Cross Education as Exercise Therapy for Knee Osteoarthritis

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Submitted in fulfilment of the requirements for the degree of
Doctor of Philosophy

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DEAKIN UNIVERSITY

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Lastly, Simone (datdat), Oscar (shoot spider man) and Max (nah man), thanks for all the omelettes, motivation and putting up with me.
Knee osteoarthritis (KOA) affects greater than 30% of the Australian population over the age of 65 years of age, with the prevalence and severity increasing in the following decades of life. KOA is the fourth most prevalent cause of disability in women and the eighth in men, to a significant cost to the community. Hallmark features of KOA are the loss in knee extensor strength, increasing knee pain severity and deficits in functional performance. Therefore there is a clear and critical need for the investigation into potential cost effective therapeutic interventions in the treatment KOA. A potential therapeutic option is the cross education phenomenon. Cross education is defined as a unilateral resistance training stimulus that results in a strength increase in both the trained muscle group and untrained contralateral homologous muscle group. Preliminary investigations suggest that in a KOA cohort, a cross education intervention may improve bilateral knee extensor strength, pain and functional performance. Therefore, the aim of this thesis was to determine the efficacy of the cross education phenomenon in improving these measurements in older adults with diagnosed unilateral KOA.

To determine the magnitude of the cross education phenomenon in KOA, study one (chapter three) investigated a 4-week unilateral knee extensor strength training intervention in a cohort with diagnosed unilateral KOA compared to a KOA and healthy age-matched control groups. The findings showed that the trained limb knee extensor strength increased by 24% (P < 0.001); further this improvement was maintained 3-months post intervention. The untrained KOA limb knee extensor strength increased by 20% (P < 0.001); further this improvement was maintained 3-months post intervention. This equated to 78.2% of the strength gain of the trained limb. However, no change in knee extensor muscle thickness, as measured by sonography, occurred in trained limb (P = 0.317), or the KOA limb (P = 0.486). Study one (chapter three) demonstrated that unilateral strength training of the contralateral limb in unilateral KOA, results is significant and sustained bilateral strength improvements.
To determine the changes in knee pain severity following the 4-week cross education intervention, study two (chapter four) investigated changes in acute pain as measured by the visual analogue scale (VAS) and short term pain as measured by the Knee Injury and Osteoarthritis Outcome Score (KOOS) pain subscale. Symptom and quality of life (QOL) KOOS subscales were also investigated. The findings showed that trained limb VAS improved by 63% (P < 0.001); further this improvement was maintained 3-months post intervention. KOA limb VAS improved by 40% (P < 0.001) and this improvement was maintained 3-months post intervention. KOOS pain-subscale improved by 29.7% (P < 0.001) with this improvement being maintained 3-months post intervention. KOOS symptoms improved by 12% (P = 0.002) and this improvement was maintained 3-months post the intervention (P > 0.876). The KOOS QOL subscale improved by 44.6% (P < 0.001) and was maintained 3-months post intervention (P = 0.551). Study two (chapter four) demonstrated that unilateral strength training of the contralateral limb in unilateral KOA, results in significant and sustained bilateral improvements to acute and short term pain, symptoms and QOL.

To determine the changes in functional performance following the 4-week cross education intervention, study three (chapter five) investigated changes in objective functional performance as measured by the Stair Climb Test (SCT) and Timed Up and Go test (TUG). Further, subjective functional performance was measured via the KOOS ADL and Sport subscales. The findings showed that the SCT improved by 20.1% (P < 0.001) and this improvement was maintained for 3-months post intervention (P = 0.505). TUG improved by 23% (P < 0.001) and surprisingly 3-months post intervention there was a further improvement in the TUG by an additional 6% (P < 0.001). The KOOS ADL subscale improved by 28.5% (P < 0.001) and this was maintained at 3-months post intervention. The KOOS Sport subscale improved by 81.9% (P < 0.001) and was similarly maintained 3-months post intervention. Study three (chapter five) demonstrated that unilateral strength training of the contralateral limb in unilateral KOA, results in significant and sustained improvements to objective and subjective measures of functional performance.
The aims of Study four (chapter six) was to determine the potential corticospinal mechanisms that modulate knee extensor weakness in KOA and their response to a 4-week cross education intervention. Transcranial magnetic stimulation (TMS) was utilised to measure motor evoked potential (MEP) amplitude, silent period (SP) and short interval cortical inhibition (SICI). Hamstring co-activation was measured as it has been implicated as a potential modulating factor in knee extensor weakness. At baseline, no differences in MEP amplitude ($P = 0.476$), SP ($P > 0.379$) and SICI ($P = 0.282$) compared to the health age-matched control group. Further, no changes in MEP amplitude ($P = 0.176$), SP ($P > 0.999$) and no change in SICI ($P = 0.287$) occurred following the intervention. No change in hamstring co-activation occurred in the trained limb ($P = 0.655$). Hamstring co-activation of the untrained limb improved by $17.6\%$ ($P = 0.019$). Study four (chapter six) indicated that knee extensor strength deficits in KOA are not modulated by supraspinal influences.

Collectively, the results from this thesis support the efficacy of cross education as a therapeutic intervention in unilateral KOA. A 4-week long knee extensor strength training intervention of the contralateral limb in a cohort with diagnosed unilateral KOA resulted in significant improvements to knee extensor strength, knee pain, functional performance, symptoms and QOL. Importantly, these results were maintained for 3-months following the intervention. While no changes were observed in neurological measurements, this finding, or absence of one, is in alignment with previous studies.
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<tr>
<td>6MWT</td>
<td>6 Minute walk test</td>
</tr>
<tr>
<td>AMT</td>
<td>Active motor threshold</td>
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<tr>
<td>ADL</td>
<td>Activity of daily living</td>
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<tr>
<td>AMI</td>
<td>Arthrogenic muscle inhibition</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>EMG</td>
<td>Electromyography</td>
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<tr>
<td>CAD</td>
<td>Central activation deficit</td>
</tr>
<tr>
<td>CSA</td>
<td>Cross sectional area</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<tr>
<td>KOA</td>
<td>Knee osteoarthritis</td>
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<tr>
<td>KL</td>
<td>Kellgren &amp; Lawerence</td>
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<tr>
<td>KOOS</td>
<td>Knee injury and Osteoarthritis Outcome Score</td>
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<td>LBP</td>
<td>Lower back pain</td>
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<tr>
<td>MCID</td>
<td>Minimum clinically important difference</td>
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<td>MVIC</td>
<td>Maximal voluntary isometric contraction</td>
</tr>
<tr>
<td>M-Wave</td>
<td>Maximal compound wave</td>
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<tr>
<td>OA</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>OARSI</td>
<td>Osteoarthritis Research Society International</td>
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<tr>
<td>QOL</td>
<td>Quality of life</td>
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<tr>
<td>SCT</td>
<td>Stair climb test</td>
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<tr>
<td>sEMG</td>
<td>Surface electromyography</td>
</tr>
<tr>
<td>SICI</td>
<td>Short-interval intracortical inhibition</td>
</tr>
<tr>
<td>RF</td>
<td>Rectus femoris</td>
</tr>
<tr>
<td>RMS</td>
<td>Root mean square</td>
</tr>
<tr>
<td>RMT</td>
<td>Resting motor threshold</td>
</tr>
<tr>
<td>RT</td>
<td>Resting twitch</td>
</tr>
<tr>
<td>SES</td>
<td>Socioeconomic status</td>
</tr>
<tr>
<td>TKR</td>
<td>Total knee replacement</td>
</tr>
<tr>
<td>TMS</td>
<td>Transcranial magnetic stimulation</td>
</tr>
<tr>
<td>TUG</td>
<td>Timed up and go</td>
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<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
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</table>
Arthritis is an umbrella term that encompasses more than 100 musculoskeletal joint conditions, of which osteoarthritis (OA) is the most prevalent form. 2.1 million Australians or 9% of the population have diagnosed OA, with the knee the most commonly affected joint (AIHW, 2015). Globally, 3.8% of the world’s population have been radiographically diagnosed with knee osteoarthritis (KOA) (Cross et al., 2014). Further, greater than 30% of the Australian and global population over the age of 65 years of age has some degree of KOA based on radiographic evidence, with the prevalence and severity increasing in the following decades of life (Litwic et al., 2013, AIHW, 2015). The prevalence of unilateral and bilateral KOA is difficult to accurately quantify, and has been largely overlooked in the literature. In a Japanese cohort the prevalence of radiographic diagnosed unilateral and bilateral KOA was 10 and 21.6% respectively (Nishimura et al., 2012). However, over a 12 year period, up to 30% of individuals with asymptomatic knees, develop radiographic evidence of unilateral KOA, and further, in individuals with radiographic evidence of unilateral KOA at baseline, up to 80% of these individuals progressed to bilateral KOA in this period of time (Metcalfe et al., 2012, Jones et al., 2013, Nishimura et al., 2011). Therefore, bilateral KOA appears to directly progress from unilateral KOA and any individual diagnosed with unilateral KOA is at high risk of developing bilateral KOA, even if no symptoms are evident in the contralateral limb (Felson and Zhang, 1998).

KOA has a very low associated mortality rate with its incidence (AIHW, 2014), however, it results in substantial knee extensor strength loss in the KOA limb (Alnahdi et al., 2012) and contralateral limb in unilateral KOA (Bade et al., 2010, Gapeyeva et al., 2007, Berth et al., 2002, Stevens-Lapsley et al., 2010, Lewek et al., 2004, Liikavainio et al., 2008), knee pain (Felson, 2005) and deficits to objective (Liikavainio et al., 2008, Bade et al., 2010, Hurley et al., 1997, Bieleman et al., 2010, Ciolac et al., 2015) and subjective functional performance (O'Reilly et al., 1998, Bieleman et al., 2009, Gapeyeva et al., 2007, Mahmoudian et al., 2014, Heiden et al., 2009, Slemenda et al., 1997). These modulating factors ultimately lead to disability, comorbidities and increased healthcare expenditure.
OA and other musculoskeletal conditions are the 4th highest health related expenditure behind cardiovascular disease (CVD), oral and mental health (AIHW, 2015). More than 8.7% of Australia’s total health expenditure, 4,690 million is spent on OA and other musculoskeletal conditions annually, of which OA accounts for 29% or 1,637 million. However, beyond the annual direct expenditure, individuals with OA are 2.4 times more likely to have CVD and diabetes, 1.5 times more likely to have lower back pain (LBP), and .65 times more likely to have mental health problems when compared to individuals without OA (AIHW, 2015). The final therapeutic option for KOA is total knee replacement (TKR) surgery. In the 10-years preceding 2015 there was a 29% increase in the rate of total knee replacements (TKR) for the treatment of KOA, this trend is expected to continue over the coming decades (AIHW, 2015).

Therefore, there is a clear and critical need for further research into the development of efficacious and cost effective rehabilitation techniques that are translatable into clinical and community environments in treating and minimizing the disability and economic impact of KOA. Current rehabilitation practice as recommended by The Royal Australian College of General Practitioners (RACGP), include exercises that focus on the KOA limb, which incorporate function movements such as sit to standing, step ups and squats, using body weight as the resistance, with a frequency of three times per week (RACGP, 2016). A possible treatment beyond current rehabilitation approaches in addressing the symptoms and disability associated with KOA is the cross education phenomenon (Scripture et al., 1894). Cross education is defined as a unilateral resistance training stimulus that results in a strength increase in both the trained muscle group and the untrained contralateral homologous muscle group (Manca et al., 2017). Whilst an interesting phenomenon in young healthy adults, the potential clinical applications of the cross education phenomenon had been highlighted by many authors over a large period of time (Farthing and Zehr, 2014, Hendy et al., 2012, Zhou, 2003, Kannus et al., 1992, Devine et al., 1981, Gregg et al., 1957, Hellebrandt, 1951)
In recent years the potential of cross education has been successfully exploited in a range of clinical populations (Magnus et al., 2013, Manca et al., 2016a, Dragert and Zehr, 2013, Kim et al., 2015). However to date, the cross education phenomenon has only been superficially exploited in bilateral KOA (Malas et al., 2013) and unilateral KOA (Onigbinde et al., 2017). In both studies there was an absence of control groups, making the quantification of the strength transfer from the trained to untrained limb as outlined by Carrol (2006) impossible. Further, to date there has been no investigation into changes in knee pain severity or functional performance following a cross education intervention in unilateral KOA.

Knee extensor strength loss is a hallmark feature of KOA (Alnahdi et al., 2012). Further, in unilateral KOA a bilateral knee extensor strength loss occurs, with the contralateral limb affected to a lesser extent (Bade et al., 2010, Gapeyeva et al., 2007, Berth et al., 2002, Stevens-Lapsley et al., 2010, Lewek et al., 2004, Liikavainio et al., 2008). Knee extensor strength loss in unilateral KOA is of critical concern as decreasing knee extensor strength has been associated with increased knee pain severity (Ruhdorfer et al., 2014, O’Reilly et al., 1998, Steidle-Kloc et al., 2015). Further, deficits in knee extensor strength of the KOA limb (Gur and Cakin, 2003, Topp et al., 2000, Rejeski et al., 1996, Brown et al., 2009, Maly et al., 2005) or the contralateral limb in unilateral KOA (Brown et al., 2009, Topp et al., 2000) are associated with deficits in functional performance. Therefore, study 1 (chapter 3) investigated a 4-week unilateral strength training intervention of the contralateral limb in an older adult cohort with diagnosed unilateral KOA, compared to a KOA control group and a healthy age-matched control group. The aims of this study were to quantify the magnitude of the transfer of knee extensor strength from the trained contralateral limb in unilateral KOA to the untrained KOA limb.

Knee pain is the dominate and most disabling symptom in KOA (Felson, 2005). Knee pain has a strong correlation to deficits in knee extensor strength (Ruhdorfer et al., 2014, O’Reilly et al., 1998, Steidle-Kloc et al., 2015), and is independently associated with deficits
in functional performance (Lohmander et al., 2004, O'Reilly et al., 1998, Cubukcu et al., 2012, McAlindon et al., 1993, Dieppe et al., 1997, Kitayuguchi et al., 2016). Knee pain severity is the strongest predictor of quality of life, and individuals with KOA have significantly lower QOL when compared to age-matched healthy controls (Jordan et al., 1997, Hawker et al., 2008). Therefore, study 2 (chapter 4) investigated changes in knee pain severity following a 4-week unilateral strength training intervention of the contralateral limb in an older adult cohort with diagnosed unilateral KOA. As knee pain severity is inversely associated with knee extensor strength, an increase in knee extensor strength of the trained contralateral limb and also the untrained KOA limb may reduce knee pain severity and improve QOL.

The primary identified causes for functional decline in KOA are pain (Gur and Cakin, 2003, Rejeski et al., 1996, Topp et al., 2000, Marks, 1994) and knee extensor strength deficits of the affected limb in unilateral KOA (Gur and Cakin, 2003, Topp et al., 2000, Rejeski et al., 1996, Brown et al., 2009, Maly et al., 2005) and the unaffected limb in unilateral KOA (Brown et al., 2009, Topp et al., 2000). A reduction in knee pain severity will not automatically lead to improvements in functional performance (White et al., 2011). However, increased knee extensor strength of either the KOA limb or contralateral limb are independently associated with improved functional performance (Valtonen et al., 2015), regardless of knee pain severity (Zhang et al., 2010, McAlindon et al., 2014, Alnahdi et al., 2012). Therefore, study 3 (chapter 5) investigated the changes in subjective and objective functional performance following a 4-week unilateral strength training intervention of the contralateral limb in an older adult cohort with diagnosed unilateral KOA.

A variety of mechanisms have been implicated in modulating knee extensor strength loss in KOA. Arthrogenic muscle inhibition (AMI) has been implicated as the primary mechanism (Rice and McNair, 2010), however, potential corticospinal influences of AMI remain unclear and largely unexplored in KOA (Hunt et al., 2011, Rice et al., 2014, Kittelson
et al., 2014). Further, hamstring co-activation has been implicated in contributing to knee extensor weakness (Busse et al., 2006), however to date it remains unclear if the cross education phenomenon can influence hamstring co-activation. Therefore, study 4 (chapter 6) investigated the corticospinal responses and the level of hamstring co-activation following a 4-week unilateral strength training intervention of the contralateral limb in an older adult cohort with diagnosed unilateral KOA.

The overall purpose of this thesis was to systematically examine the efficacy of applying the cross education phenomenon as an exercise therapy, in a clinical population suffering from radiograph diagnosed tibiofemoral unilateral KOA. Furthermore, this thesis also aimed to quantify the magnitude of the cross education phenomenon on knee extensor strength, and the effect the improvement in knee extensor strength had on knee pain severity, functional performance, symptoms and QOL. Lastly, this thesis also examined the potential corticospinal responses that may contribute to these improvements.
1.1 Primary aims of this thesis:

To quantify the effectiveness of the cross education phenomenon in unilateral KOA and to determine if it is an efficacious rehabilitation approach in improving bilateral knee extensor strength, knee pain severity, objective and subjective functional performance in patients with diagnosed unilateral KOA.

1.2 Specific aims of this thesis:

1. To determine if 4-weeks of unilateral knee extensor strength training of the contralateral limbs in unilateral KOA will impart a strength improvement to the untrained KOA limbs knee extensors. Further, to quantify the magnitude of strength transfer due to the cross education phenomenon, and the 3-month retention of knee extensor strength following completion of the intervention (Study 1).

2. To examine changes in acute and short term knee pain severity, knee symptoms and QOL, following bilateral knee extensor strength improvements due to the cross education phenomenon, and to examine if these improvements are retained for 3-months post-intervention (Study 2).

3. To examine the changes in subjective and objective functional performance, following bilateral knee extensor strength improvements and a bilateral reduction in knee pain severity following a cross education intervention, and to examine if these improvements are retained for 3-months post-intervention (Study 3).

4. To establish the potential underlying mechanisms that may modulate the improvements in knee extensor strength, knee pain severity and functional performance following the cross education intervention (Study 4).
1.3 Primary Hypothesis:

It was hypothesised that 4-weeks of unilateral knee extensor strength training in individuals with unilateral KOA would result in a larger cross education effect than seen in non-pathological populations. The improvement in knee extensor strength would be accompanied by a decrease in knee pain severity, improvements in functional performance and QOL. Furthermore, it is hypothesised that the changes in knee extensor strength, pain severity and functional performance will be modulated by improvements in corticospinal control of the knee extensors. Lastly, all improvements would be retained for 3-months following the cross education intervention.

1.4 Specific hypotheses:

1. Following 4-weeks of unilateral knee extensor strength training of the contralateral limb in unilateral KOA would increase knee extensor strength bilaterally, and that the magnitude of strength transfer from the cross education phenomenon would be greater than seen in non-pathological populations. Further, the improvements in knee extensor strength would be retained for 3-months following the intervention (Study 1).

2. Following 4-weeks of unilateral knee extensor strength training of the contralateral limb in unilateral KOA, acute and short term knee pain severity, symptoms and QOL would improve. Further, these improvements would be retained for 3-months following the intervention (Study 2).

3. Following 4-weeks of unilateral knee extensor strength training of the contralateral limb in unilateral KOA, subjective and objective functional performance would improve. Further, these improvements would be retained for 3-months following the intervention (Study 3).
4. Underpinning the improvements in knee extensor strength following the 4-week unilateral strength training intervention would be reduced hamstring co-activation, increased corticospinal excitability and reduced intracortical inhibition in the ipsilateral primary motor cortex (Study 4).
CHAPTER TWO

REVIEW OF THE LITERATURE
2.0 Overview

This chapter will begin by outlining the prevalence and economic cost of KOA, highlighting the need for efficacious and cost effective therapeutic treatments. The chapter will then briefly review aetiology of KOA, following with a thorough review of the key symptoms arising from KOA; pain; knee extensor strength; functional performance, and the interactions between these symptoms. This chapter will then explore the potential mechanisms modulating the loss in knee extensor strength and ultimately pain severity and functional performance. This chapter will introduce a novel therapeutic approach in treating the symptoms arising from KOA, the cross education phenomenon. Finally, this chapter will discuss the potential therapeutic efficacy on knee extensor strength, knee pain severity and functional performance of applying a cross education intervention in a KOA cohort with unilateral KOA.

2.1 Prevalence and economic cost of KOA

OA affects approximately 2.1 million Australians or 9% of the population, with the knee the most commonly affected joint (AIHW, 2015). Globally, 3.8% of the world’s population have been radiographically diagnosed with KOA, with higher rates seen in women (4.8%) compared to men (2.8%) (Cross et al., 2014). KOA is more commonly seen in the right knee than the left knee (23% vs 16.3%) (D'Ambrosia, 2005). More than 30% of the population over the age of 65 years of age have some degree of KOA based on assessment using the Kellgren and Lawrence (KL) scale, which is a five point likert scale which categorises KOA based on radiographic evidence, from grade 0: no radiographic evidence, to grade 4: large osteophytes, marked joint space narrowing and severe sclerosis (Kellgren & Lawrence, 1957). Further, the prevalence and severity of KOA increases in the following decades of life (Litwic et al., 2013). OA affects significantly more individuals in the lowest socioeconomic status group (SES) than the highest SES group (AIHW, 2015), which
is problematic as 61% of the treatment costs are borne by the individual affected (Economics, 2007).

Arthritis and other musculoskeletal conditions account for the 4th highest health care expenditure in Australia at 8.7% of total health expenditure, of which OA is the most common subgroup of this category, with the highest direct health expenditure at 1,637 million annually (AIHW, 2014). The highest portion of this expenditure (57%) is on hospital admitted patient services, specifically joint replacement surgery, which is the final therapeutic option for end stage OA, followed by arthroscopy for OA pain and symptom relief (AIHW, 2014). In the 10-years preceding 2015 there was a 29% increase in the rate of total knee replacements (TKR) for the treatment of KOA, which increased from 133 to 172 per 100,000 population. However, the population wide rate of TKR is misleading, as the rate of diagnosed OA is relatively low in adults below 54 years of age (9.6%) compared to older adults above >65 years of age (30.9%), the population wide rate of TKR in the older adult demographic is above 1000 TKR per 100,000 population (AIHW, 2015).

OA has a very low associated mortality rate with its incidence, of 137,854 deaths in Australia in 2007, osteoarthritis and rheumatoid arthritis were the underlying causes in only 79 instances (AIHW, 2014). However, individuals with OA have a significantly higher rate of comorbidity when compared to their healthy peers. For example, 51% of OA suffers report having CVD compared to 15% of individuals without OA; 35% report having lower back pain (LBP) compared to 15% of individuals without OA; and 18% report having mental health issues compared to 11% of individuals without OA (AIHW, 2015).

The prevalence of unilateral compared to bilateral KOA is difficult to quantify, with limited direct data available, such as the Australian Health Survey not discriminating between unilateral and bilateral KOA (AIHW). Nishimura and colleagues (2012) identified this vacuity in the literature and reported the prevalence of radiographic diagnosed unilateral and bilateral KOA at 10 and 21.6% respectively. However, over a period of time, particularly
once increasing aged is taken into account; many individuals with initially unilateral KOA will develop radiographic evidence and symptoms in the contralateral limb. Over a 12 year period, up to 30% of individuals with no KOA, develop radiographic evidence of unilateral KOA, and further, in individuals with radiographic evidence of KOA at baseline, up to 80% of these individuals progressed to bilateral KOA in this period of time (Metcalfe et al., 2012, Jones et al., 2013, Nishimura et al., 2011). Further, in the decade following TKR, up to 37% of individuals will have bilateral TKR (Ritter et al., 1994, McMahon and Block, 2003). Therefore, any individual diagnosed with unilateral KOA is at high risk of developing bilateral KOA, even if no symptoms are evident, as it is not uncommon for individuals with radiographic evidence of KOA to be asymptomatic (Felson and Zhang, 1998).

### 2.2 Aetiology of Osteoarthritis

The following subsections will briefly outline the dominate factors in the aetiology of OA. The development of KOA is multifactorial (Aspden, 2008), with both endogenous and exogenous risk factors being implicated, and logically these factors interact together for many individuals. Endogenous risk factors include age and sex, while exogenous risk factors include macro trauma and previous surgery, repetitive micro trauma, obesity and various lifestyle factors (Michael et al., 2010).

#### 2.2.1 Age

Knee osteoarthritis has often been considered a disease of the elderly and while age is the strongest predicting factor (Prieto-Alhambra et al., 2014), KOA can occur at any age and is not an inevitable consequence of aging (Anderson & Loeser, 2010). The incidence of KOA continues to rise through the lifespan, with the incidence at 3% for <44 year olds and 35.1% for >80 year olds, with the highest number of TKRs occurring at 65-69 years of age (AIHW, 2015). The reasons for the increase in incidence throughout the lifespan are multifactorial, and the adage of ‘wear and tear’ is too simple of an explanation to explain the
increasing incidence, considering a decline in physical activity as we age has an inverse relationship to the incidence of KOA (American College of Sports et al., 2009).

As we age, there is an inability of cells to maintain homeostasis under metabolic or physical stress that may account for the increased incidence of KOA (Ferrucci et al., 2001). Chondrocytes appear to be particularly vulnerable to the aging process, they play a vital role in maintaining the cartilaginous matrix, but, uniquely they rarely undergo cell division, so when chondrocytes apoptosis, the remodelling ability of cartilage is diminished (Anderson & Loeser, 2010). Compounding this, MRI studies have shown that the cartilage matrix thins with age, particularly around the patella-femoral joint (Ding, Cicuttini, Scott, Cooley, & Jones, 2005; Hudelmaier et al., 2001). This sequelae of thinner cartilage with a reduced ability to remodel under loading or stress, may partially explain the increasing incidence of KOA with increasing age. Further, age related sarcopenia of the lower limbs resulting in reduced knee extensor strength has been implicated in the progression and severity of KOA (Kim et al., 2016)

2.2.2 Sex

The incidence KOA between men and women is similar until menopause, in which the prevalence is doubled in females compared to men (AIHW, 2015, O'Connor, 2006, Srikanth et al., 2005). Concurrently, the severity becomes greater (Debi et al., 2009) and the rate of hospitalisation is around 20% higher than seen in men (AIHW, 2015). Despite this, there is still a lack of well powered studies investigating this occurrence (Hame and Alexander, 2013). It appears that the cause of this discrepancy between the sexes is multifactorial, difference in hormones, particularly the post-menopausal estrogen loss has been strongly implicated (Felson and Zhang, 1998). Further, anatomical differences may play a role, with women having wider pelvises, shorter femurs, smaller tibial condylar joints and therefore a greater Q angle at the knee joint (Conley et al., 2007). In support, due to anatomical differences, women also present with kinematic variances when compared to
men, most notably greater valgus moments (Chappell et al., 2002). Further, due to these factors, women suffer from KOA in differing locations, specifically tibial and patella cartilage loss within the knee when compared to men (Hanna et al., 2009).

### 2.2.3 Physical activity

Physical activity has been shown to have a strong correlation with the development of KOA (Felson et al., 1997), but the relationship is not a simple one, with the ‘wear and tear’ theory being unlikely at best (McAlindon et al., 1999). Mild to moderate levels of physical activity typically seen in recreational pursuits and amateur sports, appear to have little to no influence on the development of KOA regardless of the activity (Felson et al., 2007, Gross and Marti, 1997, Lequesne et al., 1997, Lane et al., 1993). Further, it has been reported that moderate levels of activity may actually decrease the incidence of KOA in some populations (Manninen et al., 2001). However, individuals who undergo professional levels of sports training and activity, with both high volume and intensity of training are more than 2-3 times likely to develop KOA than their more sedentary peers, once confounding factors such as previous injury and BMI are adjusted for (Deacon et al., 1997, Kujala et al., 1995, Kujala et al., 1994, Spector et al., 1996) Occupational levels of physical activity as seen in labouring workforces also have a significantly higher incidence of KOA (Jensen et al., 2000), and there is a dose response correlation with greater time kneeling and squatting leading to higher incidences of KOA (Jensen, 2005).

