Between-muscle differences in the adaptation to experimental pain

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1The University of Queensland, NHMRC Centre of Clinical Research Excellence in Spinal Pain, Injury and Health, School of Health and Rehabilitation Sciences, Brisbane, Australia; 2University of Nantes, Laboratory “Motricité, Interactions, Performance” (EA 4334), UFR STAPS, F-44000, Nantes, France; and 3The University of Queensland, School of Biomedical Sciences, Brisbane, Australia

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Hug F, Hodges PW, van den Hoorn W, Tucker K. Between-muscle differences in the adaptation to experimental pain. J Appl Physiol 117: 1132–1140, 2014. First published September 11, 2014; doi:10.1152/japplphysiol.00561.2014.—This study aimed to determine whether muscle stress (force per unit area) can be redistributed between individual heads of the quadriceps muscle when pain is induced into one of these heads. Elastography was used to measure muscle shear elastic modulus (an index of muscle stress). Electromyography (EMG) was recorded from vastus lateralis (VL), vastus medialis (VM), and rectus femoris (RF). In experiment I (n = 20), participants matched a knee extension force, and thus any reduction of stress within the painful muscle would require compensation by other muscles. In experiment II (n = 13), participants matched VL EMG amplitude and were free to vary external force such that intramuscle compensation would be unnecessary to maintain the experimental task. In experiments I and II, pain was induced by injection of hypertonic saline into VM or RF. Experiment III aimed to establish whether voluntary drive to the individual muscles could be controlled independently. Participants (n = 13) were asked to voluntarily reduce activation of VM or RF while maintaining knee extension force. During VM pain, there was no change in shear elastic modulus (experiments I and II) or EMG amplitude of VM (experiment II). In contrast, RF pain was associated with a reduction in RF elastic modulus (experiments I and II): −8 to −17% and EMG amplitude (experiment II). Participants could voluntarily reduce EMG amplitude of RF (−26%; P = 0.003) but not VM (experiment III). These results suggest that muscle differences in adaptation to pain might be explained by their function (monoarticular vs. biarticular) and/or the neurophysiological constraints associated to their activation.

Supersonic shear imaging

THE EFFECTS of experimentally induced pain on the motor system have been extensively studied during single-joint tasks. The observed adaptations (e.g., changes in motor unit discharge characteristics, gross muscle activity, and/or mechanical behavior) are thought to reduce stress (defined as force per unit area) within the painful region to protect from further pain and/or injury (10, 16).

Supersonic shear imaging (SSI) is an elastography technique that quantifies the shear elastic modulus (stiffness) of a localized area of tissue. This technique provides reliable measurement of muscle shear elastic modulus (15), with a strong linear relationship between shear elastic modulus and muscle stress during isometric contractions (2, 4) and passive stretching (12, 17). Therefore, SSI provides a unique opportunity to quantify if stress within muscle tissue is modified during acute pain. Taking advantage of this technique, we have previously shown no systematic reduction in stress within a painful muscle [vastus lateralis (VL) (24) or vastus medialis (VM) (11)] during isometric tasks. In these studies (11, 24) participants were instructed to match a knee extension torque before and during pain. To maintain torque a decrease in stress (i.e., force) in VL or VM (i.e., the painful muscle) would have necessitated compensation (i.e., increased stress/force) with other knee extensor muscles. Whether the central nervous system (CNS) can differentiate the activation of the individual heads of the quadriceps muscle is a matter of ongoing debate. Therefore, the absence of deloading painful tissues during pain (11, 24) may be a consequence of a limited potential to redistribute force between synergist muscles in the previous investigations.

