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Quadriceps-hamstrings intermuscular coherence during single-leg squatting 3–12 years following a youth sport-related knee injury

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ABSTRACT

The purpose of this study was to determine the degree of co-contraction as per electromyographic gamma-band intermuscular coherence of the quadricep (Q) and hamstring (H) muscles during single-leg squatting (SLS), and to assess the influence of sex and self-reported knee complaints on the association between knee injury history and medial and lateral Q-H intermuscular coherence.

Participants included 34 individuals who suffered a youth sport-related intra-articular knee injury 3–12 years previously, and 37 individuals with no knee injury history. Surface electromyographic signals were recorded from medial and lateral thigh muscles bilaterally to determine the gamma-band (30–60 Hz) intermuscular coherence between medial and lateral Q-H muscle pairs during SLS. Multivariable linear regression ($\alpha = 0.05$) was performed to investigate the relationship between knee injury history (main exposure) and medial and lateral Q-H coherence (outcome) while accounting for the influence of sex and self-reported knee pain and symptoms (covariates).

The median age of participants was 25 (range 18–30) and 67% were female. Q-H gamma-band coherence was present for 60–90% of legs. Medial and lateral Q-H coherence was higher in females compared to males. There was no evidence for an association between medial Q-H coherence, knee injury history, knee pain, or symptoms. There was evidence for an association between knee injury history and lateral Q-H coherence, which was modified by sex such that previously injured males demonstrated reduced Q-H coherence compared to uninjured males.

These finding suggest that females demonstrate a more pronounced Q-H co-contraction strategy during a SLS than males regardless of knee injury history. Further, that male who suffered a youth sport-related knee injury 3–12 years previously demonstrate less Q-H co-contraction during a SLS than uninjured males. The mechanisms behind differences in neuromuscular control between males and females as well as previously injured and uninjured males require further investigation.

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1. Introduction

Increased quadriceps-hamstrings (Q-H) muscle co-contraction during gait or other functional movements is a commonly observed neuromuscular adaptation immediately following a significant knee injury (e.g., Anterior Cruciate ligament (ACL) rupture or meniscal tear) (Rudolph, Axe, Buchanan, Scholz, & Snyder-Mackler, 2001; Hurd & Snyder-Mackler, 2007; Sturnieks, Besier, & Lloyd, 2011). This adaptation is hypothesized to be a protective adaptation of the central nervous system (CNS) to increase joint stiffness and thereby avoid excessive anterior tibial translation and/or other painful movements (Chmielewski, Rudolph, & Snyder-Mackler, 2002). Despite these immediate benefits, however, a pronounced Q-H co-contraction strategy is characteristic for individuals who show poor knee function following ACL rupture as it may hinder more effective knee stabilization strategies observed in individuals with no prior knee injury (Eastlack, Axe, & Snyder-Mackler, 1999; Rudolph et al., 2001; Chmielewski, Hurd, Rudolph, Axe, & Snyder-Mackler, 2005). Furthermore, a more pronounced Q-H co-contraction strategy that persists past the acute knee injury phase (> one year) most likely results in a permanent alteration of the magnitude and direction of forces that act across the tibio-femoral joint surfaces (Schipplein & Andriacchi, 1991; Victor, Labey, Wong, Innocenti, & Bellemans, 2010). Joint tissues that are unable to adapt to the modified mechanical environment associated with increased Q-H co-contraction may slowly degrade overtime, exposing the affected individuals to an increased risk for post-traumatic osteoarthritis (PTOA) of the knee (Andriacchi et al., 2004). Therefore, albeit protective initially, a permanent increase in Q-H co-contraction following a knee injury has been considered a maladaptive neuromuscular strategy that may impede effective knee stabilization and contribute to joint degeneration (Chmielewski et al., 2005; Tsai, McLean, Colletti, & Powers, 2012). For the design of effective neuromuscular rehabilitation aimed at improving knee stability and reducing OA risk following a knee injury, it is of importance to better understand long-term adaptations of the CNS related to controlling quadriceps and hamstrings motor unit activity (Needle, Lepley, & Grooms, 2017; An, 2018).

The few previous studies that have investigated Q-H muscle co-contraction beyond the first year following a knee injury have generally provided evidence that a more pronounced co-contraction strategy does persist in previously injured individuals (Ortiz et al., 2008; Tsai et al., 2012; Hall, Stevermer, & Gillette, 2015). These authors, however, primarily analyzed a muscle co-contraction index, that is based on the average ratio of low-pass filtered surface electromyography (sEMG) amplitudes between the quadriceps and hamstrings muscles. While such indices may or may not be a marker for knee joint forces (Winby, Gerus, Kirk, & Lloyd, 2013), this approach can only provide limited insight into neurophysiological processes that facilitate the coupling of Q-H motor unit activity following knee trauma (Pizzamiglio, De Lillo, Naeem, Abdalla, & Turner, 2017). In contrast, techniques that analyze correlations between EMG signals in the frequency domain, such as intermuscular coherence, have been successfully applied to study intermuscular coordination and may thus reveal new insights into the adaptation of Q-H co-contraction strategies post-injury (Laine & Valero-Cuevas, 2017).

For the ankle joint it has been suggested, that a co-contraction strategy between antagonistic muscles, e.g. for joint stabilization, is enabled by a stronger involvement of the motor cortex that leads to a more synchronized motor unit activity between these muscles (Nielsen & Kagamihara, 1992; Hansen, Hansen, Christensen, Petersen, & Nielsen, 2002). These findings were based on an intermuscular coherence analysis between the surface electromyography (sEMG) signals of the involved muscles (Hansen et al., 2002). EMG-EMG coherence can be used to detect coupled motor unit activity between two muscles as a result of neural inputs from different sources within the CNS (Farmer, Bremner, Halliday, Rosenberg, & Stephens, 1993; Grosse, Cassidy, & Brown, 2002). Specifically during movement, intermuscular coherence in the gamma-band (30–60 Hz) has been investigated as a marker of motor unit coupling between muscles associated with common inputs from the corticospinal tract to these muscles (Clark, Kautz, Bauer, Chen, & Christou, 2013; De Marchis, Severini, Castronovo, Schmid, & Conforto, 2015; von Tscharner, Ullrich, Mohr, Comaduran Marquez, & Nigg, 2018)

Therefore, it may be hypothesized that a persistent Q-H muscle co-contraction strategy observed in individuals following a knee injury is associated with a stronger coupling of motor unit activity between the quadricep and hamstring muscles and can be detected as an increase in gamma-band intermuscular coherence between the respective sEMG signals when compared to uninjured controls.

