Agent-dependent modulation of corticospinal excitability during painful transcutaneous electrical stimulation

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ABSTRACT

Pain has an inhibitory effect on the corticospinal excitability that has been interpreted as an evolutionary mechanism, directed to down-regulate cortical activity in order to facilitate rapid protective spinal reflexes. Here, we focused on the link between defensive mechanisms and motor system and we asked whether voluntary actions can modulate the corticospinal excitability during painful stimulations. To this aim, we manipulated the volition-related aspects of our paradigm by comparing conditions in which either the participant (self-generated action) or the experimenter (other-generated action) pressed the button to deliver painful high-intensity transcutaneous electric shocks to the right digit V. MEPs to TMS were recorded from the FDI and APB muscles of the stimulated hand. A compelling agent-dependent modulation of the corticospinal excitability was found, showing, in self-generated compared to other-generated actions, a significantly lower inhibitory effect, as measured by greater MEP amplitude. This finding suggests a top-down modulation of volitional actions on defensive mechanisms, promoting the view that predictive information from the motor system attenuates the responses to the foreseeable adverse events generated by one's own actions as compared to unpredictable events generated by someone else's actions.

1. Introduction

In the literature examining the relationship between pain and sensorimotor system, several studies demonstrated a physiological counterpart of defensive motor responses to painful stimuli, showing a consistent modulation of the primary motor cortex (M1) excitability (Burns et al., 2016). Nociceptive fingertip stimulation inhibits voluntary EMG activity of contracting muscles, the so-called cutaneous silent period (Kofler, 2003; Kofler et al., 1998). At rest condition, by using brain stimulation to evoke motor evoked potentials (MEPs) and different methods to induce pain, an inhibitory effect on the corticospinal excitability has been demonstrated. Some studies investigated the effect of short painful CO_2 laser stimulation in modulating MEP amplitude, recorded from both hands' (Algoet et al., 2018; Valeriani et al., 1999) and arms' (Valeriani et al., 2001) muscles. Other studies, employing noxious electrical fingertip stimulation found different modulation patterns on

the EMG activity of the upper-limb: they showed inhibition of the hand muscle activity and facilitation on the arm muscle activity (Kofler et al., 1998; Urban et al., 2004). In other research contexts, several studies demonstrated that the mere observation of painful stimuli delivered to another individual induces corticospinal inhibition in the observer similar to those recorded during oneself pain (Avenanti et al., 2010, 2009b; 2009a, 2006; 2005; Bucchioni et al., 2016; Bufalari et al., 2007). This has been interpreted as the physiological basis of empathy (Singer and Frith, 2005) or, more recently, as the physiological counterpart of an embodiment phenomenon related to the sense of body-ownership (Bucchioni et al., 2016). Such effects may suggest that the observed corticospinal inhibition rather than being entirely explained by a bottom-up mechanism, might instead be linked also to a top-down component, related to the pain anticipation. Coherently, through a conditioning paradigm, we recently showed that the mere expectancy of a painful stimulus may induce corticospinal inhibition, even when the

conditioning painful stimulus was not actually delivered (Fossataro et al., 2018c).

Capitalizing on this TMS literature, in the present study we focused on the link between defensive mechanisms and motor system and we asked whether voluntary actions can modulate the corticospinal excitability during painful transcutaneous electrical stimulation. The everyday experience of volitional action is strongly associated with the foreseeability of the events generated by our own action, as compared to the unpredictability of the events generated by others' actions. The tight link between volitional actions and the physical (or even moral) events they caused has been extensively investigated in the literature on motor cognition (Haggard, 2017). Here, we reasoned that the same painful (high intensity) electric shock can induce a different modulation of the corticospinal excitability, depending on whether it is perceived as the consequence of the own action or, on the contrary, as an externally generated event.

2. Materials and methods

2.1. Participants

Eighteen healthy volunteers (8 males, 20–29 years, mean $\pm$ SD 24.61 $\pm$ 2.25; educational level = 16.4 $\pm$ 2.5 years) participated in the study. All participants were right-handed, as assessed with the Edinburgh Handedness Inventory (Oldfield, 1971), naïve to the experimental procedure and, before taking part in the study, they gave written informed consent. None of them had a history of neurological, major medical or psychiatric disorders and they were free from any contraindication to TMS (Bruno et al., 2018a; Rossi et al., 2009). The experimental procedure

was approved by local ethics committee of the University of Turin (3167, February 1, 2016).

2.2. Experimental paradigm

In the present study, we investigated whether volitional actions interacted with a defensive motor response to painful stimuli. To this aim, we contrasted the MEP amplitude to single TMS pulses over the M1 (contralateral to the stimulated hand) in two different conditions, wherein high electrical stimuli could be generated either by the participant's button press (self-generated shock) or by the experimenter's button press (other-generated shock). A vocal signal "*you*" indicated that participants had to press the button with their left index finger; a vocal signal "*other*" indicated that participants had to look at a co-experimenter pressing the button. Note that, either participants or the experimenter might press the button delivering the stimulus whenever they wanted, therefore the latency between the vocal signal and the stimulus delivery was random. In control conditions, the button press did not cause the electric shock, either in self-generated (no-shock) trials or in other-generated (no-shock) trials (see Fig. 1). It is important to note that we decided to adopt no-shock trials as control condition since in a previous study it has been demonstrated that non-painful tactile stimuli do not modulate the MEP amplitude (Fossataro et al., 2018c).

