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Experimental hand and knee pain cause differential effects on corticomotor excitability

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Abstract

Acute pain elicits a well-known inhibitory effect on upper limb corticomotor excitability, whereas the temporal effects of lower-limb experimental pain and pain in a remote limb are less clear. The aim of this study was to compare the temporal corticomotor excitability changes in the upper and lower limbs in response to acute upper and lower limb pain. In a cross-over design, 13 participants (age 29±9 years; 12 male) attended two sessions where experimental pain was induced by injecting hypertonic saline into either the first dorsal interosseous (FDI) muscle or infrapatellar fat pad at the knee, inducing a short-lasting pain experience scored on a numerical rating scale (NRS). Motor evoked potentials (MEPs) in response to transcranial magnetic stimulation were recorded in the FDI and vastus lateralis (VL) muscles before, during, and following pain. Hand and knee pain NRS scores were not significantly different. Hand pain elicited a short duration inhibition of the FDI MEPs ($P<0.0001$) together with a facilitation of VL MEPs ($P=0.001$) that outlasted the duration of pain. Knee pain elicited a short-duration facilitation of VL MEPs ($P=0.003$) with no significant effect in the FDI MEPs ($P=0.46$). The findings indicate a limb-specific corticomotor response to experimental pain that may be related to limb function.

Perspective: These data demonstrate the impact of acute, experimental pain on corticomotor excitability in the upper and lower limbs. This facilitates our understanding of the effect of pain on motor control of both local and distant muscles.

Keywords: transcranial magnetic stimulation; experimental pain; corticomotor excitability; upper limb; lower limb

Introduction

It is well established that both acute and chronic pain affect various aspects of motor control and performance, including changes in muscle strength, endurance, and force control.[1,13,26] However, the neural mechanisms that underlie these changes remain incompletely understood.[7,11,29]

To study the effects of pain on the motor system, experimental models of pain have been used in healthy volunteers. The most widely used model is the injection of hypertonic saline into soft tissue structures.[13] This model has been validated and shown to cause moderate intensity pain for a short duration (15-20 mins) in both the upper and the lower limbs.[2,12] A meta-analysis[5] of studies using transcranial magnetic stimulation (TMS) to examine the effects of acute experimental muscle pain indicated a significant reduction in corticomotor excitability in both target and remote (not receiving experimental pain) muscles in the upper limb during and following pain. Furthermore, short interval intracortical inhibition (SICI) has been shown to increase in response to acute hand pain, suggesting at least part of this inhibitory effect occurs at a cortical level.[30] In contrast, in a previous study we observed an increase, rather than a decrease, in quadriceps corticomotor excitability following the induction of experimental knee pain and no change in SICI.[25] This finding raises the possibility that the motor response to pain may be different between the upper and lower limbs. However, it is not known if this difference arises due to the location of pain or the location of the target muscle.

Furthermore, knowledge of the time course of changes in corticomotor excitability during and following pain is uncertain. While some studies show an immediate reduction in corticomotor excitability during local muscle pain followed by a return to baseline once pain subsides,[10] others show a delayed inhibitory response[31,32] or a more persistent change in

corticomotor excitability that outlasts the pain experience.[5,8,28,30,33] It is not yet clear if persistent changes in corticomotor excitability may also occur in remote muscles, distant from the location of pain.

The primary aim of the current study was to examine the effect of hand and knee pain on corticomotor excitability of local and remote muscles in the upper and lower limb. These findings might provide evidence whether acute pain elicits limb-specific or more global effects on corticomotor excitability. We also examined in detail the time course of these effects during and after the pain experience, to provide clearer information on the relationship between altered corticomotor excitability and the change in pain intensity over time.

