Movement does not promote recovery of motor output following acute experimental muscle pain

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Running head: Motor output recovery following experimental pain

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ABSTRACT

Objective: To examine the effect of motor activity on the magnitude and duration of altered corticomotor output following experimental muscle pain.

Design: Experimental, pre-post test

Setting: University laboratory

Subjects: Twenty healthy individuals.

Methods: Participants were randomly allocated to a Rest or Movement group. The Rest group sat quietly, without moving for the duration of the experiment. The Movement group repeated a unimanual pattern of five sequential keystrokes as quickly and as accurately as possible immediately following the resolution of pain. Pain was induced into the right extensor carpi radialis brevis muscle by a bolus injection of 0.5ml hypertonic saline. Corticomotor output was assessed as motor evoked potentials in response to transcranial magnetic stimulation before, immediately after, and at 10, 20 and 30 minutes following pain resolution. Pain intensity was recorded every 30 seconds using an 11-point numerical rating scale.

Results: There was no difference in peak pain intensity ($P<0.09$) or duration ($P<0.2$) between groups. Corticomotor output was reduced in both groups ($P<0.002$) at 10 min ($P<0.002$), 20 min ($P<0.02$), and 30 min ($P<0.037$) following the resolution of pain relative to baseline. There was no difference between groups at any time-point.

Conclusions: Performance of motor activity immediately following the resolution of acute muscle pain did not alter the magnitude or duration of corticomotor depression. Understanding corticomotor depression in the post-pain period and what factors promote recovery has relevance for clinical pain syndromes where on-going motor dysfunction, in the absence of pain, may predispose to symptom persistence or recurrence.

Keywords: Corticomotor output; Experimental muscle pain; Motor activity; Recovery; Transcranial magnetic stimulation**.**

INTRODUCTION

When acute muscle pain is present, intracortical inhibition in the primary motor cortex (M1) is increased (1) and corticomotor output to the painful muscle is reduced (2). These changes are thought to reflect an adaptive motor strategy that restricts movement of the painful part and protects the area from further pain, damage or threat thereof (3). However, a perplexing finding from previous work is that altered intracortical activity and reduced corticomotor output persist *after* pain has resolved (2). These data suggest that although pain may provide a salient cue for rapid reorganization of the motor system, the removal of pain is insufficient to trigger a return to normal motor output.

The factors that trigger a return to normal motor output following the resolution of acute muscle pain are unknown. However, studies investigating motor output following an episode of acute muscle pain are usually conducted with the affected limb at rest (2). One possibility is that resumption of normal motor activity in the post-pain period is required to facilitate a return to normal motor output. Motor activity including motor learning (e.g. 5-finger sequence task) (4), motor practice (e.g. racquet sports, violin players) (4), skill (e.g. visuomotor tracking task) and strength training (e.g. biceps curls at one repetition max synchronized to an auditory cue) (5, 6), and even movement observation (7), is known to increase corticomotor output and reduce intracortical inhibition; such effects could counteract the changes observed following acute muscle pain. Evidence for a relationship between motor activity and recovery of corticomotor output can also be drawn from studies that have examined the effect of pain on motor learning. For example, when task performance is controlled (i.e. feedback is provided to ensure the same task is performed with and without pain), corticomotor output is reportedly unchanged in response to acute muscle pain and the characteristic increase in corticomotor output observed with motor learning is abolished, suggesting the two effects may cancel each other (8, 9). Despite this, no study has examined the impact of motor activity on the magnitude and duration of reduced corticomotor output following acute muscle pain.

The present study aimed to examine the effect of motor activity, undertaken immediately following the resolution of acute muscle pain, on the magnitude and duration of altered corticomotor output following experimental muscle pain. It was hypothesized that motor activity would promote recovery of corticomotor output (reduced magnitude and duration of corticomotor depression) in the 30 minutes following resolution of acute muscle pain when compared with a condition where the painful limb remained at rest.

METHODS

Participants

Twenty, healthy, right-handed individuals volunteered to participate and were randomly allocated to either the Rest (4 male, 6 female; 27 ± 6 years, mean $\pm$ SD) or Movement (4 male, 6 female; 27 ± 6 years) group. Participants completed a transcranial magnetic stimulation (TMS) safety screen (10) prior to commencement and had no history of musculoskeletal, neurological or upper limb conditions. All subjects received written and verbal description of experimental procedures and provided written informed consent consistent in line with the Declaration of Helsinki. Experimental procedures were approved by the local human research ethics committee (N-20130055).

