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Published in:
European Journal of Neuroscience

DOI:
[10.1111/ejn.15371](https://doi.org/10.1111/ejn.15371)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Colomer-Poveda, D., Zijdwind, I., Dolstra, J., Márquez, G., & Hortobágyi, T. (2021). Voluntary suppression of associated activity decreases force steadiness in the active hand. *European Journal of Neuroscience*, 54(3), 5075-5091. <https://doi.org/10.1111/ejn.15371>

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Voluntary suppression of associated activity decreases force steadiness in the active hand

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Edited by: Francisco Alvarez

Abstract

Unilateral muscle contractions are often accompanied by the activation of the ipsilateral hemisphere, producing associated activity (AA) in the contralateral homologous muscles. However, the functional role of AA is not fully understood. We determined the effects of voluntary suppression of AA in the first dorsal interosseous (FDI), on force steadiness during a constant force isometric contraction of the contralateral FDI. Participants ($n = 17$, 25.5 years) performed two trials of isometric FDI contractions as steadily as possible. In Trial 1, they did not receive feedback or explicit instructions for suppressing the AA in the contralateral homologous FDI. In Trial 2, participants received feedback and were asked to voluntarily suppress the AA in the contralateral nontarget FDI. During both trials, corticospinal excitability and motor cortical inhibition were measured. The results show that participants effectively suppressed the AA in the nontarget contralateral FDI (-71%), which correlated with reductions in corticospinal excitability (-57%), and the suppression was also accompanied by increases in inhibition (27%) in the ipsilateral motor cortex. The suppression of AA impaired force steadiness, but the decrease in force steadiness did not correlate with the magnitude of suppression. The results show that voluntary suppression of AA decreases force steadiness in the active hand. However, due to the lack of association between suppression and decreased steadiness, we interpret these data to mean that specific elements of the ipsilateral brain activation producing AA in younger adults are neither contributing nor detrimental to unilateral motor control during a steady isometric contraction.

KEYWORDS

contralateral activity, FDI, ipsilateral activation, mirror activity, TMS

Abbreviations: AA, Associated Activity; ADM, Abductor digiti minimi; CON, Control; CV, Coefficient of variation; EMG, Electromyography; FDI, First dorsal interosseous; IA, Ipsilateral activation; M1, Motor cortex; MEP, Motor evoked potential; $M_{\max}$, Maximal compound muscle action potential; MVC, Maximal unilateral voluntary isometric contraction; RMS, Root mean square; SICI, Short-interval intracortical inhibition; TMS, Transcranial magnetic stimulation.

1 | INTRODUCTION

It is a classical neuroscientific tenet that the control of unilateral movements relies exclusively on the activation of specific brain areas located in the hemisphere contralateral to the moving limb (Lemon, 2008). Recent evidence seems, however, to suggest that even strictly unilateral movements are often accompanied by the activation of the premotor and motor areas located in the hemisphere ipsilateral to the moving limb (Andrushko et al., 2021; Cabibel et al., 2020; Chettouf et al., 2020; Dettmers et al., 1995; Hortobágyi et al., 2003; Perez & Cohen, 2008; van Duinen et al., 2008; Waldvogel et al., 2000). Some theories propose that ipsilateral activation (IA) is a consequence of a spillover of the neural drive from the contralateral primary motor cortex through interhemispheric connections (Addamo et al., 2007; Bundy & Leuthardt, 2019; Cabibel et al., 2020; Hoy et al., 2004). Others suggest that IA is a vestigial remnant of a bilateral organisation of the motor system (Hopf et al., 1974; Maudrich et al., 2018; Sehm et al., 2016). According to both theories, an intricate network of premotor (bilateral supplementary motor area and ipsilateral premotor cortex) and contralateral motor areas inhibit the ipsilateral motor cortex (M1) through intrahemispheric and interhemispheric connections (i.e., “nonmirroring transformation network”), preventing interference with unilateral movements (Chettouf et al., 2020; Cincotta & Ziemann, 2008; Giovannelli et al., 2006; Maudrich et al., 2018). Therefore, IA tends to occur more frequently during movements that require a strong voluntary drive, which occurs in complex (Rao et al., 1993), forceful (Andrushko et al., 2021; Dettmers et al., 1995; Hortobágyi et al., 2003; Perez & Cohen, 2008; van Duinen et al., 2008) or long-lasting (Jiang et al., 2012; Liu et al., 2003; Post et al., 2009) unilateral muscle contractions. In such cases, the excitatory inputs reach the ipsilateral cortex and overcome the inhibition coming from the “nonmirroring transformation network” (Giovannelli et al., 2006), leading to a net facilitation of the ipsilateral M1, that can be measured by transcranial magnetic stimulation (TMS) or brain imaging (Hortobágyi et al., 2003; Perez & Cohen, 2008; Rao et al., 1993; van Duinen et al., 2008).

Regardless of its origin, IA is considered physiologically a nonessential by-product without a functional role in unilateral movements (Cabibel et al., 2020; Carson, 2020). However, recent studies challenge this idea by suggesting cooperation between IA and the contralateral cortex for the control of unilateral movements (Bundy & Leuthardt, 2019; Cabibel et al., 2020; Carson, 2020). For example, together with a weakly lateralised neural activation of the motor cortical areas during

unilateral movements, the neural activity of the ipsilateral hemisphere in nonhuman primates (Ames & Churchland, 2019) and humans (Bundy et al., 2018; Ganguly et al., 2009) contains task-relevant information about the kinematics of unilateral movements. Furthermore, interfering with ipsilateral M1 activation by repetitive TMS whilst performing unilateral movement sequences can increase the number of errors and impair movement timing (Chen et al., 1997). These data, together with evidence showing that IA is stronger during active than passive finger movements (Berlot et al., 2019), suggest that IA may in fact have a functional role in planning and generating unilateral voluntary movements. Indeed, it was suggested that the age-related increase in IA during unimanual movements may reflect an increased contribution of the ipsilateral motor areas to unilateral movements in compensation for the atrophy of motor cortical regions (Bodwell et al., 2003; Mattay et al., 2002; Seidler et al., 2010). Still, direct evidence in support of the functional role of IA in unilateral motor control is scarce and incompletely understood.