Although there is some indirect evidence for differential activation of the quadriceps muscles during submaximal contractions (3, 13, 14), these differences are subtle (3, 13) and/or limited to compensations between the biarticular rectus femoris (RF) muscle and the vastii (14, 21). Further, the high common drive reported between VL and VM (18) leads to the assumption that a dissociation of activity between these muscles might be difficult or might only occur with high cost to the CNS. As the volume of RF represents only ~16% of the total volume of the vastii muscles (9), RF would only have the capacity to successfully counterbalance minor changes in force produced by the vastii. Together, the inability to dissociate VL and VM activation, and the limited capacity for RF to compensate for a substantial reduction in force output from the vastii, may explain why no systematic decrease in stress within VL or VM was observed when pain was induced in these muscles while maintaining isometric knee extension torque (11, 24). However, because RF is controlled more independently from the vastii than the vastii muscles are from each other (21), it is more likely that pain in RF could be associated with systematic reduction in stress in this painful muscle and compensation by the vastii. Studying pain adaptation when pain is induced into one vastii muscle or RF during an isometric leg extension may allow us to determine whether the absence of deloading painful tissues during pain (11, 24) is a consequence of the limited potential to redistribute force between some synergist muscles. Ultimately, this work will provide insight into the developing theories of pain adaptation that predict a change in muscle stress (10). In a broader motor control context, these results will provide further evidence as to whether the individual heads of the quadriceps muscle can be independently recruited. This is particularly relevant as it is generally assumed that the altered function of a single muscle can be compensated within the same muscle group.
Here we used SSI to determine whether muscle stress could be redistributed between individual heads of the quadriceps muscle when pain is induced in one of these heads. This study involved three experiments. The first (experiment I) required participants to match an isometric knee extension force at 20% of maximum voluntary contraction force (MVC), and thus any reduction of stress within the painful muscle would require compensation by other synergist muscles. This experiment aimed to determine whether stress is reduced within RF or VM during homonymous nociceptive stimulation. We hypothesized that a decrease in RF stress would be observed during nociceptive stimulation of this muscle whereas stress in VM would not be reduced when it is the painful muscle. The second experiment (experiment II) explored whether stress within RF or VM could be reduced, independently of VL, during nociceptive stimulation of these muscles. Participants matched VL EMG amplitude (rather than knee extension force). Thus they were free to vary external force such that intermuscle compensation would be unnecessary to maintain the experimental task. We hypothesized that RF muscle activity and stress would decrease during RF pain, but VM muscle activity and stress would remain unchanged during VM pain. In the third experiment (experiment III; performed without pain) we investigated whether participants could voluntarily reduce the activation of VM or RF (with EMG feedback) while maintaining the knee extension force at 20% of MVC.

MATERIALS AND METHODS

Participants

Twenty healthy volunteers (means ± SD: age 29 ± 5 yr, weight 72 ± 10 kg, height 176 ± 11 cm; 4 females) participated in experiment I. Thirteen healthy volunteers (age 27 ± 6 yr, weight 71 ± 16 kg, height 175 ± 13 cm; 5 females) participated in experiments II and III. Participants provided informed written consent. The local ethics committee approved the experiment (The University of Queensland/CPP Nantes Ouest IV), and all procedures adhered to the Declaration of Helsinki.

Measurements

Ergometer. Participants were seated on a plinth with their back and upper legs supported. Their torso was reclined by 10° from upright and their right knee (test leg) flexed to 65° from the horizontal. A standard support strap was placed around the pelvis to minimize changes in body position throughout the experimental task, and participants crossed their arms over their chest. Isometric knee extension force was measured with a six-axis force sensor (measuring range for Fx, 500 N, resolution 0.01% of measuring range, Poitiers, France). Signals were sampled at 2,000 samples/s (Power1401 Data Acquisition System, Cambridge Electronic Design, UK, or Bagnoli 16, Delsys, Natick, MA).

Shear elastic modulus measurements. An Aixplorer ultrasound scanner (version 6; Supersonic Imagine, Aix-en-Provence, France), coupled with a linear transducer array (4–15 MHz, SuperLinear 15-4, Vermon, Tours, France) was used in shear wave elastography mode (musculoskeletal preset). As originally described by Bercoff et al. (1), the technique consists of a transient and remote mechanical vibration generated by radiation force induced by a focused ultrasonic beam (i.e., “pushing beam”). Each pushing beam generates a remote vibration that results in the propagation of a transient shear wave. Then, an ultrafast ultrasound imaging sequence is performed to acquire successive raw radiofrequency signals at a very high frame rate. A one-dimensional cross correlation of successive radiofrequency signals is used to calculate the shear wave velocity \( V_s \) along the principal axis of the probe using a time-of-flight estimation. Considering a linear (1) and elastic (5) behavior, the muscle shear elastic modulus (\( \mu \)) is calculated as follows:

\[
\mu = p V_s^2
\]

where \( p \) is the density of muscle (1,000 kg/m³). Maps of the shear elastic modulus were obtained at 1 sample/s.

