Brain Stimulation 19 (2026) 103105

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.journals.elsevier.com/brain-stimulation

MEP-independent silent periods in hand muscles elicited by transcranial magnetic stimulation of the ventral premotor cortex: a non-invasive tool to explore premotor negative motor areas

Pier Paolo Berti [a], Guido Barchiesi [b], Mara Turri [c], Roberta Volpini [c], Giancarlo Caschera [c], Roberta Spano [c], Fabio Mariotti [c], Iolanda Galdi [c], Paolo Cipriano Cecchi [a], Andreas Schwarz [a], Francesco Sala [d], Christoph Griessenauer [e], Luigi Cattaneo [f,g,*]

[a] Neurosurgery Unit, Hospital of Bolzano (SABES-ASDAA), Teaching Hospital of Paracelsus Medical University (PMU), Bolzano-Bozen, Italy
[b] Cognition in Action (CIA) Unit – PHILAB, Department of Philosophy, Università degli Studi di Milano, Milano, Italy
[c] Neurology Unit, Hospital of Bolzano (SABES-ASDAA), Teaching Hospital of Paracelsus Medical University (PMU), Bolzano-Bozen, Italy
[d] Neursurgery Unit, Civile Maggiore Hospital, University of Verona (Azienda Ospedaliera Universitaria Integrata – AOUI), Verona, Italy
[e] Department of Neurosurgery, Christian Doppler Clinic, Paracelsus Medical University, Salzburg, Austria
[f] Center for Mind/Brain Sciences (CIMeC), Italy
[g] Center for Medical Sciences (CISMed), University of Trento, Italy

A B S T R A C T

Objective: We investigate the possibility to disrupt motor activity via premotor and parietal cortex stimulation, by inducing cortical silent periods (SPs) in the voluntarily activated upper limb.
Methods: We analyzed data from 17 subjects with normal brain function, using navigated TMS (nTMS) on individual MR anatomies. We applied single-pulse biphasic stimulation at 120% of resting motor threshold (rMT) in blocks of 30 stimulations on each spot of a 10–16 point grid covering the inferior parietal and frontal lobes in the dominant hemisphere while participants performed voluntary submaximal contraction. Electromyography (EMG) was recorded bilaterally from intrinsic hand muscles.
Results: We observed SPs not preceded by a MEP in the contralateral hand in 16/17 participants. The maximum overlap, of individual areas where such MEP-independent SPs could be evoked, corresponded to the ventral precentral gyrus (MNI coordinates: [x = −57, y = 7, z = 33]). In a subset of stimulus sites, MEP-independent SPs were bilateral, with contralateral predominance. Canonical early-onset MEPs were observed in all patients, with maximum overlap over the primary motor cortex. We also observed rare contralateral late-onset (>23 ms) MEP-like responses from peri-Rolandic TMS.
Conclusions: MEP-independent SPs are systematically elicitable in healthy participants They likely reflect interference with premotor representations of ongoing movements. They offer a novel possibility to investigate higher-order motor functions in the experimental and clinical neurosciences.

1. Introduction

1.1. Negative motor responses (NMRs) and silent periods (SPs)

Negative motor responses (NMRs) are electrophysiological and behavioral phenomena defined as the transient, complete or partial, inhibition of voluntary movement without loss of consciousness [1,2] that are elicited by stimulation of the nervous system. The present work focuses on NMRs evoked by transcranial stimulation, although NMRs can be elicited by stimulation of any portion of the central and peripheral nervous system. Cortical NMRs are commonly elicited by means of invasive, direct electrical stimulation (DES) of the cortex during brain surgery or intracranial stimulations. DES-induced negative motor responses have been described since the origins of intraoperative cortical stimulation [3], but only in recent years has the scientific community become acutely aware of the relevance of NMRs in relation to motor control and cognition [4].

NMRs are observed during the voluntary contraction of a muscle and therefore require the subject to be awake and cooperative. The simplest way to observe an NMR is by having the participant perform an isometric contraction. NMRs are documented behaviorally as a drop in active posture when held against gravity [5], or instrumentally as a

* Corresponding author. Center for Mind/Brain Sciences (CIMeC) - University of Trento , Centre of Medical Sciences (CISMed) - University of Trento, Via Delle Regole 101, 38123, TRENTO, Italy.
E-mail address: luigi.cattaneo@unitn.it (L. Cattaneo).

https://doi.org/10.1016/j.brs.2026.103105
Received 18 November 2025; Received in revised form 17 April 2026; Accepted 18 April 2026
Available online 20 April 2026

pause in the ongoing EMG pattern. Such pauses in voluntary EMG are referred to as Silent Periods (SPs). SPs are a commonly observed phenomenon in clinical neurophysiology and are the expression of different possible mechanisms. A true SP can occur as a consequence of pre- or post-synaptic inhibition of neurons along motor pathways; however, pseudo-SPs can occur as a consequence of non-inhibitory mechanisms, such as synchronization of motor unit discharge or collision with antidromic stimuli [6–8]. Given these premises, non-invasive, preoperative mapping of negative motor areas (NMAs) with TMS holds strong potential for informing surgical planning. However, TMS is not as efficient as DES in eliciting pure NMRs. The apparent dissociation between intraoperative stimulation and TMS is likely due to the different stimulation protocols used in the two techniques. Intraoperative mapping usually employs 60 Hz bipolar direct electrical stimulation, delivered in variable trains of 1–5 s to identify functional sites [9,10]. Such stimulation parameters are well beyond the established safety limits for TMS. Indeed, single TMS pulses have rarely been reported to elicit pure NMRs. However, it is also worth noting that epilepsy-surgery studies have used stimulation paradigms conceptually similar to NIBS: Rubboli et al. [5] reported that single-pulse electrical stimulation of the premotor cortex could elicit silent periods without preceding MEPs in ~50% of trials, a pattern seen predominantly at lower stimulation intensities, whereas higher intensities more often produced a canonical MEP followed by a silent period. The functional interpretation of NMRs is still debated. While some authors claim that NMRs are a simple epiphenomenon of electrical stimulation over nodes of the cortical motor system that produce active movements [11], others claim that they represent a dedicated system for action inhibition [1,12]. However, the fact that NMRs occur mostly symmetrically in both hemispheres and their widespread distribution in the peri-Rolandic regions [13] make it unlikely that they exclusively represent the expression of an action inhibition network. Finally, intraoperatively defined NMRs mostly represent purely inhibitory phenomena, as they are not preceded by positive, excitatory responses, and NMRs tend to have a lower threshold than excitatory responses [10,11,14,15]. NMAs therefore represent cortical nodes in the action system that produce a pure suppression of motor output when stimulated during an active voluntary task.

From a clinical perspective, NMAs are thought to be indicative of higher-order motor functions such as movement initiation, bimanual coordination, motor awareness, hand selection, and praxis [4,16]. Lesions in NMAs can produce motor deficits with features distinct from those caused by lesions in the primary motor cortex [9,17,18].

1.2. Exploration of negative motor areas (NMAs) with non-invasive brain stimulation

A TMS-evoked SP occurs following a motor-evoked potential (MEP) after stimulation of the primary motor cortex (M1) [19]. Such an MEP-dependent cortical SP (SP) occurs contralaterally to the stimulated hemisphere but is also observed ipsilaterally to stimulation (ipsilateral SP), where it is the result of transcallosal connections to the contralateral M1 [20]. There is general consensus that MEP-dependent SPs are generated, at least their later components, by cortical inhibitory mechanisms that are different from those producing an MEP [19,21–24]. Some authors have argued that cortical SPs are maximally elicited from regions that are non-overlapping with the peak cortical regions for MEP elicitation [25], and one report identified an anterior region on the scalp from which MEP-independent SPs could be elicited [26]. To summarize the current evidence: a) TMS systematically evokes SPs in association with MEPs; b) there is general consensus that at least the later components of the SP are produced by mechanisms independent of those producing the MEP; c) sparse reports indicate that SPs can be evoked by TMS in the absence of MEPs. It still remains an open question whether SPs can be obtained by TMS in the complete absence of an MEP by stimulating NMAs in extra-M1 cortical regions, in analogy with the well-known NMRs from invasive stimulation.

1.3. Aim of the study

In the present study, we aimed to explore NMAs with TMS coupled with state-of-the-art neuronavigation of individual brain anatomies. We focused specifically on the ventral portion of the frontal and parietal lobes, where we investigated the possible existence of extra-M1, MEP-independent cortical SPs. Importantly, we investigated every participant with a dense grid of TMS targets, covering the cortical regions of interest evenly and with a sufficient spatial sampling rate (Cattaneo, 2018). We evaluated electromyographic changes in hand muscles of healthy participants following suprathreshold single-pulse navigated TMS (nTMS) applied along the precentral and postcentral gyri, premotor cortex, pars opercularis of the inferior frontal gyrus (IFG), and posterior parietal cortex (inferior parietal lobule and intraparietal sulcus). We consistently observed MEP-independent SPs in the vast majority of subjects, with maximum overlap in the ventral frontal regions. We hypothesize that developing a feasible, reproducible, and non-invasive mapping technique for NMAs with nTMS also has clinical potential, possibly to enhance preoperative planning, thereby informing treatment decisions and improving patient counselling.

