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RESEARCH ARTICLE

Is muscle strength in a painful limb affected by knee pain status of the contralateral limb? — Data from the Osteoarthritis Initiative

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ABSTRACT

Contralateral knee pain has been suggested to be associated with muscle weakness in a pain-free knee, potentially through a mechanism of central nervous inhibition. Whether contralateral knee pain also affects muscle strength in a painful knee, however, is unknown. Here we study the extent to which isometric muscle strength differs between matched painful limbs of people with unilateral knee pain vs. matched painful limbs people with bilateral knee pain. To that end, 163 participants with unilateral knee pain were identified from the Osteoarthritis Initiative. Unilaterally painful (UP) limbs were defined as having numerical rating scale (NRS) ≥4/10, infrequent/frequent pain in the painful limb, while contralateral pain-free limbs were defined by NRS = 0-1, no/infrequent pain and Western Ontario and McMaster Universities Arthritis Index (WOMAC) ≤1. The comparator group were matched bilaterally painful (BP) limbs. Maximum isometric muscle strength (N) was compared between 1:1 matched BP and UP limbs. Extensor strength was found to be lower in BP limbs than in UP limbs, (−2.9%; p = 0.39) but this difference was not statistically significant. Extensor strength was significantly lower in the UP vs. contralateral pain-free limbs (−6.2%; p < 0.001). No differences were observed between BP and contralateral painful limbs (0.6%; p = 0.87). In conclusion, the current results identify a slight reduction of maximum knee extensor strength in a painful limb, when the contralateral knee is also painful. In contrast to pain-free limbs, this effect did not reach statistical significance, but the overall findings support the concept of central nervous inhibition of muscle strength by contralateral knee pain.

1. Introduction

Findings in people with unilateral knee pain have provided evidence that central nervous inhibition may play a role in the reduction of muscle strength in a pain-free limb, when the contralateral knee is painful (Hurley and Newham, 1993; Steidle-Kloc et al., 2015). This can be potentially explained by voluntary activation deficits via central nervous system inhibition (Metcalfe et al., 2012; Pietrosimone et al., 2011), a mechanism by which "the brain" is thought to balance muscle activation level between limbs. Specifically, we previously reported significantly lower knee extensor (-5.5%; p = 0.04) and flexor strength (−8.4%; p = 0.02) in pain-free limbs of people with unilateral knee pain compared with matched limbs of people without any knee pain on either side (Steidle-Kloc et al., 2015). The magnitude of this difference was substantial and was similar to the difference in isometric strength between painful and pain-free limbs in participants with unilateral knee pain. While thigh muscle strength in pain-free limbs appears to depend on the pain status of the contralateral knee (Steidle-Kloc et al., 2015), it is currently unknown whether thigh muscle strength in a painful limb is also affected by contralateral knee pain. In the current paper, we extend on the previous work (Steidle-Kloc et al., 2015) and specifically investigate how muscle strength in a painful limb of

Abbreviations: BMI, Body mass index; BP, Limb matched painful limb in a participant with bilateral knee pain; CI, Confidence interval; EMF, Extension maximum force (N); FMF, Flexion maximum force (N); KLG, Kellgren-Lawrence grade; NRS, Numerating rating scale; OA, Osteoarthritis; OAI, Osteoarthritis Initiative; SD, Standard deviation; SFPE, Speed of force production during extension (N/s); SFPFS, peed of force production during flexion (N/s); TPEF, Time to produce 90% of max extension force (s); TPFF, Time to produce 90% of max flexion force (s); UP, Limb painful limb in a participant with unilateral knee pain; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

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participants with unilateral knee pain compares to that of a painful limb in people with bilaterally painful osteoarthritic knees.

Impairments in muscle strength have been associated with functional limitations and disability (Segal and Glass, 2011). Osteoarthritis (OA) is known to be a major cause of knee pain (Peat et al., 2001; Segal et al., 2009a), as well as a reduction in the quality of life (Bennell and Hinman, 2011). Loss of muscle strength, or muscle weakness, is considered a potentially modifiable risk factor of knee OA (Roos et al., 2011; Segal et al., 2009a) and previous studies have reported a reduction in knee pain following an increase in muscle strength with exercise training in people with symptomatic knee OA (Bennell et al., 2013; Roos et al., 2011; Ruhdorfer et al., 2013). Consequently, quadriceps muscle strengthening is recommended by current Osteoarthritis Research Society International (OARSI) treatment guidelines for knee OA (McAlindon et al., 2014). On a mechanistic level, the reduction in muscle strength with knee OA is thought to be a result of avoidance of painful movements during daily activities (Dekker et al., 1992), but as suggested above, may also be affected by inhibitory signals from the central nervous system (Hurley and Newham, 1993; Steidle-Kloc et al., 2015).

