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Elevated corticospinal excitability in patellar tendinopathy compared with other anterior knee pain or no pain

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Anterior knee pain (AKP) is a frequent clinical presentation in jumping athletes and may be aggravated by sustained sitting, stair use, and loading of the quadriceps. Corticospinal activation of the quadriceps in athletes with AKP has not yet been investigated, but is important in guiding efficacious treatment. This cross-sectional study assessed corticospinal excitability (CSE) of the quadriceps in jumping athletes using transcranial magnetic stimulation (TMS). Groups consisted of Control (no knee pain); patellar tendinopathy (PT) [localized inferior pole pain on single-leg decline squat (SLDS)]; and other AKP (nonlocalized pain around the patella). SLDS (numerical score of pain 0–10), Victorian Institute of Sport Assessment Patellar tendon (VISA-P), maximal voluntary isometric contraction (MVIC), active motor threshold (AMT), CSE, and M_{max} were tested. Twenty nine athletes participated; control $n = 8$, PT $n = 11$, AKP $n = 10$. There were no group differences in age ($P = 0.23$), body mass index ($P = 0.16$), MVIC ($P = 0.38$) or weekly activity ($P = 0.22$). PT had elevated CSE compared with controls and other AKP ($P < 0.001$), but no differences were detected between AKP and controls ($P = 0.47$). CSE appears to be greater in PT than controls and other AKP. An improved understanding of the corticospinal responses in different sources of knee pain may direct better treatment approaches.

It can be difficult for the clinician to establish and identify the key nociceptive contribution to anterior knee pain (AKP) as many structures contain nociceptors. The most commonly involved structures in nontraumatic presentations of knee pain are thought to be the patellofemoral joint (PFJ) and patellar tendon (Baquie & Brukner, 1997; Cook et al., 2000; Culvenor et al., 2011; Wood et al., 2011); however, the contribution of the fat pad to nociception (Culvenor et al., 2011; Cowan et al., 2015) and incidence of other diagnoses such as plica are unknown. Anterior knee pain can have similarities in clinical presentation including wasting of the quadriceps (Young et al., 1982; Ferretti et al., 1985; Crossley et al., 2007; Hart et al., 2012), altered muscle function (Crossley et al., 2007; Cowan et al., 2009; Rathleff et al., 2014), and pain with activity is often a hallmark feature (e.g., Kountouris & Cook, 2007; Witvrouw et al., 2014; Papadopoulos et al., 2015) but it is not known if clinically similar conditions have comparable corticospinal control of the quadriceps. Understanding how the corticospinal pathway modulates muscle activation across conditions may provide new and important information that will enable the development of targeted and effective guidelines for rehabilitation.

Anterior knee pain may be aggravated by squatting, jumping and landing and change of direction activities (e.g., Kountouris & Cook, 2007; Papadopoulos et al., 2015) and frequently has an insidious onset that may be due to overload, where clinicians may find it difficult to pinpoint the cumulative or relative overload. There are no consistent findings on imaging to confirm involvement of particular tissue in the clinical presentation, with tendon or PFJ pathology present on imaging in asymptomatic individuals (Cook et al., 2001a; Witvrouw et al., 2005; Papadopoulos et al., 2015). Palpation is of limited clinical utility as tendon palpation may induce pain in athletes for whom PT is not the cause of their AKP (Cook et al., 2001a). Patellar tendinopathy pain can be provoked on the single-leg decline squat test (Purdam et al., 2004) but is likely to be painful for other types of AKP, thus it is not diagnostic but a pain provocation test with diagnosis relying on clinician judgment.

While there are clinical similarities between different presentations of AKP, there are also some differences including pain behaviors and specific aggravating factors. PT at the proximal insertion is not common in running athletes, presumably because patellar tendon load is low during running, (Scott & Winter, 1990), yet

other AKP can be very painful during running (Besier et al., 2009). PT does not result in global joint swelling, whereas other AKP can be associated with joint swelling (Malek & Mangine, 1981). PT is associated with a warm-up phenomenon in which pain reduces during activity, but is painful the next day (Kountouris & Cook, 2007; Rudavsky & Cook, 2014), whereas clinically people with other AKP often report increasing pain during activity. While the term "jumpers knee" is used interchangeably with PT, athletes involved in jumping sports also spend a significant amount of time in knee flexion (i.e., volleyball), resulting in retropatellar compression (Wallace et al., 2002). Similarly, these athletes may also frequently land on their knees irritating other anterior knee structures.