In shock conditions, in order to have a behavioural measure of the perceived subjective pain intensity, after each electrical stimulation, participants were asked to rate the perceived pain intensity on a 0-7 Likert scale ranging from "It is not painful at all" to "It is very painful". Moreover, in order to avoid response bias and to control for phantom sensations, catch trials (without stimulation) were randomly included
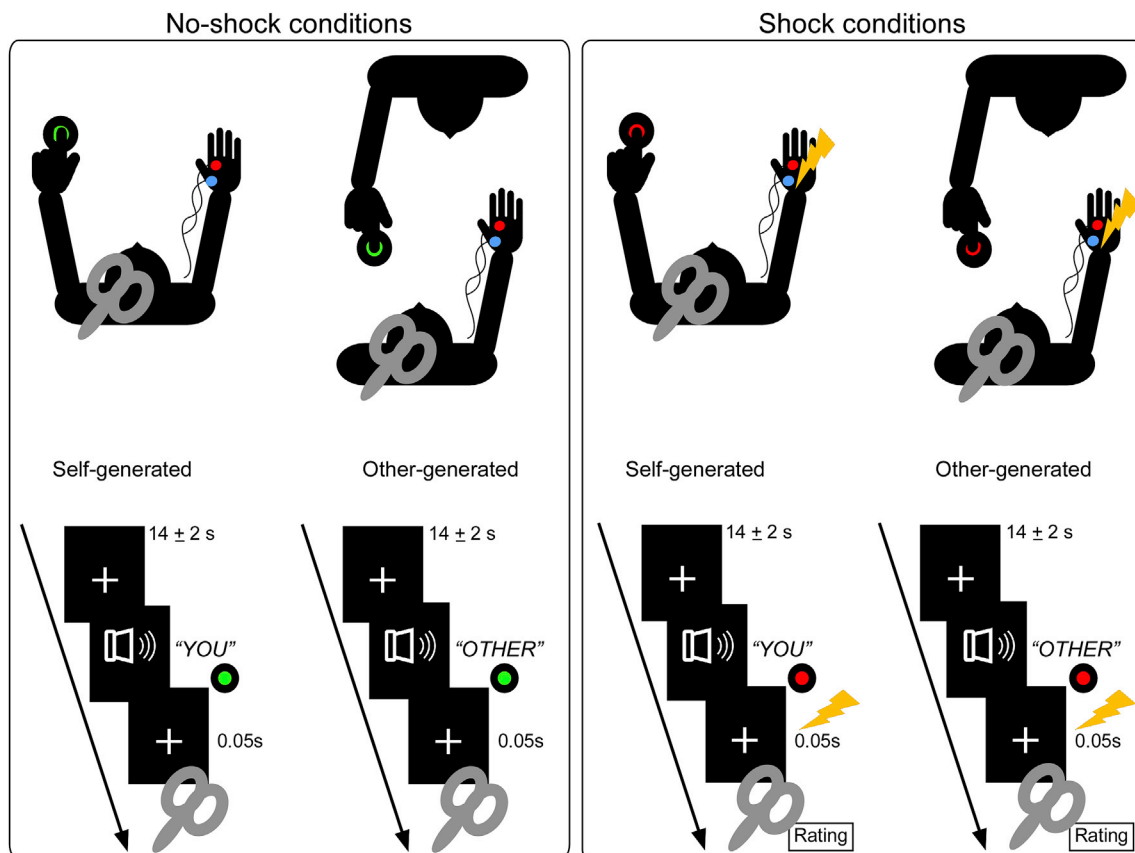
Fig. 1. Schematic representation of the experimental condition. Single-pulse TMS delivered over the participant's left M1 and MEPs recorded from the APB and FDI muscles of the right hand. Left panel shows the two no-shock conditions in which no stimuli were delivered: self-generated/no-shock and other-generated/no-shock. Right panel shows the two shock conditions in which painful stimuli were delivered: self-generated/shock and other-generated/shock. Note that in both self-generated conditions participants had to press the button with their left hand; in both other-generated conditions they did not.

and the corresponding MEPs were not considered for the analysis. Note that, during the button-pressing, the movement required to the subjects was very little. Indeed, subjects were already in position, with the left hand on the keyboard, to be ready to press the button, which needed a minimal force in order to trigger the stimulation.

The experiment consisted of two TMS sessions with a between sessions break of 20 min in order to minimize habituation and to ensure that, after the first TMS session, the corticospinal excitability came back to normal values. Within each session, the order of no-shock (A) and shock (B) blocks was counterbalanced within subjects (ABBA) resulting in a total of 48 trials: 12 trials self-generated no-shock; 12 trials other-generated no-shock; 12 trials (and 2 catch trials) self-generated shock; 12 trials (and 2 catch trials) other-generated shock. Note that participants were explicitly informed whether a shock block or a no-shock block was about to start.

The experiment was programmed by using E-prime presentation software V2.0 (Psychology Software Tool Inc., USA) in order to a) control sequence, timing and duration of the stimuli; and b) trigger TMS pulses, EMG recording and electrical stimulation delivering. Participants were comfortably seated in front of a PC screen (24 inches monitor) at a distance of ~80 cm. In order to avoid any muscles contractions, they were asked to keep their right forearm resting on a pillow.