The objective of this study was to test the hypothesis that muscle strength in a limb with a painful knee is dependent on the knee pain status of the contralateral limb. Specifically, we used a cross-sectional, matched case-control design to study to what extent isometric muscle strength differs between matched painful limbs of people with unilateral knee pain and matched painful limbs of people with bilateral knee pain.

2. Methods

2.1. The Osteoarthritis Initiative

Data used in this study were obtained from the publicly available Osteoarthritis Initiative (OAI) database on May 25th, 2014 (http://www.oai.ucsf.edu/)(Eckstein et al., 2012). The OAI study rationale and general inclusion criteria (e.g. 45–79 years of age, presence of symptoms and/or knee radiographic OA, or risk factors for developing knee OA) have been previously published (Eckstein et al., 2012). 4796 men and women were recruited at the University of Maryland, Johns Hopkins University, the Ohio State University, the University of Pittsburgh, and the Memorial Hospital of Rhode Island to participate in OAI. The study is registered at clinicaltrials.gov (ID NCT00080171) and was carried out in accordance with the IRB-approved OAI data user agreement (approval number: 10-00532).

2.2. Participant selection

4796 OAI participants completed the 2-year follow-up visit, 3386 of whom had bilateral measurement of isometric muscle strength and full demographic information available at 2-year follow-up. Participants with end-stage radiographic knee OA (Kellgren-Lawrence grade [KLG] = 4) in at least one knee were excluded from the current study. Of the remaining 3078 participants, 312 met the strict criteria for unilateral knee pain, while 433 participants met the criteria for bilateral knee pain as defined below. Pain status was assessed by rating the frequency of patients self-reported knee pain in the past 12 months in three categories: “no pain”, “infrequent pain” (pain, aching or stiffness in the past 12 months, but not on most days of a month), and “frequent pain” (pain, aching or stiffness on most days of at least one month in the past 12 months) (Eckstein et al., 2011). The participants also rated the average pain of each knee during the seven days preceding the OAI appointment, using an 11-point numerical rating scale (NRS) from 0 to 10, with values ≥4 representing a non-acceptable symptoms state (Pham and Tubach, 2009; Steidle-Kloc et al., 2015). Additionally, pain during five activities: (1) walking, (2) using stairs, (3) while in bed, (4) sitting or lying down, and (5) standing, over the seven days preceding the OAI visit was assessed for each knee using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscale (Gandek, 2015).

Participants were defined as having unilateral knee pain if they had one unilaterally painful limb with an NRS pain intensity value ≥4 (i.e. greater than the patient acceptable symptom state [PASS]) (Pham and Tubach, 2009; Steidle-Kloc et al., 2015) and either frequent pain or infrequent pain during the preceding 12 months. The contralateral pain-free limb had to meet the following criteria: an NRS pain intensity value of 0-1, either no pain or infrequent pain during the past 12 months, and a WOMAC score of 0-1. Participants were classified as having bilaterally painful limbs if they had two knees with an NRS pain intensity value ≥4, and either infrequent or frequent pain during the past 12 months in both knees (Steidle-Kloc et al., 2015).

Of the 433 participants with bilateral knee pain, 163 painful limbs could be successfully matched to painful limbs of the 312 participants with unilateral pain based on the following matching criteria: same sex, same race (White/African American), same radiographic knee OA status (KLG 0/1 [no definite radiographic OA] or KLG 2/3 [definite radiographic OA]), and comparable age (±5 years), height (±5 cm), and body mass index (BMI: ±3 kg/m^2). To ensure comparable weights for the threshold-based matching criteria age, height, and BMI, the differences between participants were normalized to a range of 0 to 1 for each of these variables. A summary of the selection process is shown in Fig. 1. Semi-quantitative readings of the radiographic disease stage of all OAI knees were performed centrally by readers from Boston University. For each knee, the KLG was determined from fixed-flexion radiographs obtained at 2-year follow up (Eckstein et al., 2012; Felson et al., 2011; Kellgren and Lawrence, 1957).

