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Observing back pain provoking lifting actions modulates corticomotor excitability of the observer's primary motor cortex

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ABSTRACT

Observing another person experiencing exogenously inflicted pain (e.g. by a sharp object penetrating a finger) modulates the excitability of the observer' primary motor cortex (M1). By contrast, far less is known about the response to endogenously evoked pain such as sudden back pain provoked by lifting a heavy object.

Here, participants ($n = 26$) observed the lifting of a heavy object. During this action the actor (1) flexed and extended the legs (LEG), (2) flexed and extended the back (BACK) or (3) flexed and extended the back which caused visible pain (BACKPAIN). Corticomotor excitability was measured by applying a single transcranial magnetic stimulation pulse to the M1 representation of the muscle erector spinae and participants scored their perception of the actor's pain on the numeric pain rating scale (NPRS).

The participants scored vicarious pain as highest during the BACKPAIN condition and lowest during the LEG condition. MEP size was significantly lower for the LEG than the BACK and BACKPAIN condition. Although we found no statistical difference in the motor-evoked potential (MEP) size between the conditions BACK and BACKPAIN, there was a significant correlation between the difference in NPRS scores between the conditions BACKPAIN and BACK and the difference in MEP size between these conditions. Participants who believed the vicarious pain to be much stronger in the BACKPAIN than in the BACK condition also exhibited higher MEPs for the BACKPAIN than the BACK condition.

Our results indicate that observing how others lift heavy objects facilitates motor representations of back muscles in the observer. Modulation occurs in a movement-specific manner and is additionally modulated by the extent to which the participants perceived the actor's pain. Our findings suggest that movement observation might be a promising paradigm to study the brain's response to back pain.

1. Introduction

Mirror neurons fire when a goal-directed action is performed and when the same action is observed (Di Pellegrino et al., 1992). These visuomotor neurons were first described in the area F5 in the premotor cortex of macaque monkeys by single-cell recordings (Di Pellegrino et al., 1992; Rizzolatti et al., 1996) and later in the inferior parietal lobe (Fogassi et al., 2005). In the case of humans, functional magnetic resonance imaging (fMRI) studies revealed that the inferior frontal gyrus and the parietal cortex have similar functional properties as mirror neurons and represent the anatomical correlates to mirror neuron areas in monkeys (Buccino et al., 2001, 2004; Grezes et al., 2003a, 2003b; Craighero et al., 2007; Lui et al., 2008). Furthermore, measuring single-neuron responses in humans showed that some cells in the supplementary motor area and the hippocampus also have mirror neuron properties (Mukamel et al., 2010).

This mirror neuron system has been widely studied with transcranial magnetic stimulation (TMS). It has been demonstrated that when the primary motor cortex (M1) is stimulated while participants observe a grasping movement the excitability of the motor cortex, quantified as the peak-to-peak amplitude of the motor-evoked potential (MEP), is increased (Fadiga et al., 1995; Strafella and Paus, 2000; Montagna et al., 2005; Borroni and Baldissera, 2008). This facilitation of M1 and the reduction of the intracortical inhibition during the observation of movements occurs in a muscle-specific way, i.e. changes in M1 only occur in the representation of muscles used in the observed action

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(Fadiga et al., 1995; Brighina et al., 2000; Gangitano et al., 2001; Aziz-Zadeh et al., 2002; Borroni et al., 2005; Montagna et al., 2005; Romani et al., 2005; Borroni and Baldissera, 2008; Alaerts et al., 2009, 2010; Hétu et al., 2010). Further TMS research has revealed that corticomotor excitability is also modulated by the temporal execution of the observed movement (Gangitano et al., 2001; Borroni et al., 2005; Montagna et al., 2005) and the required force to complete the observed action (Alaerts et al., 2010), which together implies that motor resonance emerges because the observation activates the same motor pathways as movement execution. Additional experiments with force encoding have reported that altered corticomotor excitability is already present before task relevant visual cues are available to the observer (Alaerts et al., 2012) suggesting that the observer's motor system also represents motor predictions (Alaerts et al., 2012).

However, it seems that not only motor actions are mirrored. Vicarious activity that is related to the emotions and sensations of others has also been measured in the observer (Keysers and Gazzola, 2009). Other people's sensations and feelings of pain activate the somatosensory cortex and other brain regions such as the anterior insula (AI) and rostral cingulate cortex, which contributes to empathy and social perception (Keysers et al., 2010).

In the present study, we focused on the perception of pain in others. Several fMRI studies showed that the affective part of the pain matrix (AI and anterior cingulate cortex) were involved in the participant's own pain perception but also when observing others' pain (Morrison et al., 2004; Singer et al., 2004, 2006; Botvinick et al., 2005; Jackson et al., 2005; Saarela et al., 2007; Hein and Singer, 2008; Lamm et al., 2011; Zaki et al., 2016). Other studies have supported this proposal, but they also found activity modulation in the somatosensory cortex (Jackson et al., 2006; Bufalari et al., 2007; Ogino et al., 2007; Lamm et al., 2011). Additionally, a more recent cognitive model proposes that pain is represented by a multisensory processing system with the goal to protect the body's integrity within a given environment (Legrain and Torta, 2015; Torta et al., 2017). As such, pain perception results not only from processing nociceptive stimuli in a bottom-up-fashion but is additionally modulated by top-down cognitive processes. Accordingly, observing the pain of others might activate nociceptive representations which, however, are likely to be modulated by the environmental context and the cognitive state of the observer.