2.3. Stimulation and recordings

2.3.1. Transcranial magnetic stimulation

MEPs were elicited by a single pulse transcranial magnetic stimulation (TMS) (Magstim Rapid2; Magstim Co. Ltd, Whitland, UK) with a figure-of-eight-shaped coil positioned over the left motor cortex (M1, hand area). The coil was held tangentially to the scalp with the handle pointing backwards and laterally 45° away from the mid-sagittal line, such that the flow induced by the second most effective phase of the biphasic pulse moved in a posterior anterior direction (Di Lazzaro et al., 2001; Kammer et al., 2001). In order to determine the optimal position able to elicit the greatest MEP amplitude with the lowest stimulation intensity, this orientation permits the lowest motor threshold estimation, optimizing the stimulation (Brasil-Neto et al., 1992). By moving the coil in step of 1 cm over the left motor cortex the optimal point able to activate the selected muscle was found, then the coil was fixed and held by a mechanical arm. The intensity of magnetic pulses was set at 110% of the resting motor threshold (mean ± SD 54.33% ± 9.15%, range 48–67% of the maximum stimulator output), defined as the lowest intensity of the stimulator output able to elicit five MEPs out of ten consecutive pulses with an amplitude of at list 50 μV (Rossini et al., 1994).

2.3.2. Electrical stimulation

Transcutaneous electrical stimuli consisted in constant current square-wave pulses (DS7A, Digitimer) delivered to the right digit V, using a surface bipolar electrode attached with a Velcro strap. The stimulus duration was 200 μs and the delivery occurred ~50 ms before the TMS pulse, in order to obtain the maximum pain dependent inhibition on the MEP amplitude accordingly to previous studies (Fossataro et al., 2018c; Urban et al., 2004). The mean stimulus intensities were 18.90 ± 10.61 mA, range 6.8–50 mA. The stimulation intensity was initially set at 10-fold the perceptual threshold and then individually adjusted to elicit a painful sensation of at list 4/7 (i.e. "clearly painful sensation") on a 0–7 Likert scale, where 0 is "not painful" and 7 is "the most painful imaginable". Thus, although the electrical stimulus is not pain-specific *per se* (it does not selectively activate nociceptive A-delta and C fibers), it is subjectively perceived as painful (Burin et al., 2017a). Note that, in order to minimize habituation (Torta et al., 2012; Valentini et al., 2011), stimuli were randomly delivered to three different locations of the digit V.

2.3.3. Electromyography recording

Electromyographic (EMG) activity was simultaneously recorded (MP150, Biopac System, USA), from the right Abductor Pollicis Brevis (APB) and the right First Dorsal Interosseous (FDI) muscles, using two pairs of bipolar surface electrodes with the active electrode over the muscle belly and the reference electrode over the associated joint or tendon. Our selected target muscles were APB and FDI since previous studies (Farina et al., 2001; Svensson et al., 2003; Urban et al., 2004) showed that their motor response is modulated during painful stimulation (electric shocks). Signals were amplified and digitalized with a sample rate of 10 kHz, filtered with a band-pass (10–500 Hz) and a notch (50 Hz) filter, according to the method used in previous studies (Bruno et al., 2018b, 2017; Bucchioni et al., 2016; Burin et al., 2017b; Dell'Anna et al., 2018; Fossataro et al., 2018c, 2018b; Garbarini et al., 2018), and stored for off line analysis.

2.3.4. Self-report measure

After the TMS session, all participants completed the Trait and State scale of the State-Trait-Anxiety-Inventory (STAI) (Spielberger et al., 1970; Weiner and Craighead, 2010). The STAI is a self-report questionnaire for the assessment of two different dimensions of anxiety: state and trait, by means of two scales of 20 items each. State anxiety is a measure of anxiety experienced at the time of the test, while trait anxiety is a measure of a general tendency for anxiety. Anxiety scales include items related either to the presence (e.g. "I worry too much over something that really doesn't matter") or to the absence of anxiety (e.g. "I am content; I am a steady person"). Each item is scored on a 4-point scale in terms of how often participants felt as described, from 1 indicating "Almost Never" to 4 indicating "Almost Always" (items indicating absence of anxiety are reversed scored). The total score can range from 20 to 80 and higher scores indicate greater anxiety.

2.4. Data analysis

EMG data were analysed offline using AcqKnowledge software (Biopac Systems, Inc., Santa Barbara, CA) and Statistica Software 8.0 (StatSoft, Inc., Tulsa, OK). In order to prevent contamination of MEPs by background EMG activity, the absence of any voluntary contraction in 100 ms window preceding the TMS pulse was verified by visual inspection monitoring the EMG activity online. For each muscle, all trials with any activity greater than 50 μV were excluded from the analysis (less than 2% of collected data) (Bucchioni et al., 2016; Fossataro et al., 2018c). For each participant and separately for each experimental condition the average peak-to-peak MEPs' amplitude (μV) was extracted and used as dependent variable for further analyses.

In data analyses, firstly, we used mean MEP raw values to perform comparisons between conditions, including both no-shock conditions (self-generated/other-generated) and shock conditions (self-generated/other-generated). The normal distribution of the residuals was checked by means of Shapiro-Wilk test. Since the residuals were not normally distributed ($p < .05$), a non-parametric Friedman test for differences among repeated measures was conducted. Post-hoc pairwise comparisons were performed by means of non-parametric Wilcoxon signed-rank tests. To account for multiple comparisons, the significance level (p value) was corrected using a false discovery rate (FDR) procedure (Benjamini and Hochberg, 1995).

Then, in order to obtain an 'index of MEP decrease', MEP amplitude of each shock condition, either in self-generated or in other-generated actions, was expressed as percentage of MEP decrease with respect to the relative no-shock conditions [$100-(MEP_{shock}*100)/MEP_{no-shock}$] and the resulting values were compared. As in previous analyses, parametric T-test did not run properly, due to the not-normal distribution of residuals, and the Wilcoxon signed-rank test was used.