2. Methods

2.1. Participants

We analyzed data from 17 participants (8 male, 9 female; mean age 60), recruited based on the following exclusion criteria: age <18 years; presence of brain lesions; personal or family history of epilepsy; treatment with neuroactive drugs; and metallic implants in the head and neck. The study was carried out at the neurosurgical center in Bolzano (South Tyrol Health Trust, Italy). All participants provided informed consent and were screened for potential contraindications to TMS, following established safety guidelines [27]. The study was approved by the local ethics committee (protocol N. 4/2024 bis) and conducted in accordance with the revised Declaration of Helsinki (World Medical Association, 2013). The participants in the current report were recruited as a neurologically intact control group as part of a broader study protocol, the aim of which is beyond the scope of the present work.

2.2. MRI

All patients underwent preoperative 3-T MRI scans, which included the acquisition of T1-weighted 3D MPR, T2-weighted, and FLAIR (echo train length: 48, TE: 83 ms, TR: 6800 ms, slice thickness: 3 mm, 20 diffusion directions, b-value = 1000). The T1-weighted sequences (echo train length: 1, TE: 2.67 ms, TR: 2000 ms, matrix resolution: 256 × 246, slice thickness: 1 mm) were typically utilized as the anatomical reference scan. If a T1-weighted image was not available or not compatible with the TMS machine, T2-weighted fast spin-echo sequences (TR/TE: 5200 ms/100 ms), or T2-weighted inversion recovery fast spin-echo sequences (TR/TE/TI: 6000 ms/150 ms/2000 ms) were employed. The raw DICOM images were used to reconstruct a render of the cortical surface using the mriCROn software [28]. A grid of a minimum of 12 target points was drawn to cover the ventral portion of the frontal and parietal lobes, including the caudal inferior frontal gyrus (IFG), the ventral precentral gyrus (preCG), the ventral postcentral gyrus (postCG), and the inferior parietal lobule (IPL), as shown in Fig. 1. In addition to these 12 spots, 2 extra spots corresponding to M1 and a point half-way between M1 and the inferior frontal junction were applied. The stimulation spots were positioned on the basis of individual anatomy for some major landmarks, but with some variability within macro-regions. The 12 ventral spots were located in 2 parallel rows, one at the height of the inferior frontal junction and the other midway between the first row and the sylvian fissure. The first row included spots on two fixed landmarks: the inferior frontal junction and the junction between the intraparietal and the postcentral sulci. The remaining 4 spots were put at even

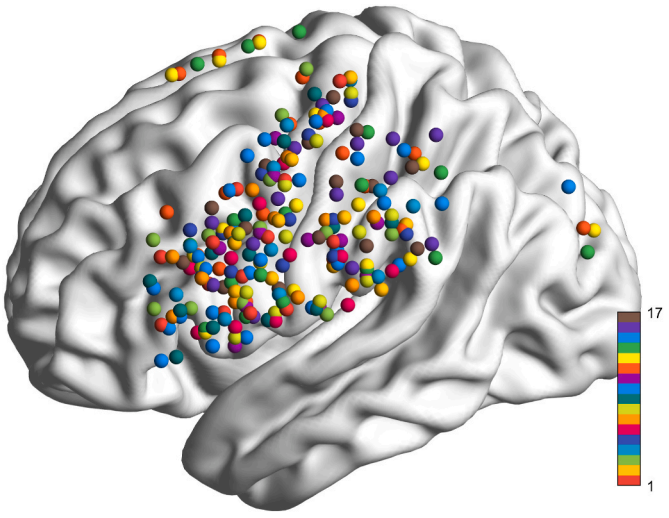

Fig. 1. MNI 152 standard brain with superimposed TMS spots. For visualization purposes, the TMS target spots are represented as 4 mm-diameter spherical ROIs. Cumulative representation showing all stimulation spots from the 17 participants (the color scale indicates the participant's number).

distances of around 1.5 cm between each other. The more ventral row of 6 spots was placed parallel to the dorsal one, around half-way between the upper row and the Silvian fissure. In some participants due to anatomical variants (e.g. split precentral sulcus, split ascending ramus of the Silvian fissure) some extra points were added, to be sure to have an even coverage of the surface, accounting for up to 3 more spots. In six participants, we also applied control stimuli to the occipital lobe and to the midline corresponding to the supplementary motor region, to control for non-specific effects of TMS (i.e., acoustic noise, trigeminal stimulation, mechanical stimulation of the skull).

2.3. nTMS mapping

Single-pulse biphasic TMS was delivered through a figure-of-eight coil (70 mm diameter of external windings) using the Nexstim NBS System 5 (Nexstim Oy, Helsinki, Finland). EMG recordings were performed bilaterally from the first dorsal interosseous (1DI) and the abductor pollicis brevis (APB) muscles by means of surface electrodes in a bipolar belly-tendon montage. The raw signal was amplified 1000-fold and digitized at 10 kHz. For the purpose of coregistration between the patient's scalp and MRI data, anatomical landmarks included the crus of the helix on both sides, the nasion, and nine additional scalp points identified by the nTMS software. The maximum stereotactic error tolerated by the system was 2 mm; stimulation was halted if this threshold was exceeded. The mapping procedure was preceded by the identification of the motor hotspot and assessment of the resting motor threshold (rMT). For each participant, the 1DI was used as the target muscle for threshold determination. The motor hotspot was operationally defined as the M1 location at which single-pulse stimulation evoked the largest and most consistently detectable MEPs in 1FDI-EMG. rMT was subsequently determined at the hotspot using the Nexstim motor-threshold search function (iterative, stepwise adjustment of stimulation intensity with repeated single pulses) and was defined as the minimum stimulator output (%MSO) required to elicit MEPs $\geq$50 μV peak-to-peak in at least 5 of 10 consecutive trials with the muscle at rest. TMS mapping was performed exclusively on the dominant hemisphere as determined by the Edinburgh Handedness Inventory (Oldfield, 1971). Stimulation was delivered tangentially over the scalp overlying the cortical region of interest with the figure-of-eight coil and the handle oriented postero-laterally at ~45° to the sagittal plane, inducing alternating current with a posterior–anterior direction of the first phase. The mapping procedure consisted of stimulating each point, in a random order, with 30 stimuli per spot. The stimulation intensity was suprathreshold and set at 120% of the rMT obtained in the 1DI muscle. We kept coil orientation constant at each grid point using the visual orientation and angulation benchmarks provided by the Nexstim NBS 5 software. The Nexstim stimulator delivers biphasic stimuli, with a first phase directed anterior–posterior. The behavioral task consisted of a submaximal isometric contraction of the hand around a small cylindrical object. Participants were instructed to squeeze at approximately 50–70% of their perceived maximal strength and to maintain a stable contraction for interval spanning from 2 to 5s, followed by a rest interval varying from 1 to 3 s. To minimize preconditioning effects, both the task interval and the timing of TMS pulses were varied across trials. Single TMS pulses were delivered manually by the operator whenever a stable contraction was obtained, based on audio and visual inspection of the online surface EMG traces. We did not systematically investigate the occurrence of neuromuscular fatigue. However, additional pauses were provided if contraction quality appeared to decline.

2.4. Data pre-processing and analysis

The EMG traces were analyzed as event-related epochs, centered on the TMS pulse. The following pre-processing steps were applied: the raw signal was individually inspected to remove artifacts (0% discard rate). The recordings consisted of a single continuous trace for each spot. The data were preprocessed with a custom-written MATLAB R2022b (The MathWorks Inc.; 2024) script and using FieldTrip [29]. The recording was downsampled to 2 kHz, band-pass filtered between 10 Hz and 1 kHz, and rectified. The rectified trace was smoothed with a 20-sample sliding window. The analysis started with the segmentation of the recordings into epochs spanning 200 ms before and 200 ms after each stimulus. Single rectified traces were then averaged within each stimulation spot. In this way, we obtained a single rectified averaged trace for each muscle at each TMS spot. Finally, the recordings from 1DI and APB were averaged to obtain a single representative trace of the distal hand muscles. The occurrence of significant post-TMS events in the averaged traces was determined by comparing post-TMS segments with the pre-TMS baseline. To do so, we constructed an “error box” based on the 200 ms pre-TMS interval: we calculated the mean value of pre-TMS EMG ±1.96 standard deviations. To define the significance of the evoked response relative to baseline noise, we utilized a standard 95% confidence interval based on the pre-event distribution. Following established bio-statistical conventions (Altman, 1991; Gardner & Altman, 1986), the threshold was set at ±1.96 standard deviations from the mean, encompassing the central 95% of the baseline variability. Any deviation in the post-TMS EMG exceeding the upper and lower bounds of the error box was considered a significant effect of TMS, provided that it lasted for 10 consecutive milliseconds (Figs. 2–5 show examples of significant events). Any event exceeding 100 ms in latency was disregarded to exclude contamination by voluntary responses to TMS-evoked sensations. Importantly, only the first post-TMS events were considered. For example, in the case of an MEP followed by an SP, only the primary positive response was considered. Conversely, in the case of a primary inhibition followed by a rebound in EMG activity, as is usually the case for SPs [6,8,30], we considered only the primary inhibitory response. Importantly, since the focus of the study was aimed at differentiating SPs that occur independently from a MEP from those that are associated to the MEP, in the mapping experiment, any SP preceded by an MEP was ignored in the main experiment. Conversely, SPs preceded by MEPs were the specific objective of control experiment 2. The data were analyzed with a custom-written MATLAB R2022b (The MathWorks Inc.; 2024) code. The code identified significant deviations outside the ±1.96 SD error box and reported the latency of the initial crossing of the limit and the area of the curve outside the error box.