Recent analyses of intermuscular coherence between two quadriceps muscles during a squatting task demonstrated a high degree of relative and absolute between-trial reliability and good sensitivity to detect a change in coherence between different squatting conditions (Mohr, Nann, von Tscharner, Eskofier, & Nigg, 2015; Mohr, Schön, von Tscharner, & Nigg, 2018). Given that a single-leg squatting (SLS) task is a common clinical test to assess knee joint function following an injury (Escamilla, 2001), high intermuscular coherence between the quadricep and hamstring muscles during this task may be a useful marker to detect abnormal co-contraction strategies. Here, it is crucial to consider males and females separately due to sex-specific neuromuscular patterns during single-leg movement tasks (Zeller, McCrory, Ben Kibler, & Uhl, 2003) as well as sex-specific adaptations to knee injuries when accomplishing single-leg movements (Yamazaki, Muneta, Ju, & Sekiya, 2010). Furthermore, if increased Q-H co-contraction during SLS is a clinically relevant strategy to cope with compromised knee function as stated initially, then Q-H intermuscular coherence should be even higher in individuals who exhibit more severe knee symptoms and/or pain.

The primary objective of this study was to assess the relationship between a history of intra-articular youth sport-related knee injury more than three years ago and gamma-band Q-H intermuscular coherence during a single-leg squat taking into consideration the influence of sex and self-reported knee symptoms and pain.

In addition to comparing previously injured individuals to a control group, it is common in clinical and rehabilitation environments to use the patient as his/her own control condition and compare muscle and joint function between the previously injured and uninjured leg. These within-subject comparisons may hold important clues about persistent neuromuscular deficits that result from a prior knee injury (Rudolph et al., 2001; Hurd & Snyder-Mackler, 2007). Therefore, the secondary objective of this study was to explore side-to-side differences in Q-H gamma-band coherence between the injured and uninjured legs in males and females.

2. Methods

2.1. Study design and participants

Participants included a subset of individuals from an ongoing longitudinal historical cohort study [The Alberta Youth Prevention of Early OA Study (PrE-OA Study)]. The Pre-OA cohort, primary outcome variables, recruitment strategies, and exclusion criteria have been described in detail previously (Whittaker, Woodhouse, Nettel-Aguirre, & Emery, 2015; Toomey et al., 2017; Whittaker, Toomey, Nettel-Aguirre, et al., 2018a; Whittaker, Toomey, Woodhouse, et al., 2018b). Briefly, the PrE-OA study includes 200 youth / young adults (aged 15 to 26); 100 participants who have suffered a sport-related knee injury three to ten years previously and 100 participants with no history of knee injury, matched for age, sex, and sport. Sport-related knee injury was defined as a clinical diagnosis of knee ligament, meniscal or other intra-articular tibiofemoral or patellofemoral injury that required both medical consultation and disrupted regular sport participation. The current study was embedded within the larger PrE-OA study and included a convenience sample of 71 individuals (34 injured, 37 uninjured) from the PrE-OA cohort, that consented to participating in an additional analysis of their leg muscle activity and lower extremity kinematics during various movements including the SLS. The biomechanical data collection for this study took place between August 2016 and October 2017 and included PrE-OA participants at varying follow-up stages of participation in the larger cohort study (e.g., year 1–3 follow-up testing). Therefore, the biomechanical data collection included individuals who had sustained knee injuries 3–12 years ago. This study was carried out in accordance with the guidelines of the University of Calgary's Conjoint Health Research Ethics Board (#E-25075) and with the Declaration of Helsinki.

2.2. Procedures

The primary data collection site for the PrE-OA study was the University of Calgary Sports Medicine Centre. After completing a study questionnaire (e.g., demographics, knee injury/surgery details, medical history) and the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire, participants' height (cm) and weight (kg) were measured. For the purposes of this study the index leg refers to the injured leg of participants with a knee injury history and the corresponding leg of their matched-control in the larger PrE-OA cohort study.

The KOOS is a self-reported outcome measure related to knee joint health and function with five subscales: pain, other symptoms, function in daily living, function in sport and recreation, and knee-related quality of life (Roos, Roos, Lohmander, Ekdahl, & Beynnon, 1998). Each item is scored on a 5-point Likert-scale ranging from no problems to extreme problems with a cumulative, normalized score for each subscale between 100 and 0, respectively. For this analysis, the KOOS pain and symptoms subscales were evaluated as these sub-scales have shown clear associations with knee injury history in the PrE-OA and other OA cohorts, and may be indicative of symptomatic PTOA (Øiestad, Holm, Engebretsen, & Risberg, 2011; Whittaker, Toomey, Woodhouse, et al., 2018b).

Biomechanical and surface EMG measurements were conducted at the University of Calgary's Human Performance Laboratory. Locations for bipolar surface EMG sensors (Ag/AgCl, 10 mm diameter, 20 mm inter-electrode distance, Norotrode Myotronics-Noromed Inc., US) were identified on the vastus lateralis (VL), vastus medialis (VM), biceps femoris (BF), and medial hamstrings (MH) of both legs according to standardized landmarks described in the widely used SENIAM guidelines for the use of surface EMG (Hermens, Freriks, & Merletti, 1999). Before sensor placement, the skin around the identified locations was shaved, lightly abraded, and cleaned with alcohol wipes to reduce skin impedance. After sensor placement, the location of the electrodes was validated according to clean, raw EMG signals during a series of test movements (i.e. squats for vasti muscles, hamstring curls for hamstrings).

Bipolar, differential EMG signals were recorded at 2400 samples per second, amplified by a factor of 1000 and bandpass-filtered between 10 and 500 Hz (Biovision, Wehrheim, Germany). Signals below 10 Hz were therefore not considered for drawing conclusions although there may be some EMG signal in the role off range of the frequency response. The measuring system was grounded by connecting the ground electrode of the system to the right tibial tuberosity. The analog EMG signals were digitized by a 12-bit A/D converter (National Instruments, Austin, TX). In addition to EMG recordings, 1D-accelerometers were taped to the lateral aspect of the right and left heel to later synchronize the EMG and motion capture systems during squatting. Heel accelerations were recorded simultaneously to EMG signals via the same data acquisition system. Following the EMG set-up, participants were equipped with sets of three retroreflective markers that were mounted on the thigh and shank segments to track three-dimensional lower limb kinematics during the squatting task.