Of the common AKP conditions, PT has two distinguishing clinical features that assist with diagnosis: (a) localized, nonradiating pain; and (b) dose-dependent load-related pain (Ferretti et al., 1990; Kountouris & Cook, 2007). All other presentations may be clinically grouped as *other* AKP because of the clinical difficulty in ascertaining the exact nociceptive structure (e.g., PFJ including chondromalacia patella, intra-articular PFJ chondropathy, fat pad, plica, etc.). The similarities in nontraumatic AKP presentations make it vital to understand if the corticospinal control over the associated quadriceps muscle is differentially modulated in PT compared with other AKP as this may influence rehabilitation.

Muscle and therefore tendon loading is driven by the corticospinal control of the muscle. Several musculoskeletal conditions have been shown to result in persistent changes in the control of the affected area and can alter the topography of the primary motor cortex (M1) (Tsao et al., 2008; Schwenkreis et al., 2010; Nijs et al., 2012). These changes may be positive and protective, or may be negative and even contribute to symptoms or resistance to rehabilitation. Nociceptive input from local tissue may result in differences in corticospinal control that can be addressed for optimal rehabilitation.

A review by Heales et al. (2014) reported bilateral sensory and motor deficits in people with unilateral tendon pain, providing rationale that corticospinal deficits might exist. Of the 20 papers included in that systematic review, 18 investigated upper limb conditions (17 lateral elbow tendinopathy and one rotator cuff), indicating a paucity of literature investigating central nervous system involvement in lower limb tendinopathies. Furthermore, it has yet to be determined if different clinical conditions at the same anatomical location impacts the corticospinal pathways.

Current approaches for managing AKP are likely to be improved with a better understanding of the contributors to pain and dysfunction. While these pain conditions have local nociceptive drivers, treatment directed solely at these local contributors have had variable results in, for example, PFJ (Crossley et al., 2001) and PT (Larsson et al., 2012), with the most effective rehabilitation strategies focusing on exercise-based therapy (Woodley et al., 2007; Crossley et al., 2015). Exercise therapy is usually directed toward the quadriceps and an improved understanding of the corticospinal control of the quadriceps may improve the understanding of the similarities or differences in various AKP presentations and treatment approaches. Therefore, the aim of this study was to determine the corticospinal excitability of the quadriceps in people with PT, in people with undefined AKP and in healthy controls. Our primary hypothesis was that corticospinal excitability would be different between those with knee pain (either PT or those with undefined anterior knee pain) and healthy controls.

Method

Active, healthy men and women aged over 18 years were recruited to participate in this cross-sectional study. Participants were recruited from sub-elite volleyball and basketball competitions and by word of mouth. Flyers were placed at venues and researchers also attended games and trainings to advise players and coaches about the study. Athletes who participated in jumping activities three times per week (e.g., two training sessions and one game) were invited to participate. Standard transcranial magnetic stimulation (TMS) exclusion criteria were applied that includes past history of epilepsy or seizure activity, heat convulsion, head injury or history of epilepsy, and seizure in first-degree relatives, psychiatric, or neurological illnesses (including brain injury or cranial surgery), metal implants in the head (outside the mouth) any metallic particles in the eye, implanted electrical biomedical device (defibrillator, acoustic device), pregnancy, use of medications that affect arousal level, excessive use of caffeine or energy drinks, sleep deprivation, and the inability to speak, read, and write English (Chipchase et al., 2012; Rossini et al., 2015), and anyone with lower limb injury (other than knee pain) within the past 12 months were also excluded. People with traumatic knee injury were excluded by telephone screening potential participants. This study was approved by university ethics committees, conformed to the declaration of Helsinki, and all athletes provided written informed consent.

Electromyography and transcranial magnetic stimulation

The area of electrode placement was shaved, abraded and cleaned with 70% isopropyl alcohol. Bipolar gel Ag-AgCl electrodes were placed over the rectus femoris muscle and the grounding electrode was placed over the patella and subsequently used as a common reference for all electrodes. sEMG signals were amplified (1000×), bandpass filtered (high pass at 13 Hz, low pass at 1000 Hz), digitized online at 2 kHz for 500 ms, recorded and analyzed using PowerLab 4/35 (ADInstruments, Bella Vista, Australia).