### 2.2.4 Trauma

Previous knee trauma is likely to be the dominate exogenous cause of KOA (Felson et al., 1997, Silverwood et al., 2015), with 12% of all diagnosed KOA being attributed to previous trauma (Brown et al., 2006). Individuals with previous knee trauma has been shown to have a 5-fold increase of developing KOA compared to no injury in a 36 year long prospective study (Gelber et al., 2000). Previous knee trauma, particularly anterior cruciate
Ligament (ACL) injuries have been shown to result in the accelerated development of post-traumatic KOA, with 30% incidence of KOA within 5-years (Frobell et al., 2013). Further, 10-20 years post ACL or menisci tear, a 50% incidence rate of KOA has been observed (Lohmander et al., 2007). Individuals over 30-years of age show the highest rate of progression (Roos et al., 1995), with older adults (50-79 years old) demonstrating a KOA incident rate of 84% within 30 months of meniscal damage (Englund et al., 2009). A similar trend is seen in younger adults (26 – 40 years old) who had sustained previous ACL injury in the previous 12 years, 82% had radiographic evidence of KOA. Importantly, 75% of this group had a significant detrimental effect on their quality of life measures, as measured by the KOOS (Lohmander, Östenberg, Englund, & Roos, 2004).

2.2.5 Obesity

Being overweight and obese is a significant risk factor for the development of KOA (Silverwood et al., 2015). Increasing population wide BMIs have been implicated in the increasing incidence of KOA (Neogi and Zhang, 2013), with overweight and obese individuals being respectively 2.18 and 2.63 more likely to have diagnosed KOA than healthy weight individuals (Blagojevic et al., 2010). Further, prolonged exposure to a high BMI throughout adulthood carries the highest risk of obesity initiated KOA, highlighting the potential importance of weight control at any age (Wills et al., 2012). However, a decrease in BMI by 2 units over a 10-year period can reduce the risk of developing symptomatic KOA in women by 50% (Christensen et al., 2007). Furthermore, there is strong evidence supporting weight loss interventions in individuals with KOA resulting in a reduction to knee pain severity and an increase in functional performance (Lee and Kean, 2012).

Increased mechanical load on the knee joint has been frequently implicated as a primary cause of obesity related KOA (Neogi and Zhang, 2013, Felson, 2013), with greater compressive and shearing forces during ambulation (Harding et al., 2016). However, body composition may be as important as BMI, with increased adipose tissue having a negative
association with cartilage loss and increased lean muscle mass reducing the loss of cartilage (Ding et al., 2013). Metabolic and inflammatory factors have also been implicated in the initiation of obesity related KOA, however their role is not entirely elucidated (Aspden, 2011).

2.3 Pathology of knee osteoarthritis

The following subsections will outline the primary pathology in KOA: knee pain severity, deficits in knee extensor strength and functional performance. Further the interactions between these factors will be outlined.

2.3.1 Pain

Pain is the dominate and most disabling symptom in KOA (Felson, 2005). Knee pain severity is the strongest predictor of quality of life, and individuals with KOA have significantly lower QOL when compared to age-matched healthy controls (Jordan et al., 1997, Hawker et al., 2008). Knee pain is the primary reason why people suffering from KOA seek primary care and pharmacological interventions (Bidaut-Russell and Gabriel, 2001). Consequently, knee pain is the primary reason why individuals suffering from KOA elect to undergo TKR surgery (Altman and Gold, 2007). While joints have excellent innervation for both nociception and proprioception (Grubb, 2004), cartilage has no nociception, and cartilage loss is often in the absence of symptoms (Felson, 2005).

There is no clear consensus in the literature as to the dominate cause of KOA pain, with mechanical factors being well established (Felson, 2013, Hunter et al., 2013), and the inflammation factors gaining traction in recent years (Scanzello and Goldring, 2012, Berenbaum, 2013). While both mechanical and inflammatory mechanisms have been implicated, it is probable that both are the dominate factor in modulating pain at differing stages of KOA, with neither being more important than the other (Felson, 2013, Berenbaum, 2013).
Regardless of the mechanisms modulating pain in KOA, pain has a strong correlation with deficits in knee extensor strength (Ruhdorfer et al., 2014, O'Reilly et al., 1998, Steidle-Kloc et al., 2015) deficits in knee extensor muscle mass (Lee et al., 2016, Sattler et al., 2012, Wang et al., 2012), and deficits in functional performance (Lohmander et al., 2004, O'Reilly et al., 1998, Cubukcu et al., 2012, McAlindon et al., 1993, Dieppe et al., 1997, Kitayuguchi et al., 2016). Unilateral KOA pain has also been implicated in deficits of the knee extensor mechanism (Rice and McNair, 2010).

Greater knee extensor strength has been associated with decreased knee pain severity (Muraki et al., 2015, Amin et al., 2009, Maurer et al., 1999, Roos et al., 2011). Supporting this, a meta-analyses has reported a small but significant decrease in knee pain severity following strength training interventions (Jansen et al., 2011). Further, a recent Cochrane review reported a land-based therapeutic exercise resulting in short term pain benefits (2-6 months). As highlighted by White and colleagues (2011) there is a common assumption that a decrease in pain severity independent from improvements in knee extensor strength will lead to an increase in functional performance. However, White and colleagues (2011) reported that nearly a quarter of participants who has a significant reduction in knee pain severity in either one or both limbs, also had a significant decrease in functional performance as measured by a walking speed test. However, these participants had also developed at least one comorbidity, highlighting why a reduction in pain may not have been accompanied by the retention or improvement in functional performance.

Knee extensor strength of the contralateral limb in unilateral KOA may also be influenced by pain severity of the KOA limb (Steidle-Kloc et al., 2015). This finding is supported by research in unilateral KOA, anterior knee pain and anterior cruciate surgery (Hart et al., 2010, Pietrosimone et al., 2011), demonstrating that pain severity in the index limb contributes to a reduction in knee extensors strength of the contralateral limb, due to the inability to fully recruit the knee extensor muscle group.
2.3.2 Knee extensor strength

Deficits in knee extensor strength are a hallmark feature of KOA, with the knee extensors of the KOA limb in unilateral KOA significantly weaker when compared to healthy age-matched controls, ranging from 10-56% (Bade et al., 2010, Gapeyeva et al., 2007, Pap et al., 2004, Palmieri-Smith et al., 2010, Hortobagyi et al., 2004, Liikavainio et al., 2008, Hurley et al., 1997, Cheing and Hui-Chan, 2001, Heiden et al., 2009, Tan et al., 1995, Diracoglu et al., 2009, Messier et al., 1992, Thomas et al., 2010, Berth et al., 2002, Jan et al., 1990, Fisher and Pendergast, 1997, Lewek et al., 2004, Hall et al., 1993, Slemenda et al., 1997, Rice et al., 2011). Further the KOA limb in unilateral KOA is significantly weaker than the contralateral limb, ranging from 18-31% (Petterson et al., 2008, Vahtrik et al., 2012, Stevens et al., 2003, Gapeyeva et al., 2007, Berth et al., 2002, Stevens-Lapsley et al., 2010, Rice et al., 2011, Skoffer et al., 2015). Interestingly, studies frequently use the contralateral limb as a control (Stevens et al., 2003, Vahtrik et al., 2012, Gapeyeva et al., 2007). However, in unilateral KOA the knee extensor strength deficit is frequently a bilateral occurrence, with the contralateral limb affected to a lesser extent (Pietrosimone et al., 2011). Therefore, using the contralateral limb as a control may be an erroneous approach as the contralateral limb in unilateral KOA is significantly weaker than healthy age-matched controls (Bade et al., 2010, Gapeyeva et al., 2007, Berth et al., 2002, Stevens-Lapsley et al., 2010, Lewek et al., 2004, Liikavainio et al., 2008). Interestingly, knee extensor weakness may be present in the KOA limb in the absence of knee pain or muscle atrophy, further highlighting the potential neurological mechanism in KOA (Slemenda et al., 1997).

Individuals with diagnosed KOA frequently have a higher BMI when compared to healthy age-matched controls (Liikavainio et al., 2008, Bade et al., 2010, Conroy et al., 2012). Increasing BMI is positively associated with greater lower limb lean muscle mass (Slemenda et al., 1998), however lower limb increased muscle mass does not correlate to increased knee extensor strength. Further, when knee extensor strength is
normalised to BMI, knee extensor strength deficits are further magnified (Hall et al., 2006, Hassan et al., 2001, Liikavainio et al., 2008). Critically, a higher BMI in relation to knee extensor strength is negatively associated with deficits in functional performance (Creamer et al., 1999).

### 2.3.3 Functional performance

Functional performance, which may also be called functional ability, capacity or status, is defined as an individual’s ability to successfully engage in activities of daily living (ADL), such as bathing, toileting, eating, transferring from beds or chairs and other general domestic tasks without assistance (Mor et al., 1989). If an individual’s functional performance declines enough to be unable to successfully engage in ADL’s, they are classed as disabled, resulting in loss of independence which often requires part to fulltime homecare or permanent institutionalisation (Fortinsky et al., 1999). Further, there is a strong correlation between disability and mortality (Manton, 1988, Covinsky et al., 1997), which may be reflected by the significantly higher rate of comorbidity in the KOA population compared to the general population (AIHW, 2015).

Functional performance can be measured by physical performance tests or self-reported subjective surveys. The Osteoarthritis Research Society International (OARSI) recommends for KOA, a minimum core set of physical performance tasks to include sit to stand, walking short distances and stair negotiation (Dobson et al., 2013), such as the stair climb test (SCT) (Lin et al., 2001) and the timed up and go test (TUG) (Podsiadlo and Richardson, 1991). Self-reported surveys include the Western Ontario and MacMaster Universities Arthritis Index of Osteoporosis (WOMAC) (Bellamy et al., 1988) or the Knee injury and Osteoarthritis Outcome Score (KOOS) (Gossec et al., 2007). However, pain is the dominate factor in determining self-reported functional performance scores (Maly et al., 2006, Stratford et al., 2006). Pain severity may partially explain why there is a disparity between self-reported functional scores and physical performance measures (Stratford et al.,
2003, Louie and Ward, 2010, Kempen et al., 1996). While self-reported surveys such as the WOMAC and KOOS are valid and reliable, functional measurements scores from these surveys should not replace physical functional performance tests (Louie and Ward, 2010).

When compared to healthy age-match controls, individuals with KOA have significant deficits on functional performance tests (Liikavainio et al., 2008, Bade et al., 2010, Hurley et al., 1997, Bieleman et al., 2010, Ciolac et al., 2015), and self-reported functional performance surveys, such as the WOMAC and KOOS (O’Reilly et al., 1998, Bieleman et al., 2009, Gapeyeva et al., 2007, Mahmoudian et al., 2014, Heiden et al., 2009, Siemenda et al., 1997). Interestingly, severity of radiographic evidence appears to have no influence on functional deficits (O’Reilly et al., 1998, McAlindon et al., 1993, Liikavainio et al., 2008, Creamer et al., 1999). However, Bade and Colleagues reported significantly worse functional performance immediately prior to TKR, which may be due to knee pain severity or increased inflammation (Cubukcu et al., 2012), however Bade and colleagues (2010) did not report pain severity, making it unclear if pain potentially influenced these findings.

The primary identified causes for functional decline in KOA are pain (Gur and Cakin, 2003, Rejeski et al., 1996, Topp et al., 2000, Marks, 1994), reduced knee extensor strength of the affected limb in unilateral KOA (Gur and Cakin, 2003, Topp et al., 2000, Rejeski et al., 1996, Brown et al., 2009, Maly et al., 2005) and the knee extensor strength of the unaffected limb in unilateral KOA (Brown et al., 2009, Topp et al., 2000). A reduction in knee pain severity will not automatically lead to improvements in functional performance (White et al., 2011). However, increased knee extensor strength of either the KOA limb or contralateral limb are independently associated with decreased stair ascension time and increased walking speed (Valtonen et al., 2015). This suggests that increasing knee extensor strength of either the KOA limb or the contralateral limb may increase functional performance, regardless of knee pain severity (Zhang et al., 2010, McAlindon et al., 2014, Alnahdi et al., 2012).
2.4 Mechanisms underpinning the loss of knee extensor strength

The primary mechanism underpinning the chronic loss of knee extensor strength throughout the progression of KOA is arthrogenic muscle inhibition (AMI) (Rice and McNair, 2010). AMI is the result of joint trauma, inflammation and pain, which are hallmark features of KOA (Fisher and Pendergast, 1997, Pietrosimone et al., 2011, Hurley and Newham, 1993b, Callaghan et al., 2014). Secondary mechanisms include the loss of knee extensor muscle cross sectional area (CSA) (Petterson et al., 2008). Further, hamstring co-activation has been implicated in contributing to knee extensor weakness (Busse et al., 2006).

2.4.1 Knee extensor CSA

The loss in CSA appears to account for less than half the knee extensor strength deficits in the KOA limb when compared to AMI (Petterson et al., 2008), however there is conflicting findings with KOA cohorts having significantly less knee extensor muscle CSA when compared to healthy age-matched controls (Toda et al., 2000, Segal and Toda, 2005), or no difference in knee extensor muscle CSA when compared to healthy age-matched controls (Slemenda et al., 1997, Liikavainio et al., 2008, Conroy et al., 2012). Greater lower extremity muscle mass also correlates strongly ($R^2 = 0.83$) with increased body weight (Slemenda et al., 1998). KOA cohorts typically have greater BMIs than healthy age-matched controls, this may explain why in some KOA cohorts no differences in lower limb muscle mass are observed (Slemenda et al., 1998). As knee extensor strength in these cohorts is significantly lower than the healthy age-matched controls, whilst the lower limb muscle mass is the same, this highlights that additional modulating factors may be responsible for the strength loss (Slemenda et al., 1997, Liikavainio et al., 2008, Conroy et al., 2012). Further, it may be possible that the increased body mass and therefore increased lower limb muscle mass, is masking muscle atrophy in these KOA cohorts.
Pain severity of the KOA limb is associated with decreased knee extensor CSA when compared to the pain free contralateral limb (Sattler et al., 2012). Pain severity also correlates to the loss of knee extensor CSA over a 2-year period (Wang et al., 2012). Further highlighting the importance of neurological factors over lower limb muscle mass in influencing knee extensor strength, a KOA cohort that underwent a weight loss intervention, had a significant reduction in lower limb lean muscle mass (Wang et al., 2007). However, this KOA cohort concurrently had a significant increase in knee extensor strength. Therefore, whilst deficits in lower limb muscle mass in a KOA cohort may be partially responsible for knee extensor strength deficits, it is unlikely that the loss in in knee extensor muscle mass is the dominate modulating factor.

2.4.2 Hamstring co-activation

Co-activation of the hamstrings during knee extensor movements is necessary for joint stability, as it acts to counter the anterior tibial shearing forces produced by the knee extensors and equalise articular surface pressure (Draganich et al., 1989, Baratta et al., 1988, Aagaard et al., 2000). Hamstring co-activation occurs in healthy knees, with 6% of maximal hamstring activation during MVICs, 12% during a sit to stand task and 11.8% during a walking task. However, in KOA, hamstring activation is significantly higher, with up to 17% during MVICs, 25% during a sit to stand task and 24% during the walking task (Busse et al., 2006, Zeni et al., 2010). High levels of hamstring co-activation have been consistently reported in knee pathology (Zeni et al., 2010, Hortobágyi et al., 2005, Lewek et al., 2006, Ramsey et al., 2007, Rudolph et al., 2007), however there is also conflicting findings, with no differences in hamstring co-activation when compared to a healthy control group (Heiden et al., 2009).

Excessive hamstring co-activation during knee extension movements manifests as decreased knee extensor strength, which is of concern as knee extensor strength is a dominate factor in functional performance (Gur and Cakin, 2003, Topp et al., 2000, Rejeski
et al., 1996, Brown et al., 2009, Maly et al., 2005). Previous training studies have reported conflicting results, with increased co-activation following a strength training intervention (de Boer et al., 2007, Simoneau et al., 2006), decreased co-activation (Hakkinen et al., 1998, Carolan and Cafarelli, 1992, Stock and Thompson, 2014), or no change (Hakkinen et al., 1998). In an attempt to resolve the inconsistent findings in hamstring co-activation a recent meta-analysis reported that changes in co-activation in the lower limbs in the elderly are inconsistent. Further, the inconsistencies appear to be due to the joint involved, ankle or knee, type of contraction and the task utilised during measurement (Arnold and Bautmans, 2014), therefore further investigation of changes in co-activation are warranted.

2.4.3 Arthrogenic muscle inhibition

The existence of AMI and its influence on knee extensor strength and activation has been well established in KOA (Callaghan et al., 2014, Stevens et al., 2003, Hurley and Newham, 1993a, Hurley et al., 1997, O’Reilly et al., 1998, Lewek et al., 2004, Pap et al., 2004, Hassan et al., 2001). AMI is thought to be a protective mechanism following joint trauma, by reducing loading onto the joint (Hart et al., 2010). However, decreased knee extensor strength has been associated with an increase (23%) in the rate of loading though the limb (Mikesky et al., 2000), which potentially may aggravate the knee joint, subsequently increasing pain and joint effusion and therefore increasing AMI.

AMI is a dominate factor in modulating knee extensor strength in KOA, and therefore is of clinical importance, despite this, the mechanisms modulating AMI have not been fully elucidated (see figure 2.1). In KOA, AMI has been attributed to joint trauma, inflammation and pain (Rice and McNair, 2010). It is unclear as to which stimulus may be the dominate modulating factor, with a complex interaction between these being likely. Pain has been independently implicated as a modulating factor of AMI, with increasing VAS scores (10mm) accompanied by a 1.6% decrease in voluntary muscle activation, as measured via the interpolated twitch technique (Callaghan et al., 2014). Pain also correlates strongly with knee
extensor strength loss in KOA, so this is not a surprising finding (Ruhdorfer et al., 2014, O’Reilly et al., 1998, Steidle-Kloc et al., 2015). However, AMI has been reported in KOA in the absence of pain and joint effusion (Hurley and Newham, 1993a). Interestingly, deficits in knee extensor strength are also observed prior to pain or radiographic evidence of structural damage in KOA and this has been emphasised as a potential risk factor for the development of KOA (Brandt et al., 1999, Slemenda et al., 1998). More so, it highlights that pain and cartilage loss may not be the dominate mechanisms modulating AMI. Swelling has been shown to provoke significant AMI, in the absence of pain and joint damage (Rice et al., 2009, Wood et al., 1988), which has been directly attributed to spinal reflex inhibition of the α-motorneuron pool.

Several authors have highlighted that the contralateral limb in unilateral KOA should not be considered uninvolved and free of impairments (Alnahdi et al., 2012, Pietrosimone et al., 2011). AMI results in knee extensor strength deficits due to the inability of the nervous system to fully activate the knee extensor muscle group (Pietrosimone et al., 2011, Hurley and Newham, 1993a). In unilateral KOA in the KOA limb is affected more severely when compared to healthy age-matched controls (-15% knee extensor activation), and while the contralateral limb is affected to a lesser extent, it is significantly worse (-6% knee extensor activation) when compared to healthy age-matched controls (Pietrosimone et al., 2011).

Further, AMI has been implicated in mitigating the benefits of knee extensor strength training (Hurley and Newham, 1993a). Mild levels of AMI do not appear to prevent strength gain (<10%); however severe levels of AMI at end stage KOA and following TKR may make resistance training largely ineffective in improving knee extensor strength (Hurley et al., 1994, Stevens et al., 2003b, Rossi et al., 2005). It is possible that high levels of AMI in KOA may minimise improvements in strength simply because of an inability to completely activate the muscle (Fitzgerald et al., 2004), particularly if knee extensor training aggravates the KOA limb increasing pain severity or swelling (Callaghan et al., 2014). The bilateral effect of AMI...
in unilateral KOA is relatively minor in the contralateral limb, suggesting that AMI should have no detrimental effect in knee extensor strength improvements following a strength training intervention. As the contralateral limb is an important factor in functional performance (Brown et al., 2009, Topp et al., 2000), a strength improvement in this limb may be beneficial to functional performance and bypass any potential negative effect of the higher levels of AMI seen in the KOA limb.

Figure 2.1 Proposed mechanisms of arthrogenic muscle inhibition (Rice and McNair, 2010). Acute joint trauma results in inflammation, swelling, laxity and receptor damage, this then via afferent pathways results in reflexive inhibition at the spinal cord (alpha motor neuron pool), which inhibits descending efferent drive from the cortex. While not pictured it appears that prolonged AMI also results in reduced excitability and increased inhibition within the motor cortex. Dark lines represent stronger evidence for their existence.
2.5 Cross Education

The ‘cross education’ phenomenon, which is also referred to as the ‘cross-training effect’ was first reported more than 120 years ago (Scripture, 1894), and is defined as a unilateral resistance training stimulus that results in a strength increase in both the trained muscle group and untrained contralateral homologous muscle group (Zhou, 2000). The cross education phenomenon has been extensively investigated in young healthy populations, using a broad range of methodologies (See Manca et al. (2017) for a detailed review). A recent meta-analysis reported that in young healthy adults the combined mean strength improvement of the untrained upper and lower limbs is 11.9%. Further, in isolation, strength improvements to the upper limb are 9.4%, and the lower limb is significantly greater at 16.4% (Manca et al., 2017). While Manca and colleagues reported that the strength transfer to the untrained limb is significantly correlated to the strength improvement in the trained limb, no percentage of strength transfer was presented, however an earlier meta-analysis calculated a pooled estimate of upper and lower limb studies and reported 52% strength transfer of the strength improvements observed in the trained limb (Carroll et al., 2006). Some caution is needed when comparing across meta-analyses, with Carroll and colleagues reported a mean strength improvement to the homologous muscle group on the untrained limb was a 7.6%, however, Manca et al. included 15 more studies that had been published in the following decade, making the comparison tenuous. Further, the greater strength improvement seen in the lower limb that Manca et al. (2017) reported may be potentially due to a greater cross education effect, or simply a greater strength gain in the trained limb.
2.5.1 Mechanisms of Cross Education

The cross education phenomenon is a neurological adaption in the absence of changes to muscle morphology (Hendy and Lamon, 2017). Transcranial magnetic stimulation (TMS) is a well-established method of investigating intracortical and corticospinal pathways that underlie neuromuscular pathways (Hallett, 2000). Cross education investigations utilising TMS have reported increased corticospinal excitability of the ipsilateral motor cortex of the trained limb (Goodwill et al., 2012, Kidgell et al., 2011); reduced corticospinal inhibition (Latella et al., 2012); reduced short interval intracortical inhibition (SICI) (Goodwill et al., 2012, Hortobagyi et al., 2011); reduced interhemispheric inhibition (Hortobagyi et al., 2011, Manca et al., 2016b), resulting in increased voluntary activation (Lee et al., 2009). Further, modulation of spinal mechanisms cannot be completely dispelled (Carroll et al., 2011).

There are two theories that may explain the neurological adaptations underpinning the cross education effect, the ‘bilateral access hypothesis’ and the ‘cross-activation’ hypothesis, (see Ruddy and Carson (2013) for a detailed review). Firstly, the cross-activation model entails that during unilateral contractions there is bilateral cortical activity in the contralateral motor cortex and ipsilateral motor cortex. With chronic training, neuroplastic changes occur in both cortices, facilitating improved task performance. The bilateral access model entails that during unilateral training, motor engrams are formed, which is the reorganisation of the movement representations within the motor cortex that both the trained and untrained limb can access (see figure 2.2).
Figure 2.2 A schematic representation the ‘bilateral access hypothesis’ and the ‘cross-activation’ hypothesis (Lee et al., 2010). MCx: motor cortex, X: represents the site of adaptation that contributes to improved performance.
2.5.2 Cross Education in clinical populations

The potential applications of cross education as an exercise therapy are not a new or novel concept (Farthing and Zehr, 2014, Hendy et al., 2012, Zhou, 2003, Kannus et al., 1992, Devine et al., 1981, Gregg et al., 1957, Hellebrandt, 1951). However, investigating the potential clinical applications of the cross education phenomenon has only recently gained traction. The cross education phenomenon has been investigated in mock immobilisation trials in healthy young adults (Farthing et al., 2009, Pearce et al., 2013, Magnus et al., 2010), distal radius fractures (Magnus et al., 2013), lower limb training post stroke (Dragert and Zehr, 2013, Kim et al., 2015), multiple sclerosis (Manca et al., 2016a), bilateral KOA (Malas et al., 2013) and unilateral KOA (Onigbinde et al., 2017).

Cross education investigations in KOA have shown promising results, with a 3-week unilateral isometric training intervention in bilateral KOA, resulting in a 38% increase in knee extensor strength in the trained limb, which imparted a 27% increase in strength of the untrained KOA limb, which correlates to a strength transfer from the trained limb of 72.4% (Malas et al., 2013). Following 6-weeks of unilateral isometric knee extensor strength training of the contralateral limb in unilateral KOA, knee extensor strength of the trained non-KOA limb increased by 21%, whilst the untrained KOA limb increased by 20%, which imparted a strength transfer from the trained limb of 95% (Onigbinde et al., 2017). Both studies have reported a contralateral knee extensor strength increase well above what is seen in young healthy adults (Manca et al., 2017), and a transfer of strength from the trained to the untrained limb well above what has been previously reported in young healthy adults (Carroll et al., 2006). There are methodological issues that may partially explain the variance in these results. Neither study incorporated a control group into the study design, which was highlighted as a limitation by Onigbinde and colleagues (2017). However, the absence of a control group means that the transfer of knee extensor strength cannot be calculated as outlined by Carroll (2006). Further, a familiarisation bias in the testing protocol may have
occurred as the exercise intervention in both studies was identical to the testing procedure. It is possible that a portion of the improvements in knee extensor strength were not due to the cross education phenomenon but improved efficiency at the testing procedure (Carroll et al., 2006).

2.5.3 Pain and Cross Education

Knee pain has been implicated as a mechanism in modulating AMI (Rice and McNair, 2010), and knee pain has a strong correlation with deficits in knee extensor strength (Ruhdorfer et al., 2014, O’Reilly et al., 1998, Steidle-Kloc et al., 2015). Malas and colleagues (2013) reported a significant reduction in knee pain severity of the trained and untrained contralateral limb in bilateral KOA following unilateral isometric strength training intervention. A small but significant reduction in knee pain severity is in alignment with previous research (Jansen et al., 2011). However, Malas and colleagues had concurrently used heat packs and therapeutic sonography concurrently with the strength training, making a correlation between improvements in knee extensor strength and changes in pain severity unviable. Regardless, it appears the application of cross education in general may have positive effects on pain severity in both the trained and untrained limbs, which is crucial as increasing pain severity is the most distressing symptom for those with KOA (Felson, 2005), and the strongest predictor of poor QOL (Jordan et al., 1997, Hawker et al., 2008). However, further research is needed to quantify the changes in KOA pain severity following a cross education intervention, and the correlation between knee extensor strength improvements and knee pain severity.

2.5.4 Functional performance and cross education

The primary identified causes for functional decline in KOA are pain (Gur and Cakin, 2003, Rejeski et al., 1996, Topp et al., 2000, Marks, 1994), reduced knee extensor strength of the affected limb in unilateral KOA (Gur and Cakin, 2003, Topp et al., 2000, Rejeski et al.,
1996, Brown et al., 2009, Maly et al., 2005) and the knee extensor strength of the unaffected limb in unilateral KOA (Brown et al., 2009, Topp et al., 2000). Cross education may positively modulate these factors, with increases in knee extensor strength of the trained and also untrained contralateral limb in bilateral and unilateral KOA being reported (Malas et al., 2013, Onigbinde et al., 2017). More so, a reduction in knee pain severity has also been reported in bilateral KOA, with a corresponding increase in functional performance as measured by a 50 step walk test (Malas et al., 2013).