One way to directly determine the functional role of IA is to see what happens to unilateral motor performance whilst IA is suppressed. During a forceful unilateral muscle contraction, associated activity (AA) arises, a proxy for IA in the brain (Zijdewind et al., 2006). AA appears in homologous muscles of the “nontarget limb” whilst the contralateral muscle pairs contract (Zijdewind et al., 2006; Zijdewind & Kernell, 2001) and can be measured by surface electromyography (EMG) (Zijdewind et al., 2006). Healthy humans are able to actively suppress AA (Addamo et al., 2010; Maudrich et al., 2020). If IA has a functional role, an active suppression of AA, its peripheral proxy, would impair motor performance in the active limb.

Therefore, the purpose of the present study was to determine the effects of suppressing AA on force steadiness (Experiment 1). This motor outcome serves as a proxy for unimanual motor performance during an isometric contraction of the first dorsal interosseous (FDI) in which the goal is to maintain a predetermined submaximal force level as steady as possible. Based on the extant data, we hypothesised that suppressing AA in the contralateral FDI would impair unilateral motor performance, which will be reflected as reduced steadiness and impaired ability to match the submaximal target force. We expect that the magnitude of suppression of AA would be associated with the reductions in force steadiness and/or the inability to reach the target force. We also probed potential mechanisms underlying the relationship between AA suppression and unimanual motor performance impairment by measuring corticospinal excitability and intracortical inhibition in

ipsilateral M1. We also performed an additional control experiment (Experiment 2) to rule out the effects of fatigue and learning as a result of task repetition, on unimanual motor performance. Although the current data are limited to healthy young adults, with these experiments, we hoped to increase our understanding of the functional role IA plays in the control of ipsilateral force, which could have a potential application in rehabilitation interventions in ageing and pathological conditions (Bundy & Leuthardt, 2019).

2 | METHODS

2.1 | Participants

Healthy volunteers ($n = 17$, $n = 15$ right-handed according to Oldfield handedness questionnaire (Oldfield, 1971) 25 ± 6 ; 10F) and additional seven (21 ± 3 ; seven right-handed; 4F) healthy volunteers with no reported contraindications to TMS and currently not taking any medications participated in Experiments 1 and 2, respectively. They all gave written informed consent for the experimental procedures that were approved by the local medical ethical committee (approval number: 2019/392-201900388). Participants were asked to refrain from consuming alcoholic or caffeinated beverages for 2 h before the experimental sessions. The experiments were performed in accordance with the latest version of the declaration of Helsinki.

2.2 | Study design

2.2.1 | Experiment 1

Participants in Experiment 1 came to the laboratory once. First, participants performed three, 3- to 5-s long, maximal unilateral voluntary isometric contractions (MVCs) of the index finger abductors of each hand with 2 min of rest between trials. Participants then received peripheral electric stimulation of the ulnar nerve in each hand separately to determine the size of the maximal compound muscle action potential ($M_{\max}$) at rest. MVC and $M_{\max}$ were measured three times: before (PRE) and after the Trial 1 of the main experimental task (MID) and after the Trial 2 of the main experimental task (POST) (Figure 1a).

The main experimental task consisted of three, 30-s long unilateral isometric index finger abductions (40%–55% MVC), separated by 5 s of rest (Figure 1b); force was optimised to produce AA and reduce fatigue in the target muscle. Most participants performed the task with the

dominant hand but to maximise AA; two participants performed the task with the nondominant hand. Therefore, we refer to the FDI that performed the task as the “target” FDI ($_{\text{target-FDI}}$) and to the contralateral one as the “nontarget” FDI ($_{\text{non-target-FDI}}$), irrespective of the laterality. Participants were instructed to abduct their target index finger to match their force with the target displayed on a computer monitor as steadily as possible. This task was repeated twice during the experimental session separated by ~ 25 min. Before the Trial 1, there was no mention of AA and no instruction was given concerning the relaxation of the contralateral nontarget hand. This Trial 1 was considered as No Suppression condition. Before the Trial 2, the concept of AA was explained to the participants by showing the EMG activity in the $_{\text{non-target-FDI}}$ whilst the target hand was contracted. Then, participants were instructed to maintain the $_{\text{target-FDI}}$ force as steadily as possible and relax the contralateral $_{\text{non-target-FDI}}$ to make the AA minimal or disappear. This Trial 2 was considered as the Suppression condition (Figure 1b). To aid participants to suppress AA in the contralateral $_{\text{non-target-FDI}}$, visual feedback of the EMG signal during Suppression condition was displayed on the lower half of the monitor. Visual feedback of the force signal produced by the target hand was displayed on the upper half of the monitor. The vertical scale of the force window was optimised for each participant and maintained constant during the No Suppression and Suppression conditions to minimise the effects of visual feedback on force steadiness (Sosnoff & Newell, 2006). During both trials, participants were continuously encouraged to contract the $_{\text{target-FDI}}$ as “steadily” as possible and in the Suppression trial; they were also reminded to “relax the contralateral hand”. During the contractions, single and paired TMS were applied over the ipsilateral M1 (to $_{\text{target-FDI}}$) to determine the effects of the instructions on corticospinal excitability measured in the $_{\text{non-target-FDI}}$.