Familiarization sessions with TMS and the maximal voluntary isometric contraction (MVIC) torque were conducted prior to the experimental testing session. The MVIC torque for the quadriceps on the tested side was recorded in N·m using an isokinetic dynamometer (Biodex system 4 Pro, 1 Biodex Medical 2 Systems, Shirley, New York, USA). The participant was seated in 90 degrees hip flexion and quadriceps were tested at 60 degrees knee extension with three efforts completed with identical instructions, vocal encouragement, and setup for each trial, with 2-min rest between efforts. MVIC torque was defined as the maximum torque recorded during these three efforts. This was also used to establish the 10%MVIC for TMS testing.

Measures of CSE were obtained using single-pulse TMS. The accuracy of TMS was optimized by aligning the coil with reference markers on a tight fitting cap worn by participants and marked with a latitude-longitude matrix, positioned with reference to the nasion-inion and interaural lines (Wilson et al., 1993).

Single-pulse stimulus-response (SR) curves were obtained during low-level isometric contractions of the quadriceps muscle group. Low-level contractions were performed by maintaining the knee joint at 60° flexion, while performing a 10% MVIC, which equated to 10 ± 2% of root mean square EMG (rmsEMG) during MVIC. The 10% isometric contraction was reported to be a pain-free task for all participants. Consistent muscle activation was confirmed by recording pre-stimulus rmsEMG throughout the session (Goodwill et al., 2012). For a single SR curve, 10 stimuli were delivered at each intensity from 90% of the participant's active motor threshold (AMT) until plateau (in 5% increments to achieve a SR curve). The AMT is the minimum threshold where a motor response (recorded by the surface electrodes on the muscle) of set amplitude can be evoked and has well established criteria (Carroll et al., 2001). The stimuli were delivered using a ramped protocol, meaning the stimulus intensity was progressively increased (Pearce et al., 2013). The amplitude of the motor response, which is termed the motor evoked potential (MEP), slope and V50 of the SR curve represent corticospinal excitability (Carroll et al., 2001) and the top represents MEP maximum.

TMS was delivered using a Magstim 200^2 stimulator connected via a BiStim unit (Magstim Co, Dyfed, UK) and a 110-mm concave double-cone coil (maximum output of 1.4 T). The motor hotspot is the location of the motor cortex that delivers an optimum stimulus for the rectus femoris muscle (with posterior-to-anterior induced current flow in the M1) and this was determined prior to the curve.

Maximal compound muscle action potential

Direct muscle responses were obtained from the rectus femoris muscle by supramaximal electrical stimulation (pulse width 2000 μs; DS7A, Digitimer, UK) of the femoral nerve under resting conditions. The site of stimulation that produced the largest M-wave was located by positioning the bipolar electrodes in the femoral triangle. An increase in current strength was applied to the femoral nerve until there was no further increase observed in the amplitude of the sEMG response (M_{MAX}; Goodwill et al., 2012; Weier et al., 2012). To ensure maximal responses, the current was increased an additional 20% and the average M_{MAX} was obtained from five stimuli, with a period of 6–9 s separating each stimulus.

Grouping by knee pain status

Participants were separated into one of three clinical groups by the same experienced sports physiotherapist (but a different researcher to the one conducting TMS testing) on clinical presentation. Patellar tendinopathy was defined as pain localized to the inferior pole of the patella reported during jumping and landing activities and during testing on the single-leg decline squat (SLDS). Participants provided a numerical pain rating score for the decline squat on an 11-point numerical rating scale (NRS), anchored at left with "0, no pain" and at right with "10, worst possible pain." Athletes with bilateral symptoms were asked to nominate their most painful knee on the SLDS and this was the testing leg (measures of quadriceps torque were taken from this side only and the contralateral hemisphere was stimulated with TMS). The clinical diagnosis of PT was supported by the presence of characteristic features on ultrasound imaging (e.g., hypoechoic area). Imaging abnormality in isolation without the clinical presentation of PT did not constitute a diagnosis of PT as jumping athletes can have tendon imaging abnormality without tendon pain (Cook et al., 2001a). Diagnosis of other AKP was made by the same physiotherapist based upon clinical presentation – radiating/nonlocalized AKP during jumping and landing activities and during testing on the SLDS (Fig. 1). This term was chosen because the specific structure is difficult to ascertain clinically when the pain is vague and no definitive clinical or imaging test exists. The SLDS was used for all participants as it elicits AKP in many conditions (however, pain only remains localized in PT). Control participants had neither pain on testing, nor tendon abnormality on ultrasound.