Malas and colleagues reported a significant improvement in time to complete the walking task in all three intervention groups, isometric, isokinetic and isotonic. However, only the isometric training group significantly increased knee extensor strength in the trained and untrained contralateral limb, which suggests that potentially something other than knee extensor strength may be responsible for the increase in functional performance seen in the isometric group. All groups were reported to have significant improvements following the cross education intervention in the WOMAC pain subscale and bilateral knee pain severity as measure by the VAS. While a reduction in knee pain severity does not automatically lead to improvements in functional performance (White et al., 2011), it may partially explain the improvement in functional performance. Secondly, the functional performance task may also have influenced the result, OARSI recommend a minimum core set of physical performance tasks to include sit to stand, walking short distances and stair negotiation (Dobson et al., 2013). The short walk test was ranked 20th most challenging out of 23 tests; the short walk test may not have been challenging enough to fully discriminate changes in functional performance.

There still exists a critical need to further investigate changes in functional performance following a cross education intervention in KOA, utilising the minimum core set of functional performance tasks. Further, there is a need to quantify the potential improvements in knee extensor strength of the trained and untrained contralateral limb and
changes in knee pain severity may have on functional performance. Currently there are no published results of functional performance changes following a cross education intervention in unilateral KOA, the largest subgroup of all musculoskeletal disorders (AIHW, 2015).

2.6 Summary

KOA affects more than 3.8% of the world’s population (Cross et al., 2014), with up to 30% of the population over the age of 65 years having radiographic evidence of KOA (Litwic et al., 2013). Age, sex, previous injury, sporting or occupational pursuits and obesity all contribute to the prevalence of KOA (Michael et al., 2010). KOA results in significant knee pain (Felson, 2005), loss in knee extensor strength (Alnahdi et al., 2012), deficits in functional performance (Liikavainio et al., 2008) and QOL (Jakobsson and Hallberg, 2002) when compared to healthy age-matched controls. TKR is the final therapeutic option for knee pain at end stage KOA (Altman and Gold, 2007).

The dominate factors in maintaining functional performance in KOA are knee pain (Gur and Cakin, 2003, Rejeski et al., 1996, Topp et al., 2000, Marks, 1994) and knee extensor strength (Gur and Cakin, 2003, Topp et al., 2000, Rejeski et al., 1996, Brown et al., 2009, Maly et al., 2005). Knee extensor strength training decreases pain in KOA (Jansen et al., 2011), however independently a reduction in knee pain severity may not increase functional performance (White et al., 2011). Increasing knee extensor strength of either the KOA limb or the contralateral limb may increase functional performance, regardless of knee pain severity (Zhang et al., 2010, McAlindon et al., 2014, Alnahdi et al., 2012). The contralateral limb in unilateral KOA has been largely ignored in the literature; however an increase in knee extensor strength of this limb may improve functional performance independently of the KOA limbs status (Brown et al., 2009, Topp et al., 2000).

The cross education phenomenon as exercise therapy in unilateral KOA may have multifactorial benefits. Cross education has been reported to improve knee extensor strength
in bilateral and unilateral KOA (Malas et al., 2013, Onigbinde et al., 2017). However, no measures of pain, functional performance or changes in AMI or co-activation have been reported to date. Therefore, this thesis aims to investigate the potential benefits that 4-weeks of unilateral strength training of the contralateral limb in unilateral KOA has on bilateral knee extensor strength, pain severity, objective and subjective functional performance, QOL, and the potential mechanisms that modulate these outcomes. To my knowledge, with the exception of knee extensor strength, no studies have investigated the interplay of these mechanisms and outcomes, and doing so may provide valuable insight into the benefits that cross education may have in unilateral KOA.
CHAPTER THREE

STUDY ONE:

CROSS EDUCATION AS EXERCISE THERAPY IMPROVES MUSCLE STRENGTH IN UNILATERAL KNEE OSTEOARTHRITIS: A RANDOMISED CONTROLLED TRIAL.
3.1 Background

The loss of knee extensor strength is a hallmark feature of KOA, which is of critical importance, as knee extensor strength is a key determinant of avoiding functional disability during the progression of KOA (Ruhdorfer et al., 2015). Atrophy of the knee extensors partially explains the loss in knee extensor strength loss during the progression of KOA (Conroy et al., 2012, Slemenda et al., 1998). However, the primary cause of knee extensor strength loss appears to be arthrogenic muscle inhibition (AMI) (Pietrosimone et al., 2011), which results in the inability of the nervous system to completely activate the knee extensors (Rice and McNair, 2010).

In unilateral KOA the knee extensor strength deficit is a bilateral occurrence, with the contralateral limb affected to a less extent (Pietrosimone et al., 2011). Knee extensor strength deficits of the KOA limb are significant, the KOA limb demonstrates deficits between 36-48% during end stage KOA when compare to healthy age-matched controls (Bade et al., 2010, Gapeyeva et al., 2007). Interestingly, studies frequently use the contralateral limb as a control (Stevens et al., 2003, Vahtrik et al., 2012, Gapeyeva et al., 2007) demonstrating strength deficits in the KOA limb ranging from 18%-31% when compared to the contralateral limb. However, some caution needs to be taken when using the contralateral limb as a control, as it does not represent normal knee extensor strength when compared to healthy age-matched controls, with knee extensor strength deficits ranging from 17-36% (Berth et al., 2002, Stevens-Lapsley et al., 2010, Gapeyeva et al., 2007).

The cross education phenomenon, is a neurological response to a unilateral strength training stimulus that results in a strength increase to both the trained and untrained contralateral homologous muscle group (Zhou, 2000), in the absence of changes to muscle morphology (Hendy and Lamon, 2017). A recent meta-analysis reported that in young healthy adults the mean strength increase of the untrained lower limb is 16.4% (Manca et al., 2017). The application of cross education as a clinical exercise therapy has been
successfully trialled in mock immobilisation (Farthing et al., 2009, Magnus et al., 2010, Pearce et al., 2013), forearm fractures (Magnus et al., 2013), bilateral KOA (Malas et al., 2013), unilateral KOA (Onigbinde et al., 2017), multiple sclerosis (Manca et al., 2016a) and stroke (Kim et al., 2015, Dragert and Zehr, 2013). The application of cross education in unilateral KOA appears to have merit; however, its potential has yet to be exploited in unilateral KOA.

Increasing knee extensor strength of both the KOA and contralateral limbs in unilateral KOA towards levels seen in healthy age-matched controls is of critical importance in reducing functional disability. The contralateral limb is the dominant predictor of functional performance; therefore, an increase in strength of this limb may be beneficial in improving functional performance. While concurrently, training the contralateral limb will bypass any potential acute aggravation from heavy load strength training the KOA limb directly and still bypass an improvement in knee extensor strength. Decreased knee extensor strength has also been previously highlighted as a risk factor for the development of KOA in the contralateral limb (Oiestad et al., 2015). Again improving knee extensor strength of this limb may provide long term benefits to attenuating or slowing the progression of KOA.

Therefore, the aims of this experimental chapter was to investigate the effects of 4-weeks of unilateral strength training of the contralateral limb in individuals with unilateral KOA, compared to untrained individuals with unilateral KOA and healthy age-matched controls on knee extensor strength. It was hypothesised that unilateral strength training of the contralateral limb in unilateral KOA would increase knee extensor strength bilaterally, and that the magnitude of improvement would be greater than 16.4% as seen in young healthy adults. Further the improvements in knee extensor strength would be retained in the three month period following the intervention.
3.2 Materials and methods

Where the methods and procedures described in this chapter are either identical or similar in the following three study chapters, the reader will be redirected to the relevant section for full comprehensive details.

3.2.1 Participants

Unilateral KOA participants and matched healthy controls were recruited via the local hospital orthopaedic clinic and local advertising. Prospective participants were required to have: 1) radiographic evidence of unilateral tibiofemoral knee osteoarthritis (KL grade 3-4); 2) independently living; 3) English speaking; 4) and have a BMI of 20 to 35; and 5) able to provide informed consent.

Healthy age-matched control participants were required to: 1) be asymptomatic for knee or hip OA, as determined by radiograph evidence of KOA or significant joint pain; 2) not be currently engaged in a strength training program; 3) independently living; 4) English speaking; 5) and have a BMI of 20 to 35; and 6) be able to provide informed consent.

Participants were excluded for the following: 1) any participant unable to attain medical clearance (uncontrolled hypertension, diabetes and angina); 2) evidence of bilateral KOA or hip OA; 3) a history of neurological disease or neurodegenerative conditions; 4) previous partial or complete knee or hip replacement to either leg; 5) any form of cognitive impairment. The study was approved by the Deakin University Human Research Ethics Committee (DUHREC, ID: 2012-230). See the appendix for copies of the Deakin University medical questionnaire (Appendix A; page 204), and the TMS safety screening form (Appendix B; page 206).
3.2.2 Experimental design

This was a non-blinded randomised control trial, with a 4-week intervention, with pre, post and a follow up assessment (3-months’ post intervention). Outcome measures of isometric knee extensor strength, and rectus femoris muscle thickness were assessed at all-time points.

A medical professional (orthopaedic surgeon) based in the ward of the recruiting hospital assessed the eligibility of the potential participant via bilateral knee radiographs and determined medical clearance for potential participants, discussed the trial and ultimately recruited participants. Potential participants were then contacted by a researcher at the university, to confirm interest in enrolment in the trial, to confirm informed consent, and to determine a suitable date for the initial assessment. As part of the initial assessment VAS and KOOS pain were utilised to ensure no pain in the contralateral knee during functional tasks. Post assessment, an independent research fellow determined allocation to either the intervention or control groups. Healthy controls contacted the university directly to discuss the requirements of the trial and to determine suitability and provided informed consent. KOA participants were allocated into a unilateral exercise group or a non-exercise control group, via simple randomisation with a 1:1 allocation. Immediately following the pre-assessment, a research fellow that was independent to the study and blinded to all attributes of the participant, determined the allocation of each participant. Allocation was implemented via a random number generator. Due to practical limitations, blinding of participants did not occur. The healthy age-matched controls were not randomised.

All participants in the exercise group participated in 12 supervised exercise sessions (3 per week for 4 weeks) of approximately 30 minutes. All exercise sessions were supervised by an experienced allied health professional. The post exercise testing occurred 3 days following the final training session. The 3 month follow up (Post3) assessment occurred as close to 12 weeks as practically possible. Participants were asked to maintain
their current physical activities throughout the duration of the study and not to commence any form of new physical activity, sport or exercise. This was assessed via a simple diary format assessed prior to each training session.

3.2.3 Study settings

KOA participants were recruited from an orthopaedic ward of a local hospital, servicing both private and public health. Advertising was also utilised within the locale of Deakin University Melbourne, Australia, to additionally recruit healthy control participants and KOA participants. Potential participants that were identified to be unable to participate in the study due to lack of transportation, were offered transport in university fleet vehicles to and from the university for all testing and training sessions. All exercise (intervention) sessions were conducted in a university rehabilitation clinic, by the same allied health professional. All assessment sessions where conducted in a physiology laboratory located in the same building.

3.2.4 Maximal strength testing

Maximal voluntary isometric contraction (MVIC) of the knee extensors and knee flexors was measured pre, immediately post intervention and at 3 months follow up, with the contralateral limb tested prior to the KOA limb at each assessment. The participants were seated with their knees flexed at 60 degrees (-30 degrees from full knee extension) and the hip joint at 85 degrees on an isokinetic dynamometer (Biodex System 4 Pro, Biodex Medical Systems, Shirley USA), which has a intraclass correlation coefficient (ICC) of .93 for knee extension and an ICC of .89 for knee flexion (Toonstra & Mattacola, 2013). Knee flexion of 60 degrees was selected to ensure consistency between testing sessions and participants, and 60 degrees of knee flexion results in the greatest force output following and bypassing any potential restriction in movement due to KOA. The researcher instructed the participant to kick (extension) or pull (flexion) "as hard as possible" for 3 seconds, with three trials being
performed, with a 2-minute rest between each trial to minimise the effect of fatigue. Knee pain was measured via VAS scale immediately following each trial, to measure the potential influence of knee pain on knee extensor strength (See section 4.2.6; P65 for full pain measurement protocol). Verbal encouragement was provided by the researchers and visual feedback of the force exerted was provided on the Biodex monitor which was located at eye level approximately 1 meter from the participant. The raw force measured by the dynamometer was recorded in newton-meters (NM) and was also normalised to each participants’ weight in kilograms (NM/KG).

### 3.2.5 Measurement of muscle thickness

Real time ultrasound has been shown to highly correlate with vastus lateralis (VL) \((r=0.94)\) and rectus femoris (RF) \((r=0.86)\) muscle thickness measurement attained with magnetic resonance imaging (MRI) (Giles, Webster, McClelland, & Cook, 2015). Therefore, using the same technique, a Nemio20 premium compact ultrasound was used to measure the thickness of the participant’s quadriceps muscle (rectus femoris) of each leg pre and post intervention. Measurements for muscle thickness were taken at the beginning of all testing sessions to ensure that exercise induced changes in muscle blood flow did not affect the measurement. All measurements where performed by the same researcher, with inter-experimenter coefficient of variation [CV] being between 2.6 and 3.8% (Scott et al., 2012).

The site of measurement was determined by marking the skin midway between the superior aspect of the patella and the anterior superior iliac spine, while the participant was in a supine position with the knee and hip in the anatomical position. The 6-8 Hz transducer probe was lubricated with transmission gel and placed lightly on the marked area of the skin. When a clear image was seen on the monitor, the pressure of the transducer to the skin was slowly reduced to ensure minimal compression of the muscle before the monitor was frozen. A cursor then marked the distance between the femur and the most superficial point of the muscle fascia, giving a distance which represented the thickness (mm) of the muscle under
the marked point on the skin. Six readings were taken on each leg and averaged to determine the final value.

### 3.2.6 Interventions

All training sessions were supervised and monitored by an accredited exercise physiologist, with verbal encourage given during in set. Participants completed a warmup that consisted of two sets of unilateral leg press (Synergy Fitness, Omni Leg Press) of the contralateral limb at progressively heavier loads (40% and 65% of 1RM). The training consisted of four sets of 6-8 repetitions of unilateral leg press of the contralateral limb at >80% 1RM. This load was initially based on an 8RM unilateral strength measurement of the trained non-KOA limb determined during the initial training session. All participants were familiarised with the technique required prior to the first training session, with the focus of the initial training session focussing on correct exercise technique to ensure no adverse effects, such as delayed onset muscle soreness or joint pain and swelling. A 3-minute recovery period occurred between each set. Participants were required to perform each repetition with a repetition timing of 3 seconds of concentric and 4 seconds of eccentric, timing was measured by a metronome. The leg press was adjusted for each participant to ensure that the knee reached a minimum of 90 degrees as measured by a goniometer (360° Baseline™ evaluation instruments). The principle of progressive overload was employed throughout the training period to maximize the training response (Kraemer and Ratamess, 2004). Specifically, when participants could complete four sets of 8 repetitions, at the beginning of the next training session, the training weight (kg) was increased. All participants completed the 12 training sessions over the 4 week period.
3.2.7 Data Analysis

MVIC was determined as the highest force (NM) recorded from 3-5 individual repetitions, until a plateau in force was observed. Knee extensor muscle girth (mm) was measured as the mean value from 6 individual recordings.

The contralateral transfer of strength was quantified using a procedure published by Carroll (2006). The magnitude of the cross education effect was calculated as the mean change of knee extensor strength of the KOA intervention group to the untrained limbs of the KOA control group.

\[
\frac{(E_{post} - E_{pre})}{E_{pre}} - \frac{(C_{post} - C_{pre})}{C_{pre}} \times 100
\]

Epost referred to the mean RM of the experimental groups untrained knee extensors post intervention. Epre referred to the mean RM of the experimental groups knee extensors pre intervention. Cpost referred to the mean RM of the control groups untrained knee extensors post intervention. Cpre referred to the mean RM of the control groups knee extensors pre intervention.

3.2.8 Statistical Analysis

Given at the time no previous study had investigated cross education in a KOA cohort, power calculations (G*Power, V3.1) were based on a meta-analysis on the effect of cross education on knee extensors strength in healthy populations (Munn et al., 2004). Based on a knee extensor cross education effect of 10.4% (standard deviation [SD] ± 7.6), an a priori power analyses with a two-tailed P-value of 0.05 and a power of 0.95 (effect size [ES] 1.31) was conducted and we estimated that 10 participants was the minimum requirements for each group. While previous KOA studies have reported low dropout rates; to ensure adequate power, we adjusted recruitment to 16 participants per group (Faul et al., 2007).
Prior to statistical analysis, normality was screened with Shapiro-Wilk and Kolmogrov-Smirnov tests. If the data was not normally distributed, frequency histograms and detrended Q-Q plots was examined to determine if non-parametric tests and ES calculations (i.e. Cohen’s d) were needed. If the data appeared normally distributed, a repeated measure analysis of variance (ANOVA) was used to determine the effect of the intervention on the dependant variables of knee extensor strength, knee flexor strength, and muscle thickness between the control and OA groups. Bonferroni post hoc test was performed on all possible comparisons to analyse any significant main effects and interactions. All dependent variables were tested for non-sphericity using Mauchly’s test. Any dependent variable not meeting the assumption of sphericity was adjusted by using the Greenhouse–Geisser correction. Linear regression analysis was also used to examine any potential association between changes in muscle strength of the trained and untrained limbs [(post strength/pre strength x 100) - 100]. Significance level was set at P <0.05 for all comparisons and all group data was provided as means ± SD.

The addition of the 3-month post intervention follow-up data was a change to the planned outcomes, due to this late inclusion, the KOA control group had undergone a follow-up intervention, intention to treat as required by DUHREC and could no longer been utilised as a control group at the 3-month post intervention assessment. Due to short intervention length and trial size, interim analyses was not planned for or occurred.

3.2.9 Participant Flow

The final numbers analysed were 16 KOA intervention, 10 KOA controls, and 12 healthy controls. Of the 74 KOA participants that expressed interest in the study, 28 were excluded for not meeting the requirements, bilateral KOA or other relevant medical issue, 5 declined to participate without reason and 11 due to distance or time. All participants in the KOA intervention group finished the study, and further 4 participants allocated to the KOA control group were lost prior to post intervention assessment due to medical issues or illness.
Of the 20 healthy controls who expressed interest in the study, 12 healthy controls completed the study, with 2 not meeting the criteria with previous lower limb surgery, 1 declined participation, and the remaining 5 had subsequent medical issues prior to the initial assessment (i.e. stroke, heart attack, deceased or limb fracture). See the participant flow graph for further details (Figure 3.1, P. 46).
Figure 3.1 Consort diagram of study flow from recruitment to data analyses.
3.3 Results

3.3.1 Baseline characteristics

Twenty-eight participants aged 55-76 years with radiographic diagnosed unilateral knee osteoarthritis (KL grade >3) and sixteen healthy age-matched controls were studied. There were no differences between groups for any characteristics including, age (P = 0.736), height (P = 0.834), weight (P = 0.703) and BMI (P = 0.869) (table 3.1).

<table>
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<th>Weight (kg)</th>
<th>BMI</th>
<th>Sex</th>
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<tbody>
<tr>
<td><strong>KOA Intervention</strong></td>
<td>N = 16</td>
<td>66.2 ± 5.6</td>
<td>169.9 ± 11.9</td>
<td>84.1 ± 12.7</td>
<td>29.1 ± 3.5</td>
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<td><strong>KOA Controls</strong></td>
<td>N = 10</td>
<td>63.7 ± 4</td>
<td>173.8 ± 9</td>
<td>88.2 ± 11.5</td>
<td>29.4 ± 3.3</td>
</tr>
<tr>
<td><strong>Healthy Controls</strong></td>
<td>N = 12</td>
<td>67 ± 6.9</td>
<td>171.1 ± 7.5</td>
<td>87.3 ± 17.9</td>
<td>29.7 ± 4.9</td>
</tr>
</tbody>
</table>

Values are mean ± SD. No significant differences between groups were observed.
3.3.2 Trained limb knee extensor strength

At baseline, there were no differences in the strength of the knee extensors for the trained limb between the KOA intervention group and the KOA control group (P > 0.999). However, at baseline, there was a significant difference in strength of the trained knee extensors between the KOA intervention group and the healthy age-matched control group (P = 0.033). Further, there was also a significant difference at baseline in the strength of the trained knee extensor between the KOA control group and the healthy age-matched controls (P = 0.042).

Following the 4-week strength training intervention, there was a main effect time (F_{(1, 35)} = 18; P < 0.001) and a group by time interaction (F_{(2, 35)} = 17; P < 0.001). Bonferroni post hoc analysis, revealed that for the trained limb in the KOA intervention group, maximum strength of the knee extensors increased by 24% (P < 0.001; M= 24, 95% CI [17, 32]), and this increase was significantly different to the KOA control group (P = 0.028). Importantly, the magnitude of change in knee extensor strength between the KOA intervention group and the healthy age-matched controls was not different (P = 0.16; Figure 3.2A, P. 50).
3.3.3 Untrained limb knee extensor strength

At baseline, there were no differences in the strength of the knee extensors for the untrained limb between the KOA intervention group and the KOA control group (P > 0.999). However, at baseline, there was a significant difference in strength of the knee extensors between the untrained KOA group and the healthy age-matched control group (P < 0.001). Further, there was also a significant difference at baseline in the strength of the knee extensor between the KOA control group and the healthy age-matched controls (P < 0.001). In addition, there was also a significant difference in strength of the knee extensors between KOA intervention groups’ KOA and contralateral limbs (P = 0.016)

Following the 4-week strength training intervention, there was a main effect for time ($F_{(1, 36)} = 11; P < 0.001$) and a group by time interaction ($F_{(2, 35)} = 17; P < 0.001$). Bonferroni post hoc analysis, revealed that for the untrained limb in the KOA intervention group, maximum strength of the knee extensors increased by 20% (P < 0.001; M= 15.3, 95% CI [8.8, 21.7]), further, this increase was significantly different to the KOA control group (P < 0.001). Furthermore, there was a significant difference following the intervention between the untrained limb in the KOA intervention group compared to the healthy age-matched controls (P = 0.001). Lastly, following the intervention no difference in strength of the knee extensors between KOA intervention groups' KOA and contralateral limbs was observed (P = 0.064; Figure 3.2B, P. 50).
Figure 3.2 Group mean (±SD) data showing knee extensor strength of the trained limb (A) and the untrained limb (B). * denotes significant baseline differences of $P < 0.001$, between the healthy control group to the KOA intervention and KOA control. † denotes significant time effect of $P < 0.001$, from baseline to post intervention for the KOA intervention. † denotes a significant group by time interaction of $P < 0.001$ to the KOA controls and healthy control groups.
3.3.4 Cross education phenomenon

Unilateral strength training of the contralateral limb in unilateral KOA resulted in a cross transfer of strength of 19.8% to the untrained KOA limb, which equated to 78.2% of the strength gain of the trained limb.

There was no relationship between the percentage of strength gained in the trained knee extensors and the percentage of the contralateral transfer of strength to the untrained knee extensors ($r^2 = 0.16; P = 0.140$; Figure 3.3). Unilateral strength training of the contralateral knee extensors resulted in an 18% strength-transfer to the untrained KOA knee extensors.

![Figure 3.3](image)

**Figure 3.3** Strength changes for the trained and untrained knee extensors in the KOA intervention group following 4 weeks of unilateral strength training.
3.3.5 Retention of knee extensor strength trained limb

Following the 3 month wash out period post intervention, there was no main effect for time observed ($F_{(1, 53)} = 0.033; P = 0.857$) and no group by time interaction was observed ($F_{(2, 53)} = 0.53; P = 0.593$). No changes in knee extensor strength were observed in the 3 months following the intervention for the trained limb ($P > 0.999; M = -4.8, 95\% \text{ CI} [-22, 13]$), and healthy age-matched control group ($P > 0.999$; Figure 3.4, p. 53). Retention of knee extensor strength in the trained limb had occurred over the 3 months following the intervention.

3.3.6 Retention of knee extensor strength untrained limb

Following the 3 month wash out period post intervention, there was no main effect for time observed ($F_{(1, 53)} = 0.033; P = 0.857$) and no group by time interaction was observed ($F_{(1, 53)} = 0.53; P = 0.593$). No changes in knee extensor strength were observed in the 3 months following the intervention for the untrained limb ($P > 0.999; M = 2.5, 95\% \text{ CI} [-15, 20]$), and healthy age-matched control group ($P > 0.999$). A significant difference between the untrained limb of the KOA intervention group and healthy age-matched controls remained ($P = 0.013$; Figure 3.4, p. 53). Retention of knee extensor strength in the untrained limb had occurred over the 3 months following the intervention.
**Figure 3.4** Group mean (±SD) data demonstrating the retention of the improvements in knee extension strength in the three months following the intervention. * denotes significant baseline difference of P < 0.05, between the KOA untrained limb and healthy control group.
3.3.7 Muscle thickness trained limb

At baseline, there were no differences in muscle thickness of the quadriceps for the trained limb between the KOA intervention group and the KOA control group (P > 0.999). Furthermore, there were no differences in muscle thickness of the quadriceps for the trained limb between the KOA intervention group and the healthy control group (P > 0.999). Again, there were no differences in muscle thickness of the quadriceps for the trained limb between the KOA control group and the healthy control group (P > 0.999).

Following the 4-week strength training intervention, there was a main effect for time (F\(_{1, 32}\) = 8.5; P = 0.006), however, there was no group by time interaction (F\(_{2, 32}\) = 0.08; P = 0.923). Bonferroni post hoc analysis revealed that for the trained limb in the KOA intervention, no significant change in quadriceps muscle thickness of the trained limb was observed (4.1%, P = 0.317; M = -0.16, 95% CI [0.4, 0.08]; Fig 3.5A, P. 55).

3.3.8 Muscle thickness untrained limb

At baseline, there were no differences in muscle thickness of the quadriceps for the untrained limb between the KOA intervention group and the KOA control group (P > 0.999). Furthermore, there were no differences in muscle thickness of the quadriceps for the untrained limb between the KOA intervention group and the healthy control group (P > 0.999). Again, there were no differences in muscle thickness of the quadriceps for the untrained limb between the KOA control group and the healthy control group (P > 0.999).

Following the 4-week strength training intervention, there was a main effect for time (F\(_{1, 41}\) = 7.3; P = 0.036), however, there was no group by time interaction (F\(_{2, 41}\) = 0.041; P = 0.96). Bonferroni post hoc analysis revealed that for the untrained limb in the KOA intervention, quadriceps muscle thickness of the untrained limb increased by 3.8% (P = 0.486; M = -0.13, 95% CI [-0.45, 0.19]; Fig 3.5B, P. 55).
Figure 3.5 Group mean (±SD) data showing muscle thickness of the quadriceps muscle group, of the trained limb (A) and the untrained limb (B). ° denotes significant time effect of P < 0.01, from baseline to post intervention for the KOA intervention group.
3.4 Discussion

The purpose of this study was to determine the clinical efficacy of unilateral knee extensor training on imparting the cross education phenomenon to the untrained limb in unilateral KOA. There were several important findings, which further validate the use of cross education in unilateral KOA, above a single previous study that investigated cross education in bilateral KOA and lacked adequate qualitative analysis (Malas et al., 2013). The main findings were that there was a significant cross education effect of 19.8%, when the untrained limb of the KOA intervention group was compared to the untrained limb in the KOA control group. Retention of the knee extensor strength gains of both the trained and untrained KOA limbs was observed three months following the intervention, with the trained limb in the KOA intervention group showing no significant difference at both the post intervention and 3-month post intervention time point, showing that the cross-transfer of strength was retained. A time effect was observed in knee extensor muscle girth for the healthy age-matched controls.