TMS experiments have demonstrated that painful stimuli (i.e. application of capsaicin or heat) induced a massive inhibition of corticomotor excitability (Farina et al., 2001, 2003; Svensson et al., 2003; Urban et al., 2004; Dube and Mercier, 2011; De Coster et al., 2014; Mahayana et al., 2014). However, not many TMS studies have investigated the perception of pain experienced by others and all previous studies used similar exogenous stimuli where a passive hand was injured by an external object. It was shown that the excitability of M1 was reduced in a muscle-specific manner when the participant observed a video of a needle deeply penetrating a certain hand muscle (Avenanti et al., 2005, 2006, 2009a, 2009b, 2010; Minio-Paluello et al., 2006, 2009). The extent to which M1 was inhibited correlated with the observer's rated sensory quality of pain attributed to the actor (Avenanti et al., 2005, 2009a, 2010). Subsequent experiments have indicated that this motor inhibition was only elicited by the observation of needles deeply penetrating hand muscles and not by the observation of needles pinpricking hand muscles, suggesting that the response is mainly related to pain perception rather than to non-painful somatosensory stimulation (Avenanti et al., 2006). The reduction in corticomotor excitability was higher in participants with a high trait-cognitive empathy and lower in participants with high personal distress and high aversion for the observed movies (Avenanti et al., 2009a). This empathetic sensorimotor resonance was maximal when the perceived similarity of the hand in the movie was high, when there could be no racial stereotypes applied (e.g. violet hand) or when the stimuli were presented in near space (e.g. within the participant's arm reach) (Avenanti et al., 2010; Mahayana et al., 2014).

We ask whether observing another person's pain modulates corticomotor excitability also when the pain is inflicted endogenously mimicking sudden back pain provoked by lifting a heavy object, which might be of clinical relevance. Lower back pain is an extremely common problem in western countries (Hoy et al., 2010) and previous research has already shown that back pain might be associated with structural and functional cortical changes which could be unravelled via a movement observation approach (Apkarian et al., 2004; Tsao et al., 2008, 2011; Wand et al., 2011; Vrana et al., 2015; Masse-Alarie et al., 2016). However, the activity of back muscles is not directly connected to a movement goal as in other studies that have investigated grasping movements (Fadiga et al., 1995; Gangitano et al., 2001; Borroni et al., 2005; Montagna et al., 2005; Borroni and Baldissera, 2008; Alaerts et al., 2009, 2010, 2012) and, therefore, it is unknown whether mirror activity would be evoked.

Here, we investigated if the activity of an axial muscle involved in postural control evoked changes in corticomotor excitability and whether this mirror activity would be modulated depending on whether or not painful movements were observed. We stimulated the erector spinae muscle, which is more challenging than muscles of the upper extremity because the representation within M1 is much smaller and located deeper in the motor cortex (Strutton et al., 2005; Goss et al., 2011, 2012). Corticomotor responses were recorded while different actors lifted a heavy object with (1) a leg-lifting technique (LEG) while keeping the back straight, (2) a back-lifting technique (BACK) while keeping the legs straight, (3) a back-lifting technique with a short sharp pain (BACKPAIN), and (4) a control condition showing no movement.

We hypothesized 1) that corticomotor excitability would be lower for the LEG than the BACK condition, an indication that trunk muscle activity is mirrored by the observer and 2) that the corticomotor excitability would be lower when observing BACKPAIN than when observing BACK due to pain related inhibition.

2. Materials and methods

2.1. Participants

35 healthy participants (17 male, 18 female, 24 ± 3 years (mean ± standard deviation)) participated in the experiment. In accordance to the Edinburgh Handedness Questionnaire (Oldfield, 1971), all participants were right-handed (laterality quotient ranging from 68% to 100%) and naïve regarding the purpose of the experiment. Written informed consent was obtained before the experiment. All participants were screened for the potential risk of adverse effects during TMS and complied with the inclusion criteria. The following exclusion criteria associated with an increased risk of adverse effects of TMS were used: pregnancy, metal implants in the head or body, migraine, history of a major head injury, seizures or a stroke, epilepsy or a family history of epilepsy, previous neurosurgery, neurological disorders, regular medication and drug abuse (Anand and Hotson, 2002). Participants with acute pain were also excluded because of the potential influence on corticomotor excitability and the rated pain intensity (Meng et al., 2013). The experimental procedure was approved by the local Ethics Committee of ETH Zurich (EK 2012-N-64) and conformed to the Declaration of Helsinki (Rickham, 1964).

2.2. Electromyography (EMG) and TMS

The preparation of EMG and TMS measurements were similar to the procedure described in Alaerts et al. (2009). EMG was recorded from the erector spinae on each side of the spine and from the first dorsal interosseous on each hand as a control measurement. Parallel-bar surface EMG sensors (Delsys, USA) were placed at the height of the third lumbar vertebra on the muscle belly of the erector spinae (3.3 ± 0.5 cm from the midline of the spinal cord) (Fig. 1A). The reference electrode (Dermatrode, American Imex, USA) was placed on

