reafference is used by the brain (Proske & Gandevia, 2012). Whatever the mechanism, the process of converting an afferent impulse stream into a sensation of limb position must be relatively direct, with little loss or distortion of information given the observed time-dependent changes (Tsay et al., 2014) in position errors. This will need to be considered in the future with the development of sophisticated prosthetic devices that deliver gradable nerve stimulation to peripheral nerves located at the stump in amputees (Dhillon & Horch, 2005) to improve user acceptance of artificial limbs.

9.4.2 Two Distinct Position Senses

Since the classic study by Goodwin et al. (1972), the muscle spindle has been viewed as the primary peripheral receptor for the signalling of positional and movement information. In their study vibration was applied to the elbow flexors in a two-arm movement tracking task. Vibrating a muscle is known to phase lock spindle afferent discharge with each vibration cycle (Capaday & Cooke, 1983). We revisited these experiments and showed that the lengthening illusion was only present in the matching task, and not in the pointing task. Similarly, the distribution of position errors following thixotropic muscle conditioning in the pointing task was not consistent with the behaviour of muscle spindles. As described by Rasman and Blouin (2016), the significance of these findings is that it demonstrates “context-dependent use of muscle spindle signals (pp. 801).” Our conclusions from these experiments extended their point by proposing the existence of two distinct position senses, one concerned with the position of one body part relative to another (i.e. used during limb matching); and, a separate position sense that determines the location of the body part in peri- and extra-personal space (i.e. when pointing to a body part).

Whether we possess two distinct position senses remains to be fully determined; however, the prioritisation of muscle spindle information, depending on the task, holds significant implications in the field of proprioceptive research. Researchers need to consider more carefully what it is they are assessing (Proske, 2015), whether they are dealing with proprioceptors or central processes or perhaps both, when selecting a task to measure

proprioception. Many position sense studies employ a repositioning task (Newcomer et al., 2000; Koumantakis et al., 2002; Descarreaux et al., 2005; Asell et al., 2006; Sheeran et al., 2012; O'Sullivan et al., 2013; Proske, 2015; Tsay et al., 2015). Such tasks require the subject to replicate a previously remembered body posture without vision; hence, it is a task concerning the location of the body part in extrapersonal space based on memory. Of the two position sense tasks used in this thesis, the pointing task would be more closely aligned with the repositioning tasks used by others, and our findings should be viewed through this lens.

Further, distinctions can also be inferred from the brain areas in which the matching and pointing processes were likely to occur. McCloskey (1973) made the observation that split-brain patients were able to perform simple forearm matching and vibration-illusion tracking tasks with reasonable accuracy. This suggests that afferent pathways for matching cross below the corpus callosum. Pointing is likely to involve a central body representation, presumably in the posterior parietal area, given that complex perceptions of hand postures, for example, require collaborative sensory information from multiple sources (Proske, 2015). The evidence suggests that proprioceptive representation involving the posterior parietal area crosses the contralateral hemisphere (Ettlinger & Kalsbeck, 1962), indicating that pointing and matching may have different central pathways.

The distribution of pointing errors in the direction of elbow extension (Walsh et al., 2013; Bellan et al., 2015; Tsay et al., 2016; Tsay et al., 2016; Tsay & Giummarra, 2016) may be related to the fact that representations of body parts do not conform to anatomical proportions (Longo & Haggard, 2010). Moreover, Bosco et al. (2000) argued that the brain does not calculate the geometry at each joint, but rather, is concerned with the limb end-point, i.e. the position of the hand (Fuentes & Bastian, 2010). Further investigations towards the relationship between limb end-point and hand/arm representation may help unify the observation of an extension-bias when pointing to the perceived position of a hidden forearm.

Several other experiments may rule out potential contributing factors to the pointing task,

namely vision, cutaneous stimulation, effort and agency. Manipulating motor commands by increased loading of the reference arm (Tsay et al., 2016), and introducing the experimenter-moved versus subject-moved pointing trials, produced pointing errors that were comparable to pointing errors without those manipulations (Tsay et al., 2016). Attempts at stimulating cutaneous receptors by stretching the skin at the elbow joint also produced no changes in pointing or matching errors as from those seen under control conditions (Tsay et al., 2016). Although, this result was considered inconclusive, as Collins et al. (2005) were able to evoke illusory movements at the elbowing during matching using a more sophisticated skin stretch protocol.

9.4.3 Body Representation

Historically, the roles of the body schema and body image have been blurred, with the terms often used interchangeably (Gallagher & Cole, 1995; Berlucchi & Aglioti, 2010; de Vignemont, 2010). In the context of this thesis, we defined *body schema* (also referred to as the postural schema) as an internal, sensorimotor representation of the body's posture (Berlucchi & Aglioti, 2010; Longo & Haggard, 2010), and *body image* as the body as perceived by its owner (Lotze & Moseley, 2007). In some instances, when sensory information from one source is absent, another representation may be substituted to re-establish motor function for basic tasks. For example, Gallagher and Cole (1995) report of patient IW, who lost all proprioceptive and tactile sensations from the neck-down due to a large-fibre sensory neuropathy. He regained the ability to walk by relying on visual feedback of his body. Indeed several studies have highlighted the distortions in the way the body feels to the pain patient in relation to the body image (Lotze & Moseley, 2007; Lewis et al., 2010; Turton et al., 2013). This may explain why the chronic pain participants showed distortions to their body image (Tsay & Giummarra, Submitted), but no apparent disturbances in position sense (Tsay & Giummarra, 2016), and possibly the body schema. The findings from Longo and Haggard (2010) would support such an interpretation. They reported distortions to the representation of the hand via pointing in healthy subjects, but no distortions when selecting images of hands that resembled the subjects' own hand. This suggests that there are differences in the sensory information used between the body image and body schema.

The investigations using thixotropic muscle conditioning in unilateral chronic pain patients had clinical relevance as it provided evidence to support that the sensorimotor disturbances associated with chronic pain take place at the central level. We propose that the contribution of muscle spindles to position sense continues to function in chronic pain, and that both painful and non-painful limbs contribute equally to position sense. Others have shown that with both proprioceptive and visual sensory feedback available, vision often overrides the former, in healthy subjects (Lackner & Taublieb, 1984; Holmes & Spence, 2005; Izumizaki et al., 2010; Guerraz et al., 2012). In the case of chronic neck pain, when visual feedback is manipulated to exaggerate neck rotation, pain occurs earlier during the neck rotation movement than without the manipulation (Harvie et al., 2015). Taken together with the present findings, it appears that higher order integration of sensory information may be responsible for the sensorimotor disturbances in chronic pain (Hodges & Tucker, 2011; Azañón et al., 2016). Hence, pain management and treatment should focus less on the proprioceptive system of chronic pain patients, but rather target the associated threat cues that can potentially trigger recurring pain symptoms (Moseley & Flor, 2012).

As there were no group differences between chronic pain and healthy control groups for the position sense tasks, we explored other mechanisms that could contribute to distortions in body representation or bodily experience. Body image disturbance was measured with body drawings, and those with severe body image distortions (multiple sites of the body) were found to have poorer interoception compared with those who had no/minor distortions. Since the retrieval of body schema information was intact, as suggested by the position sense study of chapter seven (Tsay & Giummarra, 2016), the body image is presumed to derive sensory information from sources other than proprioception to generate the perceived distortions in form of the painful body part. The site specific nature of the body image distortions in our chronic pain cohort would support further investigations into the role of nociception (Haggard et al., 2013), as well as its interactions with other sensory modalities (Azañón et al., 2016), in generating central representations of the body.

9.5 Limitations

One of the challenges with measuring position sense is that movement of the indicator arm

provides positional information used in position matching. Typically, the arms are conditioned at a set angle before being moved towards the test angle. Hence, we could not separate the effect the starting position had on the overall position errors. Movement signal generated by moving from the starting position to the test angle is used by the subject to determine arm position. One way to control for this would be to condition both arms at the test angle. However, repeated trials meant that subjects could become aware that their arms were already aligned at the start of each trial. Alternatively, matching errors could be compared by moving either the reference or indicator arm to the test angle from different directions, i.e. flexion or extension movements. However, due to time constraints, such control experiments were not carried out.

Another limitation is that the small sample sizes meant that the studies, particularly our investigation into chronic pain and position sense, were underpowered. However, we would like to emphasise that our cohort for each group ($n=15$) was consistent with other proprioceptive studies in chronic pain patients (Mientjes & Frank, 1999; O'Sullivan et al., 2003; Descarreaux et al., 2004; Pötzl et al., 2004; Descarreaux et al., 2005; Knox et al., 2006; Paulus & Brumagne, 2008; Ha et al., 2011; Mörl et al., 2011). Further, finding that there was no significant difference in position errors between pain and control groups did not appear to be due to a lack of statistical power. In the matching and pointing errors following flexion conditioning of the painful reference arm, position errors fell within a narrow range across all three groups. A similar range was present when the opposite (pain-free) arm was the reference arm. Yet during the asymmetrical conditioning experiments, there was an approximate shift of 13° between conditions despite the small sample size. A similar argument about statistical power could be made regarding the studies investigating proprioceptive drift (Chapter two, experiment three and four), matching with co-conditioning of the reference arm (Chapter three), and position errors differences between matching and pointing tasks (Chapter four), which all exhibited large differences in position error, on the order of 10° or more, between conditions, which can be reliably observed in reasonably small samples.

Perhaps the biggest limitation of this thesis is the constraints associated with psychophysical

studies. From the present work it is clear that central components play a greater role in position sense than previously thought. Matching and pointing tasks alone cannot assess the central components, leaving many unanswered questions in relation to the body representation. An additional problem was that the term “body representation” was not clearly defined in the literature (Gallagher & Cole, 1995; de Vignemont, 2010) or tangibly assessed. Moreover, others have argued for the existence of multiple body representations (Schwoebel & Coslett, 2005; Kammers et al., 2006; Longo, 2015), and it was not clear during the present experiments whether body representations such as the body schema or body image were truly assessed in the pointing trials or body drawing tasks, respectively.