3.4.1 Strength increase of the trained and untrained limb

Knee extensor strength of the trained limb significantly improved by 24%, with the untrained KOA limb improving by 20%. The magnitude of the cross education effect was calculated by the method outlined by Carroll et al. (2006), 78% of the strength improvement of the trained limb, transferred to the untrained KOA limb. The strength improvement of the untrained leg was greater than seen in a recently published meta-analysis (Manca et al., 2017), which pooled data from the lower limb of 338 subjects, showing a mean improvement of 16.4%. While both distal and proximal muscles groups were included in the analysis, no differences where shown in the magnitude of the cross education effect. While it appears the
magnitude of cross education was significantly greater in this experimental chapter, there were several variables that could explain this.

In the meta-analysis by Manca et al. (2017), the average age of the participants was 23.9 ± 3.3 years, whereas in this study, the mean age of the KOA intervention group was 66.2 ± 5.6 years, on average a greater than 40-year difference. It is well-established that sedentary behaviour becomes more common place as we age (Vandervoort, 2002), and that the loss of muscle mass and strength is a normal part of the ageing process, with muscle strength declining more rapidly than muscle mass (Goodpaster et al., 2006). This could potentially lead to a large adaptive reserve, as a detrained individual can make larger strength gains faster than a normal to well-trained individual (Hakkinen et al., 1996). Supporting this, previous evidence showed that in KOA, the loss of knee extensor strength is primarily neurological in nature and not due to muscle atrophy alone (Stevens et al., 2003, Pietrosimone et al., 2011).

Two previous studies that have investigated cross education in KOA, bilateral KOA (Malas et al., 2013), and unilateral KOA (Onigbinde et al., 2017). Both studies reported significant improvements in trained limb knee extensor strength, with Malas and colleagues reporting a 39.7% and Onigbinde and colleagues reporting a 21% increase. Further, both reported significant improvements in knee extensor strength in untrained limb 27.3% and 21% respectively. These were significantly higher than results from the previous meta-analysis (Manca et al., 2017). Both Malas et al. (2013) and Onigbinde (2017) utilised a highly specific isometric intervention that mimicked the testing procedure. The greater improvements in isometric knee extensor strength may be potentially explained due to a greater degree of familiarisation with the testing protocol are responsible for this difference (Carroll et al., 2006). Further, no control group was included in either the Malas (2013) or Onigbinde (2017) studies and neither study quantified the cross education by the method outlined by Carroll (2006).
This study also investigated cross education in bilateral KOA, with no mention of the severity of the KOA for either limb. Whereas, the current study result can be considered more robust, participants had radiographic evidence of the grade of KOA, the use of a KOA control group allows the correct determination of the cross education effect and the intervention is more general in nature, allowing greater transference into a community or clinical environment.

3.4.2 Retention of the strength gains

Investigating the retention of strength improvements following a cross education intervention is not a novel idea (Shima et al., 2002), however, to the best of my knowledge this is the first study that has investigated the retention of strength gains following a cross education intervention in a clinical cohort. Previous detraining research in cross education with a young healthy cohort has shown that over 6-weeks a significant decrease in strength of the trained limb occurred, but interestingly, the untrained limb maintained strength. This disparity possibly occurred as the trained limb had made significantly greater strength gains than the untrained limb in the young healthy cohort. Where as in the current study, the magnitude of the cross education phenomenon was high, both limbs increase in knee extensor strength to a comparable degree. Further, when compared to healthy age-matched controls, the KOA intervention group in this experimental chapter were significantly weaker prior to the intervention. It is possible that knee extensor strength was maintained as the KOA intervention group returned to normal levels of strength as seen in the healthy age-matched controls, whereas if they had achieved knee extensor strength significantly higher, the magnitude of loss may have been significant.

Previous detraining research in the same age subjects (64.4 ± 0.9) has shown that strength loss in the lower limbs was at the same rate as younger adults and as little as a 9% decrease in a 6 months period following their intervention (Sherk et al., 2012). While a shorter detraining period of 2 months also displayed a 9% loss in strength, the participants
were older (60-80 yrs old), comparable to this current study, suggesting that older adults may lose strength faster (McCartney et al., 1996). In comparison to cohorts of similar age, the retention of knee strength is impressive; however the explanation may be simple. Individuals with KOA do less incidental physical activity and less vigorous physical activity (Farr et al., 2008). Following the intervention it is possible that incidental physical activity and a return to normal recreational physical activity occurred in the KOA intervention group. This activity may have been the primary stimulus for retaining improvements made to knee extensor strength. However, a major limitation in this study is physical activity was not measured pre or post activity, so these claims cannot be substantiated.

### 3.4.3 Muscle thickness

No significant changes in knee extensor muscle thickness were observed in either the trained or untrained contralateral limb in the KOA intervention group, from pre to post intervention. The cross education phenomenon is a neurological adaptation (Carroll et al., 2006), and while current research has suggested there is a possibility muscle architecture changes (Malas et al., 2013), the majority of studies do not support this occurrence (Hendy and Lamon, 2017). A strength of this study was the measurement of knee extensor muscle thickness, as a change in cross sectional area (CSA) may impact the MVIC strength. This result supports the current research that the transfer of strength is wholly neurological in nature.

No changes in muscle thickness were observed in the KOA controls and the healthy controls from the pre to post time points, interestingly, there was no significant difference in muscle thickness between the limbs within each group and also between the three study groups as a whole. This suggest that in this population, the significant deficit in strength demonstrated in both the KOA intervention and KOA control groups when compared to the healthy control groups, was not due to differences in muscle mass, but neurological factors. This is in support of previous research that demonstrated the loss of knee extensor strength...
in KOA is primarily due to the inability activate the muscle, not atrophy on the knee extensors (Pietrosimone et al., 2011, Stevens et al., 2003).

3.4.4 Limitations

This study has several limitations that needed to be considered. First, no assessment of SES or previous occupational status were investigated, no blinding occurred, other than data analysis and group allocation, due to practical limitations. Secondly, only isometric strength measured during testing sessions and an 8RM during the first and last training sessions were taken, due to safety and ease of familiarisation in this elderly cohort. Thirdly, while physical activity was monitored during the intervention period to ensure no changes to normal physical activity, no measurement of baseline physical activity was determined prior to the intervention period, or in the three months following the intervention, prior to the final assessment. This limitation meant that we could only theorise as to the reasons of the complete retention of strength gains in the intervention group. Due to practical limitations there was no 3-month post intervention measurement of the KOA control group and no intention to treat analysis, which made it impossible to compare the KOA intervention to an equivalent control group at this time point. However, the novelty of measuring the three month detraining period in the KOA intervention and being able to compare them to a healthy control overcomes this limitation to a degree. Lastly, the relatively small sample size may limit the overall generalisability of the findings reported in this chapter, especially considering 9 participants dropout of the study due to unrelated medical reasons.

3.4.5 Conclusions

This study supported our hypothesis that four weeks of strength training of the contralateral limb in unilateral KOA would result in a significant increase in strength to both the trained and untrained limb, and that the cross education phenomenon would occur at a higher magnitude that in previous studies in young healthy subjects. The improvement in
knee extensor strength of both the trained and untrained limbs was maintained for three months following the intervention. The cross education phenomenon as an exercise therapy in improving bilateral knee extensor strength in this cohort was effective.
CHAPTER FOUR

STUDY TWO

PAIN AND QUALITY OF LIFE IMPROVES FOLLOWING CROSS EDUCATION TRAINING IN UNILATERAL KNEE OSTEOARTHRITIS: A RANDOMISED CONTROLLED TRIAL.
4.1 Introduction

Pain is a hallmark feature of KOA and is the primary reason why people suffering from KOA seek primary care and pharmacological interventions (Bidaut-Russell and Gabriel, 2001). Pain, particularly intermittent intense pain has a significant impact on QOL and individuals with KOA have significantly lower QOL when compared to age-matched healthy controls (Hawker et al., 2008). Consequently, pain is the primary reason why individuals suffering from KOA elect to have joint replacement surgery (Altman and Gold, 2007). Individuals will typically favour mental wellbeing over functional ability (Smith et al., 1999), hence, the investigation and management of pain is equally as important as improving and maintaining functional performance (Riddle and Stratford, 2014).

Knee pain severity has been shown to have a relationship with deficits in knee extensor strength (Ruhdorfer et al., 2014, O’Reilly et al., 1998, Steidle-Kloc et al., 2015). Whereas, the correlation between knee extensor strength loss and radiographic evidence of KOA, such as the K/L scale is controversial, with some authors reporting no relationship (Lewek, Rudolph, & Snyder-Mackler, 2004; Petterson, Raisis, Bodenstab, & Snyder-Mackler, 2007) while other evidence disputes this finding (Segal et al., 2009, Ruhdorfer et al., 2014).

Unilateral pain in the KOA limb has been shown to have a bilateral effect on knee extensor strength (Steidle-Kloc et al., 2015). This result supports the conclusions from a recent systematic review that investigated AMI, that reported bilateral quadriceps weakness from unilateral anterior cruciate ligament (ACL) injury (Hart et al., 2010). There is also evidence showing bilateral quadriceps weakness in unilateral KOA (Pietrosimone et al., 2011), of which pain may be a modulating mechanism (Rice and McNair, 2010). Regardless of the mechanisms modulating pain and the bilateral knee extensor strength loss, lack of quadriceps strength is correlated with increased pain and disability ($R^2 = 0.43$) (O’Reilly et al., 1998). Furthermore, pain severity is also associated with decreased functional ability independently of knee extensor strength (White et al., 2011). Previous research has reported
decreased knee pain after quadriceps training (Amin et al., 2009; Maurer, Stern, Kinossian, Cook, & Schumacher, 1999; Roos, Herzog, Block, & Bennell, 2011). However, a reduction in knee pain will not automatically lead to increases in functional ability (White et al., 2011). This leads to a potential interesting and novel outcome of cross education therapy. Increasing strength of the untrained KOA limb via the cross education phenomenon, may also lead to decreased symptoms, particularly pain. Pain being an independent variable in functional ability, may also lead to an increase in functional ability (investigated in Study 3).

Therefore, this study investigated the effect of 4 weeks of unilateral strength training of the contralateral limb in individuals with unilateral KOA, compared to both healthy age-matched controls and untrained individuals with unilateral KOA. It was hypothesised that unilateral strength training of the contralateral limb in unilateral KOA would decrease pain and improve symptoms in the untrained KOA limb as measured by a VAS and the KOOS, whilst globally improving sport and recreation and QOL.

4.2 Materials and methods

4.2.1 Participants

The participant characteristics, inclusion and exclusion criteria are identical to the protocol outlined in study one, section 3.2.1 (Page 38).

4.2.2 Experimental design

The experimental design is identical to the protocol outlined in study one, section 3.2.2 (Page 39).
4.2.3 Study settings

The study setting is identical to the protocol outlined in study one, section 3.2.3 (Page 40).

4.2.4 Interventions

The study intervention is identical to the protocol outlined in study one, section 2.3.4 (Page 42)

4.2.5 Knee extensor strength

The knee extensor strength testing protocols are identical to the protocol outlined in study one, section 3.3.5 (Page 40).

4.2.6 Measurement of knee pain using a Visual Analogue Scale (VAS)

In order to quantify acute knee pain in participants the VAS was utilised. The VAS is one of a battery surveys used to measure acute pain in clinical and research settings (Hawker et al., 2011), it is valid, reliable, simple to understand and administer (Price et al., 1983). The VAS is a 100 mm line, with the left extremity of the line marked as ‘no pain at all’ and the right extremity marked as ‘unbearable pain’, the individual then without influence from the clinician marks on the line their perception of their pain (Scott and Huskisson, 1976). The distance along the line is then measured in millimetres and recorded (See appendix D; page 214).

During each testing session, participants were asked to record their perceived knee pain, for each limb, at rest and immediately following MVIC testing. Participants were not permitted to see the previous pain score. Pain medication was recorded at each testing session to ensure that changes in medication were not mediated changes in pain perception. Measurements taken for each MVIC where then averaged to determine a final score. The
data recorded from the VAS measurements was used to ensure that pain tolerances are adhered to and to determine any correlation between pain, strength and the cross transfer of strength, and that minimum clinically important difference (MCID) in VAS pain have been achieved, which are defined as 6mm, 13mm and 21mm, if initial pain scores are <40mm, 40-70mm and >70mm respectively (Olsen et al., 2017).

4.2.7 The Knee Injury and Osteoarthritis Outcome Score (KOOS)

The KOOS is detailed knee specific questionnaire that scores 5 separate subscales: Pain, Symptoms, Function in Daily Living (ADL), Function in Sport and Recreation, and knee-related QOL (See Appendix C; page 208), with the sum of scores transformed to from a 0-100 scale (Roos and Lohmander, 2003). It measures both the short and long term consequences of KOA, whereas the other commonly used survey tool, The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) only measures long term consequences (Bellamy et al., 1988).

The KOOS was self-administered by participants at the start of each assessment (Pre, Post, 3 Months), with clarification of questions provided if needed. Participants were required to answer all questions based on their symptoms from the previous 7 days. For the purposes of this study, Pain, Symptoms and QOL data was utilised. Data and results for KOOS Function in Daily Living (ADL) and Sport and Recreation are presented in the following study 3 (Chapter 5).

4.2.8 Data analysis

The data analysis is identical to the protocol outlined in study one, section 3.3.7 (Page 43).

4.2.9 Statistical analysis

The statistical analysis is identical to the protocol outlined in study one, section 3.3.8 (Page 43).
4.2.10 Participant Flow

The participant flow is identical to the protocol outlined in study one, section 3.2.9 (Page 44).

4.3 Results

Twenty-eight participants age 55-76 years with radiographic diagnosed unilateral knee osteoarthritis (KL grade >3) and sixteen healthy age-matched controls were studied. No differences between groups for any characteristics was observed, age (P = 0.7369), height (P = 0.8344), weight (P = 0.7036) and BMI (P = 0.8694, Table 4.1, P. 68).
Table 4.1 Characteristics of participants

<table>
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<th>Healthy Controls (N = 12)</th>
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<td>Baseline</td>
<td>102 ± 37</td>
<td>99 ± 22</td>
<td>149 ± 46</td>
</tr>
<tr>
<td>Post training</td>
<td>127 ± 45*</td>
<td>98 ± 22</td>
<td>152 ± 48</td>
</tr>
<tr>
<td>Untrained knee extensor strength (nm)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>92 ± 32</td>
<td>90 ± 28</td>
<td>149 ± 46</td>
</tr>
<tr>
<td>Post training</td>
<td>111 ± 33*</td>
<td>89 ± 28</td>
<td>152 ± 48</td>
</tr>
</tbody>
</table>

Values are mean ± SD, * denotes P < 0.001 post training vs baseline.
4.3.1 VAS trained limb

At baseline, there were no differences in the VAS pain score for the trained limb between the KOA intervention group and the KOA control group (P = 0.188). There were no differences between the KOA intervention group and the healthy control group at baseline (P = 0.470). Further, there were also no differences VAS pain score between the KOA control group and the healthy control group (P > 0.999).

Following the 4-week strength training intervention, there was no main effect for time observed (F(1, 38) = 0.88; P = 0.353 however, there was group by time interaction (F(2, 38) = 4.3; P < 0.021). Bonferroni post hoc analysis, revealed that for the trained limb in the KOA intervention, the VAS pain score improved by 63% from baseline (P < 0.001; M= -3.1, 95% CI [0.49, 5.7]). This increase was significantly different to the KOA control group (P = 0.007). Further, the magnitude of change in knee pain between the KOA intervention group and the healthy age-matched controls was not different (P > 0.999; Figure 4.1, P. 70).
Figure 4.1 Group mean (±SD) data showing the VAS pain results immediately following maximal voluntary isometric contractions (MVIC) of the trained limb. No significant differences were observed at baseline or post intervention between groups. † denotes a significant group by time interaction of $P < 0.05$, between the KOA intervention and healthy control group.
4.3.2 VAS Untrained Limb

At baseline, there were no differences in the VAS pain score for the untrained limb between the KOA intervention group and the KOA control group (P = 0.991). However, at baseline, there was a significant difference in VAS pain score between the untrained KOA intervention group and the healthy age-matched control group (P < 0.001). Further, there was also a significant difference at baseline in the VAS pain score between the KOA control group and the healthy age-matched controls (P = 0.026).

Following the 4-week strength training intervention, there was a main effect time ($F_{(1, 45)} = 10; P = 0.002$), and a group by time interaction ($F_{(2, 45)} = 18; P < 0.001$). Bonferroni post hoc analysis, revealed that for the untrained limb in the KOA intervention, VAS pain score improved by 40% (P < 0.001; M = -5.3, 95% CI [2.5, 6.5]), further, this increase was significantly different to the KOA control group (P < 0.001). The magnitude of change in the VAS pain score between the KOA intervention group and the healthy age-matched controls remained different (P = 0.037). Further, VAS pain score of the KOA control remained significantly different to the healthy age-matched controls (P < 0.001; Figure 4.2, P. 72).
Figure 4.2 Group mean (±SD) data showing the VAS pain results during maximal voluntary isometric contractions (MVIC) of the untrained limb. * denotes significant baseline differences of $P < 0.05$, between the healthy control group to the KOA intervention and KOA control. ° denotes significant time effect of $P < 0.001$, from baseline to post intervention for the KOA intervention. † denotes a significant group by time interaction of $P < 0.01$, between the KOA intervention and both the KOA control and healthy control groups.
4.3.3 Pain and strength correlation

Using linear regression, there was no association between the change in knee extensor strength of the untrained limb and the change in VAS pain scores (decreasing pain) in the untrained limb, $R^2 = 0.16$, ($F_{(1, 13)} = 2.4$; $P = 0.143$; Figure 4.3). There was no association between the change in knee extensor strength of the trained limb and the change in VAS pain scores in the trained limb, $R^2 = 0.021$, ($F_{(1, 13)} = .27$; $P = 0.609$). Further, there was no association between the change in knee extensor strength of the trained limb and the change in VAS pain scores in the untrained limb, $R^2 = 0.006$, ($F_{(1, 13)} = 0.074$; $P = 0.789$).

Figure 4.3 Knee extensor change (%) for the untrained limb of the KOA intervention group and % change in VAS pain scores.
4.3.4 Trained limb retention of improvements in VAS pain

Following the 3 month wash out period post intervention, there was no main effect for time observed ($F_{(1, 51)} = 2.2; P = 0.372$) and no group by time interaction was observed ($F_{(1, 51)} = 1.0; P = 0.147$). No changes in VAS pain scores were observed in the 3 months following the intervention for the trained limb ($P > 0.999; M= 5.3, 95\% CI [2.5, 6.5]$), or the healthy age-matched control group ($P > 0.999$; Figure 4.4, P. 75). Retention of VAS pain improvements in the trained limb of the KOA intervention group over the 3-months following the 4-week intervention had occurred.

4.3.5 Untrained limb retention of improvements in VAS pain

Following the 3 month wash out period post intervention, there was no main effect for time ($F_{(1, 51)} = 2.2; P = 0.372$) and no group by time interaction was observed ($F_{(1, 51)} = 1.0; P = 0.148$). There was no changes in VAS pain scores in the 3 months following the intervention for the untrained limb ($P = 0.341; M= 0.77, 95\% CI [-0.42, 2]$) or the healthy age-matched control group ($P > 0.999$; Figure 4.4, P. 75). Retention of VAS pain improvements in the untrained limb of the KOA intervention group over the 3-months following the 4-week intervention was maintained.
Figure 4.4 Group mean (±SD) data showing the VAS pain results during maximal voluntary isometric contractions (MVIC) from the post-intervention assessment to the 3 month post-intervention assessment. * denotes significant post-intervention differences of $P < 0.05$, between the healthy control group to the KOA intervention and KOA control.
4.3.6 KOOS Pain

At baseline, there were no differences in the KOOS pain between the KOA intervention group and the KOA control group (P > 0.999). However, at baseline, there was a significant difference in KOOS pain between the KOA intervention group and the healthy age-matched control group (P < 0.001). Further, there was also a significant difference at baseline in the KOOS pain between the KOA control group and the healthy age-matched controls (P = 0.002).

Following the 4-week strength training intervention, there was a main effect for time (F$_{(2, 35)}$ = 6; P = 0.019) and a group by time interaction (F$_{(2, 35)}$ = 8.3; P = 0.001). Bonferroni post hoc analysis, revealed that for the KOA intervention group, KOOS pain improved by 29.7% (P < 0.001; M= 16, 95% CI [8.3, 24]), further, this increase was significantly different to the KOA control group (P <0.001). The magnitude of change in KOOS pain between the KOA intervention group and the healthy age-matched controls remained significantly different (P = 0.013; Figure 4.5, P. 77).
**Figure 4.5** Group mean (±SD) data showing the KOOS pain outcome scores. * denotes significant baseline differences of $P < 0.05$, between the healthy control group to the KOA intervention and KOA control. ° denotes significant time effect of $P < 0.001$, from baseline to post intervention for the KOA intervention. † denotes a significant group by time interaction of $P < 0.01$, between the KOA intervention and both the KOA control group and healthy age-matched controls.
4.3.7 Retention of improvements in KOOS pain

Following the 3 month wash out period post intervention, there was no main effect for time observed ($F_{(1, 20)} = 2.3; P = 0.996$) and no group by time interaction was observed ($F_{(1, 20)} = 0.28; P = 0.601$). There were no changes in KOOS pain scores in the 3 months following the intervention for the KOA intervention group ($P = 0.914; \text{M}= 0.51 \text{ 95% CI [-2.7, 3.7]}$) or the healthy age-matched control group ($P = 0.918$; Figure 4.6). Retention of KOOS pain improvements that occurred following the 4 week intervention had occurred.

![Graph showing KOOS pain results](image)

**Figure 4.6** Group mean (±SD) data showing the KOOS pain results from the post intervention assessment to the 3 month post intervention assessment. * denotes significant post-intervention differences of $P < 0.05$, between the healthy control group to the KOA intervention group.
4.3.8 KOOS Symptoms

At baseline, there were no differences in the KOOS symptoms between the KOA intervention group and the KOA control group (P > 0.999). However, at baseline, there was a significant difference in KOOS symptoms between the KOA intervention group and the healthy age-matched control group (P = 0.002). Further, there was also a significant difference at baseline in the KOOS symptoms between the KOA control group and the healthy age-matched controls (P = 0.001).

Following the 4 week strength-training intervention, there was no main effect for time (F(1, 35) = 1.6; P = 0.218), however, there was group by time interaction (F(2, 35) = 5.3; P = 0.001). Bonferroni post hoc analysis, revealed that for the KOA intervention group, KOOS symptoms improved by 12% (P = 0.002; M= 17, 95% CI [7.7, 25]), however, this increase was not significantly different to the KOA control group (P > 0.999). The magnitude of change in KOOS symptoms between the KOA intervention group and the healthy age-matched controls remained significantly different (P = 0.002; Figure 4.7, P. 80).
Figure 4.7 Group mean (±SD) data showing the KOOS symptoms outcome score. * denotes significant baseline differences of P < 0.01, between the healthy control group to the KOA intervention and KOA control. † denotes a significant group by time interaction of P < 0.01, between the KOA intervention and healthy control group.
4.3.9 Retention of improvements in KOOS symptoms

Following the 3 month wash out period post intervention, there was no main effect for time ($F_{(1, 20)} = 0.46; P = 0.505$) and no group by time interaction ($F_{(1, 20)} = 1.8; P = 0.197$). No changes in KOOS symptom scores were observed in the 3-months following the intervention for the KOA intervention group ($P = 0.876; M = -0.64, 95\% \text{ CI } [-4, 2.7]$) or the healthy age-matched control group ($P = 0.311$; Figure 4.8). Retention of the improvements in KOOS symptom improvements that occurred following the 4 week intervention had occurred.

![Figure 4.8](image-url)

**Figure 4.8** Group mean (±SD) data showing the KOOS symptoms results from the post intervention assessment to the 3 month post intervention assessment. * denotes significant post-intervention differences of $P < 0.02$, between the healthy control group to the KOA intervention group.
4.3.10 KOOS Quality of Life

At baseline, there were no differences in the KOOS QOL between the KOA intervention group and the KOA control group (P = 0.887). However, at baseline, there was a significant difference in KOOS QOL between the KOA intervention group and the healthy age-matched control group (P < 0.001). Further, there was also a significant difference at baseline in KOOS QOL between the KOA control group and the healthy age-matched controls (P < 0.001).

Following the 4-week strength training intervention, there was a main effect time ($F_{(1, 35)} = 5.5; P = 0.025$) and a group by time interaction ($F_{(2, 35)} = 6.3; P = 0.004$). Bonferroni post hoc analysis, revealed that for the KOA intervention group, KOOS QOL improved by 44.6% (P < 0.001; M= 15, 95% CI [7.1, 24]), further, this increase was significantly different to the KOA control group (P = 0.029). The magnitude of change in KOOS pain between the KOA intervention group and the healthy age-matched controls remained significantly different (P < 0.001; **Figure 4.9**, P. 83).
Figure 4.9 Group mean (±SD) data showing the KOOS quality of life (QOL) outcome score. * denotes significant baseline differences of $P < 0.001$, between the healthy control group to the KOA intervention and KOA control. ° denotes significant time effect of $P < 0.05$, from baseline to post intervention for the KOA intervention. † denotes a significant group by time interaction of $P < 0.01$, between the KOA intervention and KOA control groups.
4.3.11 Retention of improvements in KOOS QOL

Following the 3 month wash out period post intervention, there was no main effect for time observed ($F_{(1, 20)} = 0.49; P = 0.493$) and no group by time interaction was observed ($F_{(1, 20)} = 0.51; P = 0.484$). No changes in KOOS QOL scores were observed in the 3 months following the intervention for the KOA intervention group ($P = 0.551; M= -2.2, 95\% CI [-7.3, 3.2]$) or the healthy controls ($P > 0.999$). Retention of the improvements in KOOS QOL scores in the KOA intervention group was achieved during the 4 week intervention, however, the KOA intervention continued to score significantly lower than the healthy age-matched controls ($P < 0.001$; Figure 4.10).

**Figure 4.10** Group mean (±SD) data showing the KOOS QOL results from the post intervention assessment to the 3 month post intervention assessment.* denotes significant post-intervention differences of $P < 0.001$, between the KOA intervention group and healthy control group.
4.3 Discussion

The purpose of this study was to determine the clinical efficacy of unilateral knee extensor training on improving pain and symptoms in the untrained KOA limb via the cross education phenomenon. This is the first study to the best of the authors' knowledge that has measured the influence of the cross education phenomenon and pain in the untrained contralateral limb. There were several important and novel findings, which further validate the use of cross education in unilateral KOA.

The primary finding was there was a significant decrease in acute knee pain as measured by the VAS. Following the intervention, acute pain in the untrained KOA limb decreased by 36.5% and acute pain in the trained KOA limb decreased by 53%. Post intervention, the untrained KOA limb was still significantly different to pain measured in the age-matched healthy controls by 72%. Both limbs retained the improvements in acute pain for a 3-month period following the intervention. A significant decrease in short term pain as measured by the KOOS was observed. Following the intervention, short term pain improved by 27.9%, which was maintained for three months following the intervention, with a 3.4% improvement.

The secondary findings are there was a significant improvement in QOL of 45.6% as measured by the KOOS following the intervention. The improvement in QOL continued to improve in the three months following the intervention by an additional 15.2%. There was a significant improvement in KOOS Symptoms of 12.2%, which was retained for the 3-months following the intervention.

