Joint stiffness in a phantom limb: evidence of central nervous system involvement in rheumatoid arthritis

R. C. Haigh, C. S. McCabe, P. W. Halligan and D. R. Blake

Objective. The nature and cause of perceived joint stiffness (PJS), a well-established and defining symptom of rheumatoid arthritis (RA), remains unclear. We hypothesized that changes in the central nervous system (CNS) may determine and maintain this subjective experience of stiffness in a limb even after it is amputated. To test this hypothesis, patients with a phantom limb (PL) who had experienced characteristic RA stiffness prior to amputation were systematically investigated.

Methods. Three patients with a current diagnosis of RA and lower limb amputation were investigated to determine the nature and pattern of pain and stiffness in their PL and intact limb. In addition to standard physical examination, pain and stiffness severity was measured using visual analogue scales for both limbs. The duration and timing of stiffness were also recorded for each limb.

Results. In all three cases, the pattern of perceived RA stiffness was similar for the intact limb and the PL. All three patients described stiffness in their PL which mirrored that of physical RA joint symptoms in terms of quality, frequency, diurnal variation, location, distribution and response to medication [non-steroidal anti-inflammatory drug (NSAID), corticosteroid, opiate and disease-modifying anti-rheumatic drug (DMARD)]. Unilateral exercise (or attempted exercise) relieved stiffness only in the limb being exercised.

Conclusion. The extent to which the subjective experience of perceived stiffness could be dissociated from the assumed original peripheral source was strikingly illustrated in RA patients with phantom limbs. We suggest that the PJS characteristic of RA is generated and maintained by secondary plastic changes in the CNS, although causally related to the initial peripheral rheumatoid disease process.

The nature and cause of stiffness in rheumatoid arthritis (RA) remain unclear, although it is a cardinal diagnostic symptom [1] and is used as a clinical indicator of the extent of disease activity. Currently, two qualitatively different uses of the term are employed. Objective joint stiffness (OJS) is operationally defined as the measurable resistance to passive movement when the joint is put through a normal range of motion in the usual functional plane [2]. This objective or mechanical stiffness, however, is not equivalent to the subjective complaint of localized immobility, a perceived resistance to self-initiated movement, reported by patients with active RA [3, 4]. Using a microprocessor-controlled arthograph, it has been shown that measures of OJS do not relate to the subjective experience. Indeed, compared with non-arthritic controls, OJS was reduced in RA joints [5].

We suggest, therefore, that it is clinically useful and theoretically important to distinguish two different uses of the clinical term ‘stiffness’ in RA. We propose that the common clinical complaint of subjective rigidity and immobility be described as ‘perceived joint stiffness’ (PJS). Following the qualitative findings of Lineker et al.
[4], we take PJS to refer to the variable set of subjective sensations (i) that can be triggered by preparing to move a joint or initiating a limb movement, (ii) that is more commonly pronounced in the morning, and (iii) in which the subjective content is commonly associated with and often indistinguishable from pain or discomfort. Traditionally, PJS has been attributed to local ongoing sensory deafferentation and repetitive selective limb use [8, 9]. We therefore hypothesized that the central nervous system (CNS) is capable of generating a feedback-dependent state which can result in pathological sensations, such as pain and stiffness, that are to some extent independent of the initial peripheral pathology [7, 10]. Clinical evidence to support this proposal might be found by investigating the clinical presentation of PJS in RA patients who have undergone limb amputation but nevertheless retain an experience of a phantom limb. Indeed, by decoupling direct physical sensory feedback, such cases provide a great opportunity to understand the CNS mechanisms that may generate the characteristic subjective symptoms of PJS.

**Patients and methods**

Patients were sought who fulfilled diagnostic criteria for RA prior to undergoing limb amputation. A search was made of the local hospital’s database (RNHRD, Bath) and regional Artificial Limb Centre (Southmead Hospital, Bristol). Three patients were identified, and local ethics committee approval was given to approach them. A detailed history was taken of each patient. For example, in the foot, maximal stiffness was found to that experienced in the limb prior to amputation. The location and distribution of the stiffness was identical and carried with it the same distressing quality. The duration of stiffness in each limb was similar. The phantom ankle and knee in patients B and C felt swollen in exactly the same manner as (though independent of) normal limb RA joints. When the intact limb joint flared, the phantom limb joint also flared (Fig. 1). The stiffness reported was similar in magnitude and faded concomitantly with the intact limb. Nocturnal and diurnal variation was also present. If stiffness woke the patient at night or the intact limb was similar.