2.3. Isometric strength measurement

The quadriceps and hamstrings maximum isometric strength were assessed by the OAI using the Good Strength Chair (Metitur Oy Jyvaskyla, Finland), as described previously (Steidle-Kloc et al., 2015). The maximum force (N) was measured at 60° knee flexion, and participants were instructed to push the leg forward against the pad during extension and to pull back against the pad during flexion. Certified research technicians trained in the standardized measurement protocol recorded the greatest of three maximal efforts, as this was considered to represent each participant's maximal strength. Additional parameters of force measurements (electronically recorded variables from the same trial) were time to produce 90% of maximal force (s) and the speed of force production (N/s). After two warm-up repetitions at 50% effort, data were collected for three measurement trials for each muscle group (extensor and flexor). The coefficient of variation between two consecutive isometric strength measurements performed two weeks apart was 6.3% (SD 5.7) for knee extension strength (https://oai.epi-csf.org/datarelease/docs/StudyDesignProtocol.pdf).

2.4. Measurement of physical activity

The physical activity level of the participants was determined using the validated Physical Activity Scale for the Elderly (PASE) questionnaire (Washburn et al., 1999). The PASE is a 12-item scale that measures average daily time spent participating in three domains of activity within the past seven days: leisure activities, household activities and occupational activities (Washburn et al., 1999). Each activity was scored for frequency and hours per day