4.3.1 Improvements in pain following cross education therapy

Direct exercise therapy of the KOA limb is well established in improving KOA pain post intervention (Jansen et al., 2011), whether it is strength or aerobic based training (Roddy et al., 2005, Tanaka et al., 2013). Maurer and colleagues (1999), after 8 weeks of
knee extensor training (3 sessions per week) observed a 20.3% increase in isometric knee extension strength, with a corresponding 65% improvement in pain. While the strength improvement observed by Maurer was almost identical to this study (19.8% - see Chapter 3, Study 1), Maurer noted a 65% improvement in ‘categorical’ pain, whereas this study observed a 36.5% in the untrained KOA limb and a 53.2% in the trained limb. When comparing the WOMAC used by Maurer et al. (1999) to the KOOS used in this study, the differences were negligible with knee pain decreasing by 24.8% and 27.9% respectively. Results from the WOMAC and KOOS are directly comparable as the KOOS is an extension of the WOMAC (Roos and Toksvig-Larsen, 2003). The current study achieved the same improvement in pain symptoms in half the duration and training sessions, and this result alone potentially highlights the efficacy of the cross education phenomenon in this population. Both studies also included a follow-up assessment following the post intervention assessment with the study by Maurer and colleagues measuring pain scores at 4 weeks post intervention while the current study measured pain at 12 weeks post intervention. Interestingly both studies showed continued improvements in these periods, with Maurer observing a 15.2% and the current study observing a 3.4% increase. It is unclear if the significantly longer follow-up period would have affected this outcome.

The results from the current study were also similar to Topp et al. (2002), who utilised a WOMAC to measure changes in pain after a 16 week isometric training program (x3 training sessions weekly). A 41% improvement in pain was observed, but unfortunately no measures of knee extensor strength were taken, so it is unclear if there was a correlation between improved knee extensor strength and decreasing KOA pain. This is arguably a critical parameter of any study investigating changes in knee pain following a therapeutic exercise program, as knee strength appears to closely correlate with pain, however this relationship was not seen in this experimental chapter. A study by Amin et al. (2009) demonstrated a significant increase in KOA pain in groups when ordered from high, moderate to low levels of knee extensor strength. This correlation is well supported in the
literature, with increasing levels of knee pain resulting in greater deficits in knee extensor strength (Ruhdorfer et al., 2014, O'Reilly et al., 1998, Steidle-Kloc et al., 2015, Baker et al., 2004).

Most importantly, both the VAS for the untrained limb and KOOS pain scales met the threshold for minimum clinically important difference (MCID) in the KOA intervention group. A recent meta-analysis (Olsen et al; 2017) determined that MCID for acute pain as measured by the VAS for individuals reporting <40mm are mean decrease of 6mm (4-8mm). As the untrained limb, whilst the pain decrease following the 4-week intervention did not met the absolute threshold at 5.3mm achieved, however it did meet the 17% relative reduction, at a decrease of 40%, the relative low initial pain scores likely mediated this result, as Olsen highlighted that lower initial pain will result in smaller improvements meeting MCID, Supporting this result an early study determined VAS MCID for osteoarthritis was 15mm absolutely or 20% relatively (Tubach et al., 2012). However, to meet the criteria for MCID for KOOS pain, a 4% improvement or a 2.2 point improvement on the KOOS pain scale was required (Singh at al., 2014). As the improvement in the KOA intervention group for KOOS pain was 29.7% and an absolute improvement of 16 points, this criteria was met. Interpretation of these results suggests the invention was successful in achieving MCID in pain symptoms over the previous week, but less successful in acute knee pain during MVIC’s.

4.3.2 Knee extensor strength and pain

Potentially underpinning the improvements in pain, and by default, KOOS symptoms and QOL; it has been hypothesised that quadriceps weakness, particularly in relation to body mass (KG), may compromise knee stability (Slemenda et al., 1997) and alter gait biomechanics (Harding et al., 2012). Conversely, this hypothesis was not supported by the results in this study, with a linear regression comparing the relationship between strength improvements of the untrained limb to changes in pain as measured by the VAS showing no relationship between the two variables. End stage KOA is a multifactorial and complex
disease, with mechanical factors driving an active response to this ongoing trauma (Loeser et al., 2012), since increasing knee extensor strength has no effect on existing joint damage, strength alone is unlikely to be able to significantly reduce knee pain. However, pain also did not prevent significant increases in knee extensor strength of the untrained limb via the cross education phenomenon (Chapter 3, Study 1). It also cannot be overlooked that engaging in acute bouts of resistance training may positively alter acute pain perception regardless of any chronic change in knee extensor strength (Koltyn and Arbogast, 1998, Focht and Koltyn, 2009). However, the use of the KOOS pain sub-scale which measures the perception of pain over a week long period negates the effect of acute change in pain perception.

4.3.3 Knee Symptoms and QOL

The evidence in the literature on the QOL in people with KOA is inconsistent. While it is clear that KOA has a detrimental effect on QOL, with increasing pain and reduced function driving this deficit, the absolute deficit appears to be modulated primarily by social support (or lack of) (Jakobsson and Hallberg, 2002). While the KOA intervention group in this study made significant improvements in QOL (44.6%), they were still 44.1% below the age-matched healthy controls. These result mimic previous research that showed a 29% improvement after 8 weeks of strength training, but no comparison to an age-matched control group was conducted (McQuade and de Oliveira, 2011).

Knee symptoms significantly improved in this study by 12.2% and this was in agreement with findings from McQuade & Oliveira (2011) who reported a 16.6% improvement in symptoms, after 8 weeks of strength training. However, these results are in contrast to Topp et al. (2002), who after a 16 week intervention showed no change in any intervention group symptoms as measured by the WOMAC. As the WOMAC measures symptoms such as stiffness, the difference in survey questions might help to explain the difference in results. Again, very few studies have investigated the effects of strength training on knee symptoms, as highlighted in a detailed systematic review by Jansen et al. (Jansen
et al., 2011), with research strongly focused on pain, strength and function, making further comparisons difficult. Lastly, the improvement in KOOS QOL score of 44.6% or an increase in 18 points, met the MCID criteria of a relative improvement of 25.7% and an absolute improvement of 8 points (Singh et al., 2014).

4.3.4 Retention of improvements

It can be speculated that the retention of reduced in knee pain, and the improvement in knee symptoms, recreation and QOL was due to a potential increase in incidental activity and physical recreation. One of the limitations to this study was that no physical activity measurement was taken prior to the intervention or during the 3 months post intervention, it has been previously reported that in both bilateral and unilateral KOA a sustained and significant increases in moderate to vigorous physical activity in conjunction with a strength training program occurs (Farr et al., 2010). Interestingly, the strength training program does not replace other forms of physical activity, but increases them, which is in opposition to what occurs in elderly populations without KOA, who typically reduce incidental physical activity when engaged in a formal exercise program (Meijer et al., 1999). Whilst the finding by Farr et al. (2010) who’s study design does not directly mimic the current study, it does highlight that the 4 week bout of strength training may have had a positive residual effect on overall physical activity levels in the participants, which may partially explain the retention of benefits over the 3 months following the intervention.

4.3.5 Limitations

Pain medications were noted for all KOA participants, ensuring the same medication for each individual participant occurred at each testing session to ensure consistency. However, medication type and dosage differed between participants, as prescribed by their general practitioner or surgeon; this may have affected pain data compared to comparable previous studies. However, the use of the VAS for acute pain during each testing session
and the use of the KOOS Pain for short term pain (previous week) may partially overcome this limitation.

As previously highlighted in Study 1 (Chapter 3; Page 60) while physical activity was monitored during the intervention period to ensure no changes to normal physical activity, no measurement of baseline physical activity was determined prior to the intervention period, or in the three months following the intervention, prior to the final assessment. This limitation meant that we could only theorise as to the reasons of the complete retention of improves in pain, symptoms, recreation and QOL in the intervention group. Due to practical limitations there was no three month post intervention measurement of the KOA control group, which made it impossible to compare the KOA intervention to an equivalent control group at this time point.

4.3.6 Conclusions

The results from this study supported our hypothesis that four weeks of strength training of the contralateral limb in unilateral KOA would result in significant decreases in pain and symptoms in the untrained contralateral limb, and concurrently an increase to QOL. To the best of the author’s knowledge this was the first cross education study to demonstrate such results. Interestingly, these improvements were retained for the 3 months following the intervention, which may be explained by positive changes in incidental activity as previously demonstrated in KOA cohorts (Farr et al., 2010). The clinical applications from cross education are apparent, and further research, particularly around the limitations of this study, no measurement of physical activity and determining the mechanisms in the retention of benefits, are warranted, to ensure these benefits can be maximally exploited.
CHAPTER FIVE

STUDY THREE

CROSS EDUCATION EXERCISE THERAPY IMPROVES OBJECTIVE AND SUBJECTIVE FUNCTIONAL PERFORMANCE IN UNILATERAL KNEE OSTEOARTHRITIS.
5.1 Background

Functional capacity, which is also called functional ability or functional status, is defined as an individual's ability to successfully engage in activities of daily living (ADL's), such as bathing, toileting, eating, transferring from beds or chairs and other general domestic tasks without assistance (Mor et al., 1989). When an individual is no longer able to successfully engage in these tasks, they are classed as disabled and are high risk for the need for outpatient care, hospitalisation, nursing home admission and ultimately death.

The primary identified causes for functional decline in knee osteoarthritis (KOA) are pain (Gur and Cakin, 2003, Rejeski et al., 1996, Topp et al., 2000, Marks, 1994) and reduced knee extensor strength of either the affected limb or contralateral limb in unilateral KOA (Gur and Cakin, 2003, Topp et al., 2000, Rejeski et al., 1996, Brown et al., 2009, Maly et al., 2005). When compared to age match healthy controls, the KOA cohort is slower by 20% on the stair climb test (SCT) and 26% slower on the timed up and go (TUG). Interestingly the grade of KOA has no relationship on physical performance (Liikavainio et al., 2008). However, at end stage KOA, two weeks prior to knee replacement surgery, functional deficits are further magnified with the KOA cohort taking 89% longer to complete the SCT, 49% longer on the TUG and they covered 38% less distance during the six minute walk test (6MWT) when compared to healthy age-matched controls (Bade et al., 2010). Cubukcu (2012) theorised that pain at this time point explained the increased functional deficit prior to surgery, independently of KOA grade.

While a reduction in knee pain will not automatically lead to increases in functional ability (White et al., 2011), previous research has shown the knee extensor strength of both the KOA limb and contralateral limb are independently associated with stair ascension and walking speed (Valtonen et al., 2015). This strongly suggests that an increase in knee extensor strength following a training intervention can increase functional capacity regardless of pain (Zhang et al., 2010, McAlindon et al., 2014).
There is a dearth of evidence showing that cross education is an efficacious method of increasing strength in the trained and the untrained contralateral limb in healthy subjects (Carroll et al., 2006). A previous study investigated cross education in bilateral KOA, with promising results in improving physical function as measured by decreased time to complete a 50 foot walk test (Malas et al., 2013). Albeit, only 1 of the 5 recommended tests of physical function were performed, as recommended by the Osteoarthritis Research Society International (OARSI) guidelines (Dobson et al., 2013). Therefore, there is still a critical need to evaluate the efficacy of cross education in improving functional capacity in a unilateral KOA, utilising OARSI recommended tests, such as the TUG and SCT.

Therefore, this study investigated the influence of 4 weeks of unilateral strength training, on functional performance, as measured by the SCT, TUG and KOOS ADL. It was hypothesised that following the 4-week intervention, functional performance would increase, primarily due to the increase in knee extensor strength of both limbs and the concurrent reduction in knee pain.

5.2 Materials and methods

5.2.1 Participants

The participant characteristics, inclusion and exclusion criteria are identical to the protocol outlined in study one, section 3.2.1 (Page 38).

5.2.2 Experimental design

The experimental design is identical to the protocol outlined in study one, section 3.2.2 (Page 39).
5.2.3 Study settings

The study setting is identical to the protocol outlined in study one, section 3.2.3 (Page 40).

5.2.4 Interventions

The study intervention is identical to the protocol outlined in study one, section 2.3.4 (Page 42)

5.2.5 Stair Climb Test (SCT)

The SCT is a simple and fast functional test designed to determine a participant’s ability to ascend and descent a flight of steps, as quickly as possible, in a safe manner (Bennell et al., 2011). The participant began at the bottom of the stairs and at the researchers’ instruction, ascended the stairs, turned around at the top and descended the stairs, using the hand rail only if needed for balance or safety. Assistive devices were allowed if the participant felt they could not do the test without it. A modified SCT using 10 steps (each step 18 cm high and 28 cm deep) was used, as described by Rejeski (1995), which has excellent retest reliability (coefficient of 0.93). The participant conducted 1-trial as familiarisation, then two subsequent trials which were timed, with a 2-minute rest period between trials to reduce the influence of fatigue. With the fastest time being used for statistical analysis. The SCT has been shown to have high inter-rater reliability, 0.94 (Almeida et al., 2010).

5.2.6 Timed Up and Go (TUG)

The TUG measures the combined output of leg strength, gait, coordination and balance (Bennell et al., 2011). The test began by having the participant seated in a standard height chair (44 cm) with their feet on the floor and back against the back rest. When the participant was told to ‘go’, they rose to a standing position, walked forwards 3 meters to a
line on the floor, turned around and returned to the chair and sat back down. The test ended when they were fully seated in the chair. Participants were encouraged to move as quickly as possible during the test, but safely. No physical assistance was given unless it was required as the tester walked with the subject during the test. The participant underwent a familiarisation trial, then two timed trials. The TUG has been shown to have high inter-rater reliability, 0.99 (Podsiadlo and Richardson, 1991).

5.2.7 Data analysis

The data analysis is identical to the protocol outlined in study one, section 3.3.7 (Page 42).

5.2.8 Statistical analysis

The statistical analysis is identical to the protocol outlined in study one, section 3.3.8 (Page 43).

5.2.9 Participant Flow

The participant flow is identical to the protocol outlined in study one, section 3.2.9 (Page 38).

5.3 Results

Twenty-eight participants aged 55-76 years with radiographic diagnosed unilateral knee osteoarthritis (KL grade >3) and sixteen healthy age-matched controls were studied. No differences between groups for any characteristics was observed, age (P = 0.7369), height (P = 0.8344), weight (P = 0.7036) and BMI (P = 0.8694, Table 5.1, P. 96).
**Table 5.1 Characteristics of participants**

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</tr>
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<td><strong>BMI</strong></td>
<td>29.1 ± 3.5</td>
<td>29.4 ± 3.3</td>
<td>29.7 ± 4.9</td>
</tr>
<tr>
<td><strong>Trained knee extensor strength</strong> (nm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>102 ± 37</td>
<td>99 ± 22</td>
<td>149 ± 46</td>
</tr>
<tr>
<td>Post training</td>
<td>127 ± 45*</td>
<td>98 ± 22</td>
<td>152 ± 48</td>
</tr>
<tr>
<td><strong>Untrained knee extensor strength</strong> (nm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>92 ± 32</td>
<td>90 ± 28</td>
<td>149 ± 46</td>
</tr>
<tr>
<td>Post training</td>
<td>111 ± 33*</td>
<td>89 ± 28</td>
<td>152 ± 48</td>
</tr>
<tr>
<td><strong>Pain VAS</strong></td>
<td></td>
<td></td>
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<tr>
<td>(untrained)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>12 ± 6</td>
<td>8 ± 8</td>
<td>3 ± 2</td>
</tr>
<tr>
<td>Post training</td>
<td>7 ± 6*</td>
<td>7 ± 8</td>
<td>3 ± 2</td>
</tr>
</tbody>
</table>

Values are mean ± SD, * denotes P < 0.0001 post training vs baseline.
5.3.1 Stair climb test

At baseline, there were no differences in time to complete the SCT between the KOA intervention and KOA control group (P >0.999). However, at baseline, there was a significant difference in the time to complete the SCT between the KOA intervention group and the healthy age-matched control group (P = 0.004). Further, at baseline, there was also a significant difference in the time to complete the SCT between the KOA control group and the healthy age-matched control group (P = 0.001).

Following the 4-week strength training intervention, there was no main effect for time ($F_{(1,35)} = 3; P = 0.094$), however there was a group by time interaction ($F_{(2,35)} = 7.8; P = 0.002$). Bonferroni post hoc analysis, revealed that the KOA intervention group decreased the time to complete the SCT by 20.1% ($P < 0.001; M= 2.7, 95\% CI [1.2, 4.2]$) and this improvement was significantly different to the KOA control group ($P = 0.028$). Importantly, following the 4-week intervention the KOA intervention group was not different to the healthy age-matched control group in time to complete the SCT ($P = 0.502$; Figure 5.1, P. 98).
Figure 5.1 Group mean (±SD) data showing the time to complete the Stair Climb Test (SCT). * denotes significant baseline differences of $P < 0.01$, between the healthy control group to the KOA intervention and KOA control. ° denotes significant time effect of $P < 0.001$, from baseline to post intervention for the KOA intervention. † denotes a significant group by time interaction of $P < 0.01$, between the KOA intervention and the KOA control.
5.3.2 Trained limb knee extensor strength and the SCT

Using linear regression, there was no association between the change in knee extensor strength of the trained limb and the change in the time to complete the SCT ($R^2 = 0.00016$, $P = 0.965$).

5.3.3. Untrained limb knee extensor strength and the SCT

Using linear regression, there was no association between the change in knee extensor strength of the untrained limb and the change in the time to complete the SCT ($R^2 = 0.00096$, $P = 0.913$).

5.3.4 Trained limb VAS and the SCT

Using linear regression, there was no association between the change in knee pain severity of the trained limb and the change in the time to complete in the SCT ($R^2 = 0.2$, $P = 0.093$).

5.3.5 Untrained limb VAS and the SCT

Using linear regression, there was no association between the change in the knee pain severity untrained limbs and the change in the time to complete in the SCT ($R^2 = 0.002$, $P = 0.848$).
5.3.6 Retention of improvements in the SCT

Following the 3 month wash out period post intervention, there was no main effect for time observed ($F_{(1, 24)} = 1.1; P = 0.301$) and no group by time interaction was observed ($F_{(2, 33)} = 0.53; P = 0.591$). No changes in the time to complete the SCT were observed in the 3 months following the intervention for the KOA intervention group ($P = 0.505; M= -0.41, 95\% \text{ CI } [-1.2, 0.42]$) or the healthy age-matched control group ($P > 0.999$; **Figure 5.2**). Improvements in the time to complete the SCT in the KOA intervention group following the 4-week intervention were retained for 3-months post-intervention.

![Figure 5.2](image-url)  
**Figure 5.2** Group mean (±SD) data demonstrating the retention of the improvements in the time to complete the Stair Climb Test (SCT) in the three months following the intervention compare to an age-matched healthy control group. No significance differences were observed within or between groups.
5.3.7 Timed up and Go

At baseline, no differences in time to complete the TUG were present between the KOA intervention and KOA control groups (\(P >0.999\)). However, there was a significant difference in the time to complete the TUG between the KOA intervention group and the healthy age-matched control group (\(P = 0.036\)). Further, there was also a significant difference in the time to complete the TUG between the KOA control group and the healthy age-matched control group (\(P = 0.008\)).

Following the 4-week strength training intervention, a main effect for time was observed (\(F_{(1,35)} = 7.8; P = 0.009\)) and a group by time interaction occurred (\(F_{(2,35)} = 12; P = 0.001\)). Bonferroni post hoc analysis revealed that the KOA intervention group decreased their time to complete the TUG by 23% (\(P < 0.001; M= 1.8, 95\% \text{ CI} [0.08, 3.6]\)). Importantly, post intervention, the KOA intervention group was significantly faster than the KOA control group in the time to complete the TUG (\(P = 0.005\)). Again, the time to complete the TUG between the KOA intervention group and the healthy age-matched controls was not different (\(P > 0.999\); Figure 5.3, P. 102).
Figure 5.3 Group mean (±SD) data showing the time to complete the TUG test.* denotes significant baseline differences of $P < 0.05$, between the healthy control group to the KOA intervention and KOA control. ° denotes significant time effect of $P < 0.01$, from baseline to post intervention for the KOA intervention. † denotes a significant group by time interaction of $P < 0.01$, between the KOA intervention and the KOA control.
5.3.8 Trained limb knee extensor strength and the TUG

Using linear regression, there was no association between the change in knee extensor strength of the trained limb and the change in the time to complete the TUG ($R^2 = 0.00016$, $P = 0.966$).

5.3.9 Untrained limb knee extensor strength and the TUG

Using linear regression, there was no association between the change in knee extensor strength of the trained limb and the change in the time to complete the TUG ($R^2 = 0.0036$, $P = 0.831$).

5.3.10 Trained limb VAS and the TUG

Using linear regression, there was no association between the change in knee pain severity of the trained limb and the change in the time to complete in the SCT ($R^2 = 0.024$, $P = 0.058$).

5.3.11 Untrained limb VAS and the TUG

Using linear regression, there was no association between the change in knee pain severity of the trained limb and the change in the time to complete in the SCT ($R^2 = 0.004$, $P = 0.939$).
5.3.12 Retention of improvements in the TUG

Following the 3 month wash out period post intervention, there was a main effect for time observed ($F_{(1, 24)} = 9.2; P = 0.006$) and a group by time interaction ($F_{(1, 24)} = 6.6; P = 0.017$). The time to complete the TUG in the KOA intervention group increased by 6% compared to the post intervention measurement ($P < 0.001; M= 0.75, 95\% \text{ CI } [0.36, 1.2]$). No changes in the time to complete the TUG were observed in the 3 months following the intervention in the healthy age-matched control group ($P > 0.999$). Retention of the improvements in time to complete the TUG in the KOA intervention group was achieved during the 4 week intervention were retained. Importantly, the time to complete the TUG between the KOA intervention group and the healthy age-matched control group at 3 months’ post intervention were not different ($P > 0.999$; Figure 5.4, P. 105).
Figure 5.4 Group mean (±SD) data demonstrating the retention of the improvements in the time to complete the Timed Up and Go (TUG) in the three months following the intervention compared to an age-matched healthy control group. No significant difference post or post3 intervention were observed between groups. ° denotes significant time effect of P < 0.01, from post-intervention to 3-month post for the KOA intervention. † denotes a significant group by time interaction of P < 0.05, between the KOA intervention and the KOA control.
5.3.13 KOOS ADL

At baseline, no differences in KOOS ADL were present between the KOA intervention and KOA control groups (P >0.999). However, at baseline, there was a significant difference in KOOS ADL between the KOA intervention group and the healthy age-matched control group (P < 0.001). Further, at baseline, there was also a significant difference in KOOS ADL between the KOA control group and the healthy age-matched control group (P = 0.001).

Following the 4-week strength training intervention, a main effect for time was observed (F(1, 35) = 4.5; P = 0.042) and a group by time interaction occurred (F(2, 35) = 7.1; P = 0.003). Bonferroni post hoc analysis revealed that the KOA intervention group improved its KOOS ADL score by 28.5% (P < 0.001; M= -0.64, 95% CI [-4, 2.7]). Importantly, the KOA intervention group was significantly different from the KOA control group following the intervention (P = 0.022). Furthermore, the KOOS ADL score between the KOA intervention group and the healthy age-matched controls were significantly different post intervention (P > 0.038; Figure 5.5, P. 107).
Figure 5.5 Group mean (±SD) data showing the KOOS ADL outcome score. * denotes significant baseline differences of $P < 0.001$, between the healthy control group to the KOA intervention and KOA control. ° denotes significant time effect of $P < 0.05$, from baseline to post intervention for the KOA intervention. † denotes a significant group by time interaction of $P < 0.01$, between the KOA intervention and the KOA control.
5.3.14 Retention of improvements in the KOOS ADL

Post intervention there were differences in the KOOS ADL score between the KOA intervention group and the healthy age-matched control group (P = 0.017).

Following the 3 month wash out period post intervention, there was no main effect for time ($F_{(1, 20)} = 1.5; P = 0.233$) and no group by time interaction was observed ($F_{(1, 20)} = 0.032; P = 0.86$). No changes in KOOS ADL score occurred in the 3 months following the intervention in either the KOA intervention group (P = 0.553; M= 1.7, 95% CI [-2.4, 5.9]) or the healthy age-matched control group (P = 0.715). Significant differences between the KOA intervention group and healthy age-matched control group persisted (P = 0.014; Figure 5.6, P. 109).
Figure 5.6 Group mean (±SD) data demonstrating the retention of the improvements in the KOOS ADL score in the three months following the intervention compare to an age-matched healthy control group.* denotes significant post-intervention differences of $P < 0.05$, between the healthy control to the KOA intervention group.
5.3.15 KOOS Sport

At baseline, there were no differences in the KOOS sport between the KOA intervention group and the KOA control group (P > 0.403). However, at baseline, there was a significant difference in KOOS sport between the KOA intervention group and the healthy age-matched control group (P < 0.001). Further, there was also a significant difference at baseline in the KOOS sport between the KOA control group and the healthy age-matched controls (P < 0.001).

Following the 4-week strength training intervention, there was a main effect for time (F(1, 35) = 12; P = 0.0012) and a group by time interaction (F(2, 35) = 11; P < 0.001). Bonferroni post hoc analysis, revealed that for the KOA intervention group, KOOS sport improved by 81.9% (P < 0.001; M= 21, 95% CI [13, 29]), further, this increase was significantly different to the KOA control group (P = 0.011). The magnitude of change in KOOS pain between the KOA intervention group and the healthy age-matched controls remained significantly different (P < 0.001; Figure 5.7, P. 111).
**Figure 5.7** Group mean (±SD) data showing the KOOS sport and recreation outcome score. * denotes significant baseline differences of P < 0.001, between the healthy control group to the KOA intervention and KOA control. ° denotes significant time effect of P < 0.001, from baseline to post intervention for the KOA intervention. † denotes a significant group by time interaction of P < 0.01, between the KOA intervention and KOA control groups.
5.3.16 Retention of improvements in KOOS sport

Following the 3 month wash out period post intervention, there was no main effect for time observed ($F_{1, 20} = 2.5; P = 0.132$) and no group by time interaction was observed ($F_{1, 20} = 1.1; P = 0.341$). No changes in KOOS sport scores were observed in the 3 months following the intervention for the KOA intervention group ($P = 0.155; M = -14, 95\% CI [4.3, 31]$) or the healthy age-matched control group ($P = 0.915$). Retention of the improvements in KOOS sport scores in the KOA intervention group was achieved during the 4 week intervention, however significant differences remained between the KOA intervention group and healthy age-matched control group ($P < 0.001$; Figure 5.8).

![Graph showing KOOS sport results](image)

**Figure 5.8** Group mean ($\pm$SD) data showing the KOOS sport results from the post intervention assessment to the 3 month post intervention assessment. * denotes significant baseline differences of $P < 0.05$, between the healthy control group to the KOA intervention group.
5.4 Discussion

The purpose of this study was to determine how bilateral knee extensor strength improvements induced by the cross education phenomenon would influence functional capacity as measured by the SCT, TUG and KOOS ADL. Previously, only 1-study has investigated functional improvements in bilateral KOA due to the cross education phenomenon (Malas et al., 2013). This is the first study to the best of the author’s knowledge that measured the influence of the cross education phenomenon on functional capacity in unilateral KOA. There were several important and novel findings, which further validate the use of cross education in unilateral KOA.

The primary finding was that 4 weeks of unilateral strength training of the contralateral limb in KOA patients significantly improved and retained functional capacity as measured by the SCT, TUG and KOOS ADL. Following the intervention, the time to complete the SCT decreased by 20.1%, with no differences between the KOA intervention and healthy controls post intervention. Time to complete the TUG decreased by 23%, with no differences between the KOA intervention and healthy control post intervention. The KOOS ADL increased by 28.5% post intervention and the KOOS Sport and Recreation increased by 80.9%. All improvements where retained for 3-months post intervention.