9.6 Future Directions

One of the issues that remain unresolved is the role of body representations when pointing to the perceived location of a body part. Walsh et al. (2013) demonstrated differences at the elbow and wrist joint, using both matching and pointing tasks. Subjects were instructed to perform a 30% maximum voluntary contraction with their reference limb at the test angle. At the wrist, the muscle contraction significantly altered the perceived wrist angle compared to when the muscle was at rest. However, no illusory displacements were seen at the elbow joint in either pointing or matching tasks. Moreover, for the wrist matching errors remained close to zero, but pointing errors all lay in the direction of flexion (Walsh et al., 2013). These observations raise the possibility that the direction of the pointing errors observed throughout several studies of this thesis (Tsay et al., 2016; Tsay et al., 2016; Tsay & Giummarra, 2016) may be unique to the elbow joint and that at other joints, including the wrist, the direction of errors may be different. Why such directional biases occur at different joints is a point for future experiments.

Preliminary findings suggest that a disruption of the body representation creates a contraction or foreshortening of the body representation (Longo et al., 2009; Walsh et al., 2015). In the experiments by Longo and colleagues (2009), when dual tendon vibration was applied at the elbow joint, subjects perceived a telescoping effect on the arm; that is, the arm felt like it was shorter. However, from follow-up experiments it would appear that the telescoping effect may be caused by the displacement of the arm during dual tendon

vibration (Bellan et al., 2016). Similarly, when proprioceptive information is abolished via anaesthesia, the perceived length of the finger does not change but the width does (Walsh et al., 2015). Future investigations where proprioceptive conflict, such as those induced during simultaneous vibration of the antagonist muscles or even the generation of incongruent sensory information through alterations in visual and proprioceptive inputs (McCabe et al., 2005), or anaesthesia, may be alternate research avenues. Ultimately, the goal of such investigations is to determine the relationship between the body image, body schema and proprioception.

Finally, an interesting point was raised by a reviewer of Tsay et al. (2016, Chapter five) regarding thixotropic behaviour of muscle spindles, in particular from the secondary endings. First described by McCloskey (1973), separate lines of information are used for position and movement information. This was evident in the lack of a movement illusion invoked at low frequency (20-35 Hz) vibration, in conditions not dissimilar to the studies described in the present thesis. Yet McCloskey found large position errors at these lower frequencies. In contrast, vibration at 100 Hz generated the typical movement illusions in line with Goodwin et al. (1972), in addition to large position errors. Some years later, in an animal study, the responses of single identified afferents of muscle spindles, including primary and secondary endings, were tested for thixotropic properties (Proske et al., 1992). It was found that all primary endings exhibited such behaviour but 16 of 35 secondary endings did not. These afferents had characteristically low conduction velocities and it was speculated that the lack of a history dependence related to the location of the sensory terminals on the intrafusal fibres. Hence, thixotropic conditioning of human muscle may not engage all spindle afferents in the muscle. It raises the possibility, although unlikely, that in a pointing task there is a contribution to the position signal from spindle secondary endings which are unresponsive to the conditioning (Tsay et al., 2016). We are currently unaware of a non-invasive technique that is able to systematically locate and differentiate between single primary and secondary muscle spindle endings, although distinguishing between the two populations of secondary endings could perhaps be done using low frequency vibration. Future research in this area is warranted. Confirmation that thixotropic muscle conditioning and vibration selectively stimulate the primary endings of muscle spindles would hold

significant implications for research in this area and opens further questions as to the role of secondary endings, and how the brain uses their information.

9.7 Concluding Remarks

Each of us holds a unique and specific view of our own body. The perception of the body arises from sensations such as interoceptive awareness and the sense of limb position, enabling us to make conscious appraisals of ourselves. Since the 1970s, the muscle spindle has been considered the primary receptor in signalling position sense. Yet little is still known in regards to how the brain processes spindle, and other sensory, information to generate perceptions of limb position and the body part as a whole. The work presented in this thesis contributed some new insight into these unanswered questions.

Our investigations provided evidence in support that the brain is concerned with the signal difference coming from muscle spindles between antagonist muscles, and compares this difference between limbs in an arm matching task. Further, we uncovered evidence of two distinct forms of position sense. One is concerned with the position of a body part relative to another, while the other seems to be used in determining the location of the body part in extrapersonal space.

Finally, we provided evidence that muscle spindle function remains intact in those with chronic pain, suggesting that distortion to the body image was unlikely to rely on proprioceptive information. Hence, our work supports the existence of multiple body representations that derive or weigh information from various sources to generate the sense of the body.

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APPENDIX 1: Muscle Thixotropy as a Tool in the Study of Proprioception

Proske, U., Tsay, A. & Allen, T. (2014). "Muscle thixotropy as a tool in the study of proprioception." Exp Brain Res **232**(11): 3397-3412.

1.1 Explanatory Notes

This review paper explores the use of thixotropic muscle conditioning in measurements of proprioception. The last comprehensive review on the topic was published over a decade ago (see Proske et al., 1993).

While we provide a brief introduction and molecular basis for thixotropy, the main focus of this review was to provide evidence that spindle signals can be manipulated with muscle conditioning, generating reproducible errors in position sense, which can be studied to determine the neural mechanisms surrounding proprioception.

It should be acknowledged that the first author, Prof Uwe Proske, provided the most contribution to this paper. However, the review has been included in the appendix because it addresses many key points relating to this thesis, in particular the importance of conditioning the muscle before taking a position sense measurement.

Muscle thixotropy as a tool in the study of proprioception

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Abstract When a muscle relaxes after a contraction, cross-bridges between actin and myosin in sarcomeres detach, but about 1 % spontaneously form new, non-force-generating attachments. These bridges give muscle its thixotropic property. They remain in place for long periods if the muscle is left undisturbed and give the muscle a passive stiffness in response to a stretch. They are detached by stretch, but reform at the new length. If the muscle is then shortened, the presence of these bridges prevents muscle fibres from shortening and they fall slack. So, resting muscle can be in one of two states, where it presents in response to a stretch with a high stiffness, if no slack is present, or with a compliant response in the presence of slack. Intrafusal fibres of muscle spindles show thixotropic behaviour. For spindles, after a conditioning contraction, they are left stretch sensitive, with a high level of background discharge. Alternatively, if after the contraction the muscle is shortened, intrafusal fibres fall slack, leaving spindles with a low level of background activity and insensitivity to stretch. Muscle spindles are receptors involved in the senses of human limb position and movement. The technique of muscle conditioning can be used to help understand the contribution of muscle spindles to these senses and how the brain interprets signals arising in spindles. When, in a two-arm position-matching task, elbow muscles of the two arms are deliberately conditioned in opposite ways, the blindfolded subject makes

large position errors of which they are unaware. The evidence suggests that the brain is concerned with the difference signal coming from the antagonists acting at the elbow and with the overall difference in signal from the two arms. Another way of measuring position sense is to use a single arm and indicate its perceived position with a pointer. Here, there is no access to a signal from the other limb, and position sense relies on referral to a central map of the body, the postural schema.

Keywords Fusimotor · Position sense · Muscle spindle · Kinaesthesia · Motor command

Introduction

The term thixotropy was first applied to skeletal muscle by Lakie et al. (1984) and refers to a property of all muscles, a dry friction-like, passive stiffness which is distinct from muscle's elastic (length-dependent) and viscous (velocity-dependent) properties and which is contraction history dependent. The term 'thixotropy' comes from the Greek 'thixis', meaning touch, and 'tropos', meaning transformation. It applies to materials which change their physical properties as a result of being moved. So, for example, thick paint behaves thixotropically, becoming less viscous as a result of stirring.

This review briefly summarises the biomechanical basis of muscle thixotropy. Evidence is provided that both the ordinary or extrafusal fibres of skeletal muscle, as well as the intrafusal fibres of muscle spindles, exhibit this property. An important consequence is that the responses of muscle spindles can vary over a wide range, depending on their thixotropic state, and this has implications for reflex action and roles in proprioception.

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Following recognition of thixotropy as a fundamental property of skeletal muscle, numerous studies in the 1980s explored the consequences for neural control of muscle, culminating in a review of the topic (Proske et al. 1993). Since then interest in the subject has waned. However, more recently, there has been a resurgence of interest in the subject of proprioception, including the senses of limb position, limb movement and muscle force. There is evidence that under some conditions, all three senses are subject to the influence of thixotropy. This is particularly so for the sense of limb position, and if the thixotropic state of the muscle is not taken into account, errors can be made in the interpretation of results. One of the aims of this review is to remind readers of the effects of muscle thixotropy and to encourage them to carefully consider its influences in the design of experiments in proprioception.

Because thixotropy provides a simple means of manipulating muscle spindle sensitivity, it is hoped that this review will encourage further exploitation of the method to explore new aspects of proprioception. Despite the many recent advances in techniques available for the study of proprioception, such as new methods of neuroimaging, our knowledge about the generation of proprioceptive sensations has remained relatively rudimentary. Use of a method which permits a systematic alteration of responses of muscle stretch receptors, without actually changing the length of the muscle, may help to provide new insight into these senses.

The first two sections discuss the biomechanical basis of muscle thixotropy. This is reviewed in some depth, since any claims about its influences must rest on a thorough understanding of the phenomenon. An attempt has been made to strike a balance, providing sufficient basic facts, but without going into exhaustive detail and controversy. This aspect of the review should therefore be seen as providing an adequate but not comprehensive coverage.

The molecular basis

An early comment on what ultimately turned out to be thixotropic behaviour was made by Denny-Brown (1929). He noted that in response to a slow stretch, resting skeletal muscle does not behave as a purely elastic structure, showing an initial steep rise in tension, followed by a more gradual rise. In response to the second of two successive stretches, this initial stiffness was less and he noted that this 'preliminary rigidity' took less than one tenth of a second to appear. He attributed the behaviour to the muscle fibres themselves since during stretch of a piece of isolated tendon, the tension rise showed no preliminary rigidity.

The thixotropic behaviour of muscle was studied in more detail by Lakie et al. (1984; for a review see Proske et al.