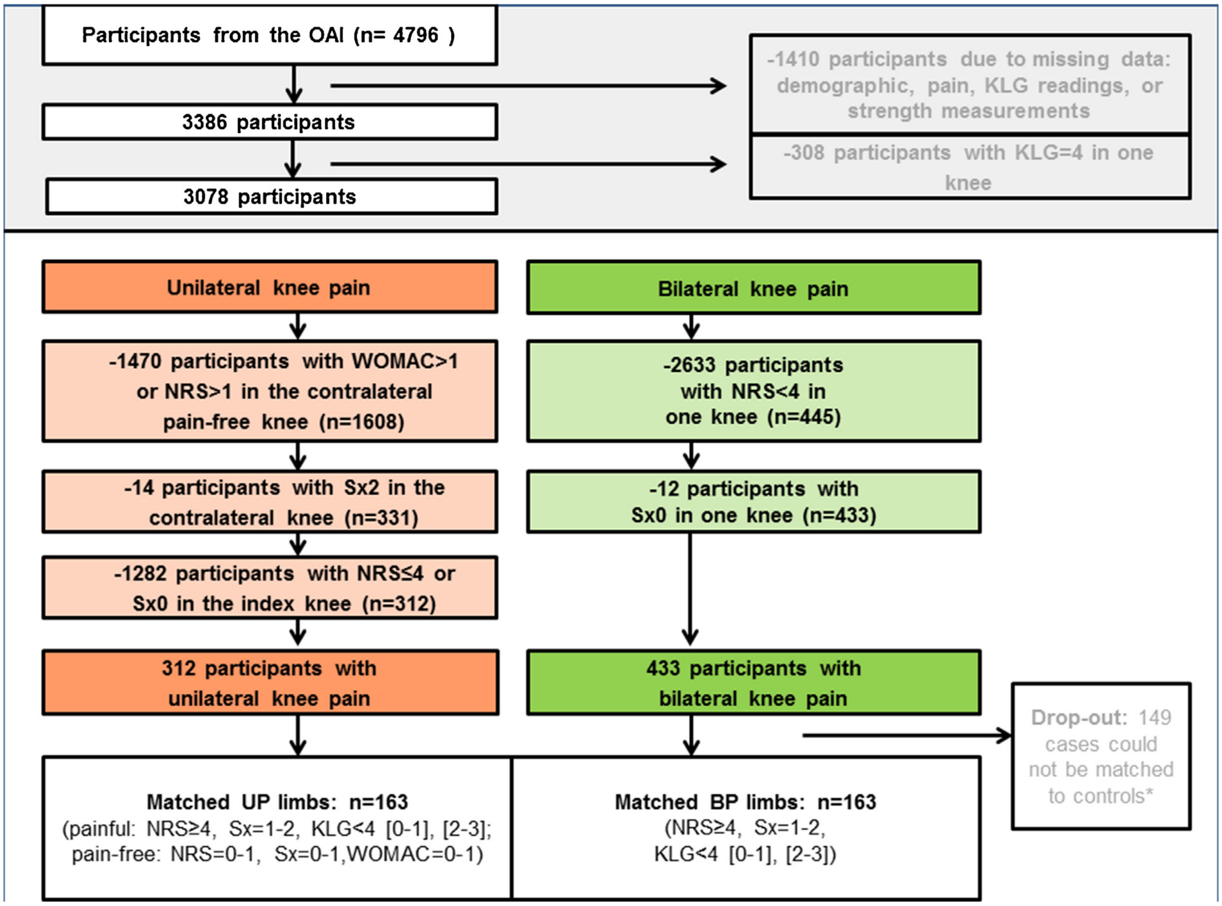

Fig. 1. Selection process of participants with unilateral and bilateral knee pain.
Abbreviations: OAI, Osteoarthritis Initiative; KLG, Kellgren-Lawrence grade; WOMAC, Western Ontario and McMaster Universities Arthritis Index; NRS, numerical rating scale: Sx = symptom status defined as pain frequency: Sx0 = no pain; Sx2 = frequent pain; [SX1 = infrequent pain as defined in the method section]; UP limb = painful limb in a participant with unilateral knee pain; BP limb = matched painful limb in a participant with bilateral knee pain.
*149 drop outs due to inability to match participants with unilateral knee pain to those with bilateral knee pain without differences in sex, race (White/African American), age (>5 years), height (>5 cm), body mass index (BMI:>3 kg/m^2) and radiographic knee OA status (Kellgren Lawrence grade [KLG] 0/1 [no definite radiographic OA] or 2/3 [definite radiographic OA]).

using a 4-point scale and a total PASE score range from 0 to >400, with a higher score indicating more frequent or intense activity.

2.5. Statistical analyses

The matching algorithm used to optimize the matching of painful limbs of participants with unilateral knee pain versus those of participants with bilateral knee pain has been described previously (Dannhauer et al., 2013; Steidle-Kloc et al., 2015). In brief, for each participant with unilateral knee pain, we identified one participant with bilateral pain and the same (or similar) demographics in the OAI database.

The primary focus of the analysis was the comparison of differences in the maximal isometric knee extension/flexion force between matched BP limbs vs. UP limbs, while differences in time to 90% strength production (s) and speed of force production (N/s) were considered exploratory outcomes.

Because the matching process was controlled for demographic factors and radiographic OA status, paired t-tests could be used, without further adjustment for demographic parameters. The absolute differences were computed by using simple subtraction (value for the UP limb of each participant subtracted from that of the matched BP limb of each participant) and the percent differences were computed by relating the above difference to the value in the UP limb. The level of significance was set at p-value < 0.05 and 95% confidence intervals (CIs) were computed for between-group differences. All statistical tests were performed using IBM SPSS (IBM Corp. Armonk, NY; USA) and Microsoft Office Excel 2010 (Microsoft Inc. Redmond, WA, USA).

3. Results

3.1. Demographics

Demographic and clinical data are presented in Table 1. Age and BMI did not differ significantly between matched pairs, as was intended per matching criteria. Participants with bilateral knee pain were slightly taller (1.8 cm; 95% CI (0.6 cm, 3.1 cm); p = 0.004) and had a slightly greater body mass (1.9 kg; (0.6 kg, 3.2 kg); p = 0.004), despite matching. Both groups included 100 women and 63 men, who were white (135) or African–American (28). Interestingly, the PASE score tended to reflect a minimally greater physical activity in participants with bilateral knee pain than in those with unilateral knee pain, but the difference (13.8) was not statistically significant (8.5%; p = 0.11). 44% of the matched knees had no definite radiographic knee OA (KLG 0/1), whereas 56% had (KLG 2/3).

Table 1
Characteristics of participants and differences between groups.

	Participants with bilateral knee pain (mean ± SD)	Participants with unilateral knee pain (mean ± SD)	Absolute Difference[a]	95% Confidence Interval[a]	Difference[a] (%)	p-value[b]
Age (years)	63.3 ± 8.7	63.4 ± 8.6	−0.1	(-0.3, 0.2)	−0.1	.58
Height (cm)	169 ± 9.2	167 ± 9.3	−1.8	(0.6, 3.1)	1.1	.004[c]
Mass (kg)	83.3 ± 15.5	81.4 ± 15.4	1.9	(0.6, 3.2)	2.3	.004[c]
BMI (kg/m^2)	29.1 ± 4.4	29.1 ± 4.5	±0.0	(0.0, 0.1)	0.1	.34
PASE score	162 ± 84.9	149 ± 69.3	13.8	(-2.3, 29.9)	8.5	.11
KLG 0/1	72	72	–	–	–	–
KLG 2/3	91	91	–	–	–	–

BMI, body mass index; PASE, physical activity scale for the elderly; KLG, Kellgren-Lawrence Grade.
[a] The absolute differences, 95% confidence intervals, and percent differences (%) were calculated using the difference for each matched pair and the average percent difference among matched pairs.
[b] p-values for paired t-tests of absolute differences.
[c] Statistically significant difference.

Table 2
Comparison of muscle strength in matched limbs of participants with bilateral and unilateral pain.

