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HIGHLIGHTS:

- Action observation and motor imagery facilitate corticomotor excitability (CE)
- Intramuscular pain reduces CE
- Action observation and motor imagery counterbalance pain-induced reduction in CE

PAIN-INDUCED REDUCTION IN CORTICOMOTOR EXCITABILITY IS COUNTERACTED BY COMBINED ACTION-OBSERVATION AND MOTOR IMAGERY

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Running title: Action observation and motor imagery counteracts pain-induced reduction in corticomotor excitability

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ABSTRACT

Musculoskeletal pain reduces corticomotor excitability (CE) and methods modulating such CE reduction remain elusive. This study aimed to modulate pain-induced CE reduction by performing action observation and motor imagery (AOMI) during experimental muscle pain. Twelve healthy subjects participated in three cross-over and randomized sessions separated by one week. During the AOMI session subjects performed an AOMI task for 10 mins. In the AOMI+PAIN session, hypertonic saline was injected in the first dorsal interosseous (FDI) muscle prior to performing the AOMI task. In the PAIN session, subjects remained at rest for 10 min or until pain-resolve after the hypertonic saline injection. CE was assessed using transcranial magnetic stimulation motor-evoked potentials (TMS-MEPs) of the FDI muscle at baseline, during, immediately after, and 10 min after AOMI and/or PAIN. Facilitated TMS-MEPs were found after two and four mins of AOMI performance (P<0.017) whereas a reduction in TMS-MEPs appeared at four mins (P<0.017) during the PAIN session. Performing the AOMI task during pain counteracted the reduction in CE, as evident by no change in TMS-MEPs during the AOMI+PAIN session (P>0.017). Pain intensity was similar between the AOMI+PAIN and PAIN sessions (P=0.71). This study, that may be considered a pilot, demonstrated the counteracting effects of AOMI on pain-induced reduction in CE and warrants further studies in a larger population.

PERSPECTIVE:

This is the first study to demonstrate a method counteracting the reduction in corticomotor excitability associated with acute pain and advances therapeutic possibilities for individuals with chronic musculoskeletal pain.

Keywords: Corticospinal excitability, mirror neuron system, experimental muscle pain, Action observation, Motor imagery

INTRODUCTION

Pain education and exercise are interventions known to assist recovery of function in patients with musculoskeletal pain [6,37]. However, it still remains unknown how to target the well-established sensorimotor changes occurring in response to acute or chronic muscle pain [45]. Acute experimental muscle pain reduces corticomotor excitability [35,46,59] and a body of evidence suggest that patients with chronic musculoskeletal pain show a reduction in corticomotor representation of the muscles in pain [57,67]. Indeed, persistent pain can alter our movement patterns and may serve to protect the painful limb against further harm [31] and as result lead to long-standing, possibly maladaptive, changes in cortical motor excitability. This notion is supported by experimental studies, where acute pain modifies movement patterns [8,34] as well as cortical motor excitability governed by the primary motor cortex (M1) [12].

The pain-induced reduction in corticomotor excitability during experimental pain is most commonly assessed using transcranial magnetic stimulation (TMS) motor-evoked potentials (MEPs). Reduced TMS-MEPs are consistently demonstrated across different experimental pain modalities such as muscle pain [35,46,58], skin pain [21], and noxious heat [68,69]. Interestingly, such pain-related reduction in corticomotor excitability is maintained at pain-resolve and lasts for up to 30 mins after pain has disappeared [46,56] suggesting that it is not pain perception per se that drives the reduction. In contrast, ballistic repetitive motor practice [13,41] and novel goal-directed motor practice [7,25], action observation

(AO) [20,33,62] and motor imagery (MI) [9,11,16,23,61] facilitate TMS-MEPs. AO and MI are considered motor simulation paradigms [32] as opposed to motor practice which is the actual execution of e.g. repetitive movements [41]. By observing or imagining movements without overt movement [19], the so-called 'action observation network' is engaged [14]. The facilitating effects of actual movement execution and AO or MI are believed to be mediated by overlapping neuroanatomical structures [14,32]. For instance, Porro et al. [48] demonstrated that activation patterns of precentral and postcentral gyri were similar between motor execution and MI of self-paced finger-to-thumb opposition movements. It is therefore not surprising that observing or imagining movement can facilitate corticomotor excitability. Early premotor cortex (PMC) studies in macaque monkey, demonstrated the so-called mirror neurons which discharge during the observation of movements performed by others [26,51]. In humans, AO and MI performance led to activation of the ventral and dorsal premotor cortex (PMC) as demonstrated by functional magnetic resonance imaging [10,14], and is considered to influence primary motor cortical (M1) excitability through strong reciprocal connections between the PMC and M1 [65,66]. Thus, there is a neuroanatomical substrate to influence MI excitability by AO and MI. Combining AO and MI (AOMI) as a task yields a greater facilitating effect on corticomotor excitability than when performed separately [19]. Furthermore, AO and MI, separately and combined, have shown similar efficacy for stroke rehabilitation [19].

This study aimed to determine the effects of performing an action observation and motor imagery (AOMI) task on corticomotor excitability during acute experimental muscle pain. It was hypothesized that (1) AOMI would counteract the reduction in corticomotor excitability during experimental muscle pain compared to baseline, and (2) AOMI would normalize the pain-induced reduction in corticomotor excitability at pain-resolve.