5.4.1 Improvements in the SCT and TUG

The baseline deficits of 36% for the SCT and 23% for the TUG when compared to the healthy age-matched controls align with previous published data. Liikavainio et al. (2008) reported functional deficits of 20% and 26% on the SCT and TUG respectively when compared to healthy age-matched controls. Differences between this study and Liikavainio et al. (2008) may be explained by differences in KOA severity. With Liikavainio et al. (2008) recruiting participants with KOA from K/L stages 1-4, whereas in the current study only KOA stages 3-4 were included. In support of this finding, at end stage KOA, two weeks prior to
knee replacement surgery, functional deficits are further magnified with the KOA cohort taking 89% longer to complete the SCT and 49% longer on the TUG when compared to healthy age-matched controls (Bade et al., 2010). Bilateral KOA shows a similar trend with the time to complete the TUG taking 36% longer and a stair climb and descent task taking 100% longer when compared to healthy age-matched controls (Hurley et al., 1997). Recently it has been shown that bilateral and unilateral KOA result in similar deficits in functional performance, enough to consider both subsets the same cohort, making this comparison valid (Messier et al., 2016).

Improvements to the SCT (20%) and TUG (23%) from baseline to post intervention also align with previous research. Gur et al. (2002) reported a 21-23% (concentric – eccentric training groups) improvement in time to complete a SCT and a 23-29% improvement in time to complete a stair descent after an eight week strength training program. While it appears the current study made the same improvements in half the training sessions and time, participants in the Gur study were on average ten years younger, this may have limited the absolute improvements, however, with the lack of a comparison within the Gur study to healthy age-match controls this is postulation at best.

The only previous study that has investigated the cross education phenomenon in KOA, measured function objectively via the time to complete a 50 foot walk test (Malas et al., 2013). While a small but significant result was found (5%), some caution in drawing conclusions is warranted. The walking activity was one of the core recommended functional tasks recommended by OARSI (Dobson et al., 2013). The short walk test was ranked 20th most challenging out of 23 tests, and potentially was not discriminate enough for the results in this test to translate across a full range of functional performance tasks.

Knee extensor strength of both the KOA limb and contralateral limb are independently associated with stair ascension and walking speed (Valtonen et al., 2015). Increasing levels of pain are also independently associated with a decline in functional
performance (White et al., 2011). Result from Study 1 (Chapter 3), showed a significant increase in knee extensor strength to both the trained limb and also the untrained KOA limb, while results from Study 2 (Chapter 4) demonstrated significantly reduced pain as measured by the VAS and KOOS Pain subscale following the cross education intervention. Therefore, it is not surprising that significant improvements in functional performance have been demonstrated in this study.

However, linear regressions comparing knee extensor strength of both the trained and untrained limbs in the KOA intervention group, to the improvements in both the SCT and TUG have been inconclusive. No relationship between changes in knee extensor strength and improvements in functional performance were observed. The same result occurred when comparing changes in knee pain as measured by VAS pain of both the trained and untrained limbs in the KOA intervention group. While the reduction in knee pain following the intervention in this experimental chapter is in alignment with previous research (Amin et al., 2009; Maurer, Stern, Kinossian, Cook, & Schumacher, 1999; Roos, Herzog, Block, & Bennell, 2011), the pain reduction was not shown to be responsible for the improvement in functional performance. This result may have been potentially mediated by the small sample size, while adequate power occurred for all primary measures, potentially not for the linear regressions.

5.4.2 Improvements in KOOS ADL and sport

The Knee injury and Osteoarthritis Outcome Score (KOOS), which incorporates The Western Ontario and McMaster Universities Arthritis Index (WOMAC) are measurement tools of functional capacity, via a subjective questionnaire (Bellamy et al., 1988, Roos et al., 1998). Caution needs to be taken in interpreting functional capacity via subjective surveys, as self-reported measurements do not correlate well with physical assessment (Alnahdi et al., 2012). Subjects tend to overestimate functional capacity in subjective surveys, with pain being the determining factor in survey outcomes (Mizner et al., 2011), this suggests that
Results from objective and subjective measurements are not directly comparable and there is a need to do both (Liikavainio et al., 2008). However in this experimental chapter results from the objective and subject measurements were similar in percentage difference between the KOA and healthy age-matched controls at baseline.

Results from the current study differ from Lund et al. (2008), with the KOOS ADL scoring lower in Lund’s study both before and after each studies 4-week intervention. However, Lund reports a much higher percentage improvement post intervention (60%), compared to the current study (28%). The differences in percentage improvement following the intervention may be explained, as Lund’s intervention was twice as long at 8 weeks in contrast to the current studies 4 week intervention, the participants starting at a lower KOOS ADL score may also influence the magnitude of improvement. Both studies retained improvements three months following the intervention.

In contrast to both the current study and Lund’s (2008) findings, no improvements in function as measured by the KOOS ADL were noted after a 6 week intervention of moderate intensity body weight exercises (Thorstensson et al., 2005). The authors postulated that this was due to the moderate training intensity used in the intervention, as a higher training intensity was not appropriate in this cohort with moderate to severe KOA. This highlights the potential of the cross education phenomenon in unilateral KOA, the contralateral limb can be trained safely at high intensity, maximising knee extensor strength improvements and functional capacity.

In the only previous cross education bilateral KOA study, a 3-week (5 days/week) knee extension strengthening program resulted in substantially improved WOMAC function scores in all intervention groups by 28.1 to 51.9% (Malas et al., 2013), a similar result to the KOOS ADL improvements in the current study. This result also highlights the importance of conducting physical measurements. The time taken to complete a 50 foot walking test decreased by 4.4 - 9%, while a significant finding, it is an 82% difference in improvements.
when compared to the subjective results, a short walking test may not be challenging enough to discriminate improvements effectively.

While it appears that sport and recreation improved dramatically in this study (80.9%), this result can be explained as the baseline score was low, particularly in relation to previously published data (McQuade and de Oliveira, 2011). The potential reasons for the improvements in sport and recreation are outlined in the following section.

5.4.3 Limitations

As previously highlighted in Study 2 (Chapter 4), whilst pain medications were noted for all KOA participants, ensuring the same medication for each individual participant occurred at each testing session to ensure consistency. However, medication type and dosage differed between participants, as prescribed by their general practitioner or surgeon. This may have affected pain data compared to comparable previous studies, as pain has a strong independent relationship on functional capacity. However, the use of the VAS for acute pain during each testing session and the use of the KOOS Pain for short term pain (previous week) may partially overcome this limitation. Lastly, without the measurement of changes in physical activity in the 3-month period following the intervention it is unclear as what may have been the dominate factor in maintaining functional performance.

5.4.5 Conclusions

The results from this study supported our hypothesis that four weeks of strength training of the contralateral limb in unilateral KOA would result in significant improvements in functional capacity as measured by the SCT, TUG and KOOS ADL. Interestingly, these improvements were retained for the 3 months following the intervention, which is in align with previous research (Lund et al., 2008). The clinical applications from cross education are apparent; the cross education phenomenon can significantly improve function while avoiding any aggravation to the KOA limb in unilateral KOA.
CHAPTER SIX

STUDY FOUR

POTENTIAL MECHANISMS UNDERLYING IMPROVEMENTS IN STRENGTH AND FUNCTIONAL PERFORMANCE FOLLOWING CROSS EDUCATION IN UNILATERAL KNEE OSTEOARTHRITIS.
6.1 Background

The chronic loss of knee extensor strength throughout the progression of knee osteoarthritis (KOA) is primarily due to the inability of the nervous system to completely activate a muscle, which is termed central activation deficit (CAD) (Rice and McNair, 2010). While the loss of muscle cross sectional area (CSA) has also been implicated in knee extensor strength loss in KOA, CAD appears to account for more than double the deficits attributed to muscle atrophy in KOA (Mizner et al., 2005).

Transcranial magnetic stimulation (TMS) is a well-established method of investigating intracortical and corticospinal pathways that underlie neuromuscular pathways and ultimately, physical function (Hallett, 2000). However, to date, TMS has only been utilised in two previous KOA studies. Firstly, a single participant case report investigating an eight week training intervention, with motor evoked potential (MEP) amplitude being the only neurological response measured (Hunt et al., 2011). Followed by a cross sectional study comparing a KOA cohort awaiting unilateral knee replacement surgery, to a healthy control comparison (Kittelson et al., 2014). Interestingly, no differences in resting motor threshold (RMT), short interval intracortical inhibition (SICI) or intracortical facilitation (ICF) were observed, and no associations between CAD and corticospinal or intracortical excitability were observed. However, there was a significant correlation between increased pain severity and increased corticospinal excitability ($R^2 = .57$), and reduced knee extensor strength and increased corticospinal excitability ($R^2 = .82$). It has been postulated that the increased levels of corticospinal excitability maybe an attempt of the nervous system to overcome spinal inhibition of the knee extensors due to the trauma, inflammation and pain of KOA (Kittelson et al., 2014, Rice et al., 2011). Further, Kittelson and colleagues postulated that the lack of difference in TMS measures between the KOA and healthy control groups suggested that cortical influences are not a dominate factor in knee extensor weakness in KOA cohorts.
A recent meta-analysis demonstrated that in a healthy population a cross education intervention will result in a reduction in intracortical inhibition, resulting in increased corticospinal excitability (Kidgell et al., 2017). Currently, no interventional studies have investigated a cross education intervention in KOA, and whether the same responses will occur as seen in healthy populations.

Hamstring co-activation has also been implicated as being involved in reduced knee extensor strength in KOA. It has been speculated that increasing levels of co-activation aid in joint stability, at the cost of knee extensor strength (Zeni et al., 2010). Conversely, mixed results have been reported, with increasing co-activation during maximal isometric knee extension (Zeni et al., 2010), and no differences in KOA co-activation when compared to a healthy control group (Heiden et al., 2009). However, to date, no study has investigated the influence of a cross education intervention on hamstring co-activation during maximal isometric contractions.

Therefore, this study investigated the corticospinal responses utilising TMS after 4-weeks of unilateral strength training of the contralateral limb in individuals with unilateral KOA, compared to both age-matched healthy controls and untrained individuals with unilateral KOA. It was hypothesised that unilateral strength training of the contralateral limb in unilateral KOA would decrease co-activation of the hamstring muscle group, increase corticospinal excitability and reduced intracortical inhibition in the ipsilateral primary motor cortex.
6.2 Materials and methods

6.2.1 Participants

The participant characteristics, inclusion and exclusion criteria are identical to the protocol outlined in study one, section 3.2.1 (Page 38).

6.2.2 Experimental design

The experimental design is identical to the protocol outlined in study one, section 3.2.2 (Page 39), with TMS measurements collected two days prior to and following completion of the intervention. The order of data collection at each assessment was subjective survey data, muscle thickness, functional measurements, strength measurements and TMS data.

6.2.3 Study settings

The study setting is identical to the protocol outlined in study one, section 3.2.3 (Page 40), with all assessment sessions being conducted in a physiology laboratory located in the same building located on the universities campus.

6.2.4 Interventions

The study intervention is identical to the protocol outlined in study one, section 2.3.4 (Page 42)

6.2.5 Recording of surface electromyography

Surface electromyography (sEMG) was recorded from the rectus femoris (RF) muscle in both legs using Ag-AgCL electrodes. Two electrodes were place 20 mm apart on the midpoint of the belly of RF, with the ground electrode placed on the lateral epicondyle of the tibia. Skin was prepared (shaven and cleaned with 70% isopropyl alcohol swabs) prior to
the placement of the electrodes to ensure a clear signal was obtained. sEMG signals were amplified (1000x) with bandpass filtering between 20 Hz and 1 kHz and digitised at 10 kHz for 1 second, recorded and analysed using PowerLab 4/35 (ADinstruments, Australia).

Surface electromyography (sEMG) was recorded from the rectus femoris (RF) muscle and bicep femoris (BF) in both legs using Ag-AgCL electrodes. Two electrodes were placed 20 mm apart on the midpoint of the belly of RF and BF, with the ground electrode placed on the lateral epicondyle of the tibia. Skin was prepared (shaven and cleaned with 70% isopropyl alcohol swabs) prior to the placement of the electrodes to ensure a clear signal was obtained. sEMG signals were amplified (1000x) with bandpass filtering between 20 Hz and 1 kHz and digitised at 10 kHz for 1 second, recorded and analysed using PowerLab 4/35 (ADinstruments, Australia).

Single and paired-pulse TMS was applied over the cortical representation of the RF, using a circular coil (90mm diameter) attached via a BiStim unit, to two magstim 200² stimulators (Magstim, Dyfed, UK). The handle of the TMS coil was positioned over the vertex of the head and in an anterior posterior orientation, so the current flows in a counter clockwise direction for innervating the left and right RF (Kidgell and Pearce, 2010). To ensure consistency during and between testing sessions, all participants were fitted with a semitransparent cap, in relation to nasion-inion and interaural lines. The cap was marked with points at 1cm intervals in a longitude-latitude matrix, to allow consistent location of the site evoking the largest MEP in the RF muscle. Single pulse, 130% of active motor threshold (AMT) and short interval paired pulse, 80% of AMT with an interstimulus interval of 3ms, stimuli was delivered to the motor area projecting to the RF (the location on the primary motor cortex that evokes the maximum MEP amplitude to RF, while minimising hamstring activity). AMT was determined by the lowest stimulus required to produce an MEP with a peak-to-peak amplitude of at least 200 μV, AMT MEP amplitudes were evaluated by producing 10 stimuli during low level voluntary knee extension (10% MVIC) (Carroll et al.,
Due to time and practical constraints, only the contralateral hemisphere to the KOA limb in the KOA cohorts was assessed.

### 6.2.6 Cortical excitability and inhibition

All MEPs derived from single and paired-pulse TMS was analysed by calculating the peak-to-peak of the biphasic spike, averaged and normalised to the $M_{\text{MAX}}$ and multiplied by 100. In order to calculate SICI, MEP amplitude was calculated as a ratio by applying the following equation:

$$\text{SICI} = \frac{\text{MEP}_{\text{pp}}}{\text{MEP}_{\text{sp}}} \times 100$$

Where;

- MEP$_{\text{pp}}$ represents the average MEP amplitude from the paired-pulse stimuli.
- MEP$_{\text{sp}}$ represents the average MEP amplitude from the single pulse stimuli.

![Sigmoidal fit to MEP size versus stimulus intensity plot](image)

**Figure 6.1** An example of a sigmoidal fit to MEP size versus stimulus intensity plot. The peak slope of the function is at its tangent at $V_{50}$ (Weier & Kidgell, 2012).
6.2.7 M-waves

Maximum compound action potential waves (M-waves) were obtained from the right and left rectus femoris muscle by direct supramaximal electrical stimulation (pulse duration 1 ms) of the femoral nerve under resting conditions. A high-voltage constant current stimulator (DS7, Digitimer®, Hertfordshire, UK) delivered each electrical pulse. Stimulation was delivered by positioning bipolar electrodes over the femoral triangle. An increase in current strength was applied until there was no further increase in sEMG amplitude ($M_{\text{MAX}}$). To ensure maximal responses, the current was increased an additional 20% and the average $M_{\text{MAX}}$ obtained from 5 stimuli were delivered and recorded at 2.0 Hz. Previous research indicates intra-participant M-wave amplitudes were reliable over 5 trials with a CoV of 0.35% (Goodwill et al., 2012).

6.2.8 Data analysis

Silent period durations were obtained from single-pulse stimuli delivered at 130% AMT during a light KNE Extension contraction (10% MVIC). The duration between the onset of the MEP and the resolution of background sEMG was visually inspected and manually cursored, with the experimenter blinded to each condition. The average from ten stimuli was used for silent period duration (Wilson et al., 1993). An example of the measurement of SPD is shown in Figure 6.4 (p. 129).

The extent of hamstring co-activation was quantified using a procedure published by Hortobagyi (2005). The magnitude of co-activation was calculated as the percentage of maximal BF RMS EMG recorded during knee extension MVIC, compared to the maximal BF RMS EMG recorded during knee flexion MVIC.

$$\text{Co-activation} = \frac{(\text{BF} / \text{BF}_{\text{max}})}{(\text{BF} / \text{RF})} \times 100$$
Peak RMS EMG of BF was recorded during a knee flexion MVIC; the peak RMS EMG for BF was also recorded during knee extension MVIC. The BF/BF$_{max}$ ratio, expressed as a percentage of total activation was then used to correctly interpret the extent of BF/RF ratio.

6.2.9 Statistical analysis

The statistical analysis is identical to the protocol outlined in study one, section 3.3.5 (Page 43).

6.2.10 Participant Flow

For a full summary of the participant flow see 3.2.9 (Page 44). However in brief, KOA participants were randomised into an experimental and control group, with a non-randomised healthy control group included. The three groups were compared via ANOVA’s comparing changes to MEP amplitude, SICI, SP of the contralateral hemisphere to the trained limb (untrained hemisphere) and hamstring co-activation of both limbs following the 4-week intervention (Figure 6.1, P. 126).
Figure 6.2 Consort diagram of study flow from recruitment to data analyses. Note: due to contrindications to TMS, participant flow differs from from studies 1-3.
6.3 Results

6.3.1 Baseline characteristics and Neurophysiological variables.

19 participants aged 55-76 years with radiographic diagnosed unilateral knee osteoarthritis (KL grade >3) and 10 healthy age-matched controls were studied. There were no differences between groups for any characteristics including, age (P = 0.816), height (P = 0.827), weight (P = 0.711) and BMI (P = 0.843, Table 6.1, P. 129).

At baseline, there were no differences in pre-stimulus MEP RMS values of the untrained limb between the KOA intervention group and the KOA control group (P > 0.925). No differences in MEP RMS between the KOA intervention group and the healthy age-matched control group (P = 0.982). No differences in MEP RMS between the KOA control group and the healthy age-matched controls (P = 0.758). Further, following the 4-week intervention no change within groups for MEP RMS for the KOA intervention group (P = 0.897), KOA control group (P = 0.942), or age-matched healthy controls (P = 0.309). No change in SICI RMS for the KOA intervention group (P > 0.999), KOA control group (P = 0.944), or age-matched healthy controls (P = 0.319, Table 6.2, P. 130).

At baseline, there were no differences in pre-stimulus SICI RMS values of the untrained limb between the KOA intervention group and the KOA control group (P > 0.973). No differences in SICI RMS between the KOA intervention group and the healthy age-matched control group (P = 0.957). No differences in SICI RMS between the KOA control group and the healthy age-matched controls (P = 0.79). Further, following the 4-week intervention no change within groups for SICI RMS for the KOA intervention group (P > 0.999), KOA control group (P = 0.944), or age-matched healthy controls (P = 0.319, Table 6.2, P. 130).
At baseline, there were no differences in MVIC hamstring EMG values of the untrained limb between the KOA intervention group and the KOA control group (P > 0.775). No differences in MVIC hamstring EMG between the KOA intervention group and the healthy age-matched control group (P = 0.397). No differences in MVIC hamstring EMG between the KOA control group and the healthy age-matched controls (P = 0.821). Further, following the 4-week intervention no change within groups for MVIC hamstring EMG for the KOA intervention group (P = 0.899), KOA control group (P = 0.899), or age-matched healthy controls (P = 0.807). No change in MVIC hamstring EMG was observed following the 4-week intervention for the trained limb in the KOA intervention group (P = 0.995), KOA control group (P > 0.999), or age-matched healthy controls (P = 0.98, Table 6.3, P. 131).

At baseline, there were no differences in MVIC quadriceps EMG values of the untrained limb between the KOA intervention group and the KOA control group (P > 0.811). No differences in MVIC quadriceps EMG between the KOA intervention group and the healthy age-matched control group (P = 0.976). No differences in MVIC quadriceps EMG between the KOA control group and the healthy age-matched controls (P = 0.994). Further, following the 4-week intervention no change within groups for MVIC quadriceps EMG for the KOA intervention group (P > 0.811), KOA control group (P > 0.999), or age-matched healthy controls (P = 0.993). No change in MVIC quadriceps EMG was observed following the 4-week intervention for the trained limb in the KOA intervention group (P > 0.999), KOA control group (P > 0.999), or age-matched healthy controls (P = 0.999, Table 6.3, P. 131).
Table 6.1 Characteristics of participants

<table>
<thead>
<tr>
<th></th>
<th>KOA Intervention (N = 11)</th>
<th>KOA Controls (N = 9)</th>
<th>Healthy Controls (N = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67 ± 5.8</td>
<td>63.7 ± 3.9</td>
<td>67 ± 6.8</td>
</tr>
<tr>
<td>Sex</td>
<td>6 (M)</td>
<td>5 (M)</td>
<td>7 (M)</td>
</tr>
<tr>
<td></td>
<td>5 (F)</td>
<td>4 (F)</td>
<td>3 (F)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174.1 ± 11.9</td>
<td>171.1 ± 7.5</td>
<td>173.3 ± 8.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>86.8 ± 13.2</td>
<td>87.3 ± 17.8</td>
<td>88.4 ± 11.9</td>
</tr>
<tr>
<td>BMI</td>
<td>28.6 ± 2.8</td>
<td>29.7 ± 4.9</td>
<td>29.4 ± 3.3</td>
</tr>
<tr>
<td>Trained knee extensor strength (nm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>102 ± 37</td>
<td>99 ± 22</td>
<td>149 ± 46</td>
</tr>
<tr>
<td>Post training</td>
<td>127 ± 45*</td>
<td>98 ± 22</td>
<td>152 ± 48</td>
</tr>
<tr>
<td>Untrained knee extensor strength (nm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>92 ± 32</td>
<td>90 ± 28</td>
<td>149 ± 46</td>
</tr>
<tr>
<td>Post training</td>
<td>111 ± 33*</td>
<td>89 ± 28</td>
<td>152 ± 48</td>
</tr>
<tr>
<td>Trained knee flexor strength (nm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>45 ± 22</td>
<td>49 ± 15</td>
<td>72 ± 11</td>
</tr>
<tr>
<td>Post training</td>
<td>48 ± 21</td>
<td>50 ± 15</td>
<td>69 ± 12</td>
</tr>
<tr>
<td>Untrained knee flexor strength (nm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>39 ± 17</td>
<td>43 ± 14</td>
<td>72 ± 11</td>
</tr>
<tr>
<td>Post training</td>
<td>41 ± 17</td>
<td>42 ± 14</td>
<td>69 ± 12</td>
</tr>
</tbody>
</table>

Values are mean ± SD, * denotes P < 0.001 post training vs baseline.
Table 6.2 Mean (±SD) raw values for neurophysiological variables.

<table>
<thead>
<tr>
<th>Group</th>
<th>MEP RMS (Pre-Stim)</th>
<th>MEP Amplitude (%Mmax)</th>
<th>SICI RMS (Pre-Stim)</th>
<th>SICI Amplitude (%Mmax)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRE</td>
<td>POST</td>
<td>PRE</td>
<td>POST</td>
</tr>
<tr>
<td>KOA Intervention</td>
<td>0.03 ± 0.11</td>
<td>0.026 ± 0.008</td>
<td>37.3 ± 16.4</td>
<td>45.4 ± 18.4</td>
</tr>
<tr>
<td></td>
<td>0.027 ± 0.014</td>
<td>0.027 ± 0.006</td>
<td>39 ± 19.2</td>
<td>47.2 ± 14.5</td>
</tr>
<tr>
<td>KOA Controls</td>
<td>0.03 ± 0.007</td>
<td>0.03 ± 0.13</td>
<td>34.1 ± 18.7</td>
<td>36.5 ± 22.2</td>
</tr>
<tr>
<td></td>
<td>0.028 ± 0.014</td>
<td>0.028 ± 0.011</td>
<td>51.1 ± 21.1</td>
<td>49.9 ± 22.5</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>0.04 ± 0.29</td>
<td>0.028 ± 0.01</td>
<td>25.4 ± 8.9</td>
<td>27.8 ± 16.0</td>
</tr>
<tr>
<td></td>
<td>0.032 ± 0.014</td>
<td>0.030 ± 0.014</td>
<td>64.1 ± 47.1</td>
<td>58.6 ± 47.4</td>
</tr>
</tbody>
</table>

No significant differences were observed for each group at each time point.
Table 6.3 Mean (±SD) raw EMG values during MVIC

<table>
<thead>
<tr>
<th>Group</th>
<th>KOA EMG (mV) (Quads)</th>
<th>KOA EMG (mV) (Hams)</th>
<th>CONTRALATERAL EMG (mV) (Quads)</th>
<th>CONTRALATERAL EMG (mV) (Hams)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRE</td>
<td>POST</td>
<td>PRE</td>
<td>POST</td>
</tr>
<tr>
<td>KOA Intervention</td>
<td>1.08 ± 0.7</td>
<td>1.23 ± 0.7</td>
<td>0.53 ± 0.3</td>
<td>0.69 ± 0.3</td>
</tr>
<tr>
<td>KOA Controls</td>
<td>1.14 ± 0.66</td>
<td>1.12 ± 0.66</td>
<td>0.66 ± 0.47</td>
<td>0.78 ± 0.65</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>1.4 ± 0.82</td>
<td>1.28 ± 0.91</td>
<td>0.8 ± 0.7</td>
<td>0.8 ± 0.6</td>
</tr>
</tbody>
</table>

No significant differences were observed for each group at each time point.
6.3.2 Untrained limb motor evoked potentials

At baseline, there were no differences in MEP amplitude for the untrained limb between the KOA intervention group and the KOA control group (P > 0.999). At baseline, there was no differences in MEP amplitude between the KOA intervention group and the healthy age-matched control group (P = 0.476). Further, at baseline, there were no differences in MEP amplitude between the KOA control group and the healthy age-matched controls (P = 0.969).

Following the 4 week strength training intervention, there was no main effect for time (F_{(1, 25)} = 0.3; P = 0.094) and no group by time interaction (F_{(1, 25)} = 3; P = 0.537). No significant change in MEP amplitude was observed for the untrained limb in the KOA intervention group (P = 0.176; M= -8.1, 95% CI [-19, 2.4]). Further, the KOA intervention group was not significantly different to the KOA control group (P > 0.999). The magnitude of change in MEP amplitude between the KOA intervention group and the healthy age-matched controls was not different (P > 0.476; Figure 6.3, P. 133).
Figure 6.3 Group mean (±SD) data showing the motor evoked potentials (MEP) at 130% stimulator intensity, of the untrained OA limbs quadriceps muscle group. MEP amplitudes are displayed as a percentage of $M_{\text{MAX}}$. There was no significant differences in MEP’s from pre to post intervention for any group.
6.3.3 Untrained limb short-interval intracortical inhibition

At baseline, there were no differences in SICI MEP amplitude for the untrained limb between the KOA intervention group and the KOA control group (P > 0.999). At baseline, there was no differences in SICI MEP amplitude between the KOA intervention group and the healthy age-matched control group (P = 0.282). Further, at baseline, there were no differences in SICI MEP amplitude between the KOA control group and the healthy age-matched controls (P = 0.422).

Following the 4 week strength training intervention, there was not a main effect for time (F(1, 27) = 0.04; P = 0.843) and no group by time interaction (F(2, 27) = 2.1; P = 0.144). No significant change in SICI MEP amplitude was observed for the untrained limb in the KOA intervention group (P = 0.287; M= -8.3, 95% CI [-21, 4]). Further, the KOA intervention group was not significantly different to the KOA control group (P > 0.999). SICI MEP amplitude between the KOA intervention group and the healthy age-matched controls was not different (P > 0.7245; Figure 6.4, P. 135).
Figure 6.4 Group mean (±SD) data showing the percentage change of short-interval intracortical inhibition (SICI) of the untrained OA limbs quadriceps muscle group in the intervention group and both control groups.
6.3.4 Silent Period

At baseline, no differences in SP duration of the untrained limb between the KOA intervention and KOA control group (P > 0.999), no difference was measured between the healthy controls and both the KOA intervention and control groups (P = 0.379).