Using B-mode ultrasound imaging, the optimal transducer location was determined for each muscle (RF and VM) as a region with a muscle thickness of at least 1.5 cm and that avoided major hypoechoic regions related to aponeurosis and tendon. The transducer was aligned approximately in parallel with the muscle fiber direction of VM (obliquus region). Because of the complex architecture of RF, the ultrasound transducer was aligned with the shortening direction of the muscle, consistent with previous work on RF (3). Previous experiments have demonstrated that muscle architecture (i.e., fusiform vs. pennate muscle) does not influence the reliability of the estimation of changes in muscle stress using SSI (4). The optimal transducer locations were marked on the skin using a waterproof marker to guide repeated placement throughout the trials.

Surface electromyography. For experiments II and III, myoelectric activity was recorded from the right (test) leg with surface EMG electrodes on VM, VL, and RF. For each muscle, a pair of self-adhesive Ag/AgCl electrodes (Blue sensor N-00-S, Ambu, Denmark) was attached to the skin with an interelectrode distance of 20 mm (center to center) (location shown in Fig. 2). Prior to electrode application, the skin was cleaned with abrasive gel (Nuprep, D.O. Weaver) and alcohol. The ground electrode (half of a Universal Electrosurgical Pad, 3M Health Care) was placed on the skin over the tibia of the right leg. EMG data were amplified 1,000 times, band-pass filtered between 20 and 500 Hz (Neurolog, Digitimer), and sampled at 2,000 samples/s using a Power1401 Data Acquisition System with Spike2 software (Cambridge Electronic Design).

Experimental pain. For experiments I and II, pain was induced by a 0.5-ml, single-bolus injection of hypertonic saline (5% NaCl) using a 25 G × 24 mm needle, into either the distal portion of RF (PainRF) or VM (PainVM). Pain intensity was rated on an 11-point numerical rating scale (NRS; anchored with “no pain” at 0 and “maximum imaginable pain” at 10). After completion of the contractions during pain, participants drew a surface representation of the region of pain directly onto their leg, and a photograph was taken.

Protocol

Experiment I. Two maximal isometric voluntary knee extensions were performed for 3 s, separated by 90 s for recovery. The maximum force was considered the best performance (maximum voluntary contraction, MVC). The experimental task required participants to match a target force set at 20% of MVC during short (12 s) constant-force isometric contractions. This contraction intensity was chosen for two reasons. First, associated with the relatively short duration of the contractions, the moderate force level limited the potential for neuromuscular fatigue that could interfere with interpretation of the data. Second, this enabled direct comparison with a previous pain experiment that served as a basis for this series of experiments (11).

For the baseline condition, participants performed 10 × 12-s contractions with a 30-s recovery period between contractions (Fig. 1). Then, muscle pain was induced into either the distal portion of RF (PainRF) or VM (PainVM) (Fig. 2A). When pain intensity was reported as at least 2/10, another 3 × 12 s isometric knee extensions was performed. The task was stopped if pain intensity dropped below 2/10. Approximately 10 min after complete resolution of pain, the protocol (including 10 baseline and 3 pain contractions) was repeated, but with hypertonic saline injected into the second muscle (either RF or VM). The order of pain location was randomized (PainRF was the first condition for 9/20 participants).
During contractions, the ultrasound transducer was placed over the distal region of RF (for both PainRF trials and their corresponding baseline trials) or over the distal portion of VM muscle belly (for both PainVM trials and their corresponding baseline trials).

**Experiments II and III.** These experiments were performed within the same session. The MVC procedures were identical to those described for experiment I. To determine the target amplitude of VL EMG for experiment II, participants first performed $3 \times 12$ s isometric reference knee extensions (30 s recovery) at 20% of MVC. The RMS EMG of VL was calculated in real time over a 200-ms window (Spike2, Cambridge electronic) and averaged across the three isometric knee extensions. The experimental task required participants to match the RMS EMG activity recorded during the preceding reference contractions (Fig. 1). For the baseline condition, participants performed $6 \times 12$ s isometric knee extensions at the VL RMS EMG target with a 30-s recovery period between contractions. In the pain trials, muscle pain was induced as described above, into either the distal portion of RF (PainRF) or VM (PainVM) (Fig. 2B). When the participants reached a pain intensity of at least 2/10, $6 \times 12$ s isometric knee extensions were performed to an intensity that matched the VL RMS EMG target. The task was stopped if pain intensity was reported below 2/10. Approximately 10 min after complete cessation of pain, the protocol (including $6 \times 12$ s baseline and $6 \times 12$ s pain contractions) was repeated, with pain induced in the second muscle (either RF or VM). The order of pain location was randomized (PainRF was the first condition for 7/13 participants). The second series of $6 \times 12$ s contractions (no pain) was considered as both the washout of the first pain condition and the baseline of the second pain condition. A final set of $6 \times 12$ s isometric knee extensions was performed $\sim 10$ min after complete cessation of pain. This condition was considered as the washout of the second pain condition (Fig. 1). During this experiment, the ultrasound transducer was relocated for each contraction, alternatively on VM and RF (the first recorded muscle was randomized) such that the shear elastic modulus of both muscles could be assessed in each condition.