METHODS

Subjects

Sample size calculations were performed based on the standardized mean difference [0.52 (-0.01, 1.06)] from a recent meta-analysis on the effect of experimental pain on MEPs [12]. With type I and type II errors set to 5% and 20%, respectively, and high correlation between repeated measures (0.8) [36], 10 subjects were needed. To account for drop-out, two extra subjects were included (20%). Sample size calculations were performed in G*Power version 3.1.9.2. (Universität Düsseldorf). Twelve pain-free, left- and right-handed subjects [2] were included (average age ± SD: 25.8 ± 3.7 years; six women). All subjects were screened for eligibility in receiving TMS, using a standardized safety questionnaire [52,53]. Handedness for each subject was determined by Edinburgh Handedness Inventory [44]. One subject was left-handed based on the laterality quotient (L.Q. = -0.8), whereas the remaining 11 were right-handed (L.Q. = 0.74 ± 0.25). One right-handed subject was excluded from all analyses due to having MEPs exceeding up to ± 27 SDs (AOMI session) of the sample mean (total n = 11). Before participating, subjects received oral and written information about the procedures and provided written informed consent. The study was approved by the local ethics committee (VN-20170006) and conducted in accordance to the Declaration of Helsinki.

Experimental design

In a cross-over and randomized design, the subjects participated in an AOMI only session (AOMI), an AOMI and pain session (AOMI+PAIN), or a pain only session (PAIN; Fig. 1). Each session was separated by at least one week and sequence of sessions was randomized. During the AOMI session, an AOMI task was performed for 10 mins. In the AOMI+PAIN task, hypertonic saline was injected into the first dorsal interosseous (FDI) muscle before performing the AOMI task for 10 mins. For the PAIN session, subjects were injected with hypertonic saline in the FDI muscle and remained at rest until pain-resolve.

Baseline corticomotor excitability was assessed by 20 TMS-MEPs and always recorded immediately after AOMI familiarization. Another 100 TMS pulses were delivered over 10 min during the AOMI and/or PAIN sessions. Twenty follow-up TMS-MEPs were recorded immediately after and 10 min after the AOMI

performance. In the AOMI+PAIN and PAIN sessions, the 20 TMS-MEPs follow-up recordings were done at pain-resolve and 10 min after pain-resolve. MEPs were recorded while observing and imagining the AOMI task during the AOMI and AOMI+PAIN sessions. For the PAIN session, MEPs were recorded while the subjects remained at rest.

Action observation and motor imagery task

The AOMI task consisted of pre-recorded video clips of index finger abductions and adductions performed by a Caucasian male or female. One trial of the AOMI task consisted of observing and imagining two index finger abductions and adductions. Subjects were familiarized with the AOMI task (three consecutive trials). The AOMI task was shown on a 17-inch monitor placed 90 cm away from the subjects (from nasion to the middle of the monitor). Each AOMI trial lasted four seconds, followed by a 2 second black screen (screenshot of the task movement is shown in Fig. 2).

The subjects were asked to imagine performing the AOMI task movement, without any volitional movement of the index finger. Since the investigator was placed immediately behind the subject, the absence of volitional movement was ensured by observation. After every 20 AOMI trials (2 mins), a screen-prompt to rate the pain intensity appeared (AOMI+PAIN and PAIN sessions) or attention to the AOMI task, as control rating. Numerical rating scale (NRS) ratings of attention were recorded, with anchors '*0*' representing '*no attention*' and '*10*' representing '*most attention imaginable'*. Attention NRS ratings were obtained at 2, 4, 6 ,8, and 10 min while performing the AOMI task. A total of 100 AOMI task trials (10 mins) were performed during the AOMI or the AOMI+PAIN session. The AOMI trials were coded in E-prime 3.0 (Psychology Software Tools, Sharpsburg, PA).

Motor evoked potentials

All TMS methods are described in accordance to the recent guidelines on TMS methodology reporting [15]. A magnetic stimulator (Magstim BiStim^2, Magstim Company, UK) was used to deliver monophasic pulses, using a focal figure-of-eight coil (D70^2, Magstim Company, UK). To induce a posterior-anterior directed current eliciting MEPs from the FDI muscle, the coil handles was pointing backwards and laterally at a 45° angle to the sagittal plane. An interstimulus interval of 5-7 seconds was used. Each subject was fitted with a swimming cap containing a pre-defined grid (1 × 1 cm squares, orientated to vertex; 0,0). The swimming cap ensured standardized orientation and location of the delivery of TMS pulses and was employed to determine the optimal scalp position and resting motor threshold (RMT) for the FDI muscle. The optimal scalp position was determined using 50% of maximum stimulator output and was defined as the site that yielded the highest and most consistent peak-to-peak amplitude MEPs in three trials. The RMT was determined based on the stimulator output intensity needed to evoke MEPs ≥ 50 µV in the FDI muscle in five out of 10 trials with the muscle at rest [55]. A stimulation intensity of 120% × RMT was used for the remaining of the session. An interstimulus interval of 5-7 seconds was used for repeated TMS-MEP recordings throughout the experimental sessions.