When a significant effect was found, Cohen's d value (calculated as within-subjects effect sizes using G*Power's matched pairs statistical tests) was reported as well.

Behavioural data for each condition (subjective ratings on the 0-7 Likert scale) were normalized in z-scores in order to obtain comparable measures among participants (Bruno et al., 2019; Bucchioni et al., 2016;

Fossataro et al., 2016a; Garbarini et al., 2014; Romano et al., 2014) and the normal distribution of the residuals was checked by means of Shapiro-Wilk test (W = 0.97; p = .45). Thus, data were analysed by means of paired T-test (two tailed). When a significant effect was found, Cohen's d value (calculated as within-subjects effect sizes using G*Power's matched pairs statistical tests) was reported as well.

Furthermore, we calculated Spearman's correlation in order to investigate whether STAI-Trait and STAI-State scores were significantly correlated to the subjective ratings on the perceived pain intensity and to the MEP amplitude changes recorded from APB and FDI muscles. In order to perform the correlation analysis, an index of agent-dependent modulation was calculated as a delta between self- and other-generated action, in both behavioural and physiological data.

3. Results

3.1. Physiological data

In the first analyses on raw data, the Friedman test on the MEPs acquired from both APB and FDI muscles showed a significant difference among the distributions of the experimental conditions [APB: $\chi^2(3)$ = 20.33; p = .00014; FDI: $\chi^2(3)$ = 24.93; p = .00001]. Wilcoxon test showed that, in both muscles, when shock conditions were compared to the corresponding no-shock conditions, significantly lower MEP amplitude was found in both self-generated condition [APB: shock vs no-shock (z = 2.89; p = .003; p after FDR correction = 0.007; dz = 0.8); FDI: shock vs no-shock (z = 3.24; p = .001; p after FDR correction = 0.004; dz = 0.98)] and other-generated condition [APB: shock vs no-shock (z = 3.59; p = .0003; p after FDR correction = 0.001; dz = 0.97); FDI: shock vs no-shock (z = 3.20; p = .001; p after FDR correction = 0.002; dz = 0.93)]. See Fig. 2A and Fig. 2B. This suggests that, in both shock conditions (irrespective of the agent of the action), painful stimulation induced a

significant decrease of the MEP amplitude compared to no-shock conditions. Importantly, when the two no-shock (control) conditions were compared, no significant difference was found (self-generated action vs other-generated action p > .5). See Fig. 2A and B. On the contrary, when the two shock conditions were compared, a significantly lower inhibition in self-generated action as compared to other-generated action was found in both APB (z = 2.37; p = .01; p after FDR correction = 0.02; dz = 0.7) and FDI (z = 2.19; p = .02; p after FDR correction = 0.03; dz = 0.87). See Fig. 2A and B.

These results were confirmed by Wilcoxon test performed on the 'index of MEPs decrease', showing a significant difference between self-generated action and other-generated action both in APB (z = 2.11; p = .0034; dz = 0.65)] and in FDI (z = 2.15; p = .031; dz = 0.85)]. See Fig. 2C and D. This suggests that the corticospinal inhibition, in response to painful stimuli, is significantly modulated by the agent of the action.

3.2. Behavioural data

In shock conditions, T-test over the subjective ratings on the perceived pain intensity showed a significant effect [t(17) = -2.5409; p = .021; dz = 0.77], suggesting that, at the behavioural level, participants reported the subjective pain perception in self-generated action as attenuated compared to the other-generated action. See Fig. 3.