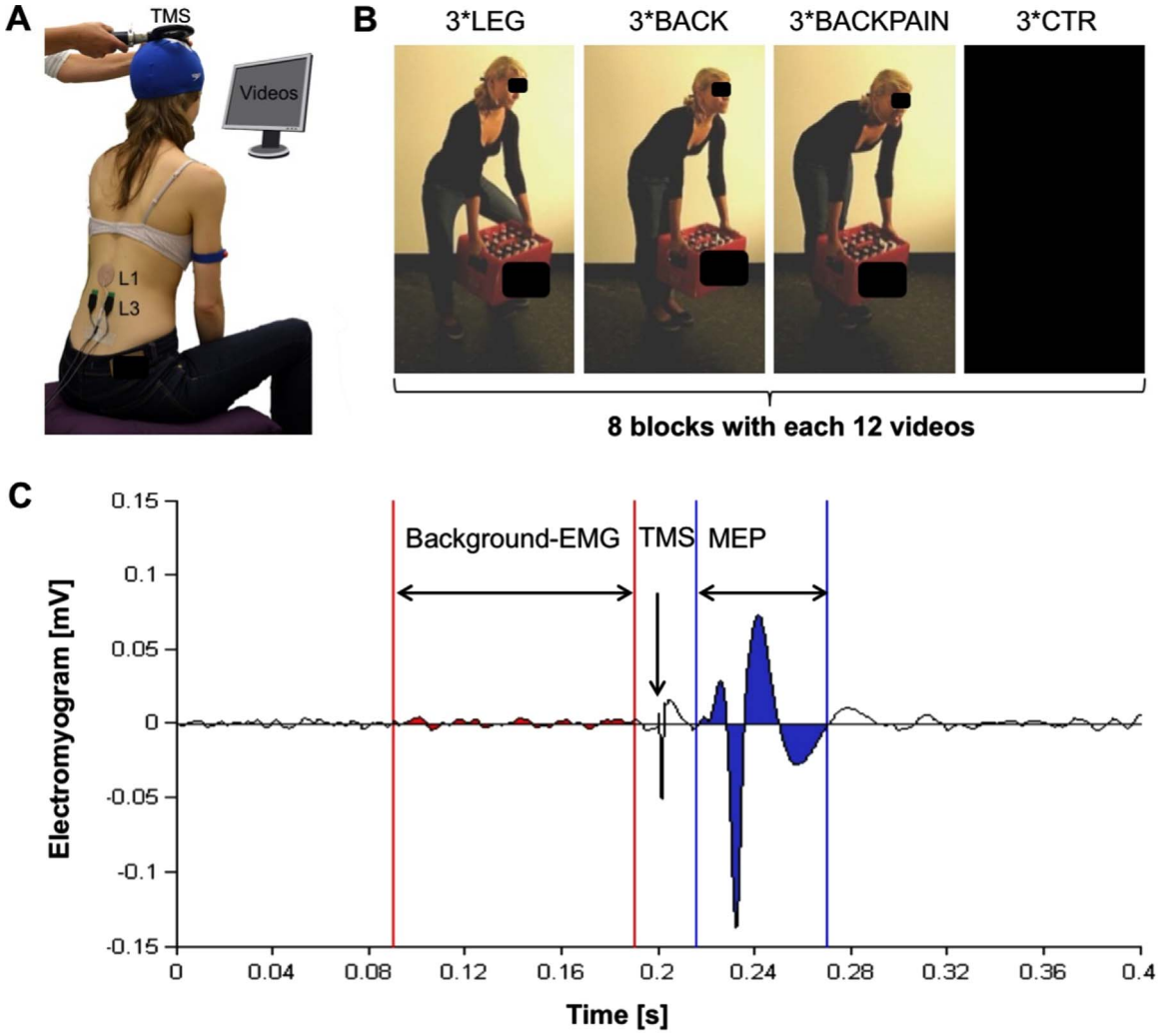

Fig. 1. Experimental paradigm. (A) Illustration of the experimental setup. Participants sat in front of the monitor. The sitting position caused a pre-activated erector spinae muscle. **(B)** Illustration of one block with 12 videos showing the four different video conditions in a"pseudo-randomized, partly blocked" order. The four conditions were: (1) lifting with flexed legs (LEG), (2) lifting with extended legs and with a "round" back (BACK), (3) lifting with a "round" back and a painful electric stimulation (BACKPAIN) and (4) a black screen as a control condition (CTR). One trial lasted about 5 s with a black screen of 1 s between each trial. One block lasted about 72 s. Transcranial magnetic stimulation (TMS) was applied TMS stimulation was applied in the middle of the lifting phase, i.e. when the back muscles of the actor in the video were highly activated and/or when the actor in the video experienced pain. **(C)** Schematic illustration of the data analysis. The red absolute area represents the background-electromyography (background-EMG) during 100 ms and the blue absolute area represents the motor-evoked potential (MEP) during 54 ms. The absolute area of the MEP per ms was corrected with the absolute area of the background-EMG per ms. The MEP and the background-EMG were normalized relative to the control condition. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the bony structure of the first lumbar vertebra (Fig. 1A). Before placing the electrodes, the skin was abraded, shaved and cleaned to achieve higher conductivity.

An eight-channel Bagnoli EMG-system (Delsys, USA) with the compatible surface EMG sensors was used for data collection. Responses were sampled at 5000 Hz (CED Power 1401-3, Cambridge Electronic Design, UK), amplified (1000x), band-pass filtered (20–450 Hz) and stored for offline analysis on a personal computer (Fujitsu Siemens Esprimo, P5720 EPA, 1280 × 1024, 50–60 Hz). Signal software (Version 5, Cambridge Electronic Design, UK) was used to trigger the TMS pulse and to record the EMG data.

TMS was applied via a 70 mm figure-of-eight coil connected to a monophasic Magstim 200 stimulator (Magstim, Dyfed UK). The coil was positioned tangentially to the scalp with the handle pointing backward and laterally at an angle of 45° away from the nasion-inion line, inducing a lateral-posterior to medial-anterior current.

For consistent MEPs, pre-activation of the paraspinal lumbar muscle was required. Participants were positioned in the thoracic upright sitting posture (Fig. 1A) causing consistent pre-activation of the lumbar erector spinae (O'Sullivan et al., 2006). To do so, the participants were seated on a small chair with their thighs angled at approximately 75° in relation to their spine and the arms hanging relaxed between the legs (Fig. 1A).

The preparation of the experiment started with finding the hotspot. The hotspot was defined as the position with the most consistent and largest MEPs in the erector spinae muscle. It was located individually for each participant, using a grid with 0.5 cm interspace that was painted onto a tight-fitting swimming cap. The starting point was the vertex (determined as the point of intersection of half of the nasion-inion line and half of the porion-porion line) and subsequently, the position of the coil was systematically varied in the anterior-posterior and medial-lateral directions in 0.5 cm steps. In the present study, the mean hotspot was found lateral to the vertex (lateral (left): 1.15 ± 0.64 cm, anterior-posterior: 0.02 ± 0.44 cm), which is consistent with previous reports (Strutton et al., 2005; Goss et al., 2012).

The next step consisted of defining the active-motor threshold (AMT) over the hotspot. Similar to previous work measuring cortico-motor excitability in back muscles (Tsao et al., 2008; Goss et al., 2011,

2012), we determined the intensity that evoked an MEP with a clear silent period after stimulation and a clear peak that was discernible from the background EMG activity in 5 out of 10 trials (Tsao et al., 2008).