Bipolar Ag/AgCl electrodes (Neuroline 720, Ambu® A/S, DK) were placed at the muscle belly of the FDI muscle, with an approximate 20 mm interelectrode distance. The reference electrode was placed at the styloid process. The electromyography (EMG) data was pre-amplified (1000x gain), analogue band-pass filtered (5 Hz-1 kHz) and sampled at 4 kHz by a 16-bit data-acquisition card (National Instruments, NI6122). Peak-to-peak TMS-MEPs were shown on-line by custom-made LabView software (Mr. Kick III, SMI, Aalborg University). A window of 100 ms pre-TMS stimulation was used to confirm that no movement (pre-contraction) or tension in the muscle was present before the stimulation. Similar to a previous protocol [35], peak-to-peak amplitude was extracted for each MEP and averaged across sequential 20 MEPs. The averaged MEPs were used for analysis. The grand mean of pain-resolve and pain-resolve+10 was used to reflect follow-up TMS-MEPs.

Hypertonic saline injection

The injection site was determined by palpation of the contracted FDI muscle. The skin was cleaned with alcohol, and pain was induced by a bolus injection of sterile hypertonic saline (0.2 mL, 5.8% NaCl) into the FDI muscle, using a 1 mL syringe with a disposable needle (27G) [35,46]. The participants assessed their pain intensity rating verbally on a NRS, with '*0*' representing '*no pain*' and '*10*' representing '*worst imaginable pain*'. NRS ratings were obtained immediately after, and 2, 4, 6 ,8, and 10 min after the injection and every minute until pain-resolve. Pain-resolve was defined as the first time the NRS scores was zero.

Statistical analyses

Normal distribution of the data was tested using Shapiro-Wilk's test for normality. Since data exhibited non-normal distribution across several time-points, all MEPs were log-transformed (base 10) and used for subsequent analyses. Pain-induced reduction in TMS-MEPs peaks from 2-4 mins [35,46] and planned contrasts were performed between baseline and 2-4 mins, as well as between baseline and follow-up measures.

To investigate if AOMI could counteract the pain-induced reduction in corticomotor excitability, a two-way repeated measures analysis of variance (RM ANOVA) was used with within-subjects factors session (AOMI, AOMI+PAIN, and PAIN) and time (baseline, 2 mins, 4 mins, and follow-up). Post hoc tests were carried out by simple main effects analyses reflecting one-way RM ANOVAs within each session and at each time-point across the three sessions. Planned contrasts were run between baseline MEPs and 2 mins or 4 mins to show the effects of AOMI, AOMI and PAIN, or pain on FDI-MEPs during experimental muscle pain. To investigate the follow-up measures (after pain-resolve), a planned contrast was also performed for baseline

versus follow-up MEPs. Planned contrast analysis was corrected for multiple contrasts by applying false discovery rate (FDR) [5].

Pain NRS scores were analyzed using a two-way RM ANOVA, with within-subjects session (AOMI+PAIN and PAIN) and time (11 time-points from immediately after injection to 15 mins post-injection). Attention NRS-ratings were analyzed using a one-way repeated RM ANOVA with time as within-subjects factor (2-10 mins of performance). FDR was applied for the NRS scores of pain and attention when appropriate.

All statistical analyses were performed in Statistical Package for Social Sciences (SPSS; version 25, IBM). Data are presented as mean and standard error of the mean (SEM).

A *P*-value < 0.05 was considered statistically significant for the two-way (MEPs and pain NRS) and one-way (attention NRS) RM ANOVAs, whereas the FDR corrected multiple contrasts were required to reach a P_{FDR}-value < 0.017 to be considered significant.

RESULTS

The baseline RMT of the FDI muscle was 43.2% ± 4.2 (AOMI), 41.7% ± 3.7 (AOMI+PAIN), and 42.5% ± 3.9 (PAIN) of maximum stimulator output. The anterior-posterior distance from vertex (0,0) for the optimal scalp position (FDI muscle) in the AOMI, AOMI+PAIN and PAIN sessions was 2.18 cm ± 0.4, 2.09 cm ± 0.30, and 1.82 cm ± 0.40, respectively. The corresponding medio-lateral distances were 4.00 cm ± 0.70, 4.18 cm ± 0.60, and 4.36 cm ± 0.80, respectively.

TMS-MEPs did not reduce in response to hypertonic saline-induced pain during AOMI

A significant interaction between session and time was found (Fig. 3; $F_{6,60} = 6.33$, $P < 0.0005$, $\eta^2_{partial} = 0.39$). Post hoc analysis revealed a session difference between baseline FDI MEPs ($F_{2,20} = 8.41$, $P = 0.002$, $\eta^2_{partial} = 0.46$), with lower baseline MEPs for the AOMI session compared to the AOMI+PAIN session (Fig. 3; $P_{FDR} < 0.017$). The baseline MEPs did not differ between the AOMI and PAIN sessions (Fig. 3, $P_{FDR} > 0.017$). Similarly, baseline measures did not differ between the AOMI+PAIN and PAIN sessions (Fig. 3, $P_{FDR} > 0.017$). At 4 mins, a difference in TMS-MEPs was found ($F_{2,20} = 5.2$, $P = 0.015$, $\eta^2_{partial} = 0.34$) with the MEPs of the AOMI session being increased compared to the PAIN session (Fig. 3; $P_{FDR} < 0.017$). Conversely, MEPs were not different between the three sessions after 2 mins (Fig. 3; $F_{2,20} = 1.2$, $P = 0.33$, $\eta^2_{partial} = 0.1$) or at follow-up measures (Fig. 3; $F_{2,20} = 0.65$, $P = 0.54$, $\eta^2_{partial} = 0.06$). During the AOMI session (Fig. 3; $F_{3,30} = 5.47$, $p = 0.004$, $\eta^2_{partial} = 0.35$), an increase in FDI MEPs was found at 2 mins and 4 mins (Fig. 3; $P_{FDR} < 0.017$) compared with baseline. During the PAIN session MEPs changed significantly over time (Fig. 3; $F_{3,30} = 4.14$, $P = 0.014$, $\eta^2_{partial} = 0.29$), with a reduction in FDI MEPs after 4 mins (Fig. 3; $P_{FDR} < 0.017$). A significant time-effect was found for the AOMI+PAIN session (Fig. 3; $F_{3,30} = 3.77$, $P = 0.02$, $\eta^2_{partial} = 0.27$), but FDR corrected planned contrasts showed no change in FDI MEPs at any time-point compared to baseline (Fig. 3; all $P_{FDR} > 0.017$). The mean raw MEPs from each session across time are available in Table 1.