Following the intervention there was no main effect for time (F(1, 21) = 0.11; P = 0.739) and no group by time interaction (F(2, 21) = 1.4; P = 0.267). No significant change in SP was observed for the untrained limb in the KOA intervention group (P > 0.999; M= 0.0079, 95% CI [-0.025, 0.04]). Further, the KOA intervention group was not significantly different to the KOA control group (P = 0.086). SP between the KOA intervention group and the healthy age-matched controls was not different (P > 0.999; Figure 6.6, P. 137).

![Figure 6.5](image)

**Figure 6.5** 5 overlayed raw MEP sweeps of one participant at 130% of AMT, illustrating an increase in MEP amplitude and the reduction in SP duration from pre intervention (**A**) to post intervention (**B**).
Figure 6.6 Group mean (±SD) data showing the SP duration at 130% stimulator intensity, of the untrained OA limbs quadriceps muscle group. There was no significant differences in SICI from pre to post intervention for any group.
6.3.5 Trained limb hamstring co-activation

At baseline, there were no differences in hamstring co-activation for the trained limb between the KOA intervention group and the KOA control group (P > 0.999). At baseline, there was no differences in hamstring co-activation between the KOA intervention group and the healthy age-matched control group (P = 0.994). At baseline, there were no differences in hamstring co-activation between the KOA control group and the healthy age-matched controls (P = 0.994). Further, there were no differences in hamstring co-activation between the KOA and trained limb in the KOA intervention group (P = 0.627).

Following the 4-week strength training intervention, there was no main effect for time (F(1, 36) = 0.58; P = 0.451) but a group by time interaction occurred (F(2, 36) = 3.8; P = 0.032). Bonferroni post hoc analysis revealed that for the trained limb in the KOA intervention group, hamstring co-activation decreased by 12% (P = 0.655; M= 3.1, 95% CI [-0.77, 6.9]). Further, this decrease was significantly different to the KOA control group (P = 0.019). Furthermore, there was no significant difference following the intervention between the trained limb in the KOA intervention group compared to the healthy age-matched controls (P > 0.999). However, a group by time interaction occurred, with the KOA intervention group reducing hamstring co-contraction compared to the healthy age-matched controls (P = 0.032; Figure 6.7A, P. 140).
6.3.6 Untrained limb hamstring co-activation

At baseline, there were no differences in hamstring co-activation for the untrained limb between the KOA intervention group and the KOA control group (P > 0.9999). However, there was a significant difference in hamstring co-activation between the KOA intervention group and the healthy age-matched control group (P = 0.0083). Further, at baseline, there was a significant difference in hamstring co-activation between the KOA control group and the healthy age-matched controls (P > 0.0068).

Following the 4-week strength training intervention, there was no main effect for time (F(1, 32) = 0.053; P = 0.8197) but a group by time interaction occurred (F(2, 32) = 5.3; P = 0.0106). Bonferroni post hoc analysis revealed that for the untrained limb in the KOA intervention group, hamstring co-activation decreased by 17.6% (P = 0.019; M= 6, 95% CI [0.8, 11]), further, this decrease was significantly different to the KOA control group (P < 0.001). Importantly, the magnitude of change in knee extensor strength between the KOA intervention group and the healthy age-matched controls was not different (P = 0.631; Figure 6.7B, P. 140).
Figure 6.7 Group mean (±SD) data showing hamstring co-activation % of the trained limb (A) and the untrained limb (B).† denotes a significant group by time interaction of $P < 0.05$, between the KOA intervention and the heathly control (A); and a significant group by time interaction of $P < 0.05$, between the KOA intervention and the KOA control (B).
6.3 Discussion

The purpose of this study was to investigate the mechanisms underlying improvements in knee extensor strength following a 4-week unilateral strength training intervention (chapter 3, Study 1). There were several important findings in this study, which further elaborate on and also support findings from previous research into TMS and hamstring co-activation in KOA.

The main finding was that there was a significant decrease in hamstring co-activation of 17.6% in the untrained KOA limb following the 4-week intervention. Post intervention, there was a significant difference in hamstring co-activation of the untrained KOA limb compared to the KOA control group and further, no difference compared to healthy age-matched controls. No significant changes were observed in trained hamstring co-activation, MEP amplitude, SICI or SP, and no significant differences to the control group. However, the between group results for all measures were similar to results from Kittelson (2014), who also showed no differences compare to healthy controls when measuring RMT, SICI and ICF.

6.3.1 Hamstring co-activation

Hamstring co-activation has previously been identified as an underlying pathology leading to decreased knee extensor strength in KOA (Hortobágyi et al., 2005; Lewek, Scholz, Rudolph, & Snyder-Mackler, 2006; Ramsey, Snyder-Mackler, Lewek, Newcomb, & Rudolph, 2007; J. A. Zeni et al., 2010). Hamstring co-activation is thought to be a compensation mechanism in KOA to add stability to the knee joint (De Luca and Mambrito, 1987, Baratta et al., 1988). However, the trade-off for increased knee stability is knee extensor weakness. Prior to knee extension occurring, the quadriceps must over power the torque created by the hamstring muscle group, reducing absolute knee extensor strength (Tillin et al., 2011), this leads to a decrease in walking speed in KOA cohorts.

Typically, hamstring co-activation studies in KOA are measured during a walking task, in which the co-activation increases with increased gait speed, with the KOA cohort having
significantly greater co-activation at all walking speeds when compared to healthy age-matched controls (J. A. Zeni et al., 2010). However, the current study measured co-activation during a MVIC, which paradoxically resulted in similar levels of co-activation compared to previous studies, where logically higher levels of force or sheering through the knee joint were expected to be observed (Hortobágyi et al., 2005; Lewek et al., 2006; Ramsey et al., 2007; J. A. Zeni et al., 2010). Potentially an MVIC in a seated and stable position results in no greater instability of the knee over a brisk walking task, hence the similarity between results.

Previous research has investigated a 4-week cross education intervention in young healthy adults and hamstring co-activation during maximal isometric knee extension (Tillin et al., 2011). Interestingly, Tillin et al. reported a different result from the current study, with no significant change in hamstring co-activation of the trained limb or the untrained limb. Whereas, the current study demonstrated a significant change in the untrained KOA limb, but no change in the trained limb. This difference may be explained as the underlying pathology in the KOA limb, resulting in greater initial levels of co-activation, especially when the significant difference to the healthy age-matched controls prior to the 4-week intervention is taken into account. Tillin et al. postulate that the change in hamstring co-activation was not due to a decrease in hamstring activation, but an increase in knee extension force, therefore changing the percentage ratio. The current study has potentially shown the same result, with no changes pre to post intervention in hamstring EMG during knee extension MVC’s. Further, the lack of change in corticospinal measurements in this experimental chapter may implicate this response being a spinal cord mechanism.

Regardless of the mechanisms mediated the extent of hamstring co-activation during an MVIC, this is the first study to the best of the authors knowledge that has shown changes in co-activation in an untrained limb following a cross education intervention.
6.3.2 Corticospinal excitability and inhibition

Baseline data from this study mimics data from a previous study comparing corticospinal excitability in a KOA cohort, who were awaiting unilateral knee replacement (Kittelson et al., 2014). Kittelson et al. found no differences in resting motor threshold (RMT), SICI or ICF compare to healthy age-matched controls. Whereas the current study found no differences in MEP amplitude at 130%, SICI or SP at baseline compared to healthy age-matched controls.

The only previous study that has investigated corticospinal excitability with a strength training intervention in KOA, was a case report Hunt et al. (2011) who reported on a single participant with unilateral KOA. Hunt reported an increase in MEP amplitude after 8 weeks of strength training. While the current study demonstrated a 21.6% increase in MEP amplitude, this result was not significant. However, the response in MEP amplitude following the 4-week intervention may suggest that some form of plasticity is occurring. However, a recent study investigating acute joint effusion to mimic chronic joint pathology found no cortical influence in knee extensor deficits, and that knee extensor deficits where likely due to spinal mediation (Rice et al., 2014), spinal mediation of knee extensor strength loss has also been implicated in KOA (Kittelson et al., 2014). Supporting this are previous training studies in first dorsal interosseous muscle (Kidgell and Pearce, 2010, Carroll et al., 2002), and biceps brachii (Jensen et al., 2005) who have shown no changes in MEP amplitude following an intervention. However, an increase in MEP amplitude has been previously show to increase in the lower limb following a training intervention, albeit in a healthy cohort (Beck et al., 2007).

Previous investigations utilising TMS in anterior cruciate ligament injury and anterior knee pain, have shown quadriceps corticospinal excitability to be higher than in healthy controls (Heroux and Tremblay, 2006, On et al., 2004). It has been postulated that the increase in corticospinal excitability, which initially appears to be paradoxical, is a mechanism of the primary motor cortex in overcoming an inhibited α-motorneuron pool (Rice and McNair, 2010).
6.3.3 Limitations

Post hoc power analysis revealed that MEP and SP measurements had reached statistical power, whereas the SICI measurement had not reached statistical power, which along with a small sample size limits the generalisability of these findings. Further, due to practical limitations retest reliability in this cohort was not able to be complete, which also may have contributed to the null findings. TMS measures were only taken from the contralateral hemisphere to the untrained limb, no TMS measurements occurred in the trained hemisphere. Taking measurements from both hemispheres would have been beneficial as the unilateral trauma from KOA has a bilateral effect and potentially corticospinal excitability of the trained hemisphere of the KOA free limb may not resemble the healthy controls. Secondly, while the measurement of hamstring co-activation during a MVIC a valid measurement of co-activation, it would have beneficial to measure co-activation during a walking task similar to previous research, as MVIC’s don’t readily mimic normal functional tasks. BF Mmax was also not recorded due to time and technical limitations. Lastly, measurement of CAD as a direct measurement of the severity of AMI in this cohort did not occur and therefore was a final limitation of this experimental chapter.

6.3.4 Conclusions

The results from this study partially supported our hypothesis, which was a novel finding, that four weeks of strength training of the contralateral limb in unilateral KOA would result in a significant bilateral reduction in hamstring co-activation. While there was no change corticospinal excitability or inhibition of the KOA knee extensor muscle group, baseline measures where not different from healthy controls. This result concurs with previous TMS research in KOA, and potentially further highlights that supraspinal influences may have minimal influence of modulating AMI. However, future research incorporating larger sample sizes is required to confirm or deny the extent of supraspinal influences.
7.1 Introduction

The studies described in this thesis thoroughly investigated the efficacy of a 4-week unilateral knee extensor strength training program of the contralateral limb in older adults with diagnosed unilateral KOA. Specifically, the effect that the intervention had on mediating the cross education phenomenon to the untrained KOA limb, and further, the influence that the bilateral knee extensor improvements that occurred had on pain, physical function, subjective outcomes as measured by the KOOS and the potential neurological responses underlying these adaptations.

This chapter will elaborate on the overarching themes arising from each experimental chapter and the interaction between these topics. Lastly, this chapter will provide an overview of how the findings from this thesis contribute to the knowledge of exploiting the cross education phenomenon in clinical rehabilitation, specifically KOA. To conclude, the chapter will outline what key questions remain unexplored and potential future directions of research arising from this thesis to continue to advance our knowledge and therefore the efficacy of cross education as a therapy in KOA.

The experimental chapters presented in this thesis contribute novel findings to previous cross education and KOA research, as this is the first application of cross education as a therapeutic approach in unilateral KOA. The primary aim of Study 1 (chapter 3) was to quantify the extent of the transfer of strength to the untrained KOA limb, after a 4-week unilateral strength-training intervention due to the cross education phenomenon. The secondary aim was to quantify the retention of the knee extensor strength gains 3-months following the completion of the training program. It was hypothesised that the cross education phenomenon would occur in a unilateral KOA cohort to a greater extent than has previously been reported in young healthy adults, and secondly, the strength gains would be retained in the 3-months following the completion of the strength training intervention. The results from this experimental chapter support both the primary and secondary hypotheses. These novel
results provide support for the use of exploiting the cross education phenomenon as an exercise therapy in unilateral KOA cohorts.

As knee extensor strength loss correlates with increasing knee pain during the progression of KOA, the aim of Study 2 (chapter 4) was to determine the influence that the improvements in knee extensor strength of both the trained and untrained limbs (Study 1), had on acute pain, as measured by the VAS, and the KOOS sub categories of pain, symptoms, sport and QOL. It was hypothesised that following the 4-week unilateral knee extensor strength training intervention a significant improvement in pain (VAS and KOOS), symptoms, sport and QOL would occur. Secondly, these improvements in subjective symptoms would be retained in the 3-months following the completion of the strength training intervention. The results from this experimental chapter supported both the primary and secondary hypotheses. Significant within group improvements in all measurements occurred in the KOA intervention group following the intervention. Further, the KOA intervention group significantly improved in all measures when compared to the KOA control group following in the intervention, with the exception of KOOS symptoms. Retention of all improvements was retained for the 3-month period following the intervention. These novel results provide further support for the use of exploiting the cross education phenomenon as an exercise therapy in unilateral KOA cohorts.

As the two dominant factors that determine physical function are pain and knee extensor strength, the aim of Study 3 (chapter 5) was to quantify the extent of improvements to functional performance as measured by the SCT, TUG and KOOS ADL, after a 4-week unilateral strength-training intervention. The secondary aim was to quantify the retention of the improvements to functional performance in the 3-months following the completion of the training program. It was hypothesised that functional performance would significantly increase towards healthy age-matched controls and be retained for the 3-month period following completion of the intervention. Secondly, the increase in functional performance will be directly attributable to the bilateral knee extensor strength improvements (Study 1) and a
bilateral decrease in knee pain (Study 2). While the results from this experimental chapter support both the primary and secondary hypotheses, the hypothesis that improvements in functional performance was attributable to increases in knee extensor strength and a decrease in knee pain was not supported. This experimental chapter robustly supports the application of cross education in unilateral KOA for improving functional performance. Most remarkably, in this cohort, the KOA intervention group returned to normal levels of functional performance as compare to the healthy age-matched controls following the intervention.

In efforts to determine the underlying mechanisms that modulated the improvements observed in studies 1-3, the aim of Study 4 (chapter 6) was to determine the response of corticospinal excitability and inhibition to a 4-week unilateral strength training intervention. Secondly, how hamstring co-activation of the untrained KOA limb responds to the 4-week unilateral strength training intervention. Further, how these underlying mechanisms may modulate knee extensor strength loss in unilateral KOA. It was hypothesised that following the 4-week unilateral strength training intervention, an increase in corticospinal excitability will be observed, with a concurrent decrease in cortical inhibition and a decrease in hamstring co-activation. The results from this experimental chapter partially support the hypotheses, with hamstring co-activation in the untrained limb being the only significant change. This experimental chapter suggests that supraspinal mechanisms are not the dominate cause of knee extensor weakness in unilateral KOA, and further investigation is warranted particularly with a larger cohort sample and reliable assessment procedures to continue to progress knowledge in this area.

Overall, when considering the 4 experimental chapters cohesively, the outcomes from a 4-week unilateral strength training intervention in a unilateral KOA cohort, provided multifactorial benefits to the participants. In only 12 training sessions, bilateral knee extensor strength, pain, function and subjective measures all significantly improved. In the case of functional performance as measured by the SCT and TUG, the KOA intervention group returned to normal levels of functional performance as seen in the healthy age-matched
controls. These results contribute broadly to cross education research and findings, and further, they highlight the potential application of cross education in individuals suffering from unilateral KOA. A cohort that is increasing in size on a community and global level, who due to the extent that KOA affects all aspects of their lives, need evidence-based research with aims of improving the quality of their lives, and applying cross education as an exercise therapy to this cohort may compliment current rehabilitation practices.

7.2 The efficacy of the cross education in clinical populations

The cross education phenomenon was first reported more than 120 years ago (Scripture, 1894), and in that time the cross education phenomenon has been extensively investigated in young healthy populations (Manca et al., 2017); however, investigations into the potential clinical applications have only recently gained traction. The potential clinical applications were first investigated by Farthing et al. (2009), who astutely investigated a 3 week period of mock immobilisation in young healthy adults. In which unilateral strength training of the free limb attenuated strength loss in the immobilised limb. Further reinforcing the clinical potential, were investigations in mock immobilisation in young healthy adults, demonstrating maintenance of strength and muscle mass (Magnus et al., 2010), and an investigation into the underlying neurological responses during immobilisation coupled with unilateral exercise (Pearce et al., 2013). Investigations then moved beyond mock trials, with research investigating unilateral strength training during distal radius fractures (Magnus et al., 2013), unilateral strength training in bilateral KOA (Malas et al., 2013), lower limb training post stroke (Dragert and Zehr, 2013, Kim et al., 2015) and multiple sclerosis (Manca et al., 2016a). Many authors over a large period of time have also postulated on the potential clinical applications of cross education (Farthing and Zehr, 2014, Hendy et al., 2012, Zhou, 2003, Kannus et al., 1992, Devine et al., 1981, Gregg et al., 1957, Hellebrandt, 1951). The application of cross education as an exercise therapy for a variety of unilateral pathologies is not a novel idea, however the application of cross education as presented in this thesis, in a cohort with unilateral KOA is novel.
Study 1 (chapter 3) demonstrated that the cross education phenomenon occurs in unilateral KOA, and that the magnitude of strength improvement to the untrained limb is greater, when compared to lower limb studies in young healthy adults, 20% compared to 16.4% (Manca et al., 2017). However, while the meta-analysis conducted by Manca and colleagues combined data for all previous lower limb studies, regardless of whether it was a proximal or distal muscle group, it was demonstrated that there was no variance in results in the lower limb when comparing proximal to distal, making this comparison valid. Previous studies that have exploited the cross education phenomenon in clinical cohorts, have shown improvements in strength of 21 to 45.5% to the untrained limb (Magnus et al., 2013, Malas et al., 2013, Manca et al., 2016a, Dragert and Zehr, 2013, Kim et al., 2015, Onigbinde et al., 2017). The results in this thesis are the lowest at 20%, which may be explained due to the heterogeneity of the pathology and the interventions. The magnitude of strength transfer due to the cross education phenomenon in clinical cohorts appears to be superior to healthy young adults. However, currently no meta-analysis exists combining results from the various cross education studies in clinical cohorts, with the exception of a systematic review in stroke (Ehrensberger et al., 2016), making an exact figure, tenuous at best. Further, several studies (Malas et al., 2013, Dragert and Zehr, 2013, Manca et al., 2016a, Onigbinde et al., 2017) did not incorporate a control group, or have been a single participant case study (Manca et al., 2016a), making the quantification of the strength transfer due to the cross education phenomenon, as developed by Carrol at al. (2006) not possible at this point in time.

7.3 Knee extensor strength following cross education

In alignment with previous research, the unilateral KOA cohort in this thesis demonstrated a significantly weaker KOA limb compared to the contralateral limb at baseline (Petterson et al., 2008, Vahtrik et al., 2012, Stevens et al., 2003, Gapeyeva et al., 2007, Berth et al., 2002, Stevens-Lapsley et al., 2010). Further, knee extensor strength of both the KOA and contralateral limbs in the KOA intervention and control groups was significantly lower than
the healthy age-matched controls at baseline (Bade et al., 2010, Gapeyeva et al., 2007, Berth et al., 2002, Stevens-Lapsley et al., 2010, Lewek et al., 2004, Liikavainio et al., 2008).

Following the 4-week intervention, knee extensor strength of the trained contralateral limb and untrained KOA limb in the KOA intervention group improved significantly. Further, following the 4-week intervention the trained limb did not significantly differ in strength to the healthy age-matched controls. While the untrained KOA limb in the KOA intervention group, had significantly improved in knee extensor strength, it still remained significantly weaker than the healthy age-matched controls. It is likely that a return to comparable knee extensor strength of the KOA limb to the level seen in healthy age-matched controls may not be a viable possibility. However, the knee extensor strength improvement to the untrained KOA limb following the 4-week intervention was greater than reported in young healthy adults (Manca et al., 2017). The magnitude of strength transfer from the trained limb was 78.2%, which is significantly higher than previously reported. Manca et al. (2017) did not report the mean transfer of strength from the trained limb, however, an earlier meta-analysis reported that the mean transfer of strength from the trained limb in young healthy adults was 52% (Carroll et al., 2006). However, caution is needed in interpreting this comparison, as it includes both upper and lower limb, in which a significantly larger cross education effect is seen in lower limbs (Manca et al., 2017). Regardless it appears that the magnitude of the cross education phenomenon was significantly greater in this thesis than seen in young healthy adults, which would explain the untrained limb increasing in strength greater than seen in the young healthy cohorts. Supporting this, Malas et al. (2013) reported a strength transfer from the trained to untrained limb of 74% in bilateral KOA, and Onigbinde (2017) reported a strength transfer from the trained to untrained limb of 95% in unilateral KOA. However, both studies lacked control groups so determination of the magnitude of the cross education effect cannot be calculated as outlined by Carrol et al. (2006).

The following subsections will allude to the potential mechanisms that have resulted in a magnified transfer of strength due to the cross education phenomenon in the unilateral KOA
cohort presented in this thesis. As it is well established that the cross education phenomenon is a neurological adaptation (Carroll et al., 2006), muscle thickness was first assessed via sonography, to ensure changes in muscle mass did not influence knee extensor strength improvements.

7.4 Knee extensor muscle thickness following cross education

No change in knee extensor muscle thickness were hypothesised or observed following the 4-week intervention. Knee extensor muscle thickness of the KOA and contralateral limbs in the KOA intervention and KOA control groups did not differ. Further muscle thickness of either limb in the KOA intervention and control groups did not significantly differ to the healthy age-matched controls at baseline. This was not a novel finding as previous research has reported no difference in muscle mass between limbs in unilateral KOA (Petterson et al., 2008), nor significant differences in muscle mass to healthy age-matched controls (Slemenda et al., 1997, Liikavainio et al., 2008). However, conflicting with the finding in this thesis is research that shows deficits in knee extensor muscle mass in KOA cohorts (Conroy et al., 2012, Toda et al., 2000, Segal and Toda, 2005). Possible reasons for this confliction may be explained by differing cohorts, KOA severity, length of time diagnosed with KOA, diet, exercise, pain levels and BMI across multiple studies.

Lower limb muscle mass does not explain knee extensor weakness in KOA (Gur and Cakin, 2003, Slemenda et al., 1997, Muraki et al., 2015). Further, greater KOA severity, as measured via radiographic evidence, paradoxically, predicted greater lean muscle mass in both sexes suffering from KOA (Scott et al., 2012). The KOA participants in this thesis, had diagnosed unilateral stage 3 or end stage KOA, which may partially explain why no differences in muscle mass were observed to the healthy age-matched controls. Pain may also explain the variance in knee extensor muscle cross sectional area; with increasing pain severity being associated with decreasing muscle mass (Lee et al., 2016). Pain in the KOA intervention and KOA control groups was lower than reported by Lee et al. (2016) which may
also partially explain why the KOA cohort in this thesis did not significantly differ in knee extensor muscle thickness of the healthy age-matched controls.

It is well established that strength deficits in KOA are primarily neurological in nature, resulting in the inability to fully activate muscle the knee extensors (Hart et al., 2010, Pietrosimone et al., 2011, Rice and McNair, 2010). Highlighting the importance of neurological factors in knee extensor strength, a KOA cohort undergoing a dietary and exercise intervention had a significant decrease in lean muscle mass following the intervention. However, concurrently a significant increase in knee extension strength was concurrently observed (Wang et al., 2007).

The KOA intervention and control groups in this thesis had significant deficits in knee extensor force, but no differences in knee extensor muscle thickness. Further, the improvements in knee extensor strength in the KOA intervention group occurred in the absence of hypertrophy. The higher magnitude of the cross education phenomenon seen in this thesis may partially be explained due to the retention of muscle mass when compared to the healthy age-matched control. Previous research has shown the primary reasons for knee extensor deficits in KOA are caused by the inability to fully recruit the knee extensors due to AMI (Pietrosimone et al., 2011), cross education has been shown to increase voluntary muscle activation, which may oppose this mechanism (Lee et al., 2009).

Regardless of the underlying mechanisms that determine knee extensor muscle mass in KOA cohorts, the loss of lower limb lean muscle mass can only partially explain knee extensor strength loss in KOA (Petterson et al., 2008). Knee pain has been implicated as factor in mediating deficits in knee extensor strength (Ruhdorfer et al., 2014, O’Reilly et al., 1998, Steidle-Kloc et al., 2015), and deficits in functional performance (McAlindon et al., 1993, Lowry et al., 2017). Therefore pain prior to the intervention and changes in pain following the intervention were measured to determine the effect a change in pain would have on knee extensor strength and functional performance.
7.5 Cross education decreases knee pain

Knee pain is strongly correlated with deficits in knee extensor strength (Ruhdorfer et al., 2014, O'Reilly et al., 1998, Steidle-Kloc et al., 2015), and deficits in knee extensor muscle mass (Lee et al., 2016, Sattler et al., 2012, Wang et al., 2012). In unilateral KOA, it has been suggested that pain has a bilateral effect (Steidle-Kloc et al., 2015), which may partially explain why the contralateral knee extensors are weaker than healthy age-matched controls in the absence of knee extensor atrophy and radiographic evidence of KOA (Bade et al., 2010, Gapeyeva et al., 2007, Berth et al., 2002, Stevens-Lapsley et al., 2010, Lewek et al., 2004, Liikavainio et al., 2008).

Knee pain is also an important factor in mediating AMI (Palmieri-Smith et al., 2013), which is the neurological inhibition of the knee extensor muscles in KOA and other knee joint trauma (Hart et al., 2010, Pietrosimone et al., 2011, Rice and McNair, 2010). It has also been previously shown that AMI result in bilateral knee extensor strength loss (Pietrosimone et al., 2011), which correlates with unilateral knee pain resulting in bilateral knee extensor deficits (Steidle-Kloc et al., 2015). Conversely, reduced knee extensor strength has also been implicated in increasing knee pain (Muraki et al., 2015). It is possible pain and the loss in knee extensor strength are a negative feedback loop, with KOA pain resulting in decreasing knee extensor strength, which then results in greater pain. Hence, independently improving either pain severity or knee extensor strength may result in a positive improvement for the other.

The KOA intervention and control groups in this thesis had significantly more pain in the KOA limb than the healthy age-matched controls, however the contralateral limb did not differ in pain to the healthy age-matched controls. Following the 4-week intervention pain of the KOA limb significantly improved from baseline. Interestingly, while pain in the trained limb was no different to the healthy age-matched controls at baseline, it significantly improved following the intervention, and was significantly lower than the pain measured in the healthy age-matched controls. A reduction in knee pain following an exercise intervention in KOA is not a novel finding (Juhl et al., 2014). However, a return to pain levels as seen in healthy age-
matched controls does not occur, and potentially is an unachievable goal at end stage KOA. A significant bilateral decrease in pain was observed, concurrently with a bilateral increase in knee extensor strength following the 4-week intervention. However, a linear regression comparing decreased knee pain of either limb to increasing knee extensor strength was no relationship was observed in the cohort presented in this thesis.

As both knee pain severity and knee extensor strength are the dominate factors mediating functional performance, this thesis investigated the influence that the 4-week cross education intervention had on objective and subjective functional performance.