Finally, after detecting AMT, a stimulation intensity of 130% of the participants' AMT was used for the experiment. In one case this intensity induced a large stimulation artefact which saturated the EMG amplifier and confounded the MEP, so that we reduced the intensity until no artefact was evoked (corresponding to 110% of the AMT). In two participants, the stimulation intensity of 130% of the AMT exceeded the maximal stimulator output. These participants were stimulated with an intensity of 125% and 122% of AMT. The mean stimulation intensity was 86 ± 9% of the stimulator's output and ranged from 65% to 100% of the stimulator's output. Due to the high stimulation intensity, all participants wore earplugs to reduce the sound of the coil.

2.3. Stimuli

The stimuli showed how the same actor lifted a heavy object in three different conditions (Fig. 1B): (1) the leg-lifting technique was used, which represents the ergonomic execution of a lifting task (LEG); (2) The back-lifting technique was used, which is characterized by a round back (BACK); (3) The back-lifting technique was again used, but with a pain stimulus applied during execution (BACKPAIN); additionally, there was (4) a control condition showing a black screen (CTR).

All lifting techniques were performed by four different actors (2 men, 2 women). When the videos were recorded, a pain stimulus mimicking sharp pain was administered using electric stimulation (Grass S48 Square Pulse Stimulator, SIU5 transformer isolation unit, and CCU1 constant current unit) at the height of the fourth to fifth lumbar vertebra and 2 cm lateral from the midline. This type of pain will evoke an instant muscle contraction very similar to that evoked by painful lifting. To determine the stimulation parameters for the sharp pain, strength duration curves were made the for Aα, Aß and Aδ fibres. As the duration of a test stimulus increases, the strength of the current required to activate a single fibre action potential decreases for all fibres. Whereas it is relatively easy to differentiate between Aß and Aδ fibres in small stimulus durations, stimulation characteristics are less pronounced in larger stimulation durations. The point where the stimulation characteristics of the three types of fibres come together on the strength duration curve was determined with a clinical stimulator (Myomed 932, Enraf Nonius, NL), this resulted in a monophasic rectangular pulse of 1 ms with an intensity of 20 mA for all actors. Importantly, each actor performed several lifting actions and the pain was induced at random trials in order to make the stimuli as realistic as possible. All actors were volunteers who were informed that they would experience random, strong pain stimuli during the lifting phase. They all agreed to this procedure and gave consent that the videos could be used for the experiment.

2.4. General procedure

The participants sat at a distance of approximately 45 cm from a Philips 170B monitor (resolution 1024 × 768 pixels; refresh frequency 60 Hz) (Fig. 1A). Video clips (Audio-Video Interleaved (AVI)) were displayed with a frame rate of 25 Hz. We used the QuickTime player 7 (Apple, CA, USA) for presentation. The monitor was connected to a personal computer (Fujitsu Siemens Esprimo, E570 E-STAR 4, 1280 × 1024, 50–60 Hz).

During the experiment, participants were instructed to remain in the previously described sitting position with pre-activated lumbar muscles (Fig. 1A). They were instructed to pay full attention to the videos. After each video clip showing a lifting action, the participants rated the observed vicarious pain on the numeric pain rating scale (NPRS). This scale ranges from 0 to 10, with 0 indicating no pain and 10 indicating the worst possible pain (Hartrick et al., 2003). The NPRS is a standard tool for pain measurement (Hartrick et al., 2003), and here it was used to measure the vicarious pain intensity of the actors in the video clips. Given the previous work from Kilner et al. (2007) and de Beukelaar et al. (2016), it is likely that prior knowledge (i.e. one lifting context might be perceived as potentially more painful than another) is integrated into movement perception and neurophysiological response of the observer.

TMS stimulation was applied in the middle of the lifting phase, i.e. when the back muscles of the actor in the video were highly activated (Fig. 1B) and/or when the actor in the video experienced pain. On average the TMS pulse was applied 1.1 s (corresponding to 28 frames) after the actor showed a first sign of pain. According to previous literature (Barchiesi and Cattaneo, 2013; Borgomaneri et al., 2015; Ubaldi et al., 2015), the timing used in the present study is unlikely to tap into fast bottom-up processes producing the automatic imitative mirroring response but rather into a slower top-down process mediated by prefrontal cortex. Importantly, when observing continuous observed movements such as predictable lifting actions, one has to keep in mind that the mirroring system is continuously anticipating the observed behaviour (Umilta et al., 2001; Kilner et al., 2007; Alaerts et al., 2012), which is not the case for apparent motion stimuli (i.e. still pictures jumping from one phase of the action to another) used in previous studies. Every participant watched 8 sets (see one example set in Fig. 1B), each presenting 12 video clips in a"pseudo-randomized, partly blocked" order, i.e. three identical video clips were shown in a row for each condition (LEG, BACK, BACKPAIN, CTR) while the order of the conditions including the CTR condition was pseudo-randomised across the 8 sets. In total, each participant received 96 single-pulses (24 per condition with an inter stimulus interval of approximately 6 s) during a period of approximately 30 min. A recent study investigated the optimal number of pulses as an outcome measure for single-pulse TMS (Chang et al., 2016). These authors showed that 21 trials are sufficient for a reliably estimating MEP amplitudes (Chang et al., 2016).

2.5. Data analysis

In eight participants (3 male, 5 female) consistent MEPs could not be found in the erector spinae muscle, even when using the maximal tolerable stimulation intensity. For one female participant our protocol was not tolerable. The data from the remaining 26 participants (14 male, 12 female, 24 ± 3 years) were included in the analysis.