Experimental protocol

In both the Rest and Movement groups, fifteen motor evoked potentials (MEPs) were recorded from the right extensor carpi radialis brevis (ECRB) muscle at baseline, immediately following the resolution of experimental muscle pain (prior to the movement task in this group) and at 10, 20, and 30 minutes follow-up (Figure 1). In the Rest group, participants sat quietly, without moving for the duration of the experiment. Particular emphasis was given to keeping the right arm completely still and relaxed at all times. Participants in the Movement group were asked to repeat a right-sided unimanual pattern of five sequential keystrokes as quickly and as accurately as possible in two 3-

minute blocks, with 1-minute rest between blocks (11). Using the numbered keys from '2' to '5' on

a standard keyboard, participants were asked to repeat the sequence '3-5-2-4-3' using their right

hand. The sequence was provided on a computer screen placed in front of each participant. Previous

studies have mapped the long finger and extensor muscles following a similar 5-finger sequence

task and have shown an increase in corticomotor excitability in both muscle groups (12). The

Movement task was completed immediately following the resolution of experimental muscle pain

and prior to recording of the 10-minute follow-up measures.

Electromyography recordings

Electromyographic (EMG) activity was recorded from the right ECRB muscle using silver/silver

chloride surface electrodes (*Medicotest 720-01-K, Ambu A/S, Ballerup, Denmark*) positioned over

the muscle belly according to previous protocols (13). EMG signals were sampled at 2 kHz and

bandpass filtered at 20 Hz–1 kHz (*EM006-01, SMI, Aalborg, Denmark*). The EMG was further

digitized by a 16-bit data-acquisition card (*National Instruments, NI6122*) and saved by custom-

made Labview software (*Mr Kick, Aalborg University*).

Transcranial magnetic stimulation

Single pulse TMS was delivered using a Magstim 200 stimulator (*Magstim Co. LtD, Dyfed, UK*)

and a figure-of-eight coil. The coil was positioned over the left hemisphere at a 45-degree angle to

the sagittal plane for each participant to preferentially induce current in a posterior-to-anterior

direction. The optimal cortical site ('hotspot') to evoke responses in right ECRB, defined as the coil

position that evoked a maximal peak-to-peak MEP for a given stimulation intensity, was

determined and marked on the scalp. Stimulator intensity was set to evoke a peak-to-peak MEP of

approximately 0.5 mV in the relaxed ECRB muscle at baseline. This intensity was kept constant

throughout the experiment. Peak-to-peak MEP amplitude was measured and averaged across trials

for each participant at each time-point. All TMS procedures adhered to the TMS checklist for methodological quality (14).

Experimental muscle pain

The site for injection of the right ECRB muscle was determined using real-time ultrasound imaging and the skin was cleaned with alcohol. Pain was induced into the muscle by a bolus injection of 0.5 ml sterile hypertonic saline (5.8 %) using a 1-ml syringe with a disposable needle (27G) (15). Pain was recorded every 30 seconds using an 11-point numerical rating scale (NRS) anchored with 'no pain' at zero and 'worst pain imaginable' at 10, immediately following injection of hypertonic saline injection until the pain returned to zero. Muscle pain was considered resolved when a participant reported a pain score of 0/10 on the NRS. To capture the characteristics and distribution of pain, the McGill pain questionnaire was administered at the end of each experiment together with pain drawings.

Data and statistical analyses

A two-way analysis of variance (ANOVA) was used to compare differences between (*Rest vs. Movement*) and within (*baseline, immediately post pain, 10, 20 and 30 minutes follow-up*) groups over time. Normality was assessed using the Shapiro-Wilk test. MEP amplitude required log transformation to meet assumptions of normality. Where appropriate, post-hoc analyses were performed using Holm-Sidak multiple comparison tests. Peak pain NRS scores, pain duration, and TMS stimulator output required to evoke a MEP of approximately 0.5 mV at baseline in ECRB, were compared between groups (Rest vs. Movement) using t-tests. Linear regression was performed to examine associations between the magnitude of the MEP depression and peak pain and duration in both groups. All data in text are presented as mean ± standard deviation (SD). Statistical significance was set at $P<0.05$.

RESULTS

Experimental pain profile

Peak pain intensity (NRS scores) following injection of hypertonic saline was 7.5 ±1.6 in the Rest group and 6.2 ± 1.7 in the Movement group ($F_{1.18}$=3.2, P<0.09, Figure 2). The average pain duration was 8.2 ± 3.6 min for the Rest group and 6.5 ±1.6 min for the Movement group ($F_{1.18}$=1.7, P<0.20, Figure 2). The words most commonly used to describe pain in response to injection of hypertonic saline on the McGill pain questionnaire in both groups were cramping (75 % of participants), heavy (75 %), aching (70%), sharp (60 %), and tiring/exhausting (40 %).