	Matched BP limb (mean ± SD)	Matched UP limb (mean ± SD)	Absolute Difference[a]	95% Confidence Interval[a]	Difference[a] (%)	p-values[b]
EMF (N)	298 ± 133	307 ± 115	−8.8	(−28.7, 11.2)	−2.9	.39
FMF (N)	121 ± 60.2	122 ± 61.4	−0.9	(−11.6, 9.7)	−0.8	.87
TFPE (s)	1.6 ± 0.7	1.6 ± 0.6	±0.0	(−0.1, 0.2)	2.5	.89
TFPF (s)	1.7 ± 0.8	1.6 ± 0.7	0.2	(0.0, 0.3)	10.3	.19
SFPE (N/s)	419 ± 341	421 ± 321	6.0	(−65.2, 77.2)	1.4	.88
SFPF (N/s)	158 ± 163	150 ± 130	11.1	(−18.3, 40.5)	7.4	.67

BP limb = painful limb in a participant with bilateral knee pain; UP limb = painful limb in a participant with unilateral knee pain; EMF, extension maximum force (N); FMF, flexion maximum force (N); TPEF, time to produce 90% of max extension force (s), TPFF, time to produce 90% of max flexion force (s); SFPE, speed of force production during extension (N/s); SFPF, speed of force production during flexion (N/s).
[a] The absolute differences, 95% confidence intervals, and percent differences (%) were calculated using the difference for each matched pair and the average percent difference among matched pairs.
[b] p-values for paired t-tests of absolute differences.

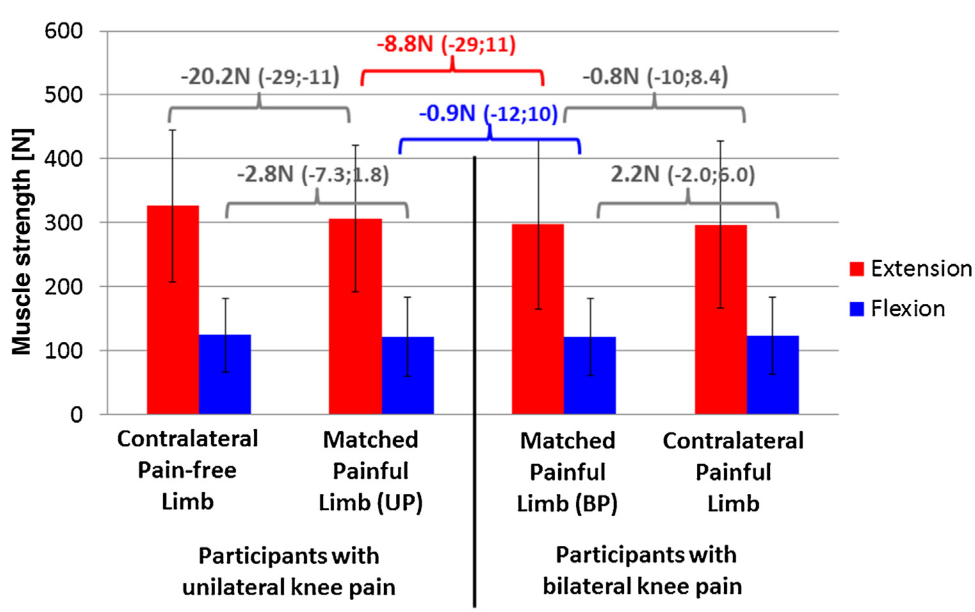

Fig. 2. Thigh muscle strength (extension and flexion) of participants with unilateral and bilateral knee pain. The brackets display the differences in Newtons (N) along with the 95% confidence interval of the difference (right vs. left column, respectively).
UP = painful limb in a participant with unilateral knee pain; BP = matched painful limb in a participant with bilateral knee pain.
Please note that for each participant with unilateral knee pain, one participant was identified with bilateral knee pain to display the same (or similar) demographics in the OAI data base (matched 1:1) for a paired comparison.

3.2. Muscle strength

The maximum extensor strength of BP limbs from participants with bilateral knee pain was 2.9% lower (-8.8N; CI (−28.7N, 11.2N)) than that in the matched UP limb from participants with unilateral knee pain; however, the difference did not reach statistical significance (p = 0.39; Table 2, Fig. 2). The maximum flexor strength in BP limbs was 0.8% lower (−0.9N; (−11.6N, 9.7N); p = 0.87) than in matched UP limbs (Table 2, Fig. 2). For comparison (within person analysis), extensor strength was 6.2% lower

Table 3
Comparison of muscle strength between painful and pain-free limbs of participants with unilateral knee pain.