3.3. Correlations

Correlation analyses between subjective ratings on the STAI scores (mean ± SD STAI-Trait = 44.77 ± 8.82; STAI-State = 32.41 ± 8.50) and both perceived pain intensity and MEP amplitude changes recorded from APB and FDI muscles, did not show any significant result. The absence of correlations with the STAI scores suggests that, even if in different experimental contexts this test was able to predict the amplitude of motor
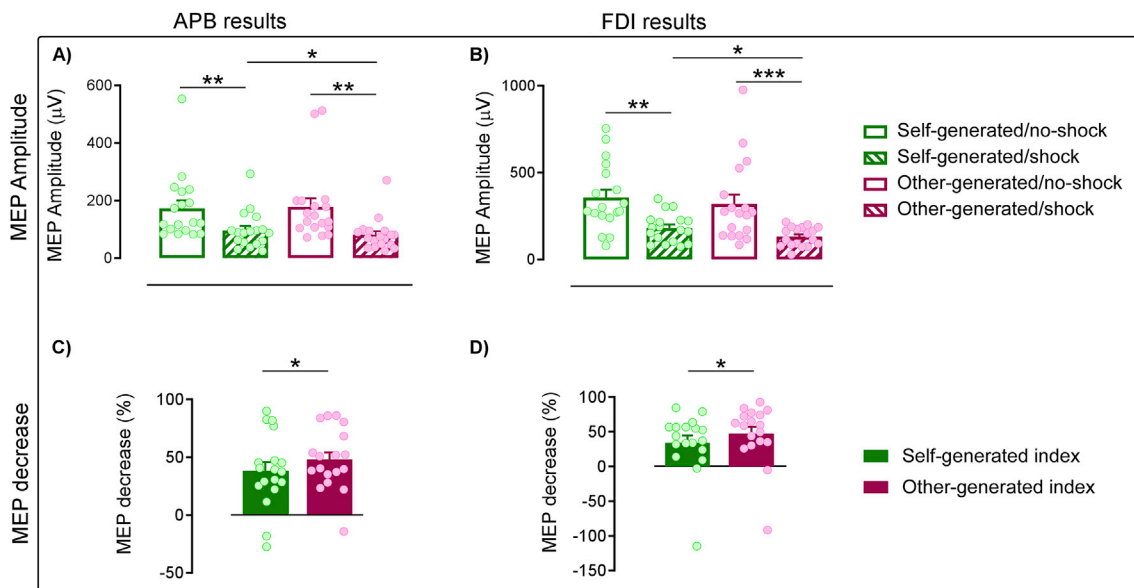
Fig. 2. Physiological results. *Top panel*, in each experimental condition, we plotted the MEP amplitude (μV), recorded in APB (**A**) and FDI (**B**) muscle. Note no differences between self-generated/no-shock [mean ± SD (μV), APB = 173.23 ± 114.96; FDI = 356.96 ± 192.01] and other-generated/no-shock [mean ± SD (μV), APB = 178.20 ± 126.79; FDI = 319.20 ± 231.29]. Significant lower MEP amplitude in shock condition compared to the corresponding no-shock condition both in APB [mean ± SD (μV): self-generated/shock = 96.32 ± 64.03; self-generated/no-shock = 173.23 ± 114.96; other-generated/shock = 80.87 ± 55.54; other-generated/no-shock = 178.21 ± 126.79] and in FDI [mean ± SD (μV): self-generated/shock = 181.67 ± 82.67; self-generated/no-shock = 356.96 ± 192.02; other-generated/shock = 132.39 ± 55.21; other-generated/no-shock = 319.21 ± 231.29]. Significant lower inhibition in self-generated/shock [mean ± SD (μV) APB = 96.32 ± 64.03; FDI = 181.67 ± 82.67] compared to other-generated/shock [mean ± SD (μV) APB = 80.87 ± 55.54; FDI = 132.39 ± 55.20]. *Bottom panel*, in each experimental condition, for both self-generated and other-generated conditions, we plotted the 'index of MEP decrease' [100-(MEPs_shock/MEPs_no-shock)] of both APB (**C**) and FDI (**D**) muscle. Note significantly lower effect in self-generated index (APB = 38.17 ± 31.72; FDI = 34.17 ± 43.75) than in other-generated index (APB = 47.93 ± 26.31; FDI = 47.41 ± 42.49) (i.e. physiological counterpart of the sensory attenuation). Error bars indicate sem. Asterisk indicates significant comparisons (*P < .05; **P < .005; ***P < .0005). Dots represent individual participants.

Behavioral results
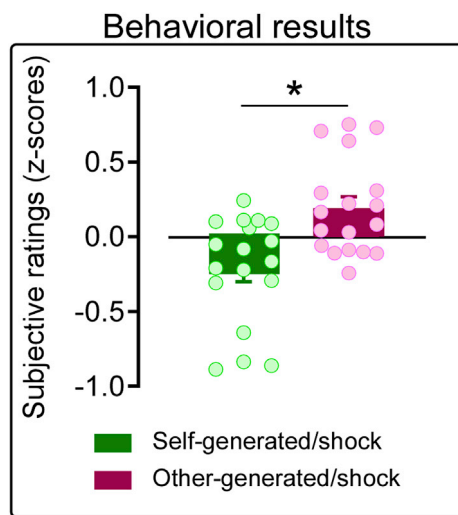
Fig. 3. Behavioural results. Significant difference between subjective ratings on the perceived painful stimuli during the two shock conditions. Note lower responses in self-generated/shock (mean ± standard deviation = −0.21 ± 0.36) compared to other-generated/shock (mean ± standard deviation = 0.19 ± 0.32) (i.e. sensory attenuation). Error bars indicate sem. Asterisk indicates the significant comparison (*P < .05). Dots represent individual participants.

defensive responses [e.g. (Fossataro et al., 2018c; Sambo and Iannetti, 2013)], no linear relationship exists between the individual anxiety profile and the agent-dependent modulation index of both subjective ratings and MEP amplitude, at least in our sample.

4. Discussion

In the present study, we focused on the interaction between defensive and motor systems, and we asked whether voluntary actions can modulate defensive motor responses to painful stimuli. To manipulate the volitional component of our paradigm, we compared conditions in which painful electric stimuli were either self-generated or other-generated and we found two main results. First, we replicated the inhibitory effect of painful electrical stimuli on the corticospinal excitability, widely demonstrated in previous physiological studies. Indeed, in both self-generated and other-generated actions, the MEP amplitude during shock conditions was significantly reduced as compared to the respective no-shock conditions. Second, and more crucial, we found an agent-dependent corticospinal excitability modulation, consisting in a significantly lower inhibitory effect (i.e. greater MEP amplitude) following self-generated than other-generated shocks. This suggests that volitional actions are effective in modulating defensive mechanisms. Similarly, in behavioural data, we found that subjective ratings on the perceived pain intensity were significantly attenuated in self-generated compared to other-generated conditions.

4.1. Inhibitory effect of painful transcutaneous electrical stimuli on the corticospinal excitability

Here, we clearly replicate the inhibitory effect of painful transcutaneous electrical stimuli on the corticospinal excitability (Fig. 2A and B). It is interesting to note that, in our sample, this effect is observed in the majority of the subjects (83.33% in APB and 88.8% in FDI) and it is present in both self- and other-generated shock conditions. Importantly, the amount of inhibition in other-generated shock condition (56.57% reduction of the MEP amplitude as compared to no-shock condition) is largely comparable to the previously described inhibitory effect in different experimental contexts in which the painful stimulus is automatically triggered (Fossataro et al., 2018c; Urban et al., 2004).