The EMG signal was bandpass-filtered (20–450 Hz) and detrended using a custom-made script (Matlab 2015b, USA). We analysed MEPs for the ipsi- and contralateral side of stimulation. As expected, the MEPs contralateral to the stimulation side were larger [$p_{laterality} \leq 0.001$, $d_{laterality} = 1.05$]. Corticomotor excitability was quantified as the absolute area under the MEP curve averaged within an interval of 16 ms (corresponding to the latency of the erector spinae muscles) and 70 ms after the TMS pulse (Fig. 1C). The background-EMG was quantified by averaging the absolute EMG activity within an interval of 110–10 ms prior to TMS stimulation (Fig. 1C).

The background-EMG was strongly correlated with the MEP size [$r = 0.63$, $p = 0.025$], which has also been shown in other studies (Hess et al., 1987; Devanne et al., 1997). Therefore, we calculated a corrected the MEP size (cMEP) by dividing the absolute area of the MEP by the background-EMG in each single trial. This approach is in line with previous literature (Watkins et al., 2003; Watkins and Paus, 2004; Sato et al., 2010; Parmigiani et al., 2015). Finally, we normalized the mean cMEP values (ncMEP) and the mean background-EMG (nEMG) of the movement observation conditions to the control condition and expressed them as a percentage: $ncMEP_{\ movement\ observation} = cMEP_{\ movement\ observation}/cMEP_{\ control} * 100$ and $nEMG_{\ movement\ observation} = background\text{-}EMG_{\ movement\ observation}/background\text{-}EMG_{\ control} * 100$. Absolute uncorrected and unnormalized MEPs as well as corrected and normalized MEPs are reported for each condition in Table 1. We also computed means of the

Table 1
Average uncorrected unnormalized motor evoked potentials (MEPs) in mV and average corrected normalized MEPs in % of the control condition. Mean ± standard deviations of the area under the MEP during 54 ms are displayed for each observation condition (lifting with flexed legs (LEG), lifting with a round back (BACK), lifting with a round back and pain (BACKPAIN) and a control condition (CTR)).

LEG	BACK	BACKPAIN	CTR
5.47 ± 2.06	5.81 ± 2.24	5.74 ± 2.05	5.83 ± 2.29
94.3 ± 19.1	98.8 ± 15.2	98.9 ± 18.8	100

NPRS within each subject and over all trials of each condition.

2.6. Statistics

Statistical tests were applied using SPSS23 (IBM, USA). We applied a Shapiro-Wilk test to check the distribution of our data, which revealed that only the background-EMG and the difference in NPRS between BACKPAIN and BACK were normally distributed [$p_{background\text{-}EMG} = 0.46$, $p_{NPRS\ BACKPAIN\ minus\ BACK} = 0.30$]. For this reason, we applied mixed-effects models, which are more robust to non-normal distributed data and show a better fit for repeated measurements than conventional ANOVAs (Gueorguieva and Krystal, 2004; Gelman and Hill, 2007). Condition (LEG, BACK, BACKPAIN) was modelled as fixed effect depending on the analysis, and subjects were modelled as a random effect with random intercepts. We chose a compound symmetry covariance structure. Post hoc tests were applied if a significant main effect was detected in a mixed-effects model. We reported either Cohen's d as a measure for effect size (small $d = 0.20$–0.49, medium $d = 0.50$–0.80, large $d > 0.80$) (Cohen, 1988) or r (small $r = 0.1$–0.29, medium $r = 0.3$–0.49, large $r > 0.5$) (Field, 2013). Furthermore, we used a Spearman's correlation to explore whether the difference in the NPRS score of the conditions BACKPAIN and BACK was related to the difference in ncMEP size between the conditions BACKPAIN and BACK. A non-parametric Spearman's correlation was applied because the difference in ncMEP size between the conditions BACKPAIN and BACK was not normally distributed according to the Shapiro-Wilk test.

3. Results

All participants ($n = 26$) observed 96 video stimuli consisting of three different lifting tasks (LEG, BACK, BACKPAIN) and a control condition. In the following sections, the NPRS, the ncMEP and the nEMG are reported for the different conditions.