	Matched UP Limb (mean ± SD)	CL pain-free limb (mean ± SD)	Absolute Difference[a]	ConfidenceInterval[a]	Difference[a] (%)	p-value[b]
EMF (N)	307 ± 115	327 ± 119	−20.2	(-29.3, 11.0)	−6.2	<.0001[c]
FMF (N)	122 ± 61.4	124 ± 57.5	−2.8	(−7.3, 1.8)	−2.2	.24
TFPE (s)	1.6 ± 0.6	1.6 ± 0.6	±0.0	(−0.1, 0.1)	2.3	.59
TFPF (s)	1.6 ± 0.7	1.5 ± 0.6	±0.0	(−0.1, 0.1)	1.7	.75
SFPE (N/s)	421 ± 321	429 ± 310	−4.4	(−40.2, 48.9)	−1.0	.80
SFPF (N/s)	150 ± 130	160 ± 126	−7.7	(−10.9, 26.4)	−5.2	.37

UP limb = painful limb in a participant with unilateral knee pain; CL = contralateral (pain free) limb to the UP limb; EMF, extension maximum force (N); FMF, flexion maximum force (N); TPEF, time to produce 90% of max extension force (s), TPFF, time to produce 90% of max flexion force (s); SFPE, speed of force production during extension (N/s); SFPF, speed of force production during flexion (N/s).
[a]The absolute differences, 95% confidence intervals, and percent differences (%) were calculated using the difference for each matched pair and the average percent difference among matched pairs.
[b]p-values for paired t-tests of absolute differences.
[c]Statistically significant difference.

Table 4
Comparison of muscle strength between limbs of participants with bilateral knee pain.

	Matched BP limb (mean ± SD)	Non-matched BP limb (mean ± SD)	Absolute Difference[a]	Confidence Interval[a]	Difference[a] (%)	p-value[b]
EMF (N)	298 ± 133	297 ± 130	0.8	(-8.4, 10.0)	0.6	.87
FMF (N)	121 ± 60.2	123 ± 59.9	−2.0	(−6.0, 2.0)	-3.2	.34
TFPE (s)	1.6 ± 0.7	1.6 ± 0.6	±0.0	(−0.1, 0.1)	0.0	.81
TFPF (s)	1.7 ± 0.8	1.6 ± 0.7	±0.0	(−0.1, 0.2)	5.1	.39
SFPE (N/s)	419 ± 341	397 ± 349	16.7	(−29.8, 63.1)	4.9	.40
SFPE (N/s)	158 ± 163	165 ± 156	−7.4	(−27.5, 12.8)	−4.5	.48

BP limb = painful limb in a participant with bilateral knee pain; FMF, flexion maximum force (N); TPEF, time to produce 90% of max extension force (s), TPFF, time to produce 90% of max flexion force (s); SFPE, speed of force production during extension (N/s); SFPF, speed of force production during flexion (N/s).
[a] The absolute differences, 95% confidence intervals, and percent differences (%) were calculated using the difference for each matched pair and the average percent difference among matched pairs.
[b] p-values for paired t-tests of absolute differences.

(−20.2N; (−29.3N, −11.0N); $p < 0.0001$) in UP limbs than in contralateral pain-free limbs, whereas flexor strength was 2.3% lower (−2.8N; (−7.3N, 1.8N); $p = 0.24$) in UP limbs than in contralateral pain-free limbs (Table 3, Fig.2). The magnitude of the difference in extensor strength between the matched BP and UP limbs was almost half of that between the painful and pain-free limbs in participants with unilateral knee pain (Tables 2 and 3). As expected, no relevant side differences in extensor or flexor strength were noted between both painful limbs in participants with bilateral knee pain (Table 4).

3.3. Speed of force production

There were no statistically significant differences in the time to produce 90% of the maximum force or the speed of force production for extension or flexion when comparing BP limbs and matched UP limbs (Table 2). However, these measures were also insensitive to differences in pain status between limbs within participants with unilateral knee pain (Table 3) and did not differ between painful limbs in participants with bilateral knee pain (Table 4).