The amplitude reduction of MEPs recorded from the stimulated hand

muscles has been described after 20–50 ms electrical stimulation (i.e. at the same short-latency employed here) of both the median nerve (Fischer and Orth, 2011; Tokimura et al., 2000) and the digits (Farina et al., 2001; Fossataro et al., 2018c; Kofler et al., 2001; Urban et al., 2004). This short-latency inhibition is compatible with the nature of electrical stimulation. Indeed, at this latency, the electrical input conveyed by large-diameter Aβ fibres, with a fast conduction velocity (>30 m/s), has enough time to reach both spinal motoneuron pools and the sensorimotor cortex before the onset of the TMS pulse (Caccia et al., 1973; Tokimura et al., 2000). Importantly, high-intensity electrical stimulation, such as that employed here, is able to modulate the MEP amplitude, while low-intensity innocuous electrical stimuli are not (Bikmullina et al., 2009; Fossataro et al., 2018c). High-intensity electrical stimulation is likely to recruit also a wide set of pain-related afferents, thus explaining the painful sensation reported by the subjects (4.62 up to 7). Importantly, as pointed out by previous research, some group III nociceptors, known to be activated by high intensity electrical stimulation, have fast conduction velocities (between 25 and 30 m/s), compatible with the latency of the present inhibition (Caccia et al., 1973; Lewin and Moshourab, 2004; Martin et al., 2008).

A recent evidence, coming from the literature studying the acoustic startle reflex [a protective behaviour, consisting in a motor activation following high-intensity auditory stimuli (Sege et al., 2018)] demonstrated that, at rest, MEPs of the left biceps were inhibited when threatening acoustic stimuli were delivered 50 ms prior to TMS pulses (Chen et al., 2016). This finding in the auditory domain, combined with previous research highlighting corticospinal inhibition following the simple observation (Avenanti et al., 2005) or expectancy (Fossataro et al., 2018c) of painful stimuli, suggests that this modulation of corticospinal excitability might represent a combined effect including both bottom-up components, related to the actual pain experience, and top-down components, related to the anticipation of potentially dangerous events.

Interestingly, a dissociation between cortical and spinal excitability has been observed as a consequence of both painful stimulation (Martin et al., 2008) and threatening auditory stimuli (Kühn et al., 2004). Crucially, this opposite modulation of motor outputs (inhibition vs facilitation) was observed by comparing MEPs evoked by TMS over M1 with those evoked by subcortical electrical stimulation (bypassing the motor cortex). Previous studies proposed that, in the brainstem, the reticular formation (RF) plays a pivotal role in orchestrating this opposite modulation of the motor system, by inhibiting the motor cortex and, at the same time, enhancing the spinal motor system excitability (Kühn et al., 2004). Such dissociation, also described as partial "motor decerebration" (Valeriani et al., 1999), has been interpreted as an evolutionary mechanism, directed to inhibit cortical activity in order to facilitate rapid protective spinal reflexes (Farina et al., 2003; Katayama et al., 1994).

4.2. Agent-dependent modulation of defensive motor responses to painful stimuli

More crucial for the purpose of the present study, our results show that inhibitory motor responses to self-generated painful stimuli are significantly attenuated compared to those triggered by other-generated ones (Fig. 2).

It is possible that a low-level movement-dependent effects could have affected our results. In the literature, some studies described a facilitation effect of the contralateral hand movement over the target one (Muellbacher et al., 2000; Tinazzi and Zanette, 1998). In contrast, other studies showed neither facilitation nor inhibition during contralateral homologous muscle activation (Chiappa et al., 1991; Samii et al., 1997). However, in the present study, the analysis of no-shock conditions did not show any significant difference on MEP amplitude between self-generated condition (in which the subjects moved the left index finger to press the button) and other-generated condition (in which they did not) (Fig. 2A and B). This negative result rules out a possible movement-dependent effect related to the contraction of the

contralateral (left) hand muscles during the button-press. We can suppose that the absence of a facilitatory effect may be due to the scarce complexity of the motor act (i.e. button press) and the minimal force requested to trigger the stimulation.

Instead, to explain the attenuation of MEPs inhibition following self-generated shock, we suggest the existence of an agent-dependent modulation of defensive mechanisms: when the electrical stimuli are self-generated, predictive information from the motor system attenuates the defensive responses to the foreseeable adverse event generated by one's own actions as compared to unpredictable sensations generated by someone else's actions. Importantly, this agent-dependent modulation was present in the 72.2% of the subjects and was recorded in both APB and FDI.

Interestingly, behavioural data paralleled the physiological results, since participants gave significantly lower ratings of the perceived pain intensity during self-generated than other-generated actions (Fig. 3). This result can be interpreted as a "sensory attenuation", well-exemplified by the fact of being unable to tickle oneself [e.g. (Blakemore et al., 2000, 1999, 1998; Burin et al., 2018, 2017c; Colle et al., 2020; Frith, 2005; Hughes et al., 2013; Kilteni et al., 2019, 2020; Kilteni and Ehrsson, 2020, 2017; Limanowski et al., 2019; Pyasik et al., 2019)]. According to the forward model of action generation, once motor programs are selected and sent to the periphery, an efference copy is formed and, based on this signal, a forward model predicts the sensory consequences of the movement (Wolpert et al., 1995). When predictions and outcomes match each other, somatosensory afferences are not fully processed because they do not add new information, thus resulting in a sensory attenuation of the perceived stimuli intensity. A similar mechanism, comparing predicted and actual sensory consequence of one's own actions, can be useful to explain our physiological results. We may speculate that, during self-generated shocks, the agent-dependent effect we observed on the motor system is mediated by a top-down modulation of brain areas predicting the sensory consequence of the movement over the RF, via