Blinding

The TMS tester remained blinded to knee pain status throughout testing. Grouping into control, PT and other AKP was conducted by a different researcher to the one that performed the TMS testing. All data were analyzed blind to knee pain status.

Demographics

Athletes were asked to complete a VISA-P, which is a questionnaire about patellar tendon pain and function that is scored between 0 and 100 with 100 being maximal pain-free function (Visentini et al., 1998). Participant age and body mass index (BMI) were also recorded.

Data analyses

Each stimulus was automatically flagged with a cursor. The peak-to-peak amplitude (top and bottom) of MEPs evoked in the period 10–50 ms after stimulation was analyzed using LabChart 8 software (ADInstruments, Bella Vista, NSW, Australia). Peak-to-peak values (μV) were averaged, normalized to M_{max} and multiplied by 100. To construct SR curves, stimulus intensity was plotted against MEP amplitude, then fitted with a nonlinear Boltzmann equation

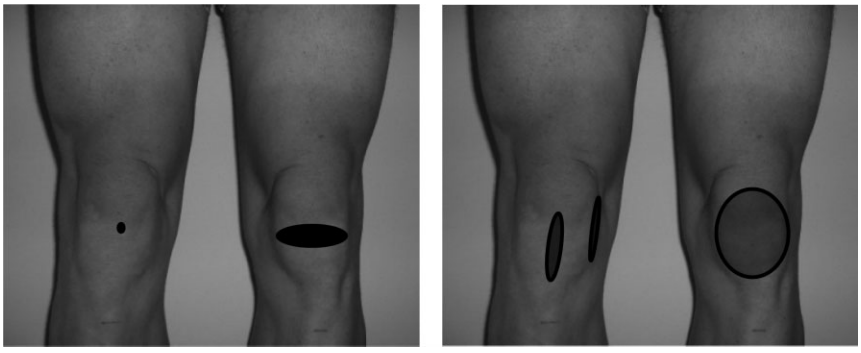

Fig. 1. Difference in the clinical presentations of patellar tendinopathy (far left) and other variations of anterior knee pain.

Table 1. Participant characteristics

	Controls	PT	AKP
Number	8 (n = 7 men, 1 woman)	11 (n = 10 men, 1 woman)	10 (n = 6 men, 4 women)
Age (median + range)	26 years (18–37)	26 years (18–37)	26.5 years (18–37)
BMI (median + range)	24.44 (21.84–27.68)	25.49 (22.95–34.91)	25.02 (19.71–29.48)
Length of time of symptoms (median months + range)	N/A	90 (5–192)	90 (12–264)
Activity details	Volleyball n = 5 Martial arts n = 1 Basketball n = 2	Volleyball n = 7 Australian football n = 1 Basketball n = 3	Volleyball n = 7 Australian football n = 1 Basketball n = 2
Number of activity minutes per week (in jumping related sport) (mean ± SD)	315 ± 26.59	312.73 ± 33.57	316.00 ± 24.70
VISA-P (mean ± SD)	97.5 ± 2.66	56 ± 18.18*	64 ± 18.85*
Pain during SLDS (mean ± SD)	0	5.36 ± 2.01*	5 ± 2.40*
MVIC torque (Nm) (median + range)	172.50 (134–284)	194.82 (113–294)	160.50 (115–303)

*Denotes significantly different from control group, no difference between PT and AKP $P < 0.05$.

AKP, anterior knee pain; BMI, body mass index; MVIC, maximal voluntary isometric contraction torque; PT, patellar tendinopathy; SD, standard deviation; SLDS, single-leg decline squat; VISA-P, Victorian Institute of Sport Assessment Patellar tendon.

Table 2. Corticospinal responses

	AMT (mean ± SD)	Slope (AU) (mean ± SD)	V50 (AU) (median + range)	Top (AU) (mean ± SD)
Control	42 ± 7.90	6.02 ± 1.54	19.06 (13.35–29.87)	57.26 ± 18.56
PT	34.5 ± 5.93	2.75 ± 0.84*	17.70 (1.44–35.92)	48.39 ± 20.03
AKP	37.1 ± 5.09	6.67 ± 2.00	18.94 (6.85–39.35)	48.73 ± 14.34

*Denotes significantly different from control and AKP $P < 0.001$, $r = 0.80$.