4. Discussion

The objective of this study was to explore the impact of contralateral knee pain on isometric thigh muscle strength in painful knees through a potential mechanism of central nervous inhibition. To achieve this, we designed a cross-sectional study comparing isometric muscle strength in unilaterally painful (UP) limbs to isometric muscle strength in bilaterally painful (BP) limbs that were 1:1 matched for relevant demographic variables. The results demonstrate that, although the difference in knee extensor strength between UP limbs and matched BP limbs did not reach statistical significance in this sample, the magnitude (% value) of the difference was almost half of that between painful vs. pain-free limbs in the participants with unilateral knee pain and amounted to a value of approximately ¾ of what may be considered clinically relevant. In the context of previous findings (Steidle-Kloc et al., 2015), the current results are suggestive of an incremental reduction in isometric knee extensor strength from pain-free limbs of bilaterally pain-free people, to pain-free limbs of unilaterally painful people, to painful limbs of unilaterally painful people, to painful limbs of bilaterally painful people. Given that no self-reported differences in daily activity levels were identified between the study participants with unilateral and bilateral pain, these finding support the concept of central nervous inhibition of muscle strength caused by contralateral knee pain, more so in pain-free than in painful limbs. Other measures, such as flexor maximum force, time to produce 90% of max extensor or flexor force (s), and speed of force production during extension or flexion (N/s) appeared to be less sensitive that the extensor maximum force, and did not differ significantly between painful and pain-free limbs in participants with unilateral knee pain, whereas the extensor maximum force did. Therefore, we recommend maximum extensor force as the primary outcome measure in future work studying the impact of knee pain on muscle function.

Several studies have investigated the relationship between muscle strength, structural pathology (e.g. radiographic stage, cartilage loss) and knee symptoms (pain and physical function) in participants with and without radiographic knee OA (Glass et al., 2013; Sattler et al., 2012). Sattler et al. (2012) found frequently painful knees to have 5.2% lower quadriceps muscle cross-sectional areas and 7.8% lower extensor muscle strength than contralateral pain-free knees with the same radiographic disease severity, whereas flexor strength, or flexor and adductor anatomical cross sectional areas were not observed to differ significantly between painful and pain-free knees within the same person. This may have to do with “antigravitational” extensor strength being a more relevant determinant of the knee joint internal forces than flexor strength. If this is the case, then there may be a closer relationship between pain and reduced extensor strength, in the context of the central nervous system acting to protect painful knee joints from large forces. In contrast, flexor muscles may be less inhibited due to their role in knee joint stabilization. While plausible, these interpretations remain speculative at this point and need to be assessed through additional experimental work.

Although strength has been related to risk of radiographic and symptomatic progression of OA (Segal and Glass, 2011), it was reported that thigh muscle strength in knee OA was much more strongly related to pain than to radiographic disease status (Ruhdorfer et al., 2014). Nevertheless, we matched painful limbs of participants with unilateral knee pain in our study to limbs of participants with bilateral knee pain by radiographic stage (KLG grade 0/1 or 2/3), to minimize the residual impact of radiographic disease severity.

In recent studies, the minimally clinically important difference (MCID) for knee extensor muscle strength was proposed to be on the order of 4% when related to self-reported knee function (Ruhdorfer et al., 2016, 2014), suggesting that a 4% reduction in muscle strength is clinically relevant in improving or deteriorating lower limb function during relevant daily activities. In the current study, we found knee extensor strength to be 2.9% lower in matched BP limbs compared to UP limbs, a value on the order of 72.5% of the suggested MCID. Within participants with unilateral knee pain, we observed a 6.2% difference in knee extensor strength between UP limbs versus contralateral pain-free limbs, a value on the order of 155% of the MCID. In our previously published study, knee extensor strength was 5.5% lower in unilaterally pain-free limbs when compared with matched bilaterally pain-free limbs (Steidle-Kloc et al., 2015), a value that is on the order of 137.5% of the proposed MCID (Ruhdorfer et al., 2016, 2014).

The underlying mechanisms behind these findings may be related to central nervous system inhibitory effects. This effect may be mediated by altered afferent signals arising from painful joints, as these afferent signals appear to cause neural inhibition of the musculature surrounding the affected knee (Héroux and Tremblay, 2006; Palmieri et al., 2004, 2003). There is also evidence that this process may influence muscle strength in the contralateral limb (Hurley and Newham, 1993). The impact on contralateral muscle strength is thought to be due to voluntary activation deficits in the context of central nervous system inhibition (Metcalfe et al., 2012; Pietrosimone et al., 2011). This mechanism enables the central nervous system to balance the muscle activation level between limbs. Considering the findings of the current and the previous study (Steidle-Kloc et al., 2015), it is conceivable that this effect of central nervous inhibition is stronger in a pain-free knee than it is in a knee in which pain is already present. Yet, the observations in this study need to be confirmed in additional larger cohorts. Furthermore, the specific mechanism by which contralateral pain affects extensor muscle strength in the contralateral limb remains to be determined.