Methods

Participants

Based on data from previous studies exploring the effect of experimental pain on corticomotor excitability in the target muscle, effects sizes of 0.52 for upper[5] and 0.61 for lower[25] limb muscles were determined. Using the lower value of 0.52, power of 0.8, and $\alpha = 0.05$, a sample size of 25 participants would be required to detect a within group change. Participants were healthy individuals who were required to be over the age of 18, currently pain free, and who had no previous hand or knee pain/injury requiring treatment by a health professional. Participants were excluded if they had any contraindications to TMS, a resting motor threshold (RMT) >75% of maximum stimulator output for either the vastus lateralis (VL) or first dorsal interosseous (FDI) muscles, or if they had a history of any neurological condition, spinal surgery, or spinal pain in the last six months with associated neurological signs or symptoms. Ethical approval was obtained from the regional ethics

committee (NTY 10/11/089) and participants provided written informed consent prior to participating.

Experimental procedure

All participants attended two sessions at least 72 hours apart. In one session, participants received experimental pain in the right hand and in the other session they received experimental pain in the right knee. The order of these sessions was randomised for each participant using a computer-generated randomisation schedule. During each session, 30 baseline motor evoked potentials (MEPs) were collected for each muscle. They were collected alternatively in sets of 10 MEPs per muscle (interstimulus interval 4.5-5.5 s), with the stimulating coil switched between each set. During alternating stimulation, the starting set always targeted the FDI muscle in the hand pain session and targeted the VL muscle in the knee pain session.

Following these baseline measurements, participants received the hypertonic saline injection. Once the needle was withdrawn, the participants were asked to rate their pain on a numerical rating scale (NRS) with 0 being no pain and 10 being the worst pain imaginable. Approximately 30 s after needle withdrawal, alternating sets of 10 MEPs were collected from the FDI and VL muscles. Participants were asked to give a rating of their hand/knee pain on the 0-10 NRS after each set of 10 MEPs (~ 1 min each). Alternating stimulation was continued until the participant gave a score of “0” on the NRS. A break of 5 mins was then given to ensure that the pain had completely subsided before a set of post-pain measures were collected. This consisted of 60 MEPs (30 for each muscle) collected in the same way as the baseline measures.

Motor evoked potentials

A Bistim 200[2] (Magstim Co, Whitland, UK) was used to deliver monophasic transcranial magnetic stimuli to the primary motor cortex. A double cone coil (100 mm) was used to elicit responses in the lower limb and a figure of eight coil (70 mm) for the upper limb. The coils were oriented to induce a posterior-anterior current, with the coils placed over the left hemisphere to elicit responses in the right hand or leg. Bipolar Ag-AgCl disc electrodes with an interelectrode distance of 2.2 cm were placed on the skin overlying the muscle bellies of the VL and the FDI. A ground electrode was placed on the proximal tibia. To ensure minimal signal impedance, electrode sites were shaved, abraded, and wiped with alcohol. All electromyography (EMG) signals were amplified (x1000), filtered (10-1000 Hz) (AMT-8, Bortec Biomedical, Canada) and sampled at 2000 Hz (Micro 1401, Cambridge Electronic Design, UK) before being stored on a computer for further analysis.

Once the electrodes were in place, the optimal site of stimulation for each muscle was determined by systematically moving the coil across the scalp until large, consistent MEPs were elicited. These sites were established as the "hot spot" for each muscle and marked on the scalp using a felt pen. The participant's RMT was then established for each muscle using a staircase method. RMT was defined as the lowest stimulation intensity that produced a MEP >50 μV in a minimum of four out of eight consecutive stimuli.[27] For both the FDI and VL muscles, stimulation intensity was set to 130% of the RMT for the remaining stimuli.

Experimental knee and hand pain

Experimental knee and hand pain were induced by injecting sterile 5.8% hypertonic saline directly into the FDI muscle for the hand and into the infra-patellar fat pad for the knee.[2,12] Injections were done under sterile conditions using a 27-gauge needle mounted on a 1 mL

syringe. The skin was cleaned thoroughly with an antiseptic prior to insertion of the needle, and new sterile needles, syringes, and latex gloves were used for each participant. For the FDI muscle injection, the hand was in a relaxed position and 0.5 mL of hypertonic saline was injected directly into the muscle. To induce knee pain, 0.25 mL of hypertonic saline was injected into the infra-patellar fat pad while the knee was in a slightly flexed position. Injections were from a medial approach with the needle inserted approximately 1 cm at a 45° angle in a posterolateral direction.