Similar pain NRS scores in the two PAIN sessions, and NRS attention scores in AOMI session

The two-way RM ANOVA on pain NRS scores did not reveal a significant session × time interaction (Fig. 4; $F_{12,132} = 0.74$, $P = 0.71$, $\eta^2_{partial} = 0.06$). Conversely, a strong effect of time was found ($F_{12,132} = 57.12$, $P < 0.005$, $\eta^2_{partial} = 0.84$). Post hoc tests showed that pain NRS scores significantly reduced after 8 mins up until pain-resolve ($P_{FDR} < 0.007$) as compared to intensity ratings immediately following the injection. The one-way RM ANOVA did not show any effect of time on the attention ratings ($F_{4,44} = 0.64$, $P = 0.64$, $\eta^2_{partial} = 0.06$) (grand mean attention rating ± SEM: 7.9 ± 0.08).

DISCUSSION

This is the first study to demonstrate a modulation of pain-induced reduction in corticomotor excitability using a paradigm based on engaging intracortical mechanisms between the PMC and M1. Results show that performing an AOMI task during acute experimental muscle pain counteract the reduction in corticomotor excitability that would otherwise occur. The current findings suggest that engaging the "action observation network" may enhance motor rehabilitation training regimes for musculoskeletal pain patients. Furthermore, this study showed that the pain intensity remained the same while performing the (AOMI) task supporting that the intensity of pain is unrelated to the change in corticomotor excitability.

Non-primary motor areas may counterbalance pain-induced corticomotor excitability reduction

The current study is the first to show that AOMI performance counteract the pain-induced reduction in corticomotor excitability. This may indicate a competitive system between efferent motor output as elicited by AOMI and TMS and afferent nociception as induced by the hypertonic saline injection. Indeed, earlier studies support that innocuous and noxious heat input affects movement preparation, in that sensory-evoked potentials and MEPs related to movement preparation reduce [42,49] or increase [39], however, this has never been explored in combination with AOMI. This opens an interesting avenue for future research to understand the possible competing nature of corticomotor facilitation by AOMI and pain-induced reduction in M1 excitability. Earlier studies employing TMS-MEPs as an outcome measure, have attempted to disentangle the influence of cortical and spinal excitability, and it is, at present, well-accepted that the reduction in TMS-MEPs due to muscle pain is of cortical origin [21,46].

At present, the functional benefits of the pain-induced reduction in corticomotor excitability is hypothetical [12] and has, until the current study, been difficult to modulate. Previously it was shown that performing a finger-tapping task immediately following an injection of hypertonic saline into the extensor

carpi radialis brevis muscle did not promote corticomotor excitability recovery [59]. This finding implies that volitional movement is not the driving factor during corticomotor excitability recovery after pain. The current study employed indirect influence on M1 excitability through AOMI. During performance of AOMI, activation of the PMC has consistently been reported [14,47]. In monkeys, reciprocal connections project from the PMC to the M1 muscle representations [65,66]. This neuroanatomical and functional connection was later demonstrated in humans using TMS [17]. The idea that the PMC can drive M1 excitability comes from earlier evidence that have investigated both ipsilateral [27] and contralateral effects [40] of PMC inhibition and the concurrent reduced response from M1 TMS stimulation. In addition, facilitation of MEPs was shown by using high-frequency rTMS [50], suggesting that facilitation of PMC excitability yields increased M1 excitability. It could be argued that differences in attention during AOMI and/or PAIN sessions [18] could explain the non-significant changes in MEPs. This is, however, unlikely since the magnitude of pain intensity is not associated with MEP reduction [35,59], and given the similar pain ratings during the AOMI+PAIN and PAIN sessions, pain intensity is not sufficient to explain the lack of MEP change during AOMI+PAIN. Furthermore, attention-ratings were recorded during the AOMI session and subjects were required to attend to rating rather than performing the AOMI task (similar to the pain sessions). It cannot be excluded that rating attention rather than pain may have influenced the MEPs differently during the AOMI and the PAIN sessions, respectively, since attention-ratings were not obtained during the PAIN sessions and vice versa. Nonetheless, perceptual and cognitive-related brain activation remain robust while performing a multisource interference task during pain [60], and rating differences are unlikely to have influenced the AOMI+PAIN session findings. As such, it is plausible, yet hypothetical, that the counteracting effect on corticomotor excitability reduction by AOMI is achieved through adjacent non-primary motor areas. This finding further adds to the idea of applying AOMI during e.g. re-acquisition of motor skills after pain. An interesting perspective for future research would be to transiently inhibit PMC excitability by rTMS [27] and subsequently perform AOMI while being in pain, to elucidate if PMC is the main driver of M1 excitability changes during AOMI performance. However, importantly, at the relevance of AOMI in clinical

pain conditions remains speculative [19], albeit promising results have been shown in for example stroke rehabilitation [24,63].