AKP, anterior knee pain; AMT, active motor threshold; AU, arbitrary units; PT, patellar tendinopathy; SD, standard deviation.

using Prism 6 (Graphpad software Inc., San Diego, California, USA; Weier et al., 2012). The slope is given in arbitrary units. V50 represents the stimulus intensity at which the MEP amplitude is 50% of the MEP_{max} (half peak slope).

Statistical analyses

Tests of normality were applied (Shapiro–Wilk normality test). Where data were normally distributed, mean and SD was calculated and data were analyzed using a one way ANOVA and post-hoc *t*-test. Where data were not normally distributed, or failed other assumptions of parametric statistics, median and range were obtained and data were analyzed using the equivalent nonparametric test (Kruskal–Wallis or Mann–Whitney U) and post-hoc analysis (Dunn's multiple comparison test or Kolmogorov–Smirnov test). Significance was set at $\alpha = 0.05$. We did not power the study *a priori* because there were no data available that provided clear expectations of the likely differences between groups and variance of the measure, and because defining a minimally important difference with these measures of corticospinal excitability is somewhat arbitrary. We planned instead to evaluate mean and standard deviation data from the first eight participants in each group, and calculate required sample size, with an alpha of 0.05 and 80% power to detect a medium size effect, on the basis of those data.

Results

Thirty-two athletes were recruited and three athletes without anterior knee pain were found to have patellar tendon abnormality on ultrasound imaging and were excluded from the control group. Therefore, twenty nine jumping athletes were included: eight controls, 11 participants with PT, and 10 with other AKP (Table 1). Because we found effect sizes greater than two, the required sample size was in fact less than our sample, so we stopped recruiting and proceeded to analysis.

The PT group included three athletes with bilateral symptoms. There were no differences between the groups for age ($p = 0.23$), BMI ($p = 0.16$), MVIC ($p = 0.38$) or duration of symptoms between the other AKP and PT groups ($p = 0.81$). The mean VISA-P score in the control group was significantly higher than the PT and other AKP group ($p < 0.001$) but there were no differences between PT and AKP groups ($p = 0.40$). The NRS of pain during SLDS scores differed between control group and the PT and AKP pain groups ($p < 0.001$) but there were no differences between PT and AKP ($p = 0.71$).

There were no differences between groups in active motor threshold ($p = 0.06$, Cohen's d 1.07, $r = 0.47$), V50 ($p = 0.58$) or the top of the curve ($p = 0.51$; Table 2). The PT group demonstrated significantly higher CSE (a steeper slope of the SR curve) than the other groups did (Table 2; $p < 0.001$; Fig. 2); however, there were no differences between groups for V50 ($p = 0.58$) of the top of the curve ($p = 0.51$). To ensure

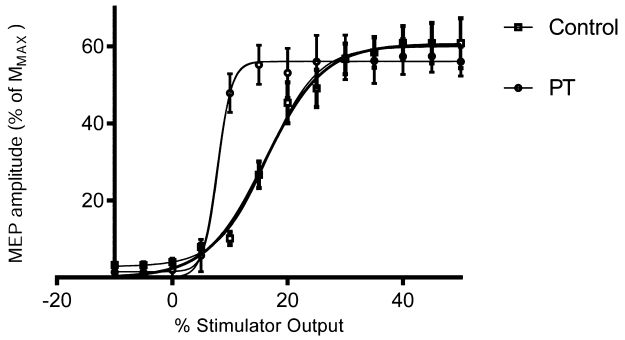

Fig. 2. Stimulus response curve data (group mean ± SEM) for the control group and the patellar tendinopathy group.

the difference between PT and the other groups did not relate to the differential distribution of men and women within the groups, a sensitivity analysis was undertaken – we repeated the analysis using only the male data. The result was unaffected.

Discussion

This study demonstrated for the first time that jumping athletes with PT experienced elevated CSE for the rectus femoris muscle compared with healthy activity matched controls and people with other AKP. This is a novel finding that may help to inform rehabilitative practices for PT, with a focus on restoring normal corticospinal control to the knee extensors.