Additionally, Experiment 1 included two further control conditions. The first control condition was performed 5 min after the No Suppression trial ($\text{CON}_{\text{NoSupp}}$) and the second one 5 min after the Suppression trial (CON_{Supp}) (Figure 1a). In both control conditions, we administered single- and paired-pulse TMS to ipsilateral M1. In each control trial, participants performed three, 30-s long contractions with the $_{\text{non-target-FDI}}$ to a level of EMG that matched the AA present during No Suppression or Suppression trials (note that although $_{\text{non-target-FDI}}$ is voluntary contracting during control conditions, the abbreviation “ $_{\text{non-target-FDI}}$ ” is maintained). During $\text{CON}_{\text{NoSupp}}$ and CON_{Supp} , the participants saw the online root mean square (rms) (time constant 100 ms) EMG of the $_{\text{non-target-FDI}}$ and were instructed to match the

FIGURE 1 Schematic view of the protocol. (a) Schematic representation of the design of the Experiment 1 ($n = 17$): Participants performed two trials of the same task. Each trial consisted of three submaximal unilateral isometric FDI contractions (30"; 40%–55% MVC) as steadily as possible. During the Trial 1 ("No Suppression"), no information was given about the contralateral homologous muscle activity. During the Trial 2 ("suppression"), participants were asked to suppress the associated activity present in the contralateral homologous FDI. After each trial, subjects were instructed to contract the non-target FDI to the level of EMG present during the No Suppression or Suppression trials (CON_{NoSupp} and CON_{Supp} respectively). During all trials, EMG and force were recorded in both hands, and single- and paired-pulse TMS were used to evoke motor evoked potential (MEPs) on the nontarget FDI. (b) Example of the main task performed during the No suppression trial and the Suppression trial of one subject. (c) Schematic representation of the design of the Experiment 2 ($n = 7$): Participants came to the laboratory twice. During the Session 1, they did three submaximal unilateral isometric FDI contractions (30"; 40%–55% MVC) twice without suppression (Trial 1: No Suppression 1; Trial 2: No Suppression 2). During Session 2, participants performed again the same task as in Session 1 but in the Trial 2 they were asked to suppress the associated activity present in the contralateral homologous FDI (Trial 1: No Suppression 3; Trial 2: Suppression). CV, Coefficient of variation; CON_{NoSupp}, control trial No Suppression; CON_{Supp}, control trial Suppression; EMG, electromyography; *target*-FDI, first dorsal interosseus that performed the task; *non-target*-FDI, contralateral first dorsal interosseus; M_{max} , maximal compound muscle action potential; MEP, motor evoked potential; MVC, maximal voluntary contraction; NS, No Suppression trial; rmsEMG, root mean square electromyography; S, Suppression trial; SICI, short-interval intracortical inhibition; TMS, transcranial magnetic stimulation

rmsEMG of the *non-target*-FDI with a target line. We performed these control conditions because a direct comparison of the TMS measurements between the No Suppression and Suppression trials would have been highly influenced by the expected differences in motoneuron

activation. The control conditions allowed us to measure the differences between TMS measurements obtained in the nontarget muscles during voluntary contractions and unintentional contractions (AA during No Suppression and Suppression) at the same level of background EMG,

either with (Suppression; $\Delta = \text{CON}_{\text{Supp}} - \text{Suppression}$) or without (No Suppression; $\Delta = \text{CON}_{\text{NoSupp}} - \text{No Suppression}$) the intention to suppress. This way, we can compare the Δ s of TMS measurements during No Suppression with those obtained during Suppression and determine if voluntary suppression of AA had any additional inhibitory effect on cortical or corticospinal excitability in addition to the reduction of motoneuron output.

2.2.2 | Experiment 2

Because the Suppression trial was always performed after the No Suppression trial, changes in force steadiness in the target hand, or in the magnitude of AA in the nontarget hand, may have been influenced by fatigue (decreasing force steadiness and increasing AA) or learning (increasing force steadiness and reducing AA) due to repeated task execution. Therefore, we performed a control experiment (Experiment 2) to rule out the effects of fatigue and learning on the results in Experiment 1. For Experiment 2 (Figure 1c), participants visited the laboratory twice. Each session started with measurements of MVCs and M_{max} in each hand. In Session 1, participants performed twice the main task (i.e., three 30-s long unilateral isometric index finger abductions at 40%–55% MVC separated by 5 s of rest) without drawing attention to the AA in the non-target-FDI or instructions about the contralateral nontarget hand in any trial (No Suppression 1 and No suppression 2). With this session, we rule out the influence of the order of sessions on the results of the experiment 1. During Session 2 (7 days later), participants repeated again the main experimental task without suppression of the AA (No Suppression 3). Then, participants performed exactly the same task but relaxing the non-target-FDI to make the AA minimal or disappear (Suppression). The Session 2 will serve to reproduce the Experiment 1. No TMS measurements were obtained in this experiment.

2.3 | Experimental set-up

Participants sat in a chair with both forearms on the armrests and the elbows flexed at $\sim 90^\circ$. In this position, participants held a force transducer in each hand with the index finger extended and parallel to horizontal bar (see Figure 2) (Sars et al., 2018; Wolkorte et al., 2015). The proximal interphalangeal joint of the index finger was taped to a C-shaped plastic piece connected to a bar with strain gauges attached to the force transducer for measuring the voluntary index finger abduction force. All the other fingers were taped around the handle of the

force transducer to ensure a consistent hand position. The force signal was amplified and sampled for off-line analysis (Power 1401, Cambridge Electronic Design, United Kingdom; sampling frequency 5000 Hz). During the MVCs and the main experimental tasks, subjects received visual feedback of their force on a monitor in front of them. Surface EMG activity was measured with four wireless sensors (37*26*15 mm, electrode material: silver; Trigno™ Wireless System, Delsys, Natick, MA, USA) placed on the muscle belly of the FDI muscle of each hand after skin preparation with alcohol. Surface EMG activity was also measured in the abductor digiti minimi (ADM) of each hand. The EMG signal was amplified ($\times 909$), band-pass-filtered (20–450 Hz) and sampled (5 kHz) using data acquisition interface and software (Power 1401, Signal v5.11, Cambridge Electronic Design Ltd, Cambridge, UK).

2.4 | Peripheral nerve electrical stimulation

M_{max} of right and left FDI was obtained via a single electrical stimulus (200- μ s duration, Digitimer DS7) delivered through two pregelled Ag-AgCl surface electrodes positioned above the ulnar nerve just proximal to the wrist. The stimulation intensity (range 30–84 mA) was set to 120% of the intensity needed to obtain the M_{max} in each muscle.