periaqueductal grey matter (PAG) [for other examples of top-down modulation of defensive subcortical responses see also (Bufacchi et al., 2017; Bufacchi and Iannetti, 2016; Fossataro et al., 2019, 2018a, 2016b, 2016a; Sambo et al., 2012b, 2012a; Sambo and Iannetti, 2013; Wallwork et al., 2016)]. Interestingly, previous studies demonstrated that the RF plays a pivotal role in the processing and response to somatosensory painful stimuli (Barik et al., 2018; Martins and Tavares, 2017; Tracey and Mantyh, 2007). By representing a key connection between the spinal neurons and higher brain regions (such as somatosensory and motor cortices, anterior cingulate cortex, and insula), RF may be considered as the "gateway" of top-down modulations of defensive responses to painful stimuli (and to other threatening sensory event), by balancing the contribution of cortical and spinal activity (Martins and Tavares, 2017). Thus, during voluntary movement, brain areas predicting the sensory consequence of the movement can down-regulate the RF activity, via PAG. This, in turn, might produce a lower inhibition of RF over the motor cortex, as supported by the enhanced MEP amplitude we found here after TMS over M1, and a lower facilitation of RF over the spinal tract, as could be investigated in future experiments, by recording reduced cervicomedullary MEP (CMEP) after electrical subcortical stimulation (Kühn et al., 2004; Martin et al., 2008) (Fig. 4).

Alternatively, one may argue that the attenuated motor inhibition in the self- compared to the other-generated conditions could be generally ascribed to either a more accurate temporal predictability or to a better cognitive controllability of action sensory consequences in the self-generated condition. The fact that the subjects could observe the other person pressing the button to trigger the stimulus seems to control for the temporal predictability. However, in the self-generated condition, subjects could actively control the timing of the stimulation, thus allowing them to choose the instant when the system was optimally tuned to receive the sensory input. This effect might be investigated by comparing the time-lag between the instruction to move and the movement itself in the self- *vs* other-generated conditions. Unfortunately, in the present
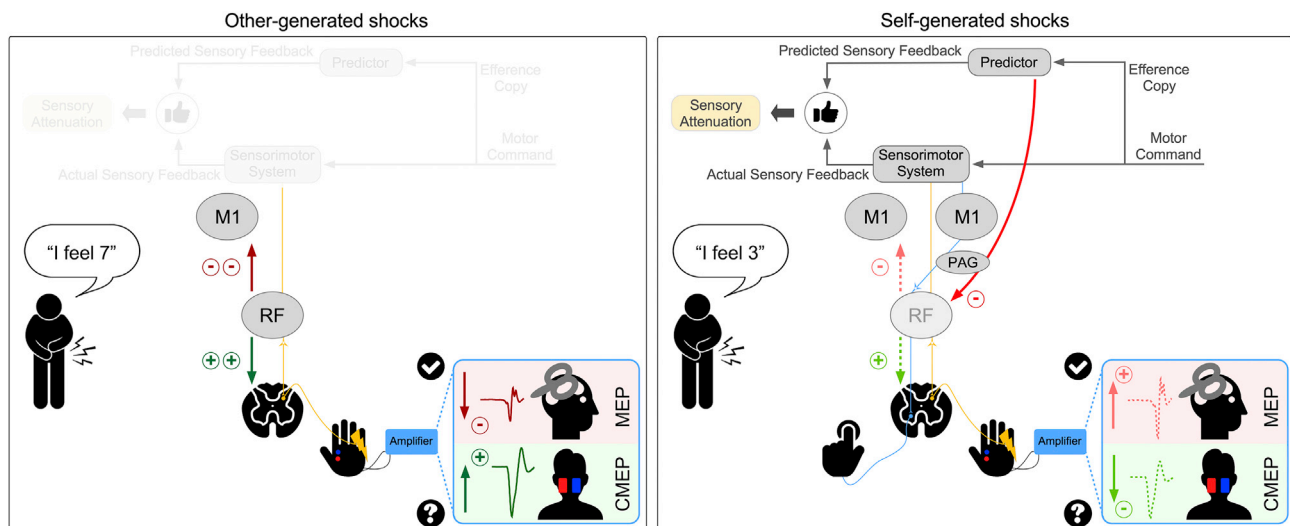
Fig. 4. Model of the perception of sensory consequences of the other-generated and the self-generated actions. *Left panel*, when other-generated electrical painful stimuli are delivered, the reticular formation (RF) may exert an opposite modulation over the motor outputs by inhibiting ("- -") the motor cortex and enhancing ("+ +") the spinal motor system. This opposite modulation between the cortical and spinal motor outputs could be tested in future experiments by comparing the amplitude of MEP (dark red) evoked by TMS over M1 with the amplitude of CMEP (dark green) evoked by subcortical electrical stimulation: the MEP amplitude should be inhibited (verified; "v") while the CMEP amplitude should be enhanced (to be verified in future experiments; "?"). The schematic representation of a man receiving pain represents the subjective perception of the perceived pain intensity (i.e. "I fell 7"). *Right panel*, when self-generated electrical painful stimuli are delivered, an internal forward model [adapted from (Blakemore et al., 2001, 1999)] makes predictions of the sensory feedback based on the motor command sent to the left hand. These predictions are then compared to the actual sensory feedback to produce the sensory prediction error. The lower the error, the greater the attenuation of the painful sensation. In case of self-generated shocks, the motor command to the left hand can be used to attenuate predictively the sensation on the right hand (i.e. "I feel 3"). Concurrently, brain areas predicting the sensory consequence of the movement can down-regulate ("-" in red) the RF activity, via PAG, producing a lower inhibition ("-" in light pink) of RF over the motor cortex and a lower facilitation ("+" in light green) of RF over the spinal tract. This should enhance the MEP amplitude evoked by TMS over M1 (verified; "v") and reduced the amplitude of cervicomedullary MEP (CMEP) evoked by electrical subcortical stimulation (to be verified in future experiments; "?").