Following the sensor set-up, participants performed a series of 45-degree SLSs at a rate of 17 squats/minute for 1 min. The squatting speed was controlled for by a metronome playing at 35 beats per minute with the instruction to synchronize the highest and lowest position of the squat with a beat. The relatively small range of motion of 45 degrees was chosen to ensure that participants with knee symptomology or poor balance would still be able to complete the SLS task. To ensure a consistent squatting depth, a string was suspended between two tripods and adjusted so that it would lightly touch the anterior aspect of the participants' knee when the knee was flexed to 45 degrees. The position of the string was confirmed prior to testing by a manual goniometer. Participants were instructed to squat down until they touched the string without deforming it and to then reverse the movement. Each participant completed a warm-up of three sets of five SLS on each leg to familiarize with the instructions, the movement task, and squatting rhythm. For the actual measurement, participants performed two 60 s trials of single-leg squatting, one for each leg. Participants were instructed to initially step onto a force plate with the leg to be measured. The step on to the force plate produces a sharp peak in both the vertical ground reaction force as well as the heel acceleration signal, which was used to synchronize the motion analysis and EMG systems during the analysis. Then, participants performed the squats while keeping their upper body straight and with their hands on their hips. During the squatting movement, EMG (2400 Hz sampling), ground reaction force (2400 Hz sampling, Kistler), and 3D

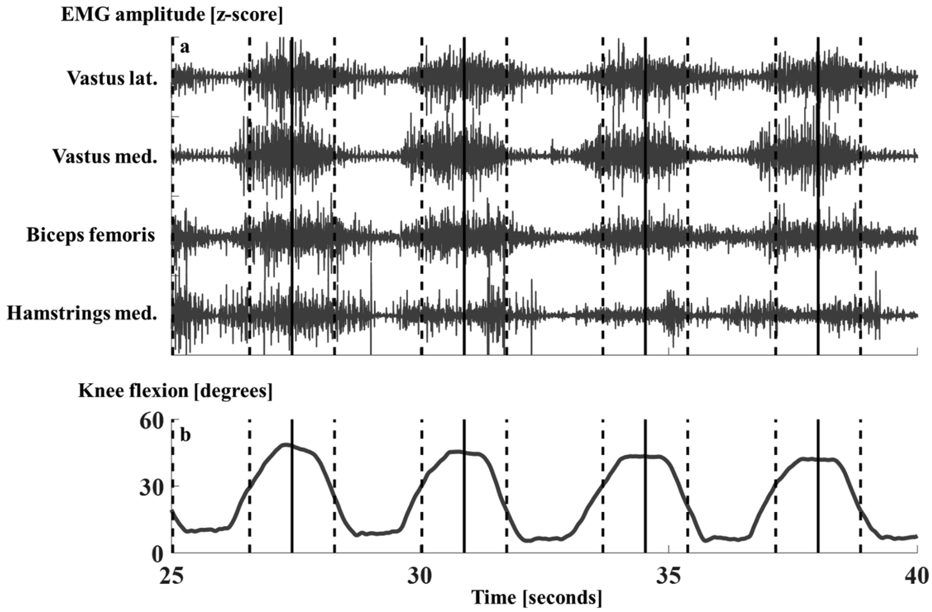

Fig. 1. Raw EMG signals of thigh muscles during single-leg squat (a). EMG amplitudes were normalized to their respective standard deviations for display purposes. Corresponding knee flexion angle in degrees (b). Solid vertical bars represent peak knee flexion. Dashed vertical bars represent analyzed data windows.

marker trajectories (240 Hz sampling, 8 cameras, Motion Analysis Corp, Santa Rosa, CA, USA) were recorded. If participants lost the squatting rhythm or had to set down their other leg to regain balance, the measurement was repeated after one minute of rest.

2.3. Data processing

The raw marker trajectories obtained from motion analyses were reconstructed using Cortex software (Motion Analysis Corp, Santa Rosa, CA). The remaining processing steps were performed using a custom-written software in MATLAB 2017a (Mathworks, Natick, MA, USA). First, the EMG and motion data were synchronized in time at the instant of the initial step onto the force plate according to a peak in the heel accelerometer signal (EMG system) and a sharp rise of the vertical ground reaction force (20 N threshold) provided by the force plate. Three-dimensional marker trajectories of the thigh and shank during squatting were low-pass filtered (fourth-order Butterworth, 10 Hz cut-off) and used to estimate the sagittal knee joint angle as described by Söderkvist and Wedin (1993) (Fig. 1b). The peak knee flexion angles during the squatting series were identified and used to extract EMG data sequences during a time window of 4096 samples (1.7 s) centered at the time of peak knee flexion. For each individual, 15 EMG data sequences were selected and further subdivided into four sequences of 1024 samples (~0.43 s) to yield 60 available data sequences. This procedure resulted in a more accurate estimate, i.e. a smaller standard error of the Fourier and coherence spectra while sacrificing frequency resolution. The resulting frequency increments of 2.3 Hz, however, were still deemed acceptable to estimate spectral variables in different frequency bands.

2.4. Intermuscular coherence analysis

After removing the mean of the raw EMG data sequences, the FFTs were computed. The power spectra for each muscle and individual were determined by multiplying the FFT (*F*) of each sequence with its complex conjugate (* *operator*) and averaging across all data sequences (Fig. 2a). Intermuscular coherence of the raw, unrectified EMG signals as a function of frequency λ (coherence spectrum) for each muscle pair was computed from the average cross-spectra normalized by the corresponding power spectra across s = 60 data sequences (Rosenberg, Amjad, Breeze, Brillinger, & Halliday, 1989):

$$coherence(\lambda) = \frac{|\overline{F_{VL}(\lambda)\bullet F_{VM}(\lambda)^{*}}|^{2}}{\overline{(F_{VL}(\lambda)\bullet F_{VL}(\lambda)^{*})}\bullet\overline{(F_{VM}(\lambda)\bullet F_{VM}(\lambda)^{*})}} \quad (1)$$

Due to the averaging procedure, the coherence between two signals decays with an increasing number of analyzed sequences unless the phase shift relationship between the signals remains constant. In consequence, even signals with no phase correlation can show a high level of coherence by chance if the number of analyzed sequences is small ($s < 10$). Therefore, a threshold coherence must be established, where the coherence spectrum above this threshold value represents a significant phase correlation between the two analyzed signals. The reference coherence was determined as a function of the number of analyzed sequences as introduced by Rosenberg and colleagues (Rosenberg et al., 1989):