1993). They pointed out that the motion produced by rhythmic torques applied to the relaxed human wrist depended on the history of movement. They concluded that the source of the thixotropic stiffness changes most probably resided in the muscle, although it has been claimed that thixotropic behaviour can be demonstrated by movement of joints after severance of all muscular attachments (Wiegner 1987).

An explanation of the molecular basis for thixotropy was provided by Hill (1968). He proposed that in sarcomeres of resting striated muscle, a small population of long-lived myosin cross-bridges are attached to the actin filaments. The response of the muscle to stretch was attributed to the spring-like property of these linkages. The elasticity is short range because the cross-bridges can only be displaced by a small amount before their elastic limit is reached and they detach. These cross-bridges also generate a low level of resting tension which Hill called the filament resting tension (FRT).

More recent studies of the cross-bridge basis of muscle thixotropy using single frog muscle fibres have estimated that resting cross-bridges, representing the short range elastic component (SREC), account for something less than 1 % of the total number of cross-bridges in a maximally contracting muscle (Campbell and Lakie 1998). During a stretch, when the elastic limit of the SREC bridges is reached and they detach, tension does not fall to zero. To explain this behaviour, Hill (1968) suggested that detachment by stretch provided the opportunity for immediate reattachment further along the actin filament to prevent force from falling to zero and giving SREC its frictional resistance-like property. Campbell and Lakie (1998) put forward a cross-bridge population displacement mechanism to account for this behaviour.

The full recovery of SREC after a stretch is relatively slow, taking over a minute to return to near control levels (Campbell and Lakie 1998; Proske and Stuart 1985). It means that although the SREC formation rate is low, since tension does not fall to zero beyond the elastic limit during a stretch, the immediate reformation rate appears to be fast. To accommodate these somewhat contradictory behaviours under a common mechanism, it has been proposed that the formation rate of SREC bridges always remains low (Proske and Morgan 1999). Since sarcomeres in a passive muscle are not all likely to resist a stretch with the same strength, some will be stretched more than others. At stretch onset the SREC bridges in the weakest sarcomere of a myofibril will be stretched first and as they reach their elastic limit they will detach. The myofibril will continue to be stretched until its passive tension has risen sufficiently, to the point where the next weakest sarcomere begins to be stretched. This process continues from the weakest towards the strongest sarcomere, in a similar way to the response to stretch of actively contracting muscle (Morgan 1990).

With this kind of model, tension will not fall to zero after the SREC has reached its elastic limit, yet the reformation rate of cross-bridges remains low.

The idea that thixotropic behaviour of muscle derives entirely from a cross-bridge mechanism has not been universally accepted. For a review, see Proske and Morgan (1999). The two most important pieces of evidence in support of a cross-bridge mechanism are the history dependence of thixotropy and its Ca^{++} dependence. The history dependence is demonstrated by a conditioning stretch which reduces the size of the SREC. Its dependence on Ca^{++} was demonstrated by Moss et al. (1976). Skinned frog muscle fibres did not exhibit a SREC in low $[\text{Ca}^{++}]$, but if the $[\text{Ca}^{++}]$ was slightly raised to just below that required for activation, it led to recovery of a typical SREC response to stretch. So muscle thixotropy can be thought of as a $[\text{Ca}^{++}]$ mediated, low level of activation involving about 1 % of cross-bridges, cross-bridges which generate an FRT and which respond to stretch with a SREC, but which do not go through a force-generating power stroke.

A gap filament, anchoring thick filaments to the Z disc in each sarcomere, is composed of the elastic protein titin. It is believed that titin contributes significantly to muscle passive tension (Kellermayer et al. 1997). Titin shows history-dependent, viscoelastic behaviour, and it has been suggested that it is able to contribute to muscle's thixotropic property (Kellermayer et al. 2008). However, the contribution by titin appears to become significant only at long muscle lengths, a sarcomere length of 3 μm (Kellermayer et al. 1997), while the history dependence due to stable cross-bridges is restricted to shorter lengths (Whitehead et al. 2001). The final word in this debate has probably not yet been said. It may ultimately turn out that there is 'a dynamic interplay between concurrent cross-bridge and non-contractile sarcomeric components (Kellermayer et al. 2008) and that the relative contributions from the two sources change with muscle length.

The concept of slack

One important consequence of thixotropic behaviour is the ability of muscle fibres to fall slack, depending on their previous history of contraction and length changes. This aspect of thixotropy has brought with it a degree of controversy since it is not normally possible to actually see fibres lying slack. The term 'slack' is applied to the condition where a muscle fibre's actual length is greater than the distance between its points of attachment (Proske et al. 1993).

The ability of muscle to fall slack can be readily demonstrated in animal preparations. When a muscle is dissected free of surrounding tissue, but leaving its tendons

of origin and insertion attached to the skeleton, rotating the joint to stretch it will, at the limit of joint movement, define the muscle's maximum body length. At the other extreme, if the muscle is shortened sufficiently, the muscle will fall slack. In human muscle, it is necessary to resort to ultrasound to show muscles falling slack (Herbert et al. 2011).

However, slack, as such, is not the subject of discussion here. The relevant issue is slack generated by thixotropic behaviour. The presence of SREC in muscle fibres allows them to lie slack or taut at a particular length, depending on their previous history of contraction and length changes. At very long lengths, a fibre will always lie taut, no matter what its previous contraction history, and at very short lengths, it will always lie slack (González-Serratos 1971). To attribute slack to thixotropic behaviour, it is necessary to choose an intermediate length where the fibre can lie either slack or taut, depending on what has been done to it beforehand.

Slack in a muscle fibre can be introduced by stretching it, holding it at the stretched length for several seconds to allow stable cross-bridges detached by the stretch to reform and then shortening it back to the initial length (Fig. 1). The cross-bridge explanation (Lakie et al. 1984; Morgan et al. 1984) is that when stable cross-bridges have formed in a fibre at a particular length, if the fibre is then shortened, the compressive forces acting on sarcomeres may lead to detachment of some stable bridges, but too few for the muscle fibre to be able to take up the shorter length without falling slack. The persisting bridges presumably exert a pushing action, opposing passive tension and generating slack. Given the low turnover rate of SREC bridges (see above), the slack may persist in the fibre for long periods, provided the muscle is left undisturbed.

Slack can be demonstrated in single isolated fibres of frog muscle. When a fibre is contracted isometrically at 2.5 μm sarcomere length and after a few seconds is shortened to a length where, if it had shortened freely, it would have adopted a sarcomere length of 1.8 μm , the shorter length signalled by the length transducer is not the actual length adopted by the fibre, which falls slack. The presence of slack shows up as a delay in the tension rise at the onset of a tetanic isometric contraction. When a second, identical, contraction is given at that length a second later, the delay is shorter by 10 ms. Calculations show that with an unloaded shortening velocity of 10 muscle lengths per second, the 10 ms delay represents take-up of 0.6 mm of slack or 0.2 μm per sarcomere (Julian et al., unpublished observations, see Proske et al. 1993; Fig. 1).

When a muscle fibre is contracted at a given length, any pre-existing slack is taken up by actively cycling, force-generating cross-bridges. As a result, once the fibre has relaxed, it lies taut. If the fibre is then stretched, once the elastic limit of the SREC has been reached, cross-bridges

detach. If the stretch is continued, some bridges will reattach during the movement to subsequently detach again. So the process envisaged during progress of a large, slow stretch is a continuous detachment and reattachment of cross-bridges. When, at the end of a stretch, the final length has been reached and the fibre is held there for several seconds, the majority of SREC cross-bridges within the fibre will have formed at or near that length. If the fibre is then shortened back to its starting length, it will fall slack (Fig. 1, see also Morgan et al. 1984).

After removal of slack by a contraction, if the taut fibre is subjected to a series of repeated stretch–shortening movements, the initial steep rise in tension in response to the second and subsequent stretches is delayed in onset due to the take-up time of the slack, and the tension at the yield point is lower because of the slow rate of formation of the SREC bridges. In this way, the increased compliance of passive muscle after preceding movements is a combination of slack and a reduced number of SREC bridges.

Why make so much fuss about slack? It is argued here that thixotropy allows passive muscle fibres to adopt one

of two extreme states, lying slack or taut, depending on their previous history of contraction and length changes. In the next section, evidence will be provided for thixotropic behaviour by the intrafusal fibres of muscle spindles. Controlling the amount of slack in intrafusal fibres regulates the sensitivity of muscle spindles.

Thixotropy in intrafusal fibres of muscle spindles

All striated muscles exhibit thixotropic behaviour, including invertebrate muscle (Harrison 1988). It therefore comes as no surprise that the intrafusal fibres of muscle spindles show thixotropic behaviour as well. The subject of intrafusal thixotropy and muscle spindle responses has a long history. It has come under a number of different headings, such as ‘spindle post-contraction sensory discharge’, ‘post-excitatory facilitation’ and ‘spindle after effects’. In the main, the observations come from single, identified muscle spindles in animals.

An early observation made by Kuffler et al. (1951) was an increase in spindle discharge after a period of fusimotor stimulation. This increase persisted for 7 min and could be abolished by a brief stretch. It was attributed to a ‘plastic’ property of the intrafusal fibres which tended to retain their shortened state after stimulation and so maintained greater stretch on the sensory ending. That, in turn, resulted in the post-contraction sensory discharge (Hunt and Kuffler 1951).

The first time a cross-bridge mechanism was invoked for post-contraction sensory discharge was by Brown et al. (1969). They applied the ideas of Hill (1968) to muscle spindles. In response to stretch of a spindle, following a period of fusimotor stimulation, they observed a large ‘initial burst’. They proposed that the peak of this burst represented the limit of the intrafusal SREC, beyond which stable cross-bridges in intrafusal fibres became detached.

At one point, it was proposed that the intrafusal fibres of muscle spindles could be excited by stretch, like insect flight muscle. But this turned out to be another example of spindle thixotropy. Rapid, repetitive stretches of a slack spindle detaches stable cross-bridges, allowing the intrafusal fibres to shorten and take up the slack. The spindle response to a brief burst of fusimotor stimulation, which had previously been small due to the slack, now grew to become much larger because the contraction no longer had to take up any slack (Emonet-Denand et al. 1985).

