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Q1 Inverse relationship between amplitude and latency of physiological mirror activity during repetitive isometric contractions

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Abstract—Mirror Activity (MA) is a phenomenon that is characterized by involuntarily occurring muscular activity in homologous contralateral limbs during unilateral movements. Even in neurologically healthy humans, MA of a small extent has been described, which does not directly lead to visible movements, but nonetheless, it is still detectable with surface electromyography (EMG) and therefore defined as physiological MA (pMA). The present study investigated latency- and amplitude-characteristics of pMA during repetitive unimanual isometric contractions with high but constant force requirements (80% maximum force). Here, we show for the first time that pMA is not time-locked to the muscle onset of voluntarily contracting hand muscles but starts with varying and dynamically changing latencies. Following consecutive isometric unilateral contractions, the latency of pMA progressively decreases accompanied by a progressive linear increase in its amplitude possibly as a result of changes in inhibitory mechanisms involved in suppressing involuntarily occurring muscular activity. Overall, the latency and amplitude of pMA show a strong inverse relationship. Furthermore, based on the previously proposed hypothesis of motor overflow, we explored the possibility of pMA modulation through anodal and cathodal transcranial direct current stimulation (tDCS) applied to the ipsilateral primary motor cortex (M1), relative to a voluntarily contracting hand. Neither anodal nor cathodal tDCS is able to modulate amplitude or latency of pMA compared to sham tDCS. In conclusion, our results extend the existing knowledge of pMA occurring due to high-effort unilateral contractions with constant force requirements to the aspect of its latency and the inverse association with its amplitude.

Key words: mirror activity, motor overflow, latency, EMG, tDCS.

INTRODUCTION

Mirror Activity (MA) is a phenomenon that is characterized by involuntarily occurring muscular activity in homologous contralateral limbs during unilateral movements. This peculiarity of human motor control has been observed in patients with neurological disorders like Parkinson's disease (Espay et al., 2005; Cincotta et al., 2006; Ottaviani et al., 2008), Klippel–Feil syndrome (Tubbs et al., 2004) and persons suffering from congenital gene mutations (Depienne et al., 2012; Gallea et al., 2013; Franz et al., 2015). These pathological forms of MA have been termed Mirror Movements (MMs), due to the severity of unintended contralateral muscle recruitment that leads to clearly noticeable and overt involuntary movements. On the other hand, even in neurologically healthy humans, MA of a lesser extent has been described. This MA does not lead directly to overt muscle contractions and therefore visible movements, yet is still subliminally detectable using surface electromyography (EMG) and is therefore defined as physiological MA (pMA) (Cincotta and Ziemann, 2008).

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Abbreviations: A, Vargha–Delaney effect size of stochastic superiority; ATS, ANOVA-type statistic; CF, crossed facilitation; CMCT, central motor conduction time; CNS, central nervous system; FDI, first dorsal interossei muscle; IHF, interhemispheric facilitation; IHI, interhemispheric inhibition; LQ, laterality quotient; MA, mirror activity; MCT, motor conduction time; MDF, median frequency; MM, mirror movements; MVC, maximum voluntary contraction; M1, primary motor cortex; fNIRS, functional near-infrared spectroscopy; pMA, physiological mirror activity; PMCT, peripheral motor conduction time; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

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In general, it is assumed that there is an association between the prevalence of pMA and the functional requirements of unilateral motor tasks. Numerous previous studies showed that especially high force requirements led to reliable pMA observation in healthy participants (Hopf et al., 1974; Todor and Lazarus, 1986; Zijdewind and Kernell, 2001; Post et al., 2008; van Duinen et al., 2008; Sehm et al., 2010, 2016; Maudrich et al., 2017, 2018). Additionally, it was demonstrated that during unilateral contractions of hand muscles with progressively increasing force demands, the amplitude of contralateral pMA increases as a function of applied force (Sehm et al., 2010, 2016; Maudrich et al., 2017, 2018). However, it is still unknown how the amplitude of pMA changes following repetitive isometric high-force contractions with constant force demands as a function of the number of contractions.

In addition to amplitude, another parameter of critical importance regarding the temporal characterization of pMA is latency, defined as the time delay between unilateral voluntary muscle burst onset and the initial occurrence of contralateral involuntary muscular activity during sustained high-effort contractions. Indeed, surprisingly few investigations observed that pMA seems to be non-time-locked to the actively contracting hand (Mayston et al., 1999; Zijdewind and Kernell, 2001; Uttner et al., 2007; Cabib et al., 2016). In fact, one study showed that the onset of pMA compared to voluntary EMG can indeed be variable (range −14 to 14 ms) during low-force finger abductions. However, the authors concluded that pMA typically starts at about the same time (Mayston et al., 1999). Another investigation observed mean time delays between voluntary and involuntary EMG of 14.6 ms following a simple unilateral wrist extension reaction task in healthy adults (Cabib et al., 2016). However, the number of averaged trials in that study was limited (in total 13 trials). As mentioned, most previous investigations of pMA focused primarily on its amplitude changes in dependency of movement characteristics e.g. applied force (Hopf et al., 1974; Todor and Lazarus, 1986; Zijdewind and Kernell, 2001; van Duinen et al., 2008; Sehm et al., 2010, 2016; Maudrich et al., 2017, 2018). Other modulating factors are central and peripheral fatigue following repetitive exhaustive contractions (Liederman and Foley, 1987; Post et al., 2007; Cincotta and Ziemann, 2008; Post et al., 2008), increased movement frequency (Uttner et al., 2007) as well as increased cognitive load during task execution (Addamo et al., 2009). However, none of these studies further investigated pMA latency, so that the current understanding still lacks a clear and systematic description of the temporal relationship between active and mirror EMG activity. However, we see the need to complement the existing literature with regard to the underlying temporal characteristics in order to allow a more precise distinction between ongoing neurophysiological processes involved in pMA.

With respect to the underlying mechanism of pMA during strong unilateral contractions, the concept of motor overflow has been proposed (Yensen, 1965). Motor overflow is thought to be caused by variable states of interhemispheric communication transmitted through transcallosal fibers connecting bilateral motor areas as a function of relative muscular effort. During unilateral contractions with progressively increasing force requirements, this communication is characterized by a gradual shift from predominantly interhemispheric inhibition (IHI) to interhemispheric facilitation (IHF), which in turn leads to bilateral activation of motor-relevant brain regions (Perez and Cohen, 2008; Sehm et al., 2016). This hypothesis is further supported by transcranial magnetic stimulation (TMS) studies indicating an increase in excitability and reduction of intracortical inhibition of the ipsilateral primary motor cortex (M1) during effortful unilateral contractions of upper limb muscles (Tinazzi and Zanette, 1998; Muellbacher et al., 2000; Hortobagyi et al., 2003; Chiou et al., 2013). Based on these proposed mechanisms it is reasonable to assume that pMA can be modulated through the application of non-invasive brain stimulation to the ipsilateral (inactive) M1 relative to a unilaterally contracting hand. In recent years, transcranial direct current stimulation (tDCS) has been used as a tool to modulate the cortical excitability of targeted brain areas non-invasively resulting in modification of various behavioral functions (Nitsche and Paulus, 2000; Nitsche et al., 2008). We hypothesized that the spillover of the motor command from active to inactive M1 can be modulated by tDCS which results in a quantifiable modification of observable pMA. With this approach, we aimed to indirectly test the motor overflow hypothesis.

Here, we investigated the behavior of pMA-characteristics during the performance of repetitive unilateral isometric contractions of intrinsic hand muscles with high but constant force requirement. The goal of this study was to perform a systematic evaluation of latencies, defined as the time between voluntary muscle burst onset and the initial occurrence of contralateral involuntary muscular activity since we hypothesized, based on anecdotal evidence and personal observations, that pMA is not time-locked to the voluntary muscle onset (Maudrich et al., 2017, 2018). Furthermore, the possibility of pMA modulation through tDCS applied to the ipsilateral M1 with respect to a contracting hand was explored. We aimed to provide new insights into the inherent characteristics of pMA using a cross-over, double-blind, counterbalanced research design.

EXPERIMENTAL PROCEDURES

Ethical approval

The study was approved by the local ethics-committee of the University of Leipzig. According to the Declaration of Helsinki, all participants gave written informed consent to partake in the experiments and were compensated for participation.

Procedure

We used a cross-over, double-blind, counterbalanced design to apply 3 conditions (sham, anodal, cathodal) of tDCS (20 min, 1 mA) to the ipsilateral M1 while 24 male, right-handed participants performed unilateral isometric contractions of the right (dominant) hand according to a block design (see Fig. 1). During the whole experiment, neuromuscular activity was recorded non-invasively via surface EMG.

