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Movement variability and pain: Searching for a solution

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Abstract

Human movement is inherently variable. In the performance of complex, multi-joint tasks, it is possible to consistently achieve an accurate outcome (i.e. low variability of the goal: VAR_{goal}), with many different combinations of joint movements and patterns of muscle activation (i.e. variability in the elements of the movement: $VAR_{elements}$). It has been proposed that when the nervous system is challenged by acute experimental pain, $VAR_{elements}$ might increase to search for a new, less painful movement strategy and then decrease if a less painful solution is found. The changes to $VAR_{elements}$ found in situations of chronic musculoskeletal pain are more diverse. In chronic pain $VAR_{elements}$ might be reduced, increased, not changed, or a complex interaction of these possible adaptations. All previous studies that investigated $VAR_{elements}$ during pain evaluated multi-joint tasks (e.g. walking, pointing) that involve multiple elements. It was unclear whether $VAR_{elements}$ would be altered in a similar manner for simple tasks with fewer elements and thus limited potential for $VAR_{elements}$ to change.

For the series of studies included in this thesis, a simple movement task was developed that involved radial-ulnar deviation of the wrist between two target angle regions. Kinematic data were collected with 3-dimensional recording systems and $VAR_{elements}$ were considered in wrist flexion-extension and forearm pronation-supination. The effect of pain on $VAR_{elements}$ during performance of the radial-ulnar deviation task was evaluated in *Studies 1-3*, under various pain conditions.

Study 1 investigated the influence of acute experimental pain, induced with injection of hypertonic saline, on $VAR_{elements}$ during performance of the repetitive radial-ulnar deviation task. This study showed that, unlike that observed in more complex multi-joint systems, $VAR_{elements}$ was reduced during acute pain in the simple task with limited elements that could change. The most likely explanation was that the motor system constrained movement in an attempt to reduce pain or exert greater control over joint motion.

On the foundation of differences in the changes to $VAR_{elements}$ for complex and simple tasks during acute pain, *Study 2* investigated whether $VAR_{elements}$ would initially increase during acute pain to gain exposure to different movement options in a search for a less painful solution. An experimental paradigm was developed where the simple task provoked moderate pain for most movements, but a less painful or non-painful solution was available that was likely to be experienced as a result of $VAR_{elements}$ with repetition of the task. We found participants searched for, and found, a less painful movement strategy, but $VAR_{elements}$ was not used as part of this search. Participants did not select

the strategy provided as *the least painful solution* by the experimental paradigm, but found a less painful strategy with gradual changes to wrist/forearm position over multiple repetitions to explore alternative movement options. The changes to $VAR_{elements}$ when participants performed the simple task in *Studies 1* and *2* were not consistent with the strategies observed in previous studies of multi-joint tasks.

In *Study 3* participants with chronic lateral epicondylalgia (LE) and pain-free controls performed the radial-ulnar deviation task whilst gripping a load cell to a standardised force, which provoked pain for LE participants. We found no difference of $VAR_{elements}$ between the LE group and controls at the start or end of the trial, but in the LE group, $VAR_{elements}$ in the flexion-extension direction decreased over time. Participants with chronic LE moved the wrist into a more flexed wrist position and reduced $VAR_{elements}$ to allow performance of the radial-ulnar deviation task in a less painful manner.

Based on the results of *Studies 1-3* and previous investigations, it was clear that $VAR_{elements}$ could be altered during pain, but two fundamental questions remained unclear. First, what is the time-course of changes to $VAR_{elements}$ when acute pain is sustained, and second, are the changes to $VAR_{elements}$ in acute pain and chronic pain related? To answer these questions a model of pain that induces acute pain that is sustained for several days was needed.

Study 4 investigated whether an intramuscular injection of nerve growth factor (NGF) into an elbow/forearm muscle induced sustained pain that was provoked by movement and muscle contraction/stretch. Pain that was provoked by movement of the upper limb and by contraction/stretch of the injected muscle was sustained for six days. These features indicate that intramuscular injection of NGF induces pain that responds in a manner that is typical of clinical pain, and is a suitable model to study the effect of sustained lateral elbow pain on $VAR_{elements}$.

These four studies provide insight into the relationship between $VAR_{elements}$ and pain during a simple task with few elements, and offers an avenue for future work using NGF as a sustained pain model for LE. When challenged by pain, the motor system does not use $VAR_{elements}$ to search for a less painful solution for simple tasks with less capacity to change and considers multiple factors in addition to minimisation of pain and injury when selecting a movement strategy.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my research higher degree candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

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Publications during candidature

Peer-reviewed papers

Bergin MJG, Hirata R, Mista C, Christensen SW, Tucker KJ, Vicenzino B, Hodges PW & Graven-Nielsen T. Movement evoked pain and mechanical hyperalgesia after intramuscular injection of nerve growth factor: A model of sustained elbow pain. *Pain Medicine,* 16:2180-2191.

Bergin MJG, Tucker KJ, Vicenzino B, van den Hoorn W & Hodges PW. (2014). Does movement variability increase or decrease when a simple wrist task is performed during acute wrist extensor muscle pain? *European Journal of Applied Physiology*, 114:385-393.

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Bergin MJG, Elliott J & Jull G. (2011). Absence of the inferior portion of the trapezius muscle in three family members. *Manual Therapy,* 16:629-635.

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Conference abstracts

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Bergin MJG, Tucker KJ, Vicenzino B & Hodges PW (2014). Has interpretation of the motor adaptation to pain been too simplistic? *Postgraduate Research Conference of the School of Health and Rehabilitation Sciences*, Brisbane, Australia: 26 November 2014 (Podium presentation) [Pain Australia and Australian Pain Society for best presentation on pain]

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Contributor	Statement of contribution
Michael J.G. Bergin (Candidate)	Designed experiments (40%) Acquisition of data (80%) Analysis of data (55%) Interpretation of data (60%) Wrote the paper (40%)
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Contributions by others to the thesis

List the significant and substantial inputs made by others to the research, work and writing represented and/or reported in the thesis. These could include significant contributions to: the conception and design of the project; non-routine technical work; analysis and interpretation of research data; drafting significant parts of the work or critically revising it so as to contribute to the interpretation. If no one contributed significantly then state "No contributions by others."

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motor control, movement variability, motion analysis, elbow pain, lateral epicondylalgia, tennis elbow, experimental pain, sustained pain, nerve growth factor

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The aim of the wise is not to secure pleasure,

but to avoid pain.

~Aristotle

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LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
BPM	Beats per minute
CV	Coefficient of variation
DASH	Disability of arm and shoulder
DOMS	Delayed onset muscle soreness
ECR	Extensor carpi radialis
ECRB	Extensor carpi radialis brevis
ECRL	Extensor carpi radialis longus
ECU	Extensor carpi ulnaris
ED	Extensor digitorum
EMG	Electromyography
FCR	Flexor carpi radialis
FCU	Flexor carpi ulnaris
FDP	Flexor digitorum profundus

FDS	Flexor digitorum superficialis
GPT	Grooved pegboard test
ISO	Isotonic saline
MVC	Maximal voluntary contraction
NaCl	Sodium chloride
NGF	Nerve growth factor
NRS	Numerical rating scale
OA	Osteoarthritis
PFPS	Patellofemoral pain syndrome
PPT	Pressure pain threshold
PRTEE	Patient rated tennis elbow evaluation
PT	Pronator teres
RMS	Root-mean squared
ROM	Range of motion
RT	Reaction time
SD	Standard deviation
SOM	Speed of movement
SRT	Simple reaction time
TMS	Transcranial magnetic stimulation
VAR_{goal}	Variability of the goal
$VAR_{elements}$	Variability of the elements
VAS	Visual analogue scale
2-D	Two-dimensional
3-D	Three-dimensional

1 Introduction

Musculoskeletal conditions are a worldwide public health problem, accounting for 6.7% of the global burden of disease (Australian Institute of Health and Welfare [AIHW], 2014). In 2011-12 an estimated 6.1 million Australians (28% of the total population) were affected by musculoskeletal conditions such as lateral epicondylalgia (tennis elbow) and osteoarthritis of the knee (Australian Bureau of Statistics [ABS], 2012). Musculoskeletal conditions can have a major impact on the health and overall quality of life of an individual. The pain and functional limitations imposed by arthritis (Murphy et al. 2012), spinal pain (Linton, 2000), and neck and low back pain (Holmberg and Thelin, 2006) can be detrimental to a person's self-esteem and image, leading to negative emotional status, anxiety, depression, and feelings of helplessness (Sheehy et al. 2006). Musculoskeletal conditions affect the capacity of working-age people to gain employment (Lacaille et al. 2007) and are the most frequent cause of sickness and absence from work (Brage et al. 2010). These individual factors place a high economic burden on the community due to lost productivity and the use of hospital and primary care services (Australian Institute of Health and Welfare [AIHW], 2005). As a result of their relatively high prevalence, impact on the individual and society, and long-lasting and generally non-fatal nature, musculoskeletal conditions have been an Australian National Health Priority Area since 2002 (Australian Institute of Health and Welfare [AIHW], 2005). Although musculoskeletal conditions are diverse and can affect any region of the body, a consistent feature is musculoskeletal pain and impaired physical function.

By definition, acute episodes of musculoskeletal pain are of "recent onset and probable limited duration that usually has an identifiable temporal and causal relationship to injury or disease" (Ready and Edwards, 1992), and typically resolve within days or weeks of onset. However, in many cases acute pain "persists beyond the time of healing of an injury and frequently there may not be a clearly identifiable cause", and develops into a chronic musculoskeletal pain condition. In 2007 an estimated 3.2 million Australians were living with chronic pain, which is expected to increase to 3.8 million people in 2020 and 5.0 million people in 2050 (Access Economics, 2007). Chronic pain contributed to a total economic impact of $34.3 billion in 2007, approximately 62% of which was related to musculoskeletal conditions (Access Economics, 2007).

A visible manifestation of both acute and chronic musculoskeletal pain is that it changes the way we move (e.g. limping after a sprained ankle). Changes to movement patterns are likely beneficial in the acute phase of pain if they limit mechanical loading of painful structures (e.g. joint surfaces,

tendons) in an attempt to reduce pain, limit further injury, and facilitate tissue healing (Hodges and Tucker, 2011). However, it has been postulated that the changes to movement that present in the acute phase might contribute to the development of chronic musculoskeletal pain conditions if they are sustained past the initial period of tissue healing (i.e. beyond when adaptation is necessary and/or in excess of what is necessary). One way in which movement adapts to pain, which could have both positive and negative consequences, and that has received infrequent attention in the pain literature, is the potential to change movement variability.

Movement variability refers to trial-to-trial variation in the patterns of muscle activation and motion of joints and body segments between each repetition of an otherwise consistent task (Preatoni et al. 2013). Movement variability can be broadly classified according to two components; variability in the outcome of a task relative to its goal (VAR_{goal}) and variability of the elements (e.g. muscles, joints; $VAR_{elements}$) that make up the movement. For instance, when pointing to a target it is possible to consistently achieve an accurate outcome (i.e. low VAR_{goal}) with many different combinations of joint movements and patterns of muscle activation (i.e. $VAR_{elements}$). $VAR_{elements}$ is possible because of the complexity and redundancy (i.e. multiple ways that a movement can be performed) of the nervous system and musculoskeletal system (Bernstein, 1967; Bartlett et al. 2007).

Movement variability was once considered an unwanted feature of movement (Fitts, 1954). However, Nikolai Bernstein's seminal work (1967) demonstrated that professional blacksmiths could perform a hammering task accurately despite variability in the movement patterns of the upper limb during the task, and challenged the belief that $VAR_{elements}$ was detrimental to optimal function. Since this work, it has gradually been accepted that $VAR_{elements}$ is a potentially beneficial feature of normal, healthy movement. Despite the numerous studies that have evaluated $VAR_{elements}$ in non-painful and painful situations since the work of Bernstein (1967), our understanding of $VAR_{elements}$ is incomplete and not straightforward. A contemporary view of $VAR_{elements}$ is that it can be both beneficial and detrimental. Beneficial $VAR_{elements}$ is thought to lie between two limits (i.e. between an upper limit and lower limit) (Stergiou et al. 2006) that are not fixed and likely influenced by a unique combination of factors, including the task goal, the environment in which the task is performed, and the individual who performs the task. Conversely, detrimental $VAR_{elements}$ can be above (i.e. too much $VAR_{elements}$) or below (i.e. too little $VAR_{elements}$) the two limits of beneficial $VAR_{elements}$.

Beneficial $VAR_{elements}$ (i.e. between the upper and lower limits) might have several positive consequences for the nervous system and musculoskeletal system (Table 1-1). First, $VAR_{elements}$ may allow the motor system to explore different movement patterns to find the optimal strategy among the many options that are available (Dingwell et al. 2001; Riley and Turvey, 2002; Preatoni et al. 2013). Second, $VAR_{elements}$ may facilitate the distribution of stresses more broadly between different tissues (e.g. muscles, joint surfaces) and thus reduce the cumulative load on specific tissues (Hamill et al. 1999; Srinivasan and Mathiassen, 2012). However, there might be immediate and long-term consequences to function if $VAR_{elements}$ increases or decreases outside the limits.

An increase of $VAR_{elements}$ above the upper limit might reflect compromised control of the numerous muscles and joints/body segments involved in the task. This poor control might have several consequences, such as greater potential for movement error (e.g. less successful attainment of a task goal) and uncontrolled/excessive loading of soft tissues with the potential for tissue damage and acute pain. Conversely, a decrease of $VAR_{elements}$ below the lower limit might compromise the ability of the nervous system to learn new skills and adapt movements in new contexts (Wu et al. 2014). Further, decreased $VAR_{elements}$ might reduce the net area of joint structures over which normal loads are applied during repetitive tasks, thereby increasing the cumulative load on specific tissues, with the potential for acute pain or damage. Thus, both too much and too little $VAR_{elements}$ in non-painful situations may compromise healthy distribution of loads and contribute to the development of acute pain and injury (e.g. through uncontrolled or excessive loading of soft tissues). During an episode of acute pain or injury, changes to $VAR_{elements}$ might have a beneficial or detrimental role. For instance, two related goals of the nervous system during acute pain are likely to be reduction of pain intensity and prevention of further injury (Hodges and Tucker, 2011). These two goals could potentially be achieved with several different *beneficial* changes to $VAR_{elements}$. First, in the presence of acute pain, an increase of $VAR_{elements}$ may enable the motor system to search for a new, less painful movement strategy that has less potential to provoke pain and injury (Moseley and Hodges, 2006; Madeleine et al. 2008a; Hodges and Tucker, 2011). The hypothesis that the motor system uses $VAR_{elements}$ to search for a less painful movement strategy during acute pain is based on studies that found $VAR_{elements}$ increased when multi-joint tasks were performed during acute experimental pain at the low back (Moseley and Hodges 2006) and shoulder (Madeleine et al. 2008a). After this initial increase in $VAR_{elements}$ (interpreted as the initial search for a new movement strategy), $VAR_{elements}$ may decrease so the less painful pattern is used more frequently for subsequent repetitions of the task (Moseley and Hodges, 2006). Second, the nervous system might increase $VAR_{elements}$ to distribute stresses over a greater

surface area of soft tissues relative to pain-free situations. This could have the short-term benefit of reducing the relative frequency and likelihood that painful tissue regions are loaded during repetitive tasks. Although these hypotheses are elegant, it remains unclear whether the interpretation is accurate.

Conversely, an initial increase of $VAR_{elements}$ during acute pain/injury might be *detrimental* to function. $VAR_{elements}$ above an upper limit of beneficial variability might reflect compromised control of the multiple task elements involved in a task due to poor sensory or motor processing, or sensorimotor integration (Brumagne et al. 2004; Dessureault et al. 2008; Malmstrom et al. 2013) or impaired joint stability following damage to important stabilising structures (e.g. anterior cruciate ligament rupture at the knee (Georgoulis et al. 2006)). Excessive $VAR_{elements}$ could lead to uncontrolled motion of joints and body segments with greater potential for error and uncontrolled/excessive loading of soft tissues with the potential for further damage and pain. To minimize the potential for damage/pain as a consequence of poor sensorimotor function or impaired joint stability, the motor system might proactively reduce $VAR_{elements}$ (Hamill et al. 1999). However, it is unclear whether the motor system uses this strategy of reduced $VAR_{elements}$ and whether it is beneficial or detrimental in the short-term and long-term.

These changes to $VAR_{elements}$ during acute pain (i.e. increase or decrease) might be beneficial in the short-term to satisfy the immediate goals of the nervous system (e.g. reduce pain and limit the potential for further injury), but they might have long-term consequences. For instance, if sustained for an excessive period of time, they could potentially contribute to the development of chronic pain (Hamill et al. 1999; Heiderscheit et al. 2002). However, the relationship between altered $VAR_{elements}$ in acute pain and the development of chronic/persistent pain has not been studied. Although there are several interpretations for the changes to $VAR_{elements}$ in acute experimental pain, the results have been reasonably straightforward. That is, $VAR_{elements}$ is increased during acute pain (Moseley and Hodges, 2006; Madeleine et al. 2008a). Further, as no pain models are currently available that induces acute nociception/pain that is sustained for up to a week, it is unclear how $VAR_{elements}$ is influenced when pain does not resolve within days and is sustained.

A number of studies have evaluated $VAR_{elements}$ during chronic/persistent pain of the knee (Hamill et al. 1999; Heiderscheit et al. 2002; Georgoulis et al. 2006; Yakhdani et al. 2010; Cunningham et al. 2014), shoulder (Madeleine et al. 2008a,b; Madeleine and Madsen, 2009; Lomond and Côté 2010) and low back (Lamoth et al. 2006; van den Hoorn et al, 2012), and the results from these

studies are conflicting. A commonly reported finding is that $VAR_{elements}$ is reduced during chronic/persistent pain. This reduced $VAR_{elements}$ may reflect a maladaptive process that persists from the acute phase of pain (Srinivasan and Mathiassen, 2012). Conversely, a reduction of $VAR_{elements}$ may reduce the potential for error in control of painful and damaged joints (Côté et al. 2005) and in doing so improve function and reduce pain (Yakhdani et al. 2010).

In other situations there might be reduced $VAR_{elements}$ of the painful joint but increased $VAR_{elements}$ of functionally related non-painful joints (Lamoth et al. 2006; Madeleine and Madsen, 2009). In this context, increased $VAR_{elements}$ might reflect a strategy to compensate for less variable movement of the painful joints, and allow maintenance of the task (Lamoth et al. 2006). However, in other contexts $VAR_{elements}$ of a painful/damaged joint might be no different to healthy control participants (Ferber et al. 2005; Lewek et al. 2006). It is also possible that changes (i.e. increase or decrease) or no change to $VAR_{elements}$ might reflect a continuum of adaptations in different phases of chronic pain. For instance, $VAR_{elements}$ might be initially increased in the affected knee of participants with knee osteoarthritis due to poor neuromuscular control of the joint, and then reduced to a magnitude similar to healthy control participants (Lewek et al. 2006) or even lower (Yakhdani et al. 2010) as a protective strategy to reduce the potential to load the injured tissue and minimise pain during movement.

A simple decrease, increase, or no change to $VAR_{elements}$ in chronic pain described above occurs in a handful of situations. However, most studies found complex and diverse changes to $VAR_{elements}$ during tasks such as running (Hamill et al. 1999; Heiderscheit et al. 2002; Cunningham et al. 2014) and upper limb movements (Madeleine et al. 2008a,b; Lomond and Côté, 2010). These diverse changes to $VAR_{elements}$ include an increase, decrease, or no change for specific sub-phases, directions of movement, and kinematic parameters of the same task.

Previous studies of movement variability during acute and chronic pain have provided important insight. However, several gaps remain and thus we have an incomplete understanding of changes to movement variability and the motor adaptation to pain. The overall objective of this thesis was to use carefully controlled experimental models to resolve important questions and uncertainties regarding movement variability in the context of acute and chronic pain.

Table 1-1. Current hypotheses regarding the potential beneficial and detrimental consequences of $VAR_{elements}$ in healthy situations and during pain.

Potential benefits of $VAR_{elements}$ in normal/healthy situations

- Allow the motor system to explore different movement options to find an optimal movement strategy
- Facilitate the distribution of stresses over a greater surface area of soft-tissues

The drivers and potential consequences of <u>increased</u> $VAR_{elements}$ during pain

Beneficial consequences

- Facilitate a search for a new, less painful strategy to reduce pain and protect injured soft-tissues
- Distribute stresses more broadly to reduce the frequency that painful/damaged tissues are loaded
- In chronic pain, increased $VAR_{elements}$ of a non-painful joint/region might be a compensatory strategy for reduced $VAR_{elements}$ of a painful joint/region

Detrimental consequences

- Poor control of the muscles and joints/body segments involved in movement, which might contribute to:
    - Greater potential for movement error
    - Uncontrolled soft-tissue loading
- Greater potential for tissue damage and pain if an increase of $VAR_{elements}$ is sustained

The drivers and potential consequences of <u>decreased</u> $VAR_{elements}$ during pain

Beneficial consequences

- Use a less painful movement option more frequently (if the nervous system finds a less painful strategy) during acute pain
- Distribute stresses over fewer tissues to decrease likelihood that damaged tissues are loaded during acute pain
- Reduce potential for error in control of damaged joints/regions during acute pain

Detrimental consequences

- Compromise the ability to learn new skills and adapt movements to new contexts
- Reduce the surface area of soft-tissue loading and increase cumulative loading of specific tissues, with the potential for tissue damage and pain

2 Background

2.1 Movement variability

2.1.1 Introduction

Variability is an intrinsic property of the nervous system that is present at all levels of movement organisation, from the firing rate of individual neurons (Faisal et al. 2008) to coordinated movements of multiple body segments involved with tasks such as reaching (Messier and Kalaska, 1999) and walking (Preatoni et al. 2013). Variability was once considered an unwanted feature of the nervous system that should be minimised (Fitts, 1954). A contemporary view is that variability may have the potential to both positively and negatively affect normal, healthy function at different levels of movement organisation (e.g. from neuron firing rate to the kinematics of joints and body segments), at different times, and in different contexts. For example, at the level of the neuron, variability of neuronal firing rate may interfere with efficient and effective signal transmission (Faisal et al. 2008), but might also have a positive effect on function by enhancing the sensitivity of the neuron (Stein et al. 2005).

Changes to the movement of body segments that occur between each repetition of a task, termed *movement variability*, is now considered a potentially important and inherent characteristic of normal movement that arises due to the complexity of the musculoskeletal system and the redundancy of its degrees of freedom (e.g. Bernstein, 1967; Riley and Turvey, 2002; Bartlett et al. 2007). However, like neuronal variability, movement variability is also postulated to have positive or negative consequences for function. For instance, movement variability may be a necessary component to enable learning (Wu et al. 2014). Alternatively, movement variability might reflect poor control of movement that is the inevitable consequence of noise in sensory or motor processing, or sensorimotor integration (Wu et al. 2014).

Whether movement variability is good or bad depends on the specific component of movement, the amount of variability, and the timing within a movement task. The following sections outline the need to consider each of these aspects.

2.1.2 Components of movement variability

When performing a repetitive task (e.g. pointing to a target; Figure 2-1) it is possible to achieve an accurate outcome on each repetition with an infinite number of potential combinations of joint excursions and muscle activation patterns (Preatoni et al. 2013). The variability that is present in the performance of any task can be broadly characterised by two components.

The first component is variability in the outcome of a task relative to its goal. Humans perform tasks to achieve a specific goal and variability of the goal (VAR_{goal}) is minimised (if this is required for the task) to ensure accurate and consistent performance of the task. For example, the goal of a repetitive pointing task may be to touch the centre of a button on each repetition (inset, Figure 2-1). Depending on the task constraints/condition, this goal might not be achieved with each repetition of the pointing movement. VAR_{goal} can be quantified in several ways. First, the task outcome can be described in a dichotomous manner with repetitions classed as "successful" (e.g. centre of button touched) or "unsuccessful" (e.g. centre of button not touched). Second, a continuous measure of the magnitude of VAR_{goal} can be used, such as the amplitude of the end-point error during a repetitive pointing task (Trommershauser et al. 2005) which reflects the spatial difference in the outcome of the task relative to the goal.

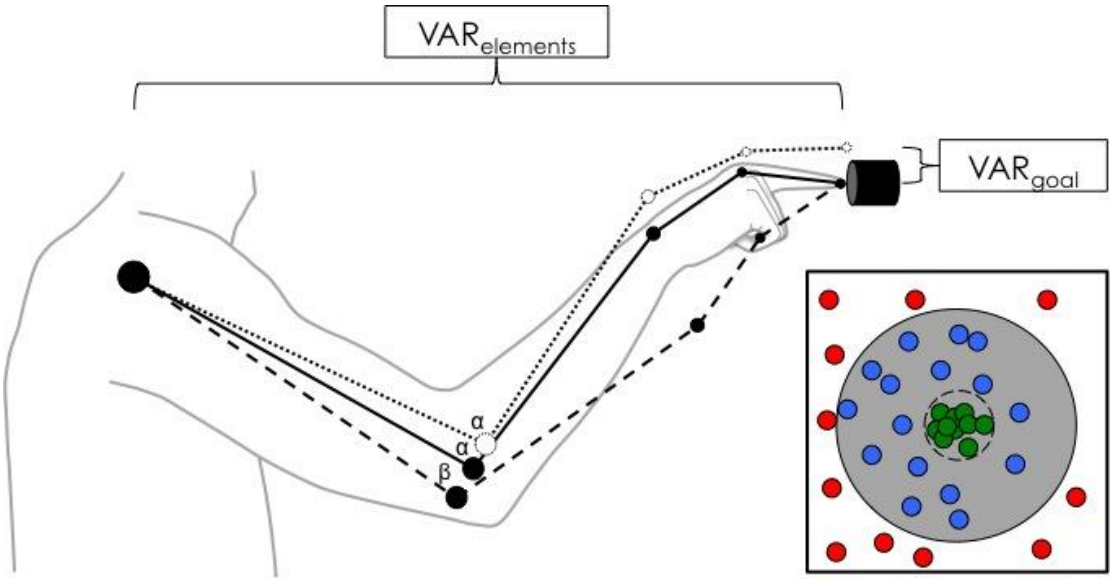

Figure 2-1. Upper limb pointing task towards a button. A sagittal view of several possible upper limb orientations to achieve a target (goal) (circles and lines define the joints and segments of the arm, forearm, wrist and finger). The stick diagrams with solid circles represent various segment interactions that maintain successful attainment of the goal, whereas the open circles and dotted line represent a segment interaction where the goal was not achieved. The centre of the button (i.e. the goal) might be touched on most repetitions (green circles) but on some movements the edge of the button might be touched (blue circles) or missed altogether (red circles).

The second component of movement variability that must be considered is variability of the elements of a movement i.e. $VAR_{elements}$. The elements of a movement refer to the individual

muscles and joints (and coordination between them) that contribute to performance of a task. For example, in a pointing task (Figure 2-1) the coordinated activation of upper limb muscles (e.g. deltoid, biceps brachii) effects movement at the shoulder, elbow, wrist and joints of the hand and fingers. With each repetition of a task it is possible to continue to achieve the task goal, despite alteration in the specific patterns of muscle activation and kinematics of individual joints (and coordination between joints) because of redundancy in the motor system (many muscles, joint and control strategies available to achieve the same outcome) (Bernstein, 1967). Motor redundancy means that at each level of the motor system (muscles, joints, etc) and central movement organisation there are many more elements contributing to performance of a task than are necessary (Latash et al. 2002). As such, it is not necessary to maintain an identical coordination of segments between repetitions (i.e. no $VAR_{elements}$) to successfully perform a task (Preatoni et al. 2013). Further, there may be positive and negative consequences for $VAR_{elements}$.

The relationship between VAR_{goal} and $VAR_{elements}$ is described in the uncontrolled manifold hypothesis (Scholz and Schöner, 1999). It proposes that in most situations the nervous system does not specify exactly how the elements (e.g. muscles, joints) involved in the goal-directed movement interact during the task, but does specify the attainment of the goal (Scholz and Schöner, 1999). That is, the nervous system aims to constrain the variation in the goal, but allows variation in the path to attain the goal. Further, the uncontrolled manifold hypothesis suggests that $VAR_{elements}$ can be partitioned into two broad categories based on its effect on successful achievement of a task goal (Latash, 2012). First, "good" $VAR_{elements}$ does not affect the outcome of the task (i.e. does not increase outcome variability) and is permitted by the nervous system because it provides potential benefits (section 2.1.3). Second, "bad" $VAR_{elements}$ causes a deviation from the final task goal (e.g. end-point error) and is thus minimised by the nervous system. The uncontrolled manifold hypothesis is supported by the minimum intervention principle, which proposes that the nervous system only corrects movement that is detrimental to successful achievement of the task goal (Todorov, 2002). Even in this context the effect of $VAR_{elements}$ is not straightforward. For instance, a specific component of $VAR_{elements}$ may have positive consequences for some individuals, but not others. Results from studies on pistol shooting (Arutyunyan et al. 1969), throwing (Kudo et al. 2000) and reaching (Messier and Kalaska, 1999) imply that "good" $VAR_{elements}$ may be required to maintain accurate performance of a task for some individuals. In a study of the accuracy of pistol shooting (Arutyunyan et al. 1969), skilled marksmen were able to reduce errors in the final pointing position of the hand by using more variable movements of the arms, whereas novice marksmen were unable to produce such adjustments and therefore exhibited more variable end-point positions.

2.1.3 Beneficial effects of $VAR_{elements}$

$VAR_{elements}$ may have beneficial consequences for the nervous system and/or musculoskeletal system in several ways. These are outlined below.

2.1.3.1 Role of $VAR_{elements}$ in adaptation and learning

$VAR_{elements}$ is thought to underpin the exploration of different movement strategies, which is thought necessary to refine movement. For instance, it may be functionally relevant to find the strategy among the many available that optimises features such as energy efficiency (Anderson and Pandy, 2001), accurate achievement of the task goal (Kording and Wolpert, 2004), and musculoskeletal health (Dingwell et al. 2001; Riley and Turvey, 2002; Preatoni et al. 2013). This flexibility allows the nervous system to learn a novel movement (Wu et al. 2014), adapt to changes in the environment (e.g. walking or running on different surfaces), alter the speed at which a continuous task is performed (e.g. moving the fingers faster or slower), change the context of a task (e.g. walking on level ground to walking up an incline) (Diedrich and Warren, 1995), and respond to changes in an individual that may be immediate (e.g. walking with and without a heavy bag) or more long-term (e.g. increase in body weight). This exploration may have a specific benefit in the presence of acute pain, and will be discussed in more detail below (Section 2.2.3).

2.1.3.2 Role of $VAR_{elements}$ in load sharing

$VAR_{elements}$ may be beneficial from a musculoskeletal health perspective as it may allow variation of tissue loads between repetitions and distribution of stresses more broadly between different tissues (e.g. sharing of load between different muscles, areas of joint contact/pressure distribution), and thus reduce the cumulative load on any particular tissues (Hamill et al. 1999; Srinivasan and Mathiassen, 2012).

2.1.4 Negative effects of $VAR_{elements}$

$VAR_{elements}$ may have negative consequences for the nervous system and/or musculoskeletal system in several ways. First, it may reflect a situation where the nervous system is unable to minimise "bad" $VAR_{elements}$ (Latash, 2012), which causes a deviation from the intended movement trajectory and less successful achievement of the task goal. Thus, there is greater potential for error, which may occur due to compromised availability, quality, and/or use of sensory information, such as proprioception (Brumagne et al. 2004; Malmstrom et al. 2013). Second, $VAR_{elements}$ may result in uncontrolled tissue loading, which may lead to a greater potential to overload specific tissues or joint surfaces. This potential negative consequence appears to directly contradict the earlier

suggestion that $VAR_{elements}$ may have a beneficial role in load sharing (Section 2.1.3). However, it is currently unclear what amount of $VAR_{elements}$ is beneficial or detrimental to load sharing in the nervous system, and likely needs to be balanced with other requirements (e.g. learn new movements, adapt to changes in the environment). Therefore the positive and negative effects of $VAR_{elements}$ must be balanced by the nervous system.

2.1.5 Balance between positive and negative effects of $VAR_{elements}$

It has been proposed that the optimal amount of movement variability within the nervous system (i.e. $VAR_{elements}$ that is beneficial to function) lies between two limits (Stergiou et al. 2006). This implies there are negative consequences of both too much and too little variation to normal function.

$VAR_{elements}$ above the upper limit implies that the motor system is too unstable and noisy, whereas $VAR_{elements}$ below the lower limit indicates the system is too stereotypical, less likely to exhibit exploratory behaviour, and thus less capable of adapting to perturbations (Stergiou et al. 2006) and more likely to overload specific tissues (Hamill, 2012). However, it is unclear what magnitude of $VAR_{elements}$ should be deemed optimal, and at what point $VAR_{elements}$ crosses an upper or lower limit to become too much or too little, respectively. One metric to classify $VAR_{elements}$ as beneficial or detrimental to the nervous system and musculoskeletal system could be the observed effect on achievement of the task goal. According to the uncontrolled manifold hypothesis (section 2.1.2), $VAR_{elements}$ is classified as "good" if the goal continues to be achieved and "bad" if the goal is not achieved (Latash, 2012). It is possible that in some situations there might be an increase of "good" $VAR_{elements}$ with continued achievement of the task goal, but the $VAR_{elements}$ is excessive and reflects poor control of the elements, which may lead to suboptimal biomechanics (e.g. joint loading, muscle activation patterns) and subsequent pain and/or injury.

Another consideration is that the amount of $VAR_{elements}$ during pain may be detrimental or beneficial to the system depending on the point in time (i.e. from the initial painful insult or episode) at which $VAR_{elements}$ is considered. For instance, at the onset of pain an increase of $VAR_{elements}$ may be beneficial if it underlies a search for a less painful movement strategy (Moseley and Hodges, 2006; Madeleine et al. 2008a), but in the long-term it could be detrimental for the system if it were excessive and resulted in impaired control of joints and body segments during movement. Whether $VAR_{elements}$ is beneficial or detrimental must be considered with respect to its observed effect on the movement (Davids et al. 2006), its effect on the dynamics of the system (Vaillancourt and Newell, 2003), and the time-point at which it is measured.

2.2 Altered movement variability in pain and injury

2.2.1 Theories of the motor adaptation to pain

A key protective function of the nervous system is its ability to detect noxious and potentially tissue-damaging stimuli, and then determine whether the situation may damage musculoskeletal tissues. In a normal physiological and adaptive situation this process requires activation of peripheral nociceptors situated in soft tissues (e.g. muscle, tendon, ligament), transmission of nociceptive signals, and integration of this information within multiple brain areas, which ultimately allows the perception of pain. The painful experience is influenced by contextual and cognitive factors (Lee and Tracey, 2013). If the nervous system concludes that a situation is, or may be, detrimental to the tissues and action is required, then the motor system is one of the key systems available to enable such action – to alter movement to reduce the potential for further pain or injury. The aversive nature of pain facilitates learning, which affects future decisions in selecting actions that will prevent potential pain and injury (Redgrave et al. 2008).

Acute pain is defined as "pain of recent onset and probable limited duration that usually has an identifiable temporal and causal relationship to injury or disease" (Ready and Edwards, 1992). In this case the roles of motor adaptation is clear; to remove or reduce the threat to the tissues indicated by the nociceptive input or the potential threat. In many cases, pain that occurs following an acute injury might persist for several months, and no longer serves a protective role, leading to chronic pain (Kehlet et al. 2006; Woolf and Ma, 2007). In this context the role of input from peripheral nociceptors may be less important or non-existent, and the relationship between pain and motor adaptation becomes more complex. Chronic pain "commonly persists beyond the time of healing of an injury and frequently there may not be any clearly identifiable cause" (Ready and Edwards, 1992). Adaptation in movement may exceed what is necessary to protect the tissues, may be maintained beyond when it is necessary, or may be completely inappropriate (Hodges and Smeets, 2015).

Several theories attempt to explain the motor adaptation to pain and its potential role in the transition from acute to chronic pain. Notable examples include the *vicious cycle theory* (Roland, 1986), *pain adaptation theory* (Lund et al. 1991), and more contemporary theories of adaptation to pain (Murray and Peck, 2010; Hodges and Tucker, 2011).

The *vicious cycle theory* proposes that activation of muscles that are painful or that move the painful region increase in a stereotypical manner (Roland, 1986). A sustained increase of muscle activity contributes to ischaemia and accumulation of pain metabolites, and subsequent increased muscle activity, which leads to a self-perpetuating cycle of sustained pain. Although plausible, and examples have been presented (Svensson et al. 1997; Sessle, 1999), not all evidence supports this

hypothesis of a systematic increase of agonist muscle activity. Similar to the vicious cycle theory, the *pain adaptation theory* proposes that the nervous system attempts to reduce pain and injury, but rather than a systematic increase in activity, it is achieved by a combination of reduced activity of muscles that are painful or that produce a painful movement, and increased activity of antagonist muscles (Lund et al. 1991). Although there are data that support this proposal, a stereotypical increase or decrease of muscle activity during pain predicted by this theory is not universally observed. For instance, muscle activity may increase (Del Santo et al. 2007; Sessle, 1999; Svensson et al. 1997), decrease (Del Santo et al. 2007; Farina et al. 2005) or not change (Farina et al. 2004; Matre et al. 1999; Schulte et al. 2004) during experimental pain in humans. To account for the diverse changes to movement during pain that are not explained by the *vicious cycle* or *pain adaptation* theories, Hodges and Tucker (2011) developed a more contemporary theory of the motor adaptation to pain (Figure 2-2). This theory proposes that pain is associated with a change of motor behaviour that: i) involves redistribution of activity within and between muscles; ii) changes the mechanical behaviour of the system, such as modified movement and stiffness; iii) leads to "protection" from further pain or injury, or the threat/anticipation of pain or injury; iv) is explained by changes at multiple levels of the nervous system that may be competitive or complimentary; and v) that is beneficial in the short-term, but with potential long-term consequences due to altered loading of the tissues (Hodges and Tucker, 2011). A key premise of this theory is that the redistribution of muscle activity leads to a unique and flexible change of mechanical behaviour that is dependent on the individual person and the specific task that is performed.

There are several ways in which the motor system may adapt mechanical behaviour to change loading of painful structures and protect the musculoskeletal system from further pain and/or injury (Hodges and Tucker, 2011). These adaptations include reduced displacement (Schaible and Grubb, 1993; Svensson et al. 1996; Friel et al. 2004) and velocity (Svensson et al. 1996) of movement, changed direction of force (Tucker and Hodges, 2010), removal of the body part from the painful situation (Clarke and Harris, 2004), or complete avoidance of a movement or task for some individuals or in some situations.

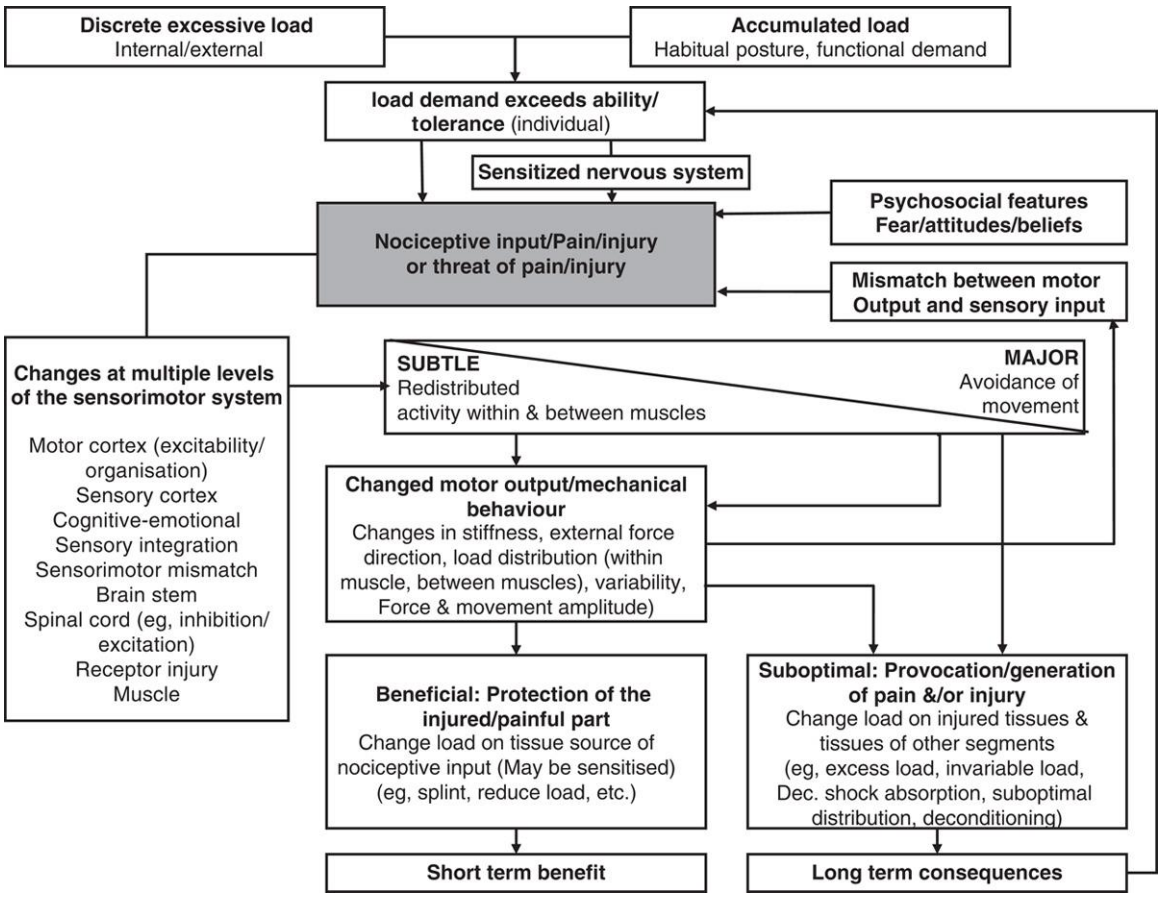

Figure 2-2. The modified pain adaptation theory (Hodges and Tucker, 2011). Figure from Hodges and Smeets (2015). Reprinted with permission.

Changes in $VAR_{elements}$ have been reported in pain and could be involved in several ways, including a beneficial role in development of the motor adaptation to pain, a negative consequence of nociception or the perception of pain, or simply an epiphenomenon that occurs in association with the painful experience but does not have a beneficial or detrimental role. The following sections will outline data from previous studies that have investigated the effect of pain on $VAR_{elements}$, with the aim to articulate the diversity and heterogeneity of findings and interpretation of the studies.

2.2.2 Quantification of movement variability during pain

Studies that have investigated the influence of pain on movement variability have used many different methods to calculate and quantify $VAR_{elements}$. These methods are summarized in Table 2-1, and discussed in detail for studies that investigated movement variability during acute (section 2.2.3) and chronic (section 2.2.5) pain.

Table 2-1. Methods used to quantify movement variability in previous studies that investigated the influence of pain on movement variability. Table adapted from Srinivasan and Mathiassen (2012). Reprinted with permission.

Study	**Participants**	**Task**	**Data**	**Movement variability metric(s)**
Cunningham et al (2014)	Unilateral PFPS (n=20) Healthy controls (n=21)	Running on a treadmill: 15 min at a self-selected speed	Kinematics: Thigh, knee, ankle EMG: N/A	Coupling angle variability between knee-ankle couplings quantified using vector coding
Ferber et al (2005)	Chronic foot pain (n=11) Healthy controls (n=11)	Running on a runway: 8 trials at 3.65 m/s	Kinematics: Lower leg, ankle EMG: N/A	Coupling angle variability between lower leg-ankle couplings quantified using vector coding
Georgoulis et al (2006)	Unilateral rupture of anterior cruciate ligament (n=10)	Walking on a treadmill: 2 min walks at 100%, 120% and 80% of a self-selected speed	Kinematics: Knee EMG: N/A	Regularity of knee flexion-extension angular displacement quantified using approximate entropy
Hamill et al (1999)	Unilateral PFPS (n=not given) Healthy controls (n=not given)	Running on a runway: 10 trials at 2.5 m/s, 3 m/s and 3.5 m/s	Kinematics: Thigh, lower leg, ankle EMG: N/A	Coupling angle variability between thigh-lower leg-ankle couplings quantified using continuous relative phase
Heiderscheit et al (2002)	Unilateral PFPS (n=8) Healthy controls (n=8)	Running on a treadmill: 20 s at fixed (2.68 m/s) and self-selected speeds	Kinematics: Thigh, lower leg, ankle EMG: N/A Other: Stride length and duration	Kinematics: Coupling angle variability between thigh-lower leg-ankle couplings quantified using vector coding Other: Variability of stride length and stride duration quantified using SD

Lamoth et al (2006)	Chronic non-specific low back pain (n=19) Healthy controls (n=17)	Walking on a treadmill: 3 min at 12 speeds, from 0.39 to 1.94 m/s (increments of 0.22 m/s)	Kinematics: Trunk, pelvis EMG: Erector spinae (bilaterally: Th12, L2, L4)	Kinematics: Coupling angle variability of trunk –pelvis couplings quantified using continuous relative Fourier phase
Lewek et al (2006)	Unilateral medial knee OA (n=15) Healthy controls (n=15)	Walking on a runway: 10 trials at self-selected speed	Kinematics: Knee EMG: Vastus medialis, vastus lateralis, hamstrings (medial, lateral), gastrocnemius (medial, lateral)	Kinematics: Variability of the knee (sagital and frontal planes) quantified using phase angle (knee angle vs. angular velocity of the knee)
Lomond and Cote (2010)	Chronic neck-shoulder pain (n=16) Healthy controls (n=16)	Repetitive reaching at shoulder height: 1 Hz until exhaustion	Kinematics: Shoulder, elbow, index finger-tip EMG: Trapezius (upper and lower fibres), anterior deltoid, supraspinatus, infraspinatus	All: Variability quantified for each kinematic variable and muscle activation using SD expressed as a percentage of average calculated across each block
Madeleine and Madsen (2009)	Neck-shoulder pain (n=6) Healthy participants (n=12)	Deboning: 6 trials of 35-50 s work cycles	Kinematics: Head-shoulder, shoulder-hip, elbow-hip displacement EMG: N/A	Kinematics: Variability for each kinematic variable quantified using SD, coefficient of variation, sample entropy, approximate entropy
Madeleine et al (2008a) [acute pain experiment]	Healthy participants (n=20)	Simulated cutting: Baseline trial – 3 min of work; Pain trial – 3 min work during acute experimental pain	Kinematics: Right arm, trunk EMG: Deltoid (anterior, middle), trapezius, infraspinatus Other: Duration of each cycle of the task	All: Variability for each kinematic variable (arm and trunk: starting position, acceleration, range of motion), EMG variable, and task duration were quantified using SD

Madeleine et al (2008a) [chronic pain experiment]	Chronic neck-shoulder pain (n=12) Healthy controls (n=6)	Simulated cutting: 3 trials of 3 min work	Kinematics: Right arm, trunk EMG: Deltoid (anterior, middle), trapezius, infraspinatus Other: Duration of each cycle of the task	All: Variability for each kinematic variable (arm and trunk: starting position, acceleration, range of motion), EMG variable, and task duration were quantified using SD
Madeleine et al (2008b)	Experiment 1: Butchers with <1 month experience (n=12) Experiment 2: Butchers with no experience (n=20) and experience (n=6)	Simulated cutting: Experiment 1 – 3 trials of 3 min work (recorded in the 1st and 6th month of employment Experiment 2 – 1 trial of 3 min work.	Kinematics: Right arm, trunk EMG: Deltoid (anterior, middle), trapezius, infraspinatus Other: Duration of each cycle of the task	All: Variability for each kinematic variable (arm and trunk: starting position, acceleration, range of motion), EMG variable, and task duration were quantified using SD
Moseley and Hodges (2006)	Healthy participants (n=16)	Shoulder flexion and extension: Baseline – 40 movements Pain trials – 70 movements, painful stimuli delivered to the abdominal muscle Washout trials – 70 pain-free movements	Kinematics: N/A EMG: Right deltoid (anterior, posterior fibres), right obliquus externus (OE)	Variability in the timing of the onset of activity in OE relative to onset of activity in anterior/ posterior deltoid quantified using SD
Van den Hoorn et al (2012)	Chronic non-specific low back pain (n=13) Healthy controls (n=12)	Walking on a treadmill: 3 min at 12 speeds from 0.5 to 1.72 m/s (increments of 0.11 m/s)	Kinematics: Trunk, thorax, pelvis EMG: N/A	Variability of the pelvis and thorax rotations quantified as the median of deviations from the mean; relationships between pelvis and thorax variability assessed by Pearson correlations

Yakhdani et al (2010)	Unilateral knee OA (n=14) Healthy controls (n=12)	Walking on a treadmill: 4 min at 7 speeds from 0.17 to 1.5 m/s (increments of 0.22 m/s)	Kinematics: Knee EMG: N/A	Variability of knee angular velocity (sagital plane) quantified using SD

PFPS – patellofemoral pain syndrome; EMG – electromyography; SD – standard deviation; N/A – not applicable; Th12 – twelfth thoracic vertebra; L2 – second lumbar vertebra; L4 – fourth lumbar vertebra; RMS – root mean square.

2.2.3 Movement variability during acute pain

Variation in movement may change in a number of ways in acute pain, including an increase, decrease, or no change to $VAR_{elements}$ and VAR_{goal}. Changes to $VAR_{elements}$ could be beneficial or detrimental to function or they could be a non-specific change that simply occurs as a consequence of pain but does not have any impact on function or provides no benefit or cost to the nervous system.

Moseley and Hodges (2006) investigated $VAR_{elements}$ in the timing of a postural strategy recorded in trials before, during, and after painful electric shocks were delivered to the low back. This postural strategy involves feedforward activation of the abdominal muscles in response to rapid arm movements that challenge the stability of the spine in predictable manner for the nervous system (Hodges and Richardson, 1996). Each trial involved 70 repetitions of the rapid arm movement. They found $VAR_{elements}$ of the postural strategy initially increased during the first 10 repetitions of the painful trials, but had returned to the baseline (i.e. pre-pain) levels by the final 10 repetitions of the painful trial, and then increased in the first 10 repetitions of the post-pain trial (Figure 2-3). However, in a sub-group of participants, after the cessation of painful electric shocks there was no increase in $VAR_{elements}$ of the postural strategy and the control strategy that was adopted during pain continued during the post-pain trial when painful electric shocks were not applied to the low back (Moseley and Hodges, 2006). Further, these participants had "unhealthy" beliefs about back pain, which was quantified with the Back Beliefs Questionnaire, Survey of Pain Attitudes, and the Pain Catastrophizing Scale. It was thought this sub-group of participants, for whom $VAR_{elements}$ did not return to baseline, failed to explore new options after the resolution of pain by increased $VAR_{elements}$. Instead, they may have become "stuck" using a postural strategy with reduced $VAR_{elements}$ during acute pain that persisted once the painful stimulus was removed (Moseley and Hodges, 2006). Thus, $VAR_{elements}$ might respond differently for different participants; after resolution of acute experimental pain (Moseley and Hodges, 2006) but also *during* acute pain.

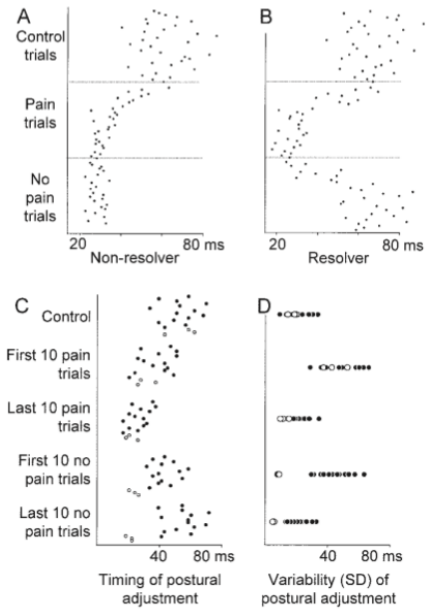

Figure 2-3. Data from Moseley and Hodges (2006). Reprinted with permission.

Madeleine et al (2008a) investigated $VAR_{elements}$ when healthy participants performed a standardised cutting task with the upper limb during acute experimental shoulder pain induced by injection of hypertonic saline. Relative motion between the right arm and trunk were expressed for the upper arm as anatomical flexion-extension, abduction-adduction and medial-lateral rotation, and for the trunk as flexion-extension, lateral flexion, and transverse rotation. Four kinematic parameters were determined in three-dimensions for the right arm and trunk: starting position, acceleration throughout the cycle, range of motion, and total area under the movement curve versus time. $VAR_{elements}$ of arm and trunk movement was quantified as the standard deviation (SD) of the kinematic parameters. They found that variability of arm starting position in the flexion-extension and rotation directions was greater during acute experimental pain than the baseline (i.e. pre-pain) trial. Further, variability of arm range of motion and acceleration of arm movement were greater during acute pain than the pre-pain trial, but were not influenced by the direction of movement (i.e. flexion-extension, abduction-adduction, or rotation). The authors proposed that the increase of $VAR_{elements}$ during acute pain might have allowed the motor system to explore alternative movement solutions to reduce pain (Madeleine et al. 2008a).