2.5 | Transcranial magnetic stimulation

In Experiment 1, single- and paired-pulses were delivered from a Magstim 200 stimulator (Magstim Company, Dyfed, UK) through an 80-mm figure-of-eight coil oriented with the handle at $\sim 45^\circ$ posterolaterally to the midline. The coil was placed on the scalp over an optimal spot relative to the M1 by exploring the estimated centre of the non-target-FDI cortical representation and marking this spot with a permanent marker where a known suprathereshold intensity stimulus produced the largest response. The resting motor threshold and the active motor threshold were obtained and used to set the stimulation intensity during the experiment. Resting and active motor thresholds were, respectively, defined as the minimal stimulation intensity producing three out of five motor evoked potentials (MEPs) of a peak-to-peak amplitude of at least 50 μ V at rest or 200 μ V during a 5% MVC. Three single- and three-paired-pulse stimulations were obtained during each of the three 30-s unilateral isometric index finger abductions performed in each experimental or control protocols. For paired-pulse stimulation, the

FIGURE 2 Schematic view of the set-up

intensity of the conditioning stimulus was set at $\sim 70\%$ of the active motor threshold whilst the intensity for the test stimulus, delivered 3 ms later, was set at 120% of the resting motor threshold in order to measure short-interval intracortical inhibition (SICI) (Kujirai et al., 1993).

2.6 | Data analysis

We measured the peak-to-peak amplitudes of MVCs and $M_{\max}$. In addition, we measured the rmsEMG of the FDI during MVC in a window of 500 ms around the peak force value of each hand. The maximum MVC of each hand and its corresponding rmsEMG value and the mean $M_{\max}$ amplitude of three attempts of each set of measurements (PRE, MID and POST) were used as the reference value for the analysis. During each 30-s long isometric contraction, the mean force and force steadiness (measured as the coefficient of variation [CV] of force) and the rmsEMG of the target-FDI were measured (30-s windows) and averaged. In the non-target-FDI , the EMG activity and force were measured as the rmsEMG and mean force in windows of 500 ms before each single- or paired-pulse TMS and then averaged for each condition (No Suppression, $\text{CON}_{\text{NoSupp}}$ and Suppression or CON_{Supp}). We expressed force and rmsEMG data during tasks as a percentage of PRE MVC (No Suppression and $\text{CON}_{\text{NoSupp}}$) or MID MVC (Suppression and CON_{Supp}) of each FDI. The peak-to-peak amplitude of each MEP was measured, and SICI was calculated as the ratio between conditioned and test MEP of each block and expressed as a % of the test MEP, such that a greater value means less inhibition and vice versa. Because $M_{\max}$ did not change significantly during the experimental session, the MEP

amplitudes were expressed in mV and not normalised to $M_{\max}$. For calculating ΔMEP and ΔSICI , the mean value of MEP or SICI during the experimental condition was subtracted from the mean value obtained during its paired control condition in each subject. EMG-based measures were also obtained in the ADM to test the effects of voluntary suppression of AA of the non-target-FDI over a heterologous muscle. Results from the ADM follow a similar trend as in the FDI; these data are presented in Tables S6 and S7 in supporting information.

2.7 | Statistics

Normality was tested using the Kolmogorov-Smirnov test. When data were not normally distributed, we used a nonparametric Friedman test to compare more than two conditions or a Wilcoxon signed-rank test when only two conditions were compared. When significant differences were found in the Friedman test, post hoc or planned comparisons (No Suppression vs. $\text{CON}_{\text{NoSupp}}$; Suppression vs. CON_{Supp} ; No Suppression vs. Suppression) were made with Wilcoxon signed-rank tests. When data were normally distributed, we used a one-way repeated measures analysis of variance with time (PRE, MID, POST for MVC and $M_{\max}$ data) or condition as factor (with Bonferroni correction for post hoc analyses) or a paired T test when only two conditions were compared. Effect sizes are presented as Cohen's d for the paired comparisons. For CV of force, the target-FDI and the AA of the non-target-FDI , we calculated the difference between the values obtained during the No Suppression and the Suppression trial and used these values to calculate the Spearman correlation

coefficient (ρ). Additionally, we calculated the correlation between the change (in %) from the No Suppression trial to the Suppression trial between non-target-FDI AA and MEP amplitude and between MEP amplitude and SICI with Pearson correlation analysis or Spearman correlation coefficient depending on data distribution. The level of significance was set at $P < 0.05$ except for when Wilcoxon signed-rank tests were used for three comparisons, where the significance level was corrected for multiple comparisons and set at $P < 0.017$. Unless indicated otherwise, data are reported as means and SD. SPSS 20.0 software (SPSS, Chicago, IL) was used for statistical analysis.

3 | RESULTS

3.1 | Experiment one

3.1.1 | Target hand

MVC and $M_{\max}$

There was a reduction in MVC force from PRE to MID (-7.3% ; $P = 0.001$; $d = 0.27$) and from PRE to POST (-8% ; $P = 0.001$; $d = 0.29$; Table 1 and Figure 3). However, there were no changes in the rmsEMG or $M_{\max}$ amplitude (See Table S4 in supporting information for statistics results). These data suggest only minimal fatigue in the target hand during the Experiment 1.

Task—rmsEMG and force

The rmsEMG of the target-FDI (13.5% ; $P = 0.011$; $d = 0.42$) during the 30-s submaximal contraction increased from the No Suppression trial to the Suppression trial (Table 2). Mean force during No Suppression and Suppression was not different ($P = 0.91$; $d = 0.01$). However, force CV increased from No Suppression trial to Suppression trial (22.2% ; $P = 0.001$; $d = 0.47$; Table 2 and Figure 4). These data suggest a decrease in steadiness when participants suppressed the AA in the non-target-FDI .

3.1.2 | Nontarget hand

MVC and $M_{\max}$

MVC force decreased from PRE to POST (-5.9% ; $P = 0.01$; $d = 0.26$) and from MID to POST (-3.1% ; $P = 0.04$; $d = 0.11$). MVC rmsEMG in the non-target-FDI decreased from PRE to MID (-11.6% ; $P = 0.02$; $d = 0.35$; Table 1 and Figure 3). There were no changes in $M_{\max}$ amplitude (Table 1). As in the target hand, these data suggest minimal fatigue in the nontarget hand during the Experiment 1.