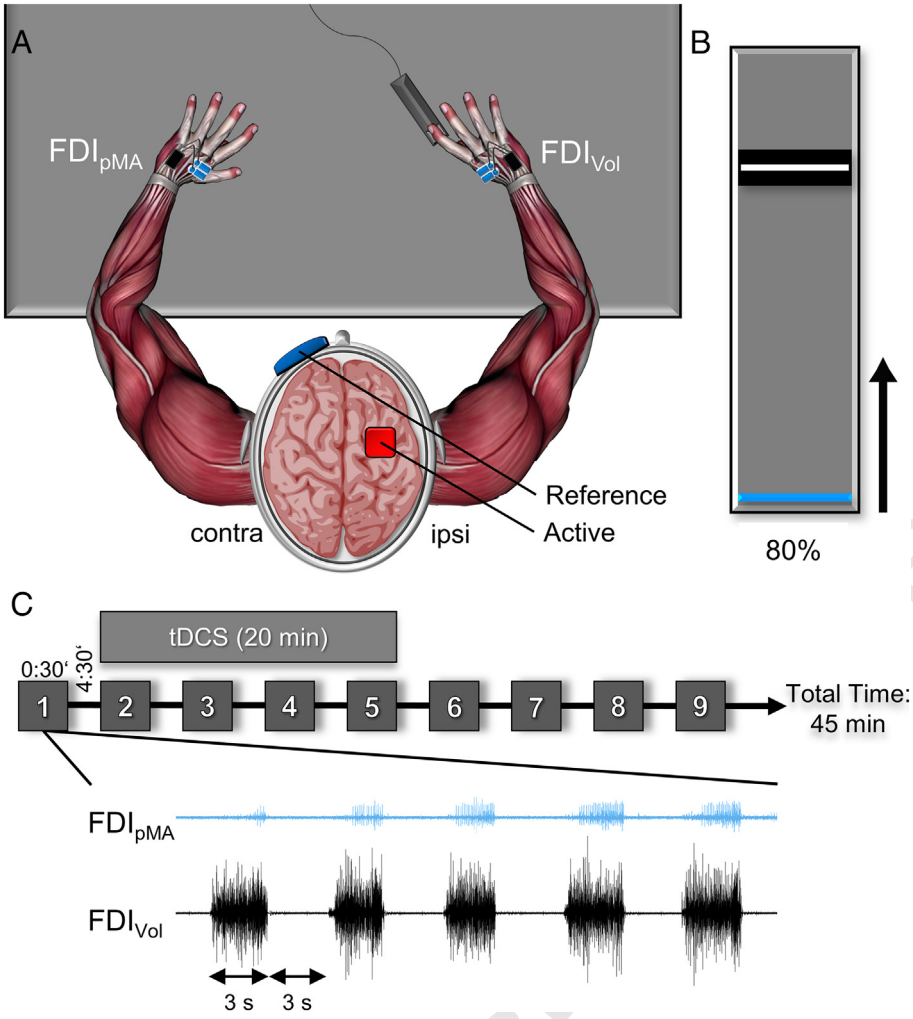

Fig. 1. Experimental Setup. (A) Unilateral force task and tDCS montage. The active tDCS-electrode was placed on the ipsilateral primary motor cortex (M1) relative to the contracting (right) hand. The reference electrode was placed contralateral supraorbital. **(B)** Visual feedback was provided during force task performance where the goal was to move the bar into the target field as quickly and precisely as possible by means of applying force on the force sensor (representing 80% MVC). **(C)** Block design overview. Every session consisted of nine force blocks, each requiring five isometric unilateral contractions (3 s) separated by 3 s of rest. In between each force block, a resting period of 4:30 min was implemented. The total time to complete one session was 45 min.

Experimental sessions were separated by 48 h. to avoid confounding effects of central and peripheral fatigue on subsequent performances. Additionally, daytime of experimental sessions were kept constant intra-individually and participants were instructed to sleep at least 7 h on the night prior to testing, in order to minimize the influence of these confounding factors, which have been shown to affect the variability and response to tDCS (Li et al., 2015; Thair et al., 2017).

Participants

Twenty-four healthy male adults participated in this study (median (interquartile range (IQR)), age: 28 (7.5) years). We recruited only male participants in order to account for possible gender-related differences in brain structure and function (Grabowska, 2017), which might have influenced the motor behavior under investigation. All participants were right-handed according to the Oldfield handedness inventory (Oldfield, 1971) (laterality quotient: 90 (20)) and none of them had any history of playing musical instruments. Participants were either recruited from the local Max-Planck Institute database or through public advertisement. In addition, participants were instructed to avoid alcohol and caffeine intake 24 h prior to experimental sessions due to its well-known influences on force production and central nervous system (CNS) functioning (Pesta et al., 2013).

Behavioral experiment

All experimental sessions consisted of an identical unilateral force generation task. Participants were instructed to sit comfortably in a chair while both of their arms were resting on a table in front of them. The actively contracting (right) hand was used to operate a custom-made force sensor to perform an isometric pinch-task by simultaneously contracting the thumb and index finger while the resting (left) hand remained relaxed (see Fig. 1A). Participants were instructed to focus solely on the active hand while no feedback of ongoing pMA was provided in order to avoid intentional inhibition of involuntarily occurring muscular activity. At no time during the experiments, were the subjects aware of the study interest, i.e. involuntary muscular activity of the resting hand.

Visual feedback during the pinch force task was provided on a PC using Presentation 16.5 (NeuroBehavioral Systems, Albany, USA). The screen presented a target field and a horizontal bar, with the goal being to move the bar into the target field as quickly and precisely as possible by the exertion of force on the force sensor. Target field, as well as the force required to reach it, was adjusted to individual MVC values, representing 80% MVC (see Fig. 1B). Applied force was displayed on the PC monitor at 60 Hz with a sampling frequency of 800 Hz.

Prior to testing, a maximum force test was conducted for both the right and left hand separately. Participants exerted individual maximum voluntary contraction force 3 times (5 s duration for each repetition) with a 1 min resting period in between contractions. To warrant the best effort, participants were verbally encouraged by the researcher following a standardized protocol. The best trial of each participant was defined as individual maximum voluntary contraction (MVC).

The subsequent task utilized a block design comprising of a constant force level (80% MVC) relative to each individuals MVC value. For one block, five isometric contractions were performed using the right hand. One contraction lasted for 3 s with 3 s rest in between contractions. Since all participants performed 5 contractions per block, this results in a total duration of 30 s per block. Each block was followed by a 4:30 min resting-period to allow for partial recovery. In total, each participant performed 9 blocks. The first block was performed without stimulation as a baseline. The following 4 blocks were performed while one of the 3 tDCS conditions (sham, anodal, cathodal, see section: Transcranial Direct Current Stimulation) was applied. The last 4 blocks again were performed without any further stimulation. Taken together, the time to complete the force task was 45 min (see Fig. 1C).

EMG recordings and analysis

Surface EMG was recorded on a wireless Desktop Direct Transmission System (NORAXON Inc., Scottsdale, USA). EMG signals were obtained from bilateral first dorsal interossei muscles (FDI) using bipolar surface electrodes (Ag/AgCl; diameter: 10 mm). Inter-electrode distances were standardized at 20 mm and electrodes were attached in parallel to muscle fiber orientation. Electrode positioning was individually determined by tape-measurements performed relative to surface anatomical landmarks (half of the distance between caput os metacarpale I & II during “L-position” of the thumb and index finger). This was done to minimize intra-individual electrode placement differences during repeated experimental sessions. This setup allowed us to capture EMG activity over the voluntarily contracting FDI (FDI_{Vol}) as well as subliminal pMA over the homologous FDI (FDI_{pMA}) of the relaxed limb. EMG data were recorded with a sampling frequency of 1500 Hz, band-pass filtered at 10–500 Hz, input impedance >100 MΩ, Common Mode Rejection Ratio (CMRR) > 100 dB and a gain of 500.

Subsequent processing of EMG data was performed using custom-written code implemented in MATLAB (v. R2017b, The MathWorks Inc., Natick, USA). Conditioning of EMG data from FDI_{Vol} consisted of rectification as well as the application of the Teager–Kaiser energy operator, which has been shown to improve muscle onset detection (Solnik et al., 2010). EMG signals from FDI_{pMA} were rectified without any further signal conditioning. This approach was implemented motivated by the observation that pMA shows a saw-tooth-like behavior (Zijdewind and Kernell, 2001) and the concern that further smoothing of the data might have led to delayed pMA-onset determination due to the elimination of physiological meaningful EMG-spikes. Additionally, both EMG signals (FDI_{Vol} and FDI_{pMA}) were overlaid and time-locked to preserve the temporal relationship between voluntary and involuntary muscular activity.