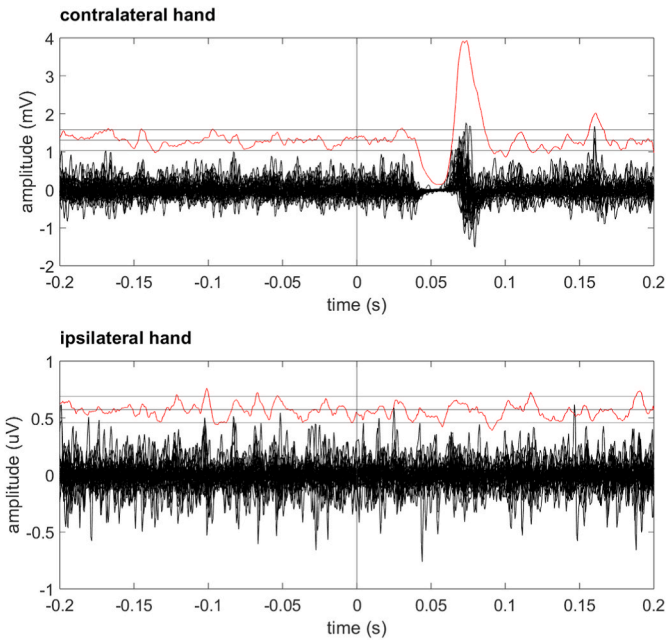

Fig. 2. Representative image of a complete MEP-independent SP from a single subject. (Subjj #13, spot #2). The black lines indicate the recordings from the APB and 1DI muscles superimposed and aligned to the time of TMS (t = 0). The red lines represent the rectified, smoothed and averaged compound EMG. The horizontal black lines indicate the "error box" for the rectified trace (baseline mean±1.96*baseline SD). Note that for illustration purposes the rectified trace and corresponding error boxes have been rescaled 5x for appropriate comparison with the raw traces.

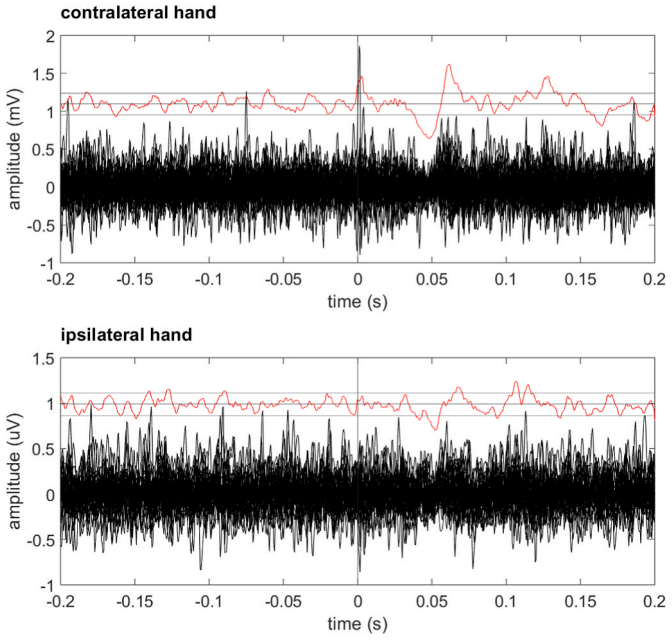

Fig. 3. Representative image of a partial SP from a single subject. (Subj #2). Conventions as in Fig. 2.

2.5. Topography of the post-TMS events

All individual brain scans were preprocessed using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) with the following steps: 1) segmentation and transformation into Montreal Neurological Institute (MNI) standard space to obtain 1 mm voxel MNI-normalized images. The coordinates of the target points, generated as an image in the subject's native MRI space by the Nexstim neuronavigation system, were transformed into MNI space using the individually obtained transformation matrix. Note that in one left-handed participant, the right hemisphere was stimulated, and the relative coordinates were flipped to the left hemisphere for consistency in the analysis. The final results of the mapping procedure for each individual stimulation spot were, therefore, the set of x, y, and z coordinates in MNI space, the polarity of the effect (inhibitory, null, or excitatory), and the latency and area of the inhibitory responses (SPs). For illustration purposes, the cortical targets were visualized with the BrainNet Viewer (http://www.

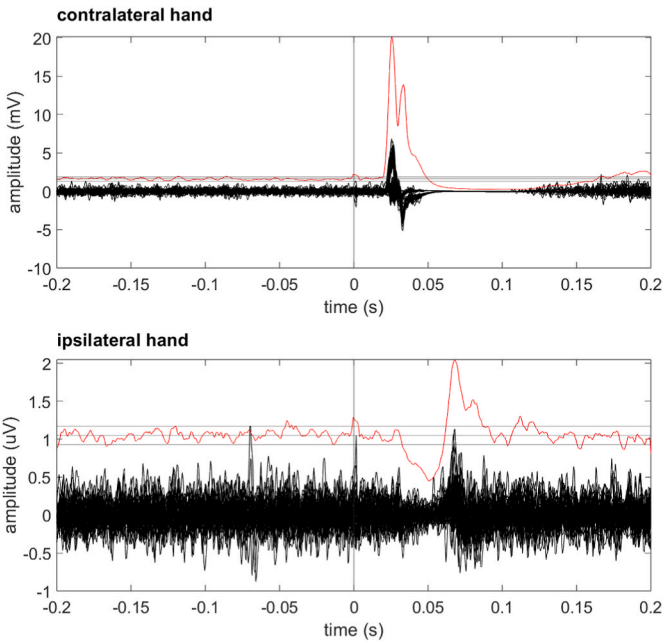

Fig. 4. Representative image of an early-onset MEP from a single subject. (onset latency: 19 ms, Subj #2) Conventions as in Fig. 2.

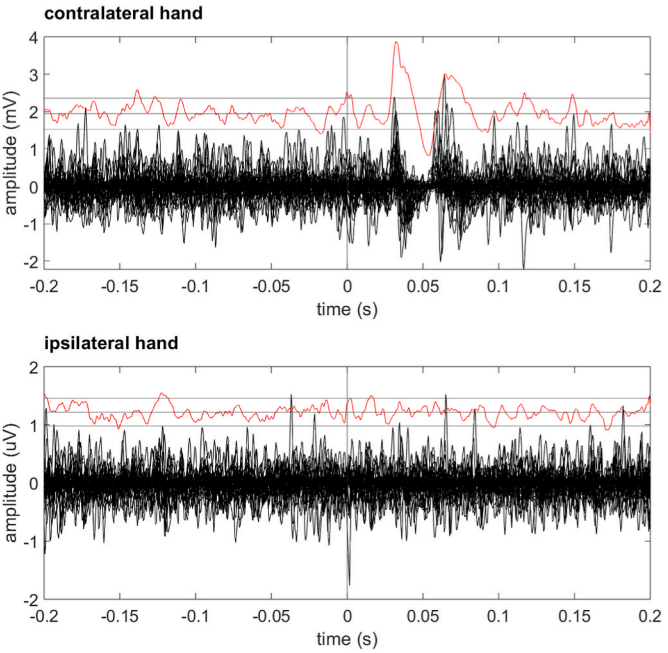

Fig. 5. Representative image of a late-onset MEP from a single subject. (onset latency: 29 ms, Subj #15) Conventions as in Fig. 2.

nitrc.org/projects/bnv/) (Xia et al., 2013). The cumulative grid of all TMS spots is shown in Fig. 1. To produce population-level data, we could not use the single spots because TMS targets from a single subject do not represent independent data points. This part of the analysis was carried out with a custom-written Python script, using the Nilearn (Machine learning for NeuroImaging in Python) toolbox (Abraham et al., 2014). To obtain quantitative spatial information at the group level, we first analyzed each subject by extracting the spots that produced a given type of response (e.g., contralateral MEP-independent SP). We projected these coordinates onto the surface of the pial-left surface template from FreeSurfer and interpolated an area around those spots with a 10 mm margin from each coordinate. All individual surfaces were then superimposed to produce a heatmap of subject overlap, and a local maximum was identified. Finally, the topography of local maxima for each post-TMS effect was compared with the parcellation of the premotor and parietal cortices of the Julich brain atlas (Amunts et al., 2020).