An interesting qualitative observation of the data from Madeleine et al (2008a), that was not discussed therein, is the potential for different movement strategies used by separate sub-groups of participants during acute experimental pain. In some cases, it appears that approximately half of the participants *did* change $VAR_{elements}$ between the pre-pain and pain trial, whereas the other participants *did not* change $VAR_{elements}$. Unlike Moseley and Hodges (2006), Madeleine et al

(2008a) did not consider the potential for different strategies (i.e. changes to $VAR_{elements}$) to be used by different participants.

There are four different interpretations for the changes to $VAR_{elements}$ in acute pain. First, $VAR_{elements}$ at the onset of acute pain may be a purposeful adaptation that allows the motor system to experiment with different movement options and search for a new, less painful movement strategy (Moseley and Hodges, 2006; Murray and Peck, 2007; Madeleine et al. 2008a; Hodges and Tucker, 2011). This adaptation might have the short-term benefit that the nervous system acts to reduce pain by altering the mechanical behaviour of the body to find a new movement solution (Hodges and Tucker, 2011; Srinivasan and Mathiassen, 2012). If the search for a less painful movement strategy is successful (i.e. a less painful solution is found), the nervous system might decrease $VAR_{elements}$ to improve the likelihood that the less painful solution is used more often for subsequent repetitions of the task (Hamill et al. 1999; Moseley and Hodges, 2006). A reduction of $VAR_{elements}$ after a search might be beneficial in the short-term if the resultant movement strategy is less provocative of pain and reduces the potential for further pain and injury. This hypothesis is consistent with the recent theory of the motor adaptation to pain (Hodges and Tucker, 2011).

Second, an increase of $VAR_{elements}$ may allow broader distribution of stresses over different tissues (e.g. sharing of load between different muscles, areas of joint contact) between repetitions of a task. This adaptation could be beneficial in the short-term as more tissues would be loaded relative to pain-free situations, thus reducing the likelihood and relative frequency of loading the painful tissues. This interpretation implies tissues that are loaded less often (or not at all) during normal pain-free movement may be loaded more frequently (or start to be loaded), which might have negative consequences in the long-term. For instance, if tissues that are unaccustomed to regular loading are suddenly (i.e. with onset of pain) loaded more frequently, they may be unable to withstand the applied stresses, thereby leading to damage.

Third, the increase of $VAR_{elements}$ during pain might reflect error in performance of the task. An increase of $VAR_{elements}$ may be detrimental to normal function if it surpasses an upper limit of optimal variability that implies the motor system is too unstable or noisy. This situation could arise due to compromised sensory or motor processing, or sensorimotor integration. Further, "bad" $VAR_{elements}$, as opposed to "good" $VAR_{elements}$ (Latash, 2012) might increase during acute pain. If "bad" $VAR_{elements}$ did increase, then according to the uncontrolled manifold hypothesis there would be an increase in "error" of the task goal. However, the effect of the observed increase of $VAR_{elements}$ (whether "good" or "bad") found in the previous studies (Moseley and Hodges, 2006; Madeleine et al. 2008a) on the task goal is unclear as the studies did not report whether the task goal was affected during pain.

Fourth, it is possible the increased $VAR_{elements}$ during acute pain might reflect a situation where the nervous system was simply responding to a change in context in which the task was being performed (i.e. transition between no pain and pain, and vice versa) and that provided no real benefit to the nervous system or musculoskeletal system. For instance, Moseley and Hodges (2006) found that $VAR_{elements}$ was increased at the start of both the pain and post-pain trials compared to baseline and the end of the pain and post-pain trials (Figure 2-3). If the increased $VAR_{elements}$ was solely due to the presence of pain, then the increase of $VAR_{elements}$ between the end of the painful trial and the start of the post-pain trial would not have been expected. Alternatively, the change in $VAR_{elements}$ found between painful and non-painful trials in Moseley and Hodges (2006) could reflect an ongoing learning response that might occur due to the expectation of pain.

2.2.4 Do all movement tasks adapt in a similar manner during acute pain?

A consistent finding of the two studies that evaluated $VAR_{elements}$ during acute pain is that $VAR_{elements}$ was increased. Madeleine et al. (2008a) evaluated movement $VAR_{elements}$ of the arm during an upper limb cutting task and Moseley and Hodges (2006) studied $VAR_{elements}$ in the timing of the postural response to rapid unilateral arm movements. Although these tasks involve distinct regions of the body (i.e. upper limb and trunk), a common feature is the involvement of multiple joints and muscles (i.e. elements). For instance, the upper limb cutting task involves movement at the shoulder, elbow and wrist joints, and the muscles that span these joints. In these multi-joint tasks there is considerable redundancy of the nervous system and musculoskeletal system, which allows great potential for variation and thus considerable $VAR_{elements}$ are available to alter movement strategy. This raises the possibility that a task that involves many elements might demonstrate different changes to $VAR_{elements}$ in acute pain compared to simple tasks that involve fewer elements.

Relative to multi-joint tasks, simple tasks have fewer movement options, and thus fewer elements for which $VAR_{elements}$ might be increased during acute pain. Even with fewer options in a simple task, the motor system is expected to use the same strategy of increased $VAR_{elements}$ to find an alternative solution. It is unclear whether an increase in $VAR_{elements}$ during acute pain is limited to complex multi-joint systems where multiple options (i.e. muscles, joints) are available to maintain the goal. We do not know whether the same principles (i.e. the adaptation found during multi-joint tasks) can be applied to simple systems with fewer elements where there are limited options for variation. A theory of the motor adaptation to pain (Hodges and Tucker, 2011) assumes that different tasks may adapt differently, so changes to $VAR_{elements}$ during acute pain are likely specific to the task and the environment in which it is performed.

It was the contention of this thesis that challenging the nervous system to adapt in a task with few available options (i.e. elements) would lead to a clearer understanding of the purpose and mechanism of adaptation to pain. The unique step made in this thesis is to challenge the system to adapt when there are limited elements.

The aim of Study 1 (Chapter 4) was to investigate whether attainment of the task goal and $VAR_{elements}$ changes in the presence of acute pain, and whether this variability changes over time with repetition of the task.

The aim of Study 2 (Chapter 5) was to investigate whether $VAR_{elements}$ would initially increase during acute experimental pain in the search for a new, less painful movement strategy; and if a less painful strategy was experienced during acute pain, to evaluate if this strategy would be selected more frequently than other options.

2.2.5 Movement variability during chronic/persistent pain

Several studies have evaluated movement variability in persistent/chronic musculoskeletal pain conditions of the neck/shoulder (Madeleine et al. 2008a; Madeleine et al. 2008b; Madeleine and Madsen, 2009; Lomond and Côté, 2010), low back (Lamoth et al. 2006; van den Hoorn et al, 2012), and lower limb (Hamill et al. 1999; Heiderscheit et al. 2002; Ferber et al. 2005; Georgoulis et al. 2006; Yakhdani et al. 2010; Cunningham et al. 2014). In situations of chronic pain $VAR_{elements}$ of the affected limb or body region might be decreased, increased, or not changed compared to healthy control participants and/or the unaffected limb. Changes to $VAR_{elements}$ in chronic pain might be linked to an adaptation that starts in the acute phase of pain (section 2.2.3) and remains in (or even contribute to the transition to) a chronic musculoskeletal pain condition. The different changes to $VAR_{elements}$ that have been found in chronic/persistent pain are discussed in the following sections.

2.2.5.1 Reduced variability

A commonly reported finding is that $VAR_{elements}$ is reduced when people with chronic pain of the knee (Hamill et al. 1999; Heiderscheit et al. 2002; Georgoulis et al. 2006; Yakhdani et al. 2010), shoulder (Madeleine et al. 2008a; Madeleine et al. 2008b; Madeleine and Madsen, 2009) and low back (Lamoth et al. 2006; van den Hoorn et al, 2012) perform multi-joint tasks. Closer inspection of the results indicates only two studies (Yakhdani et al. 2010; van den Hoorn et al. 2012) found a simple reduction of $VAR_{elements}$ during chronic pain and that more complex changes

to $VAR_{elements}$ occurred in most studies (e.g. Hamill et al. 1999; Heiderscheit et al. 2002; Madeleine et al. 2008a,b). Despite these complex changes to $VAR_{elements}$, the breadth of change was not discussed in most studies. Studies that only report decreased $VAR_{elements}$ will be discussed in this section. Other studies that report a combination of changes in $VAR_{elements}$ will be discussed in subsequent sections.

To investigate whether $VAR_{elements}$ was altered in chronic knee osteoarthritis (OA), Yakhdani et al (2010) studied treadmill walking in participants with chronic unilateral knee OA and healthy controls. Participants with knee OA performed the walking task before and after joint replacement surgery, and the control group participated in two experimental sessions. Variability of knee angular velocity in the flexion-extension direction was calculated just after heel strike. Yakhdani et al (2010) found participants with unilateral knee OA had less $VAR_{elements}$ of the affected knee than control participants before and after joint replacement surgery. Further, they found a positive correlation between the magnitude of knee $VAR_{elements}$ and the number of falls experienced by participants in the year preceding the first experimental session. This suggests that reduced variability in participants with unilateral knee OA appears to reduce fall risk. They argued that reduced $VAR_{elements}$ might have been a beneficial strategy to avoid falling (Hausdorff, 2007), rather than a sign of pain/pathology (Heiderscheit, 2002). The authors suggested that the relationship between reduced $VAR_{elements}$ and reduced falls risk might involve participants paying more attention to the motor task and/or using greater muscle co-contraction (Yakhdani et al. 2010). Conversely, participants who had high knee $VAR_{elements}$ had an increased risk of falls, which suggests they had poor movement control, perhaps due to compromised sensory information or less co-contraction (Yakhdani et al. 2010).

Further, van den Hoorn et al (2012) evaluated movement variability of the trunk in participants with chronic low back pain and healthy controls during a treadmill-walking task at twelve speeds between 0.5 m/s and 1.72 m/s. They found trunk variability in the transverse plane (quantified as residual rotation) was lower in the LBP group than controls for all walking speeds.

There are several explanations for reduced $VAR_{elements}$ in chronic musculoskeletal pain conditions that are consistent with Hodges and Tucker (2011) theory of the motor adaptation to pain and that could potentially have positive and negative consequences.

2.2.5.1.1 Positive consequences of reduced variability in chronic pain

In chronic musculoskeletal pain conditions it might be more difficult to control the painful or damaged joint due to compromised sensory information (e.g. proprioception; Dessureault et al. 2008; Malmstrom et al. 2013), altered patterns of muscle activation (Alizadehkhaiyat et al. 2007;

Rojas et al. 2007), and damage to important stabilising structures such as ligaments (Georgoulis et al. 2006). For instance, sensory feedback is important for the effective modulation and fine-tuning of neuromuscular control (Lamoth et al. 2006). In situations where it is more difficult to control a painful/damaged joint, a reduction of $VAR_{elements}$ might be considered beneficial for several reasons. First, a decrease of $VAR_{elements}$ might improve stability of painful joint(s) and thus improve overall function. For instance, knee OA is typically associated with pain and knee instability during walking (Fitzgerald et al. 2004) with buckling (or giving way) of the knee. In unilateral knee OA reduced $VAR_{elements}$ appears to reduce falls risk (Yakhdani et al. 2010). Second, a decrease of $VAR_{elements}$ to improve control of a painful/injured joint might be beneficial to ensure the task goal continues to be achieved. For instance, neuromuscular control of the upper limb might be compromised in chronic shoulder pain, with altered timing of muscle activation and impaired coordination between joints of the upper limb. If participants with poor neuromuscular control due to chronic shoulder pain were to perform a repetitive reaching task towards a target goal, attainment of the target goal might be affected. A reduction of $VAR_{elements}$ might improve control of the upper limb and ensure the task is completed accurately. This idea is congruent with the "minimum variance model", which predicts that the motor system activates muscles in a manner that minimizes end-point error of the final hand position in pointing movements (Harris and Wolpert, 1998).

Alternatively, a decrease of $VAR_{elements}$ might be beneficial to minimize loading of painful/damaged structures, such as specific regions of tendon and joints surfaces, and enable pain-free or less-painful performance of the task. This adaptation might be related to an adaptation that commences in the acute phase of pain. That is, one interpretation of increased $VAR_{elements}$ in acute experimental pain (section 2.2.2) is that it reflects a search for a new, less painful movement strategy (Moseley and Hodges, 2006). If this interpretation is correct, once the nervous system has finished its search, $VAR_{elements}$ may decrease so the less painful strategy is used more often for subsequent movements (Moseley and Hodges, 2006). This strategy of reduced $VAR_{elements}$ might be beneficial in the short-term to reduce pain and minimise loading of injured structures to facilitate tissue healing.

In some situations (e.g. recalcitrant pain or slow tissue healing), an altered movement pattern with reduced $VAR_{elements}$ could remain despite resolution of pain, which may lead to long-term pain and injury due to repeated loading of structures (Hodges and Tucker, 2011). Alternatively, pain and tissue damage might clearly motivate an adaptation (i.e. changed $VAR_{elements}$), but recovery of pain and resolution of tissue damage may not be a potent stimulus to resolve the adaptation and increase $VAR_{elements}$ to be within 'normal' levels. For instance, Yakhdani

et al (2010) found participants who had joint replacement surgery for knee OA continued to walk with less $VAR_{elements}$ of knee angular velocity in the flexion-extension direction than controls despite resolution of pain and normalisation of joint stability after surgery. They proposed the continued reduction of $VAR_{elements}$ even after surgery to reduce pain and improve stability might suggest participants persisted in using the same strategy (i.e. reduced $VAR_{elements}$ to improve control) even when it was no longer required. Another possibility is that $VAR_{elements}$ was reduced prior to onset of OA and was not related to joint replacement surgery.

2.2.5.1.2 Negative consequences of reduced variability in chronic pain

Although it is possible that reduced $VAR_{elements}$ might be beneficial in chronic/persistent pain, there are two possible situations where reduced $VAR_{elements}$ might have negative consequences.

First, if pain subsides and tissue healing resolves, it is likely ideal for $VAR_{elements}$ to increase so that it is within the two limits of beneficial $VAR_{elements}$. For instance, Heiderscheit (2000) studied the gait of participants with unilateral anterior knee pain before and after the application of a patellar taping procedure that has been shown to reduce knee pain (Cowan et al. 2002; Callahan et al. 2002). They found that $VAR_{elements}$ of the pain group was initially less than the healthy control group, but application of the patellar tape was associated with an increase of $VAR_{elements}$ to the same magnitude of that in the controls (Heiderscheit, 2000). In some situations of recalcitrant pain and/or compromised tissue healing the motor system might become "stuck" using the same movement pattern with reduced $VAR_{elements}$ (i.e. below the lower limit of beneficial $VAR_{elements}$) for an extended period of time (Moseley and Hodges, 2006; Srivinivasan and Mathiassen, 2012). A sustained period of low $VAR_{elements}$ (i.e. that outlasts its potential benefits) could become problematic. For instance, if reduced variation is maintained, the same soft tissue structures would be consistently loaded, which may increase cumulative loading of focal sections of tendon or a joint complex (Hamill et al. 1999). This process of repeated loading could lead to degeneration and contribute to the development of an overuse injury (e.g. lateral epicondylalgia) with chronic musculoskeletal pain (Bartlett et al. 2007; Hamill et al. 2012). This interpretation is consistent with the *variability-overuse hypothesis* (Wheat, 2005; Bartlett et al. 2007) and *loss of complexity hypothesis* (Lipsitz et al. 2002; Hamill et al. 2012), which suggest that injury will emerge once the reduction of $VAR_{elements}$ reaches a critical threshold/limit.

Second, it has been proposed that in non-painful situations $VAR_{elements}$ facilitates the distribution of stresses across multiple tissues (e.g. tendon, ligament) (Hamill et al. 1999). This implies that a sustained period of reduced $VAR_{elements}$ during pain leads to stresses being applied

across fewer tissues near the painful region. In this context, reduced $VAR_{elements}$ during pain might lead to *stress shielding*, where greater loads are imposed on some tissues (or specific regions of tissues), while other tissues are subject to less loading (Haraldsson et al. 2005). As mechanical loading is essential for the health of musculoskeletal soft-tissues, such as tendons, a reduction of applied stresses to focal tissue regions might contribute to structural weakening of the tissues and lead to further pain and injury (Wang, 2006; Langberg et al. 2007). For instance, stress shielding is thought to contribute to degenerative changes in the common extensor tendon of participants with chronic lateral epicondylalgia (i.e. tennis elbow) (Regan et al. 1992; Haraldsson et al. 2005; Arnoczky et al. 2007).

2.2.5.2 Reduced $VAR_{elements}$ of the painful joint and increased $VAR_{elements}$ of the unaffected joint

In some situations there might be reduced $VAR_{elements}$ of the painful joint/region in chronic/persistent pain, but with a concomitant increase in $VAR_{elements}$ of the non-painful joints that are involved in the task (Lamoth et al. 2006; Madeleine and Madsen, 2009). For example, in a study similar to van den Hoorn et al (2012) (see section 2.2.5.1), $VAR_{elements}$ of the thoracic, lumbar and pelvic regions were quantified for transverse rotation and trunk flexion-extension in participants with non-specific low back pain and healthy controls during a treadmill-walking task (Lamoth et al, 2006). Participants with low back pain had reduced $VAR_{elements}$ of lumbar transverse rotation and increased $VAR_{elements}$ of thoracic flexion-extension movement compared to controls.

In another study, male slaughterhouse workers with chronic neck/shoulder pain and healthy controls performed a manual deboning task that involved multiple cuts and typically lasted 35-50 seconds (Madeleine and Madsen, 2009). $VAR_{elements}$ of upper limb movements were quantified as the standard deviation (SD) and coefficient of variation (CV) for vertical displacement of relative movement between the head-shoulder, shoulder-elbow, and elbow-hip. Participants with neck/shoulder pain had less CV of head-shoulder and shoulder-hip displacement and increased SD of elbow-hip displacement than healthy controls. These data indicate $VAR_{elements}$ was reduced for segments that involved motion of the painful neck/shoulder region (i.e. head-shoulder and shoulder-hip), and increased for movement of non-painful segments.

As discussed above (section 2.2.5.1), it is possible the reduction of $VAR_{elements}$ at the painful joint/region reflected an increase in stability to improve function, to ensure maintenance of the goal, and/or to minimise loading of painful structures to reduce pain and allow tissue healing. These explanations do not incorporate the increase of $VAR_{elements}$ found for the non-painful joint/region that were functionally related to the painful joint/region.

There are four possible explanations for the increased $VAR_{elements}$ found in Lamoth et al. (2006) and Madeleine and Madsen (2009). First, in both studies the increased $VAR_{elements}$ for non-painful joints might be a strategy to compensate for more rigid and less variable movement patterns of the painful joint. For instance, Lamoth et al (2006) suggested the increase of $VAR_{elements}$ in the thoracic region might have been a strategy to compensate for the reduced $VAR_{elements}$ of the lumbar region. Second, it might reflect a strategy to distribute stresses over a broader surface area (e.g. different muscles, areas of joint contact) between repetitions of the task (Hamill et al. 1999). This strategy could have a beneficial effect if it reduces the frequency with which stresses are applied to injured structures (Cunningham et al. 2014). Third, an increase of $VAR_{elements}$ in chronic musculoskeletal pain conditions might suggest the motor system retains flexibility to explore alternative movement patterns, as for non-painful situations. A similar change of $VAR_{elements}$ might be used during acute experimental pain to search for a new, less painful strategy (Moseley and Hodges, 2006), but has not been observed in chronic pain. Fourth, increased $VAR_{elements}$ might reflect a situation where the motor system has greater difficulty controlling movement of the painful region (Lomond and Côté, 2010). In this context, the nervous system is unable to effectively adapt to poor neuromuscular control, perhaps due to compromised proprioception (Brumagne et al. 2004) or altered patterns of muscle activation (Cunningham et al (2014).

2.2.5.3 No change to variability during chronic pain

Two studies found $VAR_{elements}$ of the affected lower limb was not affected in chronic/persistent pain (Ferber et al. 2005; Lewek et al. 2006). For instance, Lewek et al (2006) measured knee movement variability during gait in participants with unilateral medial knee OA and healthy controls, and studied whether it was influenced by muscle activity, frontal plane laxity, and pain. Knee $VAR_{elements}$ was assessed in the sagittal plane (i.e. knee flexion-extension) and frontal plane (i.e. knee abduction-adduction) with phase angle (i.e. knee angle vs. angular velocity of the knee) during early stance. The authors hypothesised that the affected knee would have less $VAR_{elements}$ of frontal/sagittal plane motion during walking than the unaffected knee and both knees of healthy control participants. Further, they expected that pain, frontal plane joint laxity, and muscular co-contraction during walking would provide insight into the mechanism underlying alteration in knee motion variability. In the frontal plane (i.e. abduction-adduction) there was no difference in $VAR_{elements}$ between the affected knee and the control group. However, within the OA group $VAR_{elements}$ in the frontal plane of the affected knee was less than the unaffected knee. Further, in the frontal plane there was a significant relationship between the magnitude of $VAR_{elements}$ in the affected knee, and knee joint laxity and co-contraction of the medial muscles. In

the sagittal plane (i.e. flexion-extension), $VAR_{elements}$ was not different between the affected and unaffected knees, or the control participants.

The authors proposed that in unilateral knee OA, an initial increase in laxity of the affected knee was associated with increased $VAR_{elements}$, which might reflect inadequate neuromuscular control of the knee. However, as OA progresses, the motor system might use a protective strategy of greater co-contraction of the medial leg muscles to reduce $VAR_{elements}$. A reduction of $VAR_{elements}$ in this context might have the benefit of improving control of the knee and minimising pain during gait. In an attempt to explain these results in the context of their own data, Yakhdani et al (2010) suggested that $VAR_{elements}$ is initially increased in the affected knee of participants with knee OA, and is then actively reduced to that of healthy participants (Lewek et al. 2006) or even lower (Yakhdani et al. 2010).

2.2.5.4 Altered $VAR_{elements}$ for some features of movement, but not others

The majority of studies that investigated $VAR_{elements}$ in chronic pain found diverse changes that were not consistent for all features of movement. As discussed above, most studies evaluated $VAR_{elements}$ during complex, multi-joint tasks with multiple elements. These multi-joint tasks (e.g. walking, running, reaching), and the elements that are involved, are described and quantified in a number of ways. A task will often include several phases of movement. For instance, running tasks are often described according to the stride cycle i.e. from the initial contact of one foot (often heel strike) until the subsequent initial contact of the same foot. The stride cycle can be further divided into a stance phase (i.e. while the foot is in contact with the ground) and swing phase (i.e. while the foot does not contact with the ground). In studies of chronic pain and $VAR_{elements}$, these phases have been sub-divided even further. For instance, in Hamill et al (1999) the stance phase was sub-divided into four sub-phases based on key events that occurred at the foot in the frontal plane (foot contact to neutral position, neutral position to maximum eversion, maximum eversion to neutral position, neutral position to toe off). Another way to describe the movement (or element) is with kinematic parameters. For example, Madeleine et al (2008a,b) quantified $VAR_{elements}$ for several kinematic parameters of upper limb movement during a standardised cutting task, including the starting position of the upper limb joints in three-dimensional space, range of motion of each joint, and acceleration throughout the cycle of each joint. The direction in which movement of a joint or body region occurs is also used as a descriptor. For example, movement of the hip/thigh during running has been analysed in flexion-extension, abduction-adduction, and medial-lateral rotation (Heiderscheit et al. 2002).

Each of these features (i.e. characteristics and directions) within an entire movement cycle or within specific phase(s) are 'elements' that can vary between repetitions of a task. Given the multiple ways movement can be quantified and described, it is not surprising that $VAR_{elements}$ of these features do not change in a uniform or stereotypical manner. The complex changes to $VAR_{elements}$ (i.e. not a simple decrease, increase, or no change) of these features of movement in chronic pain are discussed below.

Hamill et al (1999) were one of the first to evaluate changes to $VAR_{elements}$ in chronic pain. They studied variability in the coordination between different lower limb segments during running in participants with patellofemoral pain syndrome (PFPS) and healthy controls. $VAR_{elements}$ was analysed over the entire stride cycle, and divided into the swing phase and four sub-phases of stance based on foot movements (i.e. foot contact to neutral position, neutral position to maximum eversion, maximum eversion to neutral position, neutral position to toe off). Coupling angle variability was calculated for four segment-direction pairs: thigh flexion/extension – tibial rotation, thigh rotation – tibial rotation, thigh abduction-adduction – tibial rotation, and tibial rotation – foot eversion/inversion. This resulted in twenty combinations for which variability was compared between the two groups. Participants with PFPS had a clear reduction of $VAR_{elements}$ during terminal stance (i.e. neutral position to toe off sub-phase) and the swing phase of running for several couplings (Figure 2-4).

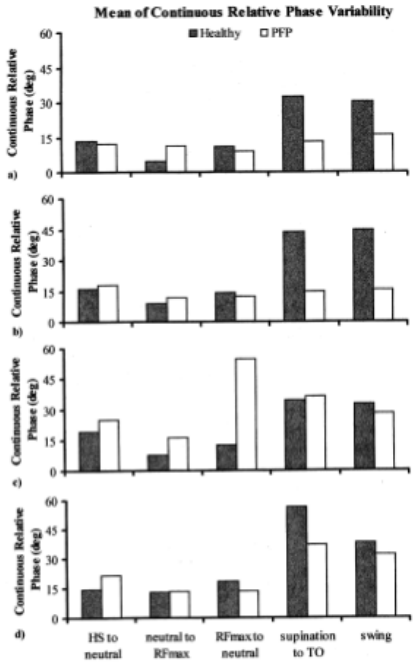

Fig. 7. Continous relative phase (CRP) variability at discrete intervals of the stance phase during running: (a) $Th_{F/E}$–Tib_{Rot}; (b) Th_{Rot}–Tib_{Rot}; (c) $Th_{Ab/Ad}$–Tib_{Rot}; and (d) Tib_{Rot}–$Ft_{Ev/In}$. The comparison is between individuals with and without patellofemoral pain (PFP). Note the discrepancy in the CRP variability present between the two data sets during terminal stance. HS = heel-strike, RF_{max} = maximum subtalar joint eversion, TO = toe-off.

Figure 2-4. Data from Hamill et al. (1999). Reprinted with permission.

Based on these select comparisons, the authors proposed that coordinative $VAR_{elements}$ was reduced in PFPS, which might reflect an inflexible pattern of coordination between joints/segments of the lower limb. They suggested this could be a beneficial adaptation that allowed participants to walk with reduced pain. Alternatively, the decreased $VAR_{elements}$ could be detrimental if it increased the load applied to soft tissues, which if repeated may result in degenerative changes. That is, reduced $VAR_{elements}$ in chronic pain may compound the original issue of pain/pathology due to localised application of stress to the tissues.

$VAR_{elements}$ was either increased or not changed during other sub-phases of stance for most other couplings. Despite the diverse changes for the numerous comparisons, the authors focused their interpretation and discussion on the comparisons for which $VAR_{elements}$ of the PFPS group was less than controls. Hamill et al. (1999) did not consider instances when $VAR_{elements}$ was greater in the PFPS group than the healthy control group, such as the coupling between thigh abduction-adduction and tibial rotation for the 'maximum eversion to neutral position' sub-phase. Further, it appears that there is a lack of statistical tests performed on the data to determine differences between groups (i.e. no mention of statistical testing within the article), and the lack of error bars (or other measures of within-group variability) in figures, makes it difficult to interpret the data in more detail (Figure 2-4).

Heiderscheit et al (2002) also studied variability in the coordination between different lower limb segments during running in participants with PFPS and healthy controls. $VAR_{elements}$ was analysed over the entire stride cycle, and divided into five sub-phases that each contained a functional event in the stride cycle: mid-stance, toe-off, swing acceleration, swing deceleration, heel-strike. Coupling angle variability was calculated for four segment-direction pairs: thigh; flexion/extension – tibial rotation, thigh rotation – tibial rotation, tibial rotation – ankle eversion/inversion, tibial flexion/extension – ankle eversion/inversion, tibial flexion/extension – ankle, and plantarflexion/dorsiflexion. This resulted in thirty combinations for which $VAR_{elements}$ was compared between the two groups. There were no differences in $VAR_{elements}$ between the affected lower limb in the PFPS group and the unaffected lower limb or either limb of the control group when the couplings were compared across the entire stride cycle. Further, despite comparisons being made between the PFPS group and controls for thirty phase/coupling combinations, $VAR_{elements}$ was reduced in the PFPS group for only one (i.e. thigh rotation – tibial rotation coupling for the phase that contained heel strike) phase/coupling combination. No other phase/coupling combinations were different between the two groups. The authors suggested the lack of further differences in joint coordination between groups might have been due to the limited

pain experienced by participants with PFPS at the fixed (group mean: 2.4/10) and preferred (group mean: 1.9/10) running speeds.

In another study of coupling variability of lower limb segments during running, Cunningham et al (2014) investigated $VAR_{elements}$ of female recreational runners who had PFPS and healthy controls when they ran on a treadmill for 15 minutes at a self-selected pace. Participants in the PFPS group were included if they reported >3/10 pain (on a 0-10 VAS) when running during the previous week, and during the treadmill running protocol during the experimental session. Although the participants ran for 15 minutes, data were analysed from one 10-second epoch for the PFPS group when participants reported the highest pain rating, but when their fatigue rating was <14 on the 15-point Borg Scale (6 = 'no exertion'; 20 = 'exhaustion' (Borg, 1982)). The average time period for the PFPS epoch was the 11^{th} minute of running, so this was chosen for the control group analysis. Variability of the coupling angle of six knee-ankle combinations were calculated over (i) the entire stride cycle, (ii) the stance phase and swing phase, individually, and (iii) over five phases of the stride cycle. Of the 48 coupling angle variability measures that were calculated, 46 of them were greater for the PFPS group, but only 7 of these couplings were statistically significant. The authors noted that the increased $VAR_{elements}$ observed in this study suggest the PFPS group that reports with greater pain intensity may exhibit coordinative structures different than that observed previously in Heiderscheit et al (2002). This suggests that contrary to Hamill (1999) and Heiderscheit (2002), $VAR_{elements}$ in PFPS was increased or not changed. Clearly, the diverse results from these studies indicate that changes to $VAR_{elements}$ in chronic pain are not straightforward. A limitation of Cunningham et al. (2014) was the concomitant presence of pain and fatigue (Borg: PFPS group = 12.4 ± 0.8; control group = 12.2 ± 0.9) for the epoch of the running task that was chosen for analysis. This fatigue rating on the 15-point Borg scale reflects 70% effort and is described as a "somewhat hard – steady pace" (Borg, 1982). Although the fatigue ratings were not different between the two groups, it is unclear whether the differences in $VAR_{elements}$ between the groups were due to the specific effect of knee pain experienced by PFPS participants during the running task or the combined effect of pain and fatigue.

A notable difference between these studies that evaluated changes to $VAR_{elements}$ in chronic PFPS is the potential role of pain. In Heiderscheit et al (2002) participants reported low pain (1.9/10 and 2.4/10 when running at the preferred and fixed speeds, respectively), whereas participants reported moderate pain (4.3/10) during the running task in Cunningham et al (2014). Conversely, Hamill et al (1999) did not report whether participants experienced pain during the running task.

The preceding discussion has focussed on changes to $VAR_{elements}$ in chronic pain conditions of the lower limb (Hamill et al. 1999; Heiderscheit et al. 2002; Cunningham et al. 2014). Diverse

changes to $VAR_{elements}$ for different features of movement in chronic neck/shoulder pain have also been observed (Madeleine et al. 2008a; Madeleine et al. 2008b). For example, in Madeleine et al. (2008a) participants with chronic neck/shoulder pain and healthy control participants performed a standardised cutting task with the upper limb that represented a common work task in the meat industry. Three 3-minute trials of the task were performed with a 5-minute break between each trial. Relative motion between the right arm and trunk were expressed for the upper arm as anatomical flexion-extension, abduction-adduction and medial-lateral rotation, and for the trunk as flexion-extension, lateral flexion, and transverse rotation. Four kinematic parameters were determined in three-dimensions for the right arm and trunk: starting position, acceleration throughout the cycle, range of motion, and total area under the movement curve versus time. $VAR_{elements}$ of arm and trunk movement was quantified as the standard deviation (SD) of the kinematic parameters. They found SD of arm acceleration was less for the patients than controls in the flexion-extension and rotation directions. However, no other parameters were different between the two groups.

Madeleine et al (2008b) conducted a study with the same protocol (i.e. task, arm/trunk recordings, and quantification of $VAR_{elements}$). They studied people who had worked for 6 months at a meat processing plant and compared workers who had developed neck/shoulder pain in that time and those who did not experience pain. It was found that SD of starting position was less in the presence of pain compared to participants without pain. Despite the numerous features of movement that were recorded, this was the only feature of movement that was different for participants with pain.

As introduced above (section 2.2.5.1) the conclusions of many studies that evaluated $VAR_{elements}$ in chronic pain did not discuss the diverse changes to $VAR_{elements}$ that are evident on close inspection of the data. Rather than a stereotypical and predictable decrease of $VAR_{elements}$ for all features of movement, changes to $VAR_{elements}$ in chronic pain (i.e. increase, decrease) are specific to the direction of movement and kinematic parameter that is measured within specific phases of a task. It is likely these changes to $VAR_{elements}$ (i.e. decrease or increase) for specific movement features have the same possible positive and negative consequences to function as discussed above. However, it is inviting to speculate why $VAR_{elements}$ might change for some features of movement but not others.

One possible explanation for the specificity of changes to $VAR_{elements}$ in chronic pain might relate to the capacity of a task element (e.g. flexion-extension movement in the middle phase of a task) to undergo a change in $VAR_{elements}$. That is, some elements of a task might be tightly constrained by the nervous system and not able to change, whereas other elements might be more flexible and able to increase or decrease according to the requirements of the system. Chronic pain

might induce different effects on specific elements of movement, which could influence whether $VAR_{elements}$ does or does not change. Another possible explanation is that specific changes to $VAR_{elements}$ might relate to the functional requirements of separate features of movement for specific phases and whether the changes to $VAR_{elements}$ would be beneficial or detrimental to the nervous system and musculoskeletal system. In the context of running in participants with PFPS, changes to $VAR_{elements}$ might relate to the loads that are applied to soft tissues during different movement phases. For instance, $VAR_{elements}$ may be reduced during the initial or final sub-phase of stance (Hamill et al. 1999; Heiderscheit et al. 2002) as this is when most stress is applied to the patellofemoral joint and is likely to be most painful (Teng and Powers, 2014). This implies that during chronic pain, changes to $VAR_{elements}$ depend on the effect on pain/pathology and function. Further, for the cutting task in Madeleine et al (2008a), it might have been beneficial to decrease $VAR_{elements}$ of arm acceleration, but not other kinematic parameters, to optimise or maintain function. This might relate the minimum jerk theory (Flash and Hogan, 1986), which proposes that upper limb movements are optimised according to smoothness of acceleration during the task.

2.2.5.5 Change in variability with repetition of the task

Most studies did not assess changes to $VAR_{elements}$ between the start and end of the trials. Lomond and Côté (2010), however, studied a repetitive reaching task performed by participants with chronic neck/shoulder pain and healthy controls. Participants in both groups performed the task until they could no longer maintain the correct frequency (i.e. one movement per second), or reported high pain (>8/10 on an 11-point NRS) or excessive fatigue (>8/10 on an 11-point Borg scale). $VAR_{elements}$ of the upper limb joints (in this case the shoulder, elbow, and fingertip) were calculated in three movement directions (i.e. anterior-posterior, medio-lateral, superior-inferior) at the start (first 30 seconds) and end (final 30 seconds) of the trial. Participants with chronic neck/shoulder pain had greater $VAR_{elements}$ of the shoulder in the anterior-posterior and superior-inferior directions than healthy controls, but $VAR_{elements}$ also changed with repetition of the task. Shoulder $VAR_{elements}$ in the anterior-posterior direction decreased in both groups between the start and end of the trial, and superior-inferior elbow $VAR_{elements}$ increased with repetition. These data suggest $VAR_{elements}$ can change in the short-term (i.e. within several minutes of performing an experimental task) for participants with chronic musculoskeletal pain, in addition to changes of $VAR_{elements}$ in the transition from acute to chronic pain.

There are several possible explanations for the change in $VAR_{elements}$ of certain kinematic parameters with repetition of the reaching task. The reduction of shoulder $VAR_{elements}$ in the anterior-posterior direction may reflect an adaptation in which participants learnt, through repetition

of the task, to decrease $VAR_{elements}$ in an attempt to reduce pain and/or minimise loading of painful/injured tissues. However, this decrease of $VAR_{elements}$ was also found in the healthy control group, which suggests the decrease of $VAR_{elements}$ was not due to pain. Further, the increase of shoulder $VAR_{elements}$ in the superior-inferior direction might suggest people with chronic neck/shoulder pain retain the flexibility to explore different movement options like non-painful (Dingwell et al. 2001) and painful (Moseley and Hodges, 2006; Madeleine et al. 2008a) situations. However, as participants in both groups experienced fatigue during the task, it is unclear whether the changes to $VAR_{elements}$ between the start and end of the task were due to fatigue or pain/pathology. It is unlikely that pain was the sole factor in the change to $VAR_{elements}$ because it was found for both groups, which suggests that fatigue may have been the main driver for the change to $VAR_{elements}$.

2.2.5.6 Summary of findings from chronic pain

As discussed in the preceding sections, changes to $VAR_{elements}$ in chronic/persistent pain are diverse. There might be a simple reduction of $VAR_{elements}$ (Yakhdani et al. 2010; van den Hoorn et al. 2012), reduced $VAR_{elements}$ of the painful joint and increased $VAR_{elements}$ of functionally-related non-painful joints (Lamoth et al. 2006; Madeleine and Madsen, 2009), no change to $VAR_{elements}$ (Lewek et al. 2006), altered $VAR_{elements}$ for some features of movement but not others (Hamill et al. 1999; Heiderscheit et al. 2002; Madeleine et al. 2008a,b; Cunningham et al. 2014), and changed $VAR_{elements}$ with repetition of a task (Lomond and Côté, 2010). Whether these potential changes (or lack of changes) to $VAR_{elements}$ are beneficial or detrimental to function are likely influenced by the context in which the task is performed. Further, the possible changes to $VAR_{elements}$ probably depend on the extent of control the nervous system imposes on the specific element, and the effect that changed $VAR_{elements}$ of the element will have on pain and function.

Although these studies of complex multi-joint tasks during chronic musculoskeletal pain provide important insight, interpretation is limited by two factors. First, the reporting of pain within the studies was unclear. Of the 12 studies that evaluated $VAR_{elements}$ during chronic pain, 9 reported pain intensity at inclusion in the study, and 6 reported pain intensity during performance of the task(s). Further, when studies *did* report pain intensity, in some cases the pain intensity during performance of the task was low. For instance, the average pain intensity experienced by participants with PFPS during performance of the walking task was 2.4 ± 1.0 /10 (fixed speed) and 1.9 ± 0.9/10 (preferred speed) in Hamill et al (1999), and 1.9/10 in Heiderscheit et al (2002). Changes to $VAR_{elements}$ in chronic pain might be different if the task provokes more pain (e.g. 4.3/10 pain in Cunningham et al. (2014)). Second, two studies reported fatigue during performance of the

tasks (Lomond and Côté, 2010; Cunningham et al. 2014) and no other studies indicated whether fatigue was recorded. As discussed above, it is unclear whether the changes to $VAR_{elements}$ in chronic pain that were observed in these studies were due to the specific effect of pain, or the combined effect of pain and fatigue.

2.2.6 Do all movement tasks adapt in a similar manner during chronic /persistent pain?

As discussed in the previous sections, $VAR_{elements}$ may change in several ways during chronic/persistent pain. A common feature of studies that investigated the effect of chronic pain on $VAR_{elements}$ is the evaluation of tasks that involved multiple joints and muscles (i.e. elements), such as walking and reaching. As discussed above, multi-joint tasks have considerable redundancy of the nervous system, musculoskeletal system and motor control strategies, which allows great potential for variation, and thus considerable $VAR_{elements}$ are available to alter movement strategy. The different changes to $VAR_{elements}$ found in previous studies might be explained by the capacity of a specific task element to be varied. However, this has not been the focus of studies in the past. One way to consider this possibility is to study a simple motor task. Simple tasks have fewer movement options, and thus fewer elements for which variability can be altered during chronic/persistent pain. A key issue to enable resolution of these questions was to identify a chronic musculoskeletal pain condition that provided an ideal model to understand the relationship between movement variability and chronic pain. Lateral epicondylalgia ('tennis elbow') was identified as a viable option and the basis for selection of this condition is discussed in the following sections.

The aim of Study 3 (Chapter 6) was to investigate whether $VAR_{elements}$ changes for participants with chronic lateral epicondylalgia, and whether this variability changes over time with repetition of the task.

2.3 Lateral epicondylalgia

2.3.1 Introduction

Lateral epicondylalgia (LE) (or tennis elbow) is a musculoskeletal condition characterized by pain over the lateral epicondyle of the humerus during gripping and other manual tasks that require movement of the wrist, hand and fingers. It is a common condition that has an annual incidence of 4-7 cases per 1000 patients in general practice (Hamilton 1986; Smidt et al. 2006) and 1-3% within the general population (Allander, 1974; Kivi, 1983; Walker-Bone et al. 2004; Shiri et

al. 2006). An acute episode of LE typically transitions to a chronic musculoskeletal pain condition (Smidt et al. 2006). It has been estimated that 5-10% of patients develop recalcitrant symptoms and eventually undergo surgical intervention (Boyd and McLeod, 1973; Coonrad and Hooper, 1973; Nirschl and Pettrone, 1979; Baker et al. 2000). This concurs with other data from randomised clinical trials that indicate 89% of individuals report recovery by one year regardless of treatment (Smidt et al. 2006), leaving ~10% with recalcitrant symptoms.

2.3.2 Pathophysiology

Lateral epicondylalgia is relatively simple to diagnose clinically; but, it has a complex pathophysiology. Coombes et al. (2009) proposed that LE comprises three inter-related components: i) local tendon pathology; ii) sensory system changes (including proprioceptive deficits, hyperalgesia and changes in processing of pain/nociceptive inputs); and iii) motor system impairments (Figure 2-5). It is likely that each case of LE will have a unique contribution from each component of the model, and this reflects the heterogeneous nature of this clinical population (Coombes et al. 2009).

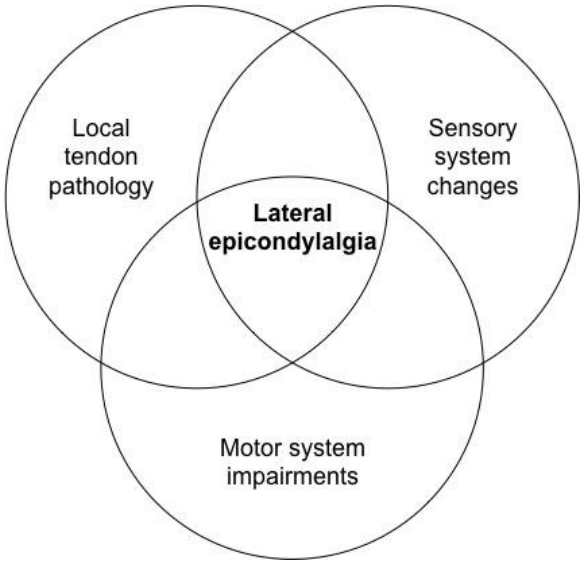

Figure 2-5. An integrated model of lateral epicondylalgia (Coombes et al. 2009). Reprinted with permission.

2.3.2.1 Local tendon pathology

Lateral epicondylalgia is an overuse injury in which the ability of the common extensor tendon, particularly the extensor carpi radialis brevis (ECRB) musculotendinous unit to heal via natural processes is compromised (Nirschl 1992; Fredberg and Stengaard-Pedersen, 2008). The pathophysiology is thought to be degenerative, rather than inflammatory, because of the presence of

degenerative changes of the deep and anterior fibres of the common extensor tendon at its attachment to the lateral epicondyle of the humerus (Regan et al. 1992; Connell et al. 2001) and the consistent absence of inflammatory cells in histological studies (Alfredson et al. 2000; Benjamin et al. 2006; Fredberg and Stengaard-Pedersen, 2008). In normal circumstances, tendons are strengthened by uniform functional mechanical loading during muscle activation and movement (Wang, 2006; Langberg et al. 2007) that alters their composition and structure (Wang et al. 2000; Cook and Purdam 2009). Non-uniform loading of the common extensor tendon contributes to degeneration and structural weakening of the tendon which makes it more susceptible to overload and explains the degenerative changes found in chronic LE (Regan et al. 1992; Haraldsson et al. 2005; Arnoczky et al. 2007).

2.3.2.1.1 How do the local tendon changes relate to variability?

As discussed earlier (section 2.1.3), $VAR_{elements}$ may provide a benefit for the musculoskeletal system by distributing stresses between different soft-tissues with the potential to reduce cumulative tissue load (Hamill et al. 1999). No studies have yet considered the potential association of $VAR_{elements}$ and chronic LE. A biologically plausible mechanism for the development of chronic LE is that decreased $VAR_{elements}$ during repetitive upper limb tasks may contribute to non-uniform loading of the common extensor tendon and the degenerative changes that are implicated in this condition. It is also possible that $VAR_{elements}$ is within normal limits prior to the onset of the degenerative tendon changes associated with LE, and changes only once pain and/or degenerative changes of the tendon are present. Finally, $VAR_{elements}$ might be no different to healthy individuals and unrelated to LE. Changes to $VAR_{elements}$ have been identified in chronic musculoskeletal pain conditions of the knee (Hamill et al. 1999; Heiderscheit et al. 2002; Georgoulis et al. 2006; Lewek et al. 2006; Yakhdani et al. 2010; Cunningham et al. 2014), shoulder (Madeleine et al. 2008a,b; Madeleine and Madsen, 2009; Lomond and Côté, 2010), and low back (Lamoth et al. 2006; van den Hoorn et al. 2012) and these changes have been implicated in the underlying pathology (see section 2.2.4). As no studies have evaluated $VAR_{elements}$ in chronic LE it remains unclear whether this critical feature of healthy movement is related to onset or persistence of this common and costly problem.

2.3.2.2 Sensory system changes

Changes to the sensory elements of the peripheral and central nervous systems have been identified in chronic LE and theories have been proposed to explain their likely contribution to the development and maintenance of pain (Wright, 1999).

2.3.2.2.1 Proprioception of the elbow

Proprioception is a critical component of the sensory system that allows individuals to sense the relative position of joints and limbs in static and dynamic situations (Proske et al. 2000), and provide a sense of effort and weight perception (Gandevia, 1996). Ongoing proprioceptive information is important for the effective modulation and fine-tuning of neuromuscular control (Lamoth et al. 2006). However, in situations of acute and chronic pain, proprioceptive information may be compromised. Two studies have evaluated proprioception in participants with LE compared to controls (Dessureault et al. 2008; Juul-Kristensen et al. 2008). In Juul-Kristensen et al (2008), proprioceptive ability at the elbow was quantified as i) absolute error and ii) variable error, for joint position sense and threshold to detect a passive movement. Absolute error and variable error of threshold to detect a passive movement were greater in the affected elbow of LE participants than controls, and there was a tendency toward a greater absolute error of joint position sense compared to controls. Interestingly, differences between the affected and unaffected elbows in the LE group were not significant. In Dessureault et al (2008) proprioceptive acuity of effort and weight perception were evaluated with a weight discrimination task. They found proprioception was decreased in the affected arm of the LE group, which the authors suggested could affect force perception during functional tasks. A reduced ability to perceive force during tasks could have detrimental consequences to the musculoskeletal system, such as the potential for overload of specific soft tissues with subsequent pain and injury. These data indicate that altered proprioception in LE concurs with studies in other clinical populations, such as whiplash at the neck (Sterling et al. 2003) and low back pain (Brumagne et al. 2004).

2.3.2.2.2 Pain free grip

Pain-free grip reflects the amount of force that can be generated at the point at which pain is perceived during gripping with the affected upper limb (Coombes et al. 2009). This measure is recommended as a critical component of diagnosis of LE (Bisset et al. 2006). Participants are instructed to gradually increase grip force until they experience the first onset of lateral elbow pain, at which point they stop gripping. Typically, pain-free grip force of the affected upper limb in LE is reduced by 43-64% relative to the unaffected side (Abbott et al. 2001; Vicenzino et al. 2001; Sran et al. 2002; Paungmali et al. 2004; Bisset et al. 2006). Gripping is thought to be painful for participants with chronic LE as a result of activation of the ECRB muscle. In normal situations (i.e. in the absence of pain), gripping involves coordinated activation of the wrist/finger extensor muscles (ECRB, extensor carpi radialis longus (ECRL), extensor carpi ulnaris (ECU), and extensor

digitorum (ED)) and wrist flexor muscles (flexor carpi radialis (FCR), flexor carpi ulnaris (FCU)) to counteract wrist flexion moments caused by activation of finger flexor muscles (i.e. flexor digitorum superficialis (FDS), flexor digitorum profundus (FDP)), to optimize the muscle length for producing force (i.e. the length-tension relationship) (Snijders et al. 1987; Shimose et al. 2011) and to stabilize wrist position (Snijders et al. 1987; Johanson et al. 1998). ECRB attaches to several structures around the elbow, including the lateral epicondyle, intermuscular septum, lateral collateral ligament and annular ligament, via the common extensor tendon (Stoeckart et al. 1989; Milz et al. 2004). When ECRB is activated during gripping under normal circumstances (i.e. in the absence of pain or degenerative changes), the extensive attachments of the common extensor tendon allows distribution and dissipation of stresses across a broad area and limits its susceptibility to overload (Coombes et al. 2009). However, if the cellular organization of the common extensor tendon is disrupted due to non-uniform loading, stresses would be applied over a smaller region of tendon when ECRB is activated during gripping. This could explain the characteristic pain caused by gripping in LE. This provocation may underpin a number of changes in motor system function in LE. A prime example is that the motor system may attempt to reduce pain with gripping by alteration of wrist position. Bisset et al (2006) found that participants with unilateral chronic LE performed a gripping task in a less extended wrist position (i.e. 11° less extension) than pain-free control participants. The optimal wrist posture for maximal grip force in healthy participants is reported to be slight extension; wrist flexion was shown to reduce maximal force development as a consequence of the effect of wrist position on the length-tension properties of the finger flexor muscles (Mogk and Keir, 2003). It is inviting to speculate that people with LE might grip in a more flexed wrist position to reduce painful loading of the damaged common extensor tendon as a result of activation of ECRB and other wrist extensor muscles.

2.3.2.2.3 Mechanical hyperalgesia

Mechanical hyperalgesia (i.e. enhanced sensitivity to mechanical stimuli that are painful) is consistently found in participants with unilateral LE. A standard method to assess the presence of mechanical hyperalgesia is to test pressure pain thresholds (PPT). PPT testing involves application of pressure via a probe at a constant rate, and the participant is instructed to press a button when the pressure sensation first changes to one of pressure plus pain, at which point the application of pressure is ceased. PPTs over the lateral epicondyle of the affected elbow are usually 45-54% less than the unaffected elbow of participants with LE (Wright et al. 1994; Vicenzino et al. 2001; Sran et al. 2002; Pienimaki et al. 2002). Interestingly, mechanical hyperalgesia of both the affected and unaffected upper limbs has been found in participants with unilateral LE (Slater et al. 2005; Ruiz-

Ruiz et al. 2011; Coombes et al. 2012). Bilateral mechanical hyperalgesia, along with provocation of symptoms from regions that are spatially distant from the affected elbow (e.g. cervical spine, neural tissues of the upper limb) are characteristic of secondary hyperalgesia, which is defined as enhanced sensitivity to painful stimuli over an area extending beyond the injured segment (Graven-Nielsen, 2006).

2.3.2.2.4 How might the sensory system changes relate to $VAR_{elements}$?

Changes to the sensory system in chronic LE might influence $VAR_{elements}$ when people with chronic LE perform tasks with the upper limb. For instance, impaired proprioception in chronic LE (Dessureault et al. 2008; Juul-Kristensen et al. 2008) might lead to uncontrolled joint/segment motion and inefficient loading of soft-tissues of the upper limb (see section 2.1.4). Further, the sensitivity of the pain system in chronic LE (Bisset et al. 2006; Coombes et al. 2012) is likely to influence $VAR_{elements}$. Although there is no direct evidence that links sensory changes in chronic LE to $VAR_{elements}$, there is a large body of evidence that indicates $VAR_{elements}$ is altered in other chronic musculoskeletal pain conditions of the neck/shoulder, low back, and lower limb (see section 2.2.5 for a detailed discussion). Thus, we contend it is likely that $VAR_{elements}$ will be affected in chronic LE compared to healthy control participants due to sensory changes. However, it is unclear whether the sensory changes would directly influence $VAR_{elements}$, or whether the sensory changes represent an intermediate step, whereby compromised sensory information contributes to poor motor output, with ensuing changes to $VAR_{elements}$. It is therefore critical to consider both the sensory and motor impairments in chronic LE to better understand their impact on movement control.