Time–domain analysis

For each burst of the FDI_{Vol}, voluntary muscle on- and offsets were defined manually by visual inspection of the EMG traces, performed by a single trained researcher. Participants were instructed to keep all muscles of the upper extremity as relaxed as possible in between every contraction. However, through initial automated onset detection, we experienced issues regarding pre-burst spikes unrelated to the actual burst of interest, leading to incorrect contraction onset detection in some cases. Therefore, we opted for manual onset detection because all bursts of interest were still clearly distinguishable by eye through visual inspection of a trained rater and apparent to identify because of the high muscular activation necessary to reach the required high force demand (80% MVC). Such unrelated pre-burst spikes, however, were not common for the pMA where we used an automated algorithm. Latency of pMA was subsequently defined automatically during the delay between burst-onset of FDI_{Vol} and the time point, at which muscular activity in the contralateral (resting) FDI_{pMA} exceeded a threshold of its own mean baseline activity (1000 ms pre-FDI_{Vol} burst onset) + 2 SD for a time window of at least 10 ms (see Fig. 2).

Mean EMG amplitudes of FDI_{Vol}, as well as FDI_{pMA}, were computed by the estimation of root mean square (RMS) values (30 ms). Mean EMG amplitudes of the FDI_{Vol} were computed over the time window from manually determined muscle-onset until manually determined muscle-offset. With regard to pMA, latencies were taken into account so that mean EMG amplitudes of FDI_{pMA} were computed over the time window from the previously determined point of significant elevation of neuromuscular activity above the mean of 1000 ms pre-FDI_{Vol} burst onset +2 SD until the muscle-offset of FDI_{Vol}.

All EMG amplitudes were normalized with respect to individual MVC values measured at the beginning of every session for each hand separately. MVC values were estimated by the mean EMG activity over a time window of 500 ms during maximum unilateral force production for FDI_{Vol} and FDI_{pMA}, respectively.

Frequency-domain analysis

Unrectified EMG signals of every determined EMG-burst (i.e. 45 per session and subject) were used for frequency analysis by means of Fast Fourier transform function implemented in MATLAB with epoch lengths of 1500 samples (1000 ms), taken from the stationary part of the EMG-burst signal. The median frequency (MDF) of every burst of FDI_{Vol} as well as FDI_{pMA} was defined separately by the frequency at which the power-frequency-spectrum reaches 50% of the total power within the epoch (Phinyomark et al., 2012). The parameter of MDF has been used in many previous investigations of stationary (isometric) signals to quantify fatigue related shifts of the power-frequency-spectrum to the left (Cifrek et al., 2009; Phinyomark et al., 2012).

Transcranial direct current stimulation

Transcranial direct current stimulation was applied using a DC-Stimulator Plus (neuroConn GmbH, Ilmenau, Germany). The active electrode (5 cm × 5 cm) was placed on the ipsilateral (right) M1 hand area relative to the contracting hand with the cable connection pointing towards the vertex. Neuronavigation (Brainsight TMS, Rogue Research, Montreal, QC,

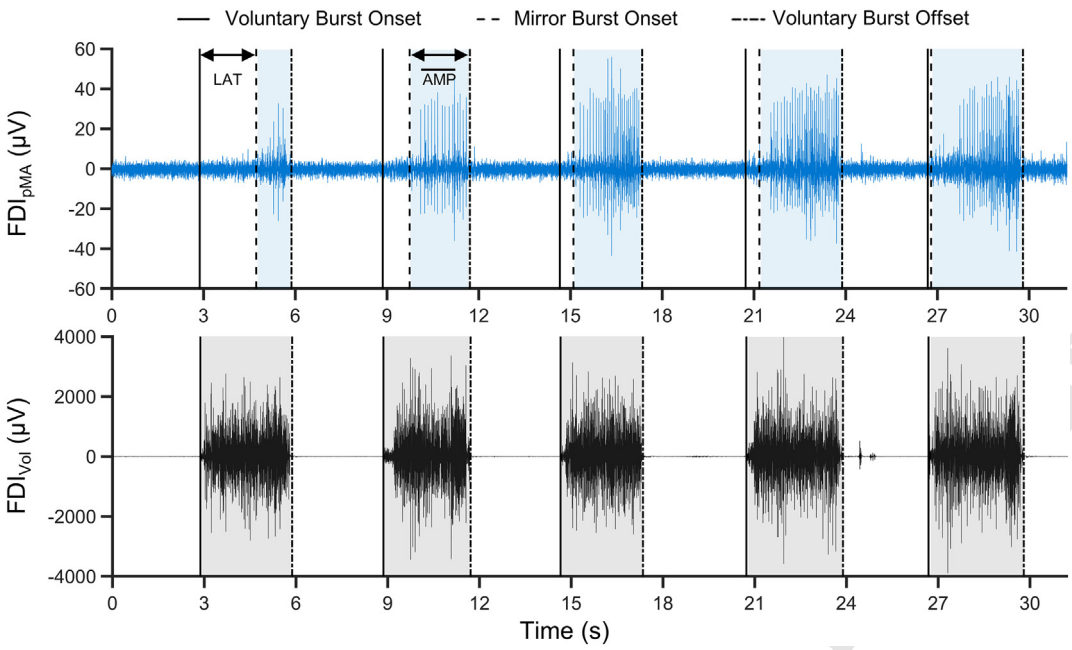

Fig. 2. Exemplary EMG-Recording of voluntary (FDI$_{Vol}$) and involuntary (FDI$_{pMA}$) muscular activity. Note the different scaling of the EMG-traces and the decrease of latencies of FDI$_{pMA}$ with each consecutive isometric contraction of FDI$_{Vol}$. LAT = latency, AMP = amplitude of pMA.

Canada) was used for the purpose of accurate intra-individual electrode positioning during the repeated experimental session. For all participants, the following MNI (Montreal Neurological Institute) M1-coordinates taken from a recent meta-analysis (Mayka et al., 2006) overlaid on an MNI-152 brain template were chosen: 37, −21, 58 (*x*, *y*, *z*). The reference electrode (10 cm × 10 cm) was placed on the contralateral (left) supraorbital cortex with the cable connection pointing upwards. Electrodes were inserted in saline-soaked sponges and elastic bands were used to fix the electrodes on the participants head.

With respect to the anodal and cathodal stimulation condition, the current intensity was set at 1 mA for a duration of 20 min with a ramp-up and ramp-down phase of 30 s, respectively. This results in a current density of 0.04 mA/cm^2 under the target electrode and 0.01 mA/cm^2 under the reference electrode. During the sham-condition, the current was ramped-up for 30 s, held constant at 1 mA for 30 s and ramped-down for 30 s. This short duration of stimulation has been shown to elicit no changes in cortical excitability while it may provide the same tingling sensation on the scalp of the participant (Nitsche et al., 2008).

tDCS conditions (anodal, cathodal, sham) were randomly assigned within participants. Immediately after the termination of tDCS participants were asked to rate the level of perceived sensation in relation to the stimulation (0 = no sensation, 10 = unbearable sensation) on a visual analog scale (VAS). Researchers, as well as participants, were blinded during the experiments.

Statistics

All statistical analyses were conducted using RStudio (v. 3.2.3, R Foundation of Statistical Computing, Vienna, Austria (R Core Team, 2015)). We used non-parametric methods to account for the non-normal distribution of the data. Normality was assessed through Lilliefors-testing (α = 0.05), resulting in 53% of the variables beeing classified as non-normally distributed (all $p < 0.005$). The R-package 'nparLD' was implemented to non-parametrically analyze the data according to a rank-based repeated measures design using ANOVA-type statistics (ATS), with the denominator degrees of freedom set to infinity (Brunner et al., 2002; Noguchi et al., 2012). The effect size *A*, a measure of stochastic superiority was computed for pairwise post-hoc comparisons of the ATS (Vargha and Delaney, 2000). The interpretation benchmarks of *A* are small effect ~0.56, medium effect ~0.64, large effect ~0.71. The statistical threshold for all analyses was set at $p < 0.05$ and was appropriately Bonferroni adjusted to correct for multiple post-hoc comparisons. No outliers were removed from the analyses.

Maximum force values during MVC testing and self-reported tDCS-sensations were analyzed by means of two separate Friedman test of variance by ranks with the factor STIM (sham, anodal, cathodal).

Contraction-wise analysis

Prior to further statistical analyses every 1st, 2nd, 3rd, 4th & 5th contraction of each force block were averaged for each participant separately (see Fig. 3A). This was done in order to analyze the dynamic behavior of FDI$_{pMA}$ parameters during five repetitive contractions within force blocks.