After the completion of experiment II, additional tasks were performed to test the participants’ ability to voluntarily reduce activity of the RF or VM muscles while maintaining the knee extension force at 20% of MVC (experiment III). First, participants performed $6 \times 12$ s isometric knee extensions (30 s recovery) at 20% of MVC (i.e., force feedback), and the mean RF and VM RMS EMG amplitudes were calculated. Then, participants performed two trials of $3 \times 20$-s isometric knee extensions (30 s recovery between the contractions and 3 min recovery between the 2 trials) during which they were asked to voluntarily reduce either RF (referred to as “RF trials”) or VM (referred to as “VM trials”) EMG amplitude while maintaining the knee extension force within $\pm 5\%$ of the target force. The order of the RF and VM trials was randomized. Feedback of both EMG amplitude of the targeted muscle (EMG RMS calculated online over a 200-ms window using Spike2 software, Cambridge Electronic Design) and force was provided to the participants. Participants were instructed to attempt to reduce the activity of the targeted muscle while maintaining force by altering their motor strategy, using any means possible, while remaining in the seated position. For each trial, the lowest EMG amplitude produced by the targeted muscle (VM or RF) over a 3-s window, when the force was maintained within $\pm 5\%$ of the target force, was calculated.

**Data Processing**

All the data were processed using Matlab (version R2012a, The Mathworks).

*Shear elastic modulus.* For experiments I and II, muscle shear elastic modulus was analyzed from the middle 8 s (8 images) of the 12-s contractions. SS1 recordings were exported in mp4 format and sequenced in png. Image processing converted the colored map into shear elastic modulus values. Before analysis of the shear elastic modulus, the map was inspected for artefacts. If artefacts were present in any image, the region of interest (ROI) was reduced in size to remove the area of artefact from all images within that contraction. The average areas of the ROIs used for analysis were $\approx 15$ and $\approx 20$ mm$^2$ for RF and VM, respectively. The shear elastic modulus was averaged across the ROI and between the eight images to provide a representative value for each contraction. For each location, the average value calculated over the baseline contractions and over the pain contractions was considered for further analysis.

*Surface electromyography.* EMG signals were rectified and low-pass filtered (4 Hz, Butterworth filter, 2nd order). EMG amplitude was considered as the washout of the second pain condition (Fig. 1). WO, washout. *These contractions performed to determine the target amplitude of VL EMG.
participants for the PainRF and PainVM, respectively. As our hypoth-
eses do not imply a comparison between PainRF and PainVM trials,
thus data were available for analysis from 18 and 19 participants.

Statistical Analysis

Data distributions consistently passed the Shapiro-Wilk normality test and are therefore reported as means ± SD throughout the text and the figures. Significance was set at P < 0.05. Cohen’s d values (SD of the difference used for standardization) are reported as measures of effect size, with 0.2, 0.5, and 0.8 as small, moderate, and large effect, respectively (6).

Experiment I. Three participants did not complete all conditions: one participant did not experience pain during PainRF following the hypertonic saline injection, and two participants felt mild dizziness following their second pain injection (one each in PainRF and PainVM). Thus data were available for analysis from 18 and 19 participants for the PainRF and PainVM, respectively. As our hypotheses do not imply a comparison between PainRF and PainVM trials, and because including both PainRF and PainVM trials would reduce the sample size as a result of casewise deletion of missing values (by the 3 participants discussed above), data were analyzed separately. Thus, for both PainRF and PainVM trials, shear elastic modulus and knee extension force (in % of MVC) were compared between conditions (baseline and pain) using paired t-tests.