2.3.2.3 Motor system impairments

There is considerable evidence of changes to the motor system in chronic LE. These changes might occur at any point along the motor pathway (e.g. cortical, subcortical, patterns of muscle activation), and contribute to functional limitations (e.g. altered fine motor control of the hand and fingers, reduced upper limb strength). These potential changes are outlined below.

2.3.2.3.1 Changes at the motor cortex

Transcranial magnetic stimulation (TMS) has been used to measure the excitability (Dessureault et al. 2008; Schabrun et al. in press) and organization (Schabrun et al. in press) of motor cortical cells that project to the forearm muscles in participants with chronic LE and healthy controls. TMS applied over the motor cortex allows indirect stimulation of cells that elicit excitatory and inhibitory responses in muscles activated by the specific cortical area that is

stimulated. These responses are recorded via electromyography (EMG) of the target muscles.

For instance, in Dessureault et al (2008) TMS was applied over the primary motor cortex to assess four measures of corticomotor excitability (i.e. resting motor threshold, stimulus-response curve, silent period, and maximum evoked potential). Muscle activity of the extensor carpi radialis (ECR) muscle was recorded bilaterally with surface electrodes. The Grooved Pegboard Test (GPT) was used to measure manual dexterity. The GPT requires participants to insert 25 pegs into randomly positioned slots as quickly as possible. There were no differences between arms or groups for any measure of corticomotor excitability or manual dexterity. There was a correlation between the resting motor threshold and manual dexterity in the LE group (but not the control group), which indicates that lower motor thresholds were associated with better performance on the GPT. The authors did not offer insight into a potential mechanism that relates corticomotor excitability to fine motor control of the upper limb in participants with chronic LE.

Schabrun et al. (in press) investigated the excitability and organization of the primary motor cortex in participants with chronic LE and healthy controls. EMG was recorded from ECR and ED with surface electrodes. The cortical representations of ECRB and ED were more excitable, less separated, and contained fewer discrete TMS-evoked peaks in participants with chronic LE than healthy controls. They proposed that the less discrete (i.e. less separated) representations of ECRB and ED might reflect greater overlap and blurring of the spatial territory of each muscle. Less separation between the cortical representations of the ECRB and ED, and fewer peaks within the representations, could lead to dysfunctional muscle activation patterns of the forearm muscles and contribute to the motor dysfunction found in chronic LE (Schabrun et al. in press).

2.3.2.3.2 Changes to muscle activation

Patterns of muscle activation can be measured with recordings of the electrical activity of muscles (i.e. EMG) using surface electrodes placed on the skin overlying target muscles or with fine-wire electrodes that are inserted into muscles via the skin. Several studies have evaluated simple tasks such as wrist extension (Rojas et al. 2007), gripping (Alizadehkhaiyat et al. 2007), and gripping whilst performing isometric wrist flexion-extension movement (Blanchette and Normand, 2011) and found diverse changes to activation patterns of the forearm muscles in chronic LE.

In Alizadehkhaiyat et al. (2007), participants with chronic LE and healthy controls performed a constant gripping task at 50% of their maximal voluntary contraction (MVC) until exhaustion. Muscle activity was recorded from ECR, ED, FCU, and FDS with surface electrodes. The root-mean-squared (RMS)-amplitude of activation for each muscle was calculated over 5-second intervals and normalized to the starting amplitude. Alizadehkhaiyat et al. (2007) found the

amplitude of ECR activity in the LE group was less than controls, whereas activation amplitude of the other muscles was similar in both groups. The authors suggested the decrease of ECR activity might be a protective strategy that occurs due to pain, but did not propose why the strategy would be protective. The intensity of the constant gripping task (i.e. 50% MVC) would likely provoke pain in approximately half of the participants. It is unclear whether the constant gripping task was painful as pain scores were not reported, and indirect calculation is not possible as pain-free grip values are not reported. Despite this lack of information, one possibility is that activity of ECR was decreased in participants with LE to limit painful loading of the common extensor tendon, as discussed above (section 2.3.2.2.2).

Activation of ECR was also reduced in Rojas et al (2007). In this study, activity of the wrist extensor muscles (i.e. ECR, ED and ECU) were recorded with surface electrodes during a resisted wrist extension task. The activity of each muscle was normalized with respect to the sum of the activity of individual muscles during the task. Participants with LE had less contribution of ECR and greater contribution of ECU during the wrist extension task. Rojas et al. (2007) did not suggest why these altered patterns of muscle activation may have been present. It is tempting to speculate that ECR was activated less for participants with LE to reduce loading of the damaged common extensor tendon and limit pain. Further, the greater contribution of ECU might be a compensatory mechanism to maintain wrist extension force despite the reduced activation of ECR. As pain intensity was not recorded during the wrist extension task, it is unclear whether the altered activation pattern of the forearm muscles reduced pain.

Conversely, activation of ECRB might not change for participants with LE. For instance, in Blanchette and Normand (2011), participants with LE performed a gripping task whilst doing isometric wrist flexion and extension. They found the amplitude of ECRB activation was no different between the affected and unaffected upper limbs in participants with LE. However, there is evidence of sensory and motor deficits of both the affected and unaffected upper limbs of participants with chronic LE compared to healthy controls (Heales et al. 2013). Therefore, as there was no healthy control group in Blanchette and Normand (2011), it is impossible to determine if there were deficits of both the affected and unaffected limbs that could explain the lack differences in activation of ECRB. That is, it is possible that activation of ECRB *was* altered in the affected upper limb, but ECRB activation was similarly altered in the unaffected upper limb.

Two studies evaluated a single-handed backhand tennis stroke (Kelley et al. 1994; Bauer and Murray, 1998). Kelley et al. (1994) recorded muscle activity from five forearm muscles (ECRB, ECRL, ED, FCR, and pronator teres (PT)) with intramuscular fine-wire electrodes during the single-handed backhand tennis stroke. The stroke was divided into six phases (preparation, early

acceleration, late acceleration, ball impact, early follow through, late follow through) for analysis. Muscle activity was normalized to the peak signal recorded during a maximal manual muscle test. There were complex changes to the patterns of forearm muscle activation between the two groups. Compared to controls, the LE group had greater activation of ECRL and FCR for the preparation phase, greater activation of ECRB, ECRL and PT during ball impact, and greater activity in ECRB and PT for early follow through. There were no differences between the groups for the early acceleration or the late follow through phases. The differences in patterns of muscle activation for differences phases of the tennis stroke might relate to different functional requirements of each phase. For instance, greater activation of the wrist extensor muscles might be required at the ball impact phase relative to the preparation and follow-through phases.

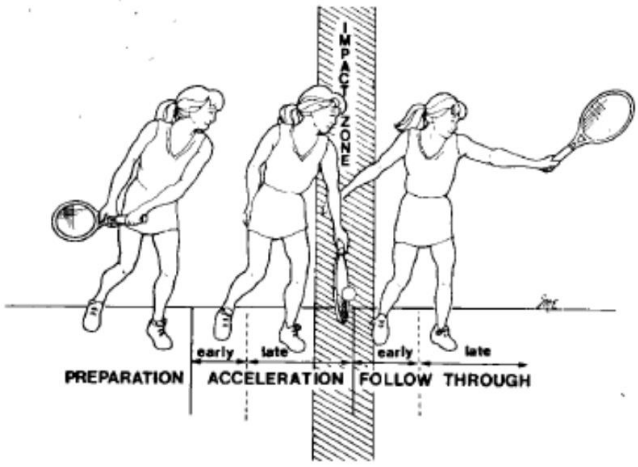

Figure 1. The six phases of the single-handed backhand tennis stroke.

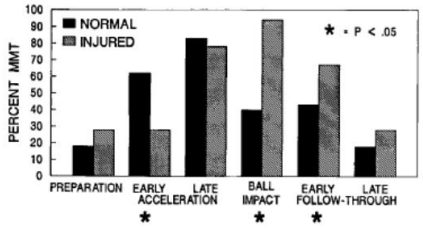

Figure 2. The EMG activity for extensor carpi radialis brevis muscle in normal and injured subjects.

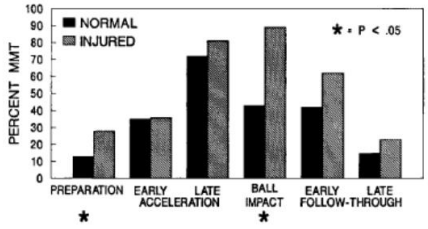

Figure 3. The EMG activity for extensor carpi radialis longus muscle in normal and injured subjects.

Figure 2-6. Data from Kelley et al. (1994). Reprinted with permission.

In Bauer and Murray (1999), participants with LE and healthy age-matched controls performed a single-handed backhand tennis stroke at three ball speeds (low 11.94 m/s, medium 17.13 m/s, high 22.95 m/s) and three racquet head locations (central, long axis, torsional). EMG was recorded from ECRB, FCU and triceps brachii with surface electrodes. They found ECRB was activated for a longer duration and with greater amplitude in the LE group for each ball speed and each racket location compared to healthy controls.

The altered muscle activation patterns in participants with chronic LE during the various tasks can be interpreted in two ways. First, reduced activation of the wrist/finger extensor muscles that attach to the common extensor tendon (i.e. ECRB, ED and ECU) could be a beneficial adaptation in chronic LE. For instance, activation of the wrist/finger extensors during various tasks in chronic LE likely result in elbow pain due to ineffective transmission of stresses within the

common extensor tendon. Therefore, reduced activation of the wrist/finger extensors could minimize stresses within the tendon and limit provocation of pain. Alternatively, reduced (or increased) activation of the wrist/finger extensor muscles and altered activation of other forearm muscles could be a detrimental adaptation. Altered patterns of forearm muscle activation might contribute to stress shielding of the common extensor tendon (i.e. disruption of beneficial mechanical loading of tendon), which could lead to further degenerative changes. Second, greater activation of ECRB (and other wrist/finger extensors) could be a beneficial adaptation. For instance, there was greater activation of ECRB during the ball impact phase of a backhand tennis stroke for participants with chronic LE compared to controls (Kelley et al. 1994; Bauer and Murray, 1998). This strategy might prevent forceful wrist flexion at ball impact, thereby reducing the potential for further damage or provocation of pain due to stretch of the common extensor tendon and/or muscle fibres. Alternatively, greater (and longer) activation of the wrist/finger extensor muscles could be detrimental if it increases stress in the damaged common extensor tendon and provokes pain (Bauer et al. 1999).

The potential beneficial and detrimental consequences of alterations to patterns of forearm muscle activation must be considered in the context of the effect on pain and function. A limitation of studies that investigated changes to forearm muscle activation in participants with chronic LE is that they did not report the pain intensity participants experienced during the tasks. Therefore, we do not know the relationship between pain intensity and the observed changes to patterns of forearm muscle activation in chronic LE and thus not in a position to determine if these changes are beneficial or detrimental. Further, there is significant heterogeneity between the studies, such as the muscles that were recorded, the method of normalization of muscle activity (e.g. maximal signal recorded during MVC, muscle activity at the start of the contraction), and the tasks that were studied (e.g. gripping, wrist extension, backhand tennis strokes). For these reasons, it is difficult to conclude with certainty what effect the changes to forearm muscle activation will have on pain and function. Despite these factors, it is clear that activity of the forearm muscles can be altered in chronic LE, which might have implications for $VAR_{elements}$.

2.3.2.3.3 Altered fine motor control

Despite the changes to activation patterns of the forearm muscles in participants with LE, only two studies have evaluated whether deficits of fine motor control are also present (Skinner and Curwin, 2007; Dessureault et al. 2008). In Skinner and Curwin (2007), fine motor control of both upper limbs was examined in participants with LE and healthy controls. Two measures of dexterity were used. First, the Purdue pegboard test required participants to place as many pins into small

pinholes as possible over a 30 s period in three trials. Participants in the LE group placed 5 fewer pins over the three trials. Second, the Complete Manual Dexterity Test required participants to use their fingers to turn over medium-sized cylindrical blocks and then reach forward to place each block consecutively into one of 60 wells. The total time to complete four trials of the test was recorded. Participants in the LE group were 51.03 seconds slower to complete the four trials than the control group. These data suggest participants with LE have impaired fine motor control. Interestingly, there was no difference between the affected and unaffected upper limbs for either task. However, as noted above, bilateral sensory and motor deficits are found in LE, which might explain why both upper limbs were affected for the tests of fine motor control. The authors suggested the mechanisms underlying the decrease in fine motor control in LE might relate to cortical reorganisation of the sensory and motor areas. This proposal is congruent with data that shows smudging of the cortical representation of back muscles in low back pain (Tsao et al. 2010) and less discrete localisation of cortical representations of upper limb muscles in chronic LE (Schabrun et al. in press), that are discussed above.

As discussed above (section 2.3.2.3.1), Dessureault et al (2008) used the GPT to measure manual dexterity in participants with chronic LE and healthy controls. Contrary to Skinner and Curwin (2007), this study did not find any differences in manual dexterity between groups or arms. However, as noted above participants who had a lower motor thresholds of the ECRB muscle performed better on the GPT. The authors noted the differences between performed of the GPT in their study and performance on the Purdue pegboard test in Skinner and Curwin (2007). They suggested one possible explanation for the differences in findings might be the properties of the Purdue and GPT themselves. Though both tests involve rapidly placing pegs in the pegboard, the GPT requires a degree of peg manipulation, whereas the Purdue test involves more hand transport and distance with less peg manipulation (Dessureault et al. 2008).

2.3.2.3.4 Reaction time and speed of movement

Two studies (Pienimaki et al. 1997; Bisset et al. 2006) investigated reaction time and speed of movement with several tests in participants with chronic LE and healthy controls. These tests included simple reaction time (SRT), and the reaction time (RT) and speed of movement (SOM) to move to a target with one choice (RT1, SOM1) or two choices (RT2, SOM2). Both studies found delayed reaction time and reduced speed of movement in the affected arm of participants with chronic LE compared to controls. However, the deficits reported in Pienimaki et al (1997) were more pronounced than those found in Bisset et al (2006). Bisset et al (2006) suggested these differences might relate to the younger and predominantly female group of participants with chronic

LE who also had symptoms for longer than the participants in Pienimaki et al (1997).

2.3.2.3.5 Muscle strength deficits

Although gripping is a provocative manoeuvre for participants with chronic LE, several studies have tested maximal grip strength. Maximal grip strength of the affected upper limb of participants with chronic LE can be reduced (Slater et al. 2005; Alizadehkhaiyat et al. 2007) or not different (Bisset et al. 2006) compared to healthy controls. There are several possible explanations for the reduced maximal grip strength in this context. First, pain elicited during the gripping task might be the limiting factor. That is, it might be possible to grip to the same extent with both the affected and unaffected upper limbs, but participants stop gripping with the affected upper limb prematurely due to the presence of pain. Conversely, the maximal force-generating capacity of the forearm muscles in the affected upper limb might become weaker due to disuse secondary to pain. The lack of differences in maximal grip strength found in Bisset et al (2006) suggests the presence of pain/pathology in the affected upper limb of participants with chronic LE might not always affect the capacity to generate maximal force.

In addition to deficits of grip strength, generalized strength deficits of wrist flexion (Alizadehkhaiyat et al. 2007) and extension (Slater et al. 2005; Alizadehkhaiyat et al. 2007), elbow flexion and extension (Coombes et al. 2012b) and abduction, internal rotation and external rotation of the shoulder (Alizadehkhaiyat et al. 2007) have been found in the affected upper limb of LE participants compared to pain-free controls. As discussed above, the generalised strength deficits of the upper limb in participants with chronic LE might relate to provocation of pain during the task or a long-standing process of disuse secondary to elbow pain. These strength deficits of the upper limb might remain for several months despite attenuation or resolution of pain (Alizadehkhaiyat et al. 2008). This suggests pain might be a potent stimulus to induce upper limb strength deficits in chronic LE, but resolution of pain might not be an effective stimulus for strength to return to normal. Alternatively, weakness of upper limb muscles might predispose people to LE.

2.3.2.3.6 How might the motor system changes relate to variability?

The preceding sections have discussed the diverse changes to the motor system found in chronic LE, such as altered excitability and organization of cells in the motor cortex that project to the forearm muscles (Dessureault et al. 2008; Schabrun et al. in press), altered pattern of forearm muscle activation during simple (Alizadehkhaiyat et al. 2007; Rojas et al. 2007) and complex (Kelley et al. 1994; Bauer and Murray, 1998) tasks, and the alterations to fine motor control (Skinner and Curwin, 2007) and strength deficits (Slater et al. 2005; Alizadehkhaiyat et al. 2007;

Coombes et al. 2012b) that might impact on functional activities. There is likely a complex interplay between changes at different organizational levels of the motor system that might aim to maintain function, limit loading of painful structures, and minimize pain. For instance, although central control mechanisms are thought to contribute to altered movement variability during pain, no studies to date have specifically investigated the link between changes to movement variability and central (cortical) involvement or correlates of pain adaptations.

The diverse changes to the motor system in chronic LE might impact on $VAR_{elements}$ in several ways. For instance, skilled movements of the upper limb require coordinated activation patterns of the forearm muscles. As these activation patterns can be altered in chronic LE, there might be uncontrolled motion of the upper limb with an associated increase of $VAR_{elements}$. If $VAR_{elements}$ becomes excessive, it could lead to uncontrolled loading of soft tissues with the potential for further pain and injury. In response to uncontrolled motion, the motor system might reduce $VAR_{elements}$ as a protective mechanism. However, if reduced $VAR_{elements}$ is maintained for an excessive period of time, the same soft tissues may be loaded repeatedly, which might contribute to degeneration and further pain/injury.

From the perspective of maintenance of functional tasks, both too much and too little $VAR_{elements}$ might contribute to impairments. For instance, excessive $VAR_{elements}$ might imply uncontrolled joint motion, which could lead to poor performance in tasks that require fine motor control, such as the Purdue pegboard test (Skinner and Curwin, 2007). Conversely, too little $VAR_{elements}$ in participants with chronic LE could explain difficulties learning a novel task that requires effective coordination of the upper limb muscles (e.g. Purdue pegboard test). For instance, in non-painful situations $VAR_{elements}$ was found to be beneficial in motor learning and adaptation (Wu et al. 2014).

2.3.3 Transition from acute lateral elbow pain to chronic LE

Studies of the pathophysiological changes associated with lateral elbow pain have focused on participants with chronic LE. However, no studies have evaluated whether similar changes are found in acute lateral elbow pain, or how they evolve over time in the transition to chronic LE. It is the contention of this thesis that better understanding of the motor adaptation associated with acute lateral elbow pain will lead to a better understanding of how and why acute lateral elbow pain transitions to a chronic musculoskeletal pain condition. One possibility to address the issue of the specific role of nociception/pain in the development of motor deficits, without the confounding effect of tissue damage and any associated psychological factors, is to examine the effects of an experimental model of sustained elbow pain. Ideally, an experimental model of elbow pain would

induce pain that is sustained for several days to replicate the ongoing aspect of pain/nociception at the start of acute LE, and that is provoked by contraction/stretch of the forearm muscles and functional activities that involved the upper limb. An adequate model of sustained elbow pain is not currently available.

A model of sustained elbow pain would also be of benefit to investigate the possible relationship between changes to $VAR_{elements}$ in acute pain and changes in chronic/persistent pain. It is unclear how $VAR_{elements}$ is altered when acute pain is sustained for several days, weeks, and months in the transition to a chronic musculoskeletal pain condition. As no studies have evaluated $VAR_{elements}$ in the transition from acute to chronic pain, whether the variation contributes to the transition to chronicity/persistence of pain remains speculative. Investigation of the relationship between changes to $VAR_{elements}$ and the transition from acute to chronic pain could be addressed with longitudinal studies, with participants recruited immediately after they sustain an acute injury and then assessed at specific time-points over a certain period (e.g. 3-6 months post-injury). Interpretation of such a study would be challenging because of the potential heterogeneity of the participants in terms of injury, healing, and other factors such as psychosocial features. Therefore, other models in which nociceptive input can be controlled may be more ideal.

A priority is to develop an experimental model of sustained pain. Potential models of sustained elbow pain are introduced in Chapter 3 and steps towards development of a suitable model are discussed in Chapter 7.

The aim of study 4 (Chapter 7) was to investigate the development of an experimental model that induces pain that is sustained for several days and provoked by movement and muscle contraction.

2.4 Aims

The specific aims of this thesis were:

1. To investigate whether the goal of a simple task could be maintained during acute experimentally induced pain (*Studies 1 and 2*) and in those with chronic musculoskeletal pain (*Study 3*).
2. To investigate whether $VAR_{elements}$ would increase for a simple task performed during acute experimental pain, and whether $VAR_{elements}$ changes over time with repetition of the task (*Study 1*).
3. To investigate whether $VAR_{elements}$ would initially increase during acute experimental pain in the search for a new, less painful movement strategy (*Study 2*).
4. If a less painful strategy was experienced during acute pain, to evaluate if this strategy would be selected more frequently than other options (*Study 2*).
5. To investigate whether participants with chronic LE perform a simple task that provokes elbow pain with altered $VAR_{elements}$ and in a different wrist position than healthy controls (*Study 3*).
6. To investigate whether pain intensity during a simple task affects wrist position and the magnitude of $VAR_{elements}$ in participants with chronic LE (*Study 3*).
7. To characterise the parameters of an experimental model of pain that induces sustained pain for several days, and that is provoked by movement and muscle contraction (*Study 4*).

3 Methods

The overall objective of this thesis was to investigate the effect of pain on movement variability during performance of a simple movement task. This chapter provides details and rationale for selection of the task (section 3.1), the equipment used to record movement (section 3.2), the analysis and quantification of movement and $VAR_{elements}$ (section 3.3), and the models of experimental and clinical pain (section 3.4) that were used in this thesis.

3.1 Development of an experimental model to evaluate movement variability

3.1.1 Introduction

As discussed in Chapter 2, previous studies that consider the influence of pain on movement variability during dynamic motor tasks have focused on multi-joint tasks (e.g. pointing (Lomond and Côté, 2010), cutting (Madeleine et al. 2008a), and walking (Hamill et al. 1999)). As these movement tasks involve multiple elements (i.e. muscles, joints) the nervous system has great scope to vary the combinations of joint movements and muscle activation patterns (i.e. $VAR_{elements}$) used to complete the task. It is unclear whether $VAR_{elements}$ is altered in a similar manner when simple tasks, with fewer elements and therefore fewer alternative movement strategies, are performed during pain.

3.1.2 Essential criteria of the simple movement task

To address the aims of this thesis (section 2.4) a "simple" movement task that could be used for *Studies 1-3* was required. This simple task needed to fulfil three essential criteria:

> ***Criterion 1: The simple movement task needed to have few 'elements' (i.e. muscles, joints), with substantially fewer options than the multi-joint tasks that have been used in previous investigations of movement variability during pain;*** *and*
>
> ***Criterion 2: The primary motion of the task should occur at one joint only, but with potential for movement in secondary directions at the same joint or joint complex.***

A repetitive task that involved wrist radial-ulnar deviation fulfilled *Criteria 1 and 2*. Relative to a multi-joint task such as pointing (Lomond and Côté, 2010) radial-ulnar deviation

involves fewer elements (*Criterion 1*) and involves movement at the wrist joint in one plane (i.e. radial-ulnar deviation) and has capacity for movement in secondary motion planes (i.e. wrist flexion-extension, forearm pronation-supination) (*Criterion 2*).

Criterion 3: The potential for movement in secondary directions (i.e. flexion-extension and pronation-supination) needed to be equally likely in all movement directions (i.e. flexion vs. extension; pronation vs. supination)

Criterion 3 was important because we wanted to determine whether a change in movement during pain was a purposeful adaptation by the nervous system. It was necessary to minimise the potential impact of other factors (e.g. restriction from passive structures, or bias secondary to gravity) that could influence movement. If these factors were not controlled then it would be difficult to delineate whether changes to movement during pain were due to a purposeful change by the motor system, or primarily due to these other factors.

Criterion 3 was fulfilled by having the wrist supported in mid-position between pronation and supination during performance of the radial-ulnar deviation task (Figure 3-1). This position was ideal because the potential for movement in secondary motion planes was equally likely in both directions (i.e. flexion vs. extension, and pronation vs. supination) for two reasons. First, as this position is not at the end of range of motion for neither pronation nor supination, there was no bias by restriction of passive structures (e.g. ligaments, joint capsule). Second, as the directions of secondary motion (i.e. flexion-extension and pronation-supination) were not aligned with the gravity vector, there was no bias for movement to occur in one direction compared to the other (e.g. greater flexion range of motion (ROM) than extension, or vice versa), as would occur if the direction of secondary motion was aligned with the gravity vector such that gravity pulled the joint in one direction.

Repetitive wrist radial-ulnar deviation movement with the forearm supported midway between pronation and supination fulfilled *Criteria 1-3* of the simple movement task. To ensure the task was standardised between participants, conditions, and experiments, *Criteria 4-7* were developed. Pilot testing was done to evaluate several features of the simple task. The following sections discuss *Criteria 4-7* and the results of the pilot trials.

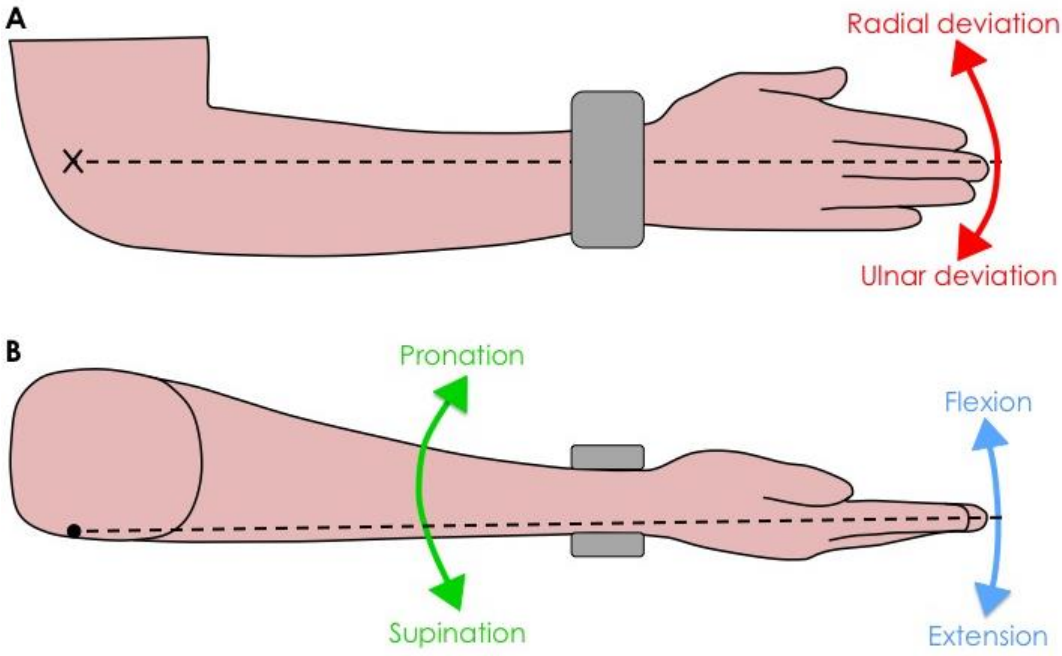

Figure 3-1. Experimental setup showing the position of the upper limb from the side view (A) and top view (B). As participants performed the repetitive radial-ulnar deviation task, there was unconstrained motion of the wrist/forearm in flexion-extension and pronation-supination.

3.1.3 Pilot trials of the simple task protocol

Pilot testing involved three participants (age = 22 ± 1 years (mean ± SD)) who each performed three trials of the radial-ulnar deviation task. Participants sat in an upright posture with the forearm resting on a table and supported in mid-position between pronation and supination. The elbow was positioned at approximately 90° flexion (Figure 3-1). The forearm was secured with an adjustable clamp at the wrist/forearm. This position allowed unconstrained wrist motion and forearm pronation-supination but prevented movement of the more proximal segments of the upper limb that could affect performance of the radial-ulnar deviation task. A similar upper limb setup has been used previously in studies that investigated variability in muscle activation (Bawa et al. 2000; Birch et al. 2000).

The experimental task involved repeated radial-ulnar deviation of the wrist between two target angle regions (Figure 3-2) that were displayed on a computer screen positioned approximately 60 cm in front of the participant. Participants were instructed to move as accurately as possible between an ulnar deviation target angle region and a radial deviation target angle region (Figure 3-2). Different angles for the ulnar and radial target angle regions were used in the pilot trials to determine what ROM could be consistently achieved. The positions of the target angle regions were calculated from each participant's maximum radial deviation ROM and ulnar deviation ROM.

Each trial was performed at a different rate in time with a metronome (Trial 1: 120 beats per minute (bpm), Trial 2 = 90 bpm, Trial 3 = 60 bpm). Note, Trial 1 and Trial 2 were performed in one pilot session, and Trial 3 was performed by the same participants in another pilot session. Different movement rates (i.e. 120 bpm, 90 bpm, and 60 bpm) were tested because it was identified that it might affect the magnitude of $VAR_{elements}$, the ease with which participants could move between the radial and ulnar target angle regions, and the number of repetitions that could be sustained with consistent performance of the simple task. For instance, walking/running at different speeds during pain influences $VAR_{elements}$ (Heiderscheit et al. 2002; van den Hoorn et al. 2012). The trials were performed until participants verbally reported they could no longer maintain the correct movement rate or radial-ulnar deviation ROM due to perceived fatigue. Participants were given a break of at least 2 minutes between trials to ensure they felt their perceived fatigue had resolved and they could perform the next trial of the task at the correct rate and ROM. A bi-axial electrogoniometer (SG65, Biometrics Ltd., Newport, UK) was used to measure radial-ulnar deviation and flexion-extension motion of the wrist for the trials performed at 120 bpm and 90 bpm. Detailed information about the electrogoniometer is provided in Section 3.2.2.

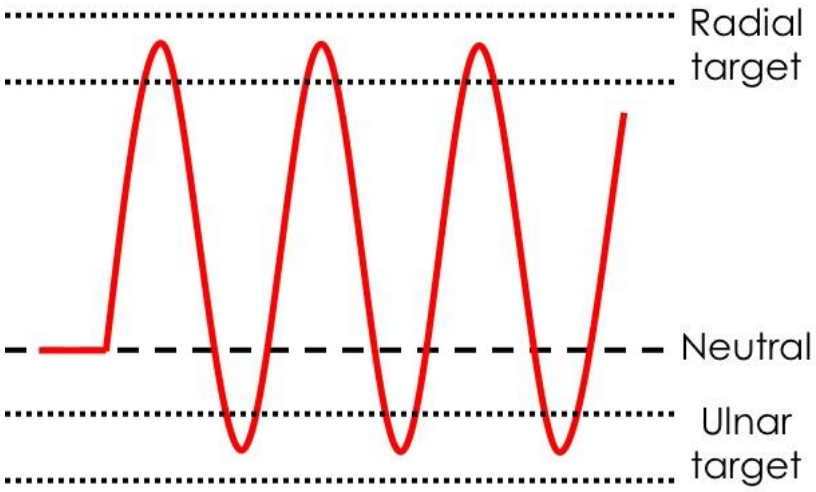

Figure 3-2. Information shown on the feedback screen during the radial-ulnar deviation task. The red line represents three complete repetitions of the radial-ulnar deviation task. Participants were instructed to perform the task in such a way that they terminated movement in both directions (i.e. ulnar to radial, and radial to ulnar) within the target angle regions (i.e. between the dotted lines).

Criterion 4: Performance of the task in the absence of pain needed to involve between-repetition $VAR_{elements}$ in secondary directions of movement.

To allow investigation of whether there was an increase, decrease, or no change of $VAR_{elements}$ during pain it was necessary to determine the magnitude of $VAR_{elements}$ in secondary movement planes when the simple task was performed in the absence of pain. It was expected that $VAR_{elements}$ would be present in the secondary movement planes (i.e. flexion-extension and pronation-supination) during the radial-ulnar deviation task. However, prior to this thesis, the radial-ulnar deviation task had not been used to study movement variability. Therefore, it was unclear how much $VAR_{elements}$ would be present in wrist flexion-extension and forearm pronation-supination, both in the absence of pain and during pain. The magnitude of $VAR_{elements}$ in the wrist flexion-extension direction was evaluated during pilot testing. Recording of $VAR_{elements}$ in forearm pronation-supination during pilot testing was not possible due to limitation of the electrogoniometers used in the trials (section 3.2.2).

It was decided *a priori* that wrist flexion-extension angle would be calculated for the first 50 repetitions at the times that the wrist crossed the neutral position of the radial-ulnar deviation motion when moving from ulnar deviation to radial deviation. The data were analysed offline. To quantify $VAR_{elements}$ in the pilot trials SD of the wrist flexion-extension angle, and absolute range of motion of the wrist angle (i.e. the difference between the maximum and minimum wrist flexion-extension angle recorded over the 50 repetitions) were calculated. The magnitude of $VAR_{elements}$ (i.e. SD (absolute range of motion)) for each trial is as follows: Trial 1 (120 bpm) = 2.9° (12.6°); Trial 2 (90 bpm) = 3.0° (14.0°). These data suggest that $VAR_{elements}$ was similar when quantified by SD and absolute range of motion. Thus, the different rates at which the simple task was performed did not affect $VAR_{elements}$ and did not contribute heavily to our decision-making for the final protocol of the task.

Criterion 5: Participants needed to move through a specific joint angle on all repetitions of the task while moving through a consistent and repeatable ROM.

It was important to develop a repetitive radial-ulnar deviation task where the wrist consistently crossed the neutral radial-ulnar position (i.e. a discrete joint position) when moving through a consistent and repeatable ROM. The neutral position was chosen as it is a standard and repeatable position in the radial-ulnar deviation range that would be consistently crossed by all participants.

It was important for *Criterion 5* to be met for two reasons. First, it allowed measurement of $VAR_{elements}$ (position in directions other than the primary movement direction) at a consistent joint position (in the primary movement plane) for all repetitions of each condition (e.g. both with and without pain) in *Studies 1-3*. Second, it would allow a transient painful stimulus to be applied at a consistent joint position (in the primary plane of motion) during performance of the task in *Study 2*.

It was possible participants would not move their wrist into enough ulnar deviation range and consistently cross the neutral radial-ulnar deviation neutral position if the ulnar deviation target was set too close to the neutral position. This would pose a large problem, as we needed participants to consistently cross neutral to allow calculation of $VAR_{elements}$ at a standardised radial-ulnar deviation angle. Thus careful selection of the radial-ulnar deviation angles for the target angle regions was critical. It was unclear what ROM was achievable and would enable completion of sufficient repetitions to enable adaptation to occur with pain and derive a clear measure of $VAR_{elements}$, but that ensured the neutral radial-ulnar position was crossed consistently. It was found that a radial deviation target range set at 80-100% of maximum radial deviation ROM and an ulnar deviation target range set at 20-40% of maximum ROM in the ulnar deviation direction could be achieved during the radial-ulnar deviation task for all participants during pilot testing. The targets were standardised to a percentage of maximal range, rather than absolute ROM, to account for differences in the maximal range that was achievable by each participant.

The total ROM was biased towards movement into radial deviation (i.e. 80-100% maximum ROM) than ulnar deviation (i.e. 20-40% maximum ROM) as the focus of the simple task was movement from ulnar deviation towards radial deviation. On questioning after the pilot trials, participants reported that it was easier to move between the radial and ulnar targets when the task was performed at 90 bpm than trials at 120 bpm.

Other positions of the ulnar target were trialled. When the target was set in greater ulnar deviation ROM (e.g. 40-60% maximum ulnar deviation ROM), participants had difficulty maintaining the correct frequency of movement and were unable to consistently achieve the radial deviation target angle region. An ulnar target range set to 10-30% of maximum ulnar deviation ROM was also piloted, but participants did not move far enough into ulnar deviation to reach the ulnar target and the amount of undershoot meant the radial-ulnar neutral was not consistently crossed.

Further pilot testing of the specific experimental protocols for *Study 2* (i.e. acute pain induced with electrical stimulation) and *Study 3* (i.e. participants with chronic LE) at the time of data collection showed that participants did not consistently reach the radial deviation target set to

80-100% of maximum ROM. For this reason, a radial deviation target of 60-80% was used for *Studies 2-3*.

Criterion 6: A sufficient number of repetitions of the simple task needed to be performed to allow calculation of $VAR_{elements}$ but that could be sustained with consistent performance of the task.

The number of repetitions required to achieve stable task performance and allow calculation of $VAR_{elements}$ depends on the task, the individual participant, and the parameter that is studied (Preatoni, 2010; Preatoni et al. 2013). We needed to determine the number of repetitions of the simple task that could be sustained with consistent performance, but provided sufficient repetitions to allow calculation of $VAR_{elements}$ (Hamill and McNiven, 1990). Trials were performed at 120 bpm and 90 bpm (as described above). Trial 3 at 60 bpm was trialled on a separate day as it was identified after the initial pilot session that a slower movement rate (i.e. 60 bpm) might allow participants to complete more repetitions that at 120 bpm and 90 bpm, and thus could be useful for *Studies 1-3*. In all trials participants were asked to report when they first considered that they would not be able to sustain performance of the task in a consistent manner (which we considered to provide a subjective perception of fatigue). Participants performed more repetitions of the radial-ulnar deviation task at the correct movement rate and range of motion when it was performed at 120 bpm (71 ± 4 repetitions (mean and SD)) and 90 bpm (69 ± 6 repetitions) than when it was performed at 60 bpm (53 ± 11 repetitions). Based on these trials we decided that trials performed at either 120 bpm or 90 bpm would allow performance of a greater number of repetitions before stoppage of the task.

Criterion 7: The task needed to provoke pain when performed by participants with chronic LE.

Criterion 7 was important so that we could study the interaction between chronic clinical pain and $VAR_{elements}$ during the simple task in *Study 3*. It was predicted that repetitive radial-ulnar deviation movement would provoke pain when performed by participants with chronic LE in *Study 3* as people with chronic LE commonly report pain with movement of the wrist and forearm (Vicenzino, 2003). Further, radial-ulnar deviation movement in a vertical direction against gravity is primarily generated by activation of ECRB, ECRL and FCR (Standring, 2005). Of particular interest, the common extensor tendon, to which ECRB and ECRL attach, is implicated in the

development and persistence of chronic LE (Nirschl, 1992; Fredberg and Stengaard-Pedersen, 2008). It was likely that activation of ECRB and ECRL during performance of the radial-ulnar deviation task would provoke pain in participants with chronic LE. However, it was unclear whether this task would provoke pain of sufficient intensity to find changes to $VAR_{elements}$. For instance, it has been proposed that low pain intensity in participants with chronic knee pain (1.9/10) might explain the lack of differences in $VAR_{elements}$ of lower limb joint coordination compared to healthy controls (Heiderscheit et al. 2002). This suggests that more intense pain might be required to observe a change in $VAR_{elements}$ during chronic pain (Cunningham et al. 2014). Gripping with the fingers is a provocative manoeuvre in participants with chronic LE (Coombes et al. 2009). Thus, it was possible to induce more intense pain during the radial-ulnar deviation task with the addition of a gripping component. Pilot testing in participants with chronic LE (n=4) found the repetitive radial-ulnar deviation task with the fingers relaxed (i.e. as for the other pilot trials discussed above) provoked pain of low intensity (0.6 ± 0.9 /10 (mean ± 95% CI)). When the radial-ulnar deviation task was performed whilst gripping a small load cell it provoked pain intensity of 3.2 ± 1.9 /10. This variant of the simple task (i.e. radial-ulnar deviation with a gripping component) was used in *Study 3*.

3.1.4 Final protocol of the simple movement task derived from pilot testing

The following parameters were used for the repetitive radial-ulnar deviation task based on the results of pilot testing:

- Movement rate: 90 bpm
- Range of motion:

  Radial deviation target = 80-100% maximum radial deviation ROM (*Study 1*)
  = 60-80% maximum radial deviation ROM (*Studies 2-3*)

  Ulnar deviation target = 20-40% of maximum ulnar deviation ROM (*Studies 1-3*)
- Number of repetitions: ≤ 60 to ensure participants maintain the correct movement rate and move between radial and ulnar deviation target regions.

3.1.5 Alternatives to the radial-ulnar deviation task that were considered during development

Although repetitive radial-ulnar deviation was selected as the simple movement task for these studies, repetitive wrist flexion-extension (Figure 3-3) also fulfilled *Criteria 1-2* of a simple movement task in this thesis and a protocol could have been devised to satisfy *Criteria 4-7*.

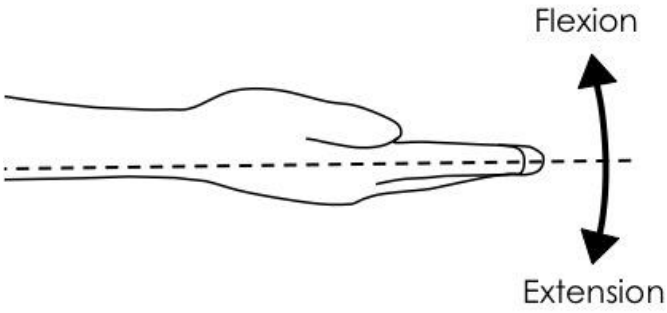

Figure 3-3. Wrist flexion-extension, an alternative simple movement task that was considered for the studies in this thesis.

A wrist flexion-extension task could be performed with the forearm supported in pronation, supination, or neutral. In this context, the primary motion would be wrist flexion-extension and secondary movement directions would be wrist radial-ulnar deviation and forearm pronation-supination. However, none of the three possible forearm positions (i.e. pronation, supination, or neutral) satisfy *Criterion 3*, i.e. the potential for movement in secondary directions needed to be equally likely in all movement planes. If a wrist flexion-extension task was performed with the forearm in a pronated or supinated position, movement in the secondary directions could only occur in the opposite direction (i.e. supination or pronation, respectively) and movement in the pronation-supination plane would not be equally likely in both directions. If wrist flexion-extension was performed with the forearm in neutral rotation then there would be freedom to move into both pronation and supination, and movement would be equally likely in both directions. However, in a neutral forearm position, the wrist radial-ulnar deviation plane is aligned with the gravity vector. Thus, the wrist would naturally move into a relative ulnar deviation position due to gravity and this would influence $VAR_{elements}$ in the radial-ulnar deviation plane. For these reasons a wrist flexion-extension task was not selected. In contrast, the radial-ulnar deviation task with the forearm midway between pronation and supination did satisfy *Criteria 1-8* and was used for *Studies 1-3* in this thesis (section 3.1.1).

3.2 Recording wrist/forearm movements

3.2.1 Introduction

Several motion analysis systems were used to record wrist/forearm movements to suit the requirements of each study. The following sections describe the rationale and parameters used for each system.

3.2.2 Electrogoniometers

In *Studies 1 and 3* an electrogoniometer (SG65, Biometrics Ltd., Newport, UK) was used to provide participants with real-time feedback of radial-ulnar deviation movement during the movement task. The electrogoniometer consists of two endblocks (i.e. rigid pieces of composite plastic that were attached to the participant's hand and forearm) connected by a composite wire that has a series of strain sensors mounted around its circumference (SG65, Biometrics Ltd, Newport, UK). These sensors measure the change in strain along the length of the composite wire as the relative position of the two endblocks changes with movement. The changes in strain are converted to angular data to describe the direction and magnitude of joint movement. The electrogoniometer has an accuracy of ± 2° measured over a range of ± 90° for movement in a single plane (Biometrics, 2002).

To record wrist radial-ulnar deviation movement the two endblocks of the electrogoniometer were attached to the skin either side of the wrist joint (Figure 3-4). The endblocks were placed on the ulnar border of the forearm and hand. As the electrogoniometers are sensitive to two directions of motion, the different orientations made no difference to the recordings – in each set up a different channel was aligned to the direction of primary motion. The signal from the electrogoniometer was recorded at 100 Hz using a Power1401 Data Acquisition system and Spike2 software (Cambridge Electronical Design, Cambridge, UK).

Although the electrogoniometer was suitable to provide feedback of radial-ulnar deviation position, it was not used to provide data for detailed analysis of wrist kinematics for two reasons. First, although the electrogoniometer can record movement in the wrist radial-ulnar deviation and flexion-extension directions, it was unable to record movement in rotation (i.e. forearm pronation-supination). Second, the accuracy of the electrogoniometer (i.e. ± 2°) was deemed unacceptable for the studies in this thesis, as more accurate measures of joint angle (i.e. wrist flexion-extension and forearm pronation-supination) to calculate $VAR_{elements}$, which occurred in the sub-degree range. Subsequently, an additional system with greater resolution and the potential to measure movement in 3-dimensions was required.

3.2.3 Vicon-Nexus 3-dimensional motion analysis

In *Studies 1 and 3* movements of the wrist and forearm were recorded by an 8-camera 3-D motion analysis system (T040, Vicon Motion Systems Ltd. Oxford, UK) at a sampling rate of 200 Hz. This system has an accuracy of <1 mm (T040, Vicon Motion Systems Ltd, Oxford, UK). Clusters of four non-collinear markers were attached to the dorsum of the hand between the 2nd and 3rd metacarpals (*Studies 1 and 3*; Figure 3-4) and the palmar surface of the forearm immediately

proximal to the wrist joint (*Study 3* only; Figure 3-4). The clusters were placed to ensure they did not restrict motion of the wrist and forearm during the radial-ulnar deviation task. Although the Vicon-nexus system could provide accurate measurements of wrist/forearm motion in *Studies 1 and 3*, it was not suitable for *Study 2* because it could not be integrated with Matlab 7.14 (The Mathworks, Natick, MA, USA) to allow delivery of painful electrical stimuli (see Chapter 5). Further, the Vicon-nexus system was not used to provide feedback of radial-ulnar deviation position during the task (i.e. instead of using the electrogoniometers) because the system could not provide real-time feedback of joint angles which was critical for the task in *Studies 1 and 3*.

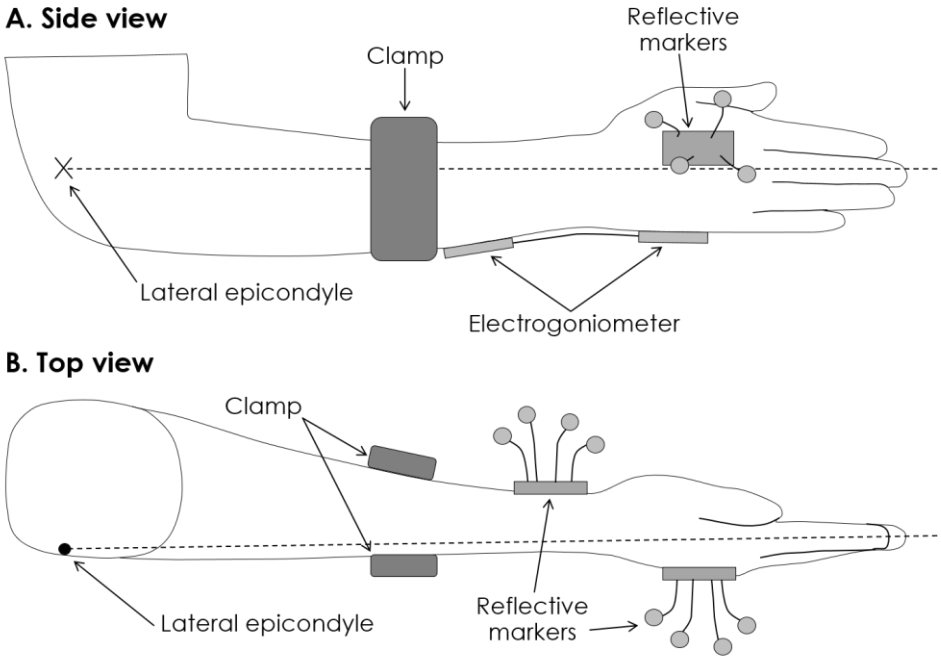

Figure 3-4. Experimental setup for *Studies 1 and 3* showing the position of the upper limb from the side (A) and top (B) view for performance of the radial-ulnar deviation task. Note the hand cluster (but not the forearm cluster) was used to record movement in *Study 1*.

3.2.4 SK7 SHAKE sensor

In *Study 2* a small motion sensor (SK7 SHAKE, SNMH Engineering Services, Dublin, Ireland) was attached to the ulnar border of the right hand to measure wrist radial-ulnar deviation and flexion-extension, and forearm pronation-supination. The motion sensor signal was recorded at a sampling rate of 100 Hz using a data acquisition system (PCI-6035E, National Instruments, TX, USA) and Matlab. The SK7 SHAKE sensor contains a triple axis linear accelerometer with a configurable full range scale of ±6 g and an output resolution of 1 mg (SK7 SHAKE User Manual, 2006). This system was used, rather than the electrogoniometer or Vicon-nexus, as it allowed real-time recording and analysis of movement data within Matlab. Further, it was necessary to use

Matlab for data collection and analysis as the protocol used for *Study 2* required delivery of painful electrical stimuli to the elbow as participants moved through a specific angle during the movement task in *Study 2* (see Chapter 5 for details).

3.3 Analysis and quantification of movement variability

3.3.1 Introduction

VAR_{goal} and $VAR_{elements}$ can be represented in several ways. Conventional measures of variation, such as SD or CV have primarily been used to quantify $VAR_{elements}$ (Riley and Turvey, 2002), but over the last fifteen years more complex non-linear measures have been used (e.g. continuous relative phase (Hamill et al. 1999), sample entropy (Hamill et al. 2000), and Lyapunov exponents (Rosenstein et al. 1993)). The ultimate choice of which measure of $VAR_{elements}$ to use depends on the research question and the task that is studied (Hamill et al. 2000). Several linear and non-linear measures were used to quantify VAR_{goal} and $VAR_{elements}$ in this thesis. These include linear measurement of between-repetition standard deviation and nonlinear measures to quantify the mean distance between successive repetitions (delta angle, sum of path length). Average vector length was calculated to quantify change of wrist/forearm position between the non-painful and painful trials in *Study 2*. Each measure is discussed in detail in the following sections.

3.3.2 Data extracted from the kinematic recordings

Wrist/forearm angles in three dimensions (i.e. wrist radial-ulnar deviation, wrist flexion-extension, and forearm pronation-supination) were extracted from the movement recordings at discrete points during the radial-ulnar deviation movement cycle. To calculate VAR_{goal}, wrist radial-ulnar deviation angle was calculated at the point of maximum displacement in the ulnar and radial deviation directions for each repetition. $VAR_{elements}$ was calculated from recordings of motion in planes other than that of the primary task (i.e. flexion-extension and pronation-supination). For each repetition the wrist flexion-extension and forearm pronation-supination angle was determined as the wrist crossed the neutral radial-ulnar position when moving from the ulnar target towards the radial target (Figure 3-5).