Possible stimulation-induced differences between total time spent within the visual target field and total length of the EMG burst of FDI$_{Vol}$ were analyzed with two separate non-parametric repeated measures ATS comprising two within-subject (sub-plot) factors: STIM (sham, anodal, cathodal) and CONTRACTION (1st–5th).

Amplitudes and latencies of FDI$_{pMA}$ as well as MDF of EMG-bursts of FDI$_{Vol}$ and FDI$_{pMA}$ were subsequently analyzed contraction-wise by means of separate non-parametric repeated measures ATS with two within-subject (sub-plot) factors: STIM (sham, anodal, cathodal) and CONTRACTION (1st–5th). Here, the significance level was Bonferroni adjusted for 5 pairwise post-hoc comparisons (Contraction 1 vs. Contraction 2, Contraction 2 vs.

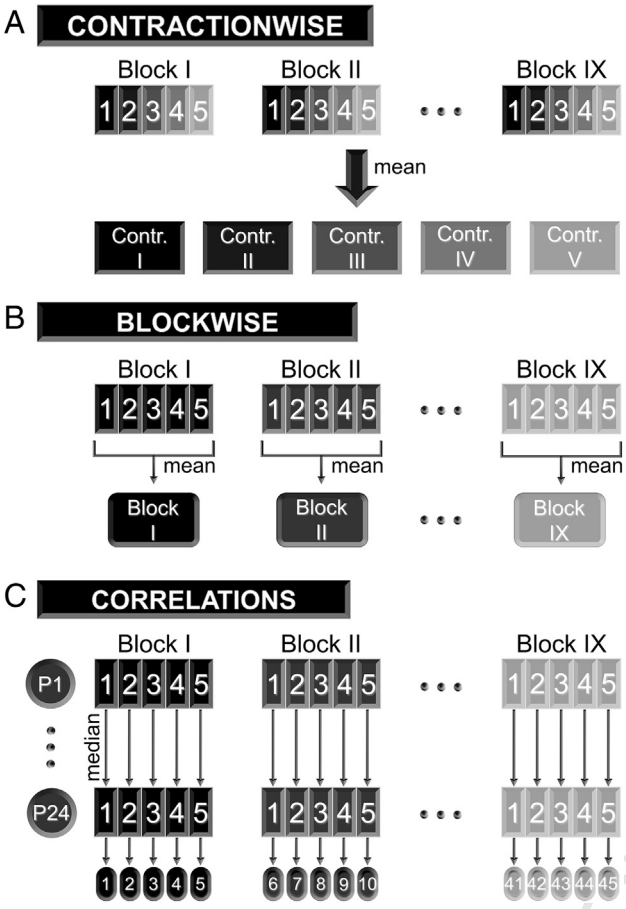

Fig. 3. Statistical procedure overview. (A) Parameter generation for contraction-wise analyses. Every 1st, 2nd, 3rd, 4th & 5th contraction of each force block were averaged for each participant separately resulting in five levels for the factor CONTRACTION. **(B)** Parameter generation for block-wise analyses. All five contractions for each force block were averaged separately resulting in nine levels for the factor BLOCK. **(C)** Median values across participants (n = 24) for all 45 contractions within one experimental session used for correlation analyses. P = participant.

Contraction 3, Contraction 3 vs. Contraction 4, Contraction 4 vs. Contraction 5 & Contraction 1 vs. Contraction 5; $p_{adj} < 0.01$).

To further investigate possible tDCS-evoked effects on amplitudes and latencies of pMA we conducted separate non-parametric repeated measures ATS with two within-subject (sub-plot) factors: STIM (sham, anodal, cathodal) and CONTRACTION (1st–5th) limited to the 4 force blocks during which tDCS was applied (Block II, III, IV, V). Here, the significance level was Bonferroni adjusted for five pair-wise post-hoc comparisons (Contraction 1 vs. Contraction 2, Contraction 2 vs. Contraction 3, Contraction 3 vs. Contraction 4, Contraction 4 vs. Contraction 5 & Contraction 1 vs. Contraction 5; $p_{adj} < 0.01$).

Block-wise analysis

We further averaged amplitudes and latencies of FDI_{pMA} of all five contractions for each force block separately (see Fig. 3B) to analyze the behavior of these parameters across the whole experimental session (change in parameters from block 1 to block 9). Accordingly, we used separate non-parametric repeated measures ATS with two within-subject (sub-plot) factors: STIM (sham, anodal, cathodal) and BLOCK (I–IX). Pre-planned post-hoc comparisons between the first and fifth (baseline vs. last stimulation block) and the first and last block (baseline vs. the last block of the experimental session) were conducted. Accordingly, the significance level was adjusted to $p_{adj} = 0.025$.

Additionally, we focused on these force blocks which were measured during tDCS-application by conducting separate non-parametric repeated measures ATS with two within-subject (sub-plot) factors: STIM (sham, anodal, cathodal) and BLOCK (II - V).

Correlation analysis

Finally, Spearman rank correlation coefficients were computed to non-parametrically test for linear relationships between amplitude and latencies of FDI_{pMA} for each stimulation condition (sham, anodal, cathodal) as well as amplitude and MDF of the FDI_{pMA} muscle burst, separately. Therefore, the median values of these three parameters of every 1st–45th contraction (9 blocks × 5 contractions) were computed across participants, respectively (see Fig. 3C). 95% confidence intervals (CI) of Spearman's rank correlation coefficients were determined by bootstrapping with 5000 permutations.

RESULTS

Maximum force values measured during MVC testing showed no significant differences between all three stimulation condition sessions ($\chi^2(2) = 5.20$, $p = 0.074$).

Furthermore, we found no significant differences in self-reported perceived sensation of tDCS between stimulation conditions ($\chi^2(2) = 2.60$, $p = 0.273$). Hence, we achieved successful sham-control during the experiments.

Additionally, there were no significant difference in the time spent within the visual target field (corresponding to 80% MVC displayed on a PC screen) between stimulation conditions ($F_{1.886, \infty} = 0.488$, $p = 0.602$) and no interaction effect ($F_{4.476, \infty} = 0.614$, $p = 0.671$).

The total length of the FDI_{Vol} EMG-burst showed no difference between stimulation conditions ($F_{1.560, \infty} = 2.639$, $p = 0.085$) and no interaction effect was observed ($F_{4.559, \infty} = 0.574$, $p = 0.704$).

Amplitude of pMA

Contraction-wise within blocks comparisons of FDI_{pMA} showed a highly significant time effect (see Fig. 5), more precisely a linear increase in amplitude ($F_{1.666, \infty} = 92.141$, $p = 1.958^{-34}$). However, no effect of stimulation condition ($F_{1.893, \infty} = 0.160$, $p = 0.840$) and no interaction effect were observed ($F_{3.712, \infty} = 1.185$, $p = 0.315$). For pairwise post-hoc comparison statistics please see Table 1.

Contraction-wise within tDCS-stimulated blocks (block II–V) comparison of FDI_{pMA} again showed a highly significant increase in amplitude ($F_{1.488, \infty} = 57.881$, $p = 6.178^{-20}$). However, no effect of stimulation condition ($F_{1.982, \infty} =$

Table 1. Pairwise post-hoc comparisons of the within-subject (sub-plot) factor CONTRACTION and BLOCK (* = significant comparison, significance level Bonferroni-adjusted to p = 0.01, † = significant comparison, significance level Bonferroni-adjusted to p = 0.025, [a]ANOVA-type statistic, [b]degrees of freedom of the central F distribution [c]Vargha-Delaney effect size of stochastic superiority, interpretation benchmarks of *A* are: small ~0.56, medium ~0.64, large ~0.71 (Vargha and Delaney, 2000).

PAIRWISE COMPARISON	AMPLITUDE				LATENCY			
	p	F [a]	df [b]	*A* [c]	p	F	df	*A*
(CONTRACTION)								
1–2	4.526^{-9}*	34.38	1.00	0.57	0.001*	10.68	1.00	0.56
2–3	1.287^{-11}*	45.84	1.00	0.55	0.839	0.04	1.00	0.50
3–4	1.316^{-22}*	95.73	1.00	0.56	0.018	5.54	1.00	0.56
4–5	1.352^{-10}*	41.23	1.00	0.55	0.077	3.14	1.00	0.54
1–5	2.453^{-29}*	126.45	1.00	0.72	2.180^{-8}*	31.33	1.00	0.66
(BLOCK)								
1–5	0.021†	5.29	1.00	0.57	0.022†	5.28	1.00	0.58
1–9	2.253^{-7}†	26.80	1.00	0.67	4.789^{-4}†	12.20	1.00	0.64

0.234, p = 0.790) and no interaction effect were observed ($F_{3.343, \infty} = 0.714$, p = 0.558).