Data Processing and Analysis

A pain profile for the hand and knee was created by averaging participants' pain NRS scores following injection. Paired *T*-tests were used to compare pain duration, maximum NRS scores of pain intensity, and the TMS stimulation parameters between the hand and knee pain sessions.

To analyse MEPs in the FDI and VL muscles, 50 ms of EMG preceding the stimulus artefact was first visually checked for contamination by voluntary muscle activity. Responses were removed from further analysis if muscle activation within the EMG signal was detected (FDI: 42 out of 2210 MEPs removed [1.9%]; VL: 9 out of 2330 MEPs removed [<1%]). The maximum peak-to-peak amplitude of each remaining MEP was then determined.

Given the different duration of pain for each participant, to examine the time course of changes in corticomotor excitability during the experience of pain, the time of each participant's MEPs were expressed as a *per cent* of their total pain duration based on when the first stimulus in each block of 10 MEPs was delivered. Pain duration was defined as the time from needle withdrawal until the pain NRS reached 0. MEP amplitudes were then

averaged in 3 blocks: 0-33, 33-66, and 66-100% of pain duration. MEP amplitudes obtained at the baseline and post-pain periods were also averaged.

Statistical analysis

Normality of the data distributions was checked using Kolmogorov-Smirnov tests. Given the non-normal distribution of a number of the MEP amplitudes, Friedman tests were used to determine the effect of time (baseline, 0-33%, 33-66%, 66-100%, post-pain) on FDI and VL MEP amplitude during both hand and knee pain. Significant main effects of time were further investigated using Wilcoxon Signed Rank tests comparing the pain and post-pain time periods to baseline. Effect sizes of the change in MEP amplitude from baseline to the subsequent time periods were determined using Cohen's *d* and interpreted according to Hopkins.[16] Correlations (Spearman's rho) were also made between the peak pain rating and change in MEP amplitude from baseline to the 0-33% time period.

The alpha level for all statistical tests was set to 0.05. Data are presented as mean and standard deviation (SD). Statistical analyses were performed using SPSS v26 (IBM).

Results

Over the recruitment period, 13 people (average age 29±9 years, body mass index 22.7±1.6 kg/m^2, 12 male, 12 right-handed) volunteered to participate in the study; a further potential participant was excluded due to a high RMT in the VL muscle. All participants were pain-free on the day of testing. One of the participants had a mild vasovagal response during experimental hand pain and took no further part in the study. One participant sustained a fibular fracture before taking part in the second session (knee pain) and their data was only available for the first session (hand pain). One participant's data from the FDI was excluded during the knee pain session due to saturation of the EMG signal. Therefore, the final

analyses were performed on 10-12 participants, depending on the outcome measure. Several participants had difficulty keeping the FDI muscle relaxed following injection of hypertonic saline into the FDI. For these participants (*n*=7), the first set of MEPs obtained during pain were delayed 1-3 mins until muscle relaxation was achieved, which was monitored in real time on an oscilloscope.

Details of experimental pain and the stimulation parameters for the hand and knee pain sessions are shown in Table 1, while average pain profiles for the two locations are shown in Figure 1. There were no significant differences in pain intensity or duration, or any stimulation parameters between the two sessions (all $P>0.05$).

Knee pain

Example FDI and VL MEPs from the knee pain session are shown in Figure 2, while group MEP amplitudes are shown in Figure 3 (top). In the knee pain session, there was a significant effect of time for VL MEP amplitude ($P=0.003$) but not for FDI MEP amplitude ($P=0.46$). For the VL MEPs, there was a significant increase in MEP amplitude compared to baseline at 0-33% ($P=0.006$; effect size [ES]=1.03) and 33-66% ($P=0.01$; ES=0.62) pain duration, reflecting large and medium effect sizes, respectively. VL MEP amplitude at 66-100% pain duration ($P=0.08$; ES=0.56) and at post-pain ($P=0.18$; ES=0.34) were not significantly different to baseline.