Experiment II. One participant did not maintain VL EMG consistently within the target range (error >10%), and their data were discarded, leaving data for analysis from 12 participants. As for experiment I, data were analyzed separately for each pain location (PainRF and PainVM). Isometric knee extension force (in % of MVC) and VL EMG amplitude (feedback) were compared between conditions (baseline, pain, washout) with a repeated-measures ANOVA. To assess the putative difference in muscle coordination strategy between the force-matched contractions and VL EMG-matched contractions (6 contractions of the first baseline condition), normalized EMG amplitude was compared between muscles (RF and VM, within factor) and conditions (force-matched vs. VL EMG-matched, within factor) with a repeated-measures ANOVA. To determine the adaptations during pain, both shear elastic modulus and normalized EMG amplitude were compared between muscles (RF and VM; within factor) and conditions (baseline, pain, washout; within factor) using a repeated-measures ANOVA. Post hoc analyses were performed using the Fisher LSD test. Finally, the relationship between changes in muscle shear elastic modulus during pain (in kPa, if any) and changes in RF EMG amplitude (in %EMGmax) or changes in knee extension force (in % of MVC) was tested using Pearson’s correlation coefficient.

Experiment III. Finally, potential changes in EMG amplitude when participants attempted to voluntarily change RF or VM EMG were tested using a repeated-measures ANOVA (muscles and conditions as within factor) for each trial (VM and RF trial), separately. Post hoc analyses were performed using the Fisher LSD test.

RESULTS

Experiment I

Pain intensity and location. In some participants, pain intensity was reported below 2/10 before completion of the three pain contractions, and subsequently the pain trial was ceased. For PainRF, trials were ceased after two contractions in nine participants, and one contraction in one participant. For PainVM, trials were ceased after two contractions in eight participants, and after one contraction in two participants. The mean pain intensity reported during the pain trials (where pain was reported ≥2/10) was 4.1 ± 1.2 for PainRF and 4.2 ± 1.1 for PainVM. Pain was reported around the site of the hypertonic saline injection, except for two participants who reported pain in an area that also extended over the patella during PainVM (Fig. 2A).

Knee extension force. The target force level was accurately matched between conditions [standard error of measurement (SE) between baseline and pain conditions was 2.2% and 1.5% for PainRF and PainVM, respectively]. There was no significant difference between conditions for PainRF (20.7 ± 1.2 vs. 20.8 ± 1.3% of MVC for baseline and pain, respectively; P = 0.25; d = 0.27) or PainVM (20.7 ± 1.3 vs. 20.7 ± 1.5% of MVC; P = 0.89; d = 0.03).

Muscle shear elastic modulus. A representative example of the shear elastic modulus map is depicted in Fig. 3. During the baseline contractions the mean shear elastic modulus was 25.5 ± 12.1 kPa in RF, and this decreased significantly to 21.0 ± 12.5 kPa (i.e., −17 ± 33%; P = 0.021; d = −0.60; Fig. 4A) when nociceptive stimulation was induced in this muscle. The decrease in shear elastic modulus indicates that the force produced by RF during homonymous muscle pain decreased...
from that in the baseline condition. In contrast, when noiceptive stimulation was induced in VM, there was no significant change in shear elastic modulus (32.3 ± 12.5 vs. 31.0 ± 13.3 kPa for the baseline and pain conditions, respectively; P = 0.23; d = −0.19; Fig. 4B).

**Experiment II**

*Pain intensity and location.* In some participants, pain intensity was reported below 2/10 before completion of the six Pain contractions, and the trial was ceased. For PainRF, trials were ceased after four contractions (i.e., 2 SSI measurements per muscle) in four participants. For PainVM, trials were ceased after four contractions in four participants, and after five contractions in one participant. The mean pain intensity reported during the Pain trials (where pain was reported ≥2/10) was 3.8 ± 1.1 for PainRF and 4.4 ± 1.3 for PainVM. Pain was perceived around the site of the saline injection, except for one participant who reported pain in an area that extended over the patella during PainVM (Fig. 2B).

*Knee extension force.* In contrast to experiment I, participants were asked to maintain VL EMG activity during experiment II. Thus knee extension force could change. There was a significant main effect of condition during PainRF (P = 0.0004). Knee extension force was less when pain was induced by saline injection into RF (15.6 ± 5.6% of MVC) than the preceding baseline trial (18.8 ± 5.9% of MVC; P = 0.0001, d = −1.17). Force remained lower during washout (16.8 ± 5.7% of MVC) compared with the baseline (P = 0.008; d = −0.78). No change in force was observed between baseline, pain, and washout conditions when pain was induced in VM, i.e., PainVM (main effect of condition: P = 0.29) (Fig. 5).