New insight into the mechanism underlying spindle responses to brief bursts of fusimotor stimulation was provided by Morgan et al. (1984). They demonstrated that the depressed response of a slack spindle to a brief burst of fusimotor stimulation could be converted into a delay in the onset of the afferent response to a period of sustained

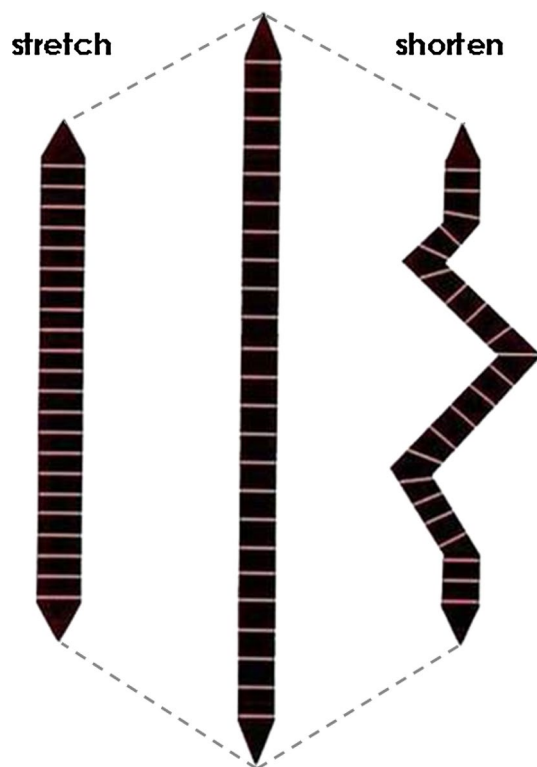


Fig. 1 Introducing slack in muscle fibres. The muscle fibre (or the whole muscle) is stretched, held at the stretched length for several seconds, to allow stable cross-bridges detached by the stretch to reattach at the longer length, and is then shortened back to its original length. During shortening, the compressive forces acting on the fibre are insufficient to detach all stable bridges. Their splinting action on the fibre leads it to be unable to take up the shorter length and it falls slack

fusimotor stimulation. Whether at the outset the spindle was slack or taut affected the delay, but not the size of the spindle response to the fusimotor stimulation (see also Gregory et al. 1986).

An aspect of spindle thixotropy which emerged at this time was its length dependence. It is a point to keep in mind in the design of experiments, when considering possible thixotropic influences. The evidence is that a spindle, when held at a moderate length, say on the ascending limb of the muscle's length–tension curve, will retain its slack over hundreds of seconds, provided it is left undisturbed. The slack can be demonstrated by the presence of a delay in the onset of a response to fusimotor stimulation ('latency shift', Morgan et al. 1984; Gregory et al. 1986). If the muscle is held at a longer length, near the optimum for a contraction, the latency shift is smaller. If it is held longer again, approaching the maximum body length of the muscle, the latency shift is very small and rapidly disappears. So at long muscle lengths spindle thixotropy effects are small and transient. The reason for this is the rising passive tension in the muscle.

If the intrafusal fibres, stiffened by the presence of stable cross-bridges, lie slack, they are subject to lateral compressive forces from surrounding connective tissue as well as from adjacent muscle fibres, tending to straighten them out. These forces may result in the detachment of stable cross-bridges, allowing the intrafusal fibres to shorten and take up some of the slack. This effect becomes more pronounced at longer muscle lengths where there is more passive tension, and a point can be reached where any developing slack is rapidly taken up and, as a result, history-dependent effects disappear.

While so far the discussion has centred on the thixotropic behaviour of intrafusal fibres, there is evidence that contractions of extrafusal fibres are able to influence the thixotropic state of spindles (Gregory et al. 1986). If a spindle has its intrafusal fibres lying slack, an extrafusal contraction is able to remove some of the slack, most probably as a result of the compressive forces exerted by the contracting extrafusal fibres detaching some of the intrafusal stable cross-bridges. In addition, as the muscle relaxes and the tendon recoils, it will stretch spindles to lead to further detachment of intrafusal cross-bridges and the removal of slack.

An important aspect of spindle responses is their background discharge. The level of background activity is believed to signal the length of the muscle and therefore limb position (Goodwin et al. 1972; Clark et al. 1985). The level of background activity is determined by the strain exerted by the intrafusal fibres on the spiral sensory ending. A simple mechanical model treats the sensory region of the intrafusal fibre as a spring (Matthews 1964). The annulo-spiral sensory ending overlying this region will have a spiral spacing determined by passive forces in the intrafusal fibre. When the muscle is contracted at fusimotor strength, at the initial length or at a shorter length ('hold short', Fig. 2), the contraction removes any pre-existing slack in intrafusal fibres, raises intrafusal passive tension and the level of strain on the sensory ending. This opens the sensory spirals and the background rate rises. Alternatively, if the muscle is stretched, contracted at the stretched length and held there for several seconds, stable cross-bridges will form at the longer length ('hold long', Fig. 2). On return to

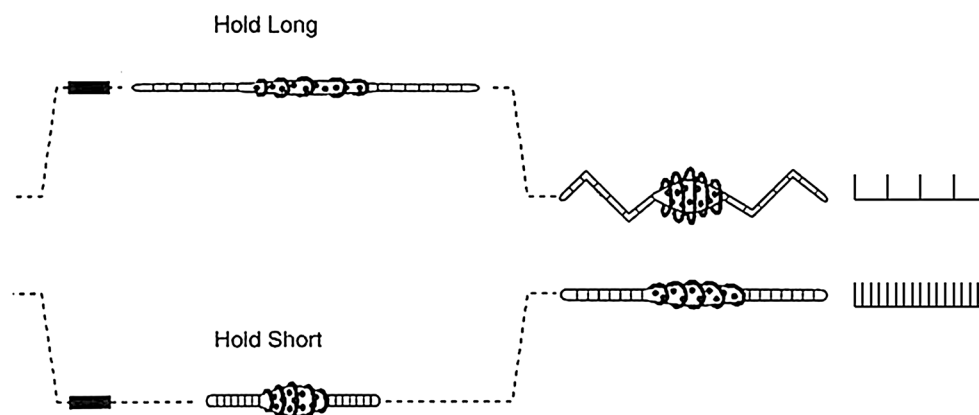


Fig. 2 Thixotropic behaviour of intrafusal fibres of muscle spindles. The diagram of the muscle spindle has been simplified by showing only a single intrafusal fibre. When the muscle is stretched and stimulated at fusimotor strength (black bar), all stable cross-bridges form at the longer length ('Hold Long'). Returning the muscle to its original length leads the intrafusal fibre to fall slack, as a result of the splinting action of the persisting bridges. That, in turn, releases any tension on the spindle sensory ending and the generation of only

a low level of background activity. Alternatively, if the muscle is shortened and contracted (black bar), the stable bridges all form at the shorter length ('Hold Short'). Stretching the muscle back to its original length leads to a rise in intrafusal passive tension, as a result of the stiffening effect of the stable bridges. This strains the spindle sensory ending, leading background rates to be high. Redrawn from Proske (1995)

the initial length, the intrafusal fibres, stiffened by the stable cross-bridges, are unable to shorten themselves and fall slack. That lowers their passive tension and the sensory spirals close, lowering background discharge rates. While the background activity of the majority of spindle primary and secondary endings is subject to thixotropic influences, some secondary endings show no thixotropic behaviour (Proske et al. 1992). These are endings typically served by afferent axons with diameters at the lower end of the Group II distribution. These axons are postulated to terminate in polar regions of the intrafusal fibres (Banks et al. 1982), overlying or distal to the region of slack and therefore unaffected by it.

Muscle spindles contribute to spinal reflex action, as well as proprioception. Inevitably, their thixotropic behaviour exerts its influence on both roles. While the subject of reflex action is peripheral to the main theme of this review, it deserves brief mention. In human subjects, a conditioning voluntary contraction of the triceps surae muscle enhanced the amplitude of the tendon jerk elicited by a tap of the Achilles tendon (Gregory et al. 1987) and reduced the size of the H (Hoffman) reflex (Gregory et al. 1990; Polus et al. 1991). Evidence has been provided that changes in spindle resting discharge, evoked by muscle conditioning, exert an influence on the H reflex. The reflex becomes depressed after conditioning which raises spindle background discharge (Wood et al. 1996). This depression is called post-activation depression (Hultborn et al. 1996). Finally, there is evidence of changes in human cortical excitability depending on the form of muscle conditioning. A rise in spindle background activity, produced by a conditioning muscle contraction, increased the size of the motor-evoked potential recorded in wrist flexor muscles in response to transcranial magnetic stimulation (Stuart et al. 2002).

While the foundations for our understanding of the influences of muscle thixotropy on the responses of muscle spindles rest on observations in animals, in recent years a body of evidence has been compiled in support of the thixotropic behaviour of human spindles. This is important background information since the work on proprioception uses human subjects. It has proved difficult to obtain detailed information on the thixotropic behaviour of identified human spindles since it requires microneurographic recordings of functionally single afferents. The technique relies on achieving stable recording conditions, and observing the responses to conditioning contractions is difficult because of the risk of dislodgement of the recording electrode. Nevertheless, a number of successful recordings have been achieved.

The first report was by Hagbarth et al. (1985) who recorded multi-unit activity of stretch receptors in human finger flexor muscles. Responses to muscle twitch contractions suggested the majority of afferents were muscle spindles. Afferent responses to torque pulses decreased following a large finger extension which was likely to introduce

slack into the muscle and its spindles. Afferent responses increased following a passive finger flexion. These changes persisted when spindles were functionally de-efferented by a nerve block proximal to the recording site, implying a peripheral mechanism and not reflex action.