AOMI induces strong facilitation of corticomotor excitability

The current findings demonstrate that AOMI induces a strong facilitation in corticomotor excitability, which has previously been demonstrated for AO [20,62], MI [54,61], and combined AOMI [43,73,74]. Corticomotor excitability facilitation in response to AO is currently believed to be driven by both cortical [62] and spinal [3] mechanisms, whereas MI is mainly of cortical origin given the lack of H-reflex response during performance [1]. Thus, the facilitation observed in the current study is likely mediated through both cortical and spinal influences.

Traditionally, AO and MI have been explored separately as external versus internal motor simulation paradigms, respectively [71]. However, since neural structures that become activated during performance of either AO or MI and motor execution largely overlap [32], and holds true for the upper [22] and lower limbs [70], an influential review suggested the combination of AO and MI, as a superior technique in engaging brain areas associated with action preparation [71].

Furthermore, the facilitatory effects of AOMI has been well-established in motor tasks relating to both simple and sequential finger movements [73,74], as well as motor tasks requiring fine motor control [43]. Further research is needed to elucidate if the reversal of the reduction in corticomotor excitability carries over into performance measures and the possible clinical benefit.

Acute experimental muscle pain reduces corticomotor excitability

The current data from the experimental pain session supports earlier findings from our group [35,46] and others [21,59,68,69]. It is well-known that the corticomotor excitability reduction in response to acute experimental pain is robust [12], and is believed to be mediated through facilitatory glutamate-mediated and inhibitory gamma-aminobutyric acid-mediated intracortical networks [58]. The present findings also confirm the previously reported temporal profile of corticomotor reduction and a return to baseline within the first 10 mins following hypertonic saline injection into a muscle [35]. However, earlier evidence has demonstrated a lasting reduction in corticomotor excitability for up to 30 mins post pain-resolve [46,57]. Whereas pain exerts a robust reduction effect on corticomotor output that may last up to 30 mins post pain-resolve, it remains elusive if choice of TMS stimulation paradigm (TMS stimulation every 6th second in the current study) influences corticomotor excitability recovery. It is possible that the constant barrage of magnetic pulses during this study is enough to induce M1 excitability recovery towards baseline values. Regardless, the current study supports the reduction in corticomotor excitability by acute muscle pain, and earlier findings on a return-towards-baseline MEPs at post-measures [35].

Limitations

Special consideration must be made with regards to the difference at baseline between AOMI and AOMI+PAIN. The current study was a planned randomized cross-over design and a difference in baseline cortical excitability was an unexpected finding. Prior studies have shown good to excellent reliability in corticomotor excitability measures such as RMT for baseline recordings in healthy subjects [36,38] though recent evidence suggests optimization of methodological and statistical methods [4]. One possibility is that the facilitation in corticomotor excitability is due to lower corticomotor excitability at baseline as compared to the AOMI+PAIN session. While this cannot be excluded, the conclusion on the counteracting effects of AOMI on the pain-induced reduction in corticomotor excitability remains unaffected, since the baseline MEPs were lower only in the AOMI session. The low sample size of the current study makes it unfeasible to

generalize the current findings. This may remain a point of contention, but the study was powered to detect the pain-induced reduction in corticomotor excitability. Furthermore, findings from our group [35,46] others [12,59] show a similar degree of corticomotor excitability reduction with similar groups. The low sample size is a product of often highly correlated measures (MEPs over time) [36], moderate effect of pain on MEPs [12], and the increased power that repeated measures designs offer to detect changes in outcome variables [30]. Considering these strengths to the current study design and the fact that two control conditions were included to account for each constituent of the combined session (AOMI+PAIN), the lack of facilitation or reduction of MEPs during the AOMI+PAIN session is unlikely a result of random factors such as between-subjects variation in TMS response [72] or a low sample size. An additional control for the PAIN session was not included as ample evidence is available showing that non-painful isotonic saline injections does not modulate TMS-MEPs [46,56,64]. Despite being an acute experimental pain model, the hypertonic saline model has been shown to induce both local and referred pain [29], as found in e.g. osteoarthritis and fibromyalgia patients [28] underscoring its relevance in musculoskeletal pain research.

In summary, this study provides the first evidence that corticomotor excitability reduction is attenuated by performing AOMI during acute muscle pain potentially through interaction with non-primary motor cortical areas. Additional studies in larger cohorts are needed to confirm these novel findings.