Correlations between the peak pain rating and the change in MEP amplitude from baseline to 0-33% pain duration were not significant for the VL (Spearman's rho=0.23; $P=0.49$) or FDI (Spearman's rho=-0.51; $P=0.07$) muscles.

Hand pain

FDI and VL MEP amplitude in the hand pain session are shown in Figure 3 (bottom). There was a significant effect of time for FDI ($P<0.001$) and VL ($P=0.001$) MEP amplitude. For the FDI, there was a significant reduction in MEP amplitude compared to baseline at 0-33% ($P=0.004$; ES=0.74), 33-66% ($P=0.005$; ES=0.73), and 66-100% ($P=0.013$; ES=0.72) pain duration. All the effect sizes are considered medium. FDI MEP amplitude recovered towards baseline levels at post-pain ($P=0.07$; ES=0.55). For the VL muscle, there was a significant increase in MEP amplitude compared to baseline at 0-33% ($P=0.002$; ES=1.31), 33-66% ($P=0.003$; ES=1.00), and 66-100% ($P=0.009$; ES=1.13) pain duration, as well as at the post-pain time period ($P=0.003$; ES=0.82). All the effect sizes are considered large.

Correlations between the peak pain rating and the change in MEP amplitude from baseline to 0-33% pain duration revealed a significant negative relationship for the FDI muscle (Spearman's rho=-0.64; $P=0.03$). That is, those with a higher peak hand pain rating had a larger inhibition of FDI MEP amplitude. The correlation for the VL muscle was not significant (Spearman's rho=0.29; $P=0.37$).

Discussion

This study confirms our previous work and that of others that corticomotor excitability of VL increased during experimental knee pain while corticomotor excitability of FDI is significantly reduced during hand pain. We extend these findings to show that hand pain also resulted in an increase in VL MEP amplitude but knee pain had no effect on the FDI corticomotor excitability. Thus, the corticomotor response to pain appears to differ according to pain location and the muscle tested.

Only two studies have examined the effect of experimental lower limb pain.[3,25] Our previous study[25] mirrored the current results that knee pain gave rise to a large, significant increase in quadriceps corticomotor excitability and then returned to baseline after pain subsided. In that study, no significant change in biceps femoris (BF) or tibialis anterior (TA) corticomotor excitability were observed, although these muscles were not specifically targeted. In contrast, Billot et al.[3] found that cutaneous heat pain over the TA muscle gave rise to a small but significant reduction in TA MEP amplitude. Potential reasons for these different findings are the type of pain induced (heat versus chemical pain), the location of pain on the lower limb (proximal versus distal), and the structure involved (cutaneous versus joint pain). This current study also found that FDI MEPs were unaffected by knee pain, indicating that knee pain has no remote effect on corticomotor excitability of the FDI muscle.

Our results in the FDI in response to hand pain are consistent with many previous studies involving the upper limb that have shown a significant decrease in corticomotor excitability during experimental muscle pain.[5] The current study is the first to examine the effects of hand pain on corticomotor excitability in a distant limb muscle, and clearly shows there is not a global inhibitory response to hand pain, but rather a more limb specific response is elicited. Previous studies that have examined the effect of acute pain on remote muscles have all targeted muscles on the same limb as that experiencing pain, and typically show a reduction[10,18,34] or no change[8,10,19,25] in corticomotor excitability, whereas we showed that hand pain gave rise to an increase in VL corticomotor excitability. It is notable that the effect size of this increase was considered large and was significantly correlated with the peak pain rating, and therefore appears to be a robust response that is related to the extent of nociceptive stimulation.