Block-wise comparison over the whole experiment again indicates a significant time effect i.e. increase in amplitude ($F_{3.501, \infty} = 13.356$, p = 8.404^{-10}) without a significant effect of stimulation condition ($F_{1.877, \infty} = 0.472$, p = 0.611) or interaction effect ($F_{7.675, \infty} = 1.193$, p = 0.299). For pairwise post-hoc comparisons please see Table 1.

Block-wise comparison over stimulated force blocks (block II – V) again indicates a significant time effect i.e. increase in amplitude ($F_{2.236, \infty} = 4.923$, p = 0.005) without a significant effect of stimulation condition ($F_{1.968, \infty} = 0.268$, p = 0.762) or interaction effect ($F_{3.899, \infty} = 1.145$, p = 0.333).

Latency of pMA

Contraction-wise within blocks comparisons of FDI_{pMA} showed a highly significant time effect (see Fig. 5), i.e. a linear decrease in latency ($F_{2.903, \infty} = 13.392$, p = 1.587^{-8}) within force blocks. However, no effect of stimulation condition ($F_{1.653, \infty} = 1.656$, p = 0.196) and no interaction effect were observed ($F_{5.491, \infty} = 0.713$, p = 0.627). For pairwise post-hoc comparison statistics please see Table 1.

Contraction-wise within tDCS-stimulated blocks (block II–V) comparison of FDI_{pMA} again showed a highly significant decrease in latency ($F_{2.774, \infty} = 7.195$, p = 1.312^{-4}). However, no effect of stimulation condition ($F_{1.737, \infty} =$ 0.110, p = 0.869) and no interaction effect were observed ($F_{5.460, \infty} = 1.574$, p = 0.157).

Block-wise comparisons over the whole experiment again indicated a significant time effect i.e. decrease in latency of FDI_{pMA} ($F_{5.373, \infty} = 5.048$, p = 7.741^{-5}) without a significant effect of stimulation condition ($F_{1.656, \infty} = 1.209$, p = 0.293) or interaction effect ($F_{7.041, \infty} = 1.079$, p = 0.374). For pairwise post-hoc comparison statistics please see Table 1.

Block-wise comparison over stimulated force blocks (block II – V) again indicates a significant time effect i.e. decrease in latency of FDI_{pMA} ($F_{2.905, \infty} = 2.640$, p = 0.049) without a significant effect of stimulation condition ($F_{1.718, \infty} = 0.001$, p = 0.999) or interaction effect ($F_{4.200, \infty} = 0.404$, p = 0.815).

For a descriptive overview of determined latencies within one experimental session (1st–45th contraction) for all stimulation conditions please refer to Table 2.

Median frequency

The MDF of FDI_{Vol} showed a highly significant time effect ($F_{1.528, \infty} = 28.256$, p = 1.667^{-10}), i.e. a linear decrease with each consecutive contraction (see Fig. 6). Again, no effect of stimulation condition ($F_{1.882, \infty} = 0.331$, p = 0.705) or interaction effect was observed ($F_{3.864, \infty} = 0.860$, p = 0.484). For pairwise post-hoc comparisons of MDF of FDI_{Vol} please refer to Table 3.

In the case of MDF (FDI_{pMA}) no significant effect of time ($F_{1.766, \infty} = 2.673$, p = 0.076) or stimulation condition ($F_{1.972, \infty} = 0.579$, p = 0.558) was found. While the global ATS indicated a significant interaction effect ($F_{4.338, \infty} =$ 2.982, p = 0.015), none of the post-hoc comparisons survived after Bonferroni correction.

Correlations

Amplitude and latency of FDI_{pMA} showed a strong inverse relationship during sham (ρ (24) = −0.678, p = 3.082^{-7}, 95%CI [−0.837, −0.438]; see Fig. 7A) and anodal tDCS (ρ (24) = −0.489, p = 6.472^{-4}, 95%CI [−0.743, −0.169]; see Fig. 7C), meaning that longer latencies correspond to lower amplitudes and vice versa. Surprisingly, this relationship failed to reach significance during the cathodal tDCS (ρ (24) = −0.2609, p = 0.0834, 95%CI [−0.527, 0.046]; see Fig. 7E).

Table 2. Descriptive statistics (n = 24) of determined latencies for all stimulation conditions.

CONDITION	MEDIAN	IQR	MIN	MAX
Sham	198 ms	74.5 ms	112 ms	401 ms
Anodal	213 ms	80.3 ms	132 ms	537 ms
Cathodal	210 ms	58.8 ms	103 ms	352 ms

Table 3. Pairwise post-hoc comparisons of the within-subject (sub-plot) factor CONTRACTION (* = significant comparison, significance level Bonferroni-adjusted to p = 0.01, [a]ANOVA-type statistic, [b]degrees of freedom of the central F distribution [c]Vargha-Delaney effect size of stochastic superiority, interpretation benchmarks of *A* are: small ~0.56, medium ~0.64, large ~0.71 (Vargha and Delaney, 2000).

PAIRWISE COMPARISON (CONTRACTION)	MDF FDI_{Vol}			
	p	F [a]	df [b]	*A* [c]
1–2	3.561^{-8}*	30.38	1.00	0.56
2–3	8.081^{-4}*	11.22	1.00	0.55
3–4	6.898^{-5}*	15.84	1.00	0.53
4–5	0.031	4.66	1.00	0.52
1–5	9.158^{-10}*	37.50	1.00	0.66

Furthermore, we found strong positive correlations between amplitude and MDF of FDI_{pMA} for all three stimulation conditions (sham: ρ (24) = 0.602, p = 1.220^{-5}, 95%CI [0.374, 0.759]; anodal: ρ (24) = 0.701, p = 8.325^{-8}, 95%CI [0.487, 0.845]; cathodal: ρ (24) = 0.651, p = 1.278^{-6}, 95% CI [0.426, 0.794], see Fig. 7B/D/F). This indicates that an increase in the amplitude of pMA is accompanied by an increase in MDF of the underlying muscular burst.

DISCUSSION

Here, we show for the first time as a part of a systematic evaluation that pMA is not time-locked to the onset of contracting muscle bursts but starts after varying latencies during the performance of unilateral isometric contractions. These latencies show a dynamic behavior as a function of repeated muscular effort. Furthermore, we provide evidence that the amplitude of pMA increases linearly following repetitive unilateral contractions even under constant (but high) force requirements. Additionally, we show that amplitude and latency of pMA are inversely related as they both seem to reflect the result of decreasing central inhibition on involuntarily occurring muscular activity. This effect might be mediated by an increased central effort to maintain force requirements in the actively contracting hand and/or a buildup of fatigue. This inverse relationship persisted after the application of anodal tDCS but was not observed following cathodal tDCS. Lastly, we report that neither anodal nor cathodal tDCS of the ipsilateral M1 relative to a unilaterally contracting hand significantly modulated amplitude or latency of pMA by itself compared to sham stimulation. This holds true a) within force blocks, b) block-wise over the course of the whole experiment as well as c) when exclusively looking at stimulated force blocks.

Latency and amplitude of pMA

As mentioned, the vast majority of previous investigations regarding pMA focused primarily on its amplitude changes or amount of involuntary muscular activity in dependency of movement characteristics e.g. applied force (Hopf et al., 1974; Todor and Lazarus, 1986; Zijdewind and Kernell, 2001; van Duinen et al., 2008; Sehm et al., 2010, 2016; Maudrich et al., 2017, 2018) or central and peripheral fatigue as a result of repetitive exhaustive contractions (Liederman and Foley, 1987; Post et al., 2007; Cincotta and Ziemann, 2008; Post et al., 2008), while disregarding its latency or rather not systematically evaluating it. However, our results clearly show that pMA always starts after voluntary muscle burst onset and never precedes it, i.e. occurs with positive latencies (please see Table 3).