Task—AA and associated force

non-target-FDI AA (i.e., rmsEMG in the non-target-FDI during the task) was lower during the Suppression trial compared with the No Suppression trial (-71% ; $Z = -3.15$; $P = 0.002$), but it was not different during No Suppression and $\text{CON}_{\text{NoSupp}}$ or Suppression and CON_{Supp} (Table 2 and Figure 5). The magnitude of suppression of the non-target-FDI AA and the change in the CV of the force exerted by the target-FDI from the No Suppression to the Suppression trial did not correlate ($\rho = -0.18$; $P = 0.48$). Mean associated force was lower during the Suppression trial vs. No Suppression trial (-106% ; $Z = -2.96$; $P = 0.003$; Figure 5). Altogether, these data suggest that AA was present in the contralateral FDI, and when instructed, participants effectively suppressed it.

Task—MEP amplitude and SICI

The non-target-FDI MEP amplitudes were lower during the Suppression trial compared with the No Suppression trial (-57% ; $P = 0.001$; $d = 1.58$; Table 2 and Figure 6). However, ΔMEP did not differ between No Suppression and Suppression (-0.3 ± 1.6 mV vs. 0.1 ± 1.6 mV). The reduction (in %) from No Suppression to Suppression in AA correlated with the reduction in the MEP amplitude in the non-target-FDI ($r = 0.56$; $P = 0.020$) (See Figure S7 in supporting information).

Three subjects were excluded from the analysis of SICI in the non-target-FDI , because they showed a facilitation instead of inhibition of more than 115% of test MEP in one or more conditions. In the non-target-FDI , inhibition was greater during Suppression compared to No Suppression (27% ; $P = 0.045$; $d = 0.34$; Table 2 and Figure 6). However, ΔSICI did not differ between No Suppression and Suppression ($-9.2 \pm 19\%$ vs. $-2.6 \pm 14.7\%$). The change (in %) in MEP amplitude from No Suppression to Suppression correlated with the change in SICI in the non-target-FDI ($\rho = 0.58$; $P = 0.03$) (See Figure S8 in supporting information). These data suggest that AA suppression reduced corticospinal excitability and increased intracortical inhibition.

3.2 | Experiment two

3.2.1 | Target hand

MVC and $M_{\max}$

During Session 1, MVC force decreased from PRE to MID (-8% ; $P = 0.03$; $d = 0.29$) but no changes occurred during Session 2 (Table 1). rmsEMG and $M_{\max}$ did not change across sessions (Table 1; see also Table S5 in supporting information for statistics results). These data

TABLE 1 MVC force, rmsEMG and $M_{\max}$ values during both experiments

	Session 1			Session 2		
	PRE	MID	POST	PRE	MID	POST
Experiment 1						
Target hand						
MVC (N)	30.45 ± 8.43	28.22 ± 8.07 ^a	28.01 ± 8.10 ^a	-	-	-
MVC FDI rmsEMG (mV)	0.67 ± 0.35	0.64 ± 0.34	0.63 ± 0.34	-	-	-
FDI $M_{\max}$ (mV)	7.06 ± 2.83 (median = 7.13)	6.99 ± 3.09 (median = 6.63)	7.10 ± 3.06 (median = 7.12)	-	-	-
Nontarget hand						
MVC (N)	39.01 ± 8.62	37.89 ± 9.23	36.72 ± 8.56 ^{a, b}	-	-	-
MVC FDI rmsEMG (mV)	1.12 ± 0.39	0.99 ± 0.36 ^a	0.98 ± 0.36	-	-	-
FDI $M_{\max}$ (mV)	9.92 ± 0.80 (median = 10.26)	9.95 ± 0.71 (median = 10.26)	9.89 ± 0.89 (median = 10.26)	-	-	-
Experiment 2						
Target hand						
MVC (N)	28.50 ± 8.20	26.22 ± 6.72 ^a	25.70 ± 6.75	29.87 ± 9.75	29.04 ± 8.49	27.73 ± 8.50
MVC FDI rmsEMG (mV)	0.60 ± 0.19	0.51 ± 0.18	0.50 ± 0.16	0.67 ± 0.36	0.65 ± 0.33	0.63 ± 0.35
FDI $M_{\max}$ (mV)	7.55 ± 2.97	7.51 ± 2.99	7.51 ± 2.73	6.96 ± 3.29	6.99 ± 3.11	6.85 ± 2.82
Nontarget hand						
MVC (N)	44.97 ± 14.44	43.05 ± 15.08	41.93 ± 15.21	44.72 ± 15.83 (median = 37.32)	42.41 ± 14.64 (median = 35.13)	41.75 ± 14.71 (median = 35.87)
MVC FDI rmsEMG (mV)	1.02 ± 0.37	0.95 ± 0.35	0.84 ± 0.40 ^a	0.80 ± 0.25	0.76 ± 0.28	0.70 ± 0.25
FDI $M_{\max}$ (mV)	9.39 ± 2.16 (median = 10.24)	9.44 ± 1.90 (median = 10.20)	9.06 ± 2.74 (median = 9.94)	9.08 ± 2.74 (median = 10.25)	9.21 ± 1.36 (median = 10.21)	9.23 ± 2.22 (median = 10.02)

Note: Values are mean ± SD, except for nonparametric variables, where median is also shown.

Abbreviations: FDI, first dorsal interosseous; $M_{\max}$: Maximal compound muscle action potential; MVC, maximal voluntary contraction; rmsEMG: root mean square electromyography.

^aRepresents $P < 0.05$ from PRE.

^bRepresents $P < 0.05$ from MID.

FIGURE 3 Maximal index finger abduction force of the nontarget (left column) and target (right column) hand (a, b) and rmsEMG of the FDI (c, d) during maximal index finger abduction. Figure shows mean (black lines) and individual values (grey lines) ($n = 17$). MVC, maximal voluntary contraction; rmsEMG, root mean squared EMG; FDI, first dorsal interosseus

suggest that fatigue in the target hand was minimal during both sessions.