Recovery of corticomotor excitability is not influenced by motor activity

The average stimulator output required to evoke a MEP of approximately 0.5 mV peak-to-peak amplitude in right ECRB was 53.6 ± 8.9 in the Rest group and 49.5 ± 9.5 in the Movement group ($F_{1.18}$=0.98, P<0.33). MEP amplitude was reduced in both groups (effect of time $F_{4.72}$=4.6, P<0.002; Figure 3) at 10 min (post-hoc: P<0.002), 20 min (post-hoc: P<0.02), and 30 min (post-hoc: P<0.037) following the resolution of pain relative to baseline. MEP amplitude was not reduced immediately following pain compared with baseline (post-hoc: P<0.33). However, this was due to two individuals who showed initial facilitation at this time-point in the Movement group (Figure 4A and B). Excluding these subjects from the MEP analysis did not reveal a difference between the Rest and Movement groups ($F_{1.64}$=0.23, P<0.63). There was no difference in the magnitude of MEP depression immediately following resolution of muscle pain based on gender when the two individuals who showed large facilitatory responses (both male) were removed (Male: -31 ± 18 %; Female: mean -27 ± 27 %). There was no association between the magnitude of MEP depression and peak pain or pain duration in either group (Rest: peak pain r=0.068, p=0.85; duration r=0.45, p=0.19; Movement: peak pain r=0.21, p=0.56; r=0.09, p=0.81).

DISCUSSION

Contrary to the hypothesis, performance of motor activity immediately following the resolution of acute muscle pain did not alter the magnitude or duration of corticomotor depression. These data suggest that a return to normal corticomotor output following pain: i) may depend on motor activity of a type or duration not examined here or that is delivered earlier than the post-pain period (i.e. immediately before or during pain), ii) may rely on cues other than motor activity (e.g. removal of threat), or iii) is reliant on the resolution of neurophysiological mechanisms that are time dependent. Understanding corticomotor depression in the post-pain period and what factors promote recovery has relevance for clinical pain where on-going motor dysfunction, in the absence of pain, may predispose to symptom persistence or recurrence.

A recent meta-analysis demonstrates a moderate reduction in corticomotor output, measured using TMS, *during* acute muscle pain when motor evoked potentials (MEPs) are elicited with the target muscle at rest but not under active contraction (2). Moreover, a strong reduction in corticomotor output in the *post-pain* period (0-30 minutes after the resolution of pain) was demonstrated when MEPs are elicited both at rest and under active contraction (2). Thus, corticomotor output is suppressed in the post-pain period and this effect appears to: i) persist for at least 30 minutes following pain (most studies cease recording at this time-point regardless of return to normal motor output), ii) be stronger than that which is present during muscle pain, and iii) be unaffected by the amount of motor activity required to measure MEPs under active contraction. The reason for maintained suppression of corticomotor output once pain has resolved is unclear. However, it has been hypothesized that suppression persists in the post-pain period as a defense against the threat of further pain and injury (16). Importantly, it has also been hypothesized that reduced corticomotor output that persists once pain has resolved in clinical populations could lead to sustained changes in movement patterns that alter loading on surrounding tissues, decrease movement variability, and predispose to persistent or recurrence of pain (16). As a result,

understanding the factors that promote a return to normal corticomotor output could have relevance in the treatment and prevention of musculoskeletal pain.

Counteracting the suppression of corticomotor output with motor activity is one strategy that could reduce the magnitude or duration of corticomotor suppression following acute muscle pain. Motor activity in a variety of forms has been repeatedly shown to increase corticomotor output in target muscles and adjacent task-related muscles (4). Indeed, a previous study using a similar 5-finger sequence task showed an increase in corticomotor excitability of the long finger flexors and extensors using TMS (12). It is therefore surprising that motor activity immediately following the resolution of pain in the current study had no effect on the magnitude or duration of corticomotor suppression. There are several possible explanations for this lack of effect. First, it is possible that a motor intervention may need to be delivered earlier (i.e. immediately preceding or during pain) to interfere with the development of corticomotor suppression. This is supported by data from studies that examined the effect of motor learning on pain and showed no change in corticomotor output (i.e. an absence of the characteristic decrease in corticomotor output expected with pain and an absence of the characteristic increase expected with motor learning, suggesting effects are cancelled out) when the task was performed during pain (8, 9). Similarly, a particular type of motor activity (e.g. motor learning, motor control, strength), specifically targeted to the painful muscle, may be required. Future studies should explore the optimal timeframe and type of motor intervention that best promotes a return to normal corticomotor output following pain. This information is important given that general advice to stay active is provided in most clinical guidelines for the management of acute clinical pain, yet it is unknown what type, how much or precisely when, motor activity should be adopted to improve clinical outcomes.