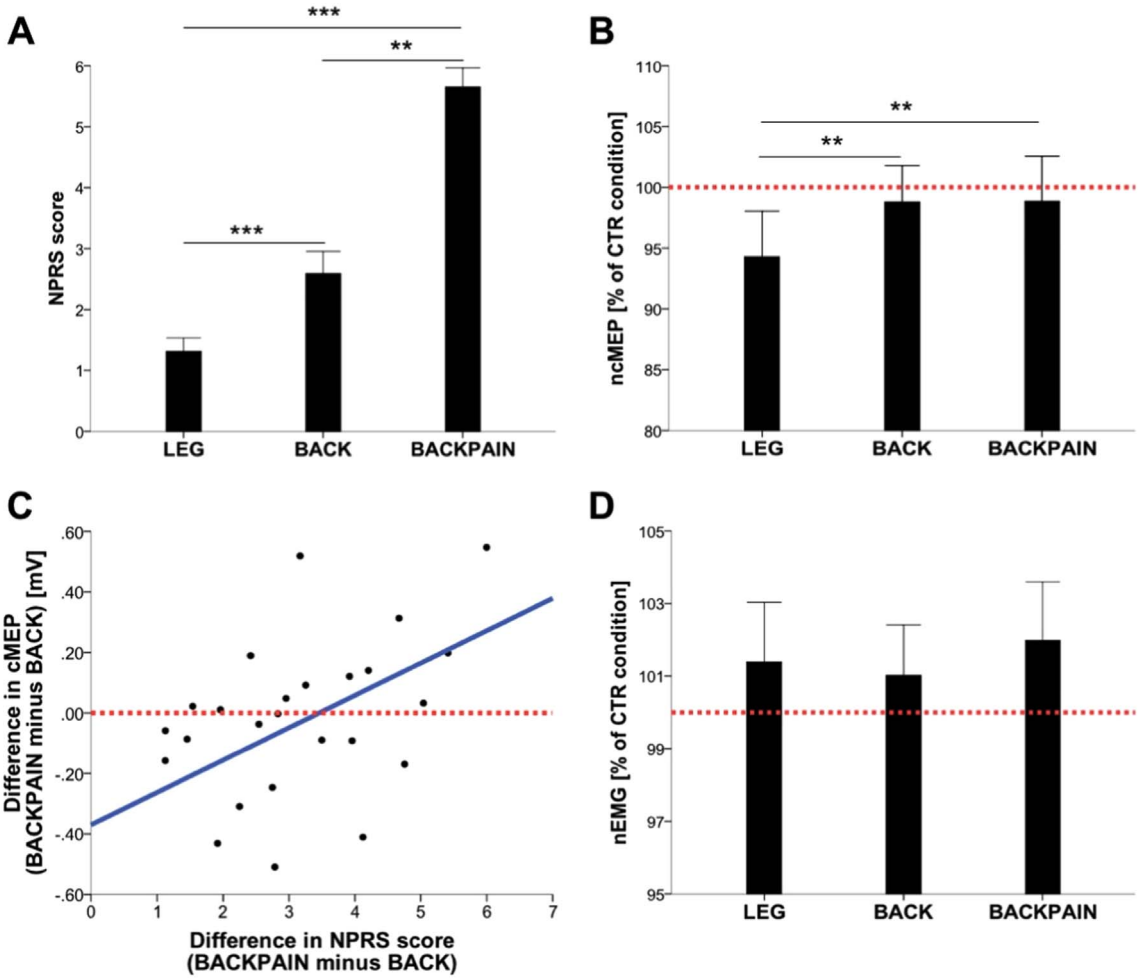

Fig. 2. Results. (A) The average of the numeric pain rating scale (NPRS) score for the three different lifting conditions (lifting with flexed legs (LEG), lifting with a round back (BACK), lifting with a round back and pain (BACKPAIN)). **(B)** The average of the normalized corrected motor-evoked potential (ncMEP) size as a % of the control condition for the three different lifting conditions. The red line indicates the level of the control condition. **(C)** Relationship between the differences in the NPRS scores (BACKPAIN - BACK) and the differences in ncMEP areas (BACKPAIN - BACK). The red line indicates no change in cMEP size between the conditions BACKPAIN and BACK. A moderate significant positive correlation was found [$rho = 0.480$, $p = 0.013$]. **(D)** The mean of the normalized background-EMG (nEMG) as a % of the control condition for the three different lifting conditions. No differences were found [$p = 0.786$]. The red line indicates the level of the control condition. All error bars represent the standard error of the mean. *** $p \leq 0.001$, ** $p \leq 0.025$ and * $p \leq 0.05$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.1. Vicarious pain perception

Fig. 2A shows that the BACKPAIN condition resulted in a moderate level of vicarious pain intensity, whilst the BACK condition showed a low level of vicarious pain intensity. The lowest vicarious pain intensity was reported in the LEG condition. The NPRS differed significantly between the three conditions [$F_{Condition}$ (2, 50) = 91.6, $p_{Condition} \leq 0.001$]. Post-hoc tests revealed that the BACKPAIN condition was perceived as being more painful than the BACK and LEG conditions [$p_{BACKPAIN\text{-}BACK} \leq 0.001$, $d_{BACKPAIN\text{-}BACK} = 3.2$; $p_{BACKPAIN\text{-}LEG} \leq 0.001$, $d_{BACK\text{-}LEG} = 1.8$], and that the BACK condition was perceived as being more painful than the LEG condition [$p_{BACK\text{-}LEG} \leq 0.001$, $d_{BACK\text{-}LEG} = 0.8$]. Effect sizes indicate strong effects for all comparisons. Furthermore, there were no significant gender differences [F_{Gender} (1, 24) = 0.5, $p_{Gender} = 0.502$, $F_{Gender*Condition}$ (2, 48) = 1.2, $p_{Gender*Condition} = 0.311$] amongst the three different movement observation conditions in the perception of vicarious pain.

3.2. Corticomotor excitability

Fig. 2B shows that the average corticomotor excitability of all movement observation conditions (LEG, BACK, BACKPAIN) were smaller than the control condition (CTR). The lowest corticomotor excitability was observed in the LEG condition and the highest in the BACKPAIN condition. The ncMEP differed significantly between the three conditions [$F_{Condition}$ (2, 50) = 3.7, $p_{Condition} = 0.030$]. The LEG condition differed significantly from the BACK and BACKPAIN condition [$p_{LEG\text{-}BACK} = 0.024$, $p_{LEG\text{-}BACKPAIN} = 0.022$, $d_{LEG\text{-}BACK} = -0.26$, $d_{LEG\text{-}BACKPAIN} = -0.24$], while the BACK and the BACKPAIN conditions did not differ [$p = 0.977$] (Fig. 2B). All effect sizes from the pre-planned comparisons were considered small. We find similar effects in the ipsilateral erector spinae muscle [$F_{Condition}$ (2, 46) = 3.9, $p_{Condition} = 0.028$, $p_{LEG\text{-}BACK} = 0.022$, $p_{LEG\text{-}BACKPAIN} = 0.019$, $d_{LEG\text{-}BACK} = -0.48$, $d_{LEG\text{-}BACKPAIN} = -0.45$]. Therefore, we only show data from the contralateral muscle in Fig. 2B.

We conducted a control analysis for the contralateral first dorsal interosseous muscle to investigate muscle specificity. The highest corticomotor excitability was observed for the BACKPAIN condition [96.2% ± 18.6%] and lowest for the LEG condition [87.6% ± 21.5%]. This difference between the LEG and BACKPAIN condition was statistically significant [$F_{Condition}$ (2, 50) = 3.6, $p_{Condition} = 0.035$, $p_{LEG\text{-}BACKPAIN} = 0.010$, $d_{LEG\text{-}BACKPAIN} = -0.39$]. The difference between the LEG and BACK condition [$p_{LEG\text{-}BACK} = 0.20$] and BACK and BACKPAIN [$p_{BACK\text{-}BACKPAIN} = 0.17$] was not significant.