Task—rmsEMG and force

The rmsEMG of the $_{\text{target}}$ FDI, mean force and CV were not different between trials (Table 3). These data suggest that steadiness was not affected by accumulated fatigue from previous trials, but the low sample size prevented to replicate the increase in the CV during the Suppression trial present in the Experiment 1.

Suppression 3 and Suppression (-83% ; $Z = -2.37$; $P = 0.018$; Table 3). Associated force did not differ between No Suppression 1 and No Suppression 2, No Suppression 1 and No Suppression 3 but neither between No Suppression 3 and Suppression (-111% ; $Z = -2.20$; $P = 0.028$; Table 3). These data suggest that reductions in AA were not related to learning by repeated execution of the task, but the low sample size prevented to replicate the effects of voluntary suppression by the subjects on AA and associated force found in the Experiment 1.

3.2.2 | Nontarget hand

MVC and M_{max}

MVC force did not change during Session 1 (Table 1). During Session 1, there was a significant reduction in rmsEMG in the $_{\text{non-target}}$ FDI from PRE to POST (-17.7% ; $P = 0.04$; $d = 0.47$) but no changes during the Session 2 (Table 1). M_{max} was stable across sessions (Table 1). As with the target hand, these data suggest that fatigue was present albeit minimal.

Task—AA and associated force

There were no differences in $_{\text{non-target}}$ FDI AA between No Suppression 1 and No Suppression 2, No Suppression 1 and No Suppression 3 but neither between No

4 | DISCUSSION

We determined the effects of voluntarily suppressing AA in the nontarget FDI on the force steadiness during a constant force isometric contraction of the contralateral FDI. When instructed, participants were able to suppress AA in the $_{\text{non-target}}$ FDI. The reduction in motoneuron output when AA was suppressed was related to reductions in corticospinal excitability and was also accompanied by increases in intracortical inhibition in ipsilateral M1. In partial agreement with the hypothesis, suppression of AA impaired force steadiness but not the ability to reach the required submaximal force level ($\sim 46\%$ of MVC). However, the magnitude of impairment in force steadiness was unrelated to the magnitude of suppression

TABLE 2 rmsEMG, force and TMS measurements values in both hands in Experiment 1

	No suppression	CON _{NoSupp}	Suppression	CON _{Supp}
Target hand				
FDI rmsEMG (% MVC rmsEMG)	56 ± 18	-	64 ± 20 ^a	-
Task force (% MVC)	46 ± 7	-	46 ± 7	-
Force CV (%)	6.32 ± 2.80	-	7.74 ± 3.14 ^a	-
Nontarget hand				
FDI AA (% MVC rmsEMG)	3.54 ± 3.47 (median = 3.28)	3.63 ± 3.49 (median = 3.32)	1.02 ± 0.65 ^a (median = 0.87)	1.02 ± 0.60 (median = 0.89)
Associated Force (% MVC)	2.18 ± 2.88 (median = 1.28)	2.79 ± 3.22 (median = 1.61)	-0.12 ± 0.46 ^a (median = -0.02)	0.19 ± 0.30 (median = 0.14)
FDI MEP amplitude (mV)	4.61 ± 2.01	4.28 ± 2.41	1.99 ± 1.20 ^a	2.06 ± 1.22
FDI SICl (% test MEP)	66 ± 26	57 ± 24	57 ± 26 ^a	55 ± 26

Note: Values are mean ± SD, except for nonparametric variables, where median is also shown.
Abbreviations: CV, coefficient of variation; FDI, first dorsal interosseous; MEP, motor evoked potential; MVC, maximal voluntary contraction; rmsEMG, root mean square electromyography; SICl, short-interval intracortical inhibition.

^aRepresents $P < 0.05$ from No Suppression.

of AA. Although these results do not preclude a functional role of IA in the control of force generation, the data suggest that the specific elements of the IA producing AA are neither contributing nor detrimental to the task.

During forceful unilateral muscle contractions, IA may inadvertently activate contralateral homologous muscles, producing AA (Zijdewind et al., 2006). As with IA, AA increases with task complexity (Watanabe et al., 2017), level of voluntary drive (Todor & Lazarus, 1986; Watanabe et al., 2017) and contraction duration (Post et al., 2008; Zijdewind & Kernell, 2001). In the present study, three 30-s-long submaximal (~46% of MVC) unilateral FDI contractions produced an AA of 3.5% (0.7%–13.4%) of the maximum rmsEMG amplitude of the non-target-FDI. This level of AA produced an associated force of 2.2% (0%–8.9%) of MVC force. Despite the large between-participant variability that accompanies AA (Post et al., 2008; Sars et al., 2018; Zijdewind & Kernell, 2001), AA amplitude was similar to that reported in a recent study (2.2% [0.6%–6%] of MVC rmsEMG) in which participants performed a similar task (30, 5-s FDI contractions at ~40% of MVC force) (Maudrich et al., 2020). However, similarly to previous studies (Addamo et al., 2010; Maudrich et al., 2020), our data show that explaining the concept of AA to participants and asking them to relax the contralateral hand during unilateral contractions reduced the level of AA in the non-target-FDI to a mean of 1.02% (0.5%–3.36%) of MVC. However, although of lower amplitude, rmsEMG was also present in the nontarget hand ADM (i.e., AA), and our results show a trend for a reduction in the AA present in the nontarget hand ADM from the No Suppression to the Suppression trial (See Table S7 in supporting information; note that although the value of AA in the ADM [3.5%] was equal to that present in the FDI [3.5%], the ADM was normalised with the maximum ADM rmsEMG during an FDI MVC in which the ADM is not agonist or synergist). These data suggest that suppression of AA might not be focal and limited to the homologous non-target-FDI. Instead, the data imply a general suppression of AA in at least two hand muscles even though AA feedback displayed to participants was only from non-target-FDI. Participants always performed the Suppression trial after the No Suppression trial (Addamo et al., 2010; Maudrich et al., 2020); learning related to the repeated execution of steadiness task could have also contributed to the reduction in AA (Bologna et al., 2012; Watanabe et al., 2017). However, data from a control experiment in a subsample of seven participants showed that AA was not reduced when participants repeated the steadiness task without suppression, during the same or a subsequent session (No Suppression 1, No Suppression 2