A second explanation for our findings is that motor activity does not provide a sufficient trigger for return to normal corticomotor output. It is possible that other factors, such as removal of threat, the stress response or psychosocial determinants are more important in driving the return to normal output. Indeed, these factors are known to correlate with recovery of function in some

people with clinical musculoskeletal pain [e.g.](17-19). However, this possibility has yet to be explored in response to acute muscle pain.

Finally, it is plausible that recovery of corticomotor output following acute muscle pain is related to time-dependent neurophysiological mechanisms. For example, it has recently been shown that circuits involved in sensorimotor integration (short-and long-latency afferent inhibition) exhibit less inhibition in response to acute muscle pain, but only once pain has resolved (20). These mechanisms are hypothesized to contribute to recovery of corticomotor output following pain. Eventual recovery may reflect a balance between the mechanisms involved in recovery (20) and those involved in generating a protective motor strategy (reduced corticomotor output) (1), causing corticomotor suppression to persist early after the resolution of pain. If this is the case, interventions that enhance the excitability of networks involved in sensorimotor integration may be more effective at promoting recovery following acute muscle pain.

This study has several limitations. First, data was collected on a relatively small sample. Although it is possible our sample was underpowered to detect an effect between groups, the data showed no evidence of a trend for an effect of group on corticomotor output over time (P<0.97). Second, a vehicle control was not included. Vehicle controls are commonly used in experimental pain studies and rarely, if ever, show an effect (21, 22). For example, previous studies of similar methodology have demonstrated no effect of intramuscular isotonic saline solution on the amplitude or latency of MEPs from upper limb muscles (23, 24). Further, corticomotor output has been shown to be stable during 30 minutes of controlled, quiet sitting (25) and is reliable over short (0-4 days) and long (0-14 days, 0-1 months) intervals (26, 27). Taken together, these findings indicate that the measures used in this study to evaluate corticomotor output are not sensitive to time effects. Thus, our findings are unlikely to be replicated in a no-pain control condition. Finally, it is unknown how these findings may translate to other forms of pain such as acute inflammatory or cutaneous pain or in individuals who experience an acute exacerbation of a chronic musculoskeletal pain condition.

Future studies should seek to examine corticomotor excitability and motor activity in these pain populations.

Conclusion

This pilot study is the first to examine the effect of a motor task performed immediately following the resolution of acute muscle pain on the magnitude and duration of corticomotor suppression. These data suggest that this intervention does not affect corticomotor output in the 30 minutes following resolution of acute muscle pain. Future studies should seek to determine whether different motor interventions applied at different stages of pain (i.e. immediately before or during), or other external triggers, are more effective at promoting recovery of corticomotor output following pain. Such data may have relevance for the treatment and prevention of clinical pain syndromes where persistence of altered corticomotor output could underpin persistence and recurrence of pain.

Author contributions

SS, TSP, and TG designed the study. SS and TSP collected the data. SS analyzed the data and drafted the manuscript. SS, TSP, and TG discussed the results, edited the manuscript, and approved the final version.

FIGURE LEGENDS

Figure 1. Experimental protocol for the Rest (top) and Movement (bottom) groups. A 1-minute rest period was applied between the two movement blocks in the Movement group.

Figure 2. Mean of pain intensity rated on the 11-point numerical rating scale (NRS) every 30 s from the time of hypertonic saline injection into the right extensor carpi radialis brevis muscle until each participant reported 0 for the Rest (filled circles; +SD) and Movement (open circles; -SD) groups.

Figure 3. Mean (+ SD) MEP amplitude at each time point in the Rest group (filled circles; -SD) and the Movement group (open circles; +SD). The grey box indicates the time of pain induced by hypertonic saline injection into the right extensor carpi radialis brevis muscle. Reduction in MEP amplitude from baseline (*, $P < 0.05$).