To explore whether the difference in the NPRS score of the conditions BACKPAIN and BACK was associated to the difference in ncMEP size between the conditions BACKPAIN and BACK, we calculated the Spearman's rank correlation coefficient [$rho = 0.480$, $p = 0.013$]. Fig. 2C illustrates a moderate significant positive relationship between these two variables, which indicates that participants who rated the BACKPAIN clearly more painful than the BACK condition, exhibited also an increased ncMEP responses when observing BACKPAIN compared to BACK. By contrast subject, who gave a similar score to BACK and BACKPAIN showed a reduction of ncMEP sizes for BACKPAIN compared to BACK. We conducted the same analysis for the contralateral first dorsal interosseous muscle and found no significant correlation [$rho = 0.071$, $p = 0.73$]. The MEP response was in neither case directly influenced by the absolute value of vicarious pain [$rho_{erector\ spinae} \geq 0.353$, $p_{erector\ spinae} \geq 0.07$, $rho_{first\ dorsal\ interosseous} \geq 0.027$, $p_{first\ dorsal\ interosseous} \geq 0.533$] probably also due to high between-subjects variability in the NPRS ratings.

3.3. Background-EMG

As a control measurement, we also analysed the nEMG during the presentation of the videos. The means of the three movement observation conditions were slightly (< 2%) larger than those in the CTR condition, but no statistical differences were detected between the three conditions [$F_{Condition}$ (2, 50) = 0.242, $p_{Condition} = 0.786$] (Fig. 2D).

4. Discussion

We first investigated if the activity of an axial muscle involved in postural control is also mirrored and second, if mirror activity is modulated depending on whether or not the actor in the video experienced pain caused by the lifting action. Our results showed less corticomotor excitability quantified as the MEP evoked in the muscle erector spinae in the condition LEG than in the condition BACK and BACKPAIN. This suggests that, during movement observation, corticomotor excitability of an axial muscle, such as the muscle erector spinae, is also modulated in a movement-specific manner. We found no difference between the latter painful and the painless lifting conditions at the group level. However, there was a significant correlation between rating the perceived vicarious pain higher for the BACKPAIN relative to the BACK condition (NPRS score difference) and MEP modulation such that participants who rated BACKPAIN as clearly more painful than BACK exhibited also significantly larger MEP amplitudes in response to BACKPAIN than to BACK. These findings indicate that changes of corticomotor excitability in response to observing painful movements is modulated by the amount of the perceived vicarious pain.

4.1. Corticomotor excitability

We assume that the leg muscles are most active during the execution of a lifting action with flexing and extending the legs (LEG) (Dolan et al., 1994; Van Dieen et al., 1999; Mayer et al., 2013) and that back muscles are most active during the execution of a lifting action with flexing and extending the back (BACK). We found that the corticomotor excitability of the axial erector spinae muscle, was lower in the condition LEG than in the condition BACK and BACKPAIN. Based on these findings, we believe that there is no principle difference in the modulation of corticomotor excitability between axial and distal muscles during movement observation as suggested by others (Strafella and Paus, 2000; Hétu et al., 2010).

At first sight it might be surprising that corticomotor excitability for the BACK and BACKPAIN conditions was very similar to the CTR condition. However, this finding is in line with a recent study showing that corticomotor excitability remains elevated when the control condition is intermixed with the movement observation conditions compared to measuring the excitability before and after the experimental blocks (Bunday et al., 2016). This indicates that conditions which do not show movement might leave the participant in an uncontrolled cognitive state, making it difficult to develop a strong a-priori hypothesis regarding the expected level of corticomotor excitability in the blank screen condition. However, we would like to emphasise that comparing conditions which show different action types is a valid approach to measure how M1 is modulated by movement observation.

We found no significant difference between the painful and the pain-free lifting techniques at the group level but corticomotor excitability was modulated by the extent to which the participants perceived the actor's pain (see 3.2). This differs from previous studies which found a general reduction of corticomotor excitability in the contralateral muscle when participants observed others in pain (Avenanti et al., 2005, 2006, 2009a, 2010; Minio-Paluello et al., 2006, 2009; De Coster et al., 2014; Mahayana et al., 2014). However, all previous studies examining pain perception in others used an *exogenous* "flesh and bone" pain stimulus (i.e. a video clip showing a needle deeply penetrating the right first dorsal interosseous while the hand is passive) (Avenanti et al., 2005, 2006, 2009a, 2010; Minio-Paluello et al., 2006, 2009; De Coster et al., 2014; Mahayana et al., 2014). Also, in all of these previous studies the actor's hand did not produce any reaction to pain or

withdrawal movement. In our study, the vicarious pain intensity rating of the painful condition (NPRS 0–10, 6 ± 2) was very similar to that reported by Avenanti et al. (2009a) (Visual-analogue-scale 0–10, 7 ± 2), however, our stimuli showed no "flesh and bone" pain induced by an external object but a *reaction* to endogenously caused back pain: The most obvious reaction of the actor was a brief "freeze" of the movement accompanied with a change of the facial expression. We therefore propose that the increased excitability in BACKPAIN compared to BACK in participants with increased pain ratings in BACKPAIN compared to BACK might mirror a sudden increase of muscle activity which is typically observed in acute lower back pain (Van Dieen et al., 2003; Lamoth et al., 2004; Jacobs et al., 2011). This interpretation is also in line with the cognitive model of pain (Legrain and Torta, 2015; Torta et al., 2017), which proposes that pain perception is a multisensory process important for adapting sensorimotor functions of the body when encountering a potentially threatening environment. Event-related brain potentials elicited by nociceptive stimuli were shown to be influenced by the salience of the stimulus (bottom-up control) and by the subject's goals and motivation (top-down control) (Legrain et al., 2012). Accordingly, the observer's response in M1 might be "context dependent", i.e. it differs when observing pain caused by exogenous "flesh and bone" stimuli where a body part is threatened by a dangerous object in the environment (Avenanti et al., 2005, 2006, 2009a, 2010; Minio-Paluello et al., 2006, 2009; De Coster et al., 2014; Mahayana et al., 2014) versus endogenously caused back pain.