FIGURE 4 Target hand values of mean force (a) and force CV (b) during the No suppression and Suppression trials. Figure shows mean (bars) and individual (lines) values ($n = 17$). CV, coefficient of variation; MVC, maximal voluntary contraction

FIGURE 5 Nontarget hand FDI associated activity (a) and associated force (b) during the No suppression and Suppression trials. Figure shows mean (bars) and individual (lines) values ($n = 17$). FDI, first dorsal interosseous; MVC, maximal voluntary contraction

and No Suppression 3: 8.9%, 7% and 9%). Together, these results suggest that the voluntary suppression did in fact reduce AA.

During a unilateral movement, a complex network of cortical areas inhibits ipsilateral M1 to reduce interference with movement (Chettouf et al., 2020; Cincotta & Ziemann, 2008; Giovannelli et al., 2006; Maudrich et al., 2018). AA during unilateral movements therefore has been interpreted as the consequence of an overload of the “nonmirroring transformation network”, in which excitatory inputs exceed inhibitory inputs reaching ipsilateral M1, resulting in net facilitation (Maudrich et al., 2018; Sehm et al., 2016). However, the results of the present and previous studies (Addamo et al., 2010; Maudrich et al., 2020) show that AA could be suppressed, suggesting that volition can effectively modulate this suppression network. During Suppression trials, an increase in the inhibitory inputs to ipsilateral M1 would overcome

excitatory inputs, reducing AA. The present results show that corticospinal excitability decreased and intracortical inhibition increased in contralateral homologous and nonhomologous muscles during Suppression trials. However, the reduction in corticospinal excitability was expected due to the differences in motoneuron output consequent to suppressing AA. Indeed, the reductions in MEP amplitude correlated with decreases in AA (FDI: $r = 0.56$). Because it is not possible to test corticospinal excitability during No Suppression and Suppression trials without differences in motoneuron output, we used an alternative approach to determine if suppression of AA had additional inhibitory effects on corticospinal excitability besides the reduction in motoneuron output (see Section 2 for a thorough explanation). The data revealed no differences in Δ MEP between No Suppression and Suppression, suggesting that changes in corticospinal excitability were highly influenced by

FIGURE 6 MEP (a), SICI (b), ΔMEP (c) and ΔSICI (d) in the nontarget FDI ($n = 17$ for MEPs and ΔMEP and $n = 14$ for SICI and ΔSICI). FDI, first dorsal interosseus; MEP, motor evoked potential; SICI, short-interval intracortical inhibition

changes in motoneuron output. Notwithstanding, at the cortical level our results show an increase in SICI. Although the increase in SICI can be influenced by the decrease in test MEP amplitude, as suggested by the correlation between changes in SICI and MEP amplitude ($\rho = 0.58$; $P = 0.03$), intracortical inhibition tends to be greater with larger and not smaller test MEPs (Daskalakis et al., 2002; Roshan et al., 2003). Therefore, our results may suggest an increase in the efficacy of intracortical inhibitory interneurons during Suppression trials. The mechanisms mediating the increase in intracortical inhibition in ipsilateral M1 during voluntary suppression of AA could be similar to those that increase SICI in contralateral M1 during inhibition of voluntary movements in a Go/NoGo reaction task (Sohn et al., 2002). Indeed, voluntary suppression of AA is associated with increases in relative δ power in frontal areas (Maudrich et al., 2020), and δ power has been associated with motor inhibition (Kaiser et al., 2019). A plausible scenario is therefore an increase in the influence from frontal areas to the ipsilateral M1 to increase SICI (Sohn et al., 2002) and prevent motor output during Suppression trials. However, because we found no differences in ΔSICI between No Suppression and Suppression, changes in SICI could also be influenced by differences

in motoneuron output between No Suppression and Suppression trials (Ortu et al., 2008).

Beyond elucidating the mechanism underlying AA suppression, the present study also aimed to examine the functional role of IA in unilateral motor control. To this aim, we determined the effects of suppressing AA, a peripheral proxy of IA in the brain (Zijdewind et al., 2006), on force steadiness during an isometric contraction of the FDI in which the goal is to maintain force as steady as possible. We found that voluntarily suppressing AA made the force unsteady without affecting submaximal force production ($\sim 46\%$ of MVC during No Suppression and Suppression). In addition to suppressing AA, fatigue from the previous trial could influence force steadiness during Suppression trials (Hunter & Enoka, 2003). Indeed, despite the inclusion of a rest period (~ 25 min), target-FDI force decreased from PRE to MID (-7% , $P = 0.001$), suggesting that the No Suppression trial induced fatigue, albeit minimal. However, the results from Experiment 2, in which participants performed two consecutive identical trials without suppression, showed that force steadiness as measured by the coefficient of variation did not change from the No Suppression 1 (6.5%) to the No Suppression 2 trial (6%). These results suggest that fatigue was probably not

TABLE 3 rmsEMG and force measurements values in both hands and both sessions of the Experiment 2

	Session 1		Session 2	
	No suppression 1	No suppression 2	No suppression 3	Suppression
Target hand				
FDI rmsEMG (% MVC rmsEMG)	71 ± 19	78 ± 21	70 ± 25	76 ± 19
Task force (% MVC)	52 ± 3	52 ± 3	53 ± 3	53 ± 4
Force CV (%)	6.54 ± 2.92	5.98 ± 2.14	5.40 ± 2.56	5.76 ± 1.76
Nontarget hand				
Associated FDI rmsEMG (% MVC rmsEMG)	8.94 ± 13.51 (median = 4.45)	6.95 ± 9.98 (median = 2.22)	9.03 ± 13.65 (median = 2.76)	1.26 ± 0.50 (median = 1.29)
Associated force (% MVC)	5.17 ± 6.15 (median = 4.42)	4.59 ± 5.35 (median = 2.05)	3.09 ± 5.65 (median = 1.08)	-0.35 ± 0.64 (median = -0.44)