study, we did not collect such data. Even though we cannot rule out such an alternative hypothesis, previous papers explored whether putative self-attenuation reflects actor-independent, general predictive mechanisms, or whether instead it is specifically bound to the self (Kaiser and Schütz-Bosbach, 2018; Klaffehn et al., 2019; Weiss and Schütz-Bosbach, 2012). However, results reported in the literature are controversial. Through a behavioural study, Weiss and Schütz-Bosbach (2012) directly compared the perceived intensity of self-generated sounds (elicited via a button press) *vs* other-generated identical sounds, whose delivery could be anticipated or not by participants. Crucially, results revealed an attenuation of the self-generated sounds that clearly differed from the perceived loudness intensity of the same sounds when generated by another person, irrespective of the predictability of the sound-eliciting action. This suggests that the attenuation of sensory effects resulting from one's own actions is specifically bound to the self as the respective agent, instead of being related to general, agent-independent mechanisms of action preparation or predictability. Diverging evidence comes from an EEG study (Kaiser and Schütz-Bosbach, 2018). The authors compared self- and other-generated stimuli between contexts wherein both self and other's actions were driven by either internal willingness or external cues (expressed by a count-down). Results showed that the absence of external cues led to a sensory attenuation for the self-generated stimuli, while the presence of external cues resulted in the attenuation of other-generated stimuli. They suggested that the attenuation of self-generated sounds does not depend on the motor command but solely on the predictability of the outcome, concluding that, contrarily to common assumptions about the processing of self-generated sensory input, sensory attenuation is not bound to self-generation *per se*. However, different explanations of such results may be proposed. The use of a count-down to control for predictability in the externally driven context, for example, may have led to the loss of the internal state of volition (or 'urge' to move), which is crucial to build the sense of agency over an outcome (Haggard, 2017). Therefore, in the context of Kaiser and Schütz-Bosbach's study (2018), it is not possible to disentangle between the effect of predictability and agency on the amount of sensory attenuation observed. A more recent study (Klaffehn et al., 2019), by contrast, found the N1 auditory event related component to be attenuated for self-generated tones as compared to other-generated ones, even when, after the button-press, a loading bar signalled the tone occurrence. This suggest that, even when the temporal predictability between self- and external-generated actions is comparable, the sensory attenuation is bound to self-generation *per se*.

In the face of such contrasting evidence, the current state of the field does not allow to disambiguate whether sensory attenuation is best explained by self-dependent predictive mechanism or not. Furthermore, it is worth noting that all the above-mentioned studies employed auditory stimuli, on which the sensory attenuation literature focused the most. However, it is well known that somatosensory and auditory processing does not share common properties both at a peripheral and central levels. Therefore, further studies are needed to explore the role of temporal predictability and cognitive controllability in modulating the sensory attenuation phenomenon, specifically directed to investigate the somatosensory domain.

It is important to note that in our experimental paradigm we did not manipulate the delay between the movement and its consequence (i.e. between the button-press and the delivery of the tactile stimuli). However, the temporal constraints under which the sensory attenuation occurs have been wildly debated and extensively investigated within the sensory attenuation literature. Indeed, it is well known that when the sensory effects of one's own actions are artificially delayed (even by only 100 ms) their attenuation is reduced and such effects are attributed to external causes rather than the self (Bays et al., 2005; Blakemore et al., 2001, 1999). Interestingly, a recent study demonstrated that the sensory attenuation is an adaptive phenomenon since people can rapidly unlearn to attenuate touch immediately after their movement and learn to attenuate delayed touch instead, after repeated exposure to a systematic

delay between the movement and the resulting touch (Kilteni et al., 2019). Furthermore, in a different experimental context of pain stimulation, it has been shown that motor output and pain report can be influenced both by the nature of the control individuals may exercise over their pain and importantly by their dispositional phenotype (i.e. internal or external locus of control) (Wiech et al., 2006). In future studies, it would be relevant to explore whether the individual trait-like belief to have general control over one's own life may affect the sensory attenuation effects.

To conclude, we interpreted our results as an agent-dependent modulation, observable both at a physiological level, on defensive motor responses, and at a behavioural level, on subjective ratings (even though we cannot exclude that other factors, such as predictability and cognitive controllability, might have contributed to the present findings). According to an evolutionary perspective, these effects can be interpreted as an integrated mechanism advantageous for survival, designed for enhancing the salience of unpredictable environmental changes to the detriment of foreseeable events generated by one's own actions.

Declaration of competing interest

None declared.

CRediT authorship contribution statement

C. Fossataro: Conceptualization, Data curation, Methodology, Software, Formal analysis, Investigation, Writing - original draft, Visualization. **D. Burin:** Data curation, Software, Formal analysis, Investigation. **I. Ronga:** Methodology, Writing - original draft. **M. Galigani:** Data curation, Writing - review & editing. **A. Rossi Sebastiano:** Data curation, Writing - review & editing. **L. Pia:** Conceptualization, Writing - review & editing. **F. Garbarini:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration, Funding acquisition.

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