Our finding is also in line with a recent meta-analysis that has shown that patients suffering from chronic pain, especially neuropathic pain, exhibit an increased motor cortex disinhibition, suggestive of a disruption in GABA-mediated intracortical inhibition (Parker et al., 2016). A study investigating specifically a population of chronic lower back pain found an increased corticomotor excitability (Clark et al., 2011). Our results suggest that similar mechanisms might happen during the observation of painful movements, which makes it a useful tool to study the brain's response to sharp internal pain as for instance acute back pain.

A control analysis revealed also a significant modulation of the corticomotor excitability in the contralateral first dorsal interosseous such that excitability was highest when observing BACKPAIN and lowest when observing the LEG condition. However, when looking at the modulation of the corticomotor excitability as a function of the vicarious pain ratings for the BACKPAIN vs BACK condition, a significant correlation was only found for MEPs measured in the back muscles. These findings indicate that even though observing different whole-body lifting actions might modulate corticomotor excitability of a finger muscle, the direct association with individual pain ratings appears to be specific to the muscle closest to the noxious event. This is in agreement with previous studies investigating the perception of pain in others which reported a muscle specific effect (Avenanti et al., 2005, 2006, 2009a, 2009b; Mahayana et al., 2014).

Our participants differed in their vicarious pain perception but it is unclear what caused these individual differences. It is possible that mirroring the actor's motor response in the BACKPAIN vs BACK condition by modulating MEP size is important for perceiving the actor's pain. This, however, might be modulated by the cognitive or affective state of the observer (Legrain et al., 2012; Torta et al., 2017) and is probably a more cognitive type of empathy (i.e. metalizing). It has been shown that while reduced empathy, caused by the Asperger syndrome for example, reduces the pain-related modulation of M1, the neurophysiological response does not correlate with the sensory qualities of pain (Minio-Paluello et al., 2009). Nevertheless, it is currently unclear how "mirroring" of the actor's response to pain relates to empathy since previous research has suggested that even though a rapid, near-automatic sensorimotor response in the observer might be necessary for feeling empathy, it is not sufficient because "feeling the pain of another person" might be additionally influenced by processes like perspective taking or prior experience of the observer (Valentini, 2010).

4.2. Background-EMG

We showed that the nEMG remains stable over the three lifting conditions. That is why we can safely assume that our MEP results were not confounded by differential EMG activity. One reason for this result is due to our decision to pseudo-randomize conditions within a block and randomize the order of the eight blocks. Thus, possible muscular fatigue was counter-balanced across conditions. Furthermore, we corrected each MEP for the background-EMG in order to not confound the mean MEP for each participant and condition by differential EMG activity. Nevertheless, one has to keep in mind that our background-EMG was not standardized.

4.3. Pain perception

The LEG condition was perceived to be the least painful and the BACKPAIN condition the most painful. These results confirmed that our video stimuli were a suitable paradigm to test corticomotor excitability during the observation of a painful movement. Nevertheless, one has to be aware of the fact that our participants even rated the LEG and BACK condition as a little painful even though the actors showed no pain. There are three possible explanations for this: First, participants might have hesitated to rate the LEG and BACK condition with 0 (no pain) even though we instructed them that the value 0 could also be used. Second, some participants could have thought that the actors in the video suffered from slight back pain and therefore, lifted the heavy object in a correct ergonomic manner as in the condition LEG. Third, some participants might have had prior knowledge that lifting a heavy object with a round back bears the risk of provoking back pain. This knowledge might have implicitly modulated the perception and interpretation of pain in the video clips (Series and Seitz, 2013).

Even though the vicarious pain intensity was the only variable we quantified objectively, it is very likely that the overall affective states of the actors were also perceived and modulated corticomotor excitability as well. Other studies showed that both sensory (pain intensity) and affective (pain unpleasantness) dimensions of pain are present on the face of a person experiencing a painful heat stimulation or suffering from chronic pain (Saarela et al., 2007; Kunz et al., 2012).

In addition, some authors have also noted that there are differences in the perception of emotions between gender, using facial expressions and body language (Hall and Matsumoto, 2004; Alaerts et al., 2011). For our task, there were no gender differences in the three different movement observation conditions in the vicarious perception of pain. It might be that vicarious pain is differently processed than emotions such as surprise, disgust, happiness, sadness and anger, which were investigated in previous studies.

4.4. Limitations

One possible weakness of this study is that our protocol was only successful in 76% of the participants. There are two main reasons that might explain why not all of our participants responded to our protocol: First, in accordance with other studies, a pre-activation of the erector spinae muscle is needed to evoke an MEP (Ferbert et al., 1992; Taniguchi et al., 2002; Strutton et al., 2005; O'Connell et al., 2007; Kuppuswamy et al., 2008; Goss et al., 2011, 2012), but some participants were simply not able to activate the erector spinae muscle sufficiently or to hold the required position for a long enough period of time. Second, in some participants the stimulation depth of the 70 mm figure-of-eight coil might have not been deep enough due to individual anatomy. For a further study, despite being potentially more uncomfortable for the participants (Goss et al., 2011), it would be better to stimulate with an angled double-cone coil. This coil was designed for deep brain stimulation (Roth et al., 2002) and might also overcome the

issue that for some participants the maximal output of our stimulator was too low to evoke consistent MEPs in back muscles. Another weakness is that we did not asses the affective state of the participants or the perceived affective state of the actor.

4.5. Conclusion

We are the first to show that movement-specific modulation of corticomotor excitability is present in erector spinae, a back muscle that is mainly involved in postural control rather than in goal-directed movements. Furthermore, we showed that corticomotor excitability in this muscle is modulated by the level of the perceived vicarious pain intensity attributed to the actor in the video. Our results indicate that movement observation might be an interesting paradigm to study the brain's response to back pain. For future studies, it would be interesting to use a similar experimental paradigm in patients with chronic or persistent lower back pain to investigate possible functional changes in motor cortex.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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