Three years later, Edin and Vallbo (1988) published a set of recordings of finger extensor muscle spindles of human subjects that was remarkably similar to animal recordings obtained four years earlier (Morgan et al. 1984). Responses were recorded after the muscle had undergone a series of rapid, large amplitude stretches that were intended to detach stable cross-bridges. The muscle was then either held short or long for a few seconds before a slow test stretch was applied. Most primary endings of spindles and some secondary endings showed enhanced stretch responses after the muscle had been held short compared with responses when the muscle had been held long. This was typical thixotropic behaviour. In a series of experiments on the flexor digitorum profundus muscle of human subjects (Jahnke et al. 1989), the discharge of single spindles was seen to be less after a stretch of the muscle compared with after an isometric contraction. The authors made the observation that slack in a muscle after a stretch could persist despite an ongoing 5 % contraction of the muscle, and a stronger contraction was required to reset the thixotropic state.

Subsequently, Wilson et al. (1995) showed that after a voluntary contraction, there was an enhancement of background discharge of muscle spindles in ankle and toe dorsiflexor muscles of human subjects. The mean rate increased from 2 to 5 impulses s^{-1} . Stretch of the receptor-bearing muscle reduced or eliminated the enhanced discharge. This result is important because the prevailing level of spindle background discharge is believed to signal limb position (Clark et al. 1985; Proske and Gandevia 2012). In a related experiment, Burke and Gandevia (1995) showed an increase in sensitivity of human muscle spindles to vibration at an intermediate muscle length after a voluntary contraction at a short length. The vibration response was significantly reduced when the conditioning contraction was carried out at a long length, and the muscle was then shortened back to the intermediate length.

To summarise, a number of aspects of thixotropic behaviour have now been demonstrated for human spindles, giving us confidence that the knowledge base provided by animal experiments can be reliably applied to human subjects.

Muscle thixotropy and the senses of limb position and movement

It is generally accepted that proprioception comprises the senses of position and movement, the senses of force, effort

and heaviness, and the sense of balance. Here, the discussion will be restricted to the senses of position and movement since sensations associated with active force generation would not be expected to be subject to the influences of thixotropy (but see Luu et al. 2011).

Thixotropy and limb position sense

Definitive evidence for a role for muscle spindles in the senses of limb position and movement was provided by Goodwin et al. (1972) using muscle vibration. The first report that muscle thixotropy could influence limb position sense was by Gregory et al. (1988). A parallel series of experiments was carried out on identified muscle spindles in an animal preparation and on limb position sense in human subjects. It was shown that conditioning contractions produced systematic changes in spindle responses of the soleus muscle in the anaesthetised cat, and similar conditioning of human elbow flexors and extensors was accompanied by changes in limb position. The underlying hypothesis was that the level of spindle resting discharge determined limb position (Clark et al. 1985). The conditioning manoeuvres altered spindle resting discharge, and this led to a change in the perceived position of the limb. When elbow flexors were contracted with the forearm held flexed, placing the arm in an intermediate test position led subjects to believe the arm was more extended than was really the case. Similarly, when the arm was held extended and elbow extensors were contracted, subjects felt it was more flexed. The authors also showed that instead of using a conditioning contraction to reset the thixotropic state of the relevant muscle, the same result could be achieved with 80 Hz vibration. Presumably, the vibration led to detachment of stable cross-bridges and their reassemblage at the conditioning length, leaving the muscle in a similar state as after a conditioning voluntary contraction. At the time, an important oversight made was not to realise that in a limb-matching task, both limbs must be put into a defined, conditioned state, since both contribute to matching errors (White and Proske 2009; Izumizaki et al. 2010).

Traps and pitfalls when measuring position sense

One of the objects of this review is to remind students of proprioception of the importance of putting a muscle into a defined thixotropic state. If that is not done, it risks misinterpretations of the data. That is, when measurements are made of position sense in a relaxed limb, or when the subject supports the limb themselves, representing a 5 % of maximum contraction (Winter et al. 2005), it is important to know what has happened to limb muscles before the measurement. In everyday activities, we typically move our arms about with or without accompanying contractions of

elbow muscles. It means elbow muscles may lie slack or tight, depending on the circumstances. The thixotropic state of muscles in both arms will therefore influence errors in any position-matching task.

Many accounts of observations of position sense using unconditioned muscles can be found in the literature. An example is the commonly reported finding that position sense is more accurate when measured in an active limb, compared with the passive limb (Paillard and Brouchon 1968). When position sense is measured in a passive limb with muscles conditioned beforehand, position errors are no larger than when limb muscles are contracting (Ansems et al. 2006; Allen et al. 2010).

The idea that signals of central origin, generating a sense of effort, contributed to position sense was explored by measuring position-matching errors in subjects whose arms were required to support a 2-kg load (Winter et al. 2005). Loading an arm was found to shift position errors in the direction of elbow extension, and it was concluded that position sense arose from both peripheral signals and signals of central origin. However, the measurements had been made on an unconditioned arm. If arm muscles are not intentionally conditioned with a voluntary contraction of 10 % or more of maximum, it is likely that some slack will be present in spindles (Gregory et al. 1998). Loading the arm would require the subject to increase the strength of their flexor contraction, to be able to support the load. The larger contraction risked removing any persisting slack, and this would lead to an increase in spindle discharge. As a consequence, position of the arm would be perceived as more extended. So, rather than an effort signal accounting for the load-dependent changes in position sense, it was the increase in afferent signals accompanying the changed thixotropic state that was responsible. This conclusion was confirmed when the experiments were repeated but with muscles of both arms systematically conditioned before applying the load (Allen et al. 2007; Walsh et al. 2013).

Thixotropy and movement sense

In the original experiments of Goodwin et al. (1972), muscle vibration produced an illusion predominantly of movement, but including a component of limb displacement. The movement illusion is presumably generated largely by the primary endings of muscle spindles (Roll et al. 1989), the illusion of displaced position by both primary endings and secondary endings (McCloskey 1973). The question has been raised whether the senses of position and movement comprise two components of the one sense, (kinaesthesia, Bastian 1880) given that both are generated by spindles, or whether they should be considered separate senses. A contribution to this debate is provided by muscle thixotropy. The background discharge of primary and secondary

endings of spindles can be increased with a conditioning contraction and this leads to a perceived change in position of the limb without any accompanying sensation of movement (Gregory et al. 1988). The fact that the two senses can be manipulated independently in this way supports the idea of their being separate.

There is relatively little information in the literature on muscle thixotropy and the sense of movement. The effects of muscle conditioning have been studied on movement sensations generated by vibration of arm muscles (Gooley et al. 2000). After a conditioning contraction of elbow muscles of both arms with the arms held flexed, 70 Hz vibration of elbow flexors at an intermediate length produced an illusion of the arm moving into extension which the subject was asked to track with their other arm. The average tracking speed by seven subjects was 1.3° per second. When the arms were contracted with the arm held extended, vibration at the intermediate length led to a halving of the perceived movement speed, 0.7° per second. This was presumably because the extension conditioning had introduced some slack in elbow flexors and the response of the slack spindles to vibration was weaker.

The movement illusion produced by vibration of one arm has been shown to be dependent on movement of the other arm (Izumizaki et al. 2010). The perceived speed of movement into extension produced by vibration of elbow flexors of one arm was reduced by half if at the same time the other, non-vibrated arm was moved into extension. If, on the other hand, the movement of the non-vibrated arm was into flexion, the perceived speed of movement of the vibrated arm nearly doubled. The result suggests that the movement illusion represents a difference signal calculated from the inputs coming from both arms. Extension of the non-vibrated arm stretches its flexors, raising their proprioceptive discharge and reduces the difference signal from the two arms. Similarly, shortening the non-vibrated arm reduces its proprioceptive signal in flexors and, as a result, the difference signal is increased.

This experiment was recently taken one step further by Hakuta et al. (2014). They showed that the illusion of movement and position change during vibration of reference elbow flexors was significantly reduced if, at the same time, the indicator flexors were vibrated as well. The authors concluded that what subjects felt was, at least in part, a difference signal calculated centrally from the inputs from both arms.

Vibrating a muscle typically generates a tonic vibration reflex (TVR) which is the vibration equivalent of the phasic stretch reflex or tendon jerk, a local segmental reflex. Hakuta et al. made the additional observation that when both arms were vibrated, leading to a reduction of the vibration illusion, there was no accompanying reduction in the TVR. The observation is a reminder of the diversity

of actions by afferents of muscle spindles; during the two-arm vibration, the segmental reflex effects continued unimpeded, while the centrally generated sensation was reduced. The observation also supported the view that the size of the afferent response to vibration was not reduced in any way by simultaneous vibration of the two limbs.

Up to this point, the sense of movement has been described in circumstances involving proprioceptive signals from both arms. A measure frequently used as a neurological test in the clinic is to impose small movements at a joint and ask subjects to declare when they feel the movement and to indicate its direction. Here, presumably it is the dynamic sensitivity of muscle spindles and perhaps skin stretch receptors that determines the value of threshold. In a laboratory simulation of this test, subjects have their forearm strapped to a servomotor that generates small, reproducible movements. Subjects are asked whether a movement has occurred and, if so, to indicate its direction. For such measurements of detection threshold, thixotropy plays an important role. When measurements are made with the contraction history of elbow muscles unknown, threshold values several times higher are obtained, compared with values when muscles have been conditioned to remove any slack (Hall and McCloskey 1983; Wise et al. 1996). Presumably in the unconditioned muscles, slack must be taken up by the movement before receptors are stimulated.

An area of controversy concerns the changes in movement detection threshold measured when the muscles acting at the joint being tested are contracting. A fall in detection threshold has been reported (Taylor and McCloskey 1992) as well as a rise (Wise et al. 1998). One possible explanation is that with muscles in an unconditioned state, the contraction removes slack in muscle spindles, leading to a lowering of threshold. A rise in threshold can be accounted for by the reduced movement sensitivity of muscle spindles during ongoing fusimotor activity (Wise et al. 1999).

To conclude, movement sense, like position sense, is strongly dependent on the way the muscles acting at a joint have been conditioned, and at the elbow joint, it is not only the form of conditioning that matters but the input coming from both arms. This latter point comes up again in measurements of position sense.