In general, motor conduction time (MCT), i.e. the time it takes to transmit the motor command from brain to muscle (from cortical M1-neurons to muscle fibers), reflects the sum of central motor conduction time (CMCT, from cortical neurons to spinal motor neurons) and peripheral motor conduction time (PMCT, from spinal nerve root through α-motoneuron to muscle fiber) (Udupa and Chen, 2013). Previous investigations estimated mean CMCT in healthy adults of 7.2 ms and PMCT (with regard to the FDI muscle) of 15.2 ms (Jaiser et al., 2015). Accordingly, an MCT of <25 ms is assumed to be the physiological default. Furthermore, it has been shown that IHF mediated through transcallosal fibers connecting somatotopic muscle representation areas of M1 takes ~10 ms (Hanajima et al., 2001). In summary, the hypothetical time for unrestricted motor overflow during unilateral contractions to occur (spillover of the motor command from the active M1 transcallosally mediated to the ipsilateral (inactive) M1 to muscle fibers of the inactive FDI) would take ~35 ms (10 ms IHF + 25 ms MCT). Under this assumption of uninhibited motor overflow, our results, showing median latencies of pMA longer than 150 ms, point to the prevalence of inhibitory mechanisms controlling the spillover to the ipsilateral hemisphere, which seem to subside over time during repetitive sustained isometric contractions. Indeed, it is generally accepted that the suppression of involuntary pMA is not orchestrated by a specific command area or a single underlying brain structure but rather requires a complex interplay and a precisely communicating network comprising of a multitude of different motor areas (Debaere et al., 2001; Swinnen, 2002), higher order motor/executive areas (Wenderoth et al., 2005; Poisson et al., 2013; Maudrich et al., 2018), as well as potentially, spinal mechanisms (Carson, 2005; Sehm et al., 2010) in order to inhibit intrinsically favored mirroring tendencies and eventually restrict the motor command towards the voluntary contracting limb.

Until now, numerous investigations of pMA confirmed that the amplitude of pMA increases with increasing force demands of unilateral isometric contractions (Todor and Lazarus, 1986; Aranyi and Rosler, 2002; Zijdewind et al., 2006; van Duinen et al., 2008; Sehm et al., 2010, 2016; Maudrich et al., 2017, 2018). Here, we provide evidence that even under continuous, high (80% MVC) force demands, the amplitude of pMA increases linearly following repetitive unilateral contractions (see Fig. 4). This linear increase of pMA amplitude within force blocks was highly significant independent of tDCS application to the ipsilateral M1 (see Fig. 5). An increase in the amplitude of the EMG burst of FDI_{pMA} could generally be the result of additional recruitment of higher threshold motor units or an increase in motor unit firing rates. This assumption is supported by strong positive associations of amplitude and MDF of FDI_{pMA}, independent of stimulation condition, meaning that higher amplitudes are associated with higher MDF of the same muscle (see Fig. 7). An

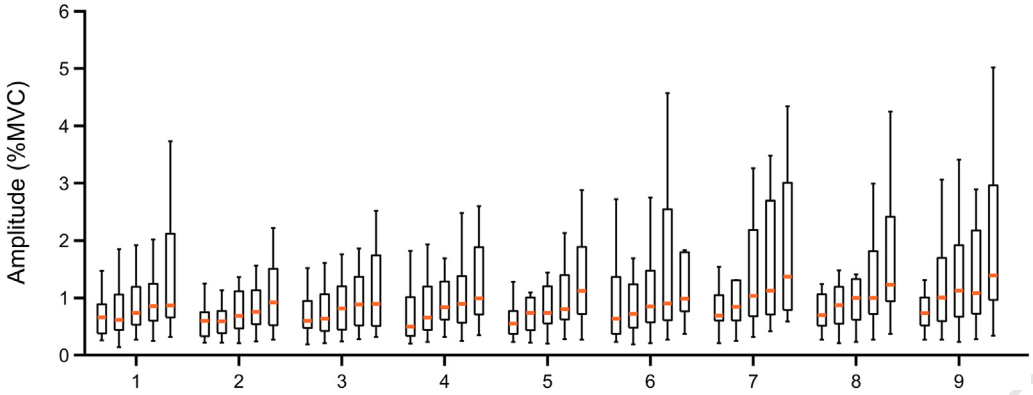

Fig. 4. Dynamic changes in the amplitude of pMA. Time-course of the amplitude of FDI_{pMA} within the sham-condition session. Displayed are boxplots with median values of all 24 subjects.

upward shift of the MDF reflects an increase in the total power spectrum of the underlying EMG burst that could be the result of progressive increases in the firing frequency of motor units initially recruited or an additional number of recruited motor units (Moritani and Muro, 1987). Overall, one can assume that the motor command from the brain through the spinal cord to FDI_{pMA} increases progressively with each consecutive unilateral contraction, again pointing to a failure to produce adequate inhibition of mirroring tendencies.

The observed dynamic behavior of amplitude and latency of pMA is further accompanied by a linear decrease in the MDF of FDI_{Vol} with each consecutive contraction which generally reflects a fatigue-related downward shift of the power-spectrum of stationary (isometric) signals (Cifrek et al., 2009; Phinyomark et al., 2012). This observation, seen independent of stimulation condition, implies peripheral fatigue of FDI_{Vol} due to high force-requirements (80% MVC) within our experiments. We hypothesize that this peripheral fatigue might be at least partially driven by central fatigue and concomitant decrease of pMA-inhibition resulting in more involuntarily spillover of the initially lateralized motor command. Indeed, there is evidence for a progressive, fatigue-induced increase in the amount of pMA during either maintained unilateral contractions with maximum force (2 min) or repeated submaximal fatiguing contractions (Zijdewind and Kernell, 2001; Post et al., 2008). One explanation for this observation might be that due to muscle fatigue of the actively contracting hand, more motor units have to be recruited in order to maintain desired force requirements, consequently leading to an increase in overall neural drive with a higher potential for bilateral activation of motor relevant brain areas (Post et al., 2008). Additionally, further studies indicated that ipsilateral motor and frontal areas gradually increase their activity (as quantified by an increase in cerebral oxygenation measured by functional near-infrared spectroscopy (fNIRS)) during unilateral exhaustive force tasks of the upper limb (Shibuya et al., 2008; Kuboyama and

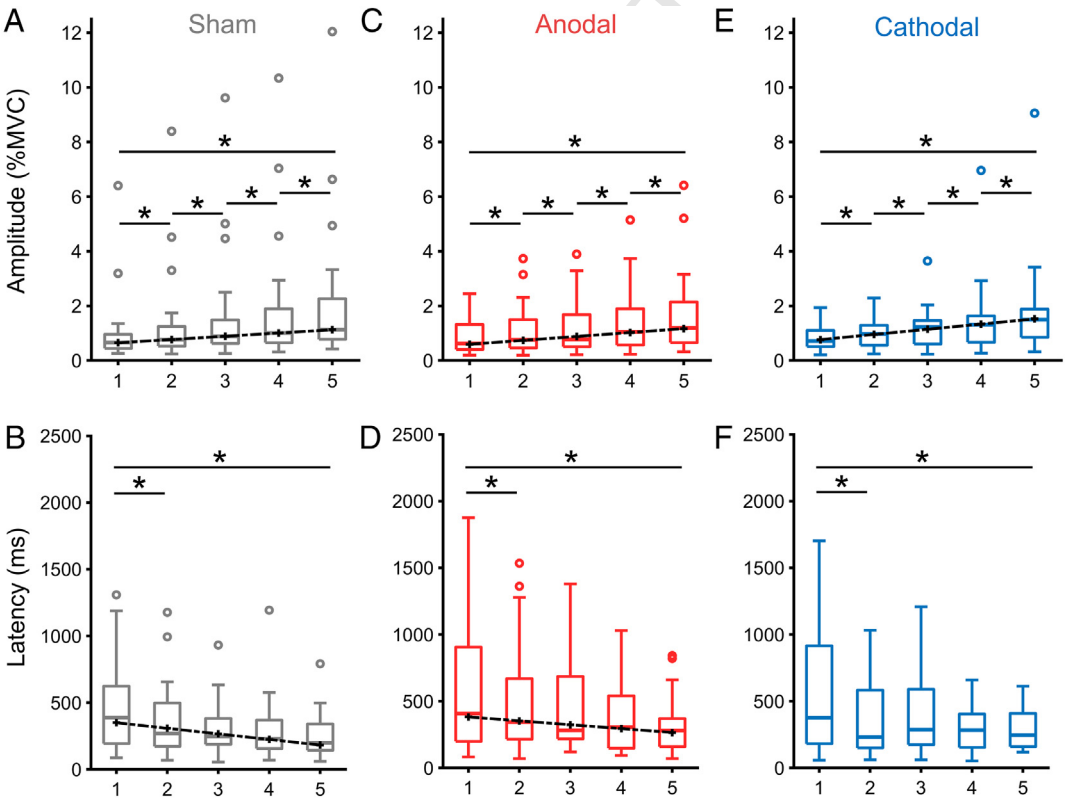

Fig. 5. Contraction-wise analysis of amplitude and latency of FDI_{pMA}. A linear increase of amplitude and a linear decrease of latency are observable for sham **(A)** & **(B)**, anodal **(C)** & **(D)** and cathodal stimulation condition **(E)** & **(F)**. * indicates significant post-hoc pairwise comparisons, significance level Bonferroni adjusted to $p < 0.01$. R^2 indicates the coefficient of determination of the linear trend line fitted through median values. **A**: $R^2 = 0.9993$*, **B**: $R^2 = 0.8277$*, **C**: $R^2 = 0.9379$*, **D**: $R^2 = 0.7482$*, **E**: $R^2 = 0.9712$*, **F**: $R^2 = 0.3414$ n.s.