The alterations in MEP amplitude over time following hand and knee pain were similar but reciprocal in nature. For both FDI and VL muscles, MEP amplitude immediately changed with pain onset, then slowly returned towards baseline. These alterations were seen consistently across all participants, although the extent of inhibition/facilitation varied between individuals. While VL MEP amplitude fully returned to baseline levels after the cessation of knee pain, the FDI was only 62% of baseline MEP amplitude when hand pain subsided and the remote increase in VL MEP amplitude persisted at least 5 minutes after hand pain had subsided. A number of previous studies in the upper limb have shown that MEPs remain inhibited following resolution of acute pain,[6,20,30-33] although this is not always consistent.[10,23] The prolonged effects have been postulated to maintain the body in an adaptive state ready for further pain. Our findings demonstrate that persistent changes in corticomotor excitability that outlast the painful stimulus may also occur in remote motor representations.

Our observations provide further experimental support that the motor response to pain is more complex and variable than previously thought.[15] Rather than a uniform inhibitory response to pain that suppresses motor output globally or in the agonist muscle,[21] experimental pain appears to have different and at times competing effects (i.e. inhibition vs facilitation) at different levels of the motor system (e.g. cortex vs spinal cord) and in different muscles.[15] It is possible that these changes are adaptive and reflect the different functional roles of the upper versus lower limbs, and what may be the most appropriate response to acute pain. For example, inhibition of the upper limb muscles might only be appropriate when pain is localised, to withdraw the limb and protect it from the source of pain. In contrast, an increase in corticomotor excitability might be appropriate in the quadriceps muscles regardless of the location of pain, as these muscles are important for

locomotion and “escaping” from the source of pain, whether this pain originates in the upper or lower limb. This may be particularly important to counter the known inhibitory effects of acute lower limb pain on spinal level quadriceps excitability and muscle force.[14,24]

While we were unable to examine the specific neural pathways involved in modulation of corticomotor excitability in the current study, previous studies have investigated these in both the upper and lower limbs. The inhibitory effects of local hand pain on the FDI are at least partly mediated at a cortical level as short-interval intracortical inhibition (SICI) is increased,[30] although spinal inhibition may also occur.[20] In contrast, local knee pain does not alter VL SICI[25] and has an inhibitory rather than facilitatory effect at a spinal cord level.[24] This suggests that other subcortical (e.g. lumbar propriospinal) or cortical (e.g. intracortical facilitatory) pathways may be involved in VL MEP facilitation. It also needs to be noted that distal muscles of the upper limb, such as the FDI, much of the corticospinal input to α-motoneurons is monosynaptic.[4] However, in lower limb muscles, such as the VL, a significant portion of the corticospinal input to α-motoneurons is transmitted via lumbar group II interneurons,[22] which are thought to form part of the lumbar propriospinal network.[17] This is likely reflected in the smaller MEPs in the VL muscle, and raises the potential that some of the differences between the effects on FDI and VL MEPs are due to the different pathways and/or motor units activated by TMS. Animal studies have shown that the lumbar propriospinal interneurons receive strong excitatory input from knee joint afferents.[9] Thus, it is also possible that the increase in VL MEP amplitude observed with local (knee) pain is due to a joint nociceptor mediated increase in the excitability of lumbar propriospinal neurons. The mechanisms explaining the increase in VL corticomotor excitability with remote (hand) pain are less certain. The diffuse nature of the effect

suggests the possibility of a cortical contribution. Future studies may wish to examine these mechanisms in more detail.

The current study has some clear strengths, including a detailed exploration of the time course of MEP changes and optimised stimulation parameters for each target muscle. There were also some limitations. The sample size was smaller than estimated, particularly for some outcome measures (*n*=10), which will have reduced our statistical power to detect differences over time. Due to time constraints, we could not look at intracortical excitability as this requires the delivery of extra sets of stimuli. The majority of the participants were males, which may limit the generalisability of the findings. The tissues targeted for hand (muscle) and knee (joint) pain were different and may have influenced the findings, although Bank et al.[1] concluded the effects of experimental pain on the motor system were reasonably consistent regardless of the source of pain. There was also no control (isotonic saline) injection so we cannot rule out non-specific effects of the injections. However, previous studies have shown no change in corticomotor excitability after isotonic saline injection in both the FDI[20] and VL.[25]

In conclusion, these findings provide evidence that the corticomotor response to pain is different in the FDI muscle (inhibition to local pain only) versus the VL muscle (facilitation to both local and remote pain). These observations support the theory of motor adaptation to pain[15] and suggest pain-motor interactions are more complex than previously thought.