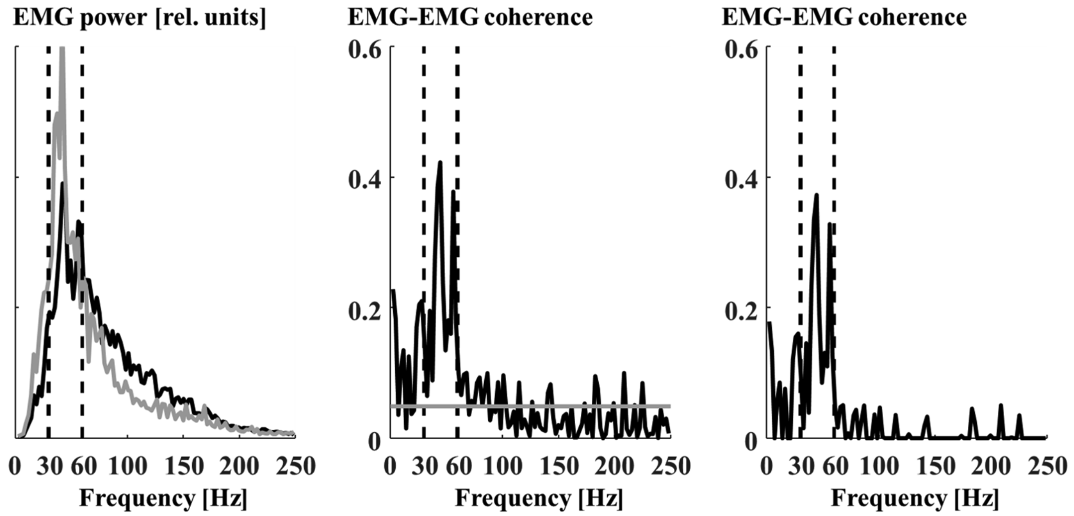

Fig. 2. Power spectra of vastus lateralis (VL, black) and biceps femoris (BF, grey), normalized to the summed power between 0 and 250 Hz (a). VL-BF intermuscular coherence spectrum (black) and coherence reference value (grey) (b). Significant VL-BF intermuscular coherence spectrum above reference value (c). Dashed vertical lines indicate the gamma-band. Spectra are displayed for one participant.

$$threshold\ \ coherence = 1 - \alpha^{1/(s-1)} \tag{2}$$

where α corresponds to the significance level that was set to 0.05. In this study, s was given by the 60 analyzed squatting sequences leading to a reference coherence of 0.0495. The reference value was subtracted from the determined coherence spectra and resulting negative values were set to zero (Fig. 2b and c). For each participant, intermuscular coherence was analyzed between the vastus lateralis and biceps femoris (VL-BF), and vastus medialis and medial hamstrings (VM-MH).

To summarize the presence and strength of significant intermuscular coherence for Q-H muscle pairs during squatting, the coherence spectra from both legs of all participants were pooled. The presence of significant coherence was then determined as the percentage of legs exhibiting intermuscular coherence above the reference value for each frequency bin (Farmer et al., 1993). To summarize the strength of intermuscular coherence across individual measurements, previous authors have recommended to first convert the raw coherence spectrum, *coherence(λ)*, into a normally distributed variable with an approximately unit standard deviation, *z-coherence(λ)*, by the following transformation (Rosenberg et al., 1989; Baker, Pinches, & Lemon, 2003):

$$z - coherence(\lambda) = \frac{\tanh^{-1}(\sqrt{coherence(\lambda)})}{\sqrt{1/2s}} \tag{3}$$

where s corresponds to the 60 analyzed data sequences that were used to compute the raw coherence. The transformed coherence spectra, *z-coherence(λ)*, were pooled across all legs and then averaged at each frequency to compare the strength and properties of Q-H intermuscular coherence between the two muscle pairs.

To investigate associations between Q-H coherence and knee injury history, sex, and KOOS scores, VL-BF and VM-MH gamma-band z-coherence was computed as the mean of the z-transformed coherence spectra between 30 and 60 Hz for each muscle pair and individual. All subsequent statistical analyses were performed on these average VL-BF and VM-MH z-transformed coherence values in the gamma-range.

2.5. Statistical analyses

Statistical analyses were performed using STATA (v.14.2, College Station, TX, USA) at a significance level of $\alpha = 0.05$. Descriptive statistics were calculated for participant characteristics (by exposure group), KOOS pain and KOOS symptoms sub-scale scores for the index leg (by injury group), and gamma-band coherence between VL-BF and VM-MH for the index and non-index leg (by injury group and sex). A Wilcoxon rank sum test was used to evaluate significant differences in the medians of KOOS sub-scale scores between injured and uninjured participants.

Regarding the first objective, multivariable linear regression (95% CI) was used to investigate the association between the predictor variables ‘injury group’ (exposure), ‘sex’, ‘KOOS symptoms,’ ‘KOOS pain’ and the two outcome variables, ‘VL-BF and VM-MH gamma-band coherence’. Regression analyses began with models that included coefficients for all predictor variables and two-way interaction terms with the exposure variable (i.e. exposure × sex, exposure × KOOS symptoms, exposure × KOOS pain). After interaction terms were evaluated for statistical significance according to likelihood ratio tests, the association between ‘injury group’ and each coherence outcome was assessed considering confounding by sex, KOOS symptoms, and KOOS pain using a stepwise elimination approach. Covariates were removed from the model if their coefficients were not statistically significant and there was no evidence that they confounded the relationship between the exposure and outcome variables. In the presence of a significant

Table 1
Participant characteristics.

Variable	Uninjured n = 33		Injured n = 31	
% female	71		65	
Age at testing in years (median, range)	25	[18 29]	24	[19 30]
Height in cm (median, range)	170	[158 194]	167	[157 196]
Weight in kg (median, range)	72.1	[54 109]	68	[49 110]
Months since injury (median, range)	n/a		98	[38 150]
Primary knee injury surgery (number)	n/a		20	
ACL reconstruction (number)	n/a		19	
Knee injury with meniscus involvement (number)	n/a		17	
Second injury to study knee (number)	n/a		5	
Contralateral knee injury (number)	n/a		5	
KOOS Symptoms (median, range)	96	[71 100]	93	[64 100]
KOOS Pain (median, range)	100	[92 100]	94	[72 100]

exposure × sex interaction, Bonferroni-corrected post-hoc comparisons (Wilcoxon rank sum tests) of coherence outcomes were conducted for all combinations of the levels of 'injury group' and 'sex'. For the VL-BF coherence outcome, all assumptions for linear regression were assessed and met. For the VM-MH coherence outcome, the distribution of residuals was right-skewed and violated the assumption of normally distributed residuals, which is important for obtaining accurate F and *t*-statistics. Therefore, a ln-transformation of the VM-MH coherence outcomes was applied to achieve normally distributed residuals.