2.6. Control experiments

We performed two control conditions. The first was to exclude the possibility that the effects could be due to non-specific TMS features such as noise, electrical stimulation of the scalp, or mechanical head displacement. We therefore applied TMS to targets over the midline of the frontal region and over the occipital cortex. In another subset of 8 participants, we constructed a recruitment curve of the MEP and of the MEP-associated SP, testing several stimulus intensities over M1, ranging from 70% to 130% of the resting motor threshold. Single TMS pulses were delivered over the 1DI muscle hotspot and the surface EMG was recorded from the 1DI and ABP muscles, in conditions identical to the ones of the main experiment, i.e. intermittent voluntary contraction of the fingers in a pinching movement. A minimum of 20 trials per stimulus intensity were obtained. Regarding data analysis, both positive (MEP) and negative (silent period) responses were taken into consideration when they exceeded the 1.96*SD error box calculated on the average trace. The amplitude of the MEPs was calculated as peak-peak amplitude of the mean recording and the magnitude of the silent periods was calculated as the area below the lower 1.96 SD line (see panel B of Fig. 8 for a representative recording). This control was performed to exclude the possibility that subthreshold stimulation of M1 could elicit a SP in the absence of an MEP.

3. Results

None of the participants reported any immediate or delayed side effects from the stimulation. We observed several patterns of EMG response to TMS in the voluntarily activated muscles. In the hand contralateral to the stimulated hemisphere, we found: A) early-onset MEPs, compatible with canonical fast corticospinal conduction (latency <23 ms); B) MEP-independent SPs, i.e., pauses in voluntary EMG not preceded by excitatory phenomena; C) late-onset (>23 ms) excitatory phenomena; and D) no effect. In the hand ipsilateral to the stimulated hemisphere, we observed three possible phenomena: A) SPs associated with contralateral MEPs; B) SPs not associated with contralateral MEPs; or C) no effect. An illustration of paradigmatic cases for each condition is provided in Figs. 2–5.

3.1. Contralateral MEP-independent SP

We found evidence of MEP-independent SPs in at least one spot of the grid in 94% of participants (16/17 subjects; subj #5 did not show any). The number of grid spots from which a SP could be elicited varied from 1 to 9, indicating considerable individual variability in the spatial extent of the NMAs. The peak overlap corresponded to the anterior portion of the precentral gyrus, at the junction with the inferior frontal sulcus at the MNI coordinates of [x = −57, y = 7, z = 33], but with considerable overlap along the mid-portion of the precentral gyrus (Fig. 6A). The mean onset latency of the contralateral MEP-independent SPs was 36.7 ms (SD = 8.0 ms). The distribution of the onset latency was unimodal, as illustrated in Fig. 7A. The duration of the MEP-independent SP was

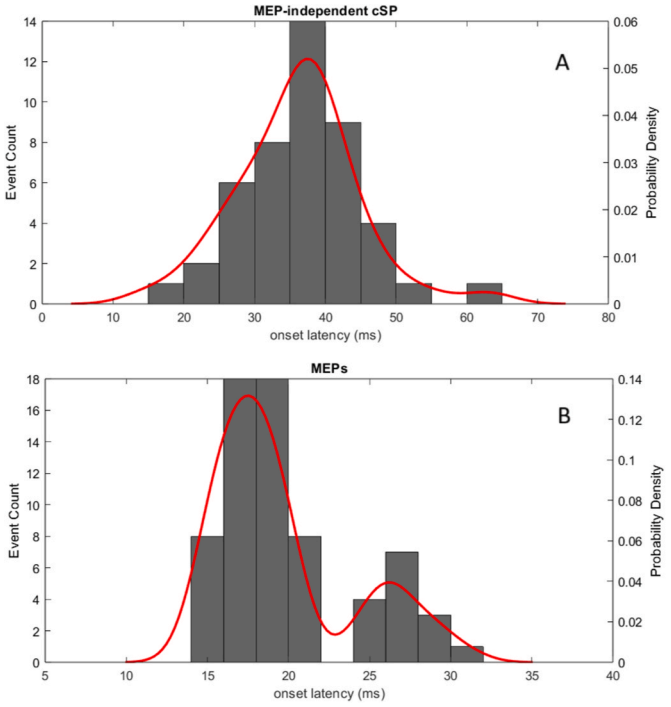

Fig. 7. Histograms showing the distribution of the number of TMS-evoked responses according to latency of onset. The grey columns indicate raw event counts and the red line indicates the kernel density estimation of event counts. The top panel refers to contralateral MEP-independent CSPs. The bottom panel refers to contralateral responses, indicating a biphasic distribution of onset latencies (the time scale on the x-axis differs between the two graphs).

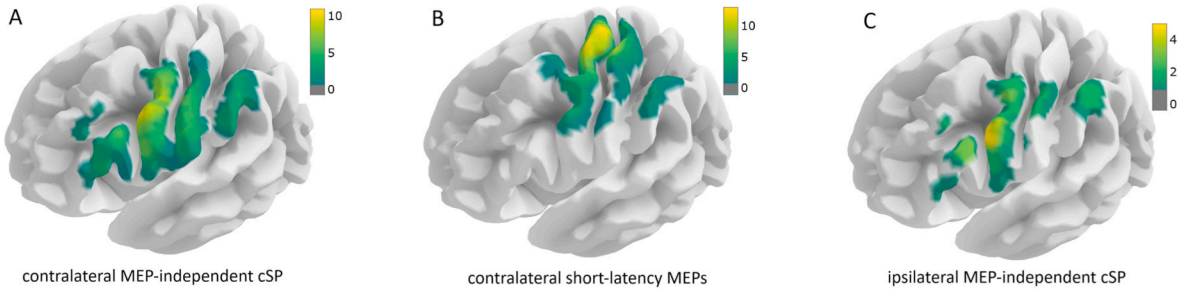

Fig. 6. Overlay maps of number of participants' cortical areas showing a specific response to TMS (note that the scale differs between the 3 maps). The coordinates of the local maxima are reported in the text.

variable, ranging from 10 to 42 ms. Note however that we established as lower cutoff for the duration of inhibitory events a 10 ms interval (see methods) and therefore we cannot exclude that possibly even shorter dips in the trace may have occurred, but they were ignored per definition to rule out random data.

The mean duration was 18.1 ms (SD = 6.8 ms). The decrease in voluntary activity was complete in only a minority of cases, while in the majority, it was an incomplete suppression of EMG (cf. Figs. 2 and 3). The maximum overlap spot co-localized with the 6v3 parcellation of the Julich atlas [31].

3.2. Contralateral MEPs

As expected, all subjects showed excitatory responses compatible with MEPs elicited from the Rolandic region by suprathreshold TMS. The latency of the MEPs showed a bimodal distribution, with an early peak around 17 ms and a late peak around 25 ms (Fig. 7B). We defined the cut-off value between early and late responses as 23 ms, based on literature descriptions of early response latency [32] and on visual inspection of the present data. Fig. 4 shows a typical early-onset MEP, and Fig. 5 shows a typical late-onset MEP. MEPs belonging to the early peak corresponded to MEPs elicited from M1, were evident in all participants, and showed maximum overlap on the hand-knob of the precentral gyrus at the coordinates [x = −37, y = −18, z = 69] (Fig. 6B). MEPs with latencies in the late peak were much less frequent (present in 7/17 participants) and did not show a consistent spatial location in the peri-Rolandic region, being distributed between the parietal, frontal opercular, and premotor regions. Their population map failed to show a consistent spatial location, with an insignificant peak overlap of only two subjects out of seven at the coordinates [x = −59, y = −32, z = 42].

3.3. Ipsilateral silent periods

We observed the systematic presence of the well-known ipsilateral silent periods [33,34] in association with contralateral early-onset MEPs. The description of these is beyond the scope of the present work. Unexpectedly, we also observed the presence of ipsilateral SPs independent of contralateral MEPs. These were never complete SPs and were observed only in association with contralateral MEP-independent SPs; they were systematically smaller and were present in only 9/17 participants. Fig. 3 illustrates the simultaneous presence of two incomplete inhibitions of EMG activity, with a prevalence on the side contralateral to TMS. The mean latency of ipsilateral MEP-independent SPs was 45.8 ms (SD = 12.0 ms), and the mean duration was 17.8 ms (SD = 8.7 ms). In no case did we find standalone ipsilateral SPs without any contralateral phenomenon. The overlap of MEP-independent ipsilateral SPs was found around the peak coordinates of [x = −57, y = 8, z = 31], which nearly overlapped with those for the MEP-independent contralateral SP. It should be noted that we never observed ipsilateral excitatory responses. Though ipsilateral MEPs have been sometimes observed in the literature, the experimental conditions adopted in the present work were not optimal to evoke them. Ipsilateral MEPs tend to occur at high stimulation intensities and high contraction levels of the target muscle. Moreover they appear more frequently in proximal muscles [35–37].