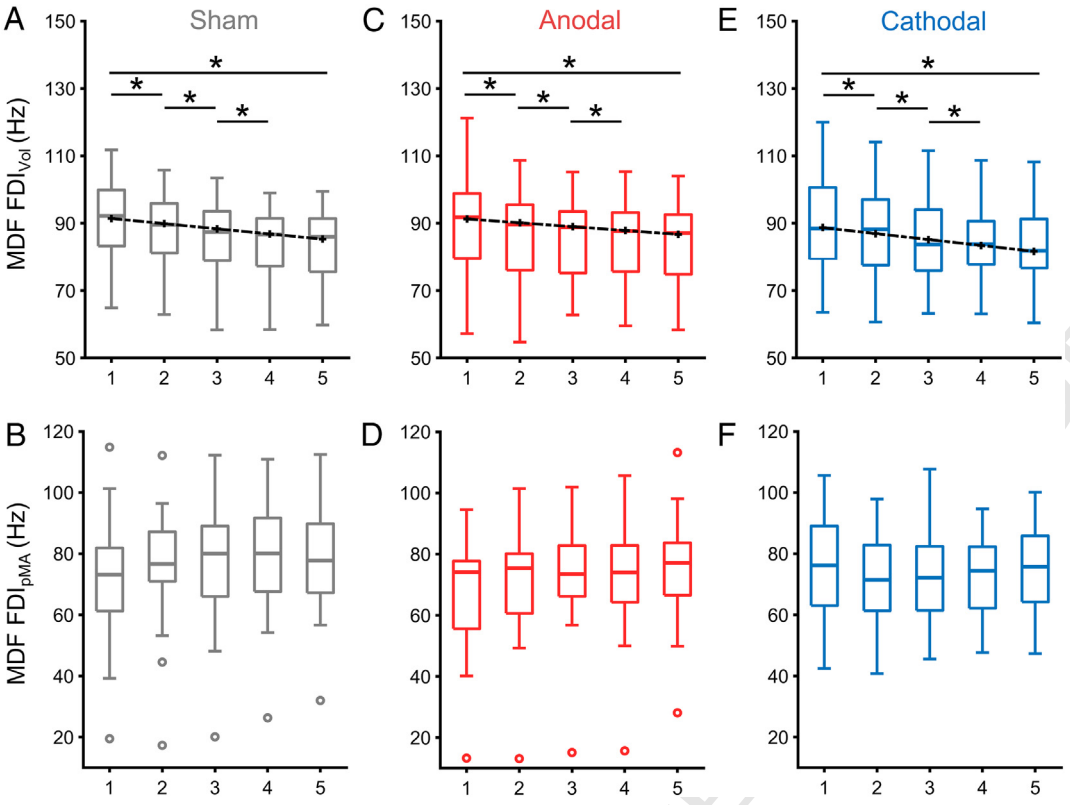

Fig. 6. Contraction-wise analysis of MDF of FDI$_{Vol}$ and FDI$_{pMA}$. A linear decrease of MDF of FDI$_{Vol}$ and increase of MDF of FDI$_{pMA}$ are observable for sham **(A)** & **(B)**, anodal **(C)** & **(D)** and cathodal stimulation condition **(E)** & **(F)**. * indicates significant post-hoc pairwise comparisons, significance level Bonferroni adjusted to $p < 0.01$. R^2 indicates the coefficient of determination of the linear trend line fitted through median values. **A**: $R^2 = 0.9234$*, **B**: $R^2 = 0.4933$ n.s., **C**: $R^2 = 0.9513$*, **D**: $R^2 = 0.2387$ n.s., **E**: $R^2 = 0.8853$*, **F**: $R^2 = 0.0239$ n.s.

Shibuya, 2015) as well as during non-exhaustive graded force generation (Derosiere et al., 2014). This increase in ipsilateral brain activity has been interpreted as a complementary attempt to support the insufficient activity of the contralateral cortex during exhaustive phases of unilateral force generation or as a result of changes in IHI between contra- and ipsilateral hemispheres. One should note, that it has also been speculated that this ipsilateral activation might be partly due to the visuo-guided control of force levels to manage task complexity and not exclusively due to the generation of force itself (Derosiere et al., 2014). Furthermore, it has been shown that the amount of ipsilateral co-activation during a unilateral isometric finger task depends on the muscle contraction force (Shibuya et al., 2014), indirectly supporting the point of high ipsilateral co-activation in our experiments due to high force requirements (80% MVC). On the contrary, there is also evidence that ipsilateral co-activation during repetitive unilateral contractions (60% MVC, 10 s duration, rest of 75 s, five sets) gradually decreases after being significantly elevated initially, which has been interpreted as an effect of accommodation to the required motor task (Shibuya, 2011). This seemingly contradictory finding might be explained by the lower force requirements (where fatigue effects are limited) in this respective investigation compared to exhaustive motor tasks implemented in the former (Shibuya et al., 2008; Kuboyama and Shibuya, 2015). The assumption of fatigue-driven reduction of ipsilateral inhibition or increase in overall central activation is further supported by the fact that block-wise pMA analysis in the present study, comparing the first and the last force block within one experimental session (in which fatigue is expected), again indicates a significant increase in amplitude and decrease of latency.

It seems like this complex inhibitory mechanism loses its efficacy over time during sustained high-effort contractions, potentially due to fatigue. This gradual loss of inhibition might result in the occurrence of pMA which progressively increases in amplitude and decreases in latency with each consecutive contraction as they both seem to share and depict identical neural processes. This assumption is further reflected in the strong inverse relationship between these two pMA parameters during the sham (no stimulation) condition, which we assume, reflects unaltered physiologically integrated processes. This inverse association between amplitude and latency slightly weakens during the anodal stimulation and fails to reach significance during the cathodal stimulation condition. This observation seems interesting at first yet we were not able to show any significant effect of both tDCS-polarities on single pMA parameters, either within-force blocks or block-wise over the whole experiment (please see section: No effect of tDCS on pMA parameters). We hypothesize that the application of tDCS might interfere with the existing network involved in suppression of pMA, which accordingly becomes slightly detuned and defused. This detuning could be responsible for the weakening of the association between amplitude and latency of pMA compared to the unaltered physiological integrated processes active during sham-stimulation.

No effect of tDCS on pMA parameters

We report that neither anodal nor cathodal tDCS (1 mA, 20 min) was able to significantly modulate latency or amplitude of pMA compared to sham. In this regard, we did not