Patellar tendinopathy appears to evoke excitatory abnormalities, evidenced by a sharp rise in the slope and immediate plateau of the SR, rather than a traditional and expected sigmoid curve (Mathias et al., 2014) observed in controls and other AKP. The slope reflects the physiological strength of corticospinal projections onto the motorneuron pool, membrane excitability, and corticospinal cell recruitment (Smith et al., 2011). Therefore, the increase in peak slope observed for the rectus femoris of people with PT indicate hyper excitability and an altered ability to modulate corticospinal control of the rectus femoris muscle. The reasons for these physiological phenomena may be protective to reduce activation or tendon load; however the lack of difference in force producing capabilities (MVIC torque) between groups does not support this explanation. Differences in MVIC torque were not observed at 60 degrees, however deficits may exist in other ranges not tested. Interestingly, the lack of strength deficit observed supports previous research where those with PT are better jumpers, termed the jumpers knee paradox (Visnes et al., 2013).

The lack of difference between groups in V50 or top indicates that there are other factors relating to PT that contribute to the different corticospinal responses. Other factors may include stage of pathology, potential changes to control of antagonist muscles, and inhibitory mechanisms. Inhibitory mechanisms (not measured in this study) also influence the slope of the SR curve because of synaptic inputs altering descending drive to the muscle. The use of single-pulse TMS provides a response that is reflective of the net excitatory drive to the muscle, but does not provide any information as to the site of contributing synaptic activities. Therefore, the slope of the SR curve is influenced by the balance between excitatory and inhibitory mechanisms so despite large forces still possible (evidenced by MVIC torque and no difference in the top), the ability to recruit the quadriceps in a smooth graded pattern may be impossible resulting in an "on or off" pattern though the net drive to the muscle is maintained. To put in a clinical context, people with PT may have difficulty grading activation of their rectus femoris muscle in functional tasks and may overshoot or undershoot recruitment compared with task demands.

It is difficult to explain the lack of differences in the CSE with pain from varied structures of AKP. Activity has been shown to influence the motor cortex (Nudo, 2003) thus was considered important as an inclusion criterion. However, activity does not appear to sufficiently explain the difference in CSE in people with PT as participants were all involved in jumping activities three times per week that did not significantly differ between groups. Clearly, enhanced CSE is not simply a consequence of having pain because the AKP group had pain of comparable intensity and duration, nor is it related to gender in this sample. It is possible however, that the differential results are due to the differing clinical presentations and reflect the more precise functional relevance of the patellar tendon to rectus femoris activation. A change in corticospinal drive reflects the predicted need for protection as hypothesized on the basis of modern models of pain and motor control (Hodges & Moseley, 2003; Moseley et al., 2003). Moreover, the testing procedure did not provoke pain, but did provoke differential corticospinal effects that would also be predicted on the basis of widespread central nervous system adaptations that are considered part of chronic pain states excitability and inhibitory mechanisms (see Wand et al., 2011; Moseley, 2012 for reviews). The current finding suggests that real-time noxious input does not mediate the effect as testing was pain-free. This study showed clear abnormalities in corticospinal function in a condition that is characterized by strictly load-dependent and localized pain, both of which are inconsistent with other chronic pain states (see Rio et al., 2014 for review).

Another consideration is that corticospinal abnormalities in people with non-PT anterior knee pain affect other quadriceps muscles such as the vastis medialis oblique (VMO). One study has reported changes in corticospinal control in the quadriceps in people with PFP (On et al., 2004). That study recorded from the VMO and vastus lateralis, rather than rectus femoris and also used the size

of MEP response as an indicator of CSE rather than a SR curve (so data were not normalized to the individuals M_{max}). Although the contrasting results of that study and ours might simply reflect different methods and analysis, it is also possible that they reflect condition-specific and nuanced alterations in cortical function, a possibility that would have potentially important implications for our understanding of knee function in both health and disease.

The active motor threshold is another representation of CSE. We did not find any differences in AMT in people with PT and controls, which contrasts with Ngomo et al.'s (2015) and Strutton et al.'s (2005) findings in rotator cuff tendinopathy and people with low back pain, respectively. However, there were differences in study design; the Ngomo et al. (2015) study compared affected and unaffected side, which, with upper limbs, would presumably involve marked use profiles because of handedness. The current study compared symptomatic PT with active, healthy age-matched controls and only collected unilateral data. It is possible, due to bilateral changes reported in tendon pathology (Docking et al., 2014), that the contralateral side may not be an ideal control. Certainly, there are other persistent pain states that are characterized by bilateral abnormalities of motor cortical excitability, even when symptoms are unilateral (Di Pietro et al., 2015). It is not known if bilateral changes in CSE exist in unilateral lower limb tendon presentations.