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FIGURE LEGENDS

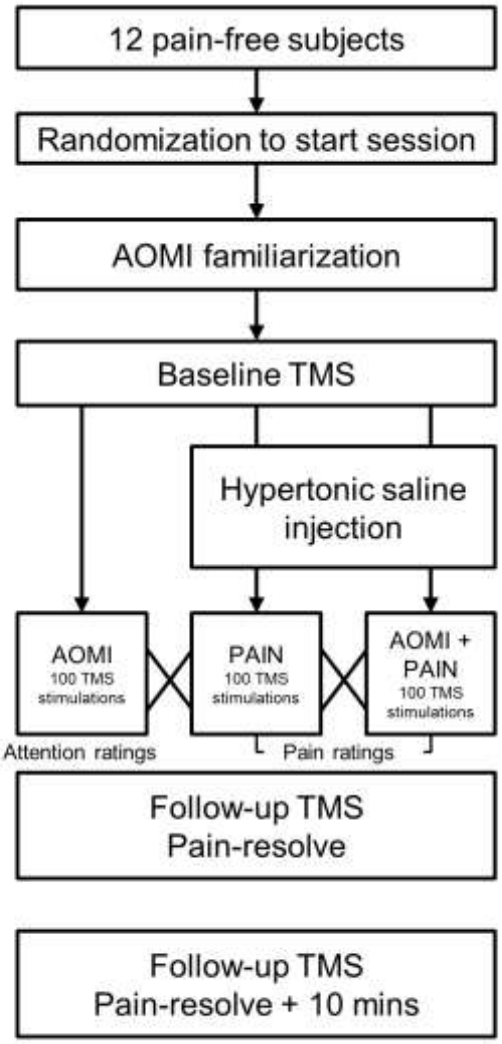

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Figure 1. Experimental design. Subjects were randomized to start with the AOMI, AOMI+PAIN, or PAIN session and then crossed over with one week in-between each session. Familiarization with the AOMI task was allowed before baseline transcranial magnetic stimulation (TMS) measures were recorded. Corticomotor excitability was assessed throughout the AOMI performance (AOMI and AOMI+PAIN

sessions) or while remaining at rest (PAIN). Pain was induced by an injection of hypertonic saline into the first dorsal interosseous (FDI) muscle. Pain intensity ratings were obtained throughout the AOMI+PAIN and PAIN sessions whereas attention ratings towards the AOMI task were recorded during the AOMI session.

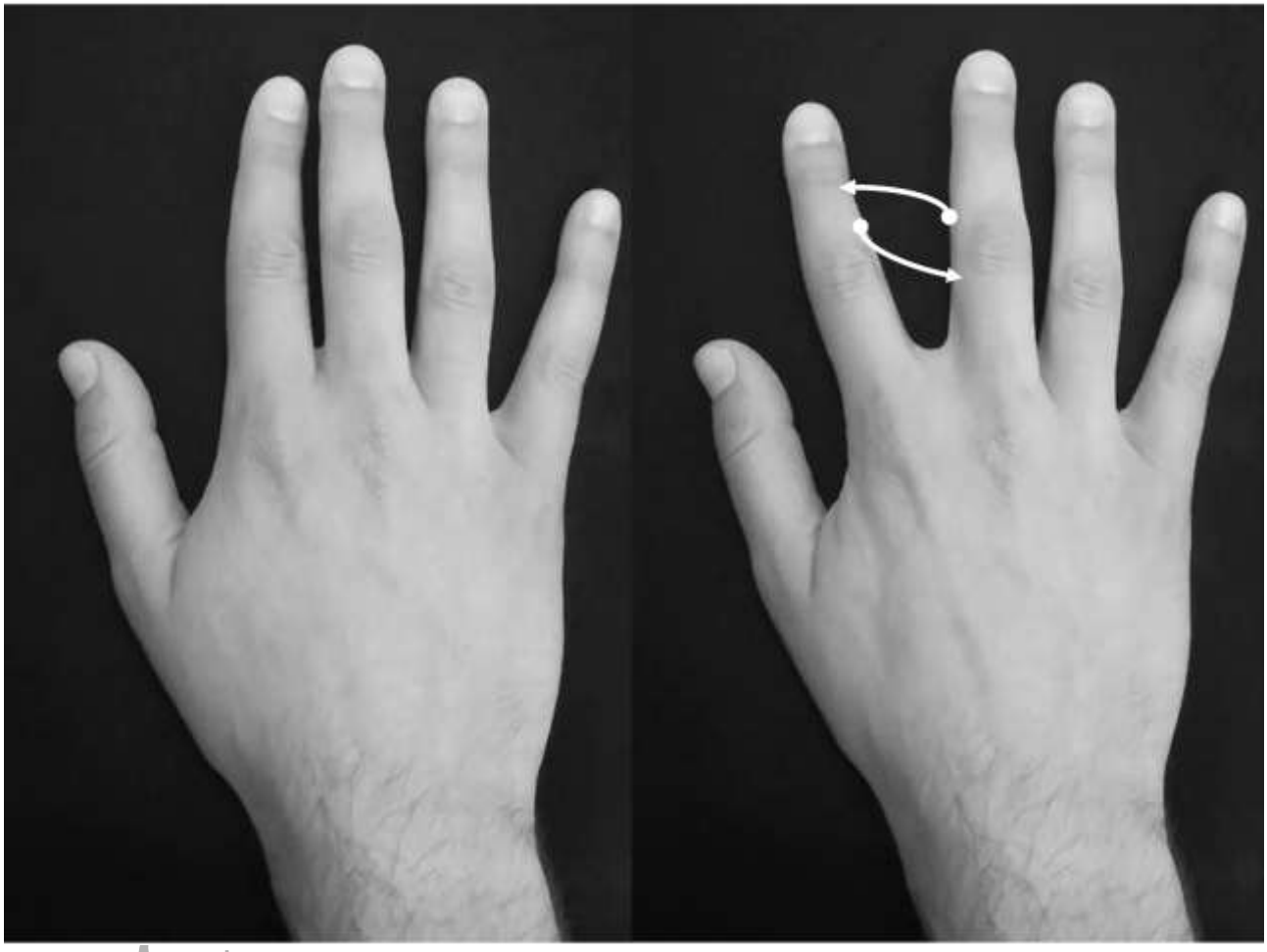

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Figure 2. Action observation and motor imagery task. Subjects observed the index finger abductions-adductions on a video clip and were explicitly instructed to imagine performing the same movement,