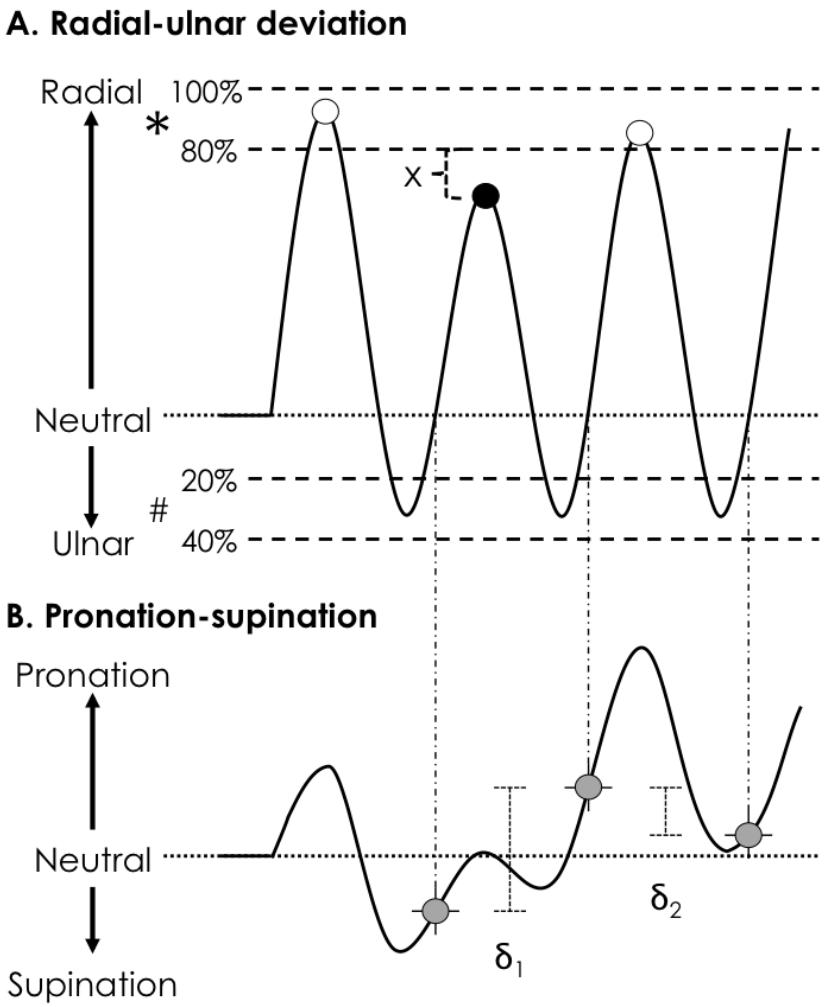

Figure 3-5. Data extracted from the kinematic recordings in *Studies 1-3.* An example of successful and unsuccessful attainment of the task goal (A) and $VAR_{elements}$ of forearm pronation-supination (B) when performing the repetitive movement task between the radial deviation (*) and ulnar deviation (#) target regions. A: White circles indicate when the radial deviation target angle region was achieved and black circles indicate when the target region was not achieved. In *Study1* the absolute error (x) was calculated for each repetition where the goal was not achieved. The error was zero for repetitions where the wrist terminated in the radial target region. B: Grey circles indicate forearm pronation-supination positions when the wrist passed through the radial-ulnar deviation neutral position. Delta angle (δ) was calculated as the absolute difference in position between consecutive repetitions. The standard deviation was also calculated to quantify $VAR_{elements}$ in a linear manner over all repetitions.

$VAR_{elements}$ was calculated at the neutral radial-ulnar deviation position for three reasons. First, as noted above (section 3.1.3) the neutral position is a standard and repeatable position in the radial-ulnar deviation range that would be consistently crossed by all participants. Second as the

neutral position is located in the middle range for all directions of motion, it is also the position with greatest potential to identify $VAR_{elements}$ in flexion-extension and pronation-supination. Third, pain intensity will likely be consistent throughout the entire radial-ulnar deviation range of motion during the repetitive movement task. Thus, the potential relationship between pain intensity and magnitude of $VAR_{elements}$ (section 2.2.5.6) will not influence $VAR_{elements}$ in the studies in this thesis. It is possible that $VAR_{elements}$ of flexion-extension and pronation-supination is inherently changed throughout the radial-ulnar deviation task, and should be considered when interpreting the results of *Studies 1-3* with respect to previous studies in the literature. Overall, the benefits outweigh the limitation of calculating $VAR_{elements}$ at the neutral radial-ulnar position for the studies in this thesis.

3.3.3 Successful attainment of the task goal

Two measures were used to quantify VAR_{goal} and quantify the extent to which participants were able to maintain accurate and consistent performance of the task during pain. First, proportion of success, represented as the proportion of repetitions (0-100%) within each trial in which the participant successfully terminated radial deviation movement within the radial deviation target angle region. Second, the total absolute error (in degrees) was calculated as the sum of the difference between the peak angle of radial deviation and the lower border of the radial target angle region for all repetitions in which the radial deviation movement failed to terminate within the target region. The absolute error was zero for repetitions where the wrist radial deviation movement terminated in the radial target region.

3.3.4 $VAR_{elements}$: Standard deviation

Linear $VAR_{elements}$ was quantified by the SD of wrist/forearm angle, which reflects the variance of wrist/forearm angle about an average position (Riley and Turvey, 2002). It is a useful measure to quantify the *magnitude* of $VAR_{elements}$ in performance of a specific task at a discrete point in time (Slifkin and Newell, 1998; Riley and Turvey, 2002). As $VAR_{elements}$ was to be quantified at a discrete wrist position (i.e. neutral radial-ulnar deviation crossing), SD was an appropriate measure for the simple task. Although SD was appropriate to quantify $VAR_{elements}$ over an entire trial or part of a trial (e.g. repetitions 1-20 of a 60-repetition trial), it does not provide information about the structure or detail of $VAR_{elements}$, such as how it changes over time between each repetition of a task.

3.3.5 $VAR_{elements}$: Delta angle

Delta angle refers to the absolute difference of wrist/forearm angle (in the secondary planes of motion) at the time of neutral crossing (in the primary motion plane) between consecutive repetitions of the simple movement task (e.g. between repetitions 1 and 2, 2 and 3, etc.). Delta angles were calculated for each trial for each participant (Figure 3-5B) and then represented as sum of delta angle, or average delta angle. Delta angle was used to quantify $VAR_{elements}$ in wrist flexion-extension and forearm pronation-supination.

3.3.6 $VAR_{elements}$: Sum of path length

Sum of path length is similar to delta angle in that it measures the absolute difference in wrist/forearm angle between consecutive repetitions. To calculate sum of path length it is first necessary to calculate the absolute difference of wrist/forearm angle in the secondary motion planes at the time of neutral crossing (in the primary motion plane), between consecutive repetitions of the radial-ulnar deviation task (Figure 3-6). It differs from delta angle because it takes into account the 'distance' each repetition is from the preceding repetition in a two-dimensional movement map (i.e. forearm pronation-supination angle plotted against wrist flexion-extension angle). Therefore, this measure takes into account changes in wrist/forearm position that occur concomitantly

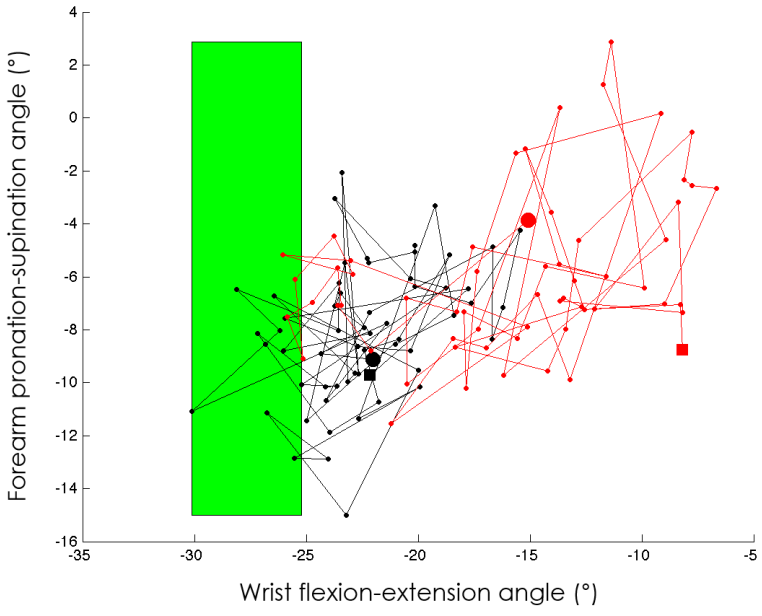

Figure 3-6. Calculation of sum of path length. The forearm pronation-supination angle was plotted against the wrist flexion-extension angle for the 60 repetitions of the Baseline trial (black), and the 60 repetitions of the Experimental trial (red). Large circles represent repetition 1, small circles represent repetitions 2-59, and squares represent repetition 60 for both trials. Lines were plotted

between consecutive repetitions of each trial. The length of individual lines (within each trial) was calculated and summed to give 'sum of path length'.

3.3.7 Change in movement strategy: Average vector length

To quantify change of movement strategy in *Study 2*, vectors were constructed between the average wrist/forearm configuration (i.e. in 2-D space derived from the flexion-extension and pronation-supination planes) of repetition of the task performed in a non-painful state (*baseline trial)*, and the position in that 2-D space during each repetition (n=60) of a *painful trial* in which acute elbow pain was induced with electrical stimulation (Figure 3-7). Each sixty-repetition trial was divided into 6 x 10-repetition epochs (i.e. epochs 1-6) and the average vector length was calculated for each epoch. Average vector length during each epoch of the painful trial relative to the non-painful baseline trial was used to represent whether participants altered wrist/forearm position during pain. It enables insight into whether a new strategy was selected during pain compared to non-painful trials.

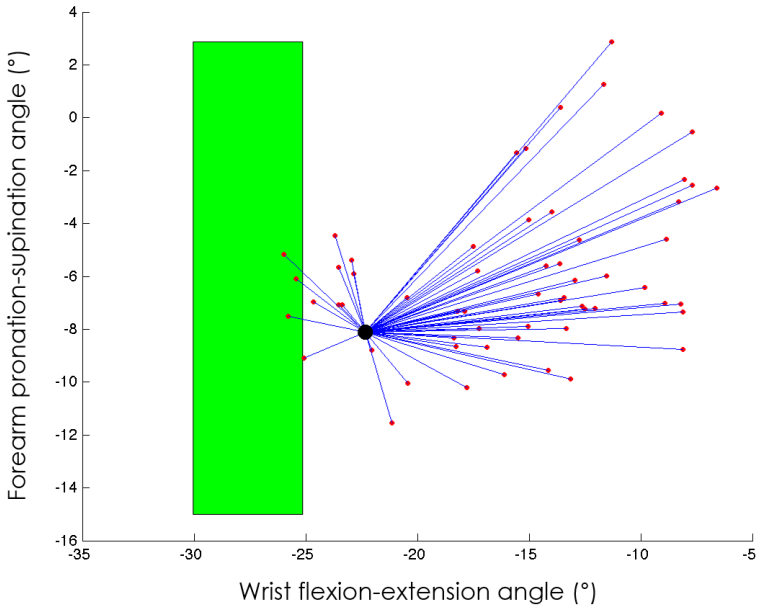

Figure 3-7. Calculation of vector lengths. The forearm pronation-supination angle was plotted against the wrist flexion-extension angle for the 60 repetitions (small black circles) and average (large black circle) of the Baseline trial, and the 60 repetitions of the Experimental trial (small red circles). Vectors (blue lines) were plotted between the average wrist/forearm position in the Baseline trial and each repetition in the Experimental trial. The length of each vector was calculated.

3.4 Experimental and clinical pain models

3.4.1 Introduction

Experimental models that stimulate nociceptive afferents can be used to induce short-term pain of a predictable duration with no long-term consequences (Graven-Nielsen, 2006). These models provide a method to study the isolated effect of nociceptive stimulation on human motor control in the absence of confounding factors such as local tissue damage, inflammation, and psychological factors (e.g. long-term fear avoidance) that could contribute to movement changes observed in chronic pain conditions (Graven-Nielsen, 2006). Although ultimately it is necessary to understand the interaction between each of these factors in determination of the motor control changes in pain, we argue that it is also important to understand the independent contribution of each factor. As the interest of this thesis was the interaction between nociceptive afferent stimulation and movement variability, the experimental pain methods used in *Studies 1, 2 and 4* are appropriate. For the studies that used experimental models to induce pain, healthy volunteers between 18-40 years of age and with no major circulatory, orthopaedic, musculoskeletal, or neurological conditions that could affect upper limb function, were included. To study the interaction between chronic pain and movement variability in *Study 3* participants with chronic LE and a healthy control group for comparison were recruited.

3.4.2 Acute pain: Injection of hypertonic saline

Injections of hypertonic saline were first used as a model of short-term deep-tissue pain in the 1930s (Kellgren, 1938; Lewis, 1938). Since then, hypertonic saline injections have been used extensively to study the interaction between acute pain and sensorimotor function, with no reported long term sequelae after more than 6000 injections across more than 130 studies (Graven-Nielsen, 2006). This model can be used to induce short-lasting, reversible pain in a variety of contexts and experimental paradigms. For instance, it can be injected into many body tissues including tendon (Gibson et al. 2006), muscle (Tucker et al. 2014), fascia (Deising et al. 2012), fat pad (Bennell et al. 2004), and ligament (Tsao et al. 2010). Further, the intensity and duration of the pain can be tailored to the individual experiment by altering the volume, concentration, method of administration (e.g. single bolus, repeated injections, continuous infusion), and infusion rate of the injection(s) (Jarvik and Wolff, 1962). The quality of the pain is comparable to acute clinical muscle pain with participants typically describing the induced pain as ‘aching’, ‘cramping’, ‘boring’, ‘drilling’, ‘taut’, ‘tight’, ‘spreading’ and ‘radiating’ when they complete the McGill Pain Questionnaire (Graven-Nielsen, 2006). Despite the many studies that have used hypertonic saline as a model of acute pain,

the exact mechanism by which it induces pain is not well understood. It is known that hypertonic saline is a non-specific model (Cairns et al. 2003) that excites both A-delta and C afferent fibres (Kumazawa and Mizumura, 1977; Hoheisel et al. 2005) when injected into muscle.

Many typical motor behaviours observed in people with clinical musculoskeletal pain have been replicated with injection of hypertonic saline. For instance, maximal wrist extension force is reduced in a model of lateral elbow pain following injection of hypertonic saline into the ECRB muscle belly (Slater et al. 2005), and muscle activation of a postural response is delayed with injection into the longissimus muscle at the low back region (Hodges et al. 2003). However, the relationship between pain and movement is unclear. Unlike musculoskeletal pain conditions where pain intensity generally increases during muscle contraction/stretch and functional activities, Tsao et al (2010) found pain intensity decreased during contraction and stretch after hypertonic saline was injected into the lumbar erector spinae muscle, but not after injection into the lumbar interspinous ligament.

In *Study 1* acute elbow pain was induced with an injection of hypertonic saline to study the effect of nociception and acute pain on movement variability. Participants received a bolus injection of hypertonic saline (0.3 ml, 5% NaCl) into the origin of the common extensor tendon near its attachment to the lateral epicondyle of the humerus.

The hypertonic saline model of acute pain was used to induce acute pain in *Study 1* for four reasons. First, injection of hypertonic saline induces tonic, moderate pain of known duration. Slater et al. (2003) studied the pain response evoked after injection of hypertonic saline into the ECRB muscle belly, the origin of the common extensor tendon near its attachment to the lateral epicondyle, and the supinator muscle. Pain lasted for approximately 10 minutes after hypertonic saline was injected into the common extensor tendon (Slater et al. 2003). This duration of pain ensures there is sufficient time for participants to complete all 45 repetitions during the painful trial of *Study 1*. Second, hypertonic saline has the benefit of inducing acute pain without damaging muscle fibres. A model that included delayed onset muscle soreness (DOMS) of the wrist extensor muscles could have been used for *Study 1*. Slater et al (2003) found an experimental model of pain that combined DOMS, induced with repeated eccentric wrist extension contractions of the forearm muscles, and hypertonic saline injection into ECRB induced more intense pain (6.94 ± 0.7) than after a single hypertonic saline injection (6.08 ± 0.5). Notwithstanding the small difference in pain intensity between the two models (i.e. 0.86/10) the combined DOMS-saline model was not appropriate for *Study 1* because the damage to contractile elements of muscle fibres by eccentric contractions (Paulsen et al. 2012) can directly influence function, which precludes investigation of the independent effects of pain/nociceptive stimulation. Third, unlike acute musculoskeletal

conditions, factors other than pain such as local tissue damage and psychological factors (e.g. fear avoidance of movement) that could underpin the movement changes are not seen after hypertonic saline injection. The lack of confounding factors is beneficial because it allowed us to study the specific effect of nociceptive stimulation and acute pain. Fourth, in *Study 1* we wanted to probe the *immediate* changes to movement variability associated with acute pain, which is not possible with acute musculoskeletal conditions.

The location of hypertonic saline injection, into the common extensor tendon at its attachment to the lateral epicondyle of the humerus, was chosen in *Study 1* for two reasons. First, the pathophysiology of chronic LE involves degeneration of the common extensor tendon, particularly at its attachment to the lateral epicondyle (i.e. the location for injection in *Study 1*). Second, pain intensity is greater (5.9 ± 0.6/10) and lasts longer (587.9 ± 33.4 seconds) after injection of hypertonic saline into the common extensor tendon near its attachment to the lateral epicondyle compared to an injection into the ECRB muscle belly (Pain intensity = 5.3 ± 0.6/10; Duration = 469.6 ± 443 seconds) (Slater et al. 2003). The duration and intensity of pain induced with hypertonic saline allowed sufficient time for participants to perform 45 repetitions of the simple movement task whilst experiencing moderate pain.

3.4.3 Acute pain: Cutaneous electrical stimulation

Electrical stimulation has been used extensively (e.g. Gasser and Erlanger, 1929; Moseley and Hodges, 2006; van Ryckeghem et al. 2012) as a non-invasive method to induce intermittent acute experimental pain. The electrical stimulation can be applied cutaneously via surface electrodes (Moseley and Hodges, 2006; Kurniawan et al. 2010) or via intramuscular electrodes (Laursen et al. 1997; Niddam et al. 2002). Care must be taken, however, to avoid stimulation of nerves (afferent or efferent) or muscle fibres as this can elicit muscle contraction (Graven-Nielsen, 2006), which would affect movement variability in our studies. To avoid the stimulation of motor activity the stimulating electrodes can be placed on the skin overlying bone (Moseley and Hodges, 2006).

One aim of *Study 2* was to determine whether a less painful movement strategy would be selected more frequently than more painful options during the radial-ulnar movement task. Thus, we needed to provoke pain at a specific point (i.e. neutral radial-ulnar deviation angle) during the wrist movement task, with an intensity that could be externally determined and varied depending on the individual participant's movement. In *Study 2* pain was experimentally induced with cutaneous electrical stimulation via a pair of surface electrodes (interelectrode distance ~10 mm) placed on the skin overlying the lateral epicondyle of the right elbow. Conversely, the two requirements of

experimental pain in *Study 2* could not be met with other pain models, such as hypertonic saline or exercise-induced DOMS.

3.4.4 Chronic pain: Lateral epicondylalgia ('tennis elbow')

The aim of *Study 3* was to investigate whether movement variability was altered in participants with chronic LE compared to healthy controls. Participants with chronic LE were included in *Study 3* if they met four inclusion criteria (Coombes et al. 2012a).

1. Unilateral elbow pain for longer than 6 weeks;
2. Worst pain intensity in the past week ≥3 on an 11-point numerical rating scale (0 = no pain; 10 = worst pain imaginable; NRS)
3. Reduced pain-free grip force (<50% compared to the unaffected arm)
4. Pain over the lateral epicondyle of the humerus provoked by at least two of; i) gripping, ii) palpation; or iii) resisted wrist/middle finger extension.

Participants were excluded if they had any of the following:

1. Received physiotherapy treatment in the preceding three months;
2. Received corticosteroid injection in the preceding six months; or
3. If participants reported any major circulatory, musculoskeletal, or neurological conditions that affected upper limb function.

A healthy control group who had no history of LE were matched to those in the LE group for age (±5 years), sex, and hand-dominance. Control participants were excluded if they reported any major circulatory, musculoskeletal, or neurological conditions that affected upper limb function.

3.4.5 Sustained pain: Intramuscular injection of nerve growth factor

Nerve growth factor (NGF) is a neurotophin, vital for the development of nerves in humans (Lewin and Mendell, 1993). In the late 1980's NGF was identified as a potential treatment for diabetic neuropathy, but in a series of clinical trials (Petty et al. 1994; Apfel et al. 2000), participants reported side effects including hyperalgesia at the injection site and generalised muscle soreness (Apfel et al. 2000). As a consequence of these side effects, intramuscular and subcutaneous injections of NGF as a treatment for diabetic neuropathy were abandoned. However, it was realised that these side effects could be taken advantage of to investigate the mechanisms underlying peripheral and central sensitization. Pain secondary to NGF injection is thought to

involve sensitisation of both peripheral nociceptors and central neurons, which have been studied in rodent models. NGF sensitizes high threshold mechanosensitive muscle nociceptors (Hoheisel et al 2005; Mann et al. 2006), which, under normal conditions do not respond to weak, everyday stimuli (e.g. muscle contraction and stretch) and require tissue-threatening stimulation to be activated (Mense, 2009). There is also evidence of sensitised central mechanisms, such as sensitization of dorsal horn neurons (Hoheisel et al. 2007; Taguchi et al. 2008), distinct areas of referred pain (Andersen et al. 2008) and spreading hyperalgesia (Hayashi et al. 2013) following intramuscular injection of NGF.

A consistent finding of human studies is that intramuscular injection of NGF induces spreading mechanical hyperalgesia at the injection site that lasts for up to 14 days (Andersen et al. 2008; Svensson et al. 2003). There have also been reports of mild muscle pain during gait (i.e. muscle contraction) that lasts 3 days after injection into tibialis anterior (Andersen et al. 2008; Hayashi et al. 2013). Similar reports of mild pain have been reported following injection into the masseter (Svensson et al. 2008) and trapezius (Gerber et al. 2011) muscles, and thoracolumbar fascia (Deising et al. 2012). It is unclear whether movement and muscle contraction at different amplitudes and intensities provokes different pain intensities.

Identification of the parameters of experimental pain induced with injection of NGF might be beneficial for future studies. For instance, an experimental model of sustained pain could be used to evaluate whether similar changes to the sensory and motor systems are found in acute lateral elbow pain and chronic LE (sections 2.3.2.2 and 2.3.2.3). Such a model might provide insight into the mechanisms underlying the transition of acute lateral elbow pain to sustained pain, and then into a chronic musculoskeletal pain condition. Further, an experimental model of sustained pain could allow investigation of the potential relationship between $VAR_{elements}$ in acute and chronic/persistent pain, which is currently poorly understood.

To be of benefit as a model of experimental pain in future studies, the NGF model would need to induce pain that is sustained for up to a week and that is provoked in a consistent manner by contraction and stretch of the upper limb muscles and functional activities of the upper limb.

Table 3-1. The benefits and drawbacks of the experimental pain models used in *Studies 1, 2, and 4*.

Acute pain: Injection of hypertonic saline

Benefits

- Used extensively (>6000 injections in >130 studies) with no reported long-term sequelae (Graven-Nielsen, 2006)
- Can be injected into many body tissues: tendon (Gibson et al. 2006), muscle (Tucker et al. 2014), fascia (Deising et al. 2012), fat pad (Bennell et al. 2004), and ligament (Tsao et al. 2010)
- The intensity and duration of induced pain may be moderated by altering the volume, concentration, method of administration (e.g. bolus, continuous infusion), and infusion rate (Jarvik and Woolf, 1962)
- The quality of induced pain is comparable to acute clinical muscle pain (Graven-Nielsen, 2006)

Drawbacks

- Cannot be used to model sustained pain because the induced pain ceases within ~5 minutes of the saline insertion into the tissue
- Pain intensity decreases or does not change during muscle contraction/stretch following injection (Tsao et al. 2010), unlike musculoskeletal pain conditions where pain intensity typically increases during these manoeuvres

Acute pain: Cutaneous electrical stimulation

Benefits

- Is a non-invasive method of inducing acute pain (i.e. does not involve an injection)
- Can externally determine pain intensity (i.e. can quickly increase/decrease stimulus intensity during the investigation) and apply painful stimuli at specific points within an individual participants movement
- Referred pain to regions away from stimulating electrodes is not expected
- Very controlled “on” and “off” times for the stimulus

Drawbacks

- Muscle contraction can be elicited if stimulating electrodes are placed within or overlying muscle (Graven-Nielsen, 2006), but can be avoided by placing electrodes on the skin overlying bones (Moseley and Hodges, 2006)

Sustained pain: Intramuscular injection of nerve growth factor

Benefits

- Can be used to induce sustained muscle pain (Gerber et al. 2011) and mechanical hyperalgesia (Hayashi et al. 2013) that lasts for approximately one week

Drawbacks

- Does not induce pain of moderate-high intensity at the dosages tested thus far, unlike hypertonic saline
- Does not induce pain immediately after injection
- Limited evidence of pain response when injected into tendon or ligament

4 Does movement variability increase or decrease when simple wrist task is performed during acute wrist extensor muscle pain?

4.1 Abstract

Purpose: The goal of complex tasks can be maintained despite variability in the movements of the multiple body segments involved in the task ($VAR_{elements}$). This variability increases in acute pain and may enable the nervous system to search for less painful/injurious movement options. It is unclear whether $VAR_{elements}$ increases when pain challenges simple tasks with fewer movement options, yet maintain successful attainment of the goal. We hypothesised that during acute pain related to a simple movement: 1) The task goal would be maintained; 2) $VAR_{elements}$ would be increased; and 3) if $VAR_{elements}$ increased during pain, it would decrease over time.

Methods: Movements of the right wrist/forearm were recorded with a 3-dimentional motion analysis system and during a repetitive radial-ulnar deviation task between two target angle ranges (the task goal). We measured success of attaining the goal (repetitions that reached the target range and total absolute error in degrees), and variability in the motion of wrist flexion-extension and forearm pronation-supination ($VAR_{elements}$). Fourteen healthy participants performed the task in one session before, during, and after wrist extensor muscle pain induced with hypertonic saline, and in another session without pain.

Results: The task goal was maintained during acute pain. However, $VAR_{elements}$ in other motion planes either reduced (pronation-supination) or did not change (flexion-extension). Thus, variability of task elements is constrained, rather than increased, in simple tasks.

Conclusions: These data suggest the nervous system adapts simple tasks with limited degrees of freedom by reduction of $VAR_{elements}$ rather than the increase observed for more complex tasks.

4.2 Introduction

Flexibility or variability in the performance of voluntary and postural tasks is thought to underpin the exploration of different movement strategies (Dingwell et al. 2001; Riley and Turvey, 2002). In complex multi-joint tasks (e.g. pointing to a target) it is possible to achieve an outcome that is accurate and consistent (i.e. high probability of successful achievement of a task objective: the goal) with many different combinations of joint excursions and muscle activation patterns (i.e. high variability of the "elements": $VAR_{elements}$). The uncontrolled manifold hypothesis (Scholz and Schöner, 1999) suggests the nervous system allows the elements of a task to vary, provided this variability does not compromise successful completion of the task (i.e. lower goal attainment). $VAR_{elements}$ can be partitioned into two components (Latash, 2012); "bad" variability leads to reduced success in attaining a goal, while "good" variability does not affect the goal, and may have the benefit of a broader distribution of stresses between tissues (e.g. muscles, joint surfaces) with the potential to reduce cumulative tissue load (Hamill et al. 1999). In the presence of acute pain, increased $VAR_{elements}$ may also enable the nervous system to explore new movement options and find a more optimal solution that has less potential to provoke pain/injury (Moseley and Hodges, 2006; Madeleine et al. 2008a; Hodges and Tucker, 2011). Consistent with these hypotheses, the goal of an upper limb task is maintained despite changes in muscle activation/movement of the trunk or shoulder ($VAR_{elements}$) during pain in those regions (Moseley and Hodges, 2006; Madeleine et al. 2008a). Although considerable variability of the elements is possible without compromising goal attainment in multi-joint movements it is unclear whether $VAR_{elements}$ increases when pain challenges simple tasks that involve a simple joint complex.

Relative to multi-joint tasks, simple tasks have fewer movement options, and thus fewer elements for which variability can be increased, yet maintain successful attainment of the task goal. Although variability of this limited number of elements could still be increased, it is not known whether this occurs. If a simple wrist radial-ulnar movement becomes painful, in order to achieve a specific intended movement (i.e. the task goal), fewer segments/options are available to compensate. As such $VAR_{elements}$ is limited to joint motion in planes other than that of the primary task (i.e. flexion-extension or pronation-supination). It has previously been hypothesised that acute pain motivates the nervous system to increase $VAR_{elements}$ and search for less painful movement strategies (Moseley and Hodges, 2006; Madeleine et al. 2008a; Hodges and Tucker 2011). Even with fewer options in a simple task, the nervous system is expected to use the same strategy of increased $VAR_{elements}$ to find an alternative solution. For instance, a recent study (Singh et al. 2010) found the motor system increased $VAR_{elements}$ during a simple force-matching task with few elements (i.e. application of pressure with middle and index fingers to match a target force) to

maintain successful completion of the task when one of the elements (i.e. index finger) was fatigued. However, it is unclear whether an increase in $VAR_{elements}$ during acute pain is limited to complex multi-joint systems where multiple options (i.e. muscles, joints) are available to maintain the goal. When few options are available in a simple task, $VAR_{elements}$ might not change during pain.

If $VAR_{elements}$ increases with acute pain in a simple system, then it follows that after this initial increase (i.e. the searching), $VAR_{elements}$ would decrease and return to the amount of variability present at baseline (i.e. before pain) if a new less painful strategy is found, or if a better option is not available. Such time-dependent change in $VAR_{elements}$ has been observed in a multi-joint system (Moseley and Hodges, 2006). However, it is unclear whether adaptation in $VAR_{elements}$, if present, shares this time-dependency in simple wrist movements.

We studied a simple, repetitive wrist movement (radial-ulnar deviation) between target angle regions with and without experimental muscle pain to test the hypotheses that: 1) The task goal would be maintained during pain; 2) this would be accompanied by increased $VAR_{elements}$; and 3) if $VAR_{elements}$ increased during pain, it would be greatest at the onset of pain and decrease over time. This study focused on the magnitude of movement variability, not the structure of variability.

4.3 Methods

4.3.1 Participants

Fourteen healthy volunteers (6 females and 8 males; age 24.5 ± 3 years (mean ± SD)) with no history of upper limb pain or dysfunction attended two testing sessions approximately 2 months apart. All participants were right-handed. Participants were excluded if they reported any major circulatory, orthopaedic, musculoskeletal, or neurological conditions that affected upper limb function. However, all participants met the inclusion criteria for each session and none were excluded, and there was no change in general health status between sessions. Informed consent was obtained from all participants. All procedures were approved by the Institutional Medical Research Ethics Committee (Project number: 2004000654) and conformed to the Declaration of Helsinki.

4.3.2 Measurements

A cluster of four reflective markers was attached to the dorsum of the right hand between the 2nd and 3rd metacarpals (Figure 4-1) to represent wrist/forearm flexion-extension and pronation-supination. Movements of the cluster were recorded by an 8-camera 3D motion analysis system (T040, Vicon Motion Systems Ltd. Oxford, UK) at a sampling rate of 200 Hz. An electrogoniometer (SG65, Biometrics Ltd., Newport, UK) was attached to the ulnar surface of the

hand and distal end of the forearm to provide feedback of radial-ulnar deviation position during the experimental tasks (Figure 4-1a). The electrogoniometer signal was recorded at 100 Hz using a Power1401 Data Acquisition system and Spike2 software (Cambridge Electronical Design, Cambridge, UK). The motion system was synchronized by remotely starting the recording within Spike2 software.

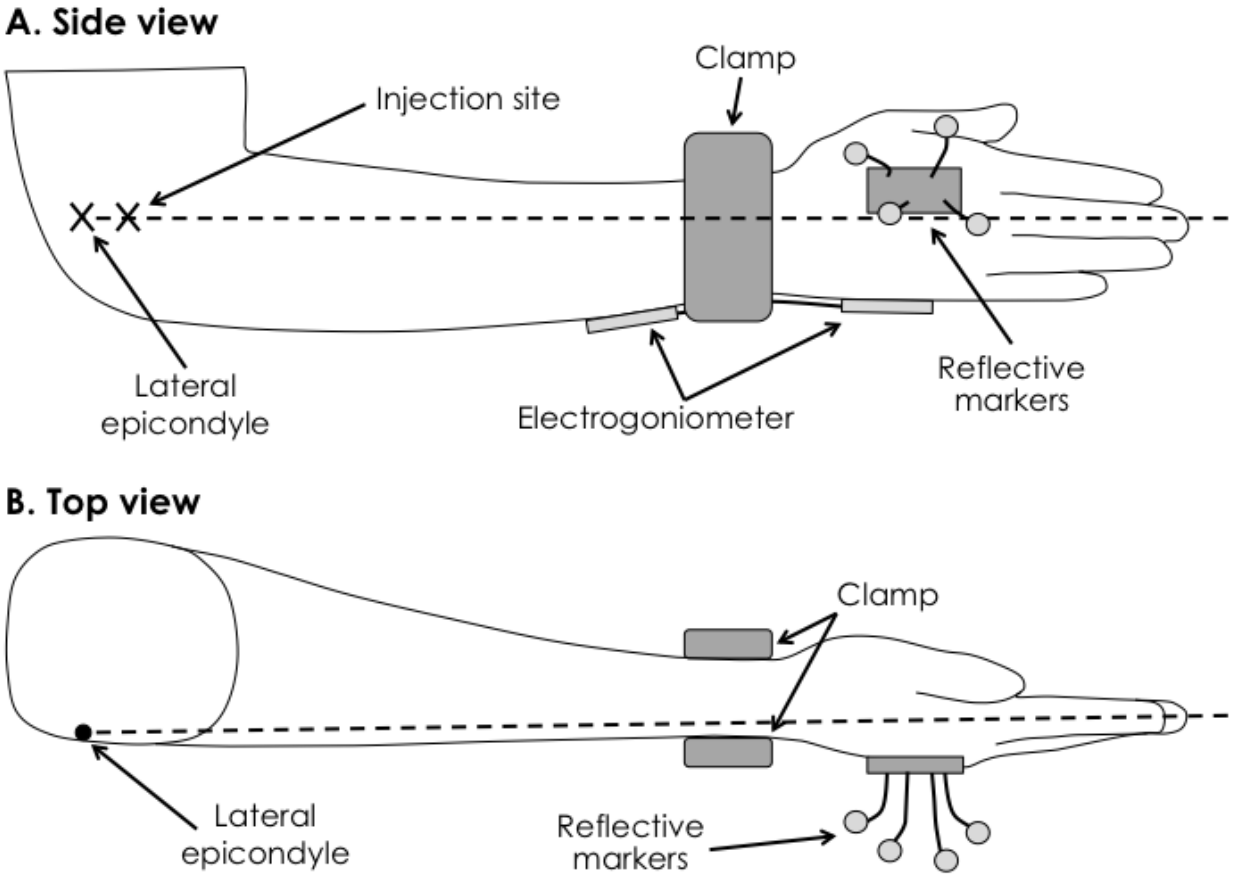

Figure 4-1. Experiment setup showing the position of the upper limb from the side view (A) and top view (B). Note the dashed line indicating the neutral position of the wrist and forearm.

4.3.3 Procedures

Participants sat in an upright posture with their right forearm resting on a table and supported in mid-position between pronation and supination with the elbow in approximately 90° flexion (Figure 4-1). The forearm was secured with an adjustable clamp immediately proximal to the wrist. This position allowed unconstrained wrist motion and forearm pronation-supination but prevented movement of the upper limb that could affect performance of the radial-ulnar deviation task.

Prior to the experimental trials the neutral position of the wrist and forearm, and the maximal ROM for radial and ulnar deviation, were recorded. The neutral position was measured

using a handheld goniometer with the wrist and forearm in the mid position of flexion and extension, radial and ulnar deviation, and forearm pronation and supination (Figure 4-1).

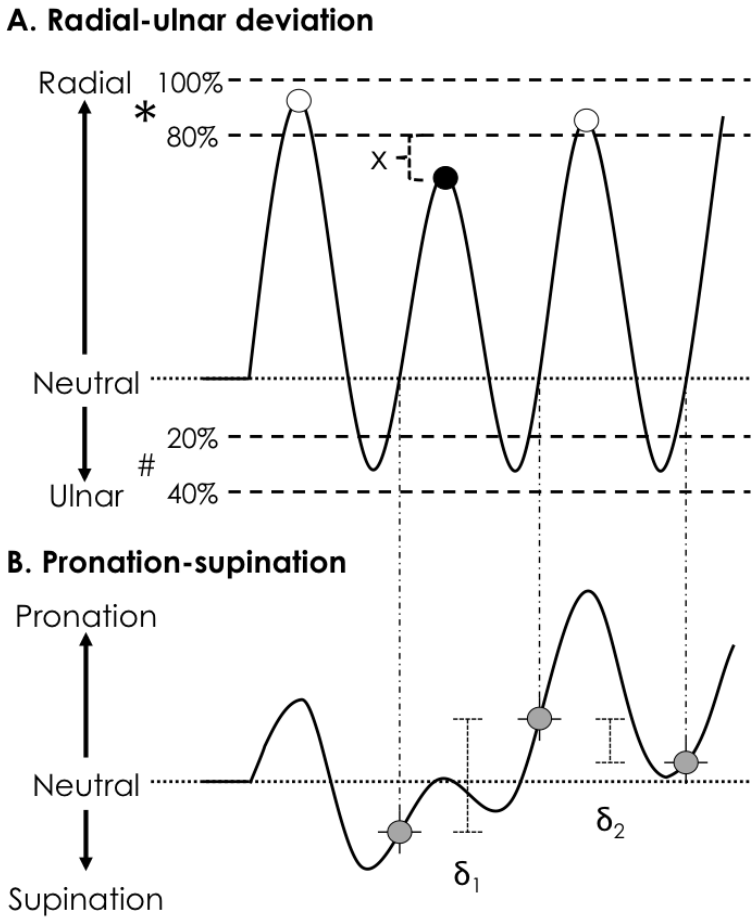

Figure 4-2. Data extracted from the kinematic recordings – *Study 1*. An example of successful and unsuccessful attainment of the task goal (A) and $VAR_{elements}$ of forearm pronation-supination (B) when performing the repetitive movement task between the radial deviation (*) and ulnar deviation (#) target regions. A: White circles indicate when the task was performed accurately and black circles indicate when it was not. The absolute error (x) was calculated for each repetition. B: Grey circles indicate forearm pronation-supination positions when the wrist passed through the neutral angle in the direction of ulnar to radial deviation. Delta angle (δ) was calculated as the absolute difference in position between consecutive repetitions. The standard deviation was also calculated to quantify the variability in a linear manner over all repetitions.

The experimental task involved repeated radial-ulnar deviation of the wrist between two target angle regions (Figure 4-2a) that were displayed on a computer screen positioned approximately 60 cm in front of the participant. Participants were instructed to move as accurately as possible from a target angle region 20-40% of their maximal ulnar deviation range to 80-100% of their maximal radial deviation range (Figure 4-2a) in time with a metronome (90 beats per minute).

The targets were standardised to a percentage of maximal range, rather than absolute range of motion, to account for differences in the maximal range that was achievable by each participant. Emphasis was placed on reaching the target angle region in the radial deviation direction. Participants practiced the task at the start of each session until it was completed at the correct frequency and between the two target angle regions. Data from this practice period were not analysed. Forty-five repetitions were recorded in each condition (see below) which started and finished with the wrist and forearm in the neutral position. Pilot testing (n=3) indicated that 45 repetitions at a rate of 90 beats per minute could be completed easily without any perception of fatigue of the forearm muscles and was a comfortable rate to perform the task.

In one experimental session the movements were performed within three conditions; before, during and after experimental pain was induced by injection of hypertonic saline (0.3 ml, 5% NaCl) into the common extensor tendon near its attachment to the lateral epicondyle of the right humerus (Figure 4-1a). The common extensor tendon gives rise to the ECRL and ECRB muscles, which, along with FCR, produce radial deviation of the wrist (Standring 2005). It was expected that acute wrist extensor muscle pain would stimulate the nervous system to search for a new, less painful movement solution. Similar changes to motor control of the wrist following injection of hypertonic saline into the common extensor tendon have been found previously, such as reduced maximal wrist extension force (Slater et al. 2003). The location for injection was identified by palpation of the elbow at rest and during a gentle wrist extensor muscle contraction. The needle (25G x 25 mm) was directed in an antero-medial direction towards the cubital fossa. The radial-ulnar deviation task in the trial during pain was initiated once the participant reported a pain intensity of ≥2 on an 11-point numerical rating scale (NRS) (0 = no pain; 10 = worst pain imaginable). In the other experimental session, three sets of movements were performed as for the pain session, but the middle condition was performed without experimental pain. This session was included to determine how much $VAR_{elements}$ could be expected by repetition of the movements, but in the absence of pain. Participants were asked at the end of each 45-repetition trial whether they perceived any sense of fatigue in the forearm or wrist.

4.3.4 Additional experiment

The extent to which the pronation-supination position of the forearm could be changed, yet still maintain the goal (the target range in the radial-ulnar deviation direction) of the simple task was studied in two healthy participants. These participants performed two blocks of 10 repetitions that started with the wrist/forearm in neutral flexion-extension and neutral pronation-supination, and moved incrementally toward the limit of pronation (block 1) or supination (block 2) with each

repetition. The pronation-supination position at the peak radial deviation position was calculated for each repetition and is presented in Figure 4-3. These data show that pronation-supination angle could deviate by more than 15° in either direction from neutral and the participant retained the ability to move the wrist to the target angle range for radial deviation.

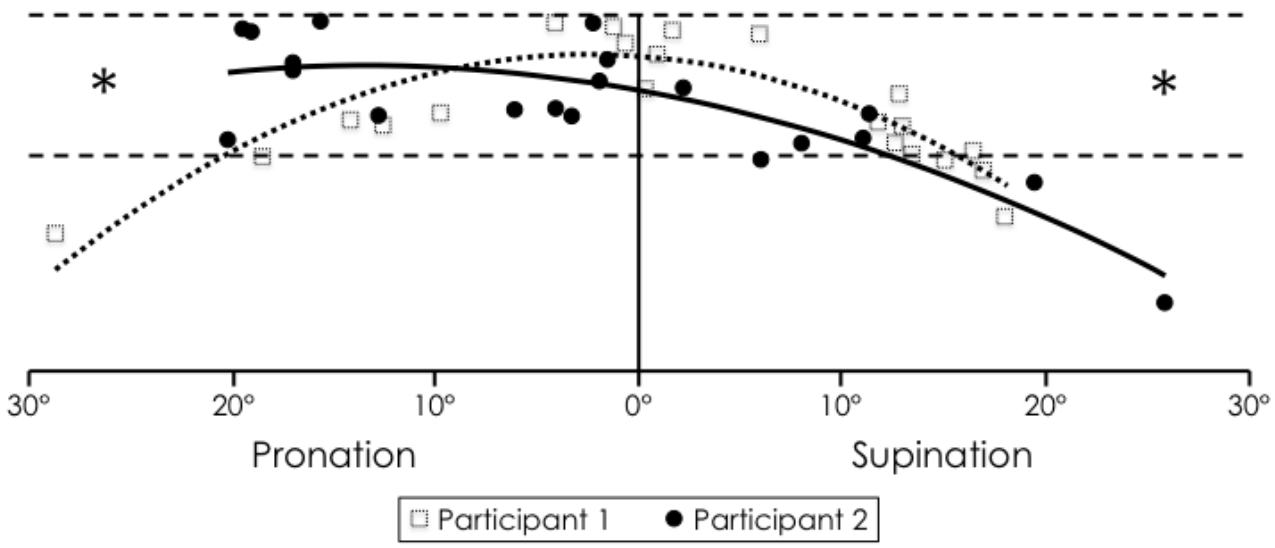

Figure 4-3. Data from an additional experiment – *Study 1*. Two additional participants who performed 20 repetitions of the simple task towards the radial deviation target range (*) at different positions of forearm pronation-supination. Each data point represents the forearm pronation-supination position at the time of peak radial deviation range for each repetition. The data show that variation in the angle of the forearm between ~20° pronation and ~10° supination plane was possible without compromising the potential to complete the radial deviation task.

4.3.5 Data analysis

Data was analysed within each condition for repetitions 1-15 and 26-40. Data are reported from 13 (of 14 participants) as one participant felt faint following the injection of hypertonic saline and withdrew from the study.

For analysis of successful attainment of the goal radial-ulnar deviation angle data recorded with the electrogoniometers were analysed offline using Spike2 software. Successful attainment of the goal was measured in two ways. First, *proportion of success* represented the proportion of repetitions within each of the three conditions in which the participant successfully moved their wrist to the radial deviation target angle region (Figure 4-2a). Second, the *total absolute error* (in degrees) was calculated as the sum of the difference between the peak angle of radial deviation and the lower limit of the target angle region for all repetitions in which the radial deviation angle failed to terminate within the target region (Figure 4-2a). Data were normalised to the maximum

proportion of success and maximum *total absolute error* across conditions within each session for each participant.

$VAR_{elements}$ was quantified as variability in the motion of the wrist/forearm in the planes other that of the primary task (i.e. wrist flexion-extension and forearm pronation-supination), and was calculated from the reflective marker cluster attached to the hand using Matlab 7.14 (The Mathworks, Natick, MA, USA). The instantaneous angle of the wrist/forearm in flexion-extension and pronation-supination for each repetition (in each condition) was calculated at the point where the wrist angle passed through the zero position of the radial-ulnar angle when moving from the target region in the ulnar direction towards the target region in the radial deviation direction (Figure 4-2b). The "zero"/neutral position of radial-ulnar deviation was chosen as it is a standard and repeatable position in the radial-ulnar deviation range of motion that was consistently crossed by all participants, and by virtue of its location in the middle range for several directions of motion it is also the position with greatest potential for movement to be modified in other planes. $VAR_{elements}$ was quantified in two ways: i) as the *standard deviation* of the angle and ii) as the sum of the absolute difference in angle (*sum of delta angle*), of wrist flexion-extension or wrist/forearm pronation-supination at radial-ulnar zero position between consecutive repetitions (Figure 4-2b). The latter measure quantifies the total $VAR_{elements}$ between consecutive repetitions. Data were normalised to the maximum values recorded across conditions within each session for each participant.

Data were normalised to maximum for several reasons. First, this method allows comparison between the two testing sessions, which was an important factor in our analysis and interpretation. Second, it reduces variation between individual participants.

4.3.6 Statistical analysis

Statistical analysis was performed using Statistica 9 (Statsoft, Tulsa, OK, USA). According to a Kolmogorov-Smirnov test all data were normally distributed (all $p > 0.20$). Pain intensity during the start and end of the painful trial was compared using a Student's t-test for dependent samples. The *proportion of success* and *total absolute error* of successful attainment of the goal, and the *standard deviation* and *sum of delta angle* of $VAR_{elements}$, were compared between sessions (pain vs. control), between conditions (pre-pain vs. pain vs. post-pain [pain session]; trial 1 vs. 2 vs. 3 [control session]) and between repetitions (early [reps 1-15] vs. late [reps 26-40]) using repeated-measures analysis of variance (ANOVA). Post-hoc testing was undertaken using Fisher's least significant difference test. Significance level was set at $p < 0.05$. Data are presented as mean ± 95% confidence intervals (1.96 * SD) throughout the text and figures.

4.4 Results

Pain measures

Pain intensity did not differ between the early phase (initial 15 repetitions) and late phase (final 15 repetitions) of the painful trial ($p = 0.66$), with an average pain intensity of 4.9 ± 0.8 and 5.1 ± 0.9, respectively. No participants reported fatigue of the forearm or wrist during either testing session.

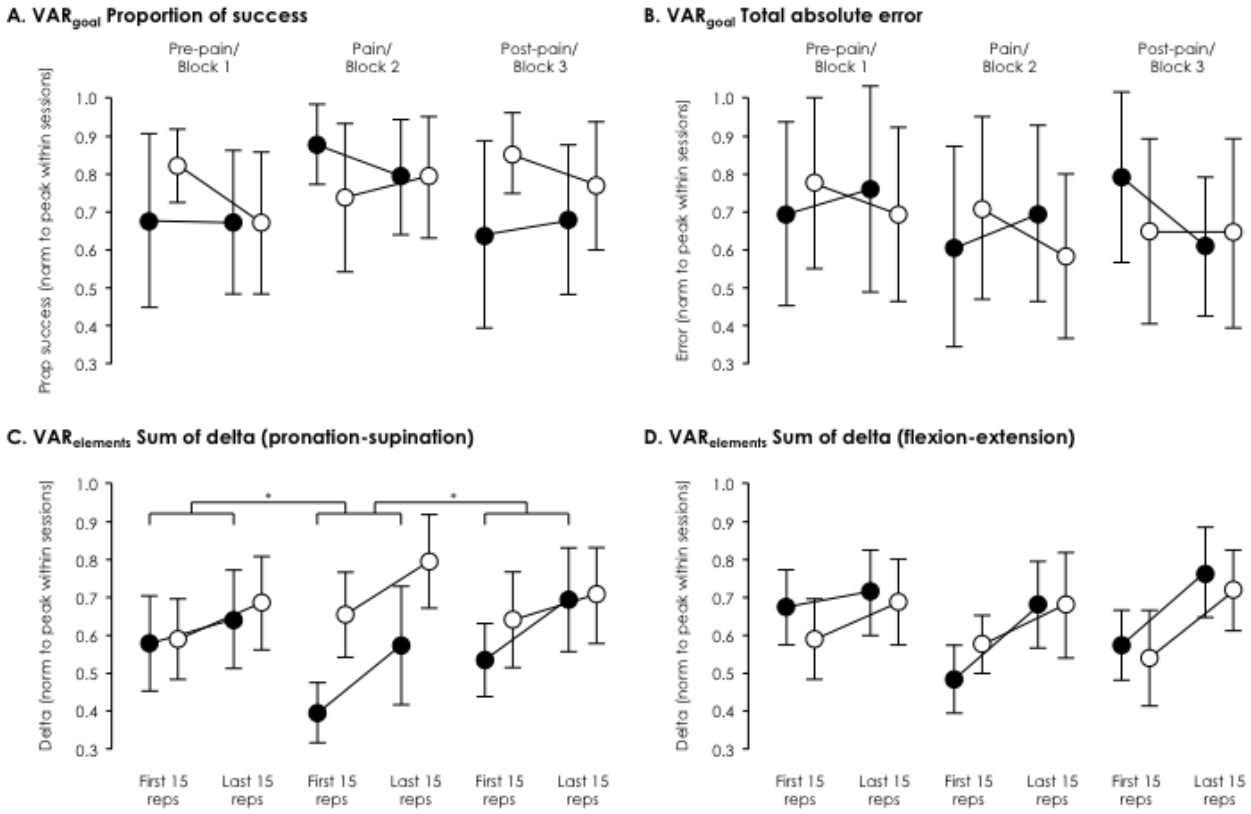

Figure 4-4. Group data for attainment of the goal and $VAR_{elements}$. Group mean and 95% confidence intervals during the session with experimental pain (black circles) and control session (white circles) for successful attainment of the goal, represented by *proportion of success* (A) and *total absolute error* (B), and $VAR_{elements}$, represented by *sum of delta angle* for forearm pronation-supination (C) and wrist flexion-extension (D). Note the reduction of variability in the pronation-supination direction during pain. Asterisk (*) indicates significant difference ($p < 0.05$) between bracketed items.

Does attainment of the goal change during an experimental session, with or without wrist extensor muscle pain?

Consistent with our first hypothesis, attainment of the goal in the radial deviation direction was not affected by pain. Neither the *proportion of success* (Main effect: condition: $F = 1.58$, $p = 0.228$; Interaction: session × condition × repetitions: $F = 1.58$, $p = 0.189$) (Figure 4-4a) nor the *total absolute error* (Main effect: condition: $F = 0.59$, $p = 0.565$; Interaction: session × condition × repetitions: $F = 1.08$, $p = 0.356$) (Figure 4-4b) changed between conditions during the session in which movement was performed with pain or the control session without pain.

Does variability of the elements ($VAR_{elements}$) change during pain despite maintenance of the primary task?

Contrary to the second hypothesis, $VAR_{elements}$ expressed as *sum of delta angle* in the pronation-supination direction was less when wrist radial-ulnar deviation was performed in the presence of wrist extensor muscle pain (Interaction: session × condition: $F = 4.82$, $p = 0.017$) than that during trials before (post-hoc: $p = 0.024$) and after pain (post-hoc: $p = 0.020$) (Figure 4-4c). There was no difference in *sum of delta angle* of pronation-supination motion between the three conditions during the experimental session without pain (all post-hoc: $p > 0.100$) (Figure 4-4c). *Sum of delta* angle in the flexion-extension direction did not change between conditions regardless of whether the experimental session involved pain or not (Interaction: session × condition: $F = 1.43$, $p = 0.258$) (Figure 4-4d).

When data were analysed as the *standard deviation* of the angle in pronation-supination, there was a tendency for a reduction of variability of pronation-supination angle but this was not significant (Main effect: condition: $F = 1.30$, $p = 0.291$; Interaction: session × condition: $F = 2.71$, $p = 0.087$). Consistent with the pronation-supination data, there was no change in variability of flexion-extension with pain (Interaction: session × condition: $F = 1.00$, $p = 0.382$).

When the initial and final 15 repetitions of each condition were compared, $VAR_{elements}$ expressed as *sum of delta angle* in pronation-supination was less at the start than the end (Main effect: repetitions: $F = 16.05$, $p = 0.002$). This increase in $VAR_{elements}$ over repetitions was consistent for both sessions and all conditions (Interaction: session × condition × repetitions: $F = 0.82$, $p = 0.450$) (Figure 4-4c). However, there was no change between the initial and final 15 repetitions when variability data were analysed as *standard deviation* (Main effect: repetitions: $F = 0.08$, $p = 0.782$). $VAR_{elements}$ of flexion-extension also increased from the start to the end of the repetitions in each condition when data were analysed as *sum of delta angle* (Main effect: repetitions: $F = 46.89$, $p < 0.001$) and *standard deviation* (Main effect: repetitions: $F = 7.20$, $p =$

0.020) and was consistent for both sessions and all conditions for both *sum of delta angle* (Interaction: session × condition × repetitions: $F = 0.81$, $p = 0.456$) (Figure 4-4d), and *standard deviation* (Interaction: session × condition × repetitions: $F = 0.25$, $p = 0.784$).