Regarding the second objective, a qualitative, exploratory analysis was conducted to detect possible side-to-side differences in Q-H gamma-band coherence in injured and uninjured subjects. Specifically, side-to-side differences (index – non-index leg) were determined for each individual and then displayed as boxplots by injury group and sex.

3. Results

3.1. Participants

Participant characteristics are summarized in Table 1. After visual analysis of the raw EMG data, six participants were excluded due to poor quality/missing data for one or two muscles (amplifier defect, n = 5; data acquisition box defect, n = 1). For these reasons, a total of 64 individuals (31 injured, 33 uninjured) were included in the analyses examining EMG power and intermuscular coherence during squatting. For assessing side-to-side differences in coherence, five additional injured individuals were excluded due to a contralateral knee injury, leaving a sample of 26 previously injured participants.

Nineteen of the previously injured participants had sustained an ACL tear and all had undergone ACL reconstruction surgery. Other injuries included isolated meniscal injuries, medial or lateral collateral ligament injuries, and one fracture. KOOS pain and KOOS symptoms median scores were significantly lower in the previously injured group compared to the control group (p = 0.025) indicating more symptoms and higher pain.

3.2. Q-H intermuscular coherence during a single-leg squat

Significant intermuscular coherence in at least one frequency bin was observed for almost all investigated legs (128 and 125 out of 128 legs for VL-BF and VM-MH, respectively). The intermuscular coherence for the VL-BF and VM-MH muscle pairs, however, did not reach significance at all frequencies. Thus, at each frequency only a certain percentage of legs reached significant coherence between the quadriceps and hamstring muscles. The percentage of legs that showed a significant coherence for a specific frequency is summarized in Fig. 3 as a grey line (right y-axes). The z-transformed coherence of the legs as a function of frequency yielded an average coherence spectrum shown as black line in Fig. 3 (left y-axes).

The shape of the average coherence spectra was similar for the VL-BF and VM-MH muscle pairs with the most consistent and strongest intermuscular coherence between 30 and 60 Hz. In the same frequency range, the gamma band, the percentage of legs that showed a significant coherence of the VL-BF muscle pairs was about 90% (64 × 2 = 128 legs). About 60% of legs showed significant VM-MH gamma-band coherence. The mean peak z-coherence between 30 and 60 Hz across all legs was higher for the VL-BF muscle pair (mean ± SE = 6.5 ± 0.3) compared to VM-MH (3.6 ± 0.3).

3.3. Association between Q-H coherence, knee injury history, sex, and KOOS

The results of the multivariable analysis are presented in Table 2. Medians and ranges for VL-BF and VM-MH intermuscular coherence in the gamma-band are presented for the index leg as boxplots by injury group and sex in Fig. 4a and b. A first general observation was that Q-H gamma-band coherence values exhibited a large between-subject variability, particularly for female individuals. There was a significant interaction effect between 'injury group' and 'sex' with respect to VL-BF gamma-band coherence (p = 0.019). While females generally showed higher VL-BF coherence compared to males (injury group median difference = 5.7, p-

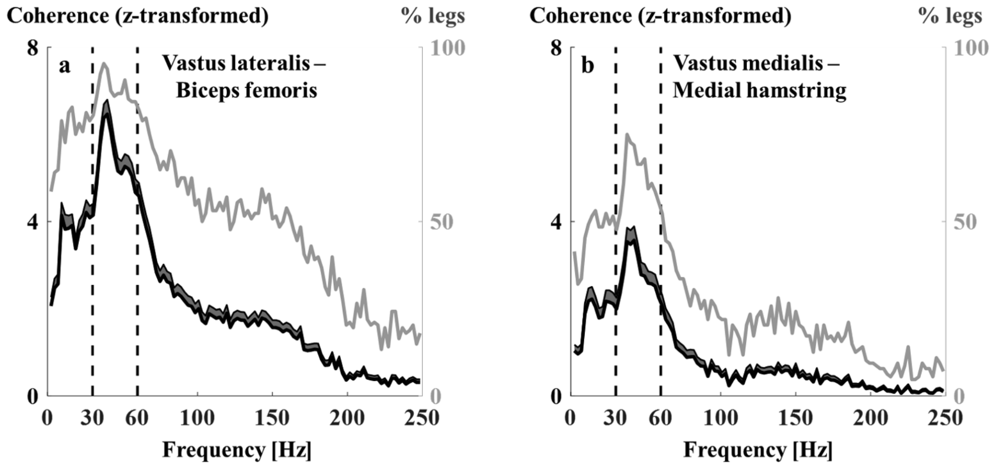

Fig. 3. Percentage of legs with significant intermuscular coherence at each frequency bin (grey lines, right y-axes) and corresponding mean z-transformed coherence spectra across legs (black lines, left y-axes) for vastus lateralis-biceps femoris (a), and vastus medialis-medial hamstrings (b). Shaded area represents one standard error computed across legs at each frequency.

Table 2
Association between previous knee injury and quadriceps-hamstrings coherence based on multivariable linear regression.

Outcome	Constant	Injury Group[a]	Sex[b]	Injury x Sex	KOOS symptoms	KOOS pain
VL-BF z-coherence	9.4 (−3.4, 22.1)	1.2 (−0.4, 2.8)	−2.1* (−4.0, −0.2)	−3.4* (−6.3, −0.6)	–	−0.0 (−0.2, 0.1)
VM-MH z-coherence[c]	0.8 (0.3, 1.3)	0.0 (−0.6, 0.7)	−1.2* (−1.8, −0.5)	–	–	–

Values represent coefficient and 95% confidence interval (CI).
*95% CI does not encompass zero.
'–' variable was removed from the model after assessing for interaction with injury group and confounding.
[a] Uninjured was used as the reference.
[b] Female sex was used as the reference.
[c] Coefficients were determined for ln(VM-MH z-coherence).

corrected < 0.001; control group median difference = 1.9, p-corrected = 0.19), the association between knee injury history and VL-BF coherence was different in males and females. Specifically, injured males showed a lower median VL-BF coherence compared to uninjured males while females in the injury group showed a slightly higher VL-BF coherence compared to the uninjured group (Fig. 4a). After correction for multiple comparisons, however, the corresponding post-hoc tests were not statistically significant (median difference males = 2.6, p-corrected = 0.18; median difference females = −1.1, p-corrected = 0.41). For the VM-MH muscle pair, ln-transformed coherence values were significantly influenced by 'sex' (p = 0.001) but not 'injury group' (p = 0.89). Fig. 4b shows that females showed a higher VM-MH coherence compared to males for both the injured group (median difference = 2.4) and uninjured group (median difference = 1.6). KOOS pain and symptoms scores did not show significant effects on VL-BF or VM-MH gamma-band coherence.