Exploring position sense using thixotropy

Now that many of the problems associated with making measurements of position sense have been recognised, the technique of putting muscles into a defined thixotropic state can be exploited to further explore this sense. Muscle conditioning allows muscle spindles to be put into one of two states: (1) where there is no slack, receptors are stretch sensitive and they generate a high level of background activity,

or alternatively, (2) where slack is present, leaving spindles with little or no background activity and a low stretch sensitivity. This ability to manipulate spindle activity at a chosen muscle length, simply by using a voluntary contraction and a stretch, represents a powerful tool for exploring new aspects of proprioception.

At the elbow, the commonly used conditioning procedure adopted before making position sense measurements is for the blindfolded subjects to hold both forearms upright, with the elbows at 90°. Subjects are asked to contract their elbow flexors, pulling the paddles supporting the forearms towards the body. This is called flexion conditioning. Alternatively, subjects lay their forearms in an extended position (0°) on the table supporting the apparatus, and they are asked to push down on the table, in the process contracting their elbow extensors. This is extension conditioning. After conditioning, the experimenter moves the reference arm to an intermediate, test angle, the subject holds it there and they match its position with their other, indicator arm. Here, it is important to remember that movement of the reference arm to the test angle and movement of the indicator to a matching position shortens and slackens the antagonists to the muscles which have been conditioned. Therefore, the proprioceptive signal coming from the arm is strongly biased in favour of activity from the muscle group which has undergone the conditioning contraction.

When muscles of both arms are conditioned identically in this way, matching errors do not reduce to zero. Typically, when the arms are flexion conditioned, the blindfolded subject makes errors of 2°–3° in the direction of flexion (Allen et al. 2007, 2010; Tsay et al. 2012). That is, the subject places their indicator arm in a slightly more flexed position relative to the reference. When both arms are extension conditioned, errors lie by a similar amount in the direction of extension. The source of these errors lies in the method of matching. After conditioning, the reference arm is moved to the test angle and held there. Once the reference arm has stopped moving, the background activity of spindles will signal the test length. Moving the indicator arm into a matching position will stretch spindles in its conditioned muscle, but here the signal will comprise both background activity as well as a component generated by the movement to the matching position. The larger signal during the move to match persuades the subject that their indicator arm is more extended than it really is, leading them to declare a match too soon, before the two arms have been accurately aligned. As a result, small errors occur, lying in the direction of flexion after flexion conditioning and in the direction of extension after extension conditioning.

Evidence that supports such an interpretation comes from experiments where the proprioceptive signals coming

from both arms are deliberately reduced by introducing slack in elbow muscles (Tsay et al. 2014). With lower spindle discharge rates, the difference in signal between the stationary reference arm and the moving indicator is smaller, resulting in errors lying closer to 0°.

The next logical step in exploring position sense is to examine the effect of making the proprioceptive signals coming from the two arms deliberately very different by conditioning arm muscles in opposite directions. If, for example, the reference arm is flexion conditioned, it will have a high flexor signal and a low extensor signal. If the indicator is extension conditioned, it will have a high extensor signal and low flexor signal. How can position be matched if the signals coming from the antagonist pairs of the two arms are very different? The answer is that large matching errors result, about 10° in the direction of extension after flexion conditioning of the reference and 10° in the direction of flexion after extension conditioning of the reference (Allen et al. 2007; White and Proske 2009). The large errors result from trying to match a high reference signal with a low indicator signal. For example, for flexion conditioning of the reference arm, the subject leaves their indicator arm too extended, trying to achieve a match with a much lower signal in the indicator flexors. The same argument applies when the reference arm is conditioned with a high extensor signal and a low flexor signal, but the errors are in the opposite direction.

It is interesting that with this technique, errors of $\pm 10^\circ$ can be generated by means of muscle conditioning. It makes for a total range of errors of 20°, representing about 25 % of the range of movements of the forearm studied in this kind of experiment, (between 90° and 0°, Allen et al. 2007). During the course of these experiments, it was thought subjects might comment about the difficulty in trying to achieve a satisfactory match when they were making such large errors. However, interrogating subjects revealed that they were no more uncertain about the position of their arms than on other occasions, despite the large disparity in forearm position (Proske and Gandevia 2009). It suggested that subjects were unaware of the size of their matching errors.

The technique of selectively conditioning one of the antagonists acting at a joint, to raise the level of its proprioceptive signal, was recently exploited in a study exploring the phenomenon of proprioceptive drift (Tsay et al. 2014). It has been known for some time that when a limb is held stationary at a particular posture, in the absence of vision, there is a perceived change in its position with time, called proprioceptive drift (Paillard and Brouchon 1968; Wann and Ibrahim 1992; Brown et al. 2003). While it has generally been assumed that proprioceptive drift arises as a result of central mechanisms, a possible alternative explanation is that the perceived shift in limb position is the result of

adaptation of the spindle receptor discharge from muscles signalling the position of the limb (Tsay et al. 2014). In support of such an explanation, it was shown that after flexion conditioning of elbow muscles, there were progressive changes in position errors, in the direction of elbow flexion, over the 30 s of visual occlusion. Importantly, when elbow muscles were extension conditioned, time-dependent errors were still present, but they were in the opposite direction, into extension (Tsay et al. 2014). The interpretation was that as the discharge from the conditioned muscle declined—as a result of receptor adaptation—this was interpreted by the brain as a less stretched muscle, that is, a more flexed or more extended elbow. In other words, thixotropy could be used to determine the direction of proprioceptive drift. It was concluded that while a contribution from central processes to proprioceptive drift could not be ruled out, an adequate peripheral mechanism was now available to account for the typical, time-dependent errors in position sense.

A new experiment

Muscle vibration is a powerful stimulus for muscle spindles (Roll et al. 1989). Some years ago, it was shown that if the two antagonists of one arm were vibrated at the same time, the illusion of movement generated depended on the difference in vibration frequency (Gilhodes et al. 1986). A higher frequency applied to flexors led to perception of arm extension, and a higher frequency applied to extensors led to perception of arm flexion. When the vibration frequency was made the same for both muscle groups, there was no movement illusion. Given that the vibration was likely to continue to increase spindle afferent discharges in both muscles, these findings suggested that the brain was not listening to the inputs from individual muscles or group of muscles, but to the difference in signal coming from the antagonist pair. Here, in a new experiment, we have used the method of muscle conditioning to arrive at the same conclusion.

With the standard flexion conditioning or extension conditioning procedure applied to muscles acting at a given joint, when, after conditioning, the limb is brought to the test angle, one of the antagonists is always left taut—with a high level of background discharge—the other slack with little or no background activity. Therefore, with this method of conditioning, the input to the central nervous system is always dominated by the signal from one member of the antagonist pair. We have recently devised a technique of conditioning where the input from both antagonists can be kept at high levels. To do that for elbow muscles, the blind-folded subject's reference arm is moved to the test angle and held fixed in position, while elbow flexors and then elbow extensors undergo isometric contractions. Since now both

muscle groups have been contracted at the same length and there is no movement after the contraction, both are in a near-identical thixotropic state, with no slack present and therefore the likelihood of a high level of background activity in both muscles. When a subject attempts to match the position of a reference arm, conditioned in this way with an indicator arm that has been flexion conditioned, position errors of 10° into flexion result (Tsay et al. 2014). Similarly, when the indicator is extension conditioned, errors of 10° into extension are observed. The result suggests that, despite both reference antagonists being in a sensitised state, the resultant signal coming from the reference arm lies close to zero, and the observed position errors arise as a result of the signal coming from the conditioned indicator arm.

Evidence for such a conclusion came from use of a new method of muscle conditioning (Tsay et al. 2014). Some of the data from this experiment are reproduced here, redrawn to bring out the key points. To aid in the description, the plot of observed errors (Fig. 4) is accompanied by a series of cartoons indicating what is happening to the muscles (Fig. 3). There are four conditioning sequences, A, B, C and D. In two of the sequences (A and B), the reference arm has both antagonists undergoing isometric contractions at the test angle, as described above. Figure 3a shows the conditioning used to produce matching errors indicated by point A in Fig. 4. Here, the indicator is flexion conditioned, that is, the arm is held at 90° and the subject is asked to attempt to flex their arm towards their body. In the meantime, reference antagonists have both been contracted at the test angle. Once relaxed, the indicator is moved into a matching position. For nine subjects, matching errors were 9.8° in the direction of flexion (Tsay et al. 2014).

The experiment is now repeated, but this time, the indicator arm is extension conditioned (Fig. 3b). For that, the indicator arm is moved into full extension (0°) and the subject is asked to push down on the supporting table, in the process contracting their elbow extensors. At the same time, reference antagonists have again been co-contracted at the test angle. The subject then moves their indicator into a matching position. For nine subjects, the matching error was 9.6° in the direction of arm extension (Tsay et al. 2014). This is shown as point B in Fig. 4.

In panel C of Fig. 3 is shown the third form of conditioning employed in this experiment. Reference and indicator muscles are initially flexion conditioned, but following conditioning, both arms are moved into full extension. The movement stretches elbow flexors and shortens extensors. The arms are left in the extended position for 6 s. A period of 6 s is sufficient for cross-bridges to reassemble at the longer length in the flexors (Morgan et al. 1984). When the arms are then moved into flexion, to a matching position, elbow flexors, stiffened by the new stable bridges,

fall slack. Since the elbow extensors are already slack, it means that at the test angle now both antagonists from both arms are slack, generating only low levels of afferent signal. When nine subjects matched their arms, following this sequence of conditioning, the errors were 0.5° in the direction of extension (Tsay et al. 2014). This is shown as point C in Fig. 4. So the slackening manoeuvre undergone by both arms has moved matching errors by 10.3° , from 9.8° into flexion to 0.5° into extension.

In the fourth sequence (D), the arrangement of the muscles is not shown in Fig. 3, just the measured errors are plotted in Fig. 4d. In this sequence, the procedure described for (C) is repeated, but starting with extension conditioning of both arms. Subsequently, the arms were flexed to 90° , held there for 6 s and then moved into a matching position. Matching errors were into extension (Tsay et al. 2014). So this time the slackening manoeuvre has moved errors by 9.5° from 9.6° into extension to 0.1° into extension.