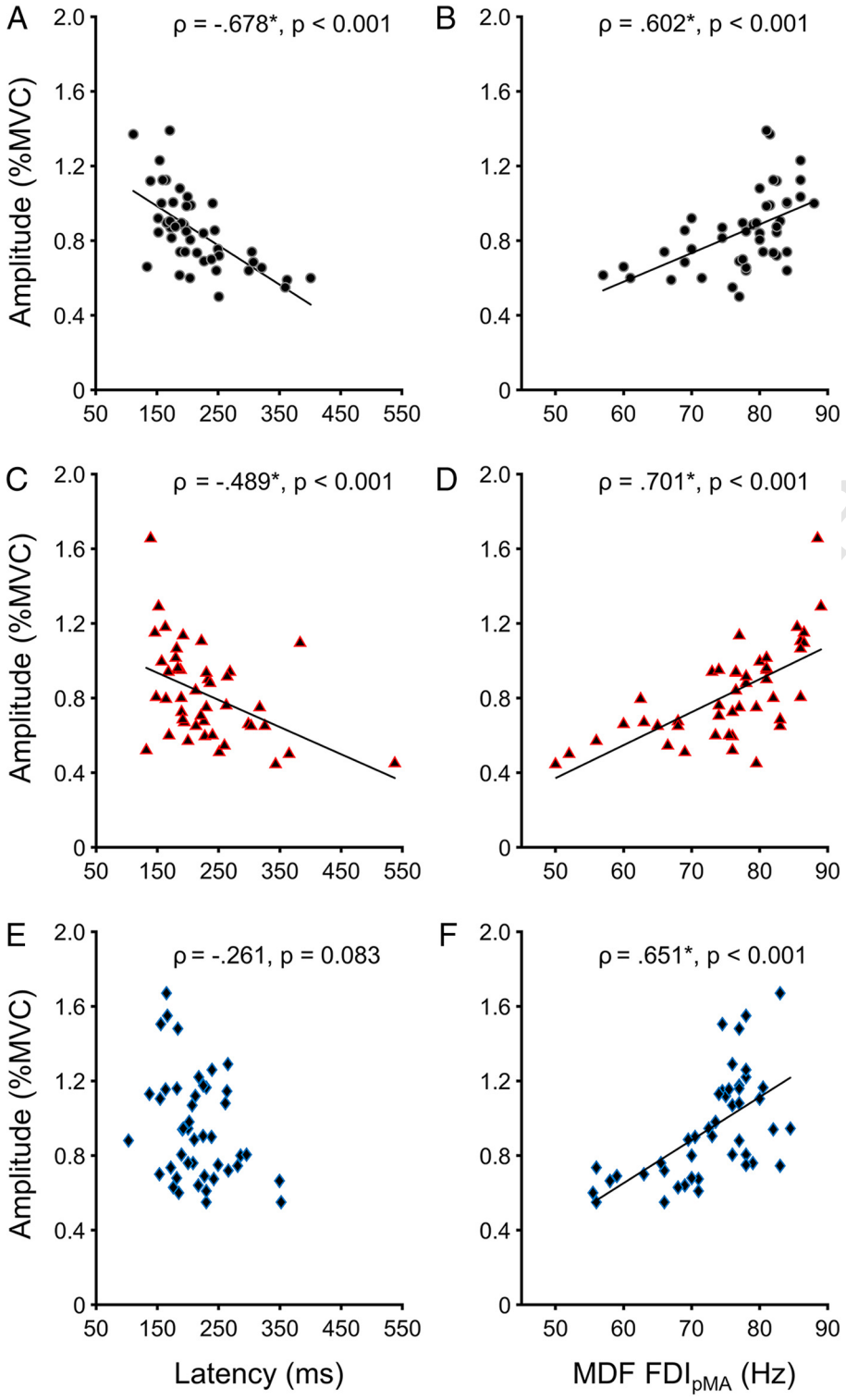

Fig. 7. Spearman rank-correlation between amplitude and latency / MDF of FDI_{pMA}. Sham **(A)** & **(B)**, anodal **(C)** & **(D)** and cathodal stimulation condition **(E)** & **(F)**. * indicates significant non-parametric associations.

observe any significant differences between the three stimulation conditions (sham, anodal, cathodal) with regard to maximum force values during MVC-testing, the time participants spent in the target field or the length of the active EMG burst of FDI_{Vol}. Several factors might have been responsible for this apparent null-effect of tDCS on pMA parameters in the present study.

Firstly, one should consider that the application of conventional tDCS implemented in the present study did not modulate cortical excitability and/or interhemispheric interactions to an extent, which would have been necessary to alter parameters of pMA. Indeed, previous studies demonstrated that traditional tDCS of one M1 (with a successful increase or decrease in its own excitability) fails to modulate excitability in the non-stimulated hemisphere (Lang et al., 2004; Tazoe et al., 2014). Nonetheless, it was observed that IHI between bilateral M1 was modulated in a polarity-dependent way so that IHI was increased during anodal tDCS and decreased during cathodal tDCS. Those after-effects on interhemispheric interactions are mainly dependent on whether or not tDCS resulted in the facilitation or inhibition of the specific M1 sending interhemispheric volleys (Tazoe et al., 2014; Davidson et al., 2016). These results indicate that interhemispheric interactions can be modified by tDCS of unilateral M1, which supports the hypothetical assumption of our study to target underlying interhemispheric mechanisms of motor overflow. On the other hand, a recent investigation using a novel approach of High-Definition tDCS (HD-tDCS) was able to show for the first-time that the modulation of the non-stimulated M1 with anodal and cathodal tDCS in combination with crossed facilitation is possible (Cabibel et al., 2018). Crossed facilitation (CF) describes the effect that unilateral contractions of upper limb muscles lead to a facilitatory effect on the contralateral homologous motor pathway (Hortobagyi et al., 2003; Carson et al., 2004). Interestingly, no polarity-specific effect of HD-tDCS on excitability in the non-stimulated hemisphere was observed. The authors attributed these findings to complex modulations of interhemispheric interactions leading ultimately to an overall facilitatory effect (IHF) on the unstimulated M1 (Cabibel et al., 2018). HD-tDCS has recently been

developed to increase the accuracy of current delivery to the brain by using arrays of smaller "high-definition" electrodes (usually a 4 × 1 electrode configuration is employed), instead of the larger pad-electrodes of conventional tDCS (Villamar et al., 2013). This extension of conventional tDCS has been shown to provide higher focality of stimulation under the target electrode (Edwards et al., 2013; DaSilva et al., 2015). Therefore, it is tempting to speculate that it might be possible to modulate pMA parameters by the application of HD-tDCS to either the ipsi- or contralateral M1 relative to a contracting limb aiming specifically at the modulation of interhemispheric interactions (i.e. IHF). Future studies should focus on this idea to shed light on this open question.

Secondly, it might be the case that ipsilateral M1 stimulation on its own, based on the theory of motor overflow, might not have been enough to interrupt the integrated complex network of brain areas involved in suppression of mirroring tendencies and therefore appears to be ineffective in modulating pMA. Indeed, one previous study already aimed to modulate pMA in healthy adults through conventional tDCS (Beaule et al., 2016). Based on an alternative hypothesis regarding the underlying mechanism of pMA (Giovannelli et al., 2006) the authors targeted the dorsal premotor cortex and indeed were able to increase pMA following cathodal stimulation (1 mA). However, a decrease in pMA, the primary aim of this study regarding its clinical application, was not achieved (Beaule et al., 2016).

In general, the existing literature on tDCS effects on motor-related behavior and functions mostly report mixed results, indicating on the one hand stimulation-dependent effects (Stagg et al., 2011) while others not reporting any effects other than on motor-evoked potentials (Horvath et al., 2015). Despite that, high response variability to tDCS is well documented but so far not well understood (Wiethoff et al., 2014). Therefore, it seems necessary to further investigate underlying physiological processes induced by tDCS to develop optimal and individually tailored stimulation protocols which induce reliable observations in the motor behavior under consideration. Furthermore, the utilization of the aforementioned advanced stimulation method of HD-tDCS combined with precise electrode placements based on the respective brain anatomy using current flow simulation software appears promising for future applications (Alam et al., 2016).

One limitation of this study is that we did not use TMS to experimentally prove tDCS-induced excitability changes in bilateral M1, restricting causal conclusions about the effectiveness of the applied transcranial stimulation. Another limitation regarding the experiment is that we exclusively focused on a single force level (80% MVC) which was held constant during task execution, potentially limiting the transfer of observed interrelations of pMA parameters to lower relative force contractions. However, the primary goal of the present study was to investigate changes in the amplitude and latency of pMA as a function of repeated muscular effort under constant force requirements. Therefore, according to the results of our previous studies, we purposely chose strong force requirements (80% MVC), as high force levels have been shown to elicit greatest pMA amplitudes (Maudrich et al., 2017, 2018). Nevertheless, future studies should focus on replicating the herein proposed pMA-characteristics as well as their dynamic behavior using multiple lower force levels (< 80% MVC). Furthermore, we did not include any brain-imaging techniques during task execution to monitor excitability changes of contra- and ipsilateral sensorimotor cortices dynamically. Future work should focus primarily on electroencephalography (EEG) and derived parameters mainly to take advantage of the high temporal resolution of EEG, in order to further characterize cortical processes involved in the phenomenon of pMA. Accordingly, an absence of related cortical processes could imply spinal mechanisms involved in the suppression of pMA that are likely to take place but remain to be backed up by empirical evidence (Carson, 2005).

In conclusion, we extend the existing knowledge of effort-related pMA to the aspect of its latency. For future investigations analyzing pMA, we propose to take the dynamic behavior of the latency into account, in order to describe ongoing neurophysiological processes more precisely and adequately. Furthermore, we provide strong evidence that even under constant and high force requirements the amplitude of pMA increases linearly as a function of repeated unilateral force productions. Additionally, we found that amplitude and latency of pMA are inversely related. This observation indicates that their dynamic behavior might be the result of changes in inhibitory mechanisms involved in suppressing involuntarily occurring muscular activity, which seem to lose efficacy with increased fatigue or increased muscular effort to maintain desired force production. Lastly, conventional tDCS applied to the ipsilateral M1 seems to be ineffective in modulating pMA parameters.

ADDITIONAL INFORMATION

Competing interests

Declarations of interest: none.

Author contributions

T.M., R.K., V.V.N, P.R., and A.V. were responsible for the conception and design of the study. T.M., R.K., V.V.N, and D.M. were responsible for acquisition, analysis and interpretation of data for the work. T.M. drafted the manuscript; T.M., R.K., V.V.N, D.M., A.V., and P.R. provided critical revision. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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