3.4. Control experiments

Regarding the first control condition, in none of the frontal and occipital control sites did we find TMS-evoked activity, neither excitatory nor inhibitory. The second control experiment showed that in none of the subjects (n = 8), TMS over M1 elicited a SP in the absence of a preceding MEP. Fig. 8 shows the population-level data and a representative recording.

3.5. Data availability

The topographic maps, the coordinates of the single TMS spots for every participant are available at the repository: https://osf.io/gv7yn.

4. Discussion

4.1. MEP-independent contralateral SPs are genuine evoked responses to cortical stimulation

The present study provides novel evidence that SPs can be consistently evoked from activated hand muscles after stimulation of the contralateral ventral premotor regions using single-pulse TMS. In only one participant out of 17 were no significant SPs elicited. The first relevant question concerns their specificity to cortical stimulation. Indeed, SPs in ongoing voluntary EMG can occur following sensory stimulation [6,7,38] and therefore could result from the activation of cutaneous afferents from the scalp. However, two lines of evidence in our study support the cortical origin of the SPs. First, if SPs were the

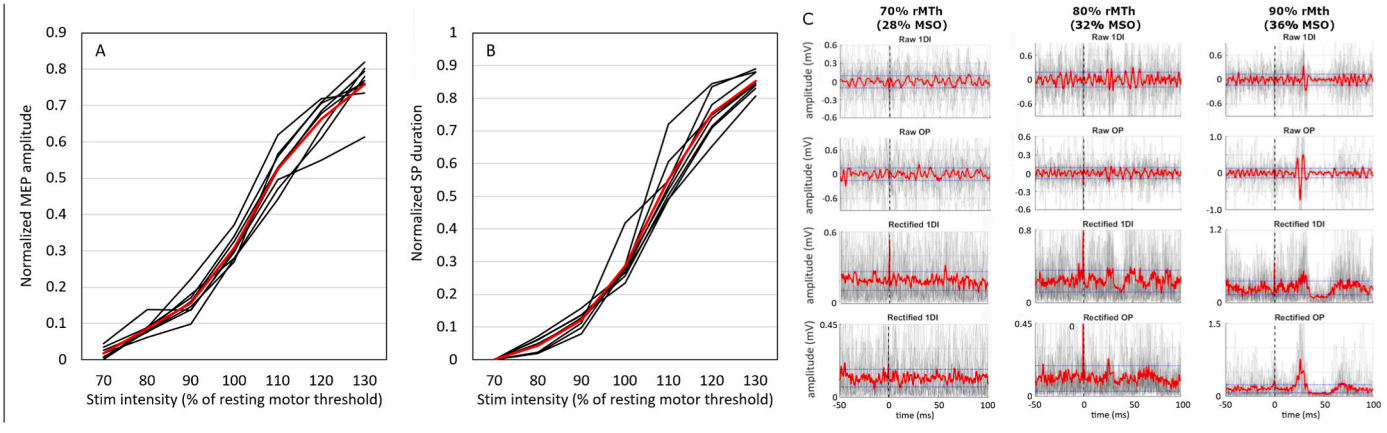

Fig. 8. Results of the control experiment #2. Panel A shows the recruitment curve of the MEP amplitude in the 8 participants. MEP amplitudes are measured positive peak-negative peak, and normalized to the maximal amplitude. Single subjects' data are shown as thin black lines, the mean value is shown as a red line. Panel B shows the recruitment curve of the silent period, measured as duration of the recording below the 1.96*SD of baseline limit. Panel C shows a representative recording of a single participant at the intensities of 70%, 80% and 90% of resting motor threshold (rMTh). Absolute intensities are indicated as maximum stimulator output (MSO). The raw and the corresponding rectified traces are indicated. The mean recordings are shown as red lines. The time of stimulation is indicated by the vertical dashed black line. The confidence intervals of the mean trace calculated on the 200 ms preceding the stimulus (mean±1.96*SD) are indicated as dashed blue lines.

result of non-specific sensory stimulation (mechanical or acoustical), they would have been consistently recorded from every stimulation site. Instead, by adopting a large stimulation grid, we demonstrated that SPs were elicited only from a limited subset of sites. Additionally, in some participants, we stimulated control regions far from the parieto-frontal cortex (i.e., the midline and the lateral occipital cortices), and these stimulations also showed no significant evoked EMG responses. Second, most responses were either exclusive to or predominant on the side contralateral to stimulation, making it highly unlikely to be a reflex behavior, which would be expected to be either bilateral or ipsilateral to the stimulated site. Finally, voluntary responses were also excluded by the fact that any event-related EMG phenomenon with a latency exceeding 100 ms was excluded from further analysis, thus cutting off any voluntary reaction to the TMS. Compared to the previous literature that seems to indicate that MEP-independent SPs are elicitable only at low threshold of intensity [23], our findings indicate that SPs can be elicited also at higher intensity of stimulation and that the most relevant parameter to elicit them without an MEP is actually cortical topography, as they localize on the inferior frontal cortex. Summing up, we show that interruptions in ongoing voluntary movements can be evoked by focal TMS over a region (the ventral premotor complex) that is topographically very distant from M1 (around 5 cm on the cortical surface). Such anatomical differentiation indicates probably a functional diversity. Both M1 and the ventral premotor cortex, if stimulated, respond with a SP, however, given the different function of the two regions, the actual physiological meaning of the two processes is probably very different (see paragraph 4.5). A SP is a transient loss of function and should be considered as a non-specific response. What our study points out is that SPs result from stimulation of the ventral precentral gyrus, with a topography, and therefore also a functional meaning, completely separate from M1. A further point of potential interest in the present findings is that for the first time we identify a physiological fingerprint of a part of the premotor cortex, which up to now has been considered as non-eloquent, in terms of direct physiological responses to TMS.

4.2. MEP-independent contralateral SPs are spatially dissociated from MEPs

We propose that the SPs described here are a different entity from the MEP-associated SPs that are commonly described following MEPs. We base this statement on anatomical and functional grounds. The hotspot for eliciting MEP-independent SPs was located in the ventral anterior portion of the precentral gyrus, around the intersection between the precentral sulcus and the inferior frontal sulcus, which was at a 51 mm Euclidean distance from the M1 hotspot for hand MEPs. However, the mere observation that SPs can be evoked from a region different from that eliciting MEPs is not sufficient to demonstrate true anatomical or functional segregation. Indeed, it is widely accepted that MEPs and MEP-dependent SPs are generated by different mechanisms, and some reports in the literature also claim that MEP-associated SP might be elicited at a lower threshold than the MEP itself directly from the hand-associated M1 [23]. Thus, the apparent presence of an SP-only region at the periphery of the MEP area could simply reflect current spread and threshold effects rather than distinct functional localization. The control experiment performed on eight participants showed that the MEP-associated SP does not have a lower threshold of elicitation compared to the MEP, and therefore, the premotor MEP-independent SPs are not likely due to current spread to M1. The spatial localization of the area from which a SP could be evoked was significantly variable between individuals, ranging from 1 spot to 7 spots per subject. We interpret such variability in terms of stimulus intensity and current spread to the cortices that generate the MEP and the SP, similarly to how MEPs were obtained in some participants over an extended frontal and parietal region due to current spread to M1 (see, for example, [39]). On the other hand, the presence of an MEP masks the possible presence of a MEP-independent SP, and not vice-versa. Therefore, the extent of the area from which a SP can be elicited depends on current spread to the precentral gyrus (the SP hotspot) but also, critically, on current spread to M1 (the MEP hotspot).

4.3. Comparison to previous literature on non-invasive stimulation

Our findings resonate with the early observations of Wassermann and colleagues [26], who first described silent periods occurring without preceding MEPs. Both studies report short-latency inhibitory phenomena (mean onset ≈ 27 ms in Wassermann et al. vs. ≈ 37 ms in our cohort) with relatively brief durations and often incomplete suppression of EMG activity, occasionally followed by a late excitatory rebound. Importantly, both studies demonstrate that these events are not ubiquitous but arise from selective cortical loci, supporting the notion that inhibitory silent periods and excitatory MEPs reflect distinct physiological substrates. However, several differences distinguish our work from this earlier report. Methodologically, we employed individual MRI-guided neuronavigation in a larger cohort (n = 17), systematically covering the entirety of the ventral parietal, central, and frontal regions with a dense grid of stimulation points. Topographically, our data indicate a specific anatomical hotspot for MEP-independent SPs in the anterior precentral gyrus near and above the inferior frontal sulcus, which is consistent with the scalp positions of the previous findings by Wassermann et al. (1993). Davey et al. [23] described the systematic presence of a low-threshold silent period not preceded by MEPs, in the same coil position that optimally evoked MEPs at higher intensities. However, the coil that was used was a 90 mm circular coil positioned laterally over the hemisphere and therefore stimulation was not focal, and therefore fully compatible with direct stimulation of the inferior frontal gyrus.