4.5 Discussion

The results of this study of a simple joint complex showed that during acute experimental pain successful attainment of the task goal was maintained; however, unlike more complex multi-joint systems (Moseley and Hodges, 2006; Madeleine et al. 2008a), the variability in the manner in which the goal was achieved (i.e. movements in other planes and other joints; $VAR_{elements}$) was reduced. The initial reduction and subsequent recovery of $VAR_{elements}$ of forearm pronation-supination contrasts evidence of an early increase in $VAR_{elements}$ during pain (Moseley and Hodges, 2006; Madeleine et al. 2008a) and subsequent reduction of $VAR_{elements}$ over time (Moseley and Hodges, 2006) when a complex multi-joint task was performed during and after acute pain. Although the nervous system appears to take advantage of variability of the multiple options available to achieve a goal in complex multi-joint movements, variability is constrained in a simple radial-ulnar deviation task with limited capacity for alternative options despite the potential to vary movement in other planes.

In support of our first hypothesis, participants continued to achieve the goal of the simple task despite acute pain. This observation concurs with some (Ingham et al. 2011), but not all previous (Boudreau et al. 2007; Salomoni and Graven-Nielsen, 2012; Salomoni et al. 2013) data of tasks that have been performed with feedback of the goal available to the participants. The failure of participants to successfully maintain the task goal in some previous studies might be explained by differences in the nature of the target or the manner in which feedback was provided. We asked participants to repetitively radially deviate their wrist to terminate within a target angle region, which by its nature allowed some scope for the wrist radial deviation position to change between repetitions, provided it was within the target region. Other work has evaluated the ability to consistently achieve a target peak acceleration of a finger movement (Ingham et al. 2011) and a sustained force (Boudreau et al. 2007; Salomoni and Graven-Nielsen, 2012; Salomoni et al. 2013). Differences in the precision required to achieve the specific goal(s) and constraints of the task may explain the difference in results.

In a system with few degrees of freedom there are limited options available to vary the performance of a task while maintaining the goal. The only options available to the nervous system in our task would be modification of wrist/forearm variability in flexion-extension and/or pronation-supination. Contrary to our second hypothesis, $VAR_{elements}$ of forearm pronation-

supination was reduced when the simple task was performed during acute pain. On the basis of data from more complex systems (Moseley and Hodges, 2006; Madeleine et al. 2008a) we predicted an increase in $VAR_{elements}$ to enable the nervous system to search for a new, less painful movement strategy (Hodges and Tucker, 2011). There are several possible explanations why $VAR_{elements}$ of forearm rotation reduced, rather than increased, in our simple task.

First, it is assumed that the nervous system searches for new less painful/injurious strategies to complete the task. It is possible that the alternative movement options available in our simple system (e.g. performance of the movement in a more flexed wrist angle) might not reduce provocation of pain and thus not present any advantage to the nervous system. In other tasks in which there is a greater range of combinations of joint excursions and muscle activation patterns available (Moseley and Hodges, 2006; Madeleine et al. 2008a), the potential to find a less provocative solution is more likely.

Second, it is reasonable to speculate that the nervous system uses an alternative solution for our simple task that involved constraint of forearm pronation-supination variability. This may have acted to minimize acute pain. Similar constraint has been observed for clinical conditions. For instance, participants with chronic knee pain exhibit constrained movement variability during gait (Hamill et al. 1999; Heiderscheit et al. 2002) and this variability increases with resolution of knee pain (Heiderscheit, 2000). Studies of complex movements during acute pain show that $VAR_{elements}$ of the painful segment (amongst the multiple segments that are available; e.g. back or shoulder in an upper limb movement task) is reduced and $VAR_{elements}$ of other non-painful segments are increased to compensate (Moseley and Hodges, 2006) to enable successful completion of the task. In our study, no other segments were available, and although we postulated that participants might increase $VAR_{elements}$ in other planes (i.e. wrist flexion-extension, forearm pronation-supination) to enable maintenance of the goal, they did not, and instead reduced $VAR_{elements}$ of pronation-supination. Thus, data from the present study imply that $VAR_{elements}$ of a painful part is reduced in acute pain and the nervous system does not appear to exploit other ways of using the segment to find a less provocative solution. It is also possible that constraint of $VAR_{elements}$ in pronation-supination minimised the area of acute wrist extensor muscle pain by reduction of spreading of the injected hypertonic saline.

Third, it could be speculated that it may not be mechanically possible to maintain successful attainment of the goal if $VAR_{elements}$ increased in other movement planes, and this may have precluded augmented variability in those planes to find a less painful solution. The nervous system may have prevented an increase of "bad" $VAR_{elements}$ to maintain accurate completion of the task as proposed by the uncontrolled manifold hypothesis (Scholz and Schöner, 1999). However, our

additional experiment in two participants confirmed that it was possible to increase pronation by approximately 20° and supination by approximately 10° (Figure 4-3) and comfortably maintain the radial target angle region. This suggests the nervous system had the capacity to change the position of the forearm and increase $VAR_{elements}$ to facilitate a search for a less painful/injurious solution, but chose not to.

Fourth, pain interferes with proprioception and this may have influenced the performance of the task (Malmstrom et al. 2013). Although reduced proprioception may be expected to increase $VAR_{elements}$, it is also possible that in view of less reliable information about joint position the nervous system might increase constraint of the task. Consistent with this proposal, people with back pain have been shown to ignore proprioceptive information from the back muscles (Brumagne et al. 2004), and other studies show reduced use of spinal movement for postural adjustments (Mok et al. 2007). This alternative requires further consideration.

We hypothesized that if $VAR_{elements}$ of forearm pronation-supination and/or wrist flexion-extension increased during pain, then $VAR_{elements}$ would be greatest at the beginning of the painful trial and subsequently decrease over repetitions in conjunction with the establishment of a new strategy for performing the simple task. As $VAR_{elements}$ of forearm rotation reduced, rather than increased, at the start of the painful trial, a further reduction towards the end of the painful trial is unlikely to have benefited the nervous system. There was a general trend for increased $VAR_{elements}$ between the start and finish of the trials, but this was present for both the painful and non-painful trials. This time-dependent change in $VAR_{elements}$ may suggest a generalised learning effect within each 45-repetition trial that is disrupted during the break between trials.

These data have possible clinical implications. The mechanisms by which the nervous system alters movement of the wrist/forearm during pain is relevant when considering the mechanisms that may underpin overuse-type injuries, that present in systems with limited degrees of freedom, such as lateral epicondylalgia (tennis elbow). If wrist/forearm variability is decreased in the acute stage of tennis elbow in a manner consistent with the present study, this could contribute to the transition to chronic tennis elbow by increasing cumulative tissue load as reduced $VAR_{elements}$ limits the sharing of load between structures. The model of hypertonic saline-induced acute pain has been used extensively and mimics several aspects of acute clinical pain (e.g. delayed muscle activation (Hodges et al. 2003)). However, the pain is short lasting (typically <5 minutes) and is not worsened by contraction/stretch (Tsao et al. 2010)).

Some limitations of the present study require consideration. We considered the magnitude of $VAR_{elements}$ at the point where the wrist passed through the neutral radial-ulnar deviation position. Other methods of analysis consider the entire time-series to evaluate coordination variability

between movement planes (Heiderscheit et al. 2002; Peters et al. 2003) and the temporal structure of repetitive movements (Preatoni et al. 2010). However, the method used in this study provided evidence of an effect of pain that answered the question posed in the study. There may have been a small learning effect that carried between the pain session (performed first) and the control session without pain. However, any learning effect was likely to be minimal given the two-month gap between the two sessions. As the variability data was normalised to the maximum values recorded during each session for each participant, this would minimise the effect of any changes between sessions. Some recent work suggests that changes to variability of muscle activation (Fedorowich et al. 2013) and force (Svendsen and Madeleine, 2010) may be gender-specific. Although these studies evaluated changes to variability due to fatigue, and not acute pain, whether gender affected the variability reported here requires further investigation with a sample selected to specifically address that issue.

4.6 Conclusion

Contrary to earlier data, which suggest that acute pain stimulates the nervous system to increase $VAR_{elements}$ during the performance of complex multi-joint tasks, we found decreased $VAR_{elements}$ when a simple task involved movement at one joint complex. This may suggest that the nervous system adapts to acute pain by altering the magnitude of $VAR_{elements}$ in a manner that is specific to the task (i.e. simple vs. complex) that is performed.

5 Has interpretation of the motor adaptation to pain been too simplistic?

5.1 Abstract

Purpose: Movement variability ($VAR_{elements}$) is increased during acute pain in complex tasks with multiple elements, but is reduced in simple tasks when the induced pain has little direct relationship to movement. We investigated whether participants searched for a less painful solution during acute experimental elbow pain and whether this was associated with increased $VAR_{elements}$.

Methods: In three experiments (*Control*, *Pain 5-1*, *Pain 5-0*), participants performed two trials (Baseline, Experimental trial) of 60 wrist radial-ulnar movements. Wrist/forearm 3-D motion was recorded. In all experiments flexion-extension angle range during the task was determined in a Baseline trial. In the *Control* experiment the Baseline and Experimental trials were identical. In the Experimental trial of the *Pain 5-1* and *Pain 5-0* experiments, elbow pain was induced by electrical stimulation when the wrist crossed radial-ulnar neutral. Stimulation intensity was determined by wrist flexion-extension angle. *Pain 5-1*: painful stimulation (~5/10) for two-thirds flexion-extension range, and less painful (~1/10) for one-third. *Pain 5-0*: painful stimulation (~5/10) for two-thirds flexion-extension range and no pain for one-third. The percentage of movements performed in the less/non-painful flexion-extension range was recorded. Sum of path length between successive repetitions in the Baseline and Experimental trials quantified $VAR_{elements}$. Average vector lengths between the average wrist/forearm angle of Baseline and wrist/forearm angle for each repetition of the Experimental trial quantified change in movement strategy during pain. Sum of path lengths and average vector lengths were calculated for six 10-repetition epochs.

Results: Average vector length was greater in the *Pain 5-1* experiment than that in the *Control* experiment for epochs 2-6 and in the *Pain 5-0* experiment than epoch 5 of the *Control* experiment, indicating a change in movement strategy. Although the new wrist/forearm position was perceived as less painful, this did not correspond to the externally determined solution region with less intense painful electrical stimulation. Interestingly, three different movement strategies were used by participants during the painful trial, and involved either no change, or a small or large change of wrist/forearm position. Participants who did not change wrist/forearm position during pain used the externally determined solution region more often than those who had a large change, but did not experience a greater reduction in pain intensity.

Conclusions: Participants searched for, and found, a less painful movement strategy during pain, but it was not the solution with complete or near complete pain reduction.

5.2 Introduction

Theories of the motor adaptation to pain (Roland, 1986; Lund et al. 1991; Murray and Peck, 2007; Hodges and Tucker, 2011) posit that movement is altered by the nervous system to reduce pain and protect structures (e.g. muscle, ligament) from further pain or injury. The motor system may adapt movement in several ways, such as reduced amplitude (Schaible and Grubb, 1993; Svensson et al. 1996) and velocity (Svensson et al. 1996), altered movement variability (Moseley and Hodges, 2006; Madeleine et al. 2008a; *Study 1*), or removal of the body part from the painful situation (Clarke and Harris, 2004). For isometric tasks that involve application of force against a fixed sensor, during pain the force may be reduced (Hug et al. 2014) or applied in a different direction (Tucker and Hodges, 2010; Hug et al. 2013) relative to non-painful trials. Although the adaptation to pain seems clear, it is unclear how and why the nervous system selects a particular movement strategy (e.g. a specific direction of knee extension force during acute pain (Tucker and Hodges, 2010)) from the many options that are available.

It has been proposed that the motor system undertakes a purposeful search for a less painful strategy by experimenting with different movement patterns (i.e. motion of body segments/joints and muscle activity; "elements"), and may take advantage of between-repetition variability of these elements ($VAR_{elements}$) in that search (Moseley and Hodges, 2006; Madeleine et al. 2008a; Hodges and Tucker, 2011). However, there is little evidence of a search or the role of $VAR_{elements}$. Although $VAR_{elements}$ is increased during acute pain in complex tasks involving multiple elements, with the potential advantage to search for new less painful solutions when pain is related to the movement (Moseley and Hodges, 2006; Madeleine et al. 2008a), $VAR_{elements}$ is reduced in simple tasks when pain is induced tonically such that the pain intensity has little direct relationship to the movement (*Study 1*). It is also unclear whether amplitude of pain reduction is the only factor considered in selection of a new movement strategy. It is plausible that if a potential movement solution achieves pain relief but is associated with a "cost" (e.g. greater energy demand), then this may influence the ultimate selection of a movement solution.

Several questions remain unanswered. First, there is little direct evidence whether changes to movement during pain reflect a *purposeful* search for a less painful solution. Second, it is unclear whether $VAR_{elements}$ is used to facilitate the search when pain is related to the task. Third, it has not

been questioned whether the search aims to simply achieve pain relief or if other factors are considered.

To investigate these questions we studied a standardized task that required wrist radial-ulnar deviation movement between two target regions. This task goal can be achieved despite variation in the alignment of the wrist/forearm in the other movement planes (flexion-extension, pronation-supination) (*Study 1*). An experimental paradigm was developed where the task provoked moderately painful stimulation as the wrist moved through the middle of the radial-ulnar range of motion, but a less painful or non-painful solution (i.e. specific wrist alignment in the flexion-extension plane) was provided that was within the range in which the participant would be expected to be exposed through normal between-repetition $VAR_{elements}$ in repetition of the task. We hypothesized that: (i) participants would continue to successfully achieve the goal of reaching the radial deviation target angle region during pain; (ii) $VAR_{elements}$ would initially increase to gain exposure to a variety of movement options in the search for a new less painful solution; and (iii) if participants experienced a substantially less painful solution (determined by the experimental paradigm) this strategy would be selected more frequently than other options.

5.3 Methods

5.3.1 Participants

Three experiments (*Control, Pain 5-1, Pain 5-0*) were conducted using separate pain protocols and different groups of participants. Ten volunteers (6 females; age 28 ± 4 years (mean ± SD)) participated in a *Control* experiment. Twenty-one volunteers (11 females; age 24 ± 6 years (mean ± SD)) participated in the *Pain 5-1* experiment (2 of these participants also participated in the *Control* experiment). Six volunteers (4 females; age 22 ± 4 years (mean ± SD)) participated in the *Pain 5-0* experiment (none had participated in the *Control* or *Pain 5-1* experiments). Different groups of volunteers were included in the *Pain 5-1* and *Pain 5-0* experiments because it was critical that participants were naive regarding the pain stimuli and potential movement strategies. All participants were naïve to the purpose of the study. Participants were excluded if they reported any major circulatory, orthopaedic, musculoskeletal or neurological conditions that affected upper limb function. Informed consent was obtained from all participants. All procedures were approved by the Institutional Medical Research Ethics Committee and conformed to the Declaration of Helsinki.

5.3.2 Procedures

Participants sat upright with their right forearm resting on a table and supported in the mid-position between pronation and supination with the elbow in approximately 90° flexion. The forearm was secured with an adjustable clamp applied to the mid region of the forearm which allowed unconstrained wrist motion and forearm pronation-supination but prevented movement of the upper limb that could affect performance of the radial-ulnar deviation task.

A motion sensor (SK7 SHAKE, SNMH Engineering Services, Dublin, Ireland) was attached to the ulnar border of the right hand to measure radial-ulnar deviation and flexion-extension of the wrist, and forearm pronation-supination. The motion sensor signal was recorded at a sampling rate of 100 Hz using a data acquisition system (PCI-6035E, National Instruments, TX, USA) and Matlab 7.14 (The Mathworks, Natick, MA, USA). The SK7 SHAKE sensor contains a triple axis linear accelerometer with a configurable full range scale of ±6 g and an output resolution of 1 mg (SK7 SHAKE User Manual, 2006).

Prior to the experimental trials, the neutral position of the wrist and forearm, and the maximal range of motion for radial and ulnar deviation, were recorded. The neutral position was measured using a handheld goniometer with the wrist and forearm in the mid position of flexion and extension, radial and ulnar deviation, and pronation and supination.

The experimental task involved repeated radial-ulnar deviation of the wrist between two target angle regions that were displayed on a computer screen positioned approximately 60 cm in front of the participant. Participants were instructed to move from a target angle region between 20-40% of their maximal ulnar deviation range to a target angle region between 60-80% of their maximal radial deviation range in time with a metronome set to 90 beats per minute (1 movement = movement from ulnar to radial target and return to ulnar target). Emphasis was placed on movement to the target angle region in the radial deviation direction. Participants practiced the task at the start of the session until it was performed at the correct frequency with successful attainment of the ulnar and radial targets for ~10 consecutive repetitions. Participants were explicitly told that the goal of the task was to terminate the radial deviation wrist movement within the radial target angle region and maintain the beat of the metronome. Data from the familiarisation period were not analysed. Two trials (i.e. “Baseline” and “Experimental” trial) of sixty repetitions were recorded for each experiment. Each trial started and finished with the wrist at the 20% ulnar deviation position, and neutral wrist flexion-extension and forearm pronation-supination. Participants were advised that each trial involved 60 repetitions and that they would be told to stop at the end of each trial. In the *Control* experiment the Baseline and Experimental trials were identical.

5.3.3 Painful electrical stimulation of the elbow

Cutaneous electrical stimulation was applied to the elbow during the Experimental trial of the *Pain 5-1* and *Pain 5-0* experiments to elicit experimental pain. This non-invasive method has been used extensively for experimental induction of pain (e.g. Gasser and Erlanger, 1929; Moseley and Hodges, 2006; van Ryckeghem et al. 2012) as it permits application of a stimulus of known intensity and duration (Handwerker et al. 1993) and is largely free of the confounding effects of stimulus habituation or sensitization (McMahon and Koltzenburg, 2005). A pair of surface electrodes (inter-electrode distance ~10 mm) was placed on the skin overlying the lateral epicondyle of the right elbow. The electrodes were placed over bone to avoid muscle contraction. Electrical stimuli were applied with increasing intensity (0–10 mV; 1-mV increments) until participants verbally rated pain intensity of 8/10 on an 11-point numerical rating scale (NRS) anchored with 'no pain' at 0 and 'maximum pain imaginable' at 10. A rating of 8/10 on the NRS was defined as the 'maximum stimulus' for each participant. Fifteen stimuli of variable stimulus intensity (range: 0 mV to 'maximum stimulus'; order randomized) were then delivered to the elbow. Participants rated their pain on the NRS after each stimulus. The pain rating was plotted against the stimulus intensity and a quadratic function fitted to determine the stimulus intensities to be used to elicit the desired pain intensity for the painful trials (Figure 5-1).

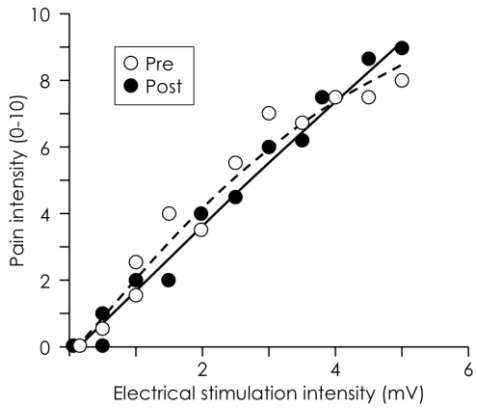

Figure 5-1. Representative data for the intensity of pain induced with electrical stimulation. Plot of pain rating (11-point numerical rating scale; 0-10) versus stimulus intensity (0-10 mV) reported by a representative participant from the *Pain 5-1* experiment in the pre-movement (white circles) and post-movement (black circles) trials. A quadratic function was fitted to the pre-movement data to determine the stimulus intensities that would be used to elicit the desired pain intensity for the painful Experimental trial.

An experimental paradigm was developed where a moderately painful stimulus (~5/10 on the NRS) was delivered to the elbow during each repetition of the wrist movement task, but a less painful stimulus (~1/10 on the NRS: *Pain 5-1* experiment) or no stimulus (0/10 on the NRS: *Pain 5-0* experiment) was delivered if the participant used a radial-ulnar deviation movement strategy with a specific alignment in the wrist flexion-extension movement plane. Several steps were undertaken to specify the characteristics of the less or non-painful movement strategy. First, when moving from the ulnar deviation target to the radial deviation target, the angle of the wrist in the flexion-extension plane was calculated as it passed through radial-ulnar neutral for each repetition of the Baseline trial. The difference (in degrees) between the maximal wrist flexion and maximal wrist extension angles recorded during this Baseline trial was defined as the 'baseline flexion-extension range' and divided into 3 equal regions (Figure 5-2). In the second 60-repetition trial (i.e. Experimental trial) painful electrical stimuli were applied to the elbow as the wrist crossed the neutral radial-ulnar deviation position. For wrist radial-ulnar deviation movements performed with the wrist aligned in two of the three regions of the flexion-extension plane (middle region and either the region in the more flexed or extended direction (randomly selected)), or outside of the baseline flexion-extension range' (i.e. greater flexion or extension wrist angles), the painful stimulus was applied at an intensity expected to evoke pain of 5/10 on the NRS when the wrist crossed the neutral radial-ulnar deviation position (Figure 5-2). A less painful stimulus (~1/10 on the NRS; *Pain 5-1*) or no stimulus (i.e. no pain; *Pain 5-0*) was delivered if the wrist was aligned within the remaining region of wrist flexion-extension allocated as the less/non-painful flexion-extension region. Participants were advised prior to the Experimental trial that they "may or may not receive painful electrical stimuli as you perform the task" and were unaware a less or non-painful movement strategy was available. After every 20 repetitions in the Experimental trial, participants were asked to verbally rate the average pain they experienced over the preceding 20 repetitions using the NRS. Participants were asked at the end of each 60-repetition trial whether they perceived any fatigue in the forearm or wrist during the task (i.e. "Did you experience any fatigue in your upper limb during the task?"). No participants reported experiencing fatigue during the task.

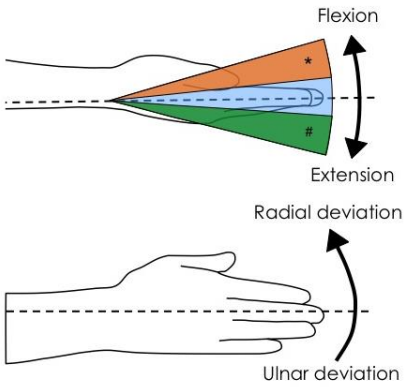

Figure 5-2. Calculation of the experimentally determined less/non-painful regions for the *Pain 5-1* and *Pain 5-0* experiments. The region in the flexion (*) or extension (#) direction was randomly assigned to be the experimentally determined solution region.

Additional measures were made after the completion of the Experimental trial to determine whether habituation or sensitization to the electrical stimuli developed during the experiments. Immediately after the completion of the Experimental trial, participants performed 5 repetitions of the radial-ulnar deviation task within each flexion-extension region (n=3) and either direction outside the 'baseline flexion-extension range' as electrical stimuli were delivered to the elbow as per the movement trials. After each 5-repetition block the participants rated the intensity of pain they had experienced for each region on the NRS. We then delivered the same fifteen stimuli of variable stimulus intensity (range: 0 mV to 'maximum stimulus'; order randomized) that were used at the start of the experiment and asked participants to rate their pain on the NRS after each stimulus. The pain rating was plotted against the stimulus intensity for each stimuli and a quadratic function fitted to the data (Figure 5-1).

Absence of habitation or sensitization would be demonstrated if: (i) the pain intensity reported during the start (i.e. repetitions 1-20) of the Experimental trial was not different to the pain intensity recorded when participants performed 5 repetitions of the radial-ulnar deviation task within the moderately painful flexion-extension regions after the Experimental trial; and (ii) there was no difference in the stimulus intensities required to elicit 5/10 and 1/10 pain before and after the movement trials.

5.3.4 Data analysis

Successful attainment of the task goal was calculated as the percentage of repetitions (0-100%) within each trial in which the participant successfully terminated radial deviation movement within the radial target angle region. For the *Control* experiment, data are reported from 9 of 10

participants as the data for 'successful attainment of the task goal' for one participant was >2 standard deviations below the group mean and considered an outlier.

The angle of the wrist/forearm in flexion-extension and pronation-supination was calculated at the point at which the wrist passed through the neutral radial-ulnar deviation position when moving from the ulnar target towards the radial target (Figure 3-5b). For comparison of the frequency of movement using the "less/non-painful movement solution" we calculated the percentage of repetitions within each trial (Baseline and Experimental trial) in which the wrist crossed the neutral radial-ulnar deviation position with wrist alignment in the flexion-extension region designated for less/no pain.

To calculate $VAR_{elements}$ between repetitions, vectors were constructed between the wrist/forearm configuration of successive repetitions (e.g. 1-2, 2-3, …) in the Baseline and Experimental trials (Figure 5-3a,d,g). The length of each vector represents the distance of the wrist/forearm between successive repetitions of the radial-ulnar deviation task, and indicates the 'path' taken within the 'movement map' (i.e. plot of flexion-extension vs. pronation-supination) for subsequent repetitions of the task. Each sixty-repetition trial was divided into 6 x 10 repetition epochs and the sum of the path length calculated for each epoch. The sum of path lengths during each epoch of the Baseline and Experimental trials were used to represent between-repetition $VAR_{elements}$ to determine whether $VAR_{elements}$ was increased as part of the search for a new, less painful movement strategy during pain.

To investigate whether wrist/forearm angle was altered during the Experimental trial relative to Baseline, vectors were constructed between the average wrist/forearm configuration (i.e. combined flexion-extension and pronation-supination position) of the Baseline trial and the position of the wrist/forearm during each repetition (n=60) of the Experimental trial, when the wrist crossed neutral radial-ulnar deviation (Figure 5-3c,f,i). The length of each vector represents the distance of the wrist/forearm (at the time of crossing the neutral radial-ulnar deviation position) during the Experimental trial from the average position during Baseline. Deviation from this average position was used to determine whether a different movement solution was selected in the Experimental trial relative to Baseline. Each 60-repetition trial was divided into 6 x 10-repetition epochs (i.e. epochs 1-6) and the average vector length calculated for each epoch. Average vector length for each epoch of the Experimental trial was used to represent the change of wrist/forearm position.

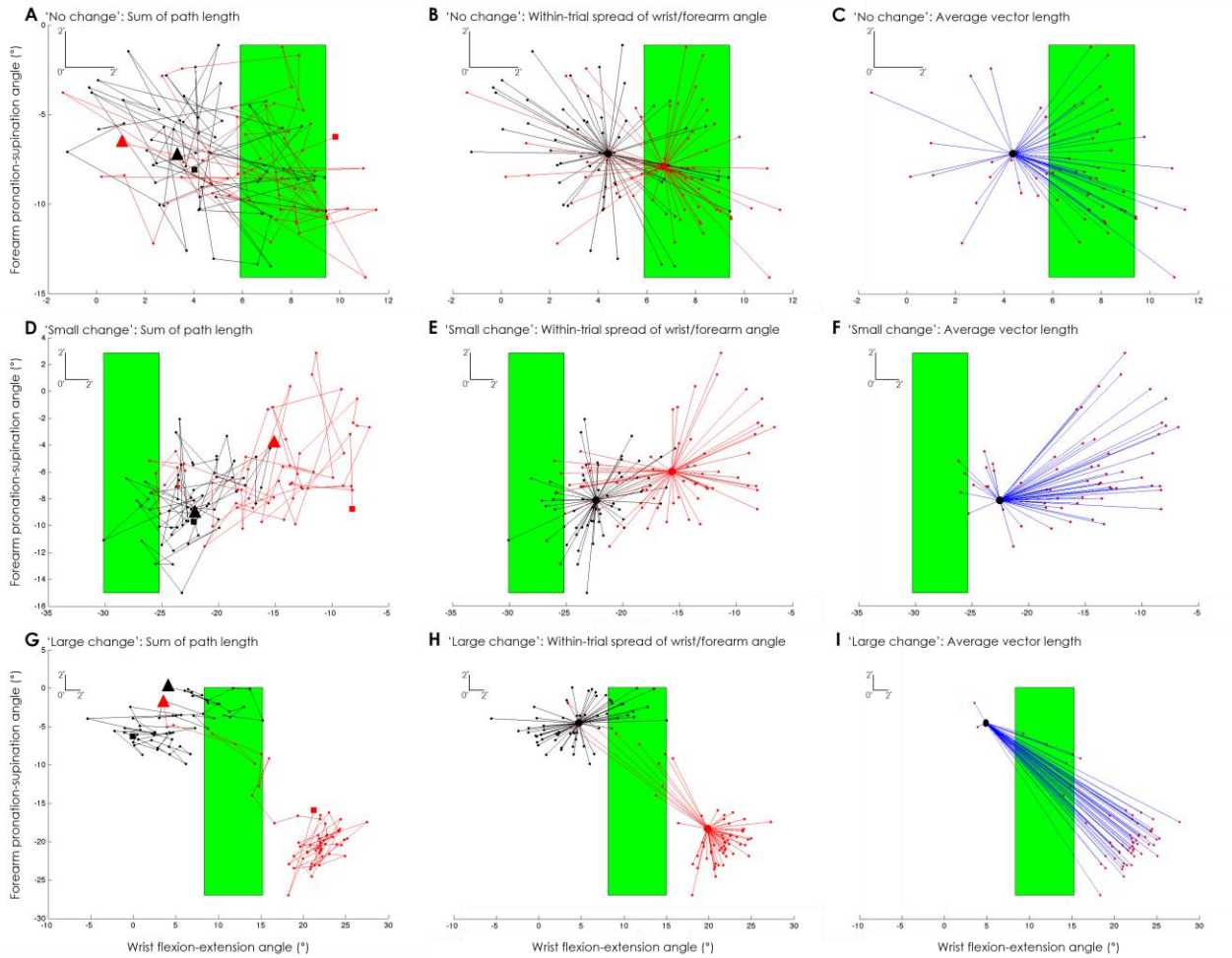

Figure 5-3. Two-dimensional movement maps that depict the three distinct movement strategies used by participants in the *Pain 5-1* and *Pain 5-0* experiments: 'no change' (a-c), 'small change' (d-f), and 'large change' (g-i). In all plots (a-i) black and red circles/lines are used for the Baseline and Experimental trials, respectively. The forearm pronation-supination angle was plotted against the flexion-extension angle for the 60 repetitions of each trial. The lines in each group of sub-plots represent different analyses. To represent 'sum of path length' lines were plotted between consecutive repetitions of each trial starting with repetition 1 (large triangles) and ending with repetition 60 (large squares) (a,d,g). To represent 'spread of wrist/forearm angles' lines were plotted between the mean wrist/forearm position (large circles) and the 60 repetitions (small circles) for each trial (b,e,h). To represent 'average vector length' vectors (blue lines) were plotted between the mean wrist/forearm position of the Baseline trial and the 60 repetitions of the Experimental trial (c,f,i). Note that different scales are used for the axes of the three movement strategies, but a scale bar is shown in the top left corner of each sub-plot that represents 2° in each direction (i.e. pronation-supination, flexion-extension). Green shaded areas represent the experimentally determined less painful movement strategy.

5.3.5 Statistical analysis

Statistical analysis was performed using Statistica 10 (Statsoft, Tulsa, OK, USA). Pain intensity during movements performed at the beginning (repetitions 1-20) and end (repetitions 41-60) of the Experimental trial were compared between experiments (*Pain 5-1* vs. *Pain 5-0*) using repeated measures analysis of variance (ANOVA). The habituation/sensitization data were compared with a t-test for dependent samples (two tails). Successful attainment of the task goal (percentage of repetitions in which participants terminated radial deviation within the target angle region) was compared between Trials (repeated measure - Baseline vs. Experimental trial) and Experiments (between-subject factor - *Control* vs. *Pain 5-1* vs. *Pain 5-0*) with repeated measures ANOVA. The sums of path lengths were compared between Trials (repeated measure - Baseline vs. Experimental trial) and Epochs (repeated measure - Epoch 1-6) and Experiments (between-subject factor - *Control* vs. *Pain 5-1* vs. *Pain 5-0*) with repeated measures ANOVA. Average vector lengths were compared between Epochs (repeated measure - Epoch 1-6) and Experiments (between-subject factor - *Control* vs. *Pain 5-1* vs. *Pain 5-0*) with repeated measures ANOVA. The percentage of repetitions in which participants experienced the solution that was externally determined by the experimental paradigm to be less/non-painful was compared between Trials (repeated measure - Baseline vs. Experimental trial) and Experiments (between-subject factor - *Pain 5-1* vs. *Pain 5-0*) with repeated measures ANOVA. Post hoc testing was undertaken using Fisher's least significant difference test. Significance was set at $p < 0.05$. Data are presented as mean ± 95% CI throughout the text and figures.

5.4 Results

Did pain intensity change from the start to the end of the Experimental trial?

Pain intensity was less at the end than the start of the painful Experimental trial (Main effect: Epoch: $p = 0.01$) for the *Pain 5-1* experiment (start: 4.3 ± 0.7; end: 3.2 ± 0.7; mean pain reduction of 1.1 ± 0.5) and *Pain 5-0* experiment (start: 4.3 ± 1.1; end: 3.7 ± 1.7; mean pain reduction of 0.6 ± 1.7). There was no evidence of habituation or sensitization to the painful stimuli during the *Pain 5-1* experiment to explain the change in reported pain. When participants rated the pain intensity elicited by electrical stimuli delivered to the elbow at a variety of intensities before and after the movement trials (Figure 5-1) the stimulus intensities required to elicit pain of 5/10 (pre: 3.3 ± 0.7 mV; post: 2.8 ± 0.5 mV; $p = 0.31$) and 1/10 (pre: 0.6 ± 0.2 mV; post: 0.7 ± 0.2 mV; $p = 0.14$) before and after the movement trials did not differ. In the *Pain 5-0* experiment there was no difference in the stimulus intensity required to elicit 5/10 pain (pre: 3.2 ± 1.3 mV; post: 3.7 ± 1.6

mV; p = 0.15). Further, when participants rated their pain intensity during movements performed after completion of the Experimental trial, for the *Pain 5-1* experiment participants rated pain of 4.4 ± 0.4 when passing through the moderate pain regions and 0.6 ± 0.3 when passing through the less painful region. For the *Pain 5-0* experiment participants rated pain of 4.3 ± 0.4 when passing through the moderate pain regions and 0.0 ± 0.0 when passing through the non-painful region.

Was attainment of the task goal affected by experimental elbow pain?

Contrary to our first hypothesis, participants did not maintain successful performance of the task during pain as consistently as they did during the baseline condition. Although the task goal was achieved consistently during the *Control* experiment without pain (Baseline = 86 ± 10%; Experimental trial = 88 ± 6%; post hoc: p = 0.53), the goal was achieved less frequently (Interaction: Experiment × Trial: p = 0.03) during the Experimental trial than Baseline for the *Pain 5-1* (Baseline = 90 ± 3%; Experimental trial = 80 ± 6%; post-hoc: p = 0.001) and *Pain 5-0* (Baseline = 95 ± 3%; Experimental trial = 82 ± 9%; post-hoc: p = 0.02) experiments.

Did $VAR_{elements}$ increase to search for a new movement solution?

During the painful Experimental trials, $VAR_{elements}$, measured as sum of path length, was greater during the middle/end of the trial (Interaction: Experiment × Epoch: p = 0.01; *Pain 5-1* experiment epochs 3,4,6: post-hoc: p < 0.025; *Pain 5-0* experiment epoch 3-6: post-hoc: p < 0.001; Figure 5-4) than the start (epoch 1), but this was not specific to the Experimental trial; the sum of path length was also greater during the middle/end epochs of the Baseline trials performed in the absence of pain (Main effect: Trial: p = 0.57; Interaction: Experiment × Trial × Epoch: p = 0.77). Taken together, contrary to our second hypothesis, this implies that $VAR_{elements}$ was not increased in the presence of pain. There was no change in sum of path length between epochs in the Control experiment (post-hoc: p > 0.20). Sum of path length was greater in the *Pain 5-0* experiment than the *Pain 5-1* and *Control* experiments for epoch 5 (post-hoc: p < 0.035), but there were no differences between experiments for any other epoch (post-hoc: p > 0.08).

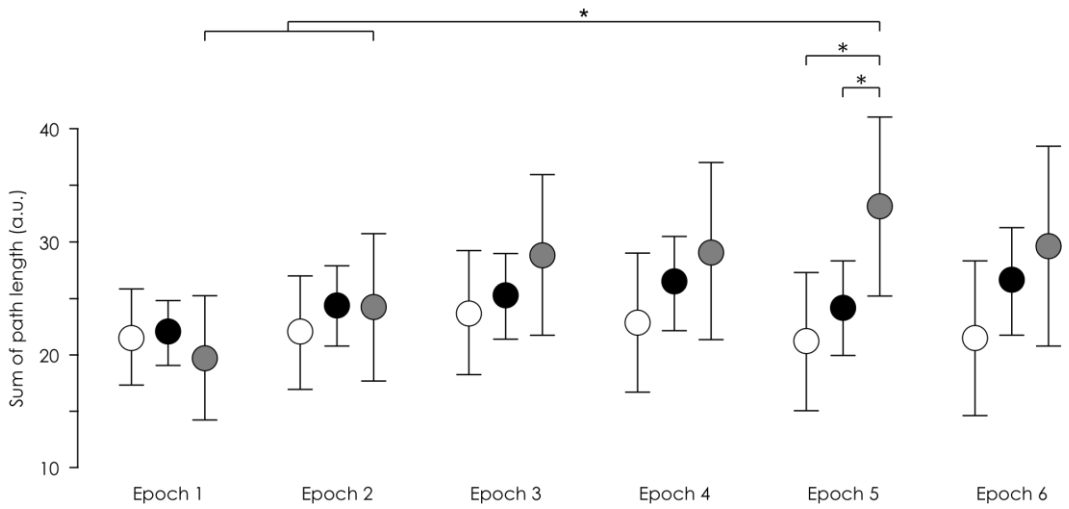

Figure 5-4. Group data for $VAR_{elements}$, measured with sum of path length. Group mean and 95% CI of sum of path length of 10-repetition epochs for the *Control* (white), *Pain 5-1* (black), and *Pain 5-0* (grey) experiments. Asterisk (*) indicates significant difference ($p < 0.05$) between bracketed items.

Was movement changed during pain?

As expected, the wrist/forearm position, as measured by average vector length, did not change between the initial and final epoch during the Experimental trial of the *Control* experiment in the absence of pain (Interaction: Experiment × Epoch: $p = 0.05$; post-hoc: $p > 0.10$; Figure 5-5). That is, the wrist/forearm configuration in the flexion-extension and pronation-supination directions remained consistent throughout the *Control* experiment.

Although average vector length was initially (i.e. epoch 1) unchanged between the three experiments (post-hoc: $p > 0.50$), as the trial progressed, average vector length was greater in the *Pain 5-1* than *Control* experiment for epochs 2-6 (post-hoc: $p < 0.05$), and greater at the end (epoch 6) than start (epochs 1-4) of the Experimental trial (post-hoc $p < 0.04$). That is, consistent with our hypothesis, wrist/forearm alignment in the flexion-extension and pronation-supination directions was changed in the Experimental trial, but this was achieved by progressively shifting the alignment away from the position used in the Baseline trial. Similarly, average vector length was greater for epoch 5 of the *Pain 5-0* experiment than epoch 5 of the *Control* experiment (post-hoc: $p = 0.03$), and average vector length was greater in epoch 5 than epochs 1-3 (post-hoc: $p < 0.02$) during *Pain 5-0*, again providing evidence of a modified movement solution.

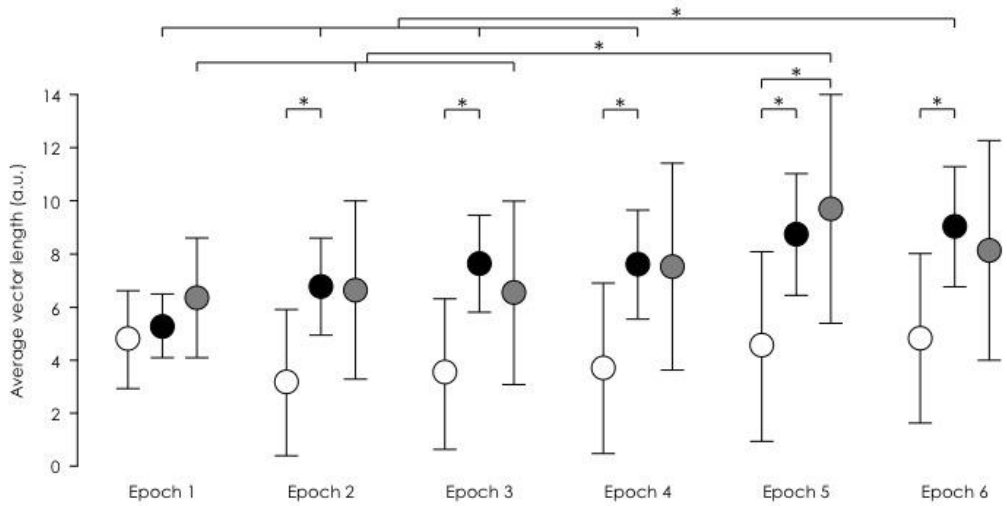

Figure 5-5. Group data for change of wrist/forearm position, measured with average vector length. Group mean and 95% CI of average vector length of 10-repetition epochs for the *Control* (white), *Pain 5-1* (black), and *Pain 5-0* (grey) experiments. Asterisk (*) indicates significant difference ($p < 0.05$) between bracketed items.

Was the experimentally determined less/non-painful option selected during the painful Experimental trials?

During the painful Experimental trials, the solution that was externally determined by the experimental paradigm to be less/non-painful was experienced (i.e. at least one repetition of the movement used the non/less painful solution) by 19 of the 21 participants in the *Pain 5-1* experiment, and all 6 participants in the *Pain 5-0* experiment. However, contrary to our third hypothesis, the experimentally determined less/non-painful movement solution was not used more frequently during the painful Experimental trial than the Baseline trial in either the *Pain 5-1* (Baseline = 27 ± 4%, Experimental trial = 21 ± 10%) and *Pain 5-0* (Baseline trial = 29 ± 11%, Experimental trial = 31 ± 17%) experiments (Main effect: Experiment: $p = 0.14$; Main effect: Trial: $p = 0.34$; Interaction: Experiment × Trial: $p = 0.23$).

What strategies were adopted to modify movement solution?

As our data showed that participants adapted movement during pain, but did not take advantage of between-repetition $VAR_{elements}$, we undertook additional qualitative and quantitative analysis to investigate the strategies used to change movement. Our major consideration was how the position of the wrist/forearm in the flexion-extension and pronation-supination directions was modified during the painful Experimental trial relative to Baseline as they attempted (not always successfully) to maintain achievement of the goal in the radial-ulnar deviation direction. Observation of the two-dimensional 'movement maps' (i.e. forearm pronation-supination vs. wrist

flexion-extension) generated for each participant revealed three distinct patterns of adaptation as shown in Figure 5-3. The first strategy involved wrist/forearm movement in the same region of map space during the Baseline and painful Experimental trials with little overall change in vector length. Participants who used a second strategy initially moved in the same map region during the painful condition but gradually moved to a new distinct region as the Experimental trial progressed with small advances with each repetition. A third strategy involved a large initial change in movement strategy where participants moved to a different map region during the painful trial on either the first or second repetition.

To quantify each strategy and measure the similarity/difference between map regions used by each participant for the Baseline and painful Experimental trials an Experimental-Baseline ratio was calculated by dividing the average vector length for the Experimental trial (i.e. average vector length of the 60 repetitions in the Experimental trial relative to the mean position in the Baseline trial) by the average vector length for the Baseline trial (i.e. average vector length of the 60 repetitions in the Baseline trial relative to the mean position in the Baseline trial). Participants were sub-grouped according to the Experimental-Baseline ratio: <1.5 = 'no change' of movement strategy; 1.5 – 4 = 'small change' of movement strategy; >4 = 'large change' of movement strategy. In the *Pain 5-1* experiment, 8 participants had 'no change', 9 participants had a 'small change', and 4 participants had a 'large change'. Data of pain intensity, attainment of the task goal, $VAR_{elements}$, average vector length, and selection of the less/non-painful region for each sub-group in the *Pain 5-1* experiment are shown in Table 5.1. In the *Pain 5-0* experiment, 2 participants had 'no change', 3 participants had a 'small change', and 1 participant had a 'large change'. In the *Control* experiment, all participants had 'no change' in movement strategy, which was expected given the Baseline and Experimental trials were identical and performed in the absence of pain.

To determine whether movement strategy influenced the frequency with which participants experienced the experimentally determined solution during the Experimental trial relative to Baseline the three sub-groups were compared with a one-way ANOVA (Factor of sub-group: No change vs. Small change vs. Large change). Participants who had 'no change' of movement strategy used the experimentally determined solution region more frequently than participants who had a 'large change' in strategy (Main effect: Sub-group: $P = 0.036$; post-hoc: $p = 0.014$) but not participants who had a small change of strategy (post-hoc: $p = 0.085$).

Next, to determine whether movement strategy influenced the change of pain intensity between the start and end of the Experimental trial the sub-groups were compared with a one-way ANOVA (Factor of sub-group: No change vs. Small change vs. Large change). There was no difference in pain reduction between the three sub-groups (Main effect: Sub-group: $P = 0.173$).

Table 5-1: Movement data for each sub-group in the *Pain 5-1* experiment

	Movement change during pain		
	'No change'	'Small change'	'Large change'
Experimental-Baseline ratio	1.28 (0.11)	2.60 (0.45)	5.80 (1.28)
Pain intensity (NRS score: 0-10)			
Start (repetitions 1-20)	4.6 (1.0)	4.0 (1.0)	4.5 (2.0)
End (repetitions 41-60)	3.1 (1.1)	2.7 (0.9)	4.4 (2.4)
Mean pain reduction	-1.6 (0.7)	-1.3(1.0)	-0.1 (0.6)
Attainment of the task goal (%)			
Baseline trial	87 (6)	90 (5)	94 (5)
Experimental trial	85 (9)	74 (9)	85 (12)
$VAR_{elements}$: Sum of path length (a.u.)			
Baseline trial	186.5 (36.7)	157.1 (20.8)	94.2 (54.7)
Experimental trial	165.8 (29.7)	184.4 (39.4)	141.0 (72.7)
Average vector length (a.u.)			
Baseline trial	3.2 (0.5)	3.5 (0.4)	2.1 (1.6)
Experimental trial	4.1 (0.5)	8.9 (1.8)	11.3 (6.7)
Less/non-painful region (%)			
Baseline trial	30 (8)	25 (7)	30 (6)
Experimental trial	37 (18)*	15 (10)	13 (5)

Data presented as mean (95% confidence interval).
Experimental-Baseline ratio – average vector length for the Experimental trial divided by the average vector length for the Baseline trial. Pain intensity – reported for the start and end of the Experimental trial, and the mean pain reduction during the trial. Attainment of the task goal – percentage of repetitions in which participants terminated radial deviation movement within the target angle region. Less/non-painful region – percentage of repetitions in which participants experienced the solution that was externally determined by the experimental paradigm to be less/non-painful.
* $P<0.05$ for comparison between the 'No change' sub-group and 'Large change' sub-group;
a.u. – arbitrary units; NRS – 11-point numerical rating scale (NRS, 0 = no pain, 10 = maximum pain imaginable)

5.5 Discussion

We hypothesised that participants would continue to achieve the task objective during pain, would use $VAR_{elements}$ to search for, and find, a less painful movement strategy, and if an option was provided that gave a large reduction in pain, this solution would be used more frequently than other movement solutions. Our data show that participants *did* seek a new solution and *achieved* a reduction in pain, but despite the substantial or complete pain reduction possible with the movement strategy externally provided by the experimental paradigm, this option was not selected and participants resolved to a solution with a more modest pain reduction. This observation has important implications for understanding the movement adaptation in the presence of nociceptive stimulation and pain. We consider the most plausible interpretation of our data is that factors in addition to reduction of pain are considered by the nervous system for the selection of a new movement solution.

The effect of experimental elbow pain on the task goal

In the present study the goal to reach the radial deviation target angle region was attained less often (~10% decrease) when pain was experienced in the *Pain 5-1* and *Pain 5-0* experiments than the *Control* experiment. This concurs with observations for some (Boudreau et al. 2007; Salomoni and Graven-Nielsen, 2012; Salomoni et al. 2013) but not all previous studies (Ingham et al. 2011; *Study 1*). There are four possible explanations for the difference between studies. First, the pain modality may be relevant. For instance, performance of the same radial-ulnar deviation task used here was maintained when acute elbow pain was induced by injection of hypertonic saline into the common extensor tendon at the elbow in an earlier study (*Study 1*). Hypertonic saline induces tonically maintained pain without clear relationship to movement, which contrasts the clear phasic relationship with the movement in the present study. Movement related pain may be more disruptive secondary to greater distraction from the task goal, or participants may have tolerated poorer task performance as a consequence of adaptation in the movement strategy. Although the radial-ulnar deviation range of motion was not related to pain intensity, participants might have anticipated a reward (i.e. reduced pain) from reduced radial deviation. Second, the emphasis placed on the goal attainment by the experimental paradigm is likely to be a determinant. Accurate task performance was emphasized as a critical aspect of the experimental paradigm by Ingham et al. (2011) who found no reduction in task accuracy with pain, but simply indicated as a target in the current study with no emphasis on importance of maintenance of goal. Third, the perceived cost/benefit of goal attainment differs between studies. If attainment of the goal was provocative of pain, this might reduce goal attainment (e.g. reduced maintenance of tongue force against a pad

coated with capsaicin (Boudreau et al. 2007)). Other work has specifically addressed the impact of benefits and/or costs associated with successful attainment, or non-attainment, of the task goal. Kurniawan et al (2010) manipulated goal attainment by providing participants with a reward (i.e. monetary reward) and penalty (i.e. painful electric stimuli) for accurate and inaccurate, respectively, pointing to a small target area in a repetitive pointing task. We encouraged participants to achieve the goal, but provided no explicit reward. In the absence of explicit benefit or cost participants in our study may have lacked motivation to maintain the task goal.

Did participants use $VAR_{elements}$ to find a new movement solution during painful trials?

It has been proposed that by taking advantage of $VAR_{elements}$, the nervous system might find an alternative movement solution that is less provocative of pain, and then once exposed to this option, may choose to use this solution more frequently to reduce pain (Moseley and Hodges, 2006). Consistent with this hypothesis several studies of multi-joint tasks have identified an initial increase in $VAR_{elements}$ of various features of movement between repetitions (Moseley and Hodges, 2006; Madeleine et al. 2008a). Although our data show increased $VAR_{elements}$ (quantified by sum of path length) over time in the *Pain 5-1* and *Pain 5-0* experiments, this was similar for the painful Experimental trial and the non-painful Baseline trial and thus does not support the hypothesis in the current paradigm. A plausible explanation is that simple movements involving few options (as opposed to the multiple available degrees of freedom in complex multi-joint tasks) may lack sufficient flexibility to increase $VAR_{elements}$ between repetitions. In a previous study of radial-ulnar deviation we showed a contrary reduction of $VAR_{elements}$ with pain (*Study 1*). However, that study involved tonic pain that was not clearly related to movement which may have precluded a search for a strategy to reduce pain (*Study 1*).

Did participants use a new movement solution during painful trials?

Despite the lack of increased $VAR_{elements}$ in the present study, participants found a new less painful movement solution. When painful electrical stimuli were applied throughout the Experimental trial in the *Pain 5-1* and *Pain 5-0* experiments, wrist/forearm position changed relative to Baseline in association with reduced pain intensity between the start and end of the trial. This involved three distinct patterns of adaptation to movement in the flexion-extension and pronation-supination directions; a large initial change in position, a progressive change in position, or a greater utilization of the experimentally provided less/non-painful position.

Instead of systematically using between-repetition $VAR_{elements}$ to search for a less painful solution, movement strategy gradually changed over multiple repetitions to explore alternative

movement options; ultimately resolving to one that was less painful. This interpretation supports the hypothesis that the motor system searches for a new, less painful movement strategy during pain (Moseley and Hodges, 2006; Madeleine et al. 2008a; Hodges and Tucker, 2011), but $VAR_{elements}$ was not used as part of this search. It is possible that changes to movement during pain would be different for movement-related stimulation of nociceptors within muscles/tendons/ligaments in contrast to the pain applied externally to the skin via surface electrodes in the *Pain 5-1* and *Pain 5-0* experiments. However, the major benefit of the pain model used in these experiments was that pain of specific intensities could be applied based on specific movements, and allowed us to answer the questions posed in this study.