*Shear elastic modulus.* Although the condition × muscle interaction was not significant (P = 0.42) during PainRF, there was a significant main effect of muscle (P = 0.0002) and condition (P = 0.004) (Fig. 6A). When pain was induced in RF the shear elastic modulus (pooled between RF and VM) was lower during pain (26.3 ± 13.0 kPa) than during baseline (30.1 ± 12.2 kPa; P = 0.006; d = −0.86) and washout (30.7 ± 13.1 kPa; P = 0.002; d = −1.05). There was no difference between washout and baseline (P = 0.66; d = 0.13). A significant correlation was found between the changes in RF shear elastic modulus during pain and the changes in knee extension force (r = 0.60, P = 0.036). Although a significant main effect of muscle was found, during PainVM (P = 0.001) there was neither a main effect of condition (P = 0.40) nor an interaction between condition × muscle (P = 0.80) (Fig. 6B).

*Electromyography.* EMG was not recorded from VM and RF for participant 1 in experiment II. Thus EMG data for these two muscles were available for 11 participants. During the first three force-matched contractions performed at 20% of MVC, EMG amplitude was 13.1 ± 3.7, 13.1 ± 4.9, and 11.9 ± 5.2% of EMGmax for VL, VM, and RF, respectively. Muscle coordination strategy did not change between the force-matched
and VL EMG-matched contractions. When VM and RF EMG amplitudes were compared between these force-matched contractions at 20% of MVC (those used to determine VL EMG level for the feedback) and the first baseline condition (when VL RMS EMG level was used as feedback), there was no systematic difference for either PainRF (main effect muscle: $P = 0.64$; main effect condition: $P = 0.59$; interaction condition $\times$ muscle: $P = 0.81$) or PainVM (main effect muscle: $P = 0.32$; main effect condition: $P = 0.56$; interaction condition $\times$ muscle: $P = 0.16$).

The target VL EMG amplitude was accurately matched between conditions (SE between baseline and pain = 0.4% and 1.8% for PainRF and PainVM, respectively). VL EMG did not differ between conditions for either PainRF (main effect condition: $P = 0.29$) or PainVM (main effect condition: $P = 0.44$).

When pain was induced in RF (PainRF) there was no effect of muscle ($P = 0.18$) on EMG amplitude. However, there was a significant condition $\times$ muscle interaction ($P = 0.013$). EMG amplitude of RF was less (8.2 $\pm$ 3.3% of EMG$_{\text{max}}$) during pain than during both baseline (12.5 $\pm$ 4.5% of EMG$_{\text{max}}$; $P < 0.0001$; $d = -0.93$) and washout (11.3 $\pm$ 4.3% of EMG$_{\text{max}}$; $P = 0.0003$; $d = -0.85$) (Fig. 7A). There was no difference in RF EMG between baseline and washout ($P = 0.10$), and no change was observed for VM EMG between any condition (all post hocs: $P > 0.15$). The changes observed in RF EMG during pain were positively correlated to the changes in RF shear elastic modulus ($r = 0.59$; $P = 0.05$). When pain was induced in VM (PainVM), no changes were observed for RF or VM EMG amplitude (effect muscle: $P = 0.18$; effect condition: $P = 0.55$; and muscle $\times$ condition interaction: $P = 0.41$) (Fig. 7B).

**Experiment III**

When the participants were asked to voluntary reduce RF EMG while maintaining the knee extension force (± 5%), there was a significant muscle $\times$ condition interaction ($P = 0.018$). RF decreased from 11.3 $\pm$ 4.9 to 8.5 $\pm$ 4.5% of EMG$_{\text{max}}$ ($P = 0.011$; $d = -1.1$ Fig. 8). EMG amplitude of neither VM ($P = 0.18$; $d = 0.37$) nor VL ($P = 0.53$, $d = 0.19$) changed significantly. During the VM trials there was neither a main effect of condition ($P = 0.18$), muscle ($P = 0.87$), or a muscle $\times$ condition interaction ($P = 0.08$). This indicates that the participants failed to voluntarily decrease VM EMG ($d = -0.38$). EMG of VL ($d = -0.12$) and RF ($d = 0.51$) were also unchanged during this task.