without overtly moving their hand. Each AOMI (Action observation combined with motor imagery) trial consisted of two index finger abductions-adductions and lasted four seconds, followed by a black screen for two seconds preceding the next AOMI trial.

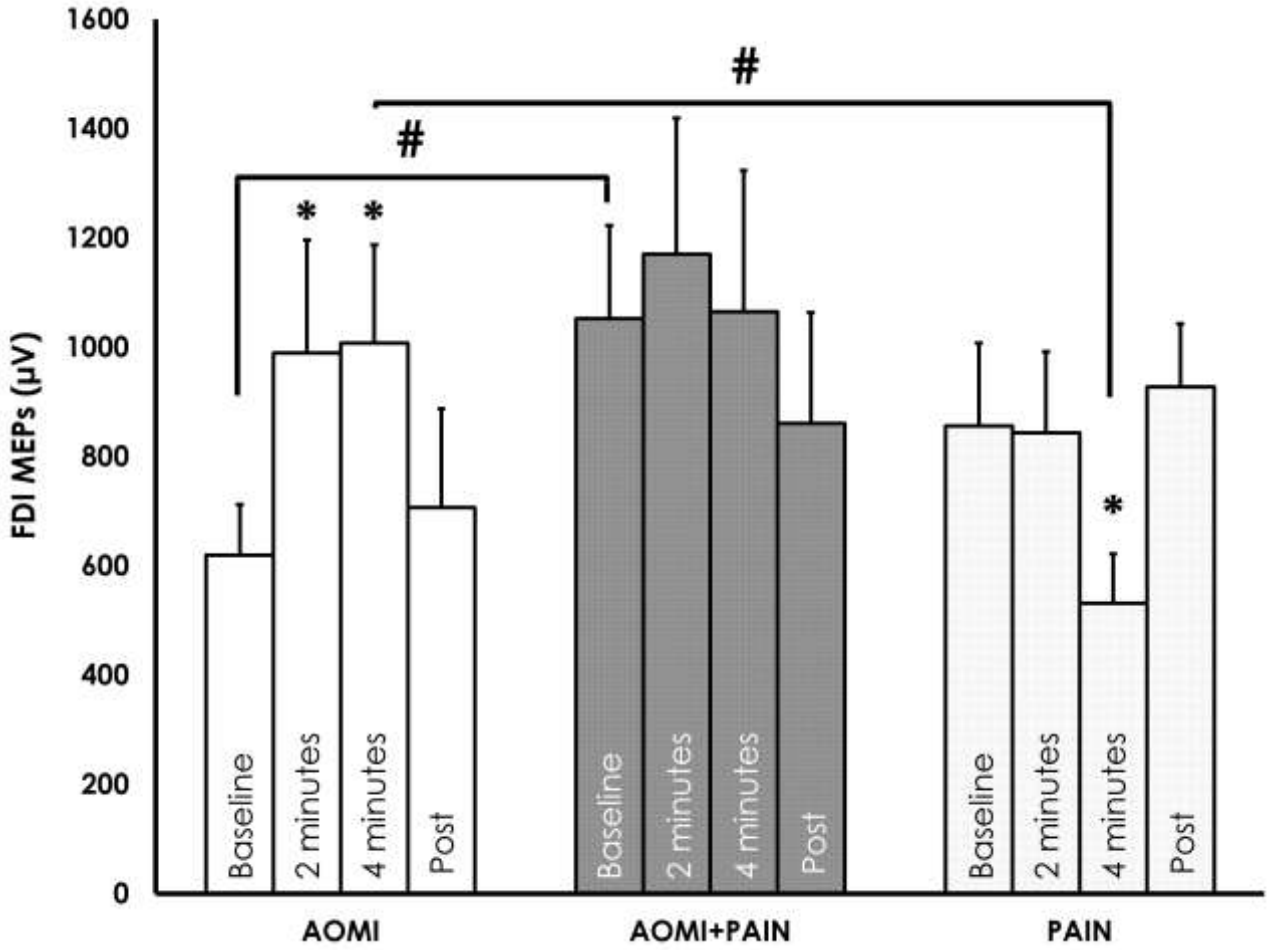

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Figure 3. Mean (+ SEM) first dorsal interosseous (FDI) motor evoked potentials (MEPs). FDI-MEPs during the AOMI (action observation combined with motor imagery, open bars), AOMI+PAIN (AOMI and injection of hypertonic saline, grey bars), and PAIN (black bars) sessions. Changes in FDI MEP compared with

baseline (*, P_{FDR} < 0.017) or compared with AOMI within the same time (#, P_{FDR} < 0.017).