Despite exposure to the externally determined movement alternative associated with complete/major pain reduction, most participants (63%) did not select this movement strategy. Instead, they achieved a lesser pain reduction using an alternative solution. In the *Pain 5-1* and *Pain 5-0* experiments a sub-group (37%) of participants used a similar movement strategy (i.e. wrist/forearm flexion-extension and pronation-supination position) in the Baseline and painful Experimental trials, and did use the less painful externally determined solution region during the Experimental trial. Despite these participants experiencing the solution region more frequently than those who had a 'large change' in strategy, these participants did not experience a larger benefit in terms of pain reduction.

Why didn't most participants select the movement strategy that was externally provided by the experimental paradigm to substantially/completely reduce pain?

It was hypothesized that participants would use the externally determined solution provided in the experimental paradigm that gave a large benefit in terms of pain relief. Although participants selected an option that was less painful, it was generally not the solution provided by the experimental paradigm. However, as discussed above, some participants did select the solution provided by the experimental paradigm, but did not experience a greater reduction in pain than other strategies. There are several possible reasons why the less painful solution we provided was not used more often. First, to maintain this experimentally applied solution, it would be necessary for participants to "realize" that pain could be reduced and which movement plane (i.e. radial-ulnar deviation, flexion-extension, or pronation-supination) determined the intensity of electrical stimulation. Participants were not informed that pain could be modified by movement strategy. Earlier work has shown that participants can change movement strategy if they are explicitly made aware of the manipulation of the task (change in load sharing between limbs when efficiency of one limb is reduced (Hu and Newell, 2011)), but they do not modify their strategy if the same

manipulation is applied without their knowledge (Hug et al. 2014). Thus, despite exposure to the benefit (i.e. reduced pain) of the experimentally applied solution, failure to repeatedly use this solution might be explained by failure to interpret the implicit relationship between movement and pain. Further, participants may have failed to learn the relationship between movement and pain in the experimental paradigm because the adaptation was not intuitive for the nervous system. Other studies with simpler solutions to reduce pain have found successful adoption of an adapted movement strategy when acute pain is induced with electrical stimulation at the end-point of a repetitive pointing task (Kurniawan et al. 2010). Taken together, these results suggest participants may require explicit feedback about the pain and task to successfully adapt to acute pain, or the solution that is provided may need to be more intuitive or natural for the nervous system (e.g. gradual change in pain over a range of motion, rather than an abrupt step change in pain).

Second, factors other than pain might be considered in selection of the preferred option for movement. An inherent assumption of the motor adaptation to pain is that during a painful episode the main priority of the nervous system is to seek a reduction in pain intensity. However, the results of this study and others (Tucker and Hodges, 2010; Hug et al. 2014) suggest otherwise. For instance, when acute pain was induced in the infrapatellar fat pad of the knee with injection of hypertonic saline, knee extension force was not applied in a direction that would be expected to consistently minimize loading of the fat pad, and thus minimize pain (Tucker and Hodges, 2010). Further, Hug et al (2014) investigated changes to muscle activation and stress (measured with electromyography and elastography, respectively) during acute pain induced by injection of hypertonic saline. They found muscle activation and stress did not change for tasks with few elements (i.e. the number of muscles and joints that may be used to perform the task), but were reduced during a task with more elements. Thus, it is likely that absolute reduction of pain intensity is not the sole consideration of the nervous system in a painful situation. The nervous system may prioritize other factors involved with movement such as optimization of end point error (Kording and Wolpert, 2004), energy usage of muscles (Anderson and Pandy, 2001), the ‘principle of minimal interaction’ (Feldman et al. 2007), and muscle force (Pandy et al. 1995). For instance, in non-painful situations it might be beneficial for the nervous system to minimize energy consumption to ensure muscles can meet the energy requirements for subsequent movements (Conley and Lindstedt, 2002; Todorov, 2002). Further, the “minimum variance model” predicts that the motor system activates muscles in a manner that minimizes end-point error of the final hand position in pointing movements (Harris and Wolpert, 1998). It is unclear how the nervous system balances these different factors (e.g. energy consumption, end-point error), and whether the weight or importance of each factor is altered in situations of acute pain or injury.

Third, the perceived *benefit* of an adaptation might be linked to the *amplitude* of the change in movement. By design, the experimentally applied solution for pain reduction was within the flexion-extension range of motion used by participants to perform the task in the non-painful Baseline trial. Our data of average vector length show that during pain the preferred solution for most participants (67%) was further from the mean wrist/forearm movement strategy than during the Baseline trial. The nervous system might perceive small adaptation as being insufficient, and more extreme adaptations may be preferred to interpret that sufficient action had been taken. Data from other studies of pain in the absence of injury (Hodges et al. 2013) or when pain is anticipated but without noxious input (Moseley et al. 2004; Tucker et al. 2012) highlight that changes to movement exceeds the adaptation required to protect the body part. Thus, despite the potential for greater pain reduction with adoption of the experimentally applied solution that was within the Baseline range of motion used to perform the task, this solution may not have been perceived as a sufficient change of strategy and a more extreme option may have been preferred, despite the lesser pain reduction.

5.6 Conclusion

This study found that participants searched for, and found, a less painful movement strategy during acute elbow pain, but $VAR_{elements}$ was not used as part of this search. Although the new movement strategy was less painful, participants did not uniformly select the experimentally determined strategy that would provide a substantial or complete reduction of pain. This suggests the nervous system may consider factors in addition to reduction of pain when selecting a new movement solution.

6 Movement variability in chronic lateral epicondylalgia: Friend or foe?

6.1 Abstract

Purpose: Changes to $VAR_{elements}$ in chronic pain have been considered during complex, multi-joint tasks, and results have been contrasting; e.g. reduced shoulder $VAR_{elements}$ during reaching vs. increased knee $VAR_{elements}$ during walking. These differences may be explained by the capacity of a specific element of a task to be varied. That is, some elements of a task may be tightly constrained by the nervous system and not able to change, whereas other may be more flexible. One way to consider this possibility is to study simple motor tasks that have few 'elements' and limited capacity to change (e.g. radial-ulnar deviation). We investigated whether participants with chronic LE had altered $VAR_{elements}$ relative to pain-free controls during a radial-ulnar deviation task, and whether pain intensity in LE participants affected wrist position and $VAR_{elements}$.

Methods: Twenty participants with chronic LE and twenty healthy controls performed 60 repetitions of the radial-ulnar deviation task that provoked moderate pain for participants with LE. Movements of the affected wrist/forearm were recorded with a 3D motion analysis system. Participants verbally rated their pain intensity (0-10) after every 20 repetitions. Control participants did not report pain. $VAR_{elements}$ was measured as the standard deviation (SD) and delta angle of motion in flexion-extension and pronation-supination. Pain intensity and $VAR_{elements}$ data were compared between the *start* (repetitions 1-20) and *end* (repetitions 41-60) of the trial, and between Groups with repeated measures ANOVA. Linear regression analysis was used to assess the relationship between pain intensity, wrist flexion-extension position, and SD of wrist flexion-extension, and the change in these three factors, in the LE group.

Results: There was no main Group effect, which indicates no difference in $VAR_{elements}$ between LE and Controls. SD of flexion-extension decreased between the *start* and *end* of the trial for the LE group, but not for Controls. In LE participants, lower pain intensity at the *start* was related to a more flexed wrist position and greater SD of flexion-extension. A greater change of wrist position into flexion was correlated with greater change in SD, and minimised pain provocation.

Conclusions: Participants with chronic LE moved the wrist into a more flexed wrist position and reduced $VAR_{elements}$ to allow performance of the task in a less provocative manner.

6.2 Introduction

The goal of motor tasks can be maintained despite variability in the multiple degrees of freedom (e.g. motion of body segments/joints and muscle activity) involved in the task. Variation in these elements of a task ($VAR_{elements}$) might be important to explore different movement options (Dingwell et al. 2001) and distribute stresses between tissues (e.g. muscles, tendons) to reduce cumulative loading (Hamill et al. 1999).

When the nervous system is challenged by acute pain it has been argued that $VAR_{elements}$ may increase to search for a less painful solution and then decrease once a less painful strategy is identified (Moseley and Hodges, 2006). However, it is not yet clear what happens to $VAR_{elements}$ during complex, multi-joint tasks if pain becomes persistent/chronic. For example, decreased $VAR_{elements}$ has been observed in chronic knee (Hamill et al. 1999; Heiderscheit et al. 2002), neck/shoulder (Madeleine et al. 2008a; Madeleine et al. 2008b; Madeleine and Madsen, 2009) and low back (Lamoth et al. 2006; van den Hoorn et al, 2012) pain. Yet, other studies report increased $VAR_{elements}$ in chronic knee (Cunningham et al. 2014) and neck/shoulder pain (Lomond and Côté, 2010), and unchanged $VAR_{elements}$ in chronic knee (Yakhdani et al. 2010) and foot pain (Ferber et al. 2005). Apart from differences in the methods used to quantify $VAR_{elements}$ these differences between studies may be explained by three factors.

First, the capacity of a specific task element to vary might underpin the degree of changes to $VAR_{elements}$. That is, some elements of a task may be restricted by the motor system depending on the underlying biomechanical constraints, and have limited capacity to change, whereas other elements may be more flexible. For instance participants with chronic neck/shoulder pain demonstrate reduced $VAR_{elements}$ for some features of an upper limb task (e.g. acceleration in the flexion-extension and rotation directions) but not others (e.g. acceleration in the abduction-adduction direction; range of motion in any direction) (Madeleine et al. 2008a). Second, consistent with other motor adaptation to pain (Hodges and Tucker, 2011), $VAR_{elements}$ might be influenced by the intensity of pain experienced during the task (Heiderscheit et al. 2002). However, this relationship has not yet been explored. Third, $VAR_{elements}$ can change over time with repetition of a task (Lomond and Côté, 2010). In that study both "fatigue" and neck/shoulder pain increased over the trial period, and either may have contributed to the decrease in $VAR_{elements}$. To investigate the potential roles of task complexity, pain intensity and fatigue, than may each affect $VAR_{elements}$ in

people with chronic pain, we studied a simple repetitive wrist radial-ulnar deviation movement that would provoke pain in participants with chronic lateral epicondylalgia.

Lateral epicondylalgia (LE) is a musculoskeletal condition characterised by lateral elbow pain provoked during gripping and manual tasks that require movement of the wrist and forearm (Coombes et al. 2009a). People with chronic LE adopt a more flexed wrist position (Bisset et al. 2006) and have reduced activation of the extensor carpi radialis (ECR) muscle (Alizadehkhaiyat et al. 2007) during gripping, which might be beneficial to reduce painful loading of the common extensor tendon at the elbow. $VAR_{elements}$ has not been considered in this chronic pain population.

We aimed to determine whether participants with chronic LE relative to pain-free participants demonstrate; (i) altered $VAR_{elements}$ during a task that involves radial-ulnar deviation movement ($VAR_{elements}$ were considered in flexion-extension and pronation-supination directions); (ii) whether LE participants performed the task in a different position of the wrist in the flexion-extension direction; (iii) whether pain intensity affected $VAR_{elements}$ and wrist flexion-extension position in participants with chronic LE; and (iv) whether $VAR_{elements}$ and wrist flexion-extension position changed over time with repetition of the task. We hypothesised that people with chronic LE would perform the radial-ulnar deviation task in a more flexed wrist position and with less $VAR_{elements}$ than pain-free controls.

6.3 Methods

6.3.1 Participants

Twenty participants with chronic LE participated in this study. Participants were recruited with newspaper advertisements and included if they had unilateral elbow pain for longer than 6 weeks, pain intensity ≥3 on an 11-point numerical rating scale within the preceding week (NRS: 0 = no pain; 10 = worst pain imaginable), reduced pain-free grip strength (<50% compared to the unaffected upper limb), and pain over the lateral epicondyle of the humerus provoked by at least two of the following manoeuvres; gripping, palpation, or resisted wrist/middle finger extension (Coombes et al. 2012a). Participants were excluded if they had bilateral upper limb pain, physiotherapy treatment in the preceding three months, or corticosteroid injection in the preceding six months. Twenty participants with no history of LE were recruited using the same strategy into a control group. Participants in either group were excluded if they reported any major circulatory, musculoskeletal (other than LE in the chronic LE group), or neurological conditions that affected upper limb function. Participants in the LE and control groups were matched for age (±5 years), sex, and hand-dominance. The matched upper limbs (i.e. according to hand-dominance) of the control group, relative to the LE group, are referred as the '*control matched affected*' and 'control

matched *unaffected*' upper limbs. Written informed consent was obtained from all participants prior to testing. Data collection was completed during one testing session for each participant. Demographic data for all participants are detailed in Table 6-1. All procedures were approved by the Institutional Medical Research Ethics Committee and conformed to the Declaration of Helsinki.

6.3.2 Assessment of pain and disability in chronic LE

Participants in the LE group completed the 'Patient rated tennis elbow evaluation' (PRTEE), which allowed quantification of pain and disability (Rompe et al. 2007). Responses were scored on a series of 11-point Likert scales to give a total score that ranged from 0 (no pain or functional limitation) to 100 (worst imaginable pain with a very significant functional limitation). In addition, an 11-point NRS was used for participants to rate the intensity of the worst pain they had experienced over the preceding week. Scores for the PRTEE and 11-point NRS are shown in Table 6-1.

6.3.3 Grip force testing

Participants performed a series of unilateral gripping tasks for both upper limbs. Grip force was measured using a load cell (Futek, Irvine, CA, USA), and recorded using a Power1401 Data Acquisition system at 100 samples/s with Spike2 software (Cambridge Electronic Design, Cambridge, UK). Participants were seated with the upper limb supported in 90° shoulder flexion, with elbow extended and forearm pronated.

Three maximal voluntary contractions (MVC) with standardised strong verbal encouragement were recorded for the unaffected upper limb of participants with LE and both upper limbs for control participants (unaffected upper limb measured first for all participants). Force was increased over ~3 seconds then held at the maximum for ~2 seconds before returning to rest. Each trial was separated by 1 minute to limit possible effects of fatigue. The maximum force achieved during the three MVC trials was used to calculate the target gripping force for control participants in the radial-ulnar deviation task.

Participants in the LE group performed three pain-free grip trials with their affected upper limb. Pain free grip is a highly reliable (ICC > 0.97; Stratford and Levy, 2004) clinical outcome measure for LE that correlates more strongly with disability and perceived improvement of symptoms than maximal grip strength (Stratford and Levy, 2004; Coombes et al. 2009a). Force was gradually increased until participants reported the first onset of pain, at which point they stopped gripping. Each trial was separated by 1 minute to limit possible effects of fatigue and sustained pain provocation from the previous trial. The average pain-free grip force recorded from the three

repetitions was used as the target force in the radial-ulnar deviation task for participants in the LE group.

Table 6-1. Participant characteristics and grip force.

	Lateral Epicondylalgia (n = 20)		Control (n = 20)	
Sex: Female	8 (40%)		8 (40%)	
Age in years	51 (4)		49 (4)	
Right arm dominant	18 (90%)		18 (90%)	
Dominant arm symptomatic	16 (80%)		n/a	
Symptom duration (weeks)	29.8 (17.1)		n/a	
PRTEE (score/100)	33.7 (6.7)		n/a	
Worst pain during the past week (NRS score 0-10)	5.1 (0.7)		No pain	
	LE Affected	LE Unaffected	Control Matched Affected	Control Matched Unaffected
Grip force (N)	84 (18)*	295 (28)	279 (29)	275 (32)

Data presented as number (% of group) or mean (95% confidence interval).

Grip force is reported for pain-free grip for LE Affected, and maximal voluntary contractions for LE Unaffected, Control Matched Affected, and Control Matched Unaffected.

* $P<0.05$ for comparison between LE Affected, and LE Unaffected and Control Matched Affected and Control Matched Unaffected; PRTEE – patient rated tennis elbow evaluation; NRS – 11-point numerical rating scale (0 = no pain, 10 = worst pain imaginable; NRS); n/a – not applicable

6.3.4 Kinematic measurements

Two clusters of four non-collinear reflective markers were attached to the upper limb to record radial-ulnar deviation and flexion-extension of the wrist, and forearm pronation-supination (Figure 6-1). One cluster was attached to the dorsum of the hand between the 2nd and 3rd metacarpals, and another was attached to the palmar surface of the forearm immediately proximal to the wrist joint. Motion of the clusters during the movement task was recorded by an 8-camera 3D motion analysis system (T040, Vicon Motion Systems Ltd. Oxford, UK) at 200 sample/s. An electrogoniometer (SG65, Biometrics Ltd., Newport, UK) was attached to the dorsal surface of the hand and distal end of the forearm to provide on-line feedback of radial-ulnar deviation position during the movement task (Figure 6-1A). The electrogoniometer signal was recorded at 100 samples/s using a Power1401 Data Acquisition system and Spike2 software (Cambridge Electronic

Design, CED, UK). The two recording systems were synchronized by remotely starting and stopping the motion analysis system recordings with Spike2 software.

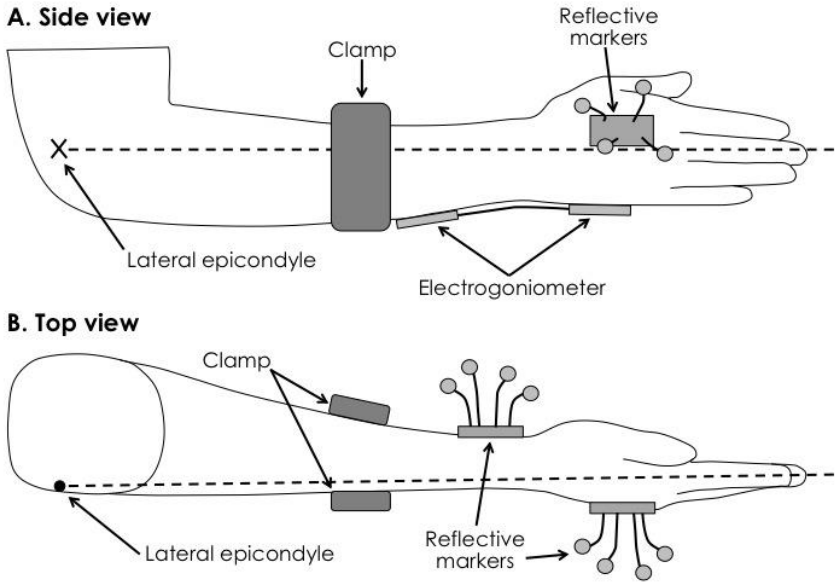

Figure 6-1. Experiment setup showing the position of the upper limb from the side (A) and top (B) view for performance of the radial-ulnar deviation task. Note the dashed line indicates the neutral position of the wrist and forearm. Also note, in *Study 3* the task radial-ulnar deviation task was performed with the elbow extended whilst gripping a load cell (not shown here).

6.3.5 Procedures

Participants sat in an upright posture with their forearm resting on a table and supported in mid-position between pronation and supination. Their elbow was positioned in relaxed extension (Figure 6-1). The forearm was secured with an adjustable clamp applied mid-way between the elbow and wrist. This setup allowed unconstrained wrist motion and forearm pronation-supination and limited the potential for arm movements that were unrelated to the experimental tasks.

Prior to the experimental trials the neutral position of the wrist and forearm, and the maximal range of motion for radial and ulnar deviation, were determined. The neutral position was measured using a handheld goniometer with the wrist and forearm in the mid position of flexion and extension, radial and ulnar deviation, and forearm pronation and supination.

The task involved repeated wrist radial-ulnar deviation movement of the *affected limb* with the elbow extended while gripping a load cell (Futek, Irvine, CA, USA). The radial-ulnar movement was between two target angle regions that were displayed on a computer screen positioned approximately 60 cm in front of the participant (*Study 1*). Participants were instructed to gradually increase their force (from zero) over ~3 seconds until they reached a target force

(achievement of the target force was indicated verbally by the experimenter). The target force for each participant in the LE group was set to his or her pain-free grip force of the affected upper limb. To determine an appropriate target force for Control participants, that reflected the pain-free grip force (as a % of their unaffected MVC) used by LE participants, the following formula was used:

$\text{Target Force}^{CPn} = (\text{MVC Unaffected}^{LEPn} / \text{MVC unaffected}^{CPn}) \times \text{Pain-Free Grip Force}^{LEPn}$,
where CPn is the control participant matched to the specific LEPn participant

Participants were asked to maintain the target grip force throughout the trial but were not given verbal or visual feedback of the force. Feedback of force was not provided as pilot testing indicated that participants failed to consistently move between the two target regions (i.e. the primary task goal) when feedback of both wrist movement and force were provided simultaneously.

Pilot testing (n=4) was undertaken to confirm that the radial-ulnar deviation movement with the addition of the grip component would provoke pain. These participants with chronic LE experienced elbow pain during performance of the task (3.2 ± 1.9 /10 (mean ± 95% CI) on the 11-point NRS).

Participants were instructed to move from a target angle region 20-40% of their maximal ulnar deviation range to a target angle region 60-80% of their maximal radial deviation range. This movement was timed with a metronome set to 90 beats per minute (1 repetition = movement from ulnar to radial target and return to ulnar target). Emphasis was placed on reaching the target angle region in the radial deviation direction. Participants practiced the task until it was consistently completed at the correct frequency and between the two target angle regions. Data from this practice period were not analysed. One trial (i.e. sixty repetitions) of the task was recorded. After every 20 repetitions, participants in both groups were asked to verbally rate the average pain they experienced (using the 11-point NRS) over the preceding 20 repetitions. Participants were asked at the end of each 60-repetition trial whether they perceived any fatigue in the forearm or wrist during the task (i.e. “Did you experience any fatigue in your upper limb during the task?”). No participants reported experiencing fatigue during the radial-ulnar deviation task.

6.3.6 Data analysis

For analysis of successful attainment of the radial deviation target angle region, radial-ulnar deviation angle data recorded with the electrogoniometer were analysed offline using Spike2 software. Successful attainment of the target region was represented as the proportion of repetitions (0-100 %) within two epochs (Start: repetitions 1-20; End: repetitions 41-60) in which the

participant successfully terminated radial deviation movement within the radial deviation target angle region.

Grip force data and angle of the wrist/forearm in flexion-extension and pronation-supination were calculated offline using Matlab 7.14 (The Mathworks, Natick, MA, USA). The grip force and wrist/forearm angles were determined when the wrist passed through the radial-ulnar neutral position, as it moved from the ulnar target towards the radial target. The radial-ulnar neutral position was chosen as it is a standard and repeatable position in the radial-ulnar deviation range of motion that has the greatest potential for movement to be modified in the flexion-extension and pronation-supination directions (*Study 1*). However, some participants failed to cross the neutral radial-ulnar position during some repetitions. As a result, the force data and wrist/forearm angles could not be calculated for all repetitions. Data from any trial with fewer than 55 (of 60) full repetitions (i.e. repetitions that crossed neutral), or more than three consecutive repetitions that did not cross neutral, were not included in the analysis. Data for repetitions where the neutral radial-ulnar position was crossed were represented within two epochs (Start: repetitions 1-20; End: repetitions 41-60).

The grip force data were analysed to determine if participants maintained the target grip force during the trial. These data were expressed as a proportion of the target force within each epoch for each participant (i.e. 100% = maintenance of the target force; <100% = less than the target force).

The mean wrist flexion-extension and forearm pronation-supination angles at the start (repetitions 1-20) and end (repetitions 41-60) were calculated when the wrist passed through the radial-ulnar neutral position, as it moved from the ulnar target towards the radial target. Positive values indicate wrist flexion and forearm pronation, whereas negative values indicate wrist extension and forearm supination, throughout the text and figures. Participants with chronic LE were sub-grouped according to whether they moved into a more flexed wrist position or more extended position between the start and end of the task. The mean change in pain intensity between the start and end of the trial for each sub-group were compared.

$VAR_{elements}$ was defined as variability in the angle of the wrist/forearm in planes other than that of the primary movement (i.e. wrist flexion-extension and forearm pronation-supination). $VAR_{elements}$ was quantified as the standard deviation of the angle (SD°), and the mean of the absolute difference in angle between consecutive repetitions of wrist flexion-extension and forearm pronation-supination (mean delta angle; Δ°). The delta angles of the repetitions were summed and divided by the number of analysed repetitions within each epoch. Mean delta angle (rather than sum of delta angle, which is conceptually similar; *Study 1*) was used to quantify $VAR_{elements}$ in the

current study to negate the effect of variation in the number of repetitions in each epoch that were calculated for some participants (as discussed above).

6.3.7 Statistical analysis

Statistical analysis was performed using Statistica 10 (Statsoft, Tulsa, OK, USA). Pain intensity in the LE group was compared between Epochs (Start vs. End) with a dependent t-test (two tail). Change in pain intensity between the start and end of the trial for participants who moved into a more flexed wrist position (n=8) and those who moved into a more extended wrist position (n=8) were compared with a dependent t-test (two tail). Note, participants in the control group did not report any pain (i.e. 11-point NRS = 0), and therefore no statistics were performed on these data. Successful attainment of the target angle region (i.e. % of analysed repetitions), target grip force data , $VAR_{elements}$ (i.e. SD°, Δ°) and mean flexion-extension and pronation-supination angle, were compared with a repeated measures ANOVA with Epoch (Start vs. End) as a within subject factor, and Group (LE vs. Control) as a between-subject factor. Post-hoc testing was undertaken using Fisher's least significant difference test. Linear regression analysis was used to assess the relationship between pain intensity, wrist flexion-extension position, and SD of wrist flexion-extension, and the change in these three factors between the start and end of the trial at group level. Pearson correlation coefficients (*r*) were then calculated for each relationship. Significance level was set at $p < 0.05$. Data are presented as mean ± 95% CI throughout the text and figures.

6.4 Results

Pain measures

Pain intensity was greater at the end (4.5 ± 0.9 /10) than at the start (2.9 ± 0.6 /10) of the trial when participants in the LE group performed the task ($P < 0.001$). Participants who selected a more flexed position had a smaller increase in pain (1.4 ± 0.6) than participants who moved into more wrist extension (2.5 ± 0.6; $P = 0.03$).

Successful attainment of the task goals

There was no difference in attainment of the target *angle* region between LE and controls at the start (LE: 91 ± 5 %; Control: 90 ± 11 %) or end (LE: 84 ± 9 %; Control: 86 ± 11 %) of the trial (Interaction - Group × Epoch: $P = 0.560$; Main effect - Group: $P = 0.928$). The target angle region was achieved less often at the end (85 ± 7 %) than the start (90 ± 6 %) of the trial for both groups (Main effect - Epoch: $P = 0.037$).

There was no difference in attainment of the target grip *force* between LE and controls at the start (LE: 63 ± 13 %; Control: 76 ± 15 %) or end (LE: 41 ± 12 %; Control: 49 ± 13 %) of the trial (Interaction - Group × Epoch: P = 0.419; Main effect - Group: P = 0.263). The target force was achieved less often at the end (70 ± 10 %) than at the start (45 ± 9 %) of the trial for both groups (Main effect - Epoch: P = 0.001).

Mean wrist/forearm angle

Wrist flexion-extension angle moved into a relatively more flexed position between the start (-3.2° ± 4.6°) and the end (-1.0° ± 5.1°) of the trial (Main effect - Epoch: P = 0.019; Interaction - Group × Epoch: P = 0.765; Figure 6-2). Forearm pronation-supination angle became relatively more pronated, from 12.8° ± 2.5° at the start to 14.4° ± 3.1° at the end of the trial (Main effect - Epoch: P = 0.004; Interaction - Group × Epoch: P = 0.589). There was no difference between LE and controls in the mean wrist flexion-extension and forearm pronation-supination angles during performance of the radial-ulnar deviation movement (Main effect - Group: both P > 0.244).

Variability of the elements

Standard deviation: flexion-extension

SD of wrist flexion-extension angle ($SD°_{flexion\text{-}extension}$) was less at the end than the start of the trial in the LE group (Interaction - Group × Epoch: P = 0.013; post-hoc: P = 0.008), but did not change between start and end in the Control group (post-hoc: P = 0.430) (Figure 6-2). However, post-hoc testing did not show differences between LE and Controls at the start (post-hoc: P = 0.109) or end (post-hoc: P = 0.542) of the trial.

Standard deviation: pronation-supination

There was no difference in SD of the pronation-supination angle ($SD°_{pronation\text{-}supination}$) when the wrist passed through neutral ulnar-radial deviation between LE and Controls (Interaction - Group × Epoch: P = 0.757; Main effect - Group: P = 0.640; Main effect - Epoch: P = 0.287) (Figure 6-2).

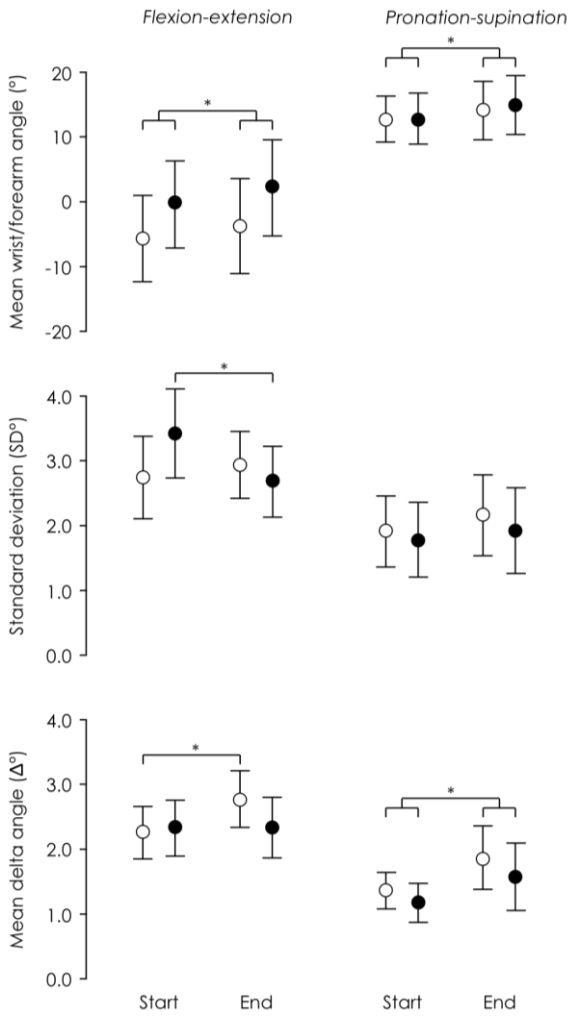

Figure 6-2. Group data for change of wrist/forearm position and $VAR_{elements}$. Group mean and 95% confidence interval of mean wrist/forearm position, standard deviation (SD), and mean delta angle (Δ°), for participants in the Control group (white) and chronic LE group (black) during performance of the radial-ulnar deviation task. For the mean wrist/forearm position, positive values indicate flexion/pronation, and negative values indicate extension/supination. Asterisk (*) indicates significant difference ($P < 0.05$) between bracketed items.

Mean delta angle: wrist flexion-extension

Mean delta angle of wrist flexion-extension ($\Delta°_{flexion\text{-}extension}$) was less at the start than the end of the trial in the Control group (Interaction - Group × Epoch: P = 0.026; post-hoc: P = 0.002). In the LE group, there was no difference in $\Delta°_{flexion\text{-}extension}$ between the start and end of the trial (post-hoc: P = 0.993). There was no difference between LE and Controls at the start (post-hoc: P = 0.816) or end (post-hoc: P = 0.151) of the trial (Figure 6-2).

Mean delta angle: pronation-supination

The mean delta angle ($\Delta°_{\text{pronation-supination)}}$ was greater at the end of the trial than the start of the trial for both groups (Main effect - Epoch: P = 0.004). No other differences in this measure were observed between groups (Interaction - Group × Epoch: P = 0.718; Main effect - Group: P = 0.337) (Figure 6-2).

Correlation between pain intensity, wrist flexion-extension positon, and $VAR_{elements}$

In LE participants, lower pain intensity at the start of the trial was related to a more flexed wrist position (r = 0.57; P = 0.02) and greater SD in the flexion-extension direction (r = 0.62; P = 0.01). A greater change of wrist position into flexion between the start and end of the trial was correlated with a greater change in SD in the flexion-extension direction (r = 0.53; P = 0.03). Correlations are shown in Figure 6-3.

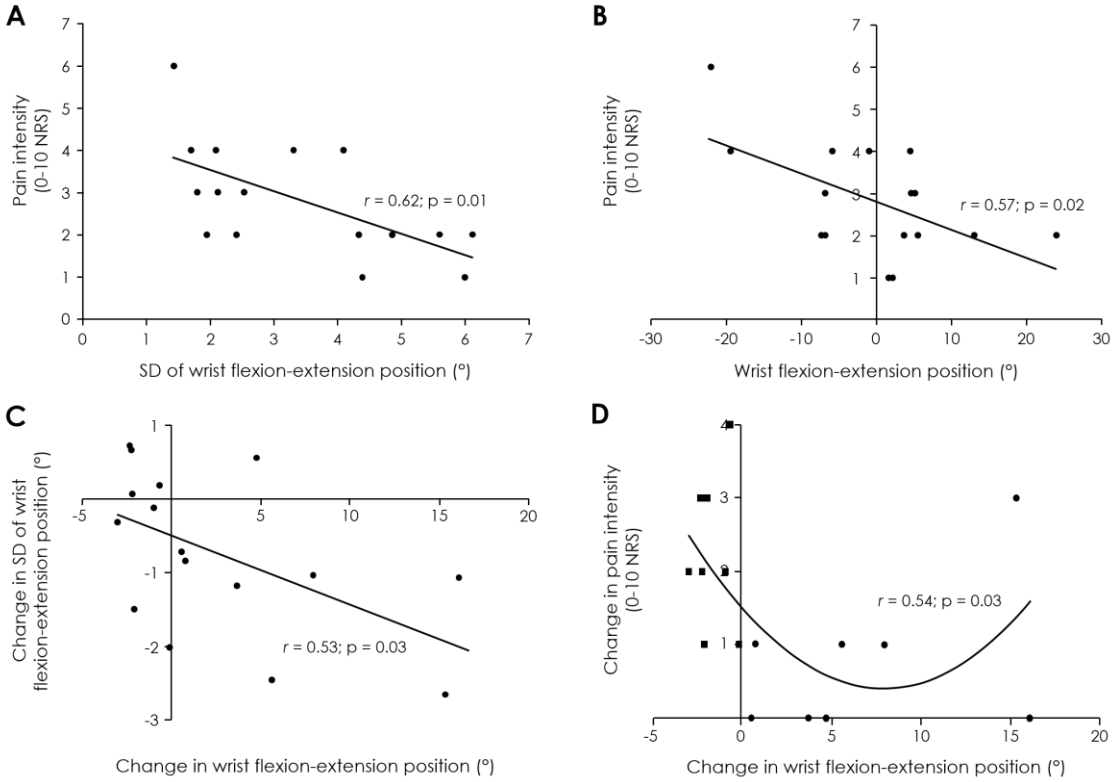

Figure 6-3. Correlations between pain intensity and movement strategy. Plots of pain rating (11-point numerical rating scale; 0-10) at the start (repetitions 1-20) of the trial versus standard deviation (SD) of wrist flexion-extension at the start of the trial (A) and wrist flexion-extension position at the start of the trial (B), change in SD of wrist flexion-extension versus change in wrist flexion-extension (C), and change in pain intensity versus change in wrist flexion-extension position (D) when participants with chronic LE performed the task. Linear functions (A-C) and a quadratic function (D) were fitted to the data. Pearson correlation coefficients (r) and two-tailed probability values (P) are shown (A-D).

6.5 Discussion

Variability of the elements ($VAR_{elements}$) in the performance of motor tasks is thought to be important for musculoskeletal health. In this study $VAR_{elements}$ of wrist/forearm angles were measured in participants with chronic LE and healthy controls during a wrist radial-ulnar deviation task. The task provoked moderate pain in participants with chronic LE. There was no difference between LE and controls in attainment of the task goals, but both groups attained the goals less often at the end than the start of the trial. Our results show there were no differences in wrist/forearm position or the magnitude of $VAR_{elements}$ between the LE group and Controls. However $SD°_{flexion\text{-}extension}$ was decreased by the end of the trial compared to the start in people with LE. Further exploration of the data revealed that participants in the LE group who moved their wrist into a more flexed position and reduced $SD°_{flexion\text{-}extension}$ had the largest reduction in pain intensity. These data suggest participants with chronic LE moved into a more flexed wrist position to minimise pain, then reduced $VAR_{elements}$ around this new wrist position so the less painful strategy was used for subsequent repetitions of the task.

Was attainment of the task goal different in chronic LE?

Successful attainment of the task goals (i.e. termination of radial deviation movement within the target region, and matching the target grip force) was not different between LE and controls. These data concur with the observation that attainment of the radial deviation target region for a similar radial-ulnar deviation movement (i.e. performed with the elbow in 90°, rather than extension) was not affected by acute experimental elbow pain induced by injection of hypertonic saline (*Study 1*). Contrary to these results, we have also shown that the radial deviation target region was attained less often when pain was induced with cutaneous electrical stimulation at the elbow (*Study 2*). One interpretation of the difference observed between studies in this thesis is that phasic pain (i.e. electrical stimulation), but not tonic pain experienced during movement (i.e. hypertonic saline, chronic LE), affects attainment of the radial deviation target angle region, possibly due to differences in distraction from the task goal by the differences in pain modalities, or by the clearer link between movement and pain in the phasic pain condition.

Participants in both groups attained the task goals less often at the end of the trial than the start. The most likely explanation for this reduction is that participants were required to maintain a target grip force, which may have diverted attention from the primary goal of terminating radial movement within the target region. An alternative explanation is that participants' motivation to perform the task accurately might have decreased from the start to the end of the trial. It is also

possible the reduction in goal attainment was related to fatigue, but this is unlikely given participants reported *no fatigue* after completion of the task. These data, combined with previous studies, suggest attainment of the goal is affected when pain is phasic (cutaneous electrical stimulation (*Study 2*)) but not tonic (i.e. chronic LE; hypertonic saline injection (*Study 1*)), and might be influenced by the participant's motivation and attention to the task.

Was $VAR_{elements}$ different between participants with chronic LE and Controls?

The effect of chronic pain/pathology on $VAR_{elements}$ has been evaluated during multi-joint tasks such as walking and reaching, and results have been contrasting (e.g. decreased (Hamill et al. 1999) vs. increased (Cunningham et al. 2014)). One factor that might influence $VAR_{elements}$ during chronic pain is the number of elements involved in a task (e.g. many elements in complex tasks vs. few elements in simple tasks) and the potential for those elements to be varied depending on the underlying biomechanical constraints. We studied a simple motor task that has few degrees of freedom and thus limited capacity for $VAR_{elements}$ to change. $VAR_{elements}$ was considered in directions other than the primary radial-ulnar motion (i.e. flexion-extension and pronation-supination).

$VAR_{elements}$ was not different between LE and Controls in the flexion-extension or pronation-supination directions at the start or end of the trial. One interpretation is that the wrist flexion-extension and forearm pronation-supination elements of the radial-ulnar deviation task are tightly constrained by the nervous system and thus not able to change in the LE group. However, contrary to this interpretation, $SD°_{flexion\text{-}extension}$ decreased between the start and end of the trial in the LE group but not Controls. The presence of ongoing pain in the LE group may motivate the nervous system to change movement strategy over time.

Was there a relationship between movement strategy and pain intensity?

We investigated whether there was a relationship between pain intensity experienced by participants with chronic LE and the different movement strategies used during the task. Participants who performed the radial-ulnar deviation task with greater $VAR_{elements}$ at the start of the trial experienced less pain. It has been proposed that $VAR_{elements}$ facilitates the distribution of stresses more broadly to reduce cumulative loading on specific tissues (Srinivasan and Mathiassen, 2012). In participants with chronic LE, greater $VAR_{elements}$ during the radial-ulnar task might be beneficial to reduce the cumulative loading on the painful/damaged regions of the common extensor tendon, with the potential for reduced pain. Alternatively, greater VAR might reflect a greater

potential to explore different options and alter movement strategy with repeated performance of the task (Moseley and Hodges, 2006).

Participants who performed the task in a more flexed wrist position at the start of the trial experienced less pain. The most likely explanation is that this strategy may have served to reduce activation of the ECRB muscle during the movement task (Alizadehkhaiyat et al. 2007; Rojas et al. 2007) to decrease painful loading of the common extensor tendon. Reduced activation of ECRB affects the coordinated activation of the forearm muscles, which is required to maintain the optimal, slightly extended wrist position during gripping (Shimose et al. 2011; Snijders et al. 1987). Less pain in a more flexed wrist position observed in the current study might explain the finding that participants with chronic LE adopted a more flexed wrist posture than healthy controls during a pain-free grip task (Bisset et al. 2006).

Interestingly, participants who moved into a more flexed position between the start and end of the trial also had the largest reduction of $VAR_{elements}$ and a lesser or no increase in pain during the task. This provides evidence that participants moved into a more flexed wrist position to minimise pain, then subsequently reduced $VAR_{elements}$ around this new wrist position to retain the less painful strategy for subsequent repetitions of the task (Moseley and Hodges, 2006). These data concur with previous studies where $VAR_{elements}$ was reduced (*Study 1*) and wrist/forearm position changed (*Study 2*) when a simple radial-ulnar task was performed during acute experimental pain. Although these correlations yielded significant relationships, they are based on a small sample size. Further studies with larger sample sizes are required to confirm the findings of this study.

6.6 Conclusion

Participants with chronic LE moved the wrist into a more flexed wrist position and reduced $VAR_{elements}$ to allow performance of the radial-ulnar deviation task in a less painful manner. This concurs with earlier studies that found when the nervous system was challenged by acute experimental pain wrist/forearm position was altered and $VAR_{elements}$ reduced during the simple task. The next step that is required is development of a model of sustained elbow pain to investigate the time-course of $VAR_{elements}$ from before the onset of pain and several days thereafter, which could provide insight into the possible relationship between $VAR_{elements}$ in acute and chronic pain.

7 Movement evoked pain and mechanical hyperalgesia after intramuscular injection of nerve growth factor: A model of sustained elbow pain

7.1 Abstract

Purpose: Lateral epicondylalgia (LE) presents as lateral elbow pain provoked by upper limb tasks. An experimental model of elbow pain provoked by movement/muscle contraction and maintained over several days is required to better understand the mechanisms underlying sustained elbow pain. This study investigated the time course and pain location induced by nerve growth factor (NGF) injection into a wrist extensor muscle, and whether movement and muscle contraction/stretch provoked pain.

Methods: On Day 0 twenty-six painfree volunteers were injected with NGF (N=13) or isotonic saline (randomized) into the extensor carpi radialis brevis (ECRB) muscle of the dominant arm. On Day 2 pain was induced in all participants by hypertonic saline injection into ECRB. A Likert scale and patient-rated tennis elbow evaluation (PRTEE) was used to assess pain and functional limitation (Days 0-10). Pain intensity during contraction and stretch of ECRB, and pressure pain thresholds were recorded before and after injections on Days 0 and 2, and Days 4 and 10.

Results: Compared with isotonic saline, NGF evoked: i) greater Likert pain ratings from 12 hours post-injection until Day 6, ii) greater PRTEE scores on Days 2 and 4, iii) greater pain during ECRB contraction/ stretch on Day 2, and iv) lower pressure pain thresholds on Day 4.

Conclusions: Intramuscular NGF injection induced elbow muscle hyperalgesia and pain that was provoked by movement and muscle contraction/stretch for several days. This study presents a novel experimental human pain model suitable to study the sustained effects of lateral elbow pain on sensorimotor function and to probe the mechanisms underlying persistent musculoskeletal pain.

7.2 Introduction

Patients with lateral epicondylalgia (LE) present with lateral elbow pain provoked by gripping and other manual tasks. Chronic LE involves sensorimotor changes, including bilateral mechanical hyperalgesia and reduced pain free grip strength (Coombes et al. 2012a), and strength deficits of wrist, elbow, and shoulder muscles (Alizadehkhaiyat et al. 2007; Coombes et al. 2012b). Whether the sensorimotor deficits found in chronic LE are a cause or effect of sustained pain and hyperalgesia remains unclear.

Experimental models of pain have been used to investigate mechanisms that underlie sensorimotor changes during acute muscle pain, such as delayed muscle activation (Hodges et al. 2003). Although these studies provide insight, interpretation is limited by the transience of the induced pain. This could explain inconsistencies between the effects of acute experimental pain and impairments of musculoskeletal pain conditions; e.g. pain provocation by muscle contraction/stretch (Tsao et al. 2010), deep-tissue hyperalgesia (Slater et al. 2003). Models of sustained pain and hyperalgesia that mimic typical behaviour of musculoskeletal pain conditions are needed to study the specific involvement of pain and nociceptive stimulation in the transition from acute to sustained musculoskeletal pain (Graven-Nielsen and Arendt-Nielsen, 2010). It is important to note that pain models cannot capture other factors that are likely involved in this transition to sustained pain, such as the affective and cognitive dimensions of pain (e.g. anxiety and depression, fear of movement and re-injury).

The combined effect of delayed onset muscle soreness (DOMS) induced by eccentric exercise of the wrist extensor muscles and intramuscular injection of hypertonic saline has been used to study sustained elbow pain. That method induced mechanical hyperalgesia for two days, and reduced grip and wrist extension force at 24 hours following exercise (Slater et al. 2005). However, damage to contractile elements by eccentric exercise (Paulsen et al. 2012) can directly influence function, which precludes investigation of the independent effects of pain/nociceptive stimulation. An alternative is nerve growth factor (NGF), an endogenous neuromodulator vital for nerve development and reconstruction (Lewin and Mendell, 1993). Intramuscular injection of NGF induces mechanical hyperalgesia for up to 14 days and mild pain during muscle contraction that lasts up to 3 days after injection into the tibialis anterior (Andersen et al. 2008; Hayashi et al. 2013), masseter (Svensson et al. 2008) and supraspinatus muscles (Gerber et al. 2011). NGF injection provides a viable method to study sustained hyperalgesia, but the pain response to muscle contraction remains unclear. A recent study found electrically-stimulated muscle contraction evoked pain that was no worse whether the muscle fascia was injected with NGF or isotonic saline (Deising et al. 2012). However, that study does not preclude provocation of NGF-induced muscle

pain by muscle contraction, as electrical stimulation was limited to twitches, which do not replicate function, and hyperalgesia of fascia might not respond similarly to muscle hyperlagesia during contraction. Investigation of pain and hyperalgesia after NGF injection into elbow muscle and the relationship to muscle contraction and function is required to determine whether NGF injection could be a suitable model to study a potential cause-effect relationship between pain and sensorimotor changes in sustained elbow pain. Intramuscular injection of NGF into elbow muscle would be a useful model of sustained elbow pain if the induced pain lasted for up to a week and was provoked in a consistent manner by contraction and stretch of the upper limb muscles and by functional activities of the upper limb.

This study investigated, in healthy subjects: 1) the time course of pain and hyperalgesia induced by injection of NGF into a wrist extensor muscle, and 2) whether movement and muscle contraction provoke pain in the NGF-induced hyperalgesic muscle.

7.3 Methods

7.3.1 Participants

Twenty-six healthy volunteers (age 25.8 ± 5.4 years (mean ± SD); 7 females) participated in this study. Participants were excluded if they had a recent history of pain that affected the upper limb and/or neck, a history of neurological, musculoskeletal or mental illness, were currently using analgesics and/or anti-inflammatory medications, or if they were participating in more than two sessions of muscle training exercises per week that involved the upper limbs. All participants were given a written and verbal explanation of the study and written informed consent was obtained prior to inclusion. The study was approved by the local ethics committee (N-201200640) and conformed to the Declaration of Helsinki. Data collection was conducted at Aalborg University, Denmark.

7.3.2 Study design

A randomized, double blind, placebo-controlled study design was used to study the nature and time course of pain induced by NGF injection. Participants attended four experimental sessions over 11 days (Figure 7-1). On Day 0, participants were randomized into one of two groups: NGF group (n = 13; 5 females) or control group (n = 13; 2 females). Participants were blinded to group allocation for the duration of the study. On Day 0 participants received an injection of NGF (NGF group) or isotonic saline (control group) into the extensor carpi radialis brevis (ECRB) muscle of the dominant upper limb. On Day 2 hypertonic saline-induced pain was evoked in the ECRB muscle of the dominant limb in all participants to investigate whether NGF injection sensitized the

muscle to chemical irritation. The behaviour of pain induced by NGF to a range of stimuli was studied to identify whether it reacted in a manner consistent with clinical pain. To address this issue, assessments of the muscle pain and functional limitation, movement-evoked pain, response to muscle contraction and stretch, and pressure pain sensitivity were performed before and after injections on Days 0 (NGF/ISO) and Day 2 (hypertonic saline), and on Days 4 and 10. Participants completed a daily diary of their elbow pain from Day 0 to Day 10.

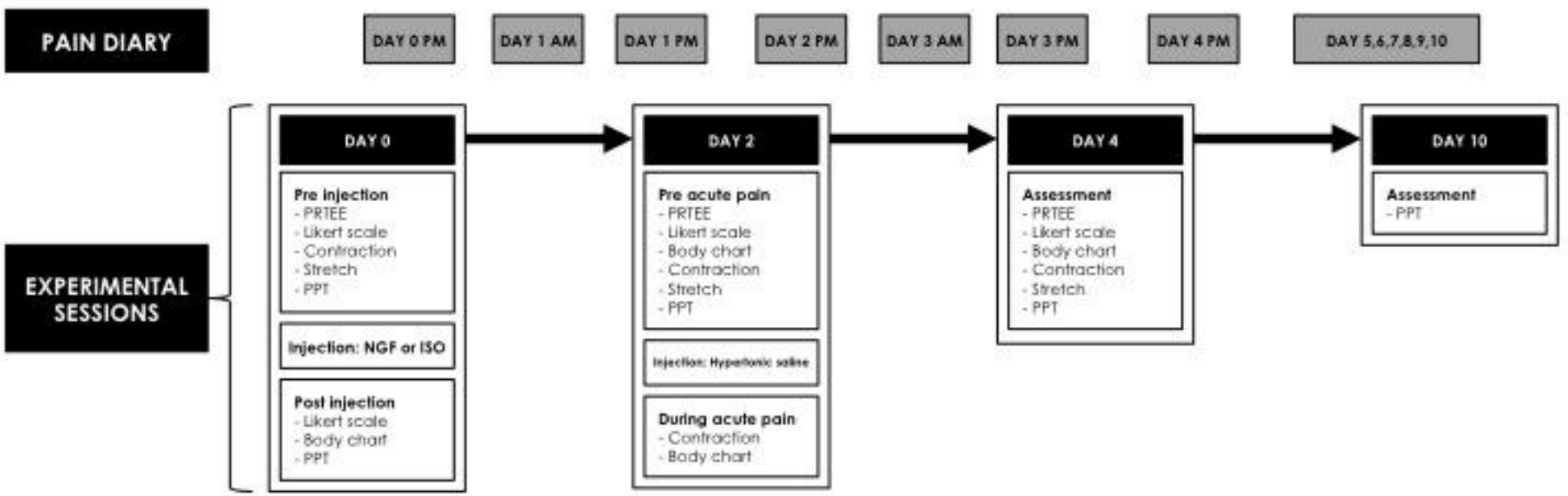

Figure 7-1. Timeline of experiment. Participants attended four experimental sessions (Days 0, 2, 4, and 10), and completed a daily diary of their elbow pain (Day 0 to Day 10) at approximately midday and in the evening of Days 0-4 and only in the evening on Days 5-10.

AM – morning; PM – evening; PRTEE – patient rated tennis elbow evaluation; PPT – pressure pain threshold; NGF – nerve growth factor; ISO – isotonic saline.

7.3.3 NGF-induced pain and hyperalgesia

A single bolus of NGF (5 μg, 0.2 ml; recombinant human NGF, prepared by the pharmacy at Aalborg University Hospital), or isotonic saline (0.2 ml 0.9%) was injected into the ECRB muscle of the dominant upper limb on Day 0. The injection site was 1 cm lateral to a point 5 cm distal to the lateral epicondyle along a line from the lateral epicondyle to the midline of the wrist. Palpation during contraction (radial deviation and extension of the wrist) and ultrasound imaging of the anatomical boundaries of the muscle confirmed that this site related to ECRB. Separate examiners prepared and administered the injection, and performed the assessments to ensure blinding of the assessor and participant.