This experiment shows that slackening flexors or extensors of both arms and therefore lowering the level of afferent discharge coming from them leads to matching errors lying close to zero. By inference, we propose that when reference muscles are co-contracted at the test angle, the net signal coming from them is also close to zero. Supporting evidence comes from a new experiment (Tsay et al., unpublished observations). Here, reference muscles were always co-contracted at the test angle, while indicator muscles had slack deliberately introduced in them. This, too, led to matching errors close to zero.

The conclusion from this experiment was that during matching, the shift in errors closer to zero after slackening indicator flexors or extensors and therefore lowering their afferent signals implies that the reference signal must also have been close to zero. Furthermore, given that the changes in errors were determined by the indicator arm, it suggests that the brain not only determines the difference in signal between the antagonists of one arm but listens to both arms and computes the difference between them. A similar conclusion was recently arrived at by Hakuta et al. (2014).

We believe that isometric conditioning of reference antagonists raises afferent activity in both muscle groups to high levels. Presumably, the streams of afferent impulses in the two muscles match one another reasonably well, sufficiently close for the difference signal coming from the arm to lie near zero. It is a little surprising given that it is likely that these are population responses from each muscle group (Bergenheim et al. 2000) and that the population discharge profiles are not likely to be identical. It may be that in interpreting the afferent activity coming from the two muscles, the brain takes into account any population differences.

Recent observations indicate future directions

So far, most of the experiments described here have been done at the elbow joint. It begs the question: can the method of muscle conditioning be applied at other joints? This is substantially an issue for future experiments, although some limited information is available from measurements at the knee (Givoni et al. 2007; Allen et al. 2010) and at the wrist (Smith et al. 2009; Walsh et al. 2013). A study of position sense at the wrist showed that when the blind-folded subject had their hand held at a particular angle, when they were asked to generate an isometric effort of 30 % of maximum in that position, they perceived a shift in location of the hand in the direction of extension for extension efforts and into flexion for flexion efforts (Smith et al. 2009). It was proposed that a centrally generated signal associated with the effort sensation contributed to position sense.

However, in those experiments, the wrist muscles had been conditioned by a series of flexion–extension movements without any conditioning contraction. It left open the question of whether some of the effort-related errors were the result of removal of slack in wrist muscles. In addition, at the forearm, it had been shown that position errors in the relaxed, supported arm were not significantly different from errors when arm muscles were contracting to support a 25 % load (Allen et al. 2010). So at the elbow, there was no evidence of a contribution from an effort signal. Because of these uncertainties, the two groups of experimenters got together and carried out a series of collaborative experiments at the elbow and wrist with muscles conditioned at each joint in identical ways (Walsh et al. 2013). The findings confirmed that isometric efforts at the elbow did not produce significant position-matching errors, while similar sized efforts at the wrist did produce such errors. It was concluded that there were systematic differences between joints in the contribution of motor command signals to position sense. In the future, similar experiments are planned for other joints with the intention of surveying the role of motor command signals in position sense across the body.

One further difference between the experiments of Allen et al. (2010) and Smith et al. (2009) was the method used for indicating the position of the limb. At the wrist, the hand was hidden from sight and the subject indicated its perceived position by rotating a pointer which was co-linear with the wrist. At the elbow, a position-matching task used both arms. Presumably, therefore, at the elbow, both arms contributed proprioceptive signals to the matching task. At the wrist, given the very different movement carried out by the hand moving the pointer, it seemed unlikely that its signals contributed to the measurement. If so, location of the reference hand must have been derived by referral to

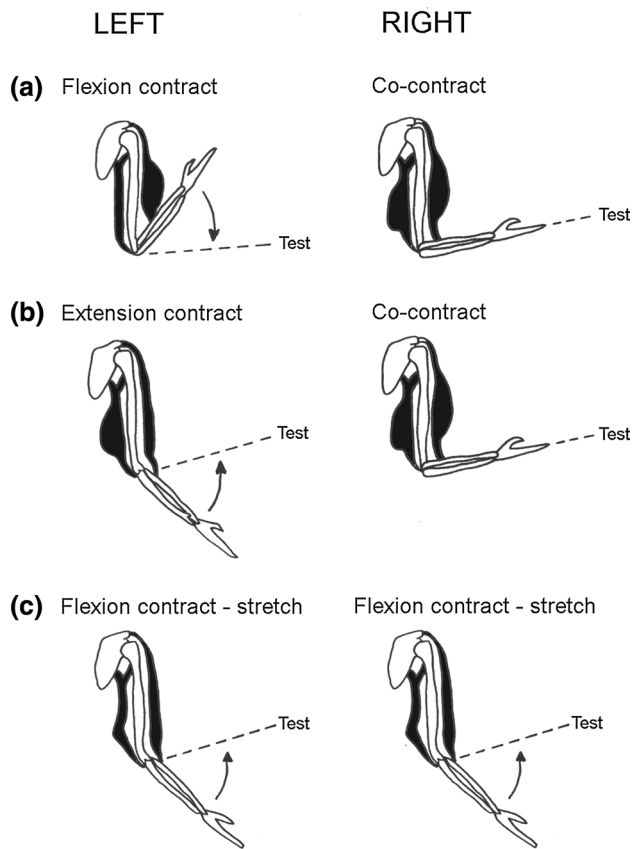


Fig. 3 Diagrammatic representations of arm muscles during conditioning procedures before a two-arm-matching task. All matching of arm positions was done by blindfolded subjects, matching in the vertical plane, while supporting their arms themselves. **a** The reference arm is the right arm, the indicator the left arm. Conditioning procedures for the right arm were the same for **a** and **b**. Here, the arm was moved by the experimenter to the test angle and held fixed in position while elbow flexors and then extensors underwent isometric contractions. Position of the indicator arm started at 90° at the elbow, that is, with the forearm in a vertical position. The subject contracted elbow flexors by trying to pull the arm towards their body. Once they had relaxed from the contraction, they moved the arm to a matching position with the reference arm (dashed line). **b** Here, the reference arm was conditioned, as above. The indicator was moved into full extension (0°) and the subject pressed the arm down on the supporting surface, in the process contracting their elbow extensors. Once they had relaxed, they were asked to move their arm to a matching position. **c** Here, both reference and indicator arms began with a flexion contraction at 90° . After they had relaxed, both arms were moved into full extension (0°) and left there for 6 s. This reset flexor cross-bridges to the longer length. The experimenter then moved the reference arm to a test angle, and the subject moved their indicator into a matching position. Redrawn from Tsay et al. (2014)

a central map of the body. It leads to the conclusion that measuring position sense in a matching task is fundamentally different from a pointing task. For that reason, in the experiments of Walsh et al. (2013), position errors were measured using both a matching task and a pointing task at the wrist and elbow.

It has recently been shown that a centrally stored model of the hand can be drawn using locations of a series of landmarks (Longo and Haggard 2010). The map is distorted and resembles a similar map drawn many years ago by Penfield and Boldrey (1937). The data suggested that the source of the distortion was clustering in the pattern of central terminations of the afferent input. The map is distinct from a conscious body image which is accurate in its representation. It seems reasonable to assume that a central stored model is used as a reference point in a limb-pointing task. We know that the map is able to rapidly change in size and shape, in response to changes in afferent input. It has been shown that the central map of the hand is continuously updated by the incoming streams of afferent information, and if the afferent pattern changes, the map changes with it (Inui et al. 2011). Therefore, it was reasonable to presume that the map was similarly updated by changes in afferent input evoked by muscle conditioning (see also Stuart et al. 2002). That conclusion was in general agreement with the observations of Walsh et al. (2013).

Evidence has already been provided for the interpretation that when elbow muscles were co-contracted at the test angle, the brain responded to the difference in signals coming from elbow muscles, not their individual values, and this was likely to lie near zero. This conclusion is consistent with the observations of Gilhodes et al. (1986) using simultaneous vibration of elbow antagonists. Vibration of both muscle groups at the same frequency abolished the vibration illusion. More recently, Longo et al. (2009) also vibrated elbow antagonists at the same time and confirmed the observations of Gilhodes et al., using a forearm-matching task. However, when subjects were asked to point with their left hand to the perceived position of the right arm, when this was being vibrated, they demonstrated significant biases in pointing errors. The direction of errors suggested that subjects perceived the vibrated arm as telescoping towards the elbow, similar to telescoping of the phantom limb seen in some amputees. They concluded that loss of coherent information about body position in space, like from co-vibration of antagonists, leads to an apparent contraction of the body representation.