**DISCUSSION**

This series of experiments has three main observations. First, RF stress significantly reduces when pain is induced in this muscle during isometric knee extension (experiment I). Second, when feedback of VL EMG activity was provided
Experiment III of RF and vastii. A disassociation seems logical given the together, these data indicate the CNS can dissociate the activity voluntarily while maintaining knee extension force. Taken force.* H11021A or VM (VM trials; experiment II) or neural drive to VL (VL). The ability to dissociate the drive of RF from the vastii (14) and moderate contraction intensities [2.5 to 40% of MVC (21)]. The ability to dissociate the drive of RF from the vastii enables reduction of stress in the painful RF while maintaining force (experiment I) or neural drive to VL (experiment II). Experiment III confirms the potential to also dissociate activity voluntarily while maintaining knee extension force. Taken together, these data indicate the CNS can dissociate the activity of RF and vastii. A disassociation seems logical given the different functional roles (knee extensor alone vs. knee extensor and hip flexor) and anatomy (mono- vs. biarticular) of the RF and vastii. Monoarticular muscles are mainly responsible for the generation of positive torque, whereas the biarticular muscles have a unique role in controlling the distribution of net moments at the joint, and thus the direction of external force (25, 26).

Performance of isometric knee extension with VL EMG feedback did not theoretically constrain RF activity. This is supported by the reduction in RF activation (EMG amplitude) during pain. Considering the total energy cost of the contraction, it may be energetically more optimal to keep this reduced RF activity during washout, but this was not observed (no difference between baseline and washout). This implies that some advantage was derived from greater activation of RF. One possibility is that there was a greater neural “cost” to maintain activity of VL with lesser RF contribution. For instance, this may have required suppression of a preferred muscle synergy. This result concurs with previous observations that patterns of muscle coordination are organized on the basis of habit rather than optimization of energy or other costs (8). Alternatively, it is possible that RF activity is needed to control stress (and thus the overall muscle stress) without changes in pelvic position that could have reduced passive stress (and thus the overall muscle stress) without change in muscle activity.

The dissociation of neural drive between RF and the vastii muscles observed here concurs with previous observations of clear dissociation between EMG activity of these muscles during knee extension performed at low [2.5 to 5% of MVC (14)] and moderate contraction intensities [~40% of MVC (21)]. The ability to dissociate the drive of RF from the vastii enables reduction of stress in the painful RF while maintaining force (experiment I) or neural drive to VL (experiment II). Experiment III confirms the potential to also dissociate activity voluntarily while maintaining knee extension force. Taken together, these data indicate the CNS can dissociate the activity of RF and vastii. A disassociation seems logical given the different functional roles (knee extensor alone vs. knee extension force). Therefore, we provided a different task goal, i.e., VL EMG amplitude rather than knee extension force. As this task does not constrain VM activity we argue that this provided a goal that can be maintained theoretically without the need for VM force. However, even in this context there was no consistent decrease in VM EMG or shear elastic modulus. This observation implies that either the CNS cannot selectively modulate the activity of VM and VL, or the cost of this strategy outweighs the benefit of reduced stress during pain. Experiment III provides evidence that the participants were also unable to voluntarily reduce the activation of VM while maintaining force, at least with the limited training used here. This concurs with studies that suggest an inability to selectively increase activation of VM over VL by alteration of lower limb position (see review by 22). Taken together, these observations provide strong evidence of an undifferentiated descending drive from the CNS to VM and VL in healthy individuals. This is consistent with the observation of highly synchronized discharge of motor units in VM and VL, which implies strong common drive to both muscles (18). Although true for healthy individuals, synchronization of motor unit discharge between the obliquus fibers of VM and VL is substantially less in people.

Reduced Stress Within RF During Homonymous Muscle Nociceptive Stimulation

When experimental pain is induced by noxious stimulation of RF, stress within this muscle decreased. This systematic decrease in RF muscle stress was observed when either knee extension force (experiment I) or VL EMG activity (experiment II) was matched between the contractions without and with pain. Reduced RF EMG in experiment II indicates the decrease in muscle stress during pain is explained (at least partly) by reduced neural drive to RF rather than subtle changes in pelvis position that could have reduced passive stress (and thus the overall muscle stress) without change in muscle activity.

The dissociation of neural drive between RF and the vastii muscles observed here concurs with previous observations of clear dissociation between EMG activity of these muscles during knee extension performed at low [2.5 to 5% of MVC (14)] and moderate contraction intensities [~40% of MVC (21)]. The ability to dissociate the drive of RF from the vastii enables reduction of stress in the painful RF while maintaining force (experiment I) or neural drive to VL (experiment II). Experiment III confirms the potential to also dissociate activity voluntarily while maintaining knee extension force. Taken together, these data indicate the CNS can dissociate the activity of RF and vastii. A disassociation seems logical given the different functional roles (knee extensor alone vs. knee extension force) and anatomy (mono- vs. biarticular) of the RF and vastii. Monoarticular muscles are mainly responsible for the generation of positive torque, whereas the biarticular muscles have a unique role in controlling the distribution of net moments at the joint, and thus the direction of external force (25, 26).