3.4. Side-to-side differences in previously injured group

Fig. 4c and d display side-to-side differences in Q-H intermuscular coherence between the index and non-index leg by injury group and sex. For both muscle pairs, the median side-to-side differences were generally close to zero indicating no systematic differences between the index and non-index leg. The one exception were male subjects in the injury group who showed a median side-to-side difference in VL-BF coherence of −1.2, as a result of lower coherence values for the injured compared to uninjured leg in 7 out of 9 injured males with no contralateral injury (Fig. 4c).

4. Discussion

This study evaluated the thigh muscle activation patterns during a SLS in participants with a previous youth sport-related knee injury 3–12 years ago in comparison to uninjured controls. Specifically, intermuscular coherence between quadriceps and hamstrings in the gamma-band frequency range was investigated as a marker for a more pronounced Q-H co-contraction strategy. Significant gamma-band intermuscular coherence between the quadricep and hamstring muscles was detected for at least two thirds of the investigated legs. However, there was no evidence to support our hypothesis that previously injured participants would generally

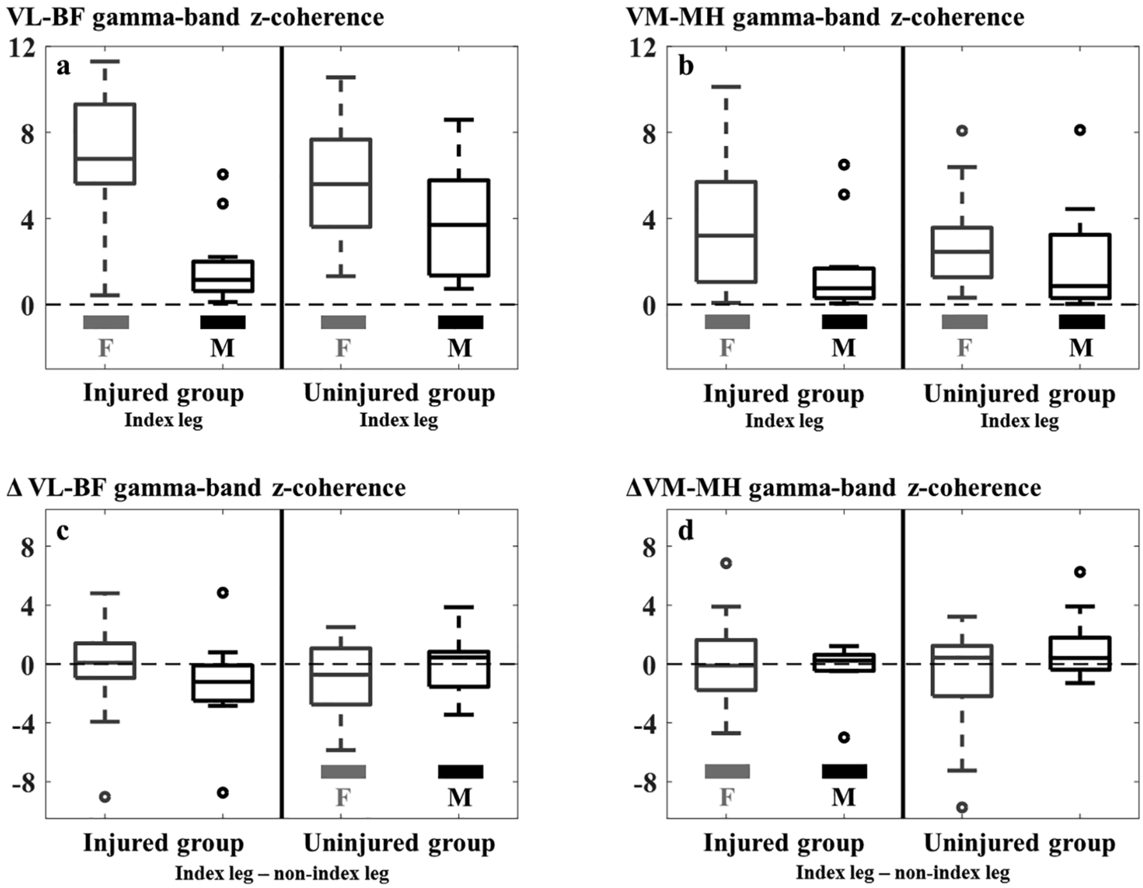

Fig. 4. Boxplots of intermuscular coherence in the gamma band (30–60 Hz) between vastus lateralis and biceps femoris (VL-BF, a) and vastus medialis and medial hamstrings (VM-MH, b) by sex. Both graphs show the results for the affected leg of the injured group and the selected leg of the uninjured group. Fig. 4c and d show the side-to-side differences between legs for the injured group (affected-unaffected leg) and uninjured group (selected – not selected leg). Grey and black boxplots present results for females (F) and males (M), respectively. All graphs show the coherence values following z-transformation.

exhibit higher Q-H gamma-band coherence compared to uninjured controls. Instead, male and female participants showed a sex-specific Q-H co-contraction strategy and possibly a sex-specific adaptation of Q-H co-contraction to a previous knee injury. These results will be discussed from a neuromuscular control perspective as well as in the context of the strengths and limitations of this study's design and methodology.

4.1. Q-H intermuscular coherence during a single-leg squat

EMG-EMG coherence has been successfully used in previous studies to identify the involvement of the corticospinal tract and other neural circuits in coordinating the muscles that produce movements or accomplish stabilizing tasks (Farmer et al., 1993; Hansen et al., 2002; Clark et al., 2013; Laine & Valero-Cuevas, 2017). During the single-leg squat investigated in this study, most of the 128 investigated legs showed significant EMG-EMG intermuscular coherence in the 30–60 Hz gamma-band between vastus lateralis and biceps femoris (~90%) and between vastus medialis and the medial hamstrings (~60%). While it is known that a large portion of the neural input to the medial and lateral quadriceps muscles is shared during squatting exercises (Chang et al., 2012; Mohr et al., 2015, 2018), the consistent motor unit coupling between the antagonistic quadriceps and hamstring muscles in the gamma-band is a novel finding. Antagonistic muscle pairs, such as vastus lateralis and biceps femoris in this study, show coupled motor unit activity if they are simultaneously activated to stabilize a common joint (De Luca & Mambrito, 1987; Nielsen & Kagamihara, 1992, 1994; Geertsen et al., 2013; Pizzamiglio et al., 2017). Combined EMG and EEG recordings during ankle muscle co-contractions have suggested that descending commands of the motor cortex are responsible for coupled motor unit activity between antagonists by suppressing spinal pathways that would otherwise inhibit their coupling (Hansen et al., 2002).