7.3.4 Questionnaires on pain intensity and functional limitation

A modified 7-point Likert scale that relates the pain intensity to specific activities (Slater et al. 2005; Andersen et al. 2008) was used to assess muscle pain intensity at the beginning of each session: 0 = 'a complete absence of pain/soreness'; 1 = 'a light pain/soreness in the muscle felt only when touched/a vague ache'; 2 = 'a moderate pain/soreness felt only when touched/a slight persistent ache'; 3 = 'a light muscle pain/soreness when lifting objects or carrying objects'; 4 = 'a light muscle pain/soreness, stiffness or weakness when moving the wrist or elbow without gripping an object'; 5 = 'a moderate muscle pain/soreness, stiffness or weakness when moving the wrist or elbow'; 6 = 'a severe muscle pain/soreness, stiffness or weakness that limits my ability to move'. The patient-rated tennis elbow evaluation (PRTEE) was used to measure pain and functional limitation (Rompe et al. 2007) at the beginning of each session. It has excellent test-retest reliability (r=0.93) and good correlation with other functional scales such as the Disability of Arm and Shoulder (DASH) questionnaire (r=0.87) in the tennis elbow population (Rompe et al. 2007). The task-related questions are scored on an 11-point Likert scale, with calculation of separate subscales for pain and function (Function A: activities specific to the upper limb; Function B: general activities), and a total score ranging from 0 (no pain and no functional limitation) to 100 (worst imaginable pain with a very significant functional limitation).

7.3.5 Location of NGF-induced pain

Participants drew the distribution of their pain induced by the injection of NGF or isotonic saline on an anatomical drawing of the upper limb at the beginning of each session. These drawings were digitized (Matlab 7.14) and the size of the painful area represented as a percentage of the total surface area of the anterior and posterior surfaces of the upper limb as represented by the drawing.

7.3.6 Pain diary

Participants completed a pain diary at approximately midday and in the evening on Days 0-4 and only in the evening on Days 5-10. The diary consisted of the 7-point modified Likert scale, an anatomical drawing of the upper limb upon which the pain area was drawn, and four questions where participants rated their pain on an 11-point numerical rating scale (NRS): i) when the arm was at rest; ii) when doing a task with repeated arm movements; iii) when pain was at its least; and iv) when pain was at its worst.

7.3.7 Contraction- and stretch-evoked pain

The influence of contraction and stretch of the ECRB muscle on pain intensity was examined for both upper limbs. Participants performed the muscle contraction tasks (i.e. wrist extension and gripping; order randomized) with the upper limb supported on a platform in 90° shoulder flexion, elbow extension and forearm pronation. Participants were instructed to maintain this upper limb position during each contraction. A force sensor (MC3A 250, AMTI, USA) was mounted above the hand being tested to record the force exerted during the wrist extension contractions. Gripping force was measured with a custom-made grip dynamometer (grip width = 64 mm), consisting of a strain gauge (CCT Transducers, Italy) interposed between two padded bars. Three maximal voluntary contractions (MVC) with strong verbal encouragement were performed for each task. Force was gradually increased to a maximum within each 5 s trial. Each trial was separated by 1 min to limit possible effects of fatigue. Immediately after each contraction the participants indicated whether pain intensity increased, decreased or was unchanged during the contraction, and verbally rated the pain intensity on an 11-point NRS anchored with ‘no pain’ at 0 and ‘maximum pain imaginable’ at 10. The maximum force achieved during the three MVC trials was used for the submaximal trials. Three submaximal contractions were performed before and after the injections. The MVC recorded on Day 0 (i.e. before NGF/ISO injection) was used to calculate the 10% MVC force target required for submaximal trials performed on Days 0, 2 and 4. A target force of 10% MVC was chosen as it was comparable to the amount of force required for many everyday tasks, and pilot tests (n=3) indicated that it allowed participants to perform three submaximal contractions without onset of forearm muscle fatigue. In the submaximal tasks participants gradually increased force from zero to the 10% MVC target (displayed on a computer screen) over 5 s, maintained the target force for 10 s, and then reduced force to zero over 5 s. Participants were instructed to match the 10% MVC target as closely as possible. Participants rested for 30 s between submaximal contractions. Immediately after each contraction the participants

indicated whether there was an increase, decrease or no change in pain intensity during the contraction, and verbally rated the pain intensity on the 11-point NRS.

For the stretching task, the upper limb was supported on a platform in 90° shoulder flexion, elbow extension, and the forearm in neutral rotation. The wrist was passively moved into flexion or ulnar deviation in separate trials (order randomized), held for 5 s, and then returned to the starting position (Palmer and Epler, 1998). One trial of each stretch (i.e. flexion, ulnar deviation) was performed at each experimental session. Immediately after each stretch, participants indicated whether there was an increase, decrease or no change in pain during the stretch, and verbally rated the pain intensity on the 11-point NRS.

7.3.8 Pressure pain sensitivity

Pressure pain thresholds (PPT) were measured bilaterally with an electronic algometer (Algometer Type II, Somedic AB, Sollentuna, Sweden) applied to the ECRB muscle (injection site), low back (3 cm lateral to the spinous process of the 4th lumbar vertebra), and over the tibialis anterior muscle belly. Pressure applied via the algometer probe (1 cm^2) was increased at a rate of 30 kPa/s, and the participant was instructed to press a button when the pressure sensation changed to one of pain, at which point the application of pressure ceased. Three measurements were recorded at each site and the mean value used for analysis. The PPT data were expressed as a percentage of the PPT measures recorded at the baseline session (Day 0 pre-injection).

7.3.9 Saline-induced muscle pain and related measures

A single bolus of hypertonic saline (0.5 ml, 5.8%) was injected into the muscle belly of ECRB (same location as NGF/ISO injection) on Day 2. The pain intensity was recorded continuously on a 10-cm electronic visual analogue scale (VAS; sampling frequency of 1 Hz), where 0 cm indicated ‘no pain’ and 10 cm ‘maximum pain imaginable’. Participants performed gripping and wrist extension tasks (see above) immediately after the injection. Participants were instructed to begin rating the saline-induced pain intensity immediately after the injection and to update their pain rating after each repetition of the gripping and wrist extension tasks until the pain ceased. The maximum VAS scores reported by each participant during each task (i.e. gripping and wrist extension) were used for further analysis. After the saline-induced pain had ceased, participants drew their pain distribution on the standardized drawing of the upper limb.

7.3.10 Statistical analysis

Statistical analysis was performed using Statistica 9 (Statsoft, Tulsa, OK, USA). According to a Kolmogorov-Smirnov test for normality the majority of PPT data, pain area data, and VAS scores during saline-induced pain were normally distributed. The contraction- and stretch-evoked pain and questionnaire data (e.g. Likert scale, PRTEE, pain at rest, worst pain) were not normally distributed and were therefore analyzed with non-parametric tests. Data are reported as mean and 95% confidence intervals or median and interquartile range when appropriate. Significance was set at $P < 0.05$ for all analyses.

Comparison of the effects of injection of NGF and ISO: To determine whether NGF injection induced muscle hyperalgesia, PPTs were compared between *sessions* (Day 0 post-injection vs. Day 2 pre-injection vs. Day 4 vs. Day 10), and between *groups* (NGF vs. ISO) with a mixed-model repeated measure analysis of variance (RM-ANOVA). To determine the time course of area of pain, these data were compared between *sessions* (Day 0 post-injection and 15 subsequent assessments) and a between-subject factor of *group* (NGF vs. ISO) with a mixed-model RM-ANOVA. A Bonferroni post-hoc test was used for the PPT and area of pain data. To determine whether pain induced by NGF was provoked by muscle contraction and stretch, the non-normally distributed NRS data during these tasks were analyzed in several ways. First, a Kruskal-Wallis test on ranks was used to test for differences between *groups/side* (Group: NGF, ISO; Side: ipsilateral, contralateral) at each *session*. This was followed by a Mann Whitney U test to probe the specific differences when significant. Second, a Friedman test was used to test for differences between *sessions* within each *group* (NGF, ISO) and *side* (ipsilateral, contralateral). This was followed by a Wilcoxon matched pairs test when significant to investigate differences between individual *sessions.* Bonferroni corrections were used to adjust p-values for multiple comparisons.

Effects of hypertonic saline: To determine whether NGF injection sensitized the muscle to chemical irritation PPTs were compared between *sides* (Ipsilateral vs. contralateral), *sessions* (Day 2 pre-injection vs. Day 2 post-injection) and a between-subject factor of *group* (NGF vs. ISO) with a mixed-model RM-ANOVA. The VAS scores during saline-induced pain were analyzed with a two-way RM-ANOVA with a between-subject factor of *group* (NGF vs. ISO), and the *task-sequence* (the task that was performed first: gripping vs. extension). A Bonferroni post-hoc test was used for the PPT and VAS scores data. An independent t-test (two tails) was used to compare the pain area data.

7.4 Results

Self-reported NGF-induced pain intensity

The 7-point Likert scale scores were higher in the NGF group than the ISO group from the evening of Day 0 until Day 6 ($P < 0.003$, Figure 7-2A). For the NGF group, peak pain was experienced on the morning of Day 2 ($P = 0.001$) and then gradually returned to zero by Day 10 ($P = 0.068$). No participants in either group reported elbow pain at rest ($P = 1.00$). When participants reported the worst pain they experienced in the preceding 12 hours (Days 0-4) or 24 hours (Days 5-10), the NRS scores were greater in the NGF group than the ISO group from the evening of Day 0 until Day 5 ($P < 0.003$, Figure 7-2B). Those in the NGF group reported greater pain with repeated arm movements than the ISO group, reflected by higher NRS scores recorded in the pain diary, between Day 0 and Day 4 ($P < 0.003$, Figure 7-2C).

The total PRTEE and component scores (Pain, upper limb activities, general activities) for participants injected with NGF were greater than those in the ISO group when measured on both Day 2 ($P < 0.001$) and Day 4 ($P < 0.001$, Figure 7-3).

Participants injected with NGF reported a larger area of pain than those injected with isotonic saline (RM-ANOVA interaction: group × session: $F_{15} = 6.29$, $P < 0.001$) from the evening of Day 0 until the evening of Day 4 (post-hoc: $P < 0.05$, Table 7-1, Figure 7-4).

Contraction-evoked pain after NGF vs. ISO

On Day 2 (before the hypertonic saline injection) participants reported greater pain provocation during maximal wrist extension contraction (i.e. higher NRS scores) for the limb injected with NGF than the limb injected in the ISO group and the contralateral limbs in either group (NGF, ISO) ($P < 0.017$, Figure 7-5). There were no differences in pain intensity evoked by contraction at 10% MVC ($P > 0.15$). No participants reported pain (NRS = 0) following muscle contraction of the contralateral limb (i.e. non-injected limb).

Stretch-evoked pain after NGF vs. ISO

When the ECRB muscle was stretched by passively moving the wrist into flexion there was greater provocation of pain (i.e. higher NRS scores) for the injected limb of the NGF group than the injected side of the ISO group, and the contralateral limb in either group (NGF, ISO) on Day 2 ($P < 0.001$, Figure 7-5). Stretch into ulnar deviation had negligible effect on pain (Figure 7-5). The stretch of the ECRB muscle in the limb contralateral to the injection did not produce pain for participants in either group (NRS = 0).

Pressure pain sensitivity after NGF vs. ISO

The RM-ANOVA of the PPTs recorded at the ipsilateral elbow showed an interaction between group and session ($F_3 = 3.19$, $P = 0.029$; Figure 7-6A). PPTs were lower in the NGF group at Day 2 than Day 0 post-injection (post-hoc: $P = 0.005$) and Day 10 (post-hoc: $P < 0.001$), and lower on Day 4 than Day 0 post-injection (post-hoc: $P = 0.027$) and Day 10 (post-hoc: $P < 0.001$). There were no such differences between sessions for the ISO group. PPT was lower for the NGF group than the ISO group on Day 4 (post-hoc: $P = 0.03$) but not at any other session (post-hoc: $P > 0.05$). For the contralateral elbow there was a main effect of session ($F_3 = 12.36$, $P < 0.001$). PPT on Day 10 was greater (regardless of group) than all other sessions (post-hoc: $P < 0.05$). As expected, PPT was not significantly affected at the low back (Figure 7-6B) or tibialis anterior (Figure 7-6C).

Effect of hypertonic saline on induced pain behaviour

There was no difference between groups (NGF: 6.6 ± 2.9 arbitrary units; ISO: 5.1 ± 3.3) with respect to the area of pain following the hypertonic saline injection (Figure 7-4). During pain induced by hypertonic saline, the peak VAS scores recorded when participants performed the submaximal contraction tasks (i.e. gripping and wrist extension) were greater for participants in the NGF group (7.3 ± 0.8 cm) than the ISO group (6.2 ± 0.6 cm; RM-ANOVA main group effect: $F_1 = 5.01$, $P = 0.036$). Hypertonic saline injection at the elbow did not change the PPTs for either group at the elbow, low back or tibialis anterior muscle (Table 7-2).

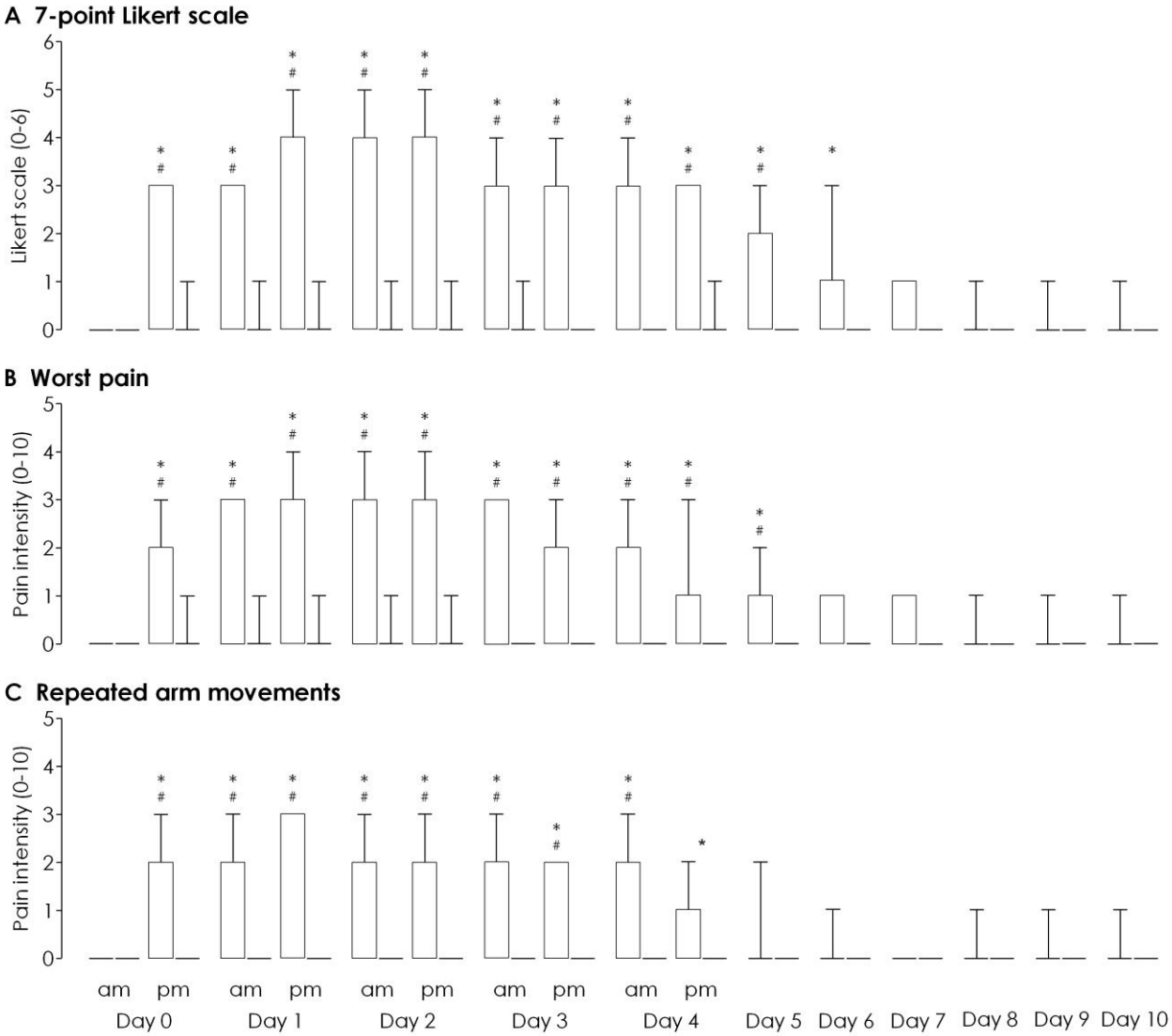

Figure 7-2. Group data for the 10-day pain diary. Median scores (75th percentile) from the 10 day pain diary for the NGF (nerve growth factor, open bars) and ISO (isotonic saline; median score was always 0, data for the 75th percentile is shown on the right side of the NGF data for each time point) groups including (**A**) the 7-point Likert scale (0 = 'a complete absence of pain/soreness'; 6 = 'a severe muscle pain/soreness, stiffness or weakness that limits my ability to move'), (**B**) the numerical rating scale of worst pain intensity (0-10), and (**C**) the numerical rating scale of the pain experienced with repeated arm movements (0-10).

* – Significant increase compared with the ISO group, Mann Whitney and Bonferroni: $P < 0.003$.

– Significant increase compared with Day 0 am, Wilcoxon and Bonferroni: $P < 0.003$.

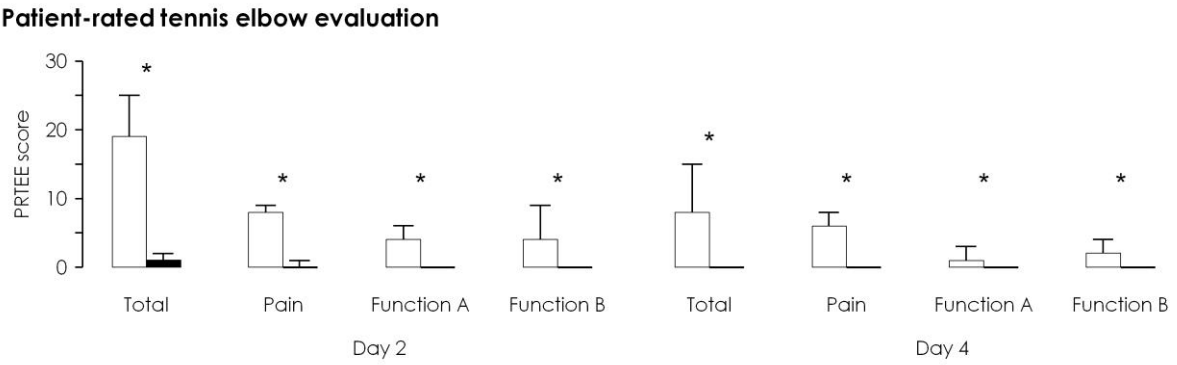

Figure 7-3. Group data for the patient rated tennis elbow evaluation (PRTEE). Median (75th percentile) total score for the PRTEE questionnaire for the NGF (nerve growth factor, open bars) and ISO (isotonic saline, solid bars) groups at Day 2 and 4. The total score is further represented by the three subscales Pain, Function A (activities specific to the upper limb), and Function B (general activities).

* – Significant increase compared with the ISO group, Mann Whitney and Bonferroni: $P < 0.017$.

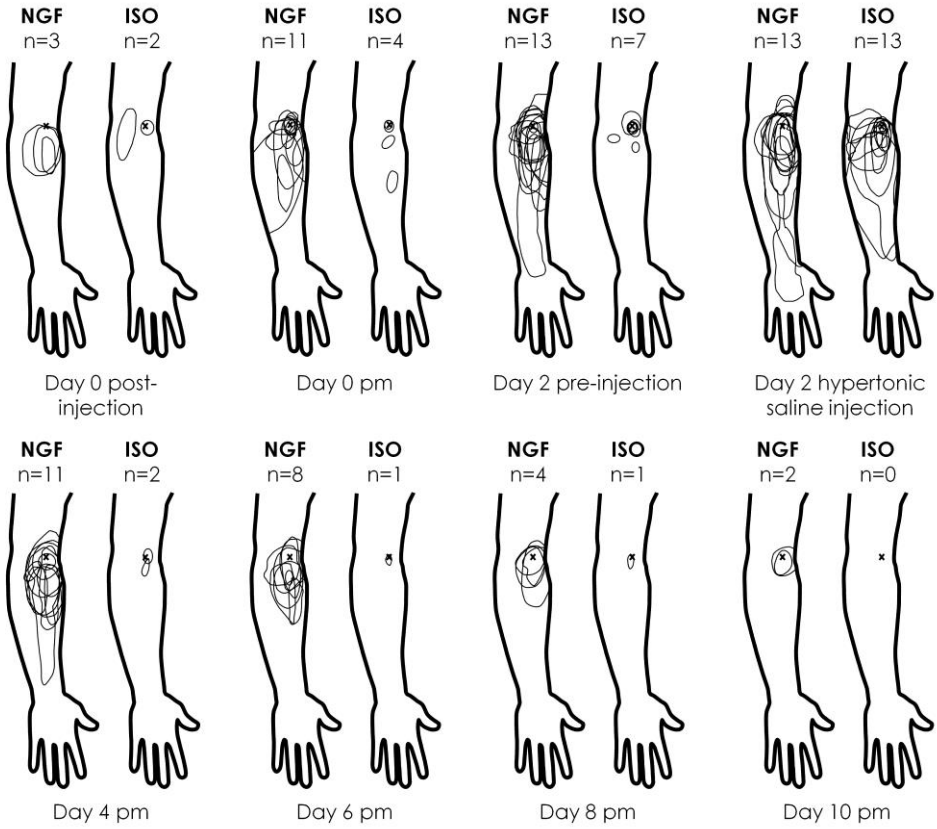

Figure 7-4. Pain chart drawings. Pain drawings of painful areas immediately after the NGF/ISO (nerve growth factor/isotonic saline) injection (Day 0 post-injection), the evening of Day 0 (Day 0 pm), before the hypertonic saline injection on Day 2 (Day 2 pre-injection), pain evoked by hypertonic saline injection (Day 2 hypertonic saline injection), and the evenings of Day 4, 6, 8 and

10. The number of participants in each group who reported pain is indicated for each time-point. The crosses indicate the injection site.

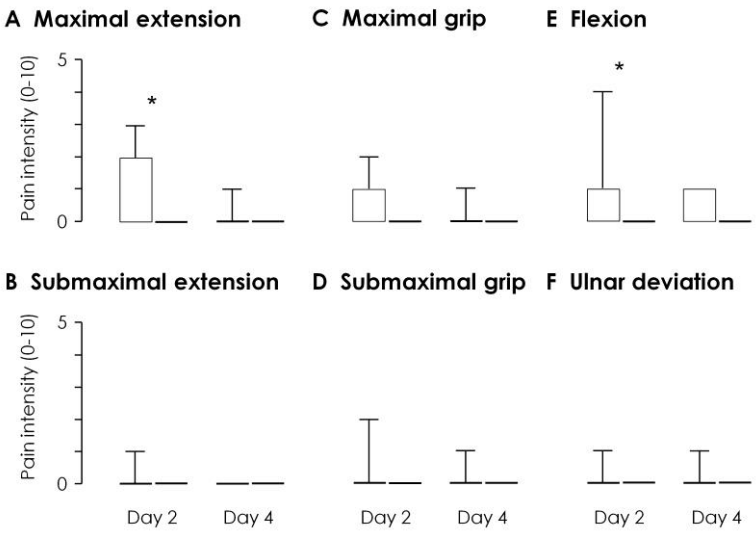

Figure 7-5. Group data for pain intensity scores during muscle contraction and stretch. Median (75^{th} percentiles) pain intensity scores on a numerical pain scale (0-10) in the NGF (nerve growth factor, open bars) and ISO (isotonic saline, solid bars) groups at Day 2 and 4 during maximal (**A**) and submaximal wrist extension (**B**), maximal (**C**) and submaximal gripping (**D**), and when ECRB was stretched by passively moving the wrist into maximal flexion (**E**), and ulnar deviation (**F**).
* – Significant increase compared with the ISO group, Mann Whitney and Bonferroni: $P < 0.017$.

Table 7-1: Size of the painful area

	Day 0		Day 1		Day 2		Day 3		Day 4		Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
	am	Pm	am	pm	am	pm	am	pm	am	pm						
NGF	0.0 (0.0)	3.4* (2.9)	4.6*,# (1.8)	5.0*,# (1.1)	5.5*,# (1.8)	5.3*,# (1.4)	4.9*,# (1.5)	4.5*,# (1.6)	3.6*,# (1.4)	4.2*,# (1.8)	2.7 (1.2)	2.2 (1.1)	1.8 (1.1)	1.2 (1.1)	0.6 (0.6)	0.3 (0.4)
ISO	0.0 (0.0)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.3 (0.2)	0.4 (0.3)	0.1 (0.1)	0.1 (0.2)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)

NGF – nerve growth factor group; ISO – isotonic saline group; Mean (95% confidence interval); * – Significantly enlarged compared with the ISO group, Bonferroni: $P < 0.05$; # – Significantly enlarged compared with Day 0 am, Bonferroni: $P < 0.05$

Table 7-2: Pressure pain thresholds for the elbow, low back and tibialis anterior

	Elbow		Low back		Tibialis anterior	
	Day 2 pre	Day 2 post	Day 2 pre	Day 2 post	Day 2 pre	Day 2 post
NGF-dominant	62.6 (13.3)	64.6 (16.6)	85.0 (9.7)	89.4 (14.4)	90.8 (10.7)	88.1 (12.3)
NGF-contralateral	92.2 (5.8)	93.1 (9.1)	93.4 (13.1)	100.1 (13.9)	89.4 (9.9)	91.8 (11.8)
ISO-dominant	85.5 (12.8)	78.3 (13.4)	97.2 (14.2)	95.9 (8.4)	99.0 (12.3)	99.1 (11.7)
ISO-contralateral	104.0 (12.7)	101.6 (12.3)	98.3 (17.9)	103.8 (22.1)	99.5 (11.5)	106.3 (8.6)

NGF – nerve growth factor group; ISO – isotonic saline group; Mean (95% confidence interval) pressure pain thresholds normalized to values recorded pre-injection on Day 0 (i.e. 0–100 %); Pre – Pre hypertonic saline injection at Day 2 ; Post – Post hypertonic saline injection at Day 2

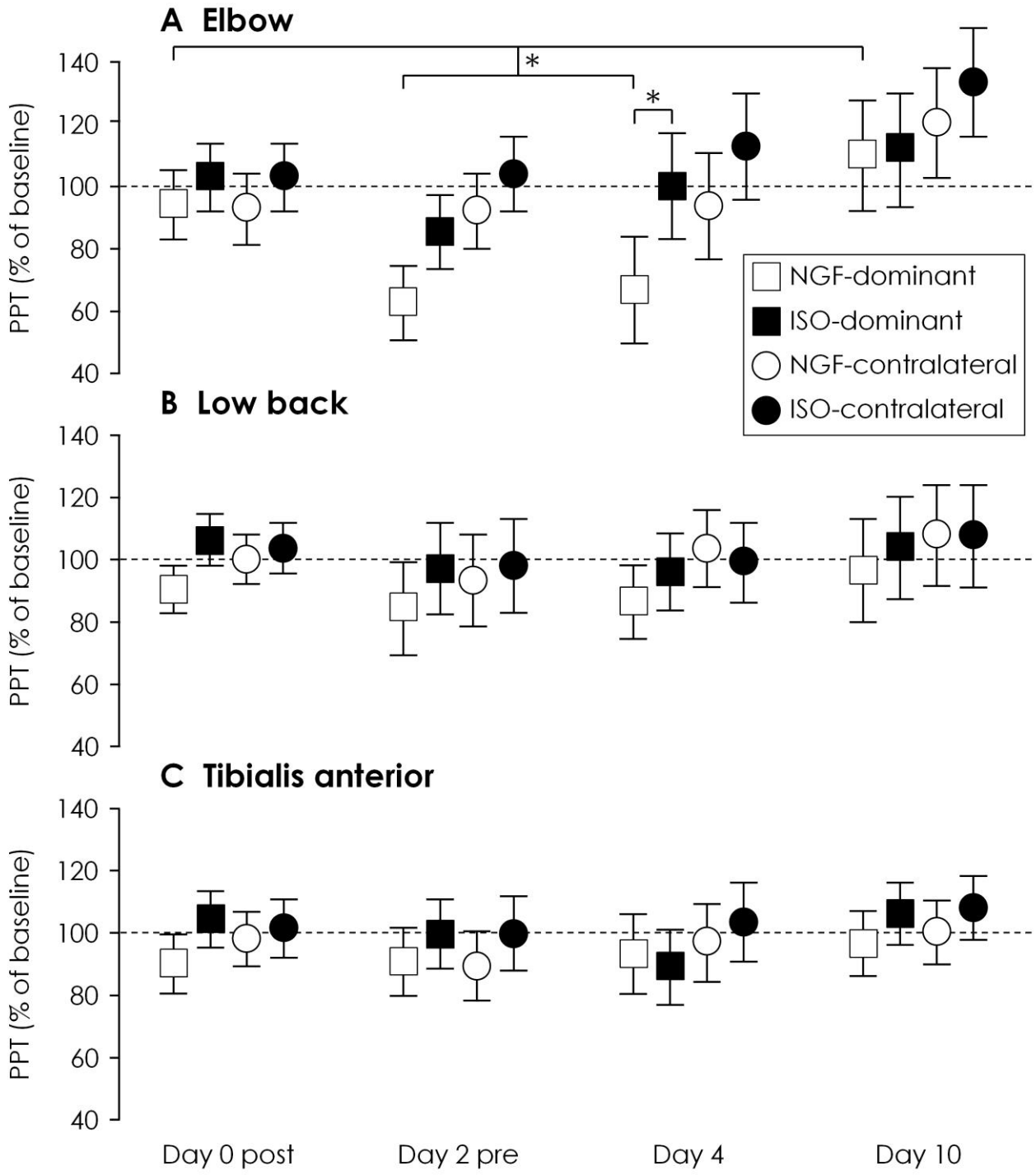

Figure 7-6. Group data for pressure pain threshold testing. Mean (95% confidence interval) of pressure pain threshold from the NGF (nerve growth factor, open bars) and ISO (isotonic saline, solid bars) groups normalized to values recorded pre-injection on Day 0 (i.e. baseline) for the elbow (**A**), low back (**B**) and tibialis anterior muscle (**C**).

* – Significant increase compared with the ISO group, Bonferroni: $P < 0.05$.

7.5 Discussion

This study is the first to demonstrate that intramuscular injection of NGF in the ECRB muscle induces lateral elbow pain and leads to reduced function lasting for several days. A unique feature of this model is the provocation of pain with movement of the upper limb and by contraction and stretch of the injected muscle. These features indicate that intramuscular injection of NGF induces pain that responds in a manner typical of sustained clinical pain, and is therefore a suitable model to study the effect of sustained lateral elbow pain on motor control of the upper limb.

Self-reported pain and functional effects of intramuscular NGF injection

Participants who received an injection of NGF reported lateral elbow pain that peaked 48 hours after injection and lasted for an average of 6 days. Although sustained pain/soreness following NGF injection has been reported, there are discrepancies between the present and previous results. A single NGF injection given into the tibialis anterior muscle induced pain that peaked after 24 hours with a lower intensity (Likert scale: 2) and lasted for 7 days (Andersen et al. 2008), whereas pain after three separate injections on consecutive days peaked 24 hours after the third injection (Likert scale: 3) and lasted for a further 14 days (Hayashi et al. 2013). Injection of NGF into ECRB induced sustained muscle pain that was more intense than after injection into tibialis anterior (i.e. higher scores on the Likert scale) but had a similar duration, which implies duration might be independent of initial pain intensity.

Data from the PRTEE, which evaluates pain and functional limitation, concurs with findings from the Likert scale. Participants injected with NGF reported greater pain and reduced function on the PRTEE (total score and sub-scales) than those in the ISO group at Day 2 and Day 4. The Day 2 PRTEE scores of individuals injected with NGF (18 ± 7) were similar to that reported by patients with mild chronic LE (24 ± 6 (mean ± SD); Coombes et al. 2012a). Thus, injection of NGF into the ECRB muscle induced comparable but slightly less functional limitation and pain after 2 days than participants with mild chronic LE who had pain for approximately 26 weeks.

The area of pain was greatest 48 hours after the NGF injection and was primarily located around the injection site. Pain spread into the proximal half of the forearm in 12/13 participants, similar to DOMS at the elbow (Slater et al. 2003). An increase in the area of pain has also been reported following injection of NGF into the tibialis anterior muscle (Hayashi et al. 2013). Increased pain area is thought to be explained by expansion of the receptive fields of nociceptive neurons with prolonged noxious input (Hoheisel et al. 1993).

Contraction-evoked pain

Maximal wrist extension of the arm injected with NGF evoked lateral elbow pain of ~2/10 from a resting intensity of zero. Similar pain intensity has been reported during contraction of leg (Andersen et al. 2008) and shoulder (Gerber et al. 2011; Nie et al. 2009) muscles that were injected with NGF. Provocation of pain with movement and muscle contraction is a feature of the NGF model of sustained pain that is not consistently associated with other common models of deep tissue pain (e.g. hypertonic saline; Tsao et al. 2010). In the present study, lateral elbow pain was only provoked by maximal wrist extension and not the 10% contraction intensity. Previous studies have reported pain (~2-3/10) during submaximal contractions of shoulder (Gerber et al. 2011; Nie et al. 2009) and lower limb muscles (Andersen et al. 2008) injected with NGF. It is unclear whether differences in contraction-evoked pain intensity between studies are due to differences in contraction intensity or the dynamic/static nature of the tasks.

Stretch-evoked pain

This is the first study to demonstrate provocation of pain by stretch of a muscle injected with NGF. This is best explained as a result of mechanical sensitization (i.e. also demonstrated by reduced PPT) of the muscle following NGF injection. Surprisingly, only the wrist flexion stretch, and not ulnar deviation stretch, was provocative. A greater range of motion is available for wrist flexion (~90°) compared to ulnar deviation (~35°) (Palmer and Epler, 1998), which may result in a greater change in muscle length and thus greater pain provocation.

Pressure pain sensitivity

Pressure pain threshold at the elbow injection site was less in the NGF group than the ISO group at Day 4. Similarly, intramuscular injection of NGF into tibialis anterior (Andersen et al. 2008; Hayashi et al. 2013), trapezius (Nie et al. 2009) and masseter (Svensson et al. 2003; Svensson et al. 2008) muscles induced mechanical hyperalgesia at the injection site that lasted for approximately one week.

Effects of superimposed injection of hypertonic saline

Intramuscular injection of hypertonic saline into ECRB elicited more intense pain during the contraction tasks in the NGF group than the ISO group, but there was no difference in the size of the painful area between the two groups. These findings concur with an earlier study that found men (but not women) reported more intense pain in the leg that was injected with NGF than the

contralateral leg injected with isotonic saline, but with no difference in the area of pain between the two legs (Andersen et al. 2008).

PPTs at the elbow were not affected by injection of hypertonic saline in either group. Injection of hypertonic saline alone (i.e. no prior injection of NGF) into ECRB (Slater et al. 2005) did not affect PPT at the injection site, which suggests that injection of hypertonic saline into ECRB does not affect PPT at the elbow, whether pre-sensitized with NGF or not.

Sensitization of peripheral and central mechanisms following NGF injection

Intramuscular injection of NGF sensitizes high threshold mechanosensitive afferent fibers (i.e. muscle nociceptors) (Hoheisel et al. 2005). Under normal conditions these muscle afferents do not respond to weak, everyday stimuli (e.g. muscle contraction, stretch) and require tissue-threatening stimulation to be activated (Mense, 2009). In the current study, contraction, stretch and direct pressure stimulation of the ECRB muscle after NGF injection evoked pain, which indicates involvement of peripheral sensitization. Evidence of sensitized central mechanisms such as sensitization of dorsal horn neurons (Hoheisel et al. 2007), distinct areas of referred pain (Andersen et al. 2008), and spreading hyperalgesia (Hayashi et al. 2013) have been found following NGF injection. The extensive spreading of pain including referred pain suggests that sensitization of central mechanisms cannot be excluded.

In the current study, an injection of hypertonic saline into pre-sensitized muscle did not induce further mechanical hyperalgesia at the elbow or referred pain, but did elicit more intense pain compared to the isotonic saline group. Hypertonic saline activates dorsal horn neurons, induces hyperalgesia one day after injection (Hoheisel et al. 2007), and produces distinct areas of referred pain (Graven-Nielsen and Arendt-Nielsen, 2010), but it does not alter the mechanical thresholds of muscle afferents (Sung et al. 2007), which suggests that hypertonic saline may sensitize central, rather than peripheral, mechanisms. Further, the strong nociceptive barrage caused by hypertonic saline may excite the pool of dorsal horn neurons to the same extent independent of a potential sensitization of the central neurons (i.e. a ceiling effect). Thus it is unclear to which degree facilitated central mechanisms was involved within the short period of NGF-induced pain.

NGF as a model of sustained elbow pain

It is critical experimental models of sustained pain reflect typical features of musculoskeletal conditions, including prolonged pain (rather than a brief, transient event) and provocation of pain with contraction, stretch and function. Data from the present study and previous reports for other muscles provide evidence that intramuscular injection of NGF more effectively replicates these

features of musculoskeletal pain conditions than injection of hypertonic saline or DOMS for several reasons. First, NGF injection induced pain that was evoked during movement for approximately one week after a single injection (Andersen et al. 2008; *Study 4*) and two weeks after multiple injections (Hayashi et al. 2013). In contrast, pain from hypertonic saline injection lasted for up to 10 minutes and DOMS-related pain was sustained for 2-3 days after exercise (Slater et al. 2005). Second, pain that is induced by injection of NGF was evoked by contraction and stretch of ECRB. This contrasts the potential for pain to decrease during contraction/stretch of a muscle injected with hypertonic saline (Tsao et al. 2010). Third, injection of NGF in the current study induced lateral elbow pain during movement of the upper limb that was more intense than exercise-induced DOMS of the wrist extensor muscles (Slater et al. 2003) and more similar in intensity to that reported by people with mild LE (Coombes et al. 2012a).

It is important to note, however, the intention of this study was to investigate whether intramuscular injection of NGF could be a suitable model of sustained lateral elbow pain, not a model of clinical chronic unilateral LE. The NGF model of sustained pain cannot replicate important features of chronic LE such as long-term pain and functional limitation (e.g. >6 weeks), anxiety, fear of movement, and fear of re-injury (Alizadehkhaiyat et al. 2007). Further, although intramuscular injection of NGF induced critical features of sustained lateral elbow pain (e.g. provocation of pain with movement of the upper limb and by contraction and stretch of the injected muscle), pain models are unlikely to precisely replicate the pain associated with clinical musculoskeletal conditions.

7.6 Conclusion

This study shows that a single intramuscular injection of NGF induces sustained elbow pain that is sustained for up to one week and provoked by contraction, stretch and functional use of the muscle. As such, this experimental pain model may be suitable to study the sustained effects of lateral elbow pain on sensorimotor function and to probe the mechanisms underlying persistent musculoskeletal pain.

8 Discussion

The overall objective of this thesis was to investigate movement variability in the context of acute and chronic pain during performance of a simple radial-ulnar deviation task with few 'elements' and thus limited capacity to change during movement.

8.1 Main findings of each study

Several studies of multi-joint tasks have found that $VAR_{elements}$ increased during acute experimental pain. *Study 1* investigated the effect of acute tonic experimental pain, induced with injection of hypertonic saline, on movement variability during the radial-ulnar deviation task. This study showed that unlike multi-joint movements with multiple elements, where $VAR_{elements}$ has been shown to increase during acute pain, $VAR_{elements}$ in the forearm pronation-supination direction was reduced in the simple task. The most likely explanation was that $VAR_{elements}$ was constrained in the simple task with limited capacity for alternative options. Constraint of $VAR_{elements}$ during acute experimental pain might have occurred for several reasons, including an attempt to reduce pain or to exert greater control over joint motion. This study provides evidence that $VAR_{elements}$ is altered differently for simple tasks compared to complex, multi-joint tasks during acute pain, at least when the pain is tonic.

For *Study 2* we modified the experimental paradigm so that the radial-ulnar deviation task provoked moderate pain only as the wrist moved through the middle of the radial-ulnar range of motion. Further, we provided a *less-painful* or *non-painful* solution that was within the participant's expected flexion-extension range. It was hypothesised that the presence of transient painful stimuli would evoke an initial increase in $VAR_{elements,}$ to assist a search for a less painful solution. Further, it was hypothesised that if participants experienced the substantially less painful solution this strategy would be selected more frequently than was observed in control trials. The findings of this study show that participants did seek a new solution. However, rather than increasing $VAR_{elements}$ to search for a less painful solution, movement strategy gradually changed with repetition of the task. The movement strategy resulted in lower reported pain levels at the end of the trial than at the beginning; however, only 37% of the participants choose to use the externally determined less-painful region more frequently during the pain trial. Three different movement strategies used by participants during the painful trial were identified based on changes of wrist/forearm position (i.e. 'no change', 'small change', and 'large change'). Participants who did not change the mean vector of wrist/forearm position during pain (37% of participants in *Pain 5-1* experiment) used the

externally determined less-painful solution more often than participants who had a large change of wrist/forearm position (63%), but did not experience a greater benefit in terms of pain reduction.

Study 3 investigated whether $VAR_{elements}$ was different between participants with chronic lateral epicondylalgia (LE) and healthy controls during the radial-ulnar deviation task whilst participants gripped a load cell. $VAR_{elements}$ was not different between the LE group and controls at the start or end of the task. In participants with chronic LE, $VAR_{elements}$ in the flexion-extension direction decreased with repetition of the task, but this was not found in healthy controls. Although these overall measures were inconsistent with our hypotheses, several features of inter-individual variation in the LE group were consistent. For participants with chronic LE there was a relationship between pain intensity and movement strategy used during the radial-ulnar task. Performance of the task in a more flexed wrist position (which is the position more commonly adopted by participants with LE with gripping in clinical studies) and with greater $VAR_{elements}$ was associated with lower reported pain scores. Further, participants with chronic LE who had the greatest reduction of $VAR_{elements}$ during the task had a smaller increase of pain intensity. The most likely explanation is that $VAR_{elements}$ decreased around a solution that was the least painful for subsequent performance of the task.

Changes to movement (e.g. movement variability, muscle activation patterns) are found in acute and chronic pain. However, it is unclear how changes in acute pain might progress to those observed in chronic pain. In *Study 4* healthy participants received an injection of nerve growth factor (NGF) or isotonic saline, and underwent several tests over a 10-day period to characterise the pain induced by the NGF injection. We found that intramuscular injection of NGF into an elbow muscle induced lateral elbow pain that lasted for approximately six days. A unique feature of this pain model was the provocation of pain with movement of the upper limb and by contraction and stretch of the injected muscle. These features indicate that intramuscular injection of NGF induces pain that responds in a manner that is typical of acute clinical pain that is sustained for several days, and is therefore a suitable model to study the effect of sustained lateral elbow pain on movement variability and other aspects of motor control of the upper limb.

8.2 Implications of this research for the understanding of how pain influences movement variability

8.2.1 Attainment of the goal in acute and chronic pain

Attainment of a goal is a behaviourally relevant feature of many tasks. However, to our knowledge no studies have considered attainment of the task goal within the context of movement

variability and pain. Two studies have considered *some* aspects of variability of the goal, such as a cutting task in a specific direction, with a target force, and in time with a metronome (Madeleine et al. 2008a) and repetitive pointing between two targets (Lomond and Côté, 2010), but unlike *Studies 1-3* did not consider attainment of the goal.

In *Studies 1-3* participants performed a standardised movement task that required wrist radial-ulnar deviation movement between two target regions. Attainment of the goal was reduced for trials performed during transient acute pain induced with electrical stimulation (*Study 2*), but was not different for tonic/constant pain induced with hypertonic saline compared to a non-painful trial (*Study 1*) or experienced by participants with chronic LE relative to pain-free controls (*Study 3*). One explanation is that electrical stimulation distracted participants from the task goal and resulted in reduced attainment of the goal.

Another factor that might contribute to our varied observations between studies, may be the perceived costs and benefits of goal attainment between studies. In *Studies 1-3* participants were encouraged to attain the task goal, but did not receive an explicit reward or penalty for achieving this goal. In the absence of explicit benefit or cost participants may have lacked motivation to attain the target during the painful trials in *Study 2* and by the end of the task in *Study 3*. It is also possible that in *Study 2* participants might have anticipated reduced pain (i.e. a benefit) from reduced radial deviation, even though radial-ulnar deviation range of motion was not related to pain intensity in any *Studies 1-3*.

8.2.2 $VAR_{elements}$ in acute pain

Two previous studies found $VAR_{elements}$ was increased during acute experimental pain (Moseley and Hodges, 2006; Madeleine et al. 2008a). It was proposed that by taking advantage of $VAR_{elements}$ during acute pain, the motor system searches for an alternative option that is less provocative of pain. If exposed to a less painful solution, the nervous system might reduce $VAR_{elements}$, so the solution is used more frequently to minimise pain (Moseley and Hodges, 2006).

The data from *Studies 1 and 2* do not support this hypothesis for a simple task. In *Study 1* $VAR_{elements}$ decreased in the pronation-supination direction and was not changed in the flexion-extension direction during acute pain. In *Study 2* $VAR_{elements}$ of wrist/forearm position was not different between painful and non-painful trials. This suggests that unlike multi-joint tasks (Moseley and Hodges, 2006; Madeleine et al. 2008a), the motor system does not increase $VAR_{elements}$ during simple tasks in acute pain to search for less painful movement strategies. Thus, changes to $VAR_{elements}$ in acute pain are not stereotypical. Whether $VAR_{elements}$ increases or decreases during acute pain likely depends on several factors, including the body region, context,

individual, and task for which $VAR_{elements}$ is recorded. This aligns with a contemporary theory of the motor adaptation to pain (Hodges and Tucker, 2011), which proposes that the neuromotor changes in pain are dependent on the individual person and the specific task that is performed.

A critical difference between *Studies 1 and 2* and previous studies (Moseley and Hodges, 2006; Madeleine et al. 2008a) is the tasks that were investigated. In *Studies 1 and 2* participants performed a simple task (wrist radial-ulnar deviation) with few elements for which $VAR_{elements}$ could change (i.e. flexion-extension, pronation-supination). In simple tasks the nervous system might exert tighter control over the fewer elements to minimise the potential for "negative" $VAR_{elements}$ to affect attainment of the goal (Scholz and Schoner, 1999). Conversely, multi-joint tasks have more elements, and thus more options for which $VAR_{elements}$ can be increased during acute pain (Moseley and Hodges, 2006; Madeleine et al. 2008a).

In *Study 1* decreased $VAR_{elements}$ during acute pain might reflect constraint of motion in the forearm pronation-supination direction to minimise provocation of pain as found in chronic pain (Hamill et al. 1999; Heiderscheit et al. 2002; Yakhdani et al. 2010). Alternatively, it might reflect increased control of the elements involved in the simple task in response to altered proprioception as a result of pain (Dessureault et al. 2008).

In *Study 2*, an experimental paradigm was developed where a less painful movement strategy (i.e. a specific benefit) was provided that would be experienced by participants through natural $VAR_{elements}$ in the flexion-extension direction during the radial-ulnar deviation task. We found that $VAR_{elements}$ of wrist/forearm position was not different between the painful and non-painful trials. This provides evidence that in simple tasks $VAR_{elements}$ does not increase to explore alternative movement options. Although $VAR_{elements}$ was not increased during the simple task participants did achieve a reduction in pain. Rather than systematically using $VAR_{elements}$ to search for a less painful solution, participants used a gradual change of wrist/forearm position over multiple repetitions. One interpretation is the motor system gradually changed movement strategy to explore alternative movement options. Thus, in *Study 2* the nervous system resolved to a less painful movement strategy, but in the context of the simple task, $VAR_{elements}$ was not used as part of this resolution. It is important to note, however, that $VAR_{elements}$ might be still be used as part of a search, but only in tasks that have multiple elements (Moseley and Hodges, 2006; Madeleine et al. 2008a) for which movement can be varied without disturbing the potential to maintain the task goal.

In *Study 2* participants used one of three different movement strategies during acute pain. One strategy involved a large change in position on either the first or second repetition of the painful trial. Another strategy involved progressive, small changes of position with each repetition. The final strategy involved minimal change in position during pain with greater utilization of the

less/non-painful solution provided in the experimental paradigm. Participants who had a minimal change of wrist/forearm position during pain used the externally determined less painful solution region more often than participants who had a large change of wrist/forearm position. However, participants who experienced the solution region did not have lower pain ratings. One possible explanation for this observation is that the nervous system may perceive small adaptations (e.g. small changes in wrist/forearm position) as being insufficient to experience less pain provocation, and more extreme adaptations may be preferred to interpret that sufficient action had been taken (Hodges et al. 2013; Moseley et al. 2004; Tucker et al. 2012). This might explain why some participants in *Study 2* used a strategy that involved a large change in position on either the first or second repetition of the painful trial. Data from other studies of pain in the absence of injury (Hodges et al. 2013) or when pain is anticipated but without noxious input (Moseley et al. 2004; Tucker et al. 2012) highlight that changes to movement can exceed the adaptation that is actually required to protect the body part.

8.2.3 $VAR_{elements}$ in chronic pain

Previous studies that evaluated movement variability in chronic pain have reported diverse results, but many concluded that $VAR_{elements}$ is decreased in individuals with chronic pain relative to those without pain. However, as discussed in detail within the Background chapter of this thesis, a simple conclusion of decreased $VAR_{elements}$ in chronic pain betrays the complexity and diversity of these data (see section 2.2.5).

In *Study 3* it was hypothesised that $VAR_{elements}$ would be less in participants with chronic LE than healthy controls during a simple movement task. Contrary to this hypothesis, $VAR_{elements}$ was not different between the two groups at the start or end of the trial. The most likely explanation for the lack of between-group differences was that participants with chronic LE did not all react uniformly and they adopted different movement strategies that were related to the intensity of pain experienced by the individual participant during the radial-ulnar task. We found that greater $VAR_{elements}$ in the flexion-extension direction at the start of the trial was associated with less provocation of pain during the radial-ulnar movement. Consistent with Moseley and Hodges (2006) we conclude that this greater $VAR_{elements}$ may have been beneficial in the exploration of different options, and the resolve to a less provocative movement strategy.

Performance of the task in a more flexed wrist posture at the start of the trial was associated with less pain. This more flexed wrist posture might be a beneficial adaptation to reduce activation of the wrist extensor muscles to minimise pain. In normal situations, the wrist extensor muscles are activated during gripping tasks to control wrist position (Snijders et al. 1987; Shimose et al. 2011).

However, participants with chronic LE have less activation of ECRB (recorded with intramuscular electrodes) and ECR (combined activation of ECRB and ECRL) during gripping (Alizadehkhaiyat et al. 2007) than healthy controls. This possible mechanism of reduced activation of ECRB as a protective mechanism to minimise pain during gripping might explain the results of Bisset et al (2006), where participants with chronic LE adopted a more flexed wrist posture than healthy controls during a pain-free grip task (i.e. ramped force applied until the first onset of pain).

Participants who moved their wrist into a more flexed position between the start and end of the trial had a greater reduction of $VAR_{elements}$ in the flexion-extension direction. The most likely explanation is that participants learnt to perform the task in a wrist position that provoked less pain (i.e. greater wrist flexion) with repetition of the task, and then reduced $VAR_{elements}$ to ensure the less painful solution was used more frequently for subsequent repetitions to minimise pain. These results in participants with chronic LE (*Study 3*) concur with the hypothesis of *Studies 1 and 2* that $VAR_{elements}$ would decrease if a less painful solution was found during acute pain. This suggests that participants with chronic LE retain the flexibility to alter $VAR_{elements}$ during performance of a painful task, with the potential benefit of reducing pain provocation. Although, these data imply a short term benefit of the change in strategy, whether these modifications have negative consequences in the long term has been proposed and is worthy of consideration.

8.3 Implications for the motor adaptation to pain

The nervous system does not use $VAR_{elements}$ to search for a less painful solution in acute pain for all movement tasks

The studies in this thesis challenge the hypothesis that the nervous system systematically increases $VAR_{elements}$ during acute pain to search for a less painful solution in all tasks (Moseley and Hodges, 2006). We demonstrated that $VAR_{elements}$ decreased (*Study 1*) or was not affected (*Study 2*) when the simple radial-ulnar deviation task was performed during acute experimental pain. The data from *Study 2* suggest the motor system searched by changing wrist/forearm position, not by increasing $VAR_{elements}$. The results of *Studies 1 and 2* contrasts previous studies that reported $VAR_{elements}$ increased when complex multi-joint tasks were challenged by acute pain (Moseley and Hodges, 2006; Madeleine et al. 2008a). As discussed above, multi-joint tasks have more elements and more options that can be varied between repetitions than simple tasks. Thus, it is possible that $VAR_{elements}$ only increases during pain to search for a less painful solution for tasks that involve enough elements that can be varied. This proposal concurs with the most recent theory of the motor adaptation to pain that proposes the nervous systems adopts a more flexible solution that is specific to the individual and task (Hodges and Tucker, 2011)

The nervous system retains the flexibility to explore less painful strategies in chronic pain

Previous studies that investigated changes to $VAR_{elements}$ in chronic pain have implied that $VAR_{elements}$ is inflexible in chronic pain (Hamill et al. 1999; Heiderscheit et al. 2002; Madeleine and Madsen, 2009). The results of *Study 3*, in which $VAR_{elements}$ reduced between the start and end of the radial-ulnar deviation task in participants with chronic LE, provide evidence that the nervous system retains some flexibility to alter $VAR_{elements}$ with repetition of a task in chronic pain. These data concur with findings that $VAR_{elements}$ changed over time when simple (*Studies 1 and 2*) and complex tasks (Moseley and Hodges, 2006) were performed during acute pain. Thus, $VAR_{elements}$ can change with repetition of a task, during simple tasks performed with acute (*Studies 1 and 2*) and chronic pain (*Study 3*) and complex, multi-joint tasks performed with acute (Moseley and Hodges, 2006) and chronic (Lomond and Côté, 2010) pain.