7.6 Cross education improves functional performance

The primary identified causes for functional decline in KOA are pain (Gur and Cakin, 2003, Rejeski et al., 1996, Topp et al., 2000, Marks, 1994) and reduced knee extensor strength of either the KOA limb or contralateral limb in unilateral KOA (Gur and Cakin, 2003, Topp et al., 2000, Rejeski et al., 1996, Brown et al., 2009, Maly et al., 2005, van der Esch et al., 2014). A reduction in knee pain does not automatically result in improvements to functional performance (White et al., 2011), however, increasing knee extensor strength following a training intervention can increase functional performance regardless of pain (Zhang et al., 2010, McAlindon et al., 2014). Increasing knee extensor strength of either the KOA or contralateral limb in unilateral KOA are independently associated with improvements in functional performance (Valtonen et al., 2015). If the cross education phenomenon did not occur in this cohort, it is likely that as long as a significant increase in knee extensor strength of the trained limb occurred, an improvement in functional performance would still occur. As the KOA intervention cohort in this thesis had undergone a significant increase in bilateral knee extensor strength (Study 1, chapter 3) and a significant decrease in knee pain (study 2, chapter 4) following a 4-week strength training intervention, a significant improvement in functional performance was hypothesised and found.
A significant deficit in functional performance as measured by the SCT, TUG and KOOS was observed at baseline in the KOA intervention and KOA control groups in alignment with previous findings (Liikavainio et al., 2008, Bade et al., 2010, Hurley et al., 1997). Following the intervention a significant improvement in the time to complete the SCT and TUG, and a significant improvement in the KOOS was observed. Critically, post intervention the KOA intervention group did not differ in time to complete the SCT and TUG compared to the healthy age-matched controls. However, a linear regression did not show a correlation between an increase in knee extensor strength or a decrease in knee pain to explain the improvements in SCT and TUG. It is unclear as to which factors have mediated the increase in functional improvements. Based on previous literature, it is likely a combination of both factors.

### 7.7 Improvements retained for 3-months following cross education therapy

Improvements in knee extensor strength, pain, KOOS and functional improvements were retained for a 3-month period following the intervention. Strength improvements to the untrained limb following unilateral strength training have been previously shown to be retained over 6-weeks in young healthy adults (Shima et al., 2002). However, in older adults, homologous to the cohort presented in this thesis, a significant detraining effect was observed in hip and knee OA, with a significant decrease in improvements at 12-weeks, and no difference to baseline at 24-weeks post intervention (van Baar et al., 2001). This finding was in alignment with comparable studies in apparently healthy older adults, with significant loss of improvements in strength, pain and function following a detraining period (Toraman and Ayceman, 2005, Sherk et al., 2012, Carvalho et al., 2009, Pereira et al., 2012, Harris et al., 2007). Therefore the retention of improvements and in the case of the TUG a significant improvement following the 12-week detraining period as seen in the cohort presented in this thesis is of interest. While no measurements of physical activity were recorded pre or post intervention, individuals with KOA accumulated significantly less physical activity than the
general population (Farr et al., 2008), however strength training increased daily physical activity following an intervention (Farr et al., 2010). Further, the loss of muscular strength can be attenuated in older adults, if daily physical activity is maintained post intervention (Harris et al., 2007, Henwood and Taaffe, 2008). These factors may explain the interesting and novel findings that have resulted in the retention of strength, pain and functional performance in this cohort following a 12 week detraining period.

In efforts to understand and therefore further exploit the potential mechanisms that modulated the improvements in strength, pain and functional performance that have been highlighted in the previous subsections, TMS was utilised to elucidate the potential neurological mechanisms underpinning these improvements.

### 7.8 TMS measurements in unilateral KOA

Currently there are two theories that may explain neurological adaptations underpinning the cross education effect, the ‘bilateral access model’ and the ‘cross-activation’ hypothesis, (see Ruddy and Carson (2013) for a detailed review). Regardless of the hypotheses presented, the cross education phenomenon appears to be a cortical response, however modulation of spinal mechanisms cannot be completely dispelled (Carroll et al., 2011). Previous research in young healthy subjects has shown mixed results demonstrating increases in corticospinal excitability following an intervention, with increases in corticospinal excitability being shown (Kidgell et al., 2011, Hortobagyi et al., 2003) or no change following the intervention (Carroll et al., 2002, Kidgell and Pearce, 2010, Jensen et al., 2005). Potentially differing muscle groups, upper limb compared to lower limb or training methodology may explain the disparity in the literature. Study 4 (chapter 5) reported no change in corticospinal excitability in the KOA cohort following the 4-week intervention, which is at odds to findings from a case report by Hunt et al. (2011). Further, the lack of significant differences in corticospinal measurements reported in this thesis in a KOA cohort when compared to healthy age-matched controls was not a novel finding. This thesis demonstrated no differences in corticospinal excitability as measured by MEP amplitude between the KOA
cohorts and the healthy controls, matching results reported by Kittelson et al. (2014). This was also not a novel finding when contrasted against other knee pathology studies when compared against healthy age-matched controls or the contralateral limb. Corticospinal excitability has been previously reported as the same or elevated during rest and maximal contractions in joint effusion (Rice et al., 2014), chronic anterior knee pain (On et al., 2004) and ACL injury (Heroux and Tremblay, 2006, Ward et al., 2016).

The results from this thesis and Kittelson et al. (2014), indicated that knee extensor strength loss associated with KOA was not cortically mediated. This is not a surprising result as previous research had indicated that AMI resulting in knee extensor strength loss in KOA and joint effusion trials may likely be spinally mediated (Rice et al., 2011, Rice et al., 2014). Spinal mediated strength loss may explain why normal levels of corticospinal excitability are observed in KOA when compared to healthy age-matched controls. While this result appears to be paradoxical initially, several authors have postulated that high levels of corticospinal excitability maybe an attempt of the nervous system to overcome spinal inhibition of the knee extensors due to the trauma, inflammation and pain of KOA (Kittelson et al., 2014, Rice et al., 2011). Further, in acute experimental effusion trials, an immediate increase in corticospinal excitability is observed (Rice et al., 2014), in KOA, it may be possible that corticospinal excitability increases over a large period of time and in correlation to the progression of KOA, however, this remains unexplored.

7.9 Cross education improves hamstring co-activation in the untrained limb

Hamstring co-activation has previously been identified as an underlying pathology leading to decreased knee extensor strength in KOA (Hortobágyi et al., 2005, Lewek et al., 2006, Ramsey et al., 2007, Zeni et al., 2010, Hubley-Kozey et al., 2008). Hamstring co-activation of the untrained KOA limb significant decreased in the KOA intervention group; however, it is unclear as to the mechanism modulating this response. It has been previously speculated that hamstring co-activation is reduced due to an increase in knee extensor strength, therefore changing the percentage ratio (Tillin et al., 2011). The significant increase
in strength in the untrained KOA limb may support this postulation. However, the investigation by Tillin et al (2011) was in young healthy adults, whereas the cohort in thesis has diagnosed KOA resulting in significant pain severity compared to the healthy age-matched controls. The significant reduction in knee pain severity of the KOA limb may have also been a factor in modulating the co-activation ratio. Pain and contraction has been previously investigated in KOA following exercise interventions (Al-Khlaifat et al., 2016, Preece et al., 2016). A reduction in co-activation was associated with decreased knee pain as measured by the KOOS and WOMAC pain subscales. However, it is unclear if the reduction in pain modulated the decrease in co-activation or a reduction in co-activation resulted in decreased knee pain.

7.10 Limitations and future directions

The limitations in this thesis must be acknowledged and considered when interpreting the findings that have been presented.

Isometric knee extensor strength is a safe, valid and reliable method of assessing knee extensor strength in KOA. However, no correlations between changes in knee extensor strength, pain or function were found. Knee extensor power has been identified as an independent determinate of function, pain and QOL (Reid et al., 2015, Calder et al., 2014). Not assessing changes in knee extensor power was a limitation of this thesis in further understanding the factors that may have modulated the changes in functional performance, pain and QOL. Therefore, future research that investigates a cross education in a KOA cohort should examine changes in knee extensor power as doing so may provide further insight into improvements in functional performance, pain and QOL following the intervention.

The retention of all improvements for the 3-month period following the intervention is a remarkable outcome; however, it remains unclear as to the factors that have modulated this result. It was postulated in the experimental chapters and previously in the general discussion that this outcome was likely due to an increase in daily physical activity following the intervention, which aligns with previous findings (Farr et al., 2010, Harris et al., 2007,
Henwood and Taaffe, 2008). However, as measurement of physical activity prior to and following the intervention did not occur, this postulation cannot be validated. It is also unclear as to potential retention of these gains beyond the 3-month period. Therefore, future research that investigates a cross education or a conventional intervention on a KOA cohort should examine changes in physical activity post intervention as these changes may be critical in sustaining the improvements from the intervention. Further, no KOA control group comparison occurred at 3-months following the intervention due to practical limitations. While this is a minor limitation as the KOA intervention group was still compared to the healthy age-matched controls, neither the less, data from the KOA control group at this time point would have made the findings more robust.

The application of cross education in clinical cohorts has yet to be fully explored or exploited (Magnus et al., 2013, Malas et al., 2013, Dragert and Zehr, 2013, Kim et al., 2015, Manca et al., 2016a). Findings arising from this thesis, coupled with previous cross education investigations in clinical cohorts, highlight the potential application cross education may have in improving the QOL of individuals who have a variety of pathology. There are still a large variety of application cross education has not been investigated in, such as hip OA, lower limb fractures, ACL recovery, dislocations or in an attempt to improve or maintain muscle mass and strength prior to or following any unilateral surgery. While the results arising from this thesis present promising outcomes for this KOA cohort, further research is warranted in investigating the economic viability and accessibility of an equivalent intervention at the community level, as the time, motivation and resources available in this thesis may not translate to this results in a community setting. Further, the investigation in lager cohort samples will enable further investigation and the ability to determine the mechanisms underlying the non-responders to the high responders within this cohort.
7.11 Conclusion

KOA is the fourth most prevalent cause of disability in women and the eighth in men (Murray and Lopez, 1997). More than 30% of the population over 65 years of age having diagnosed KOA with both the prevalence and severity significantly increasing in the following decades of life (Litwic et al., 2013). KOA results in significant deficits in knee extensor strength, pain, functional performance and QOL. There is a critical need for continuing investigations in improving deficits resulting from KOA and potentially reducing the progression and severity of KOA. The cross education phenomenon is a unilateral strength training stimulus that results in a strength increase in both the trained muscle group and untrained contralateral homologous muscle group. Cross education is potentially a viable therapeutic option in addressing strength, pain, functional deficits and QOL in unilateral KOA. To date cross education has shown promise in a variety of unilateral pathology; however, unilateral KOA had not been investigated. Therefore, this thesis investigated the efficacy of a 4-week long cross education intervention in an older adult cohort with diagnosed unilateral KOA. Following the intervention, a significant improvement in bilateral knee extensor strength, pain, functional performance and QOL was observed, further, knee extensor strength of the trained limb and functional performance matched the healthy age-matched controls. Remarkably, 3-months following the intervention all improvements were maintained. Collectively, the findings from this thesis provide novel insight into the application of cross education in a cohort with diagnosed unilateral KOA, in which the bilateral strength improvement resulted in significant and sustained improvements in all clinical measurements. The results present in this thesis contribute broadly to both cross education and KOA research. Further investigation is warranted in larger KOA cohorts in community and rehabilitation settings to ensure that these results translate meaningfully benefits to these populations.
REFERENCES


AMERICAN COLLEGE OF SPORTS, M., CHODZKO-ZAJKO, W. J., PROCTOR, D. N., FIATARONE SINGH, M. A., MINSON, C. T., NIGG, C. R., SALEM, G. J. & SKINNER,


BENNELL, K., DOBSON, F. & HINMAN, R. 2011. Measures of physical performance assessments: Self-Paced Walk Test (SPWT), Stair Climb Test (SCT), Six-Minute Walk Test (6MWT), Chair Stand Test (CST), Timed Up & Go (TUG), Sock Test, Lift and Carry Test (LCT), and Car Task. *Arthritis Care Res (Hoboken)*, 63 Suppl 11, S350-70.

BERENBAUM, F. 2013. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). *Osteoarthritis and Cartilage*, 21, 16-21.


BIELEMAN, H. J., VAN ITTERSUM, M. W., GROOTHOFF, J. W., OOSTVEEN, J. C.,
OOSTERVE LD, F. G., VAN DER SCHANS, C. P., SOER, R. & RENEMAN, M. F.
2010. Functional capacity of people with early osteoarthritis: a comparison between
subjects from the cohort hip and cohort knee (CHECK) and healthy ageing workers. *Int

BLAGOJEVIC, M., JINKS, C., JEFFERY, A. & JORDAN, K. P. 2010. Risk factors for onset of
osteoarthritis of the knee in older adults: a systematic review and meta-analysis.
*Osteoarthritis Cartilage*, 18, 24-33.

BRANDT, K. D., HEILMAN, D. K., SLEMENDA, C., KATZ, B. P., MAZZUCA, S. A.,
BRAUNSTEIN, E. M. & BYRD, D. 1999. Quadriceps strength in women with
radiographically progressive osteoarthritis of the knee and those with stable

BROWN, K., KACHELMAN, J., TOPP, R., QUESADA, P. M., NYLAND, J., MALKANI, A. &
SWANK, A. M. 2009. Predictors of functional task performance among patients

BROWN, T. D., JOHNSTON, R. C., SALTZMAN, C. L., MARSH, J. L. & BUCKWALTER, J. A.
2006. Posttraumatic osteoarthritis: a first estimate of incidence, prevalence, and
burden of disease. *J Orthop Trauma*, 20, 739-44.


CALDER, K. M., ACKER, S. M., ARORA, N., BEATTIE, K. A., CALLAGHAN, J. P., ADACHI,
J. D. & MAL Y, M. R. 2014. Knee power is an important parameter in understanding


CROSS, M., SMITH, E., HOY, D., NOLTE, S., ACKERMAN, I., FRANSEN, M., BRIDGETT, L., WILLIAMS, S., GUILLEMIN, F., HILL, C. L., LASLETT, L. L., JONES, G.,


ENGLUND, M., GUERMAZI, A., ROEMER, F. W., ALIABADI, P., YANG, M., LEWIS, C. E.,
without surgery and the development of radiographic osteoarthritis among middle-
aged and elderly persons: The Multicenter Osteoarthritis Study. Arthritis Rheum, 60,
831-9.

FARR, J. N., GOING, S. B., LOHMAN, T. G., RANKIN, L., KASLE, S., CORNETT, M. &

FARR, J. N., GOING, S. B., MCKNIGHT, P. E., KASLE, S., CUSSLER, E. C. & CORNETT, M.
2010. Progressive resistance training improves overall physical activity levels in
patients with early osteoarthritis of the knee: a randomized controlled trial. Phys Ther,
90, 356-66.

attenuates strength loss during unilateral immobilization. J Appl Physiol (1985), 106,
830-6.

FARTHING, J. P. & ZEHR, E. P. 2014. Restoring symmetry: clinical applications of cross-

statistical power analysis program for the social, behavioral, and biomedical sciences.
Behav Res Methods, 39, 175-91.


GOSSEC, L., HAWKER, G., DAVIS, A. M., MAILLEFERT, J. F., LOHMANDER, L. S.,
ALTMAN, R., CIBERE, J., CONAGHAN, P. G., HOCHBERG, M. C., JORDAN, J. M.,
KATZ, J. N., MARCH, L., MAHOMED, N., PAVELKA, K., ROOS, E. M., SUAREZ-
ALMAZOR, M. E., ZANOLI, G. & DOUGADOS, M. 2007. OMERACT/OARSI initiative
to define states of severity and indication for joint replacement in hip and knee

the literature and study utilizing electromyographic techniques. Am J Phys Med, 36,
269-80.

Wochenschr, 127, 967-77.

GRUBB, B. D. 2004. Activation of sensory neurons in the arthritic joint. Novartis Found Symp,
260, 28-36; discussion 36-48, 100-4, 277-9.

GUR, H. & CAKIN, N. 2003. Muscle mass, isokinetic torque, and functional capacity in women

combined concentric-eccentric isokinetic training: effects on functional capacity and
symptoms in patients with osteoarthrosis of the knee. Arch Phys Med Rehabil, 83,
308-16.

HAKKINEN, K., KALLINEN, M., IZQUIERDO, M., JOKEIAINEN, K., LASSILA, H., MALKIA,
antagonist EMG, muscle CSA, and force during strength training in middle-aged and


JONES, R. K., CHAPMAN, G. J., FINDLOW, A. H., FORSYTHE, L., PARKES, M. J.,

Knee pain and knee osteoarthritis severity in self-reported task specific disability: the

exercise type and dose on pain and disability in knee osteoarthritis: a systematic
review and meta-regression analysis of randomized controlled trials. Arthritis
Rheumatol, 66, 622-36.

KANNUS, P., ALOSA, D., COOK, L., JOHNSON, R. J., RENSTROM, P., POPE, M.,
exercise on the strength, power and endurance of the contralateral leg. A randomized,
controlled study using isometric and concentric isokinetic training. Eur J Appl Physiol
Occup Physiol, 64, 117-26.


KEMPEN, G. I., VAN HEUVELEN, M. J., VAN DEN BRINK, R. H., KOOIJMAN, A. C., KLEIN,
M., HOUX, P. J. & ORMEL, J. 1996. Factors affecting contrasting results between self-
reported and performance-based levels of physical limitation. Age Ageing, 25, 458-64.

Corticospinal responses following strength training: a systematic review and meta-


2012. Is knee osteoarthritis a symmetrical disease? Analysis of a 12 year prospective

MICHAEL, J. W., SCHLUTER-BRUST, K. U. & EYSEL, P. 2010. The epidemiology, etiology,


arthroplasty requires both performance-based and patient-report assessments: a

MIZNER, R. L., PETTERSON, S. C., STEVENS, J. E., VANDENBORNE, K. & SNYDER-
MACKLER, L. 2005. Early quadriceps strength loss after total knee arthroplasty. The
contributions of muscle atrophy and failure of voluntary muscle activation. *The Journal

MOR, V., MURPHY, J., MASTERS-ALLEN, S., WILLEY, C., RAZMPOUR, A., JACKSON,
Clin Epidemiol*, 42, 895-904.


MURAKI, S., AKUNE, T., TERAGUCHI, M., KAGOTANI, R., ASAI, Y., YOSHIDA, M.,
TOKIMURA, F., TANAKA, S., OKA, H., KAWAGUCHI, H., NAKAMURA, K. &


APPENDICES

Appendix A Deakin University Medical Questionnaire page 204
Appendix B TMS adult safety screening questionnaire page 206
Appendix C Knee injury and Osteoarthritis Outcome Score (KOOS) page 208
Appendix D Visual Analogue Scale (VAS) page 214
MEDICAL QUESTIONNAIRE

Responses to this questionnaire will be kept strictly confidential. The responses from this questionnaire will provide the investigators with appropriate information to establish suitability of your participation in this study. Anyone who currently has, or has had in the past, a serious musculoskeletal injury, epilepsy, are pregnant or have a cardiac pacemaker may be excluded from the study for health and safety reasons.

NAME: .................................................. AGE: ...... (yrs) GENDER: .......

BODY MASS: .......... (kg) HEIGHT: ........... (cm)

Are you currently undertaking any form of regular exercise? YES NO
If yes, briefly describe the type and amount (i.e frequency, duration) of exercise you perform.

1. Are you a smoker? YES NO (Please circle)

Has anyone ever told you that you:
2.1 Are overweight? YES NO UNKNOWN
2.2 Have high blood pressure? YES NO UNKNOWN
2.3 Have a heart condition or heart murmur? YES NO UNKNOWN
2.4 Have asthma or a respiratory condition? YES NO UNKNOWN
2.5 Have diabetes? YES NO UNKNOWN
2.6 Have a bleeding disorder (e.g. haemophilia)? YES NO UNKNOWN

Have you ever experienced:
3.1 Chest pain, chest discomfort, chest tightness or chest heaviness? YES NO UNKNOWN
3.2 Shortness of breath out of proportion to exercise undertaken? YES NO UNKNOWN
3.3 Heart palpitations (sensation of abnormally fast and/or irregular heart beat)? YES NO UNKNOWN
3.4 Episodes of fainting, collapse or loss of consciousness? YES NO UNKNOWN
3.5 Abnormal bleeding or bruising? YES NO UNKNOWN
3.6 Gastrointestinal problems? YES NO UNKNOWN
If you answer YES to any of the following, please elaborate in the space provided:

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
<th>UNKNOWN</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Do you have a family history of cardiovascular disease? (eg. heart attack, chest pain/angina, stroke)</td>
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<td>5. Do you have a family history of diabetes?</td>
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<td>6. Have you ever suffered any musculoskeletal injury?</td>
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<td>7. Have you ever experienced difficulty swallowing or any other gastrointestinal problem?</td>
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<td>8. Do you have any allergies? (including to medications)</td>
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<td>9. Are you currently on any medication?</td>
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<td>10. Are you currently taking anabolic steroids or any other performance-enhancing agents?</td>
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<td>11. Is there any other reason which you know of that would prevent you from undertaking the proposed exercise and other tests?</td>
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I believe the information I have provided to be true and correct.

SIGNED: ………………………………………………………………DATE: …………………..
### Transcranial Magnetic Stimulation (TMS) Adult Safety Screen

<table>
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<th>Name:</th>
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<tr>
<td>Date:</td>
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<tr>
<td>Age:</td>
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</table>

**Please answer the following:**

**Have you ever:**

- Had an adverse reaction to TMS? [ ] Yes [ ] No
- Had a seizure? [ ] Yes [ ] No
- Had an electroencephalogram (EEG)? [ ] Yes [ ] No
- Had a stroke? [ ] Yes [ ] No
- Had a serious head injury (include neurosurgery)? [ ] Yes [ ] No
- Had any other brain-related condition? [ ] Yes [ ] No
- Had any illness that caused brain injury? [ ] Yes [ ] No
- Do you have any metal in your head (outside the mouth) such as shrapnel, surgical clips, or fragments from welding or metalwork? [ ] Yes [ ] No
- Do you have any implanted devices such as cardiac pacemakers, medical pumps, or intracardiac lines? [ ] Yes [ ] No
- Do you suffer from frequent or severe headaches? [ ] Yes [ ] No
- Are you taking any medications? [ ] Yes [ ] No
- Are you pregnant, or is it possible that you may be pregnant? [ ] Yes [ ] No
- Does anyone in your family have epilepsy? [ ] Yes [ ] No
- Do you need further explanation of TMS and its associated risks? [ ] Yes [ ] No

*If you answered yes to any of the above, please provide details:*

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

*† For use with single-pulse TMS, paired-pulse TMS, or repetitive TM*
SUBJECT INFORMATION

Subject Details

Subject Name: ______________________________

Address: ______________________________

Phone Number: __________ Email Address: ______________________________

Sex: __________ DOB: ______________________________

Occupation: __________ Ethnic Background: ______________________________

Background information

If post-menopausal, are you receiving hormone replacement therapy?

______________________________________________________________

Do you suffer from any known neurological disorders?

______________________________________________________________

Are you currently taking any medication which influences nerve conduction or blood clotting? If so, what?

______________________________________________________________

Do you regularly drink beverages containing caffeine? If so, how many cups per day?

______________________________________________________________

Which hand do you use for most daily activities when using only one?

______________________________________________________________

Are you involved in regular physical activity? If so, what are the activity/activities, the intensity and time commitment?

Activity: ______________________________

Intensity: ______________________________

Hours per week: ______________________________

Months per year: ______________________________
KOOS KNEE SURVEY

Today's date: _____/_____/______ Date of birth: _____/_____/______
Name: ____________________________________________________

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities.

Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms

These questions should be answered thinking of your knee symptoms during the last week.

S1. Do you have swelling in your knee?
   Never    Rarely    Sometimes    Often    Always

S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?
   Never    Rarely    Sometimes    Often    Always

S3. Does your knee catch or hang up when moving?
   Never    Rarely    Sometimes    Often    Always

S4. Can you straighten your knee fully?
   Always    Often    Sometimes    Rarely    Never

S5. Can you bend your knee fully?
   Always    Often    Sometimes    Rarely    Never
Stiffness

The following questions concern the amount of joint stiffness you have experienced during the last week in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?

- None
- Mild
- Moderate
- Severe
- Extreme

S7. How severe is your knee stiffness after sitting, lying or resting later in the day?

- None
- Mild
- Moderate
- Severe
- Extreme

Pain

P1. How often do you experience knee pain?

- Never
- Monthly
- Weekly
- Daily
- Always

What amount of knee pain have you experienced the last week during the following activities?

P2. Twisting/pivoting on your knee

- None
- Mild
- Moderate
- Severe
- Extreme

P3. Straightening knee fully

- None
- Mild
- Moderate
- Severe
- Extreme

P4. Bending knee fully

- None
- Mild
- Moderate
- Severe
- Extreme

P5. Walking on flat surface

- None
- Mild
- Moderate
- Severe
- Extreme
### Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

**A1. Descending stairs**

<table>
<thead>
<tr>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
</table>

**A2. Ascending stairs**

<table>
<thead>
<tr>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
</tr>
</thead>
</table>
For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

<table>
<thead>
<tr>
<th>Activity</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Extreme</th>
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<tbody>
<tr>
<td>A3. Rising from sitting</td>
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<td>A4. Standing</td>
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<td>A5. Bending to floor/pick up an object</td>
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<tr>
<td>A6. Walking on flat surface</td>
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<td>A7. Getting in/out of car</td>
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<td>A8. Going shopping</td>
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<tr>
<td>A9. Putting on socks/stockings</td>
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<tr>
<td>A10. Rising from bed</td>
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</tbody>
</table>
A11. Taking off socks/stockings

| None | Mild | Moderate | Severe | Extreme |

A12. Lying in bed (turning over, maintaining knee position)

| None | Mild | Moderate | Severe | Extreme |

A13. Getting in/out of bath

| None | Mild | Moderate | Severe | Extreme |

A14. Sitting

| None | Mild | Moderate | Severe | Extreme |

A15. Getting on/off toilet

| None | Mild | Moderate | Severe | Extreme |

For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

| None | Mild | Moderate | Severe | Extreme |

A17. Light domestic duties (cooking, dusting, etc)

| None | Mild | Moderate | Severe | Extreme |

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the last week due to your knee.
SP1. Squatting
   None   Mild   Moderate   Severe   Extreme
   ʃ       ʃ       ʃ       ʃ       ʃ

SP2. Running
   None   Mild   Moderate   Severe   Extreme
   ʃ       ʃ       ʃ       ʃ       ʃ

SP3. Jumping
   None   Mild   Moderate   Severe   Extreme
   ʃ       ʃ       ʃ       ʃ       ʃ

SP4. Twisting/pivoting on your injured knee
   None   Mild   Moderate   Severe   Extreme
   ʃ       ʃ       ʃ       ʃ       ʃ

SP5. Kneeling
   None   Mild   Moderate   Severe   Extreme

Quality of Life

Q1. How often are you aware of your knee problem?
   Never   Monthly   Weekly   Daily   Constantly

Q2. Have you modified your life style to avoid potentially damaging activities to your knee?
   Not at all   Mildly   Moderately   Severely   Totally

Q3. How much are you troubled with lack of confidence in your knee?
   Not at all   Mildly   Moderately   Severely   Extremely

Q4. In general, how much difficulty do you have with your knee?
   None   Mild   Moderate   Severe   Extreme

Thank you very much for completing all the questions in this questionnaire
### Appendix D Visual Analogue Scale (VAS)

<table>
<thead>
<tr>
<th>Name:</th>
<th>Date:</th>
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**Limb:** RIGHT LEFT KOA Contralateral

**Instructions:** on the 100mm line below, mark or cross the line that corresponds to the pain you feel in your knee from ‘no pain at all’ to ‘unbearable pain’.

**VAS 1**

‘no pain at all’  ___________________________________________ ‘unbearable pain’

**VAS 2**

‘no pain at all’  ___________________________________________ ‘unbearable pain’

**VAS 3**

‘no pain at all’  ___________________________________________ ‘unbearable pain’

**VAS 4**

‘no pain at all’  ___________________________________________ ‘unbearable pain’

**VAS 5**

‘no pain at all’  ___________________________________________ ‘unbearable pain’