**Results**

The clinical details of the three subjects are presented in Table 1. All patients experienced a post-amputation phantom limb, a sensation of the missing limb and phantom limb pain, which is common and well described [11]. Moreover, all three patients claimed that they could voluntarily move their phantom limb. However, all subjects complained or reported, during investigation, a discernible sensation of stiffness (PJS) and inability to move the phantom limb joints freely. This was similar to that experienced in their limb prior to amputation and occurred at the same time as the stiffness in the remaining intact limb. This ‘phantom stiffness’ mirrored traditional RA joint stiffness symptoms in many, but not all aspects, as summarized in Table 2. In terms of the quality of the stiffness, all patients reported the same physical sensation of inability to move the joints freely in both the intact limb and the phantom limb. This feeling of stiffness was identical and carried with it the same distressing quality. The duration of stiffness in each limb was also similar. The phantom ankle and knee in patients B and C felt swollen in exactly the same manner as (though independent of) normal limb RA joints. When the intact limb joint flared, the phantom limb joint also flared (Fig. 1). The stiffness reported was similar in magnitude and faded concomitantly with the intact limb. Nocturnal and diurnal variation was also present. If stiffness woke the patient at night or the intact limb was similar.

**Table 1. Clinical details of patients with RA and amputation**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Disease duration (yr)</th>
<th>Reason for amputation</th>
<th>Amputation level</th>
<th>Time after amputation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>79</td>
<td>23</td>
<td>RA vasculitis and ulceration</td>
<td>Left through-knee</td>
<td>3 yr</td>
</tr>
<tr>
<td>B</td>
<td>63</td>
<td>24</td>
<td>Peripheral vascular disease</td>
<td>Right above-knee</td>
<td>4 months</td>
</tr>
<tr>
<td>C</td>
<td>77</td>
<td>25</td>
<td>Delayed non-union ankle fracture</td>
<td>Right below-knee</td>
<td>2 yr</td>
</tr>
</tbody>
</table>

**Table 2. Characteristics of stiffness in phantom limb**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Phantom swelling</th>
<th>Early morning</th>
<th>Gel phenomenon</th>
<th>NSAID</th>
<th>New DMARD</th>
<th>Corticosteroid</th>
<th>Opioid</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<td>B</td>
<td>+</td>
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<td>C</td>
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+, presence of symptom or positive response to medication; –, negative response to medication.
present in the toes located over the intact and phantom limb metatarsal joints. It was associated with a feeling of clawing of the toes, coupled with a desire to exercise. With post-rest stiffness, the usual ‘gel’ phenomenon occurred, and was similar in both intact and phantom limb. Phantom stiffness was also responsive to non-steroidal anti-inflammatory drugs (NSAIDs), mirroring the intact joints. Systemic administration of corticosterone in patient B (Fig. 1) and a new disease-modifying anti-rheumatic drug (DMARD) in patient C improved both pain and stiffness in phantom limb and intact limb joints alike.

However, the stiffness reported in the phantom limb was not simply a mirrored duplicate of stiffness in the intact limb or a somatosensory memory of stiffness of the amputated limb. When asked to exercise (with eyes closed) the existing limb while keeping their phantom limb still, the intact limb joint rapidly lost its stiffness, as indicated by scores on the VAS, but had no effect on PJS of the phantom limb (Table 3). The converse was also true: ‘exercising’ the phantom limb had no effect on stiffness in the intact joint. Furthermore, in patient B the amount of exercise required to relieve stiffness in the phantom limb was at least three times that required to relieve stiffness in the intact limb. The reduction of stiffness for similar durations of exercise was slightly less in the phantom limb. For example, the severity of stiffness (0–10 visual analogue score) before and after exercise in the intact limb was 7/10 and 4/10 respectively, and in the phantom limb it was 7/10 (before) and 5.5/10 (after).

**Discussion**

This report complements and extends previous studies of amputees, many of whom report significant levels of phantom pain. The presence and origins of arthritic symptoms in phantom limbs have not received clinical attention, nor have their implications for understanding the underlying mechanisms that generate the characteristic subjective symptoms of PJS. Consequently, there are no epidemiological studies of limb amputation in arthritis, nor are there any clinical reports describing the nature of phantom limb pain in RA patients. As PJS in these cases could not have been derived from the original peripheral pathology and the effect of limb exercise (phantom and intact limb respectively) was specific to the limb being exercised (ruling out pre-amputation memory), our findings indicate that the subjective experience of PJS is generated and maintained in the absence of continuous peripheral input from the amputated limb. If peripheral systems are not ultimately involved in generating and maintaining the subjective experience of PJS, which brain systems are involved?

Our findings are consistent with recent clinical observations and neurophysiological findings which show that neuropsychological changes in the brain are sufficient to explain some chronic pain conditions. Harris [10] proposed that many pains may have cortical origins. We suggest that PJS (a qualitatively distinct form of discomfort) could also have its origins in brain mechanisms responsible for monitoring the consequences of motor intention and, in particular, the expected or predicted sensory feedback generated at the time planned movements are initiated. These feed-forward and inverse models have been extensively reviewed by Wolpert [12].