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Figure captions

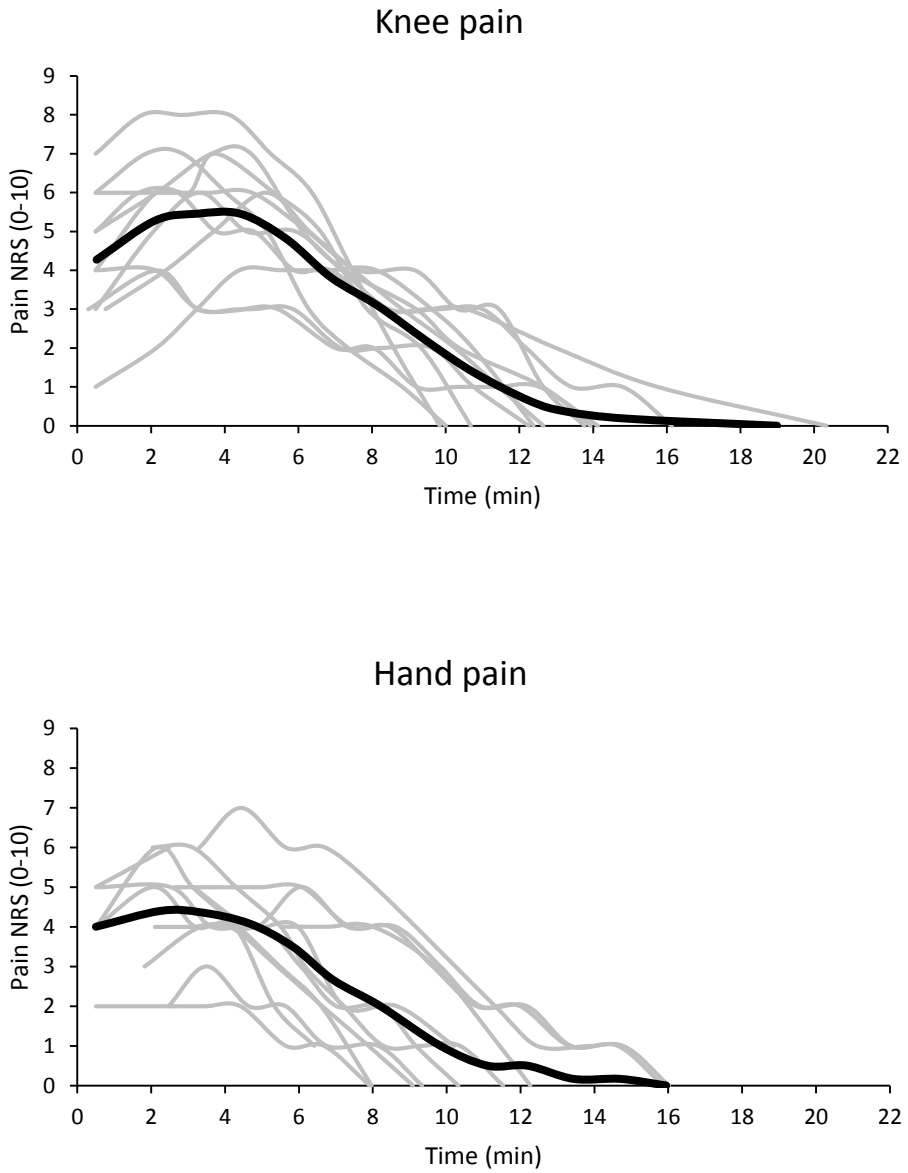
Figure 1. Pain numerical rating scale (NRS) profiles for the knee and hand pain sessions. Individual participants are shown in grey and the group average in black (smoothed lines based on NRS scores approximately every minute).

