Brain Stimulation 12 (2019) 693–701

Contents lists available at ScienceDirect

Brain Stimulation

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

Hand perceptions induced by single pulse transcranial magnetic stimulation over the primary motor cortex

Matteo Franza [a, b, c], Giuliana Sorrentino [a, b, c], Matteo Vissani [d], Andrea Serino [d], Olaf Blanke [a, b, c, e, 1], Michela Bassolino [a, b, c, *, 1]

[a] *Center for Neuroprosthetics, School of Life Science, Swiss Federal Institute of Technology (Ecole Polytechnique Fédérale de Lausanne), Campus Biotech, Geneva, Switzerland*
[b] *Laboratory of Cognitive Neuroscience, Brain Mind Institute, School of Life Science, Swiss Federal Institute of Technology (Ecole Polytechnique Fédérale de Lausanne), Campus Biotech, Geneva, Switzerland*
[c] *Center for Neuroprosthetics, School of Life Science, Swiss Federal Institute of Technology (Ecole Polytechnique Fédérale de Lausanne), Campus SUVA, Sion, Switzerland*
[d] *MySpace Lab, Department of Clinical Neuroscience, Centre Hospitalier Universitaire Vaudois (CHUV), Switzerland*
[e] *Department of Neurology, University Hospital Geneva, Switzerland*

A R T I C L E I N F O

Article history:
Received 11 April 2018
Received in revised form
20 December 2018
Accepted 21 December 2018
Available online 23 December 2018

Keywords:
Transcranial magnetic stimulation (TMS)
Primary motor cortex
Motor evoked potentials
TMS-evoked movements
TMS-evoked hand perceptions
Absolute threshold

A B S T R A C T

Background: When single pulse transcranial magnetic stimulation (TMS) is applied over the primary motor cortex (M1) with sufficient intensity, it evokes muscular contractions (motor-evoked potentials, MEPs) and muscle twitches (TMS-evoked movements). Participants may also report various hand sensations related to TMS, but the perception elicited by TMS and its relationship to MEPs and evoked movements has not been systematically studied.
Objective: The main aim of this work is to evaluate participants' kinesthetic and somatosensory hand perceptions elicited by single-pulse TMS over M1-hand area at different intensities of stimulation and their relation with MEPs and TMS-evoked movements.
Methods: We compared the number of MEPs (measured by electromyography), TMS-evoked movements (measured by an accelerometer) and participants' hand perception (measured by verbal report) elicited by TMS at different intensity of stimulation. This way, we estimated the amplitude of MEPs and the acceleration of TMS-evoked movements sufficient to trigger TMS evoked hand perceptions.
Results: We found that TMS-evoked hand perceptions are induced at 105% of the individual resting motor threshold, a value significantly different from the threshold inducing MEPs (about 100%) and TMS-evoked movements (about 110%). Our data indicate that only MEPs with an amplitude higher than 0.62 mV and TMS-evoked movements with acceleration higher than 0.42 m/s2 were associated with hand perceptions at threshold.
Conclusions: Our data reveal the main features of TMS-evoked hand perception and show that in addition to MEPs and TMS-evoked movements, this is a separate discernible response associated to single-pulse TMS over M1.

Introduction

Single-pulse transcranial magnetic stimulation (TMS) over the primary motor cortex (M1) has been extensively used to study the functional organization and the plasticity of the corticospinal motor system [1–5]. When single pulse TMS is applied over primary motor cortex, different corticospinal volleys are elicited and can be measured [6]. At the cortical level, a first descending volley is called direct wave and it is generated by fast-conducting pyramidal tract neurons and is followed by later volleys (indirect waves) mainly reflecting the transynaptic activation of pyramidal tract neurons. Spinal cord mechanisms are also recruited, involving spinal motor neurons. This cascade of events is classically evaluated at its bottom end by using motor-evoked potentials (MEPs) recorded through

* Corresponding author. School of Life Science, Swiss Federal Institute of Technology (Ecole Polytechnique Fédérale de Lausanne), Campus Biotech, Geneva, Switzerland.
E-mail address: michela.bassolino@epfl.ch (M. Bassolino).
[1] These authors contributed equally to the work.

https://doi.org/10.1016/j.brs.2018.12.972
1935-861X/

electromyography from contralateral muscles of upper or lower limbs.

Based on many studies, broadly accepted guidelines have been established [7,8]. Thus, MEPs are defined as muscular twitches characterized by liminal electromyographic (EMG) activity (peak-to-peak amplitude of 0.05 mV) and specific latencies depending on the addressed muscles, leading, for instance, to shorter latencies for the hand than for leg muscles [7]. MEP amplitude can be modulated by motor [9–11], sensory and cognitive processes. For instance, action observation/motor imagery [12,13] or stimuli presented within the peripersonal space [14–16] has been shown to increase MEP amplitude, whereas immobilization [17,18] or peripheral nerve block [19] decreases MEP amplitude. Thus, MEP amplitude is a crucial parameter to measure corticospinal excitability in a variety of experimental protocols (e.g. motor mapping, recruitment curves, [4,20–22]), with a large range of applications in clinical and experimental studies [6,23,24].

In addition, single pulse TMS over M1 has also consistently been shown to induce rapid involuntary movements in the contralateral limb (i.e. TMS-evoked movements). TMS-evoked movements have been typically measured by attaching accelerometers to the fingers and hand [10,16] or by using glove-embedded sensors [25,26]. These are smaller in amplitude and typically shorter than a passive movement [25]. Next to MEPs, TMS-evoked movements have also been used to study the functional organization of the motor system, for example after intensive motor training [11] or during action observation [27].