However, a high level of afferent activity generated simultaneously in antagonists should not be seen as a conflict situation since it is a circumstance encountered routinely in everyday life. When we are standing in the bus holding onto a handrail, we use our arm as a support, making it rigid by co-contracting elbow muscles. Presumably during such circumstances, the level of afferent signal coming from the antagonists would be expected to be high, given that during a voluntary contraction there is co-activation of fusimotor neurones (Vallbo 1971, 1974). It poses the question: do the afferent signals coming from the arm

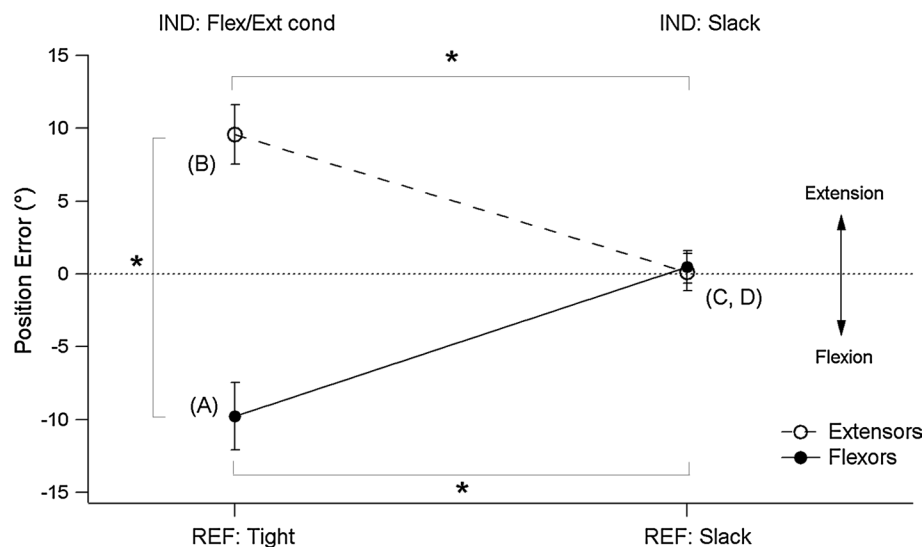


Fig. 4 Position errors at the forearm with arm muscles either tight or slack. Position errors for nine subjects after four forms of conditioning. Point A is a plot of matching errors (mean \pm SEM) after the conditioning sequence shown in Fig. 3a. Position errors were measured after both elbow muscles of the reference arm had been conditioned isometrically at the test angle (Ref: Tight) and the indicator arm flexion conditioned (IND: Flex cond, filled circle, A). Alternatively, as shown in Fig. 3b, the indicator arm was extension conditioned (IND: Ext cond, open circle, B), with the reference arm muscles again co-contracted at the test angle (Ref: Tight). For point C and shown dia-

grammatically in Fig. 3c, both arms had been flexion conditioned and then moved into full extension before matching (IND: slack, REF: slack, filled circle, C). For point D (not shown in Fig. 3) both arms had been extension conditioned and then moved into full flexion before matching (IND: slack, REF: slack, open circle, D). Trends in the data were indicated by a solid line where the conditioning procedure began with flexion conditioning and by a dashed line where it began with extension conditioning. Dotted line indicates zero error. Asterisks indicate significant differences between points. Data replotted from Tsay et al. (2014)

under such circumstances lead to perception of foreshortening of the arm? It seems unlikely.

One further difference between pointing and matching errors at the wrist and elbow is arguably the most interesting one. At the elbow, the confidence intervals for mean pointing errors were greater than for mean matching errors (Walsh et al. 2013; Fig. 4). At the wrist, the distribution of confidence intervals for pointing and matching were more nearly the same. It leads to the conclusion that at the wrist, a two-handed matching task improves accuracy over pointing, but only a little. By contrast, at the elbow-matching performance is much more consistent than for pointing. So the precision with which the position of an unseen hand or arm can be indicated with a pointer is similar for the elbow and wrist, but at the elbow, this is inherently less accurate than a comparison of signals in a two-arm-matching task. Why might that be so?

We know from experiments at the elbow that what is important is position of the hand, not the angle at the elbow. In a series of matching experiments using different arm postures, achieved by altering shoulder angles without changing elbow angle, it was found that subjects were most accurate with the arms in front, hands aligned (Gooley et al. 2000). Similarly, when subjects were asked about the position of their unseen forearm, they were less accurate in determining elbow angle than fingertip position (Fuentes

and Bastian 2010). In addition, there is animal data showing that some second-order neurones in the centrally projecting proprioceptive pathway signal the limb end point representation and not the specific geometry associated with the end point (Bosco et al. 2000). All of this suggests that the brain has assigned particular significance to the hands-in-front posture.

When we manipulate objects with our hands, or use them to fashion tools, we have our arms in front, hands aligned and palmar surfaces facing each other. We postulate that because of the importance of this posture in human behaviour, a specific neural mechanism has evolved to ensure accuracy of alignment. This mechanism makes use of proprioceptive signals from both antagonists of both arms, and the brain interprets their difference as a measure of their alignment. Experiments in which muscles of both arms have been conditioned in opposite directions, (something that is unlikely to happen in everyday life), have produced maximum matching errors of $\pm 10^\circ$, representing a total range of 20° within the working space of the arm (Allen et al. 2007; White and Proske 2009; Tsay et al. 2014). We propose that this range represents the limits of the matching mechanism, a mechanism which is based entirely on the proprioceptive signals coming from the two arms. When the arms are more than 10° apart, in the absence of vision, other mechanisms could come into play.

For example, the subject could revert to making reference to a central map.

Conclusions

Muscle thixotropy is a fundamental property, resulting from events arising at the level of the sarcomeres, and it is therefore wide ranging in its influences. The method of conditioning has allowed us to exploit the thixotropic behaviour of muscle to manipulate the afferent discharges coming from it.

The aim in this review has been to make a case for muscle thixotropy as a tool in the study of proprioception. For an arm-matching task, evidence has been provided that the relevant signal from each arm is the flexor–extensor difference. If the conditioning method is used to make the difference signal in one arm large and in the other small, then during a match, the null point, the point of minimum signal difference between the two arms, can have a large value. This leads to position errors of up to 10°, of which the brain remains unaware. The brain simply makes the assumption that when the null point has been reached, the arms are aligned. This assumption is likely to be close to correct in everyday situations. Without muscle conditioning, it is unlikely that afferent streams from the two arms are ever going to be very different. So the null point in a comparison between the two arms is always likely to lie near zero. Therefore, the conditioning method provides an opportunity to set up extreme circumstances, and the resulting position errors provide a comment on how the brain measures arm alignment.

If these ideas are correct, we are faced by the challenge of accounting for the accuracy in position matching when one arm is loaded with a weight (Allen et al. 2010) or contracting isometrically (Walsh et al. 2013). When elbow muscles of one arm contract with a force of up to 30 % of maximum, position errors in a matching task are not significantly greater than with an unloaded arm. Yet, the motor activity in the loaded arm would be expected to produce large increases in spindle discharges from fusimotor co-activation (Vallbo 1971, 1974). How a null point mechanism might work under these conditions remains to be resolved. One possibility is that a central subtraction of the fusimotor-evoked reafference takes place (Proske and Gandevia 2012). It has also been suggested that activity arising in an actively contracting muscle may no longer contribute to proprioception and the position information is coming from the stretched antagonist (Capaday and Cooke 1983).

We are beginning to learn some of the rules by which the brain makes simplifying assumptions in order to cope with the large volume of complex signals reaching it from the body periphery. Selecting the relevant parameters essential for particular tasks is one means of ensuring a prompt

response and that ultimately improves the chances of survival for the individual.

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APPENDIX 2: BodyinMind.org

Should proprioceptive training be a priority in the management of chronic pain?

Avid readers of BodyinMind.org know all too well that chronic pain can be associated with perceived distortions of the painful limb, be it in size, shape or posture [1-4]. In some cases, those with chronic pain report that they have limited awareness of the location of their painful body part [4, 5]. What they report may be a disturbance to the sense of limb position, which is a component of proprioception (or sensations derived from the body itself, such as the sense of movement and force). Efforts to potentially restore proprioceptive feedback through training have been incorporated into some chronic pain rehabilitative programs [6]. However, in the case of position sense, it is unclear how chronic pain would influence the perceived position or posture of a painful limb [7].

Let's look at the potential mechanisms. Chronic pain is associated with many changes in brain structure and function [8]. Speculatively, the changes in the brain might underpin alterations in the way proprioceptive information is processed. Alternatively, ongoing tissue damage at the site of the pain, which may involve the receptors in the muscle that provide proprioceptive information could alter proprioceptive processing.

The receptors in our muscles that respond to stretch, known as muscle spindles, are primarily responsible for signalling the sense of limb position and movement [9]. Muscle spindles increase their resting discharge in proportion to the stretch imposed on them, and this is how the brain detects that a muscle has become longer. Hence, assessing position sense is a non-invasive measure that reflects muscle spindle function and can be used in chronic pain. In these tests, the participant is blindfolded and asked to either match the position of one arm with the other, or indicate the location of the arm using a pointer. For clarification, the arm being pointed to is designated the *reference arm* and the arm (or pointer) moved to match the reference arm's location is called the *indicator*.

Manipulating spindle activity can lead to predictable errors or directional biases when we

match our arms in a position sense task [for a review, see 10]. For example, we can generate relatively accurate alignment of the arms when elbow antagonist muscles from both arms have similar net spindle activity [11, 12]; whereas large errors, in the order of 10° or more, can be produced by inducing different (i.e. high vs low) spindle activity between the arms [11]. This manipulation, called muscle conditioning, is done by performing a voluntary contraction or stretch of the muscle before taking a position sense measurement.

In our recent study [13], we investigated position sense at the forearm after muscle conditioning in 30 age- and sex-matched individuals with chronic pain primarily in one arm (upper-limb) or leg (lower-limb), and 15 people without pain. Surprisingly, matching errors were similar no matter whether the painful arm was the reference (being matched to) or the indicator arm (positioned to match the reference arm). Moreover, across different muscle conditioning techniques, i.e. presumably under a high vs low spindle activity between the arms, all participants made large matching errors. Importantly, there were no group differences found amongst those with upper- or lower-limb pain, or those without pain, in any condition. This suggests that the proprioceptive signals from the painful arm are “listened” to just as clearly and accurately as the non-painful arm during a position matching task.

We also wanted to know if chronic pain impaired the ability to indicate where the arm was in space. That is, we wanted to know what happens when position sense was determined using information from only one limb. In this task the reference arm was hidden behind a screen and participants were instructed to indicate the perceived position of their painful and non-painful arms, in separate trials, using a pointer. The results were similar across all three groups, as well as between painful and non-painful arms, reinforcing the idea that muscle spindles appear to function normally and that localising a limb in space appears to be unaffected.

Future investigations are required in order to elucidate the mechanisms involved in the bodily distortions associated with chronic pain. However, in the case of position sense, our findings seem to suggest that peripheral proprioceptive information remains intact. Hence,

proprioceptive training of position sense may not be required in the management of chronic pain.

About Anthony Tsay

Anthony is a PhD student at the School of Public Health and Preventive Medicine, Monash University. Having dabbled in everything from rowing, Taekwondo, Parkour, rock climbing, and Olympic weightlifting, it's clear that Anthony's real passion lies in human movement. No wonder his PhD focussed on proprioception (the sense of movement, position and force), and how the brain uses proprioceptive information to form a coherent mental representation of the body.

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