During SLS, the quadriceps muscle is contracting eccentrically and concentrically to perform the downwards and upwards squatting movement, respectively. At knee flexion angles of less than 45 degrees, quadriceps forces can destabilize the knee by producing an anterior pull of the tibia with respect to the femur (Li et al., 1999). The hamstring muscles have the ability to increase knee joint stability by reducing anterior tibia translation due to their posterior insertion points (More et al., 1993). Furthermore, Q-H co-contraction can support knee joint loads in the frontal plane, which are typically present during single-leg squatting (Lloyd & Buchanan, 2001; Alenezi, Herrington, Jones, & Jones, 2014). Therefore, the CNS likely uses a Q-H co-contraction strategy to stabilize the knee joint during the SLS and this may be facilitated by a common, neural input from the corticospinal tract to the quadricep and hamstring muscles.

4.2. Association between Q-H coherence and knee injury, sex, symptoms, and pain

The functional significance of intermuscular coherence is evident as the level and frequency content of coherence is often associated with the presence or absence of neurological disorder (Farmer et al., 1993), skill-level (Geertsen et al., 2013), fatigue (Castronovoa et al., 2018), or task-specific biomechanical requirements (Mohr et al., 2015; Laine & Valero-Cuevas, 2017). This study used Q-H intermuscular coherence as a potential neurophysiological marker for a pronounced Q-H co-contraction strategy in individuals 3–12 years following a previous knee injury. Despite rehabilitation and knee surgery, individuals who have sustained a knee injury, such as an ACL rupture, may suffer from persistent quadriceps muscle inhibition, knee joint instability, and deficient hamstrings reflex arcs (Ingersoll, Grindstaff, Pietrosimone, & Hart, 2008). It was hypothesized that a strategy of the CNS to compensate for these consequences of a knee injury is to increase a shared, cortical drive to the quadricep and hamstring muscles and facilitate their antagonistic co-contraction with the goal to improve joint stability. This would likely result in increased gamma-band intermuscular coherence between these muscles. The present findings, however, suggest that a more pronounced Q-H co-contraction was not generally present in all participants with a previous knee injury. The significant 'injury group × sex' interaction effect on VL-BF gamma-band coherence suggests that a previous knee injury may affect Q-H co-contraction strategies differently in males and females. Specifically, compared to uninjured controls, previously injured males showed reduced and previously injured females showed slightly increased VL-BF gamma-band coherence. In post-hoc comparisons, these trends did not reach statistical significance and should thus be interpreted with caution. Nevertheless, the exploratory analysis of side-to-side differences supported the finding that a previous knee injury in males is associated with a reduction in VL-BF gamma-band coherence. For females, side-to-side differences did not indicate a difference between the injured and uninjured leg.

These findings disagree with previous studies reporting a persistent, pronounced Q-H co-contraction strategy in a mixed group of males and females during stair ambulation (Hall et al., 2015) and in females during drop-landing tasks (Ortiz et al., 2008; Tsai et al., 2012). Possible reasons for the disagreement may include (1) that the large-between subject variability in coherence outcomes observed for females reduced the sensitivity to observe a similar significant effect of knee injury history, and/or (2) that more strenuous tasks such as drop-landings may aggravate the need for previously injured individuals to use a stronger Q-H co-contraction strategy (Ingersoll et al., 2008). Regardless, it is questionable whether a comparison of the Q-H intermuscular coherence outcomes in this study to earlier findings is appropriate. All of the above studies used a Q-H muscle co-contraction index, which assesses the magnitude of co-contraction based on a ratio between the sEMG amplitudes of the quadricep and hamstring muscles (Rudolph et al., 2001). This ratio, however, could increase simply due to an increase in hamstring EMG intensity and a constant quadricep EMG intensity. Therefore, an increase in the Q-H muscle co-contraction index in individuals with a previous knee injury may not necessarily represent a different coordination of motor unit activity between these muscles but could just reflect a stronger neural drive to the hamstring muscle as often observed following ACL injuries (Ingersoll et al., 2008).

In addition to the observed interaction between injury group and sex, both VL-BF and VM-MH gamma-band coherence were generally reduced in males compared to females. These findings corroborate previous SLS analyses, that reported sex-specific effects of a previous ACL injury on knee and hip kinematics (Yamazaki et al., 2010) as well as systematic differences in thigh muscle activation between males and females (Zeller et al., 2003). One possible interpretation of the present findings is based on the observation that during single-leg tasks, females tend to rely more on muscles surrounding the knee to control the frontal and transverse plane alignment of the lower extremity. In contrast, males may utilize a neuromuscular strategy focused on the hip musculature, which seems to be more effective in maintaining hip and knee alignment (Zeller et al., 2003; Zazulak et al., 2005; Yamazaki et al., 2010). Therefore, it may be more common for females to activate a motor program that couples the quadricep and hamstring motor unit activity via shared neural inputs from the corticospinal tract, which could explain the observed increased Q-H intermuscular coherence in the gamma-band. For male individuals, a pronounced co-contraction between quadriceps and hamstring muscles may have not been as important due to the effective use of hip muscles such as gluteus maximus for maintaining lower extremity alignment (Zazulak et al., 2005). The further reduction of VL-BF intermuscular coherence in the previously injured leg of male participants may represent a further shift of muscular control away from the knee to the hip or ankle joint as previously demonstrated in ACL-injured individuals during walking and running (Rudolph et al., 2001; Hurd & Snyder-Mackler, 2007). Since this is the first study to compare intermuscular coherence outcomes between males and females and following a knee injury, however, the neurophysiological origin of observed differences remains speculative and requires further investigation.