A limitation of this study is that, due to the strict matching criteria, some OAI participants with bilateral or unilateral knee pain could not be included. Although we initially included all limbs that fulfilled the unilateral and bilateral knee pain definitions, the matched sample consisted of n = 163 pairs which was not sufficient to establish statistical significance for pairwise differences as small as 2.9%. However, sources of bias in the current comparison were minimized by matching the participants for pertinent anthropometric and demographic parameters (age, sex, race, body size, etc.), which otherwise may have confounded associations between muscle strength and pain.

Matching for the physical activity (PASE) level was not done, but there was no statistically significant difference in PASE score between participants with bilaterally vs. unilaterally painful knees. Despite the strict matching criteria, a small, but statistically significant difference was observed for body height (1.8 cm) and body mass (1.9 kg), but these differences are of unlikely clinically relevant in the context of the question examined. Given such small differences in body height, muscle force was selected over torque as the primary analytic focus, mainly because strength is a direct measure from the Good Strength Chair, eliminating the possibility of measurement error in the calculation of torque based on participant limb length measurements.

In a cross sectional study, an association between knee height and radiographic and symptomatic knee OA was observed, with knee height of 1.9 cm greater in women and 1.7 cm greater in men being associated with a greater prevalence of radiographic knee OA and knee pain (Hunter et al., 2005). Given a difference of 1.8 cm in total body height in our study, the resulting differences in knee height likely represented a small fraction of the values reported by Hunter et al. (2005). Investigators analyzing the association of body mass with incident knee pain, stiffness, and functional difficulties in OA used a 5% threshold for their analyses (Tanamas et al., 2013), which is much larger than the difference observed in this study (2.3%) after matching limbs between groups. Therefore, the small differences in body height and mass between participants with bilateral and unilateral pain are unlikely to have influenced the study results.

An additional limitation of this study is the possible underestimation of pain status in the contralateral pain-free limb. In order to maintain an appropriate sample size to achieve statistical significance, participant limbs' were considered pain-free if they experienced no, or infrequent, pain during only 1 of the 5 activities on the WOMAC (score of 0-1). Based on the knowledge that knee pain status is associated with muscle strength, underestimation of the pain status of participants with unilateral knee pain could have decreased the significance of the difference in thigh muscle strength between UP limbs and matched BP limbs as well as the difference between UP and contralateral pain-free limbs within participants. However, to reduce the potential for underestimation of the pain-free status in the contralateral limb, additional measures were included in determining the pain-free status of these limbs (NRS pain intensity value 0-1 and either no or infrequent pain during the past 12 months).

Quadriceps weakness is thought to be associated with knee pain, functional disability, and progression of joint damage (Segal et al., 2010a,b). Muscle weakness is consistently found in patients with knee OA, and greater muscle strength has been associated with reduced risk for OA development and progression in women (Segal et al., 2010a,b; Segal et al., 2009a). Given the lack of treatment for established knee OA, the prevention of progression is of paramount importance for patients to avoid or delay pain, functional limitations and eventually arthroplasty (Schache et al., 2014). Current treatment guidelines recommend that people with or at risk for OA strengthen the quadriceps muscles (Bennell et al., 2013; Hart et al., 2010). However, it is not clear whether such recommendations may have symptom-modifying effects (Segal et al., 2009b; Segal and Glass, 2011), nor how treatments should be modified to address strength deficits when one limb is more severely affected than the other. The results of the current study suggest that, whenever possible, a similar level of strength should be maintained in both limbs, even if one knee is more painful than the other.

5. Conclusion

In conclusion, the results from the present study indicate slightly lower maximum extensor strength of matched bilaterally painful limbs (BP) when compared with unilaterally painful limbs (UP). This difference did not reach statistical significance but was ¾ of the magnitude of what may be considered clinically relevant with regard to lower limb function. In the context of previous findings, the current results are suggestive of an incremental reduction in isometric thigh muscle strength from pain-free limbs of bilaterally pain-free people, to pain-free limbs of unilaterally painful people, to painful limbs of unilaterally painful people, to painful limbs of bilaterally painful people. These findings support the possibility of central nervous system inhibition of muscle strength potentially caused by contralateral knee pain, more so in pain-free than in painful limbs.

Authors contribution

All authors have made substantial contributions to (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. Specific contributions are:

(1) The conception and design of the study: ES, FE, WW, NS
(2) Acquisition of data: ES, WW
(3) Analysis and interpretation of data: ES, KR, FE, NG, WW, NS
(4) Drafting the article: ES, FE, NS
(5) Revising the article critically for intellectual content: KR, ES, FE, NG, WW, NS
(6) Final approval of the version submitted: ES, KR, FE, NG, WW, NS
(7) Statistical expertise: ES, WW, NS

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.aanat.2018.08.003.

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