It is also possible that there may be differences in the corticospinal responses associated with tendinopathy depending upon the location and contextual factors around the injury. For example, the upper and lower limbs have different sensory representation and the upper limb is often involved in activities of daily living and self-care. This frequency of nociceptive input may drive long-term potentiation and be a point of difference between, for example, someone with PT who experiences pain during volleyball (a presumably enjoyable activity) in which they participate three times per week and someone with lateral epicondylalgia who experiences pain during manual labor (work they may not enjoy) and during simple daily tasks (lifting the kettle) that they perform frequently. Modern pain theories remind us of the potential of real-time and persistent modulatory effects of a wide range of variables on cortical protective function, not least pain and motor control. We recognize that though PT is predominantly an "athlete's condition," it remains vulnerable to such effects (Moseley et al., 2003).

There may be important clinical implications from these data. It is possible that aberrant neural control of the muscle may cause abnormal tendon loads and represent a disruption of their internal load sensing (Rio et al., 2014). Furthermore, these corticospinal changes associated with tendon pain may contribute to recalcitrance as quadriceps activation may indeed be irritating the tendon. As this was a cross-sectional study, it is unknown if these changes may precede the onset of tendon pain. Examining corticospinal changes in people with tendon pathology and no pain may contribute to our understanding of the "chicken or the egg" in pathology and pain. Whether the abnormalities we have discovered reflect an enhanced protective strategy or a risk for further pain or pathology is unknown. Rio et al. (2015) demonstrated that corticospinal measures (cortical inhibition) can be modified with a single bout of externally paced isometric exercise. Of note, externally paced strength training (using a metronome to time the contraction) has been shown to be capable of modifying CSE in healthy people and has been investigated in a randomized clinical trial in PT (Rio et al., submitted manuscript). Further studies should aim to determine if long-term changes to CSE and inhibition can be made and whether these affect clinical outcomes.

There are limitations of this study. We chose the rectus femoris muscle because it is the only one of the quadriceps muscle group where the fibers continue to become the patellar tendon (the others blend with the retinaculum), and the concept that there is preferential wasting of certain quadriceps muscles is unsupported in PFJ pain (Giles et al., 2013) and there are no data for other AKP (such as fat pad) and quadriceps wasting. It is likely that a range of knee conditions was included in the AKP pain sample and future larger studies should aim to subgroup these. This may be difficult because of the lack of agreed criterion for PFJ pain or fat pad involvement in contrast with PT; however, it may be an important progression in the management of AKP. This study utilized clinical assessment and may be strengthened by further imaging; however, the link between imaging changes in many musculo-skeletal conditions and pain remains somewhat tenuous (Rio et al., 2014). Jumping activity three times per week (e.g. two training sessions and one game in the case of basketball, volleyball, and football and three training sessions in the case of martial arts) was part of the inclusion criteria. The study would be strengthened with a more accurate quantification of jumping (e.g., number of jumps per week), though this is difficult in large studies. A physical activity questionnaire could have been used to capture overall activity and is often broken down into high, moderate, and low level; thus, it may not have contributed additional information about the "high" level (jumping). Future studies should examine other muscles including antagonists and other tendinopathies and compare with musculo-skeletal conditions that cause similar pain at the same anatomical location. We set a milestone in place *a priori* to evaluate means and variance of the key measure, the slope of the stimulus response curve. On doing so, the data clearly showed that our sample was already well powered to detect an effect. Nonetheless, it is well recognized that small samples can lead to erroneous false positives as

well as false negatives and as such, replication of this finding on a larger cohort would appear warranted. We did not match groups for gender. Although there is good evidence that CSE does not vary much between men and women it remains possible that some of the difference between control group and PT group might reflect differential distribution between groups. However, this could not impact on the difference between PT and other AKP groups, as group characteristics in terms of number of men were similar.

Perspectives

We contend that this study reinforces that it is important to look outside the tendon to improve our understanding of tendon pain and patient outcomes. The finding that CSE was abnormal in people with PT but not other AKP, may lead us to develop alternative approaches to management and prevention of PT. However, future larger studies should aim to subgroup AKP, though it does not appear possible at this time. It is possible that rehabilitation may need to utilize principles of neuroplasticity to address corticospinal response (as well as tendon-based concepts) to try to improve outcomes. Future studies should determine if these responses precede pain, are reversible with successful rehabilitation or may be a predictor of recalcitrance.

Key words: Corticospinal excitability, patellar tendinopathy, knee pain, quadriceps.

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