Although direct online stimulation of NMAs with TMS is not efficient in eliciting SPs, alternative techniques such as dual-coil TMS have consistently shown that extra-M1 cortical regions exert an inhibitory effect on corticospinal output [40–46]. In several dual-coil TMS experiments, conditioning stimuli have been applied to the ventral premotor cortex, in close proximity to the SP hotspot found in the present data, showing short-latency inhibitory effects on corticospinal excitability to hand muscles at rest [40,47–50]. Such dual-coil findings are strongly supportive of the indirect origin of the SPs observed in the present work.

4.4. Coherence of current findings with intraoperatively defined NMAs

The spatial location of the MEP-independent SP shows striking concordance with the distribution of NMRs reported in previous intraoperative mapping studies. NMAs are found in several distinct regions across the medial and lateral surfaces of both hemispheres, with a specific focus on the supplementary motor area (SMA), pre-SMA, the entire precentral gyrus (PreCG), and the caudal inferior frontal gyrus (IFG). Rech et al. [10] focused on the precentral gyrus during awake surgery in 117 patients and reported behavioral NMRs related to upper limb function within areas 6v, 6d, and 55b of the Glasser atlas parcellation of the human cerebral cortex, a distribution that is highly consistent with our findings. Recent intraoperative works have emphasized that NMRs are not limited to behavioral arrest phenomena but can also be captured through the analysis of electromyographic (EMG) patterns, which may uncover distinct underlying neural substrates [4,9,51]. Viganò et al. [51] provided a cortical surface probability-density map of hand NMRs, integrating data from three independent series [4,52,53]. Their analysis revealed a maximal density of NMRs in the dorsal premotor cortex, particularly near the junction with the inferior frontal gyrus—a distribution highly superimposable on the cluster of MEP-independent SPs described in our cohort. The differentiation between dorsal and ventral premotor contributions, as characterized by Fornia et al. [4], further enriches this interpretation. Their EMG-based analyses demonstrated that dorsal premotor sites were preferentially associated with recruitment effects and corticomotoneuronal circuit activation, whereas ventral premotor sites were more commonly linked to suppression

effects, suggesting a functional specialization for motor execution and sensorimotor integration that is fully compatible with the present results. The robustness of this spatial convergence across studies using distinct methodological approaches (behavioral vs. EMG vs. SP analysis) strongly suggests that the anterior precentral gyrus and adjacent premotor areas constitute a reproducible NMA.

4.5. Possible functional interpretation

The current data do not allow for an interpretation of the functional role of the neural system that, when activated by TMS, produces the SP in the ongoing voluntary contraction. The region of the precentral gyrus around the precentral-inferior frontal sulcus junction is located within the ventral premotor cortex (PMv), which is a pivotal node in parieto-frontal circuits controlling goal-directed upper limb movements. The role of the PMv is to translate the multisensory representations of objects and space built up in the parietal cortex into complex motor plans. More specifically, the premotor region at the level of the inferior frontal junction has been implicated in the direct control of hand movements, as shown by several TMS studies that demonstrated its direct connections to M1, carrying relevant information for object-directed actions [40,47–49]. The SP hotspot is also in close proximity to the inferior frontal junction, a region hypothesized to be a critical cortical hub for cognitive control, integrating information from attentional and motor systems. It enables flexible, goal-directed behavior by mediating processes such as task switching, response inhibition, and updating working memory. Its activity is crucial for rapidly adjusting behavior in response to changing environmental demands and internal goals [54,55].

The precentral cortex could exert its influence on spinal motor neurons to produce the SP by three mechanisms: either directly via corticospinal projections or indirectly via cortico-cortical projections to M1 or through cortico-basal ganglia-cortical loops. The current data do not allow us to discern between these three possibilities, though the long onset latency of the SPs and the considerable jitter in their onset time make a direct corticospinal effect unlikely (though do not exclude it). The indirect pathway through M1 is also favoured by current models of premotor function in primates that postulate a cortico-cortical pathway to M1 as the main mechanism by which the PMv produces actual movement [49,56,57]. The current findings are not sufficient to hypothesize a specific functional role for the SP phenomenon, because of the simplicity of the behavior tested (isometric contraction of the index finger and thumb) and the lack of control tasks. However, we should resist the simplistic interpretation that a negative phenomenon (the EMG inhibition) necessarily indicates an inhibitory function of the underlying neural system. As a matter of fact, TMS evokes non-physiological neural activity that commonly produces “loss of function” effects, with variable impacts on behavior.

4.6. Ipsilateral responses: MEP-dependent and MEP-independent SPs

Bilateral recordings of hand muscles allowed us to evaluate evoked responses ipsilateral to the stimulated hemisphere. We observed the expected ipsilateral SPs [20,33,58], which are considered an expression of transcallosal inhibitory connections between the two primary motor cortices and are necessarily associated with a contralateral MEP [33]. Indeed, we found that most TMS spots that produced an MEP were associated with an ipsilateral SP. However, we also found ipsilateral MEP-independent SPs, which were always associated with contralateral MEP-independent SPs. In no recordings did we find “standalone” ipsilateral SPs that were independent of contralateral responses. The topography of the hotspot for ipsilateral MEP-independent SPs overlapped with that of the contralateral MEP-independent SP on the ventral precentral gyrus. Taken together, these results show that the MEP-independent response was mainly contralateral but sometimes bilateral, associated with a less consistent ipsilateral inhibitory response. This finding is in agreement with data on NMRs obtained by invasive stimulation, which seem to be more lateralized to the contralateral hand when elicited by stimulation of the precentral gyrus [13].

4.7. Late-onset contralateral MEPs

Fig. 7 clearly illustrates that the contralateral excitatory responses (MEPs) belonged to two different categories according to their onset latency: the early-onset MEPs, compatible with the activation of fast corticospinal axons, were the vast majority of evoked positive responses. However, a second class of MEPs became apparent, with a latency that was incompatible with normal fast corticospinal conduction from M1 (i.e., >23 ms, as per Groppa et al. [32]). Late MEPs were uncommon events and, probably due to their low frequency, failed to show a distinct overlap hotspot. This finding in the context of the current experiment is serendipitous and requires better definition in further explorations. It should be noted that one possible source of these MEPs is the direction of the induced current with respect to the underlying gyral anatomy. It is known that stimuli with anterior-posterior induced currents generate MEPs that have shorter latencies compared to posterior-anterior currents over the central sulcus [59,60], due to preferential activation of the I1 or of later I-waves in the motor cortex. This finding, in addition to the fact that we did not find a specific topography of late-onset MEPs, but rather these were found all around the motor cortex, could indicate that these may be due to geometrical interaction of the current with the motor cortex rather than to activation of a separate corticospinal system.

4.8. Limitations of the study

One possible source of noise in the present data is that the coordinates of the stimulated spots were calculated based on a geometrical procedure, at the intersection between the line perpendicular to the coil plane, passing from the focus and the brain surface. It is well documented that, due to the anisotropy of the brain tissue, the maximum electrical field (e-field) may be slightly offset with respect to the geometrical projection point [61]. The offset however, is not systematic and depends strictly on the geometry of the underlying circuit. A second limitation regards the control experiment on M1 failed to show the occurrence of MEP-independent SP, in any of the two muscles, when the M1 hotspot was targeted. However, the literature has shown that when mapping the cortex around M1, a slight offset between the sites that most efficiently elicit an MEP and those that most efficiently elicit an SP [25]. Therefore, the lack of dissociation between MEP and SP reported in the present paper could be actually due to not having systematically explored the cortex adjacent to M1.

5. Conclusions

In this study, we describe MEP-independent SPs evoked by TMS. They consist of a transient inhibition of ongoing voluntary EMG, which occurs mainly contralaterally to the stimulated hemisphere but may also appear as a bilateral, though predominantly contralateral, response. The topographic and neurophysiological characteristics of the SP indicate that they are a separate entity compared to the SP commonly observed following an MEP. These findings have potential direct clinical applications in neurosurgical planning. There is increasing attention in the neurosurgical onco-functional balance to higher-order motor functions, and NMAs are currently seen as useful brain regions to evaluate and quantify these functions. The possibility of eliciting MEP-independent SPs expands the toolbox of non-invasive brain stimulation in the study of the cortical motor system by adding the exploration of NMAs. In this respect, our results bridge a long-standing gap between non-invasive brain stimulation and intraoperative mapping. Taken together, these results open new avenues for the use of TMS in the functional mapping of NMAs, with potential implications for both basic neurophysiology and clinical practice, particularly in the context of preoperative planning for neurosurgical patients.