Due to the lack of association between coherence outcomes and knee pain and symptoms, this study was not able to discern whether the reduced VL-BF gamma-band coherence in injured males may represent a beneficial or maladaptive neuromuscular strategy. On the one hand, a low degree of Q-H motor unit coupling may facilitate more selective motor responses of the individual quadricep and hamstring muscles and thus a better ability to react to external perturbation (Chmielewski et al., 2005; Mohr et al., 2015). On the other hand, simulation experiments have suggested that low intermuscular coherence between two co-contracting muscles is associated with out-of-phase fluctuations of the corresponding muscle forces (Santello & Fuglevand, 2004). For the knee joint it may thus be speculated, that a lower Q-H intermuscular coherence observed in injured males may result in more out-of-phase fluctuations of quadricep and hamstring muscle forces. This poor coordination of quadriceps and hamstring muscles forces may lead to relative movements of the tibia with respect to the femur (Li et al., 1999) and cause the articular cartilage to experience abnormal shear forces (Benedetti et al., 1999), a possible risk factor for knee PTOA (Chaudhari, Briant, Bevill, Koo, & Andriacchi, 2008). The effect of Q-H intermuscular coherence on the resultant forces of the knee joint, however, is virtually unknown. Since the intermuscular coherence analyzes the correlation between the phase of two raw EMG signals, the coherence value may be independent of the EMG signal amplitudes and thus the gross muscle force profiles. For now, the authors suggest that the intermuscular coherence should be understood as a marker for the organization of neural input between different muscles rather than a marker of joint force. Future studies aimed at exploring the clinical significance of Q-H intermuscular coherence should 1) implement simulations to provide insight into the relationship between Q-H motor unit coupling and knee mechanics, and 2) evaluate individuals with more acute knee injuries and thus more extreme knee symptoms and pain.

4.3. Strengths and limitations

A limitation of this study is the large variability in Q-H intermuscular coherence outcomes that remains unexplained by the investigated variables, particularly in female individuals (see Fig. 4). From a methodological perspective, there are three main factors that may influence EMG-EMG coherence spectra: Data acquisition, signal processing, and cross-talk. Cross-talk between neighbouring electrodes manifests in significant bands of coherent activity that span across the entire frequency range of the EMG spectrum (Grosse et al., 2002). However, for each measured leg, there were frequencies where low or non-significant coherences were detected (see Fig. 3), thus indicating, that there was no substantial cross-talk between the investigated Q-H muscle pairs. In contrast, due to the small distance of about 2–3 cm between the two sEMG electrodes on the hamstring muscles, it is possible that the biceps femoris EMG signal included a cross-talk component from the medial hamstrings and vice versa. This may have reduced our ability to obtain fully independent medial and lateral Q-H coherence spectra. However, in a recent study, we simulated the influence of 10% of cross-talk between the vastii muscles on their intermuscular coherence and observed a negligible effect (Mohr et al., 2018). Therefore, cross-talk between the hamstring muscles may have been present but likely had a minimal effect on this study's conclusion.

Other methodological considerations related to data acquisition and signal processing techniques and their effects on intermuscular coherence outcomes have been the topic of many recent investigations. These considerations include the effects of EMG electrode configuration on the intermuscular coherence spectrum as well as sex-specific architecture and region-specific activation of the thigh muscles (Keenan et al., 2012; Gallina, Blouin, Ivanova, & Garland, 2017; Gallina et al., 2018; Mohr et al., 2018). These are potential methodological factors that could explain the large variability in coherence outcomes but were not investigated in this study and have lowered our sensitivity to support or reject the hypothesized association between Q-H intermuscular coherence and knee injury history. Due to the novelty of this research question, future studies should be aimed at replicating the present results while further minimizing methodological influencing factors of sEMG on intermuscular coherence, potentially by using more sophisticated high-density EMG grid technology.

From a study design perspective and based on a recent review (Shanbehzadeh, Bandpei, & Ehsani, 2017), the present study is among the largest investigations of knee injury effects on quadriceps and hamstrings muscle activity. In addition to previous studies, this study also included a bilateral analysis of knee muscle activity to determine both group and side-to-side differences in muscle activity related to a previous knee injury and thus provides a full picture of knee injury effects on Q-H intermuscular coherence. The sample size of $n > 60$ enabled a sex-specific comparison of knee muscle activity between injured and uninjured legs, which is a strength of this study given the observed differences in neuromuscular control between males and females. However, the uneven distribution of males and females in this study (~70% female) resulted in a low number of available male subjects and reduced our statistical power. Therefore, the observed reduction in VL-BF coherence in previously injured males was not statistically significant and has to be confirmed by future studies. Such studies should aim to further increase the sample size of similar analyses to improve statistical power and enable the analysis of additional confounding and effect modifying variables such as injury type, time since injury, and type of sports (Whittaker, Toomey, Nettel-Aguirre, et al., 2018a). Specifically, the inclusion of multiple knee injury types may have been a source of variability, masking systematic injury effects on muscle activation strategies that are only present for some but not all injury types (e.g. ACL vs. meniscal injuries). Further, the skill level and type of skill/sport (e.g. weightlifters vs. musicians) have been shown to influence intermuscular coherence estimates and may provide further explanations of this study's findings, e.g. the large variability in gamma-band coherence in females or the reduced coherence seen in males (Semmler, Sale, Meyer, & Nordstrom, 2004; Geertsen et al., 2013). Finally, the findings of this study may not be generalizable to older, more sedentary post-injury populations. Due to the high percentage of individuals who return to sport and frequent physical participant after a knee injury in this young population (Toomey et al., 2017), 'normal' neuromuscular control may be recovered more quickly.

5. Conclusion

This study investigated the EMG-EMG intermuscular coherence between medial and lateral Q-H muscle pairs during a SLS to investigate whether an increase in Q-H co-contraction persists as a joint stabilization strategy in individuals who sustained an intra-articular knee injury 3–12 years ago. A Q-H co-contraction strategy represented by higher intermuscular coherence in the 30–60 Hz frequency range was more pronounced in female compared to male individuals. This finding suggests that compared to males, females may utilize a different neuromuscular control strategy during the SLS, that relies more heavily on coupled activity between muscles surrounding the knee. This study did not provide evidence for a pronounced Q-H muscle co-contraction strategy as assessed by an intermuscular coherence analysis more than three years following a knee injury. In contrast, male participants showed slightly reduced intermuscular coherence between vastus lateralis and biceps femoris in the injured leg. The clinical relevance of this observation with respect to knee joint stability and post-traumatic knee osteoarthritis should be the focus of subsequent studies.

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Competing interest statement

All other authors certify that they have no affiliations with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in the article. The sponsors had no involvement with respect to design, collection or data, analyses, interpretation writing or submission. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

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