Figure 2. Example motor evoked potentials (MEPs) in the first dorsal interosseous (FDI) and vastus lateralis (VL) muscles before, during, and after experimental knee and hand pain. Traces are an average of the MEPs obtained in each condition. The MEPs during pain are those obtained in the first block following the injection.

Figure 3. Individual participant motor evoked potential (MEP) amplitudes in the first dorsal interosseus (FDI) and vastus lateralis (VL) muscles during hand and knee pain. Individual responses are shown in grey and the group mean is shown in black (dashed line). * = significant difference from baseline ($P<0.05$).

Table title

Table 1. Pain and transcranial magnetic stimulation parameters for the hand and knee pain sessions. Data are mean±standard deviation.



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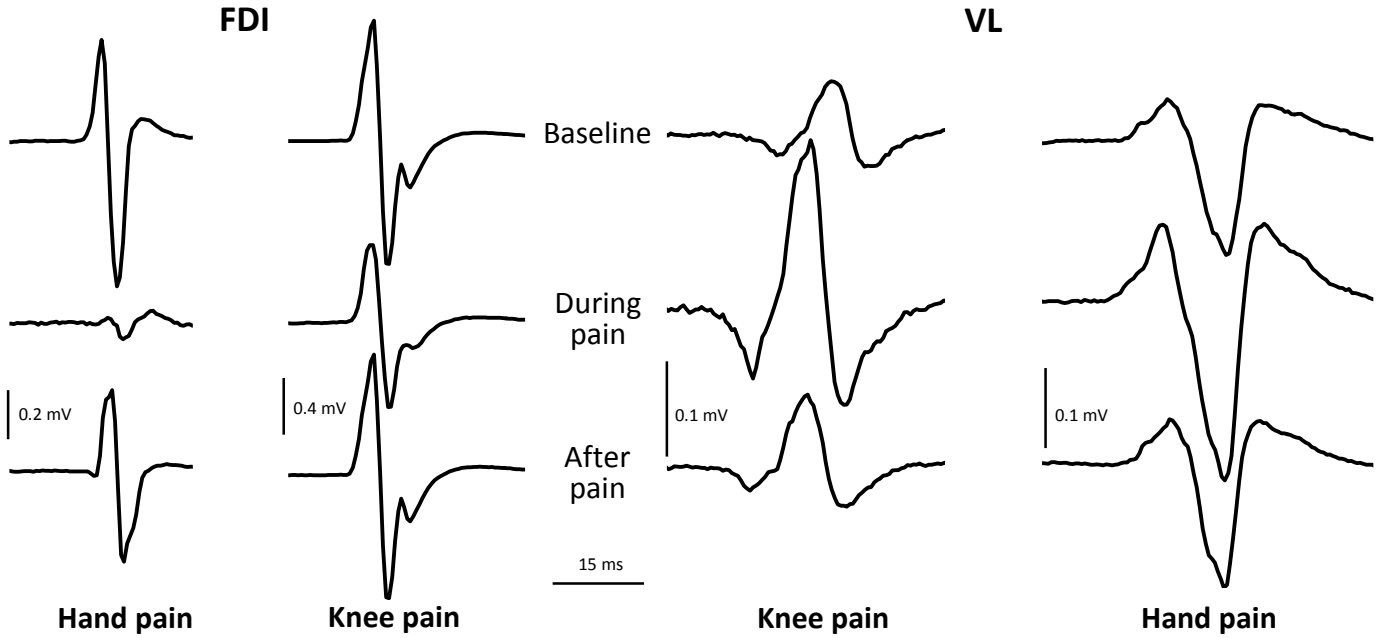