CRediT authorship contribution statement

Pier Paolo Berti: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Guido Barchiesi:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Methodology, Formal analysis, Conceptualization. **Mara Turri:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization. **Roberta Volpini:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Giancarlo Caschera:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Roberta Spano:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Fabio Mariotti:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Iolanda Galdi:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Paolo Cipriano Cecchi:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Andreas Schwarz:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization. **Francesco Sala:** Writing – review & editing, Writing – original draft, Conceptualization. **Christoph Griessenauer:** Writing – review & editing, Writing – original draft, Conceptualization. **Luigi Cattaneo:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

4. Acknowledgments

The authors thank the Department of Innovation, Research University and Museums of the Autonomous Province of Bozen/Bolzano for covering the Open Access publication costs.

References

[1] Filevich E, Kühn S, Haggard P. Negative motor phenomena in cortical stimulation: implications for inhibitory control of human action. Cortex 2012;48:1251–61. https://doi.org/10.1016/j.cortex.2012.04.014.
[2] Lüders HO, Lesser RP, Dinner DS, Morris HH, Wyllie E, Godoy J, et al. A negative motor response elicited by electrical stimulation of the human frontal cortex. Adv Neurol 1992;57:149–57.
[3] Penfield W, Boldrey E. Somatic motor and sensory representation in man. Brain 1937:389–443. https://doi.org/10.1093/brain/60.4.389.
[4] Fornia L, Rossi M, Rabuffetti M, Leonetti A, Puglisi G, Viganò L, et al. Direct electrical stimulation of premotor areas: different effects on hand muscle activity during object manipulation. Cerebr Cortex 2020;30:391–405. https://doi.org/10.1093/cercor/bhz139.
[5] Rubboli G, Tassinari CA. Negative myoclonus. An overview of its clinical features, pathophysiological mechanisms, and management. Neurophysiol Clin 2006;36:337–43. https://doi.org/10.1016/j.neucli.2006.12.001.
[6] Floeter MK. Cutaneous silent periods. Muscle Nerve 2003;28:391–401. https://doi.org/10.1002/mus.10447.
[7] Kofler M, Leis AA, Valls-Solé J. Cutaneous silent periods – part 1: update on physiological mechanisms. Clin Neurophysiol 2019;130:588–603. https://doi.org/10.1016/j.clinph.2019.01.002.
[8] Gündüz A, Aydın Ş, Kızıltan ME. Cutaneous silent period: a literature review. Neurological Sciences and Neurophysiology 2020;37:101. https://doi.org/10.4103/NSN.NSN_38_20.
[9] Fornia L, Rossi M, Rabuffetti M, Bellacicca A, Viganò L, Simone L, et al. Motor impairment evoked by direct electrical stimulation of human parietal cortex during object manipulation. Neuroimage 2022;248:118839. https://doi.org/10.1016/j.neuroimage.2021.118839.
[10] Rech F, Herbet G, Gaudeau Y, Mézières S, Moureau J-M, Moritz-Gasser S, et al. A probabilistic map of negative motor areas of the upper limb and face: a brain stimulation study. Brain 2019;142:952–65. https://doi.org/10.1093/brain/awz021.
[11] Mikuni N, Ohara S, Ikeda A, Hayashi N, Nishida N, Taki J, et al. Evidence for a wide distribution of negative motor areas in the perirolandic cortex. Clin Neurophysiol 2006;117:33–40. https://doi.org/10.1016/j.clinph.2005.08.021.
[12] Swann NC, Cai W, Conner CR, Pieters TA, Claffey MP, George JS, et al. Roles for the pre-supplementary motor area and the right inferior frontal gyrus in stopping action: electrophysiological responses and functional and structural connectivity. Neuroimage 2012;59:2860–70. https://doi.org/10.1016/j.neuroimage.2011.09.049.
[13] Borggraefe I, Catarino CB, Rémi J, Vollmar C, Peraud A, Winkler PA, et al. Lateralization of cortical negative motor areas. Clin Neurophysiol 2016;127:3314–21. https://doi.org/10.1016/j.clinph.2016.08.001.
[14] Ikeda A, Ohara S, Matsumoto R, Kunieda T, Nagamine T, Miyamoto S, et al. Role of primary sensorimotor cortices in generating inhibitory motor response in humans. Brain 2000;123:1710–21. https://doi.org/10.1093/brain/123.8.1710.
[15] Uematsu S, Lesser R, Fisher RS, Gordon B, Hara K, Krauss GL, et al. Motor and sensory cortex in humans: topography studied with chronic subdural stimulation. Neurosurgery 1992;31:59.
[16] Tariciotti L, Mattioli L, Viganò L, Gallo M, Gambaretti M, Sciortino T, et al. Object-oriented hand dexterity and grasping abilities, from the animal quarters to the neurosurgical OR: a systematic review of the underlying neural correlates in non-human, human primate and recent findings in awake brain surgery. Front Integr Neurosci 2024;18:1324581. https://doi.org/10.3389/fnint.2024.1324581.
[17] Giampiccolo D, Parisi C, Meneghelli P, Tramontano V, Basaldella F, Pasetto M, et al. Long-term motor deficit in brain tumour surgery with preserved intra-operative motor-evoked potentials. Brain Commun 2021;3:fcaa226. https://doi.org/10.1093/braincomms/fcaa226.
[18] Rossi M, Fornia L, Puglisi G, Leonetti A, Zuccon G, Fava E, et al. Assessment of the praxis circuit in glioma surgery to reduce the incidence of postoperative and long-term apraxia: a new intraoperative test. J Neurosurg 2019;130:17–27. https://doi.org/10.3171/2017.7.JNS17357.
[19] Kofler M, Ziemann U, Kimiskidis VK. Cortical silent period. In: Wassermann EM, Peterchev AV, Ziemann U, Lisanby SH, Siebner HR, Walsh V, editors. The Oxford handbook of transcranial stimulation. second ed. Oxford University Press; 2024. https://doi.org/10.1093/oxfordhb/9780198832256.013.12.
[20] Zazio A, Barchiesi G, Ferrari C, Marcantoni E, Bortoletto M. M1-P15 as a cortical marker for transcallosal inhibition: a preregistered TMS-EEG study. Front Hum Neurosci 2022;16:937515. https://doi.org/10.3389/fnhum.2022.937515.
[21] Chen R, Lozano AM, Ashby P. Mechanism of the silent period following transcranial magnetic stimulationEvidence from epidural recordings. Exp Brain Res 1999;128:539–42. https://doi.org/10.1007/s002210050878.
[22] Stetkarova I, Kofler M. Differential effect of baclofen on cortical and spinal inhibitory circuits. Clin Neurophysiol 2013;124:339–45. https://doi.org/10.1016/j.clinph.2012.07.005.
[23] Davey NJ, Romaiguère P, Maskill DW, Ellaway PH. Suppression of voluntary motor activity revealed using transcranial magnetic stimulation of the motor cortex in man. J Physiol 1994;477:223–35. https://doi.org/10.1113/jphysiol.1994.sp020186.
[24] Kallioniemi E, Säisänen L, Könönen M, Awiszus F, Julkunen P. On the estimation of silent period thresholds in transcranial magnetic stimulation. Clin Neurophysiol 2014;125:2247–52. https://doi.org/10.1016/j.clinph.2014.03.012.
[25] Pitkänen M, Kallioniemi E, Julkunen P. Extent and location of the excitatory and inhibitory cortical hand representation maps: a navigated transcranial magnetic stimulation study. Brain Topogr 2015;28:657–65. https://doi.org/10.1007/s10548-015-0442-6.
[26] Wassermann EM, Pascual-Leone A, Valls-Solé J, Toro C, Cohen LG, Hallett M. Topography of the inhibitory and excitatory responses to transcranial magnetic stimulation in a hand muscle. Electroencephalogr Clin Neurophysiol 1993;89:424–33. https://doi.org/10.1016/0168-5597(93)90116-7.
[27] Rossi S, Antal A, Bestmann S, Bikson M, Brewer C, Brockmöller J, et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: expert guidelines. Clin Neurophysiol 2021;132:269–306. https://doi.org/10.1016/J.CLINPH.2020.10.003.
[28] Rorden C, Brett M. Stereotaxic display of brain lesions. Behav Neurol 2000;12:191–200. https://doi.org/10.1155/2000/421719.
[29] Oostenveld R, Fries P, Maris E, Schoffelen J-M. FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput Intell Neurosci 2011;2011:156869. https://doi.org/10.1155/2011/156869.
[30] Türker KS, Powers RK. Black box revisited: a technique for estimating postsynaptic potentials in neurons. Trends Neurosci 2005;28:379–86. https://doi.org/10.1016/j.tins.2005.05.007.
[31] Amunts K, Mohlberg H, Bludau S, Zilles K. Julich-brain: a 3D probabilistic atlas of the human brain's cytoarchitecture. Science 2020;369:988–92. https://doi.org/10.1126/science.abb4588.
[32] Groppa S, Oliviero A, Eisen A, Quartarone A, Cohen LG, Mall V, et al. A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee. Clin Neurophysiol 2012;123:858–82. https://doi.org/10.1016/j.clinph.2012.01.010.
[33] Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD. Interhemispheric inhibition of the human motor cortex. J Physiol 1992;453:525–46. https://doi.org/10.1113/JPHYSIOL.1992.SP019243.
[34] Bortoletto M, Bonzano L, Zazio A, Ferrari C, Pedullà L, Gasparotti R, et al. Asymmetric transcallosal conduction delay leads to finer bimanual coordination. Brain Stimul 2021;14:379–88. https://doi.org/10.1016/j.brs.2021.02.002.