Figure 4. MEP amplitude expressed as a proportion of baseline for each individual in the Rest (top) and Movement (bottom) group at each time-point. The grey box indicates the time of pain induced by hypertonic saline injection into the right extensor carpi radialis brevis muscle. Note that two participants in the Movement group exhibited facilitation immediately following the resolution of pain.

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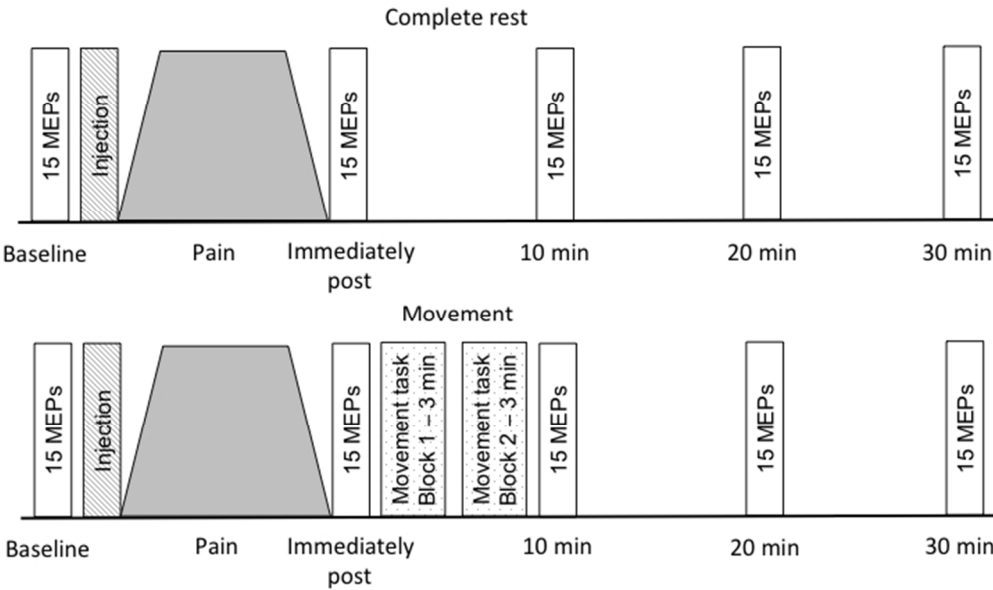
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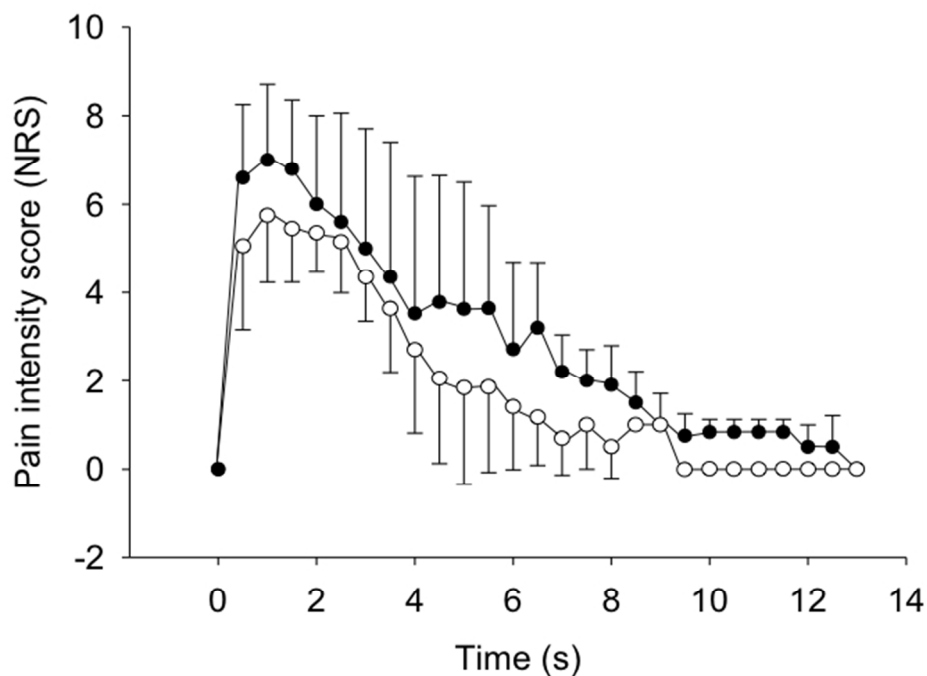
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Complete rest