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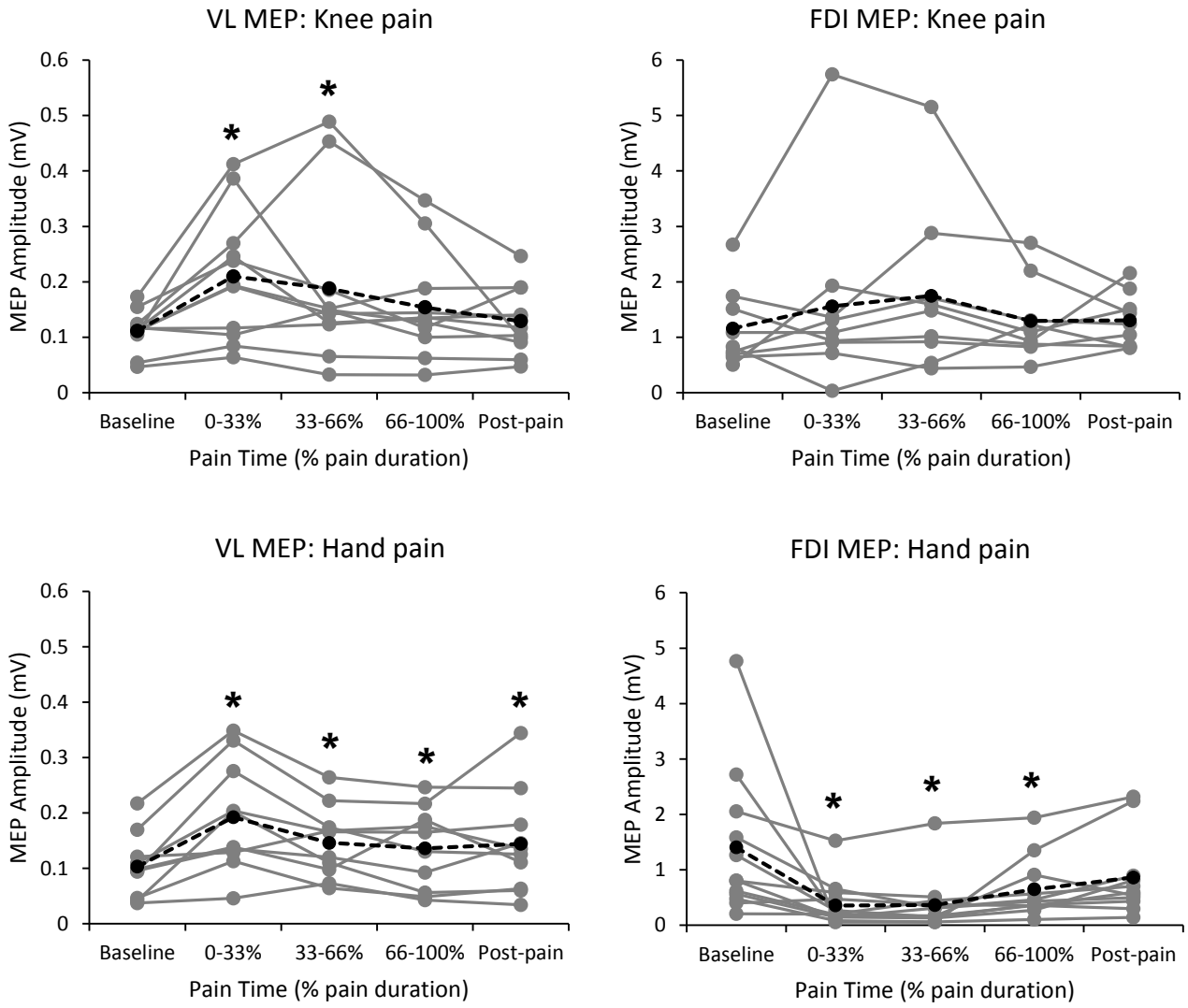

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Table 1. Pain data and transcranial magnetic stimulation parameters for the hand and knee pain sessions. Data are mean±standard deviation.

	Hand pain	**Knee pain**	***P*-value**
Peak pain (0-10)	4.8±0.4	5.9±0.4	0.06
Pain duration (mins)	11.0±0.9	13.1±0.9	0.27
FDI RMT (%)	45±10 (*n*=12)	44±10 (*n*=10)	0.32
VL RMT (%)	54±10 (*n*=12)	55±9 (*n*=11)	0.65

RMT = resting motor threshold; FDI = first dorsal interosseous; VL = vastus lateralis; MEP = motor evoked potential.