Note: Values are mean ± SD, except for nonparametric variables, where median is also shown.
Abbreviations: CV, coefficient of variation; FDI, first dorsal interosseous; MVC, maximal voluntary contraction; rmsEMG, root mean square electromyography.

contributing to decrease force steadiness in Experiment 1. Therefore, we can be fairly certain that voluntary suppression of AA underlay the impaired force steadiness during Suppression trials, assigning a functional role to AA. However, although correlation is not causation, the absence of correlation between the magnitude of suppression and the decrease in force steadiness suggests that a causative link between the two phenomena cannot be established. A potential factor that can contribute to a lack of link between the two variables is dual-tasking, as participants were asked to produce steady force in one hand whilst they tried to suppress AA in the other hand. We did not examine systematically if this increase in cognitive load contributed to a lack of association between these two factors and whether this load was specifically related to the act of suppression or a lack of association would have remained if we had asked participants to perform steady force whilst doing cognitively demanding task other than suppression. Indeed, when healthy adults were asked to produce steady force whilst doing another (cognitive task), force steadiness decreased (Lorist et al., 2002), suggesting that it was probably not the cognitive load specifically associated with suppression but the increase in cognitive load per se due to dual-tasking which could have contributed to a lack of association between the magnitude of suppression and decreased force steadiness.

We must also consider the nature of how IA produces AA in relation to the lack of relationship between AA suppression and impaired force steadiness. Nonhuman primate data revealed that the kinematics of unilateral upper arm movements can be decoded with equivalent precision from the neural information contained in the contralateral or ipsilateral motor cortex, suggesting that both contain similar task-relevant information (Ames & Churchland, 2019). This IA does not produce movements in the inactive arm because the individual neuron activation patterns during IA were different from the individual activation patterns present in the same neurons when controlling movements of their contralateral limb. It is suggested that the activation of individual neurons during ipsilateral compared to contralateral movements occupies an orthogonal subspace that contains task-relevant information without causing muscle contractions (i.e., “muscle null” dimension) (Ames & Churchland, 2019; Kaufman et al., 2014). Thus, it could be that when AA appears, it emanates from the spread of IA coded on “muscle null” to “muscle potent” dimensions, triggering motor output in the wrong muscles during unilateral demanding tasks. In this scenario, IA may have some elements functionally relevant to the task, not causing undesired movements, and other non-functionally relevant elements consequence of the spread

of the first ones to “muscle potent” dimensions. In this case, suppressing AA may affect mainly the non-functional elements of the IA, which are neither contributing nor detrimental to task performance, thus explaining the lack of correlation found in the present study.

A limitation of the present study is the use of AA as a representation of IA, which can also contribute to a lack of relationship between magnitude of AA suppression and the decrease in force steadiness. Whilst AA is consequence of IA (Zijdewind et al., 2006), suppressing AA may not have a linearly corresponding suppressing effect on IA. Indeed, there is not always AA when there is IA (Andrushko et al., 2021; Hortobágyi et al., 2003). Therefore, future studies using the suppression approach to determine a functional role of IA should use imaging techniques that allow to measure IA directly instead of using AA as a proxy. We also did not measure coactivation of the antagonist second palmar interosseous, which could have helped to interpret our data more accurately. However, it has been previously reported that during steady isometric contractions, force steadiness was not associated with differences in coactivation of the antagonist second palmar interosseous (Burnett et al., 2000). As an additional limitation, participants performed the task with their dominant ($n = 15$) or nondominant ($n = 2$) hand. Although the present study did not focus on hand lateralization, and the influence of only two subjects using the nondominant hand is likely to be marginal, future studies should use the same (dominant or nondominant) hand in order to avoid the possible influence of handedness on the results.

The current data are limited to healthy young adults. However, evidence for a more direct role of AA in movement control could be stronger in older adults with or without pathologies, including structural and functional changes in the brain, which would necessitate a heightened compensatory role of the ipsilateral hemisphere in movement control (Bueteftisch, 2015; Bundy & Leuthardt, 2019; Carson, 2020; Mattay et al., 2002; Seidler et al., 2010). In those conditions, the ipsilateral cortex is known to substantially contribute to the planning and execution of unilateral movements. However, in certain pathological conditions such as stroke, the contralesional hemisphere may play a competitive rather than a cooperative role, inhibiting the ipsilesional cortex and interfering with normal motor function (Hensel et al., 2021). In those cases, inhibiting IA during unilateral movements of the paretic side may afford clinical benefits. Therefore, future studies following the AA suppression model to elucidate the functional role of IA should focus on populations in which IA has a greater beneficial or deleterious effect on the execution of unilateral movements.

5. CONCLUSION

In conclusion, AA during unilateral isometric contractions can be suppressed by volition, accompanied by an increase in intracortical inhibition, which may contribute to prevent motor output in the “nontarget hand”. Although AA suppression was accompanied by a decrease in force steadiness, our results suggest that the specific elements of the IA producing AA in younger adults are neither contributing nor detrimental to the task.

ACKNOWLEDGEMENTS

The authors would like to express their gratitude to Giulia Visentin for her help during data collection. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

CONFLICT OF INTEREST

None of the authors declare conflict of interest.

AUTHOR CONTRIBUTIONS

D. C., I. Z, G. M. and T. H conceived and planned the experiments. D. C., J. D. and T.H. carried out the experiments. D.C. and G.M. analysed the data. D. C. interpreted the results and drafted the manuscript with input from all authors.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/ejn.15371>.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Colomer-Poveda, D., Zijdewind, I., Dolstra, J., Márquez, G., & Hortobágyi, T. (2021). Voluntary suppression of associated activity decreases force steadiness in the active hand. *European Journal of Neuroscience*, 1–17. <https://doi.org/10.1111/ejn.15371>