Performance of isometric knee extension with VL EMG feedback did not theoretically constrain RF activity. This is supported by the reduction in RF activation (EMG amplitude) during pain. Considering the total energy cost of the contraction, it may be energetically more optimal to keep this reduced RF activity during washout, but this was not observed (no difference between baseline and washout). This implies that some advantage was derived from greater activation of RF. One possibility is that there was a greater neural “cost” to maintain activity of VL with lesser RF contribution. For instance, this may have required suppression of a preferred muscle synergy. This result concurs with previous observations that patterns of muscle coordination are organized on the basis of habit rather than optimization of energy or other costs (8). Alternatively, it is possible that RF activity is needed to control stress (and thus the overall muscle stress) without change in pelvic position that could have reduced passive stress (and thus the overall muscle stress) without change in muscle activity.
with chronic patellofemoral pain (19), and greater differentiation of drive may be possible in this group. This is in line with observations of some independence of drive to VM and VL as indicated by delayed onset of VM EMG activity relative to VL during stair ascent in patients with chronic patellofemoral pain (7).

Although there was significant effect of Pain on shear elastic modulus during PainRF during experiment II, the condition × muscle interaction was not significant, which suggests that VM and RF exhibited a similar behavior (decreased stress). However, this interaction was significant for the EMG data; VM EMG was unchanged and RF EMG amplitude decreased. Consistent changes in both parameters for RF implies the CNS decreased activation of this muscle to decrease RF stress (painful muscle). Changes in VM stress, without concomitant changes in VM EMG, might be explained by the nonnegligible intermuscular force transmission (23), such that decreased force produced by RF during pain induced a lower force transmission between RF and VM. If so, this observation provides additional evidence that EMG and shear elastic modulus do not provide interchangeable information and that both measurements are necessary to fully understand the outcome of motor adaptation during pain. This is further confirmed by the moderate coefficient of correlation found between changes in RF shear elastic modulus and RF EMG activity.

Methodological Considerations

This experiment requires consideration of several methodological aspects. First, because EMG does not provide accurate information regarding muscle stress (4), this experiment used an elastography technique to test the hypothesis that muscle stress is altered during pain. As injection of hypertonic saline does not alter the shear elastic modulus measured at rest or during contraction (24), the relationship between muscle stress and shear elastic modulus is unlikely to be altered. Consequently, changes in shear elastic modulus can be interpreted as changes in muscle stress, even after the injection of saline. Second, the present study focused on the acute adaptation to pain and it is important to consider that these adaptations are likely to differ from this after a longer exposure to pain. Previous work provides some evidence for the effectiveness of biofeedback training of muscle coordination, including the ability to alter the ratio between VM and VL EMG amplitude (20). Third, adaptation to pain was studied during isometric tasks performed at ~20% of MVC. As redistribution of muscle activity among the quadriceps muscles depends on contraction intensity during fatiguing tasks (14), it is relevant to explore the present observations in tasks that require higher/lower effort and/or dynamic tasks. Finally, in the absence of direct measurements, we cannot confirm the absence of fatigue that could interfere with interpretation of the data. However, care was taken to limit fatigue. To this end, we studied short contractions (12-s) at a relatively low intensity (20% of MVC) with 30 s of recovery between each. The contractions following the pain conditions began 10 min after complete cessation of pain to provide an extra recovery period for the participants. The order of the pain conditions was randomized ensuring that fatigue, if any, did not compromise the between-muscle comparison of pain adaptations. Because the changes observed in experiment II (EMG, shear elastic modulus) recovered after pain, we are confident that fatigue, if any, did not interfere in the conclusion of this study. Finally, it is important to note that fatigue does not alter the relationship between shear elastic modulus and stress (2).

Conclusions

These results demonstrate that between-muscle differences in neuromechanical adaptation to experimental pain are likely explained by neurophysiological constraints and/or different functional roles. Consequently, pain adaptation may require consideration with reference to constraints related to the muscle system under investigation and the goal of the experimental task.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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