**Table 3. PJS severity and response to unilateral joint exercise (patient B)**

<table>
<thead>
<tr>
<th></th>
<th>Toes</th>
<th></th>
<th>Ankle</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS before exercise</td>
<td>VAS after exercise</td>
<td>VAS before exercise</td>
<td>VAS after exercise</td>
<td></td>
</tr>
<tr>
<td>Intact limb</td>
<td>7</td>
<td>4 (10)</td>
<td>7</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Phantom limb</td>
<td>7</td>
<td>6 (35)</td>
<td>7</td>
<td>6 (60)</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate duration of exercise (s) required to relieve PJS.
efferent copy of that motor command is produced in parallel. This provides the basis for predicting the consequences of the actual movement. In most cases, the normal awareness and experience of our limb is based on the predicted state rather than the actual state [13]. If the system monitoring feedback detects a deviation from the predicted state, a subjective experience of over- or undershoot is reported, as in the case of pointing or grasping [13]. Even in the absence of feedback from a physical limb (i.e. a phantom limb), motor commands from frontal brain areas can still be issued which produce a predicted state whereby the phantom is experienced as moving.

In RA, we suggest that dysfunctional proprioceptive information processing produces impaired efferent copies that are largely responsible for these patients’ experience of stiffness and indeed pain. Over time, this distorted information is used to predict the expected sensory and conscious correlates of a limb movement. Production of an impaired efferent copy will consequently activate brain areas that monitor the conflict between motor intention and appropriate sensory feedback [10, 14]. This qualitatively altered perception is experienced and reported as stiffness rather than stabbing or shooting pain because it is triggered by preparing to move a joint or initiate a limb movement and not the movement per se.

Our observation that the movement of a phantom limb fails to relieve stiffness to the same extent as movement of the intact limb highlights the importance of actual (albeit impaired) peripheral feedback in modulating stiffness symptoms. Furthermore, the lack of effect of unilateral exercise on the opposite knee joint rules out a pain-mirroring mechanism from the contralateral joint. A period of short but continuous exercise allows visualization of the moving limb—as patients do with their hands when describing stiffness in the clinic—may further enhance the modification of the efferent copy with input from another modality. Similarly, sensory interventions, such as hydrotherapy, hand immersion in hot wax and taking a shower in the morning, could provide the additional cutaneous sensory feedback required to correct inaccurate predictions of the existing efferent copy.

We consider it unlikely that the phantom RA represents a ‘somatosensory memory’. As a clinical presentation, the condition is clearly described by the patient as an experience rather than a semantic memory. This qualitative distinction by the patient also finds support in several recent functional imaging studies of phantom limb patients and referred sensations, in which experience and reported movements of the phantom limb are associated with selective activations in sensory–motor brain areas normally involved in limb movements [15–17].

The final common pathway for the generation of PJS is the conflict between the predicted (efferent copy) and actual states, caused by inaccurate sensory information. Are there conditions in RA that create these conflicts of motor and sensory information? Such incongruence may be signalled via a number of routes, and both neural mechanisms and centrally acting circulating mediators may be involved. Firstly, inappropriate cortical representations, as a consequence of impaired proprioceptive input, can generate conflict between the senses [10]. Functional imaging studies provide evidence of cortical changes at several levels in RA [18–21]. Secondly, neural mechanisms include distorted position sense [22], impaired sensory feedback from partially denervated joints [23] and the functional consequences of peripheral and CNS sensitization. Thirdly, circulating factors include inflammatory mediators and cytokines, such as tumour necrosis factor α and interleukins, which may trigger CNS centres and enhance peripheral nociceptive responses. Cytokines can recruit central stress-responsive neurotransmitter systems involved in the modulation of the immune response and in the activation of behaviours that may be adaptive during injury or inflammation [24–26]. Previous work has shown that variation in levels of these mediators, coupled to activity of the hypothalamic–pituitary–adrenal axis, may be related to the circadian pattern of stiffness [27, 28].

In conclusion, we report three patients with RA stiffness in their phantom limb. The characteristics of this PJS were very similar in some aspects, whilst crucially different in others, to that of PJS in the diseased remaining limb. On this basis, we argue that the experience of peripherally located stiffness results from impairment of central brain processes. In reformulating the accounts of both Ramachandran et al. [8] and Frith et al. [13] for phantom limb experience, we suggest that dysfunctional sensory processing in RA produces impaired efferent copies of the planned motor commands and expected sensory consequences. This is ultimately perceived as stiffness by the patient with RA.

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References