[35] Wassermann EM, Fuhr P, Cohen LG, Hallett M. Effects of transcranial magnetic stimulation on ipsilateral muscles. Neurology 1991;41. https://doi.org/10.1212/WNL.41.11.1795. 1795–1795.
[36] Maitland S, Baker SN. Ipsilateral motor evoked potentials as a measure of the reticulospinal tract in age-related strength changes. Front Aging Neurosci 2021;13. https://doi.org/10.3389/fnagi.2021.612352.
[37] Alagona G, Delvaux V, Gérard P, De Pasqua V, Pennisi G, Delwaide PJ, et al. Ipsilateral motor responses to focal transcranial magnetic stimulation in healthy subjects and acute-stroke patients. Stroke 2001;32:1304–9. https://doi.org/10.1161/01.str.32.6.1304.
[38] Cattaneo L, Macaluso GM, Pavesi G. Inhibitory reflexes in human perioral facial muscles: a single-motor unit study. Clin Neurophysiol 2007;118:794–801. https://doi.org/10.1016/j.clinph.2006.12.007.
[39] Holmes NP, Di Chiaro NV, Crowe EM, Marson B, Göbel K, Gaigalas D, et al. Transcranial magnetic stimulation over supramarginal gyrus stimulates primary motor cortex directly and impairs manual dexterity: implications for TMS focality. J Neurophysiol 2024;131:360–78. https://doi.org/10.1152/jn.00369.2023.
[40] Maule F, Barchiesi G, Brochier T, Cattaneo L. Haptic working memory for grasping: the role of the parietal operculum. Cerebr Cortex 2015;25:528–37. https://doi.org/10.1093/cercor/bht252.
[41] Byblow WD, Coxon JP, Stinear CM, Fleming MK, Williams G, Müller JFM, et al. Functional connectivity between secondary and primary motor areas underlying hand–foot coordination. J Neurophysiol 2007;98:414–22. https://doi.org/10.1152/jn.00325.2007.
[42] Civardi C, Cantello R, Asselman P, Rothwell JC. Transcranial magnetic stimulation can be used to test connections to primary motor areas from frontal and medial cortex in humans. Neuroimage 2001;14:1444–53. https://doi.org/10.1006/nimg.2001.0918.
[43] Koch G, Olmo MFD, Cheeran B, Schippling S, Caltagirone C, Driver J, et al. Functional interplay between posterior parietal and ipsilateral motor cortex revealed by twin-coil transcranial magnetic stimulation during reach planning toward contralateral space. J Neurosci 2008;28:5944–53. https://doi.org/10.1523/JNEUROSCI.0957-08.2008.
[44] Mars RB, Klein MC, Neubert FX, Olivier E, Buch ER, Boorman ED, et al. Short-latency influence of medial frontal cortex on primary motor cortex during action selection under conflict. J Neurosci 2009;29:6926–31. https://doi.org/10.1523/JNEUROSCI.1396-09.2009.
[45] Parmigiani S, Barchiesi G, Cattaneo L. The dorsal premotor cortex exerts a powerful and specific inhibitory effect on the ipsilateral corticofacial system: a dual-coil transcranial magnetic stimulation study. Exp Brain Res 2015;233:3253–60. https://doi.org/10.1007/s00221-015-4393-7.
[46] Parmigiani S, Zattera B, Barchiesi G, Cattaneo L. Spatial and temporal characteristics of set-related inhibitory and excitatory inputs from the dorsal premotor cortex to the ipsilateral motor cortex assessed by dual-coil transcranial magnetic stimulation. Brain Topogr 2018. https://doi.org/10.1007/s10548-018-0635-x.
[47] Bäumer T, Schippling S, Kroeger J, Zittel S, Koch G, Thomalla G, et al. Inhibitory and facilitatory connectivity from ventral premotor to primary motor cortex in healthy humans at rest–a bifocal TMS study. Clin Neurophysiol 2009;120:1724–31. https://doi.org/10.1016/j.clinph.2009.07.035.
[48] Cattaneo L, Barchiesi G. Transcranial magnetic mapping of the short-latency modulations of corticospinal activity from the ipsilateral hemisphere during rest. Front Neural Circ 2011;5:1–13. https://doi.org/10.3389/fncir.2011.00014.
[49] Davare M, Montague K, Olivier E, Rothwell JC, Lemon RN. Ventral premotor to primary motor cortical interactions during object-driven grasp in humans. Cortex 2009;45:1050–7. https://doi.org/10.1016/J.CORTEX.2009.02.011.
[50] de Beukelaar TT, Alaerts K, Swinnen SP, Wenderoth N. Motor facilitation during action observation: the role of M1 and PMv in grasp predictions. Cortex 2016;75:180–92. https://doi.org/10.1016/j.cortex.2015.11.009.
[51] Viganò L, Howells H, Fornia L, Rossi M, Conti Nibali M, Puglisi G, et al. Negative motor responses to direct electrical stimulation: behavioral assessment hides different effects on muscles. Cortex 2021;137:194–204. https://doi.org/10.1016/j.cortex.2021.01.005.
[52] Simone L, Fornia L, Viganò L, Sambataro F, Rossi M, Leonetti A, et al. Large scale networks for human hand-object interaction: functionally distinct roles for two premotor regions identified intraoperatively. Neuroimage 2020;204:116215. https://doi.org/10.1016/j.neuroimage.2019.116215.
[53] Viganò L, Fornia L, Rossi M, Howells H, Leonetti A, Puglisi G, et al. Anatomo-functional characterisation of the human "hand-knob": a direct electrophysiological study. Cortex 2019;113:239–54. https://doi.org/10.1016/j.cortex.2018.12.011.
[54] Brass M, Derrfuss J, Forstmann B, Von Cramon DY. The role of the inferior frontal junction area in cognitive control. Trends Cognit Sci 2005;9:314–6. https://doi.org/10.1016/j.tics.2005.05.001.
[55] Derrfuss J, Brass M, Von Cramon DY, Lohmann G, Amunts K. Neural activations at the junction of the inferior frontal sulcus and the inferior precentral sulcus: interindividual variability, reliability, and association with sulcal morphology. Hum Brain Mapp 2009;30:299–311. https://doi.org/10.1002/hbm.20501.
[56] Cattaneo L, Voss M, Brochier T, Prabhu G, Wolpert DM, Lemon RN. A cortico-cortical mechanism mediating object-driven grasp in humans. Proc Natl Acad Sci USA 2005;102:898–903. https://doi.org/10.1073/pnas.0409182102.
[57] Shimazu H, Maier MA, Cerri G, Kirkwood PA, Lemon RN. Macaque ventral premotor cortex exerts powerful facilitation of motor cortex outputs to upper limb motoneurons. J Neurosci 2004;24:1200–11. https://doi.org/10.1523/JNEUROSCI.4731-03.2004.
[58] Chen R, Yung D, Li J-Y. Organization of ipsilateral excitatory and inhibitory pathways in the human motor cortex. J Neurophysiol 2003;89:1256–64. https://doi.org/10.1152/jn.00950.2002.
[59] Sakai K, Ugawa Y, Terao Y, Hanajima R, Furubayashi T, Kanazawa I. Preferential activation of different I-waves by transcranial magnetic stimulation with a figure-of-eight-shaped coil. Exp Brain Res 1997;113:24–32. https://doi.org/10.1007/BF02454139. 113:1 1997.
[60] Di Lazzaro V, Oliviero A, Saturno E, Pilato F, Insola A, Mazzone P, et al. The effect on corticospinal volleys of reversing the direction of current induced in the motor cortex by transcranial magnetic stimulation. Exp Brain Res 2001;138:268–73. https://doi.org/10.1007/s002210100722.
[61] De Lucia M, Parker GJM, Embleton K, Newton JM, Walsh V. Diffusion tensor MRI-based estimation of the influence of brain tissue anisotropy on the effects of transcranial magnetic stimulation. Neuroimage 2007;36:1159–70. https://doi.org/10.1016/j.neuroimage.2007.03.062.