15 MEPs | Injection | Pain | 15 MEPs | 15 MEPs | 15 MEPs | 15 MEPs

Baseline   Pain   Immediately post   10 min   20 min   30 min

Movement

15 MEPs | Injection | Pain | 15 MEPs | Movement task Block 1 – 3 min | Movement task Block 2 – 3 min | 15 MEPs | 15 MEPs | 15 MEPs

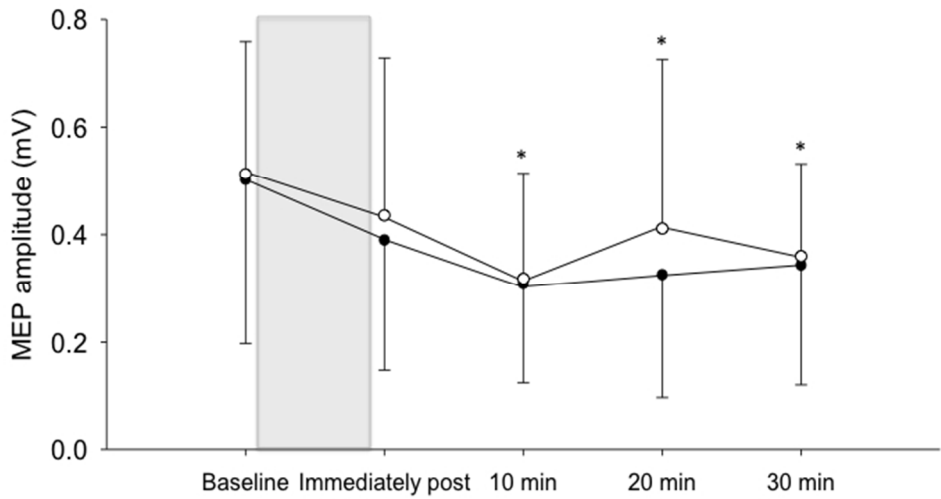Baseline   Pain   Immediately post   10 min   20 min   30 min

Experimental protocol for the Rest (top) and Movement (bottom) groups. A 1-minute rest period was applied between the two movement blocks in the Movement group.

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Mean of pain intensity rated on the 11-point numerical rating scale (NRS) every 30 s from the time of hypertonic saline injection into the right extensor carpi radialis brevis muscle until each participant reported 0 for the Rest (filled circles; +SD) and Movement (open circles; -SD) groups.

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Mean (+ SD) MEP amplitude at each time point in the Rest group (filled circles; -SD) and the Movement group (open circles; +SD). The grey box indicates the time of pain induced by hypertonic saline injection into the right extensor carpi radialis brevis muscle. Reduction in MEP amplitude from baseline (*, $P < 0.05$).

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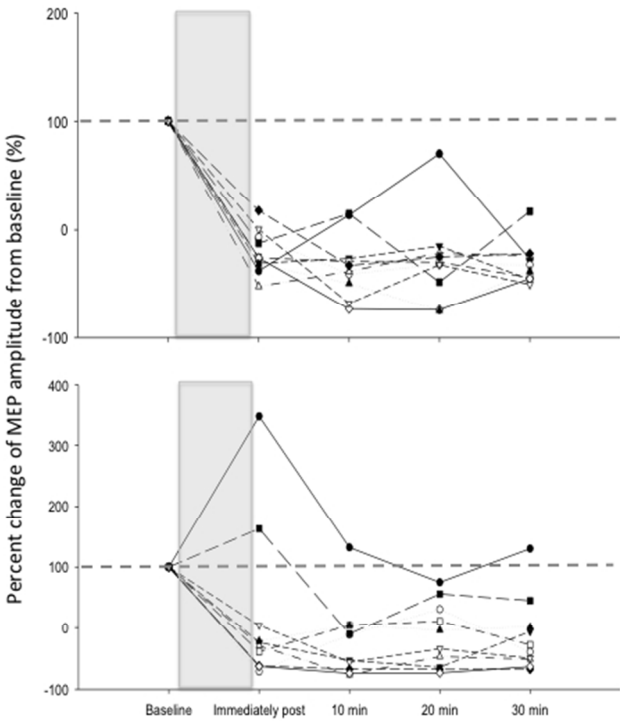
MEP amplitude expressed as a proportion of baseline for each individual in the Rest (top) and Movement (bottom) group at each time-point. The grey box indicates the time of pain induced by hypertonic saline injection into the right extensor carpi radialis brevis muscle. Note that two participants in the Movement group exhibited facilitation immediately following the resolution of pain.

254x190mm (72 x 72 DPI)