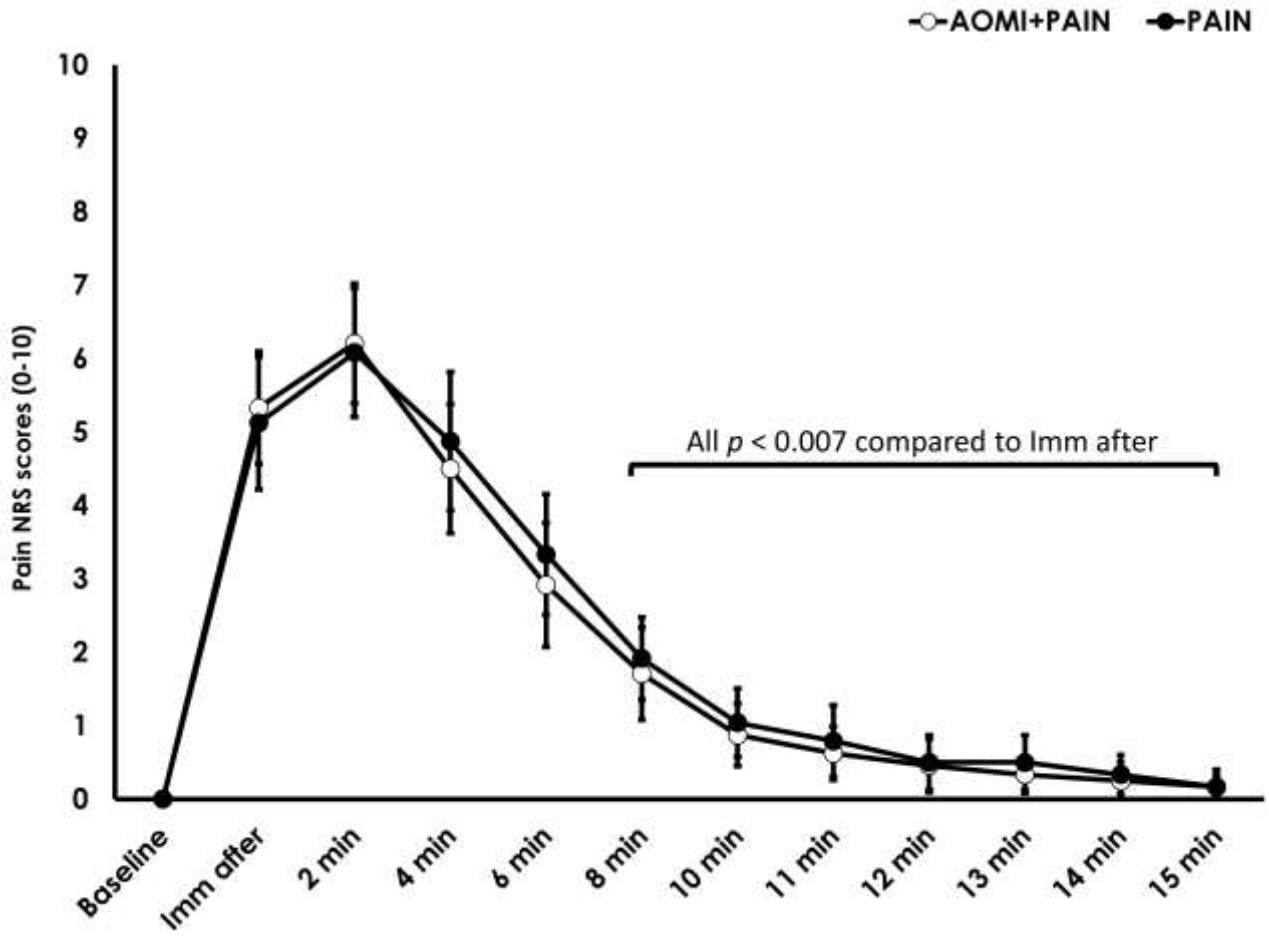

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Figure 4. Mean (+ SEM) pain numerical rating scores (NRS) following injection of hypertonic saline into the first dorsal interosseous muscle. The AOMI+PAIN (open circles) and PAIN (solid circles) sessions elicited not a significant difference in pain NRS scores (P_{FDR} = 0.71). *AOMI*: Action observation combined with motor imagery.

TABLE LEGENDS

Table 1. Mean ± SEM of raw the MEPs in each session across time. A significant baseline difference was found between the AOMI and AOMI+PAIN sessions (*Italics*). Within-session, MEPs significantly increased during the AOMI session at 2-4 mins (**Bold**), whereas MEPs significantly decreased during the PAIN session (**Bold**).

	Baseline	2 mins	4 mins	Follow-up
AOMI SESSION Motor-evoked potentials *Mean µV ± SEM*	*619.56 ± 92.75*	**989.38 ± 206.86**	**1007.8 ± 179.59**	706.75 ± 115.4
AOMI + PAIN SESSION Motor-evoked potentials *Mean µV ± SEM*	*1052 ± 170.36*	1170.6 ± 248.11	1065 ± 258.5	861.16 ± 202.24
PAIN SESSION Motor-evoked potentials *Mean µV ± SEM*	856.18 ± 151.23	843.36 ± 148.5	**531.83 ± 90.29**	927.42 ± 180.34

AOMI: Action observation combined with motor imagery; SEM: Standard error of the mean. *Note: Data analysis was performed on log-transformed MEPs.*