The nervous system likely considers several factors in the motor adaptation to pain

An inherent assumption of theories that attempt to explain the motor adaptation to pain is that a priority of the nervous system is pain reduction and prevention of further tissue damage. The different changes to $VAR_{elements}$ in *Studies 1-3* might be related to these priorities. For instance, constraint of motion could reduce pain and prevent uncontrolled joint motion that could cause future tissue damage (*Study 1*), and change of wrist/forearm position was associated with lower reported pain (*Study 2*). However, the results of *Studies 1 and 2* and previous studies (Tucker and Hodges, 2010; Hug et al. 2014) do not fully support the assumption that a reduction in pain and potential for injury are the main priorities of the nervous system during pain. For instance, although most participants in *Study 2* experienced the movement solution that would have provoked minimal (i.e. 1/10) or no pain, they did not elect to maintain this less/non painful movement strategy. Instead, they chose a movement strategy that was only moderately less painful (*Pain 5-1 experiment* = 3.2/10; *Pain 5-0 experiment* = 3.7/10). Although this strategy was less painful, it did not provide the same benefit (i.e. magnitude of pain reduction) that was possible with the externally determined solution.

Reduction of pain intensity and protection from further injury are no doubt important factors in selection of movement strategy during pain, but these two factors alone cannot fully explain the motor adaptation to pain. The most likely explanation is that the nervous system considers other factors in addition to reduction of pain and protection from further injury in selection of a new movement strategy, such as optimisation of end-point error to ensure attainment of a task goal (Kording and Wolpert, 2004), energy usage of muscles (Anderson and Pandy, 2001), and muscle

forces (Pandy et al. 1995). However, it is unclear how the nervous system balances these different factors required of movement, and whether the weight or importance of each factor is altered during acute pain or injury.

8.4 Intramuscular injection of nerve growth factor as a model of sustained elbow pain

In *Study 4* it was found that the NGF model of sustained pain reflected typical features of musculoskeletal pain conditions, including prolonged pain rather than a brief event that lasts for several minutes, and provocation of pain during muscle contraction/stretch and functional activities. After intramuscular injection of NGF into the ECRB muscle, participants reported lateral elbow pain that peaked after two days and on average lasted six days in total. It is possible to induce pain that lasts for approximately two weeks with multiple injections on separate days (Hayashi et al. 2013). Function of the upper limb was affected for up to four days after NGF injection. Scores on the PRTEE, which was used to measure pain and functional limitation, indicated that intramuscular injection of NGF induces pain and functional limitation comparable to mild chronic LE (Coombes et al. 2012a).

A critical finding of *Study 4* was that maximal wrist extension contraction provoked 2/10 elbow pain. However, submaximal wrist extension, and gripping at a maximal or submaximal intensity, did not provoke pain. Other studies have reported similar pain intensity (2-3/10) during submaximal contractions of shoulder (Nie et al. 2009; Gerber et al. 2011) and lower limb (Andersen et al. 2008) muscles following intramuscular NGF injection into those body regions. The differences in contraction-evoked pain intensity between studies are likely due to differences in contraction intensity or the dynamic/static nature of the tasks that were studied.

Study 4 and previous studies show that intramuscular injection of NGF is a more optimal model of sustained pain than other experimental pain models for several reasons. First, NGF induced pain that was evoked during movement for 1-2 weeks after single/multiple injections (*Study 4*; Andersen et al. 2008; Hayashi et al. 2012). In contrast, pain from hypertonic saline injections lasts for approximately 10 minutes (Slater et al. 2003), and pain after eccentric exercise lasts for 2-3 days (Slater et al. 2005). Second, NGF allows investigation of the isolated effect of sustained nociception/pain in the absence of injury, unlike eccentric exercise, which induces damage to muscle fibres exercise (Paulsen et al. 2012). Third, the pain provoked after NGF injection has a clear relationship to movement and muscle contraction, unlike the inconsistent relationship between pain provocation and amplitude of movement or strength of contraction after

hypertonic saline injection (Coppieters and Hodges, unpublished observations), although some data do show a contrasting decrease of pain during contraction/stretch (Tsao et al. 2010).

Intramuscular NGF is potentially useful as a model to enable future investigation of the effect of persistent exposure to pain for several days. Such studies could provide insight into the time-course of changes to movement variability, and other features of neuromuscular control (e.g. patterns of muscle activation), during sustained pain. It is critical to note, however, that the NGF model of sustained pain is not a model of chronic pain because of stark differences in the duration of pain induced by NGF (1-2 weeks) compared to chronic pain conditions (several months) and the expectation by the participants of the duration of pain, unlike clinical pain where the duration is generally unpredictable.

8.5 Methodological considerations

The studies in this thesis were carefully designed and conducted. However, it is important to recognize the limitations inherent in experimental design and analyses. In addition to the detailed consideration of these issues in each study chapter, the key limitations in regard to the overall interpretation of *Studies 1-4* are discussed in the following sections.

Participant numbers

All of the experiments included in this thesis included a relatively small number of participants. However, this is not uncommon in human neurophysiology experiments, particularly those that involve experimental induction of pain (e.g. injection of hypertonic saline, cutaneous electrical stimulation) in healthy participants. It is desirable to involve only an essential number of participants to obtain sufficient data. Even with a small sample size, the findings from our studies were consistently observed across most participants (except where variation between participants was identified as a feature of the response, see *Studies 2 and 3*) and yielded significant differences in all studies.

Experimental pain

Experimental pain models provide a standardized method to induce pain in healthy participants, which allow the investigation of specific aspects of human motor control. They are useful to study the immediate effects of acute pain on the motor control system, which could not be achieved with a clinical population where pre-pain measures are unavailable and where other effects such as injury are likely to be present and difficult to disentangle from the pain effects.

Hypertonic saline has been shown to induce pain that mimics several changes associated with clinical pain, such as impaired postural stability (Hirata et al. 2012) and delayed muscle activation (Hodges et al. 2003). However, the models cannot mimic all aspects of clinical pain, including deep tissue hyperalgesia (Gibson et al. 2006; Slater et al. 2003). Further, some data suggest that pain induced by hypertonic saline injection is reduced by muscle contraction/stretch (Tsao et al. 2010), which contrasts many clinical contexts. Despite these limitations, the acute pain induced with hypertonic saline in *Study 1* provided insight into the changes to $VAR_{elements}$ in response to a discrete noxious stimulus.

The use of electrical stimulation to induce acute pain in *Study 2* allowed application of a painful stimulus of known intensity and duration at a specific time within each repetition of the motor task (Handwerker and Kobal, 1993), and with an intensity that could be varied trial by trial. Importantly, this model is not associated with stimulus habituation and sensitization (McMahon and Koltzenburg, 2005), which was confirmed in *Study 2*. It was for these reasons electrical stimulation was critical for the experimental paradigm used in *Study 2*.

These experimental models of acute pain allow control of confounding factors other than nociception/pain, such as local tissue damage and degeneration, peripheral/central sensitization, inflammatory response, and psychosocial changes that could exert their own influence on motor behaviour. Although the ultimate goal is to understand the interaction between these different factors and their relationship to motor control changes in clinically painful musculoskeletal conditions, it is necessary to first understand the independent contribution of nociceptive stimulation.

Quantification of variability

Motion of wrist flexion-extension and forearm pronation-supination were analysed as the wrist crossed the neutral radial-ulnar deviation position when moving from the ulnar target towards the radial target. This position was chosen because it is a standard and repeatable position in the radial-ulnar deviation range. It was consistently crossed by all participants in *Studies 1 and 2*. In *Study 3* some trials were discarded because participants failed to cross the neutral position in a consistent manner.

Conventional measures of variability, such as standard deviation or coefficient of variation have primarily been used to quantify movement variability (Riley and Turvey, 2002). In contrast, in this thesis, $VAR_{elements}$ in the flexion-extension and pronation-supination directions were quantified with several linear and non-linear measures (e.g. standard deviation, sum/average delta angle, and

sum of path length). The methods used in this thesis to analyse the movement data and quantify variability allowed us to answer the specific question that were posed.

More complex non-linear measures, such as continuous relative phase (Hamill et al. 1999), sample entropy (Hamill et al. 2000), and Lyapunov exponents (Rosenstein et al. 1993) have also been used to quantify variability. One benefit of these measures is the ability to consider the entire motion signal rather than a discrete point (e.g. neutral radial-ulnar deviation position) and quantification of the structure of variability. However, these complex measures have limitations and are not appropriate for all situations. For instance, continuous relative phase is limited in quantifying non-sinusoidal movement signals and is not appropriate for most couplings between movements of the lower limb during gait (Peters et al. 2003).

Previous studies that investigated the influence of pain on movement variability evaluated variability of other task characteristics, such as velocity, acceleration, posture, and patterns of muscle activation. It is possible variability of these movement characteristics were altered when participants performed the repetitive task during acute (*Studies 1 and 2*) and chronic (*Study 3*) pain. However, the method of recording movement and quantifying variability in these studies allowed us to answer the specific questions that were posed in this thesis.

Experimental paradigm

Identification of a simple movement task with few degrees of freedom was critical for *Studies 1-3* of this thesis. The simple radial-ulnar deviation task that was ultimately chosen as it allowed investigation of the specific questions posed in this thesis. However, the task is not representative of the diverse and complex repertoire of movement performed in everyday life and for which $VAR_{elements}$ can be altered in acute and chronic pain. Future work using other experimental paradigms (e.g. lower limb, trunk) is required to determine whether the results can be extrapolated.

8.6 Future directions

The simple radial-ulnar deviation task used in *Studies 1-3* of this thesis was associated with clear differences in the changes to $VAR_{elements}$ during pain compared to complex multi-joint tasks with many elements. A focus on wrist and forearm movement allowed investigation of a simple system (i.e. fewer elements than previous studies of complex tasks) and the potential to study a provocative task in a clinical chronic pain population (i.e. lateral epicondylalgia). This paradigm proved useful to improve the understanding of changes to $VAR_{elements}$ in acute and chronic pain.

However, further investigation is needed to study the complex relationship between $VAR_{elements}$ and pain/pathology.

In what circumstances does the nervous system exploit $VAR_{elements}$ to search for a solution?

Previous studies found $VAR_{elements}$ increased during acute pain and proposed it reflected a search for a less painful solution (Moseley and Hodges, 2006; Madeleine et al. 2008a). However, the results from *Studies 1 and 2* show that during performance of the simple radial-ulnar deviation task, $VAR_{elements}$ did not increase during acute pain. These data challenge the role of $VAR_{elements}$ in exploration of alternate movement strategies in acute pain to search for a less painful solution. However, it is still possible that $VAR_{elements}$ increases during other tasks to facilitate a search for a less painful solution. Future studies should investigate the potential role of $VAR_{elements}$ in the search for a less painful solution using tasks with varying number of elements for which $VAR_{elements}$ can change and for different regions of the body. This can be done to probe whether the changes to $VAR_{elements}$ are dependent on the potential for the element(s) to change or the body region(s) involved in the task.

A novel experimental paradigm was used in *Study 2* to investigate whether the nervous system would choose to use a specific movement strategy that provoked less pain (Chapter 5). Moderately painful (~5/10) electrical stimuli were delivered to the elbow as the wrist crossed the neutral radial-ulnar deviation position. A less painful solution was provided. The less painful strategy (~1/10 or no pain) was adjacent to all other strategies that provoked moderate pain (Figure 5-2 in Chapter 5). Thus, there was a "step change" between the less/non-painful solution and all other wrist flexion-extension positions that would provoke moderate pain. Participants did not use the externally determined less painful strategy more often during the painful trials. It is possible the solution was not intuitive enough for the nervous system to find. For instance, there is some evidence that the nervous system responds better to "graded" changes than "switch" changes (i.e. on/off) for feedback of EMG amplitude to control a prosthesis (Smidt, 2014). A similar experimental paradigm to *Study 2*, but with "graded" changes to pain intensity leading to a less painful strategy, rather than a large "step change" to a less painful solution, could be used to probe this question.

In *Study 3*, participants with chronic LE who moved their wrist into a more flexed position between the start and end of the radial-ulnar task had a greater reduction of $VAR_{elements}$ in the flexion-extension direction and experienced less pain. It was proposed this change of wrist position would be expected to provoke less pain in participants with chronic LE as a result of reduced activation of the wrist extensor muscles. However, further investigation is required. A future study

could use the experimental paradigm in *Study 2* to investigate the potential of the nervous system to search for a specific less painful strategy in participants with chronic LE.

Why do different people use different movement strategies?

In *Studies 2 and 3* several sub-groups were identified based on the movement strategies used in acute experimental pain (*Study 2*) and chronic LE (*Study 3*). Sub-groups based on resolution or non-resolution of $VAR_{elements}$ in a postural control strategy after cessation of acute low back pain were identified in a previous study (Moseley and Hodges, 2006). The potential for different movement strategies that involve changes to $VAR_{elements}$ in acute and chronic pain warrants further investigation with larger sample sizes to confirm the preliminary results of these studies. Questions remain. For instance, in *Study 2*, why did some participants have no change in strategy (i.e. used a similar wrist/forearm position between the non-painful and painful trials), whereas other participants had a large change in strategy? Interestingly, participants who did not change wrist/forearm position experienced the externally determined solution region more often than participants who had a large change of wrist/forearm position, but did not get a larger benefit in terms of magnitude of pain reduction.

What factors does the motor system consider in the motor adaptation to pain?

An inherent assumption of theories of the motor adaptation to pain is that reduction of pain and minimisation of further injury are the main priorities of the nervous system. The results of *Study 2* question this assumption. A critical question for future studies is what other factors the nervous system considers in selection of a movement strategy during acute and chronic pain. This question might be answered with the development of a novel experimental paradigm that considers the interaction between pain intensity, energy expenditure, attainment of a goal, muscle force, and other factors that might influence motor adaptation.

Once it is clear *what* factors the nervous system considers for the motor adaptation to pain, it is important to investigate whether the nervous system ascribes relative weights or prioritises the different factors. These weightings could depend on the task, body region, and individual. For instance, the nervous system might have the capacity to perform a cost-benefit analysis that considers each factor and its influence on pain and movement before making a decision to change motor strategy. A potential route to investigate these questions is to design experimental paradigms where different movement strategies are beneficial or detrimental. For instance, different movement strategies might be associated with a specific benefit or cost, such as pain provocation or pain relief,

greater or less force needed to complete a task, or more or less potential for error to attain the task goal.

What is the relationship between changes to $VAR_{elements}$ in acute and chronic pain?

Changes to $VAR_{elements}$ in acute and chronic pain have been found in numerous studies, but it is unclear how the changes in acute pain relate to those found in chronic pain. A critical first step is to study changes to $VAR_{elements}$ in the same group of participants over the course of one week using the NGF model of sustained elbow pain that was characterised in *Study 4*. An important feature of this experimental pain model is that is induces pain that reflects typical features of clinical pain, including pain with muscle contraction/stretch and movement, and mechanical hyperalgesia. The NGF model of sustained elbow pain can also be applied more broadly. For instance, to investigate whether the altered patterns of forearm muscle activation in chronic LE (Alizadehkhaiyat et al. 2007; Rojas et al. 2007) are also found when at the onset of elbow pain and when it is sustained for several days.

8.7 Conclusions

The four studies in this thesis provide novel evidence of changes to movement variability in acute and chronic pain, and provide a new model of sustained pain that reflects typical features of musculoskeletal pain. The results provide strong evidence that the changes to $VAR_{elements}$ that we recorded in acute and chronic pain during simple tasks with few elements do not change in a manner identical to what has been shown for complex, multi-joint tasks. A key finding was that the nervous system searched for, and found, a less painful movement strategy during acute pain using a gradual change of wrist/forearm position. This conflicts with a key hypothesis that the nervous system uses increased $VAR_{elements}$ to search for a less painful solution during pain. A major consideration is that in selection of a movement strategy during pain the nervous system likely considers multiple factors in addition to reduction of pain and minimisation of tissue damage, including optimisation of end-point error and energy efficiency of muscles. A novel finding was that the nervous system retains the flexibility to alter $VAR_{elements}$ during chronic pain to enable performance of a task in a manner that provokes less pain. Furthermore, it presents a new model of experimental pain that will enable investigation of changes to various aspects of human motor control during sustained pain.

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APPENDIX I

Published papers

Study 1

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ORIGINAL ARTICLE

Does movement variability increase or decrease when a simple wrist task is performed during acute wrist extensor muscle pain?

Michael J. G. Bergin · Kylie J. Tucker · Bill Vicenzino · Wolbert van den Hoorn · Paul W. Hodges

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Abstract
Purpose The goal of complex tasks can be maintained despite variability in the movements of the multiple body segments involved in the task ($VAR_{elements}$). This variability increases in acute pain and may enable the nervous system to search for less painful/injurious movement options. It is unclear whether $VAR_{elements}$ increases when pain challenges simple tasks with fewer movement options, yet maintain successful attainment of the goal. We hypothesised that during acute pain related to a simple movement: (1) the task goal would be maintained; (2) $VAR_{elements}$ would be increased; and (3) if $VAR_{elements}$ increased during pain, it would decrease over time.
Methods Movements of the right wrist/forearm were recorded with a three-dimensional motion analysis system and during a repetitive radial-ulnar deviation task between two target angle ranges (the task goal). We measured success of attaining the goal (repetitions that reached the target range and total absolute error in degrees), and variability in the motion of wrist flexion–extension and forearm pronation–supination ($VAR_{elements}$). Fourteen healthy participants performed the task in one session before, during, and after wrist extensor muscle pain induced with hypertonic saline, and in another session without pain.
Results The task goal was maintained during acute pain. However, $VAR_{elements}$ in other motion planes either reduced (pronation–supination) or did not change (flexion–extension). Thus, variability of task elements is constrained, rather than increased, in simple tasks.
Conclusions These data suggest the nervous system adapts simple tasks with limited degrees of freedom by reduction of $VAR_{elements}$ rather than the increase observed for more complex tasks.

Keywords Movement variability · Motor control · Experimental pain · Hypertonic saline · Elbow · Wrist

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Introduction

Flexibility or variability in the performance of voluntary and postural tasks is thought to underpin the exploration of different movement strategies (Dingwell et al. 2001; Riley and Turvey 2002). In complex multi-joint tasks (e.g. pointing to a target) it is possible to achieve an outcome that is accurate and consistent (i.e. high probability of successful achievement of a task objective: the goal) with many different combinations of joint excursions and muscle activation patterns (i.e. high variability of the "elements": $VAR_{elements}$) (Fig. 1). The uncontrolled manifold hypothesis (Scholz and Schöner 1999) suggests the nervous system allows the elements of a task to vary, provided this variability does not compromise successful completion of the task (i.e. lower goal attainment). $VAR_{elements}$ can be partitioned into two components (Latash 2012); "bad" variability leads to reduced success in attaining a goal, while "good" variability does not affect the goal, and may have the benefit of a broader distribution of stresses between tissues (e.g. muscles, joint surfaces) with the potential to reduce cumulative tissue load (Hamill et al. 1999). In the presence of acute pain, increased $VAR_{elements}$ may also enable the nervous system to explore new movement options

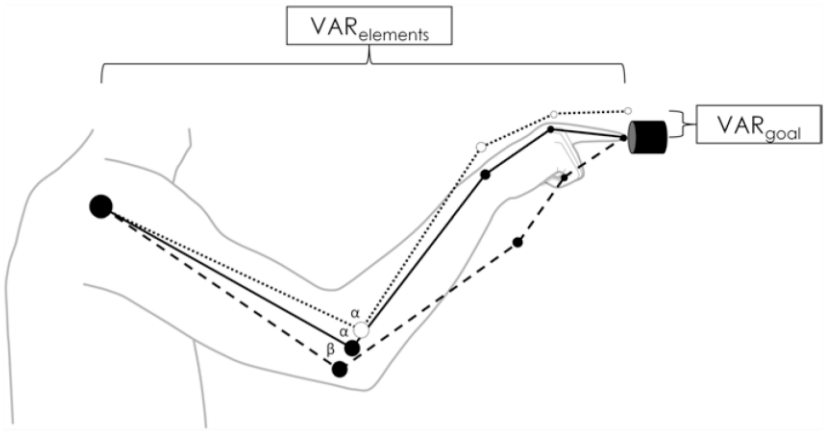

Fig. 1 Upper limb pointing task. A sagittal view of several possible upper limb orientations to achieve a target (goal) (*circles* and *lines* define the joints and segments of the arm, forearm, wrist and finger). The stick diagrams with *solid circles* represent various segment interactions ($VAR_{elements}$) that maintain successful attainment of the goal, whereas the *open circles* and *dotted line* represent a segment interaction where the goal was not achieved

and find a more optimal solution that has less potential to provoke pain/injury (Murray and Peck 2007; Hodges and Tucker 2010; Srinivasan and Mathiassen 2012). Consistent with these hypotheses, the goal of an upper limb task is maintained despite changes in muscle activation/movement of the trunk or shoulder ($VAR_{elements}$) during pain in those regions (Moseley and Hodges 2006; Madeleine et al. 2008). Although considerable variability of the elements is possible without compromising goal attainment in multi-joint movements it is unclear whether $VAR_{elements}$ increases when pain challenges simple tasks that involve a simple joint complex.

Relative to multi-joint tasks, simple tasks have fewer movement options, and thus fewer elements for which variability can be increased, yet maintain successful attainment of the task goal. Although variability of this limited number of elements could still be increased, it is not known whether this occurs. If a simple wrist radial-ulnar movement becomes painful, in order to achieve a specific intended movement (i.e. the task goal), fewer segments/options are available to compensate. As such $VAR_{elements}$ is limited to joint motion in planes other than that of the primary task (i.e. flexion–extension or pronation–supination). It has previously been hypothesised that acute pain motivates the nervous system to increase $VAR_{elements}$ and search for less painful movement strategies (Moseley and Hodges 2006; Madeleine et al. 2008; Hodges and Tucker 2010). Even with fewer options in a simple task, the nervous system is expected to use the same strategy of increased $VAR_{elements}$ to find an alternative solution. For instance, a recent study (Singh et al. 2010) found the nervous system increased $VAR_{elements}$ during a simple force-matching task with few elements (i.e. application of pressure with middle and index fingers to match a target force) to maintain successful completion of the task when one of the elements (i.e. index finger) was fatigued. However, it is unclear whether an increase in $VAR_{elements}$ during acute pain is limited to complex multi-joint systems where multiple options (i.e. muscles, joints) are available to maintain the goal. When few options are available in a simple task, $VAR_{elements}$ might not change during pain.

If $VAR_{elements}$ increases with acute pain in a simple system, then it follows that after this initial increase (i.e. the searching), $VAR_{elements}$ would decrease and return to the amount of variability present at baseline (i.e. before pain) if a new less painful strategy is found, or if a better option is not available. Such time-dependent change in $VAR_{elements}$ has been observed in a multi-joint system (Moseley and Hodges 2006). However, it is unclear whether adaptation in $VAR_{elements}$, if present, shares this time-dependency in simple wrist movements.

We studied a simple, repetitive wrist movement (radial-ulnar deviation) between target angle regions with and without experimental muscle pain to test the hypotheses that: (1) The task goal would be maintained during pain; (2) this would be accompanied by increased $VAR_{elements}$; and (3) if $VAR_{elements}$ increased during pain, it would be greatest at the onset of pain and decrease over time. This study focused on the magnitude of movement variability, not the structure of variability.

Methods

Participants

Fourteen healthy volunteers [6 females and 8 males; age 24.5 ± 3 years (mean ± SD)] with no history of upper limb pain or dysfunction attended two testing sessions approximately two months apart. All participants were right-handed. Participants were excluded if they reported any major circulatory, orthopaedic, musculoskeletal, or neurological conditions that affected upper limb function. However, all participants met the inclusion criteria for each

session and none were excluded, and there was no change in general health status between sessions. Informed consent was obtained from all participants. All procedures were approved by the Institutional Medical Research Ethics Committee (Project number: 2004000654) and conformed to the Declaration of Helsinki.

Measurements

A cluster of four reflective markers was attached to the dorsum of the right hand between the 2nd and 3rd metacarpals (Fig. 2) to represent wrist/forearm flexion–extension and pronation–supination. Movements of the cluster were recorded by an 8-camera 3D motion analysis system (T040, Vicon Motion Systems Ltd. Oxford, UK) at a sampling rate of 200 Hz. An electrogoniometer (SG65, Biometrics Ltd., Newport, UK) was attached to the ulnar surface of the hand and distal end of the forearm to provide feedback of radial-ulnar deviation position during the experimental tasks (Fig. 2a). The electrogoniometer signal was recorded at 100 Hz using a Power1401 Data Acquisition system and Spike2 software (Cambridge Electronical Design, Cambridge, UK). The motion system was synchronized by remotely starting the recording within Spike2 software.

Procedures

Participants sat in an upright posture with their right forearm resting on a table and supported in mid-position between pronation and supination with the elbow in approximately 90° flexion (Fig. 2). The forearm was secured with an adjustable clamp immediately proximal to the wrist. This position allowed unconstrained wrist motion and forearm rotation but prevented movement of the upper limb that could affect performance of the radial-ulnar deviation task.

Prior to the experimental trials the neutral position of the wrist and forearm, and the maximal range of motion for radial and ulnar deviation, were recorded. The neutral position was measured using a handheld goniometer with the wrist and forearm in the mid-position of flexion and extension, radial and ulnar deviation, and forearm pronation and supination (Fig. 2).

The experimental task involved repeated radial-ulnar deviation of the wrist between two target angle regions (Fig. 3a) that were displayed on a computer screen positioned approximately 60 cm in front of the participant. Participants were instructed to move as accurately as possible from a target angle region 20–40 % of their maximal ulnar deviation range to 80–100 % of their maximal radial deviation range (Fig. 3a) in time with a metronome (90 beats per minute). The targets were standardised to a percentage of maximal range, rather than absolute range of motion, to account for differences in the maximal range that was achievable by each participant. Emphasis was placed on reaching the target angle region in the radial deviation direction. Participants practiced the task at the start of each session until it was completed at the correct frequency and between the two target angle regions. Data from this practice period were not analysed. Forty-five repetitions were recorded in each condition (see below) which started and finished with the wrist and forearm in the neutral position. Pilot testing ($n = 3$) indicated that 45 repetitions at a rate of 90 beats per minute could be completed easily without

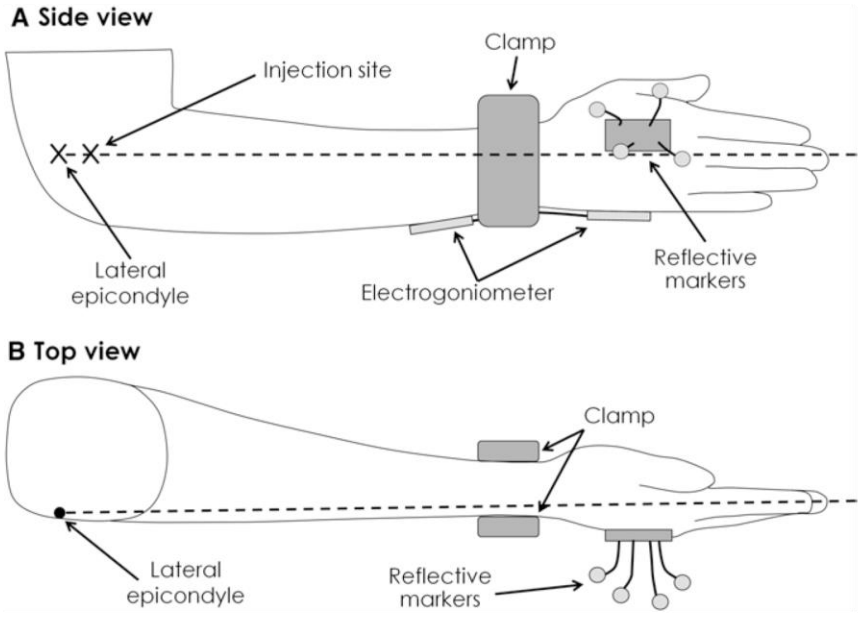

Fig. 2 Experiment setup showing the position of the upper limb from the *side view* (**a**) and *top view* (**b**). Note the *dashed line* indicating the neutral position of the wrist and forearm

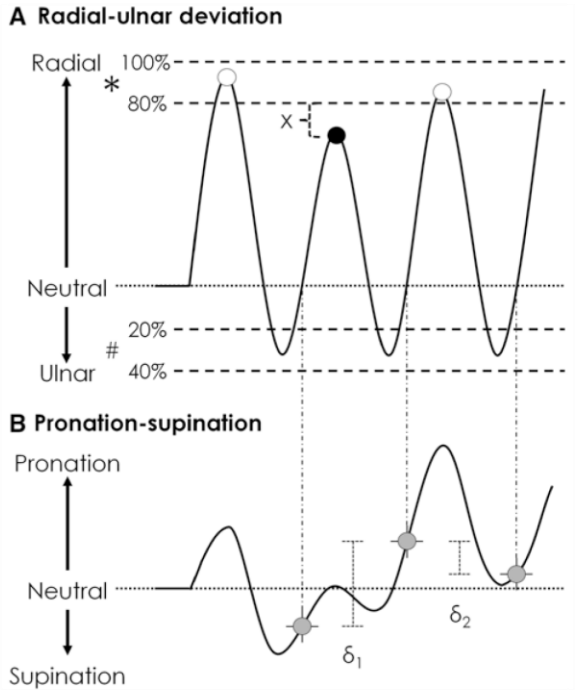

Fig. 3 An example of successful and unsuccessful attainment of the task goal (**a**) and $VAR_{elements}$ of forearm pronation–supination (**b**) when performing the repetitive movement task between the radial deviation (*asterisk*) and ulnar deviation (*hash*) target regions. **a** *White circles* indicate when the task was performed accurately and *black circles* indicate when it was not. The absolute error (*x*) was calculated for each repetition. **b** *Grey circles* indicate forearm pronation–supination positions when the wrist passed through the neutral angle in the direction of ulnar to radial deviation. Delta angle (δ) was calculated as the absolute difference in position between consecutive repetitions. The standard deviation was also calculated to quantify the variability in a linear manner over all repetitions

any perception of fatigue of the forearm muscles and was a comfortable rate to perform the task.

In one experimental session the movements were performed within three conditions; before, during and after experimental pain was induced by injection of hypertonic saline (0.3 ml, 5 % NaCl) into the common extensor tendon near its attachment to the lateral epicondyle of the right humerus (Fig. 2a). The common extensor tendon gives rise to the extensor carpi radialis and brevis muscles, which, along with flexor carpi radialis, produce radial deviation of the wrist (Standring 2005). It was expected that acute wrist extensor muscle pain would stimulate the nervous system to search for a new, less painful movement solution. Similar changes to motor control of the wrist following injection of hypertonic saline into the common extensor tendon have been found previously, such as reduced maximal wrist extension force (Slater et al. 2003). The location for injection was identified by palpation of the elbow at rest and during a gentle wrist extensor muscle contraction. The needle (25G × 25 mm) was directed in an anteromedial direction towards the cubital fossa. The radial-ulnar deviation task in the trial during pain was initiated once the participant reported a pain intensity of ≥2 on an 11-point numerical rating scale (NRS) (0 = no pain; 10 = worst pain imaginable). In the other experimental session, three sets of movements were performed as for the pain session, but the middle condition was performed without experimental pain. This session was included to determine how much variability could be expected by repetition of the movements, but in the absence of pain. Participants were asked at the end of each 45-repetition trial whether they perceived any sense of fatigue in the forearm or wrist.

Additional experiment

The extent to which the pronation–supination position of the forearm could be changed, yet still maintain the goal (the target range in the radial-ulnar deviation direction) of the simple task was studied in two healthy participants. These participants performed two blocks of 10 repetitions that started with the wrist/forearm in neutral flexion–extension and neutral pronation–supination, and moved incrementally toward the limit of pronation (block 1) or supination (block 2) with each repetition. The pronation–supination position at the peak radial deviation position was calculated for each repetition and is presented in Fig. 4. These data show that pronation–supination angle could deviate by more than 15° in either direction from neutral and the participant retained the ability to move the wrist to the target angle range for radial deviation.

Data analysis

Data were analysed within each condition for repetitions 1–15 and 26–40. Data are reported from 13 (of 14 participants) as one participant felt faint following the injection of hypertonic saline and withdrew from the study.

For analysis of successful attainment of the goal radial-ulnar deviation angle data recorded with the electrogoniometers were analysed offline using Spike2 software. Successful attainment of the goal was measured in two ways. First, proportion of success represented the proportion of repetitions within each of the three conditions in which the participant successfully moved their wrist to the radial deviation target angle region (Fig. 3a). Second, the total absolute error (in degrees) was calculated as the sum of the difference between the peak angle of radial deviation and the lower limit of the target angle region for all repetitions in which the radial deviation angle failed to terminate

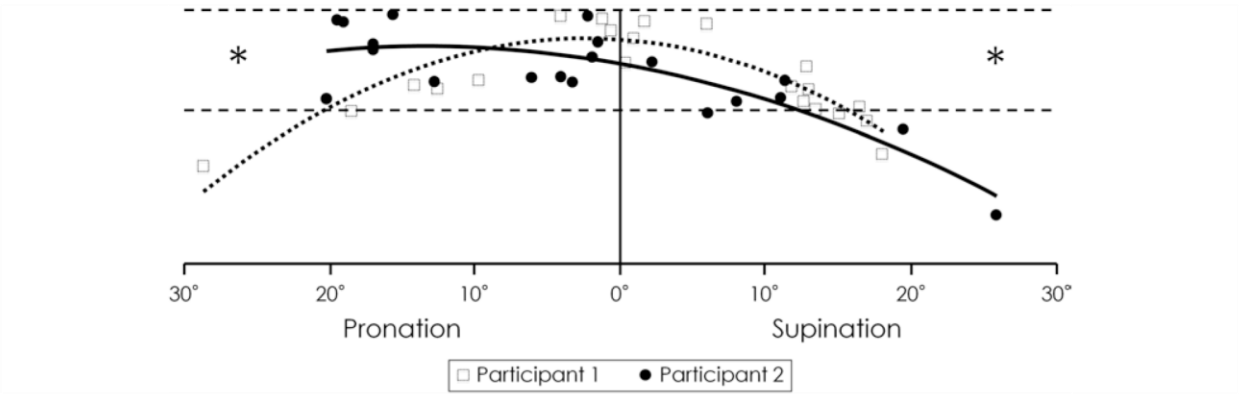

Fig. 4 Data from two additional participants who performed 20 repetitions of the simple task towards the radial deviation target range (*asterisk*) at different positions of forearm pronation–supination. Each data point represents the forearm pronation–supination position at the time of peak radial deviation range for each repetition. The data show that variation in the angle of the forearm between ~20° pronation and ~10° supination plane was possible without compromising the potential to complete the radial deviation task

within the target region (Fig. 3a). Data were normalised to the maximum proportion of success and maximum total absolute error across conditions within each session for each participant.

$VAR_{elements}$ was quantified as variability in the motion of the wrist/forearm in the planes other than that of the primary task (i.e. wrist flexion–extension and forearm pronation–supination), and was calculated from the reflective marker cluster attached to the hand using Matlab 7.14 (The Mathworks, Natick, MA, USA). The instantaneous angle of the wrist/forearm in flexion–extension and pronation–supination for each repetition (in each condition) was calculated at the point where the wrist angle passed through the zero position of the radial-ulnar angle when moving from the target region in the ulnar direction towards the target region in the radial deviation direction (Fig. 3b). The "zero"/neutral position of radial-ulnar deviation was chosen as it is a standard and repeatable position in the radial-ulnar deviation range of motion that was consistently crossed by all participants, and by virtue of its location in the middle range for several directions of motion it is also the position with greatest potential for movement to be modified in other planes. $VAR_{elements}$ was quantified in two ways: (1) as the standard deviation of the angle and (2) as the sum of the absolute difference in angle (sum of delta angle), of wrist flexion–extension or wrist/forearm pronation–supination at radial-ulnar zero position between consecutive repetitions (Fig. 3b). The latter measure quantifies the total variability between consecutive repetitions. Data were normalised to the maximum values recorded across conditions within each session for each participant.

Data were normalised to maximum for several reasons. First, this method allows comparison between the two testing sessions, which was an important factor in our analysis and interpretation. Second, it reduces variation between individual participants.

Statistical analysis

Statistical analysis was performed using Statistica 9 (Statsoft, Tulsa, OK, USA). According to a Kolmogorov–Smirnov test all data were normally distributed (all $p > 0.20$). Pain intensity during the start and end of the painful trial was compared using a Student's t test for dependent samples. The proportion of success and total absolute error of successful attainment of the goal, and the standard deviation and sum of delta angle of $VAR_{elements}$, were compared between sessions (pain vs. control), between conditions (pre-pain vs. pain vs. post-pain [pain session]; trial 1 vs. 2 vs. 3 [control session]) and between repetitions (early [reps 1–15] vs. late [reps 26–40]) using repeated-measures analysis of variance (ANOVA). Post hoc testing was undertaken using Fisher's least significant difference test. Significance level was set at $p < 0.05$. Data are presented as mean ± 95 % CI (1.96 × SD) throughout the text and figures.

Results

Pain measures

Pain intensity did not differ between the early phase (initial 15 repetitions) and late phase (final 15 repetitions) of the painful trial ($p = 0.66$), with an average pain intensity of 4.9 ± 0.8 and 5.1 ± 0.9, respectively. No participants reported fatigue of the forearm or wrist during either testing session.

Does attainment of the goal change during an experimental session, with or without wrist extensor muscle pain?

Consistent with our first hypothesis, attainment of the goal in the radial deviation direction was not affected by pain. Neither the proportion of success (Main effect: condition: $F = 1.58$, $p = 0.228$; Interaction: session × condition × repetitions: $F = 1.58$, $p = 0.189$) (Fig. 5a) nor the total absolute error (Main effect: condition: $F = 0.59$, $p = 0.565$; Interaction: session × condition × repetitions: $F = 1.08$, $p = 0.356$) (Fig. 5b) changed between conditions during the session in which movement was performed with pain or the control session without pain.

Does variability of the elements ($VAR_{elements}$) change during pain despite maintenance of the primary task?

Contrary to the second hypothesis, $VAR_{elements}$ expressed as sum of delta angle in the pronation–supination direction was less when wrist radial-ulnar deviation was performed in the presence of wrist extensor muscle pain (Interaction: session × condition: $F = 4.82$, $p = 0.017$) than that during trials before (post hoc: $p = 0.024$) and after pain (post hoc: $p = 0.020$) (Fig. 5c). There was no difference in sum of delta angle of pronation–supination motion between the three conditions during the experimental session without pain (all post hoc: $p > 0.100$) (Fig. 5c). Sum of delta angle in the flexion–extension direction did not change between conditions regardless of whether the experimental session involved pain or not (Interaction: session × condition: $F = 1.43$, $p = 0.258$) (Fig. 5d).

When data were analysed as the standard deviation of the angle in pronation–supination, there was a tendency for a reduction of variability of pronation–supination angle but this was not significant (Main effect: condition: $F = 1.30$, $p = 0.291$; Interaction: session × condition: $F = 2.71$, $p = 0.087$). Consistent with the pronation–supination data, there was no change in variability of flexion–extension with pain (Interaction: session × condition: $F = 1.00$, $p = 0.382$).

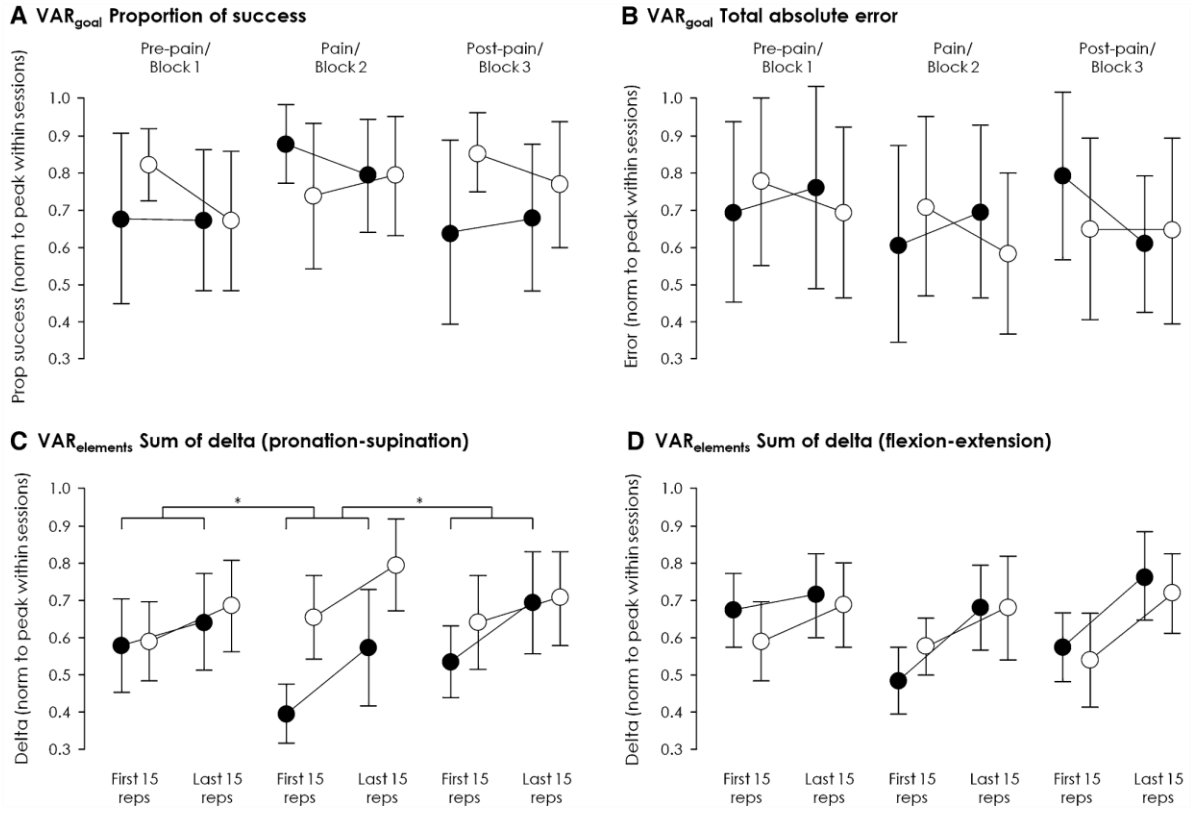

Fig. 5 Group mean and 95 % CI during the session with experimental pain (*black circles*) and control session (*white circles*) for successful attainment of the goal, represented by proportion of success (**a**) and total absolute error (**b**), and $VAR_{elements}$, represented by sum of delta angle for forearm pronation–supination (**c**) and wrist flexion–extension (**d**). Note the reduction of variability in the pronation–supination direction during pain. *Asterisk* indicates significant difference ($p < 0.05$) between *bracketed items*

When the initial and final 15 repetitions of each condition were compared, $VAR_{elements}$ expressed as sum of delta angle in pronation–supination was less at the start than the end (Main effect: repetitions: $F = 16.05$, $p = 0.002$). This increase in $VAR_{elements}$ over repetitions was consistent for both sessions and all conditions (Interaction: session × condition × repetitions: $F = 0.82$, $p = 0.450$) (Fig. 5c). However, there was no change between the initial and final 15 repetitions when variability data were analysed as standard deviation (Main effect: repetitions: $F = 0.08$, $p = 0.782$). $VAR_{elements}$ of flexion–extension also increased from the start to the end of the repetitions in each condition when data were analysed as sum of delta angle (Main effect: repetitions: $F = 46.89$, $p < 0.001$) and standard deviation (Main effect: repetitions: $F = 7.20$, $p = 0.020$) and was consistent for both sessions and all conditions for both sum of delta angle (Interaction: session × condition × repetitions: $F = 0.81$, $p = 0.456$) (Fig. 5d), and standard deviation (Interaction: session × condition × repetitions: $F = 0.25$, $p = 0.784$).

Discussion

The results of this study of a simple joint complex showed that during acute experimental pain successful attainment of the task goal was maintained; however, unlike more complex multi-joint systems (Moseley and Hodges 2006; Madeleine et al. 2008), the variability in the manner in which the goal was achieved (i.e. movements in other planes and other joints; $VAR_{elements}$) was reduced. The initial reduction and subsequent recovery of $VAR_{elements}$ of forearm pronation–supination contrasts evidence of an early increase in $VAR_{elements}$ during pain (Moseley and Hodges 2006; Madeleine et al. 2008) and subsequent reduction of $VAR_{elements}$ over time (Moseley and Hodges, 2006) when a complex multi-joint task was performed during and after acute pain. Although the nervous system appears to take advantage of variability of the multiple options available to achieve a goal in complex multi-joint movements, variability is constrained in a simple radial-ulnar deviation task with limited capacity for alternative options despite the potential to vary movement in other planes.

In support of our first hypothesis, participants continued to achieve the goal of the simple task despite acute pain. This observation concurs with some (Ingham et al. 2011), but not all previous (Boudreau et al. 2007; Salomoni and Graven-Nielsen 2012; Salomoni et al. 2013) data of tasks that have been performed with feedback of the goal available to the participants. The failure of participants to successfully maintain the task goal in some previous studies might be explained by differences in the nature of the target or the manner in which feedback was provided. We asked participants to repetitively radially deviate their wrist to terminate within a target angle region, which by its nature allowed some scope for the wrist radial deviation position to change between repetitions, provided it was within the target region. Other work has evaluated the ability to consistently achieve a target peak acceleration of a finger movement (Ingham et al. 2011) and a sustained force (Boudreau et al. 2007; Salomoni and Graven-Nielsen 2012; Salomoni et al. 2013). Differences in the precision required to achieve the specific goal(s) and constraints of the task may explain the difference in results.

In a system with few degrees of freedom there are limited options available to vary the performance of a task while maintaining the goal. The only options available to the nervous system in our task would be modification of wrist/forearm variability in flexion–extension and/or pronation–supination. Contrary to our second hypothesis, $VAR_{elements}$ of forearm pronation–supination was reduced when the simple task was performed during acute pain. On the basis of data from more complex systems (Moseley and Hodges 2006; Madeleine et al. 2008) we predicted an increase in variability of the elements to enable the nervous system to search for a new, less painful movement strategy (Hodges and Tucker 2010). There are several possible explanations why $VAR_{elements}$ of forearm rotation reduced, rather than increased, in our simple task.

First, it is assumed that the nervous system searches for new less painful/injurious strategies to complete the task. It is possible that the alternative movement options available in our simple system (e.g. performance of the movement in a more flexed wrist angle) might not reduce provocation of pain and thus not present any advantage to the nervous system. In other tasks in which there is a greater range of combinations of joint excursions and muscle activation patterns available (Moseley and Hodges 2006; Madeleine et al. 2008), the potential to find a less provocative solution is more likely.

Second, it is reasonable to speculate that the nervous system uses an alternative solution for our simple task that involved constraint of forearm pronation–supination variability. This may have acted to minimise acute pain. Similar constraint has been observed for clinical conditions. For instance, participants with chronic knee pain exhibit constrained movement variability during gait (Hamill et al. 1999; Heiderscheit et al. 2002) and this variability increases with resolution of knee pain (Heiderscheit 2000). Studies of complex movements during acute pain show that $VAR_{elements}$ of the painful segment (amongst the multiple segments that are available; e.g. back or shoulder in an upper limb movement task) is reduced and $VAR_{elements}$ of other non-painful segments are increased to compensate (Moseley and Hodges 2006) to enable successful completion of the task. In our study, no other segments were

available, and although we postulated that participants might increase $VAR_{elements}$ in other planes (i.e. wrist flexion–extension, forearm pronation–supination) to enable maintenance of the goal, they did not, and instead reduced $VAR_{elements}$ of pronation–supination. Thus, data from the present study imply that $VAR_{elements}$ of a painful part is reduced in acute pain and the nervous system does not appear to exploit other ways of using the segment to find a less provocative solution. It is also possible that constraint of $VAR_{elements}$ in pronation–supination minimised the area of acute wrist extensor muscle pain by reduction of spreading of the injected hypertonic saline.

Third, it could be speculated that it may not be mechanically possible to maintain successful attainment of the goal if $VAR_{elements}$ increased in other movement planes, and this may have precluded augmented variability in those planes to find a less painful solution. The nervous system may have prevented an increase of "bad" $VAR_{elements}$ to maintain accurate completion of the task as proposed by the uncontrolled manifold hypothesis (Scholz and Schöner 1999). However, our additional experiment in two participants confirmed that it was possible to increase pronation by approximately 20° and supination by approximately 10° (Fig. 4) and comfortably maintain the radial target angle region. This suggests the nervous system had the capacity to change the position of the forearm and increase $VAR_{elements}$ to facilitate a search for a less painful/injurious solution, but chose not to.

Fourth, pain interferes with proprioception and this may have influenced the performance of the task (Malmström et al. 2013). Although reduced proprioception may be expected to increase variability, it is also possible that in view of less reliable information about joint position the nervous system might increase constraint of the task. Consistent with this proposal, people with back pain have been shown to ignore proprioceptive information from the back muscles (Brumagne et al. 2004), and other studies show reduced use of spinal movement for postural adjustments (Mok et al. 2007). This alternative requires further consideration.

We hypothesised that if $VAR_{elements}$ of forearm rotation and/or wrist flexion–extension increased during pain, then $VAR_{elements}$ would be greatest at the beginning of the painful trial and subsequently decrease over repetitions in conjunction with the establishment of a new strategy for performing the simple task. As $VAR_{elements}$ of forearm rotation reduced, rather than increased, at the start of the painful trial, a further reduction towards the end of the painful trial is unlikely to have benefited the nervous system. There was a general trend for increased $VAR_{elements}$ between the start and finish of the trials, but this was present for both the painful and non-painful trials. This time-dependent change in $VAR_{elements}$ may suggest a generalised learning effect within each 45-repetition trial that is disrupted during the break between trials.

These data have possible clinical implications. The mechanisms by which the nervous system alters movement of the wrist/forearm during pain is relevant when considering the mechanisms that may underpin overuse-type injuries, that present in systems with limited degrees of freedom, such as lateral epicondylalgia (tennis elbow). If wrist/forearm variability is decreased in the acute stage of tennis elbow in a manner consistent with the present study, this could contribute to the transition to chronic tennis elbow by increasing cumulative tissue load as reduced $VAR_{elements}$ limits the sharing of load between structures. The model of hypertonic saline-induced acute pain has been used extensively and mimics several aspects of acute clinical pain [e.g. delayed muscle activation (Hodges et al. 2003)]. However, the pain is short lasting (typically <5 min) and is not worsened by contraction/stretch (Tsao et al. 2010).

Some limitations of the present study require consideration. We considered the magnitude of $VAR_{elements}$ at the point where the wrist passed through the neutral radial-ulnar deviation position. Other methods of analysis consider the entire time-series to evaluate coordination variability between movement planes (Heiderscheit et al. 2002; Peters et al. 2003) and the temporal structure of repetitive movements (Preatoni et al. 2010). However, the method used in this study provided evidence of an effect of pain that answered the question posed in the study. There may have been a small learning effect that carried between the pain session (performed first) and the control session without pain. However, any learning effect was likely to be minimal given the two-month gap between the two sessions. As the variability data were normalised to the maximum values recorded during each session for each participant, this would minimise the effect of any changes between sessions. Some recent work suggests that changes to variability of muscle activation (Fedorowich et al. 2013) and force (Svendsen and Madeleine 2010) may be gender-specific. Although these studies evaluated changes to variability due to fatigue, and not acute pain, whether gender affected the variability reported here requires further investigation with a sample selected to specifically address that issue.

Conclusions

Contrary to earlier data, which suggest that acute pain stimulates the nervous system to increase $VAR_{elements}$ during the performance of complex multi-joint tasks, we found decreased $VAR_{elements}$ when a simple task involved movement at one joint complex. This may suggest that the nervous system adapts to acute pain by altering the magnitude

of $VAR_{elements}$ in a manner that is specific to the task (i.e. simple vs. complex) that is performed.

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards The experiments comply with the current laws of Australia. All procedures were approved by the University of Queensland Medical Research Ethics Committee and conformed to the Declaration of Helsinki.

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