In the TMS field, specific parameters have been identified to quantify MEPs and TMS-evoked movements and facilitate the comparison among studies. For instance, the “resting motor threshold” (rMT) indicates the minimum intensity to elicit an MEP in a target muscle in half of the administered trials for a given participant at rest [7,28]. Similarly, a threshold value related to the amplitude of the recorded acceleration has also been proposed to discern actual TMS-evoked movements of the hand from signal noise (e.g. 0.09 m/s^2 in Classen et al., 1998 [10]).

Moreover, TMS-induced activation of the corticospinal motor tract may also elicit hand sensations (here called TMS-evoked hand perceptions), previously reported in seminal studies as sensations like “paraesthesias”, “tingling”, “kinesthesia” or “touch” [29–31].

However, while MEPs and TMS-evoked movements have been widely studied, leading to accepted guidelines, TMS-evoked hand perceptions were mostly neglected apart from few studies approaching this topic in amputee patients [32–34] or in healthy participants with protocols based on one specific intensity of stimulation [35,36], on anesthetic block [30,37–39], or on repetitive TMS (e.g. [37]). Systematically measuring TMS-evoked hand perceptions in healthy participants under standard conditions would be important to quantify the physiology and variety of TMS effects and investigate whether such subjective sensations following TMS over M1 lead to reliable responses.

Here we specifically investigate the occurrence of TMS-evoked hand perceptions in healthy participants after single pulse TMS administered over the dominant hand area in M1 and at different stimulation intensities. With respect to previous studies [29–31,37], we adopted a standardized protocol and a bigger sample size allowing to apply robust statistical approaches to investigate the relationship between the subjective evoked hand perceptions and objective outcomes of the TMS such as MEPs and TMS-evoked movements. We expected that M1 stimulation, at intensities that are higher than those evoking MEPs and movements, would also induce TMS-evoked hand perceptions. Moreover, we aim at investigating the exact relation between MEPs, movements, and hand perceptions. For this, we used two different approaches. First, we compared the number of MEPs, movements, and hand perceptions evoked at different intensities of M1 stimulation and, secondly, we determined the intensity necessary to elicit each response in at least half of the administered trials (absolute thresholds and logistic curve fitting). Finally, we determined the minimal amplitude of MEPs and the minimal acceleration of TMS-evoked movements sufficient to elicit TMS-evoked hand perceptions.

Methods and materials

Subjects

23 subjects took part in the study (mean age 27.1 ± 3.2 years, 13 females). All of them were right-handed, as determined by the Flinders Handedness survey [39]. No one showed any contraindication to TMS [40,41]. Participants were naive to the purpose of the study and participated after giving an informed consent. The study was conducted with the approval of the local ethics committee (PB_2016–02541, CCVEM 017/14). In a subgroup of subjects (7 participants out of the total included 23 subjects), we asked participants to specify if the reported TMS-evoked hand perception corresponded mainly to kinesthetic, somatosensory or mixed sensations (see Supplementary Materials, Fig. 1) and we further recorded TMS-evoked movements by a second accelerometer placed on the index finger (see below and Supplementary Materials, Fig. 2).

TMS and recording procedure

Subjects were seated in a chair (Brainsight, Rogue Research) with their arms resting in a prone position on a table (elbow flexion of about 90°). TMS was delivered through a figure-eight coil (wing diameter: 70 mm) connected to a single Magstim monophasic stimulator (Magstim 200^2, Magstim Co., Whitland, UK) as described previously [42]. The coil was placed tangentially to the scalp with the handle pointing backward and laterally at a 45° angle to the sagittal plane inducing a posteroanterior current in the brain [43,44]. In order to determine the optimal position for activation of the right First Dorsal Interosseus (FDI) muscle (hotspot), the coil was initially positioned 5 cm lateral and 1 cm anterior to the vertex over the left hemisphere [7]. Then, TMS pulses slightly above threshold intensity levels (45% of the maximal stimulator output, MSO) were applied by moving the coil in 0.5 cm steps around this initial estimate (around 5 pulses for each stimulated point). The hotspot was defined as the point over the scalp from which the largest and more stable MEPs were observed. The position of the hotspot was marked on the scalp with a pen and was carefully checked by the experiment to ensure the correct coil placement throughout the experiment. Resting motor threshold (rMT) of FDI muscle was determined according to standard procedure by using the software based 'adaptive method' developed by Awiszus et al., 2003 (TMS Motor Threshold Assessment Tool, http://www.clinicalresearcher.org/software.htm) [7].

MEPs were recorded by means of a surface EMG system through wireless electrodes positioned on the FDI in a tendon-belly configuration on both hands. EMG signals were amplified and bandpass filtered (1 Hz-1kHz) by a Noraxon DTS amplifier (Velamed, GmbH, Köln, Germany). The signals were sampled at 3000 Hz, digitized using a laboratory interface (Power1401; Cambridge Electronics Design CED), and stored on a personal computer for display and later off-line data analysis (Signal and Matlab software). Each recording epoch lasted 1500 ms, from −300 ms before to 1200 ms after the TMS pulse. Trials with EMG background activity (>0.05 mV) preceding the TMS pulse of 100 ms in the stimulated or the non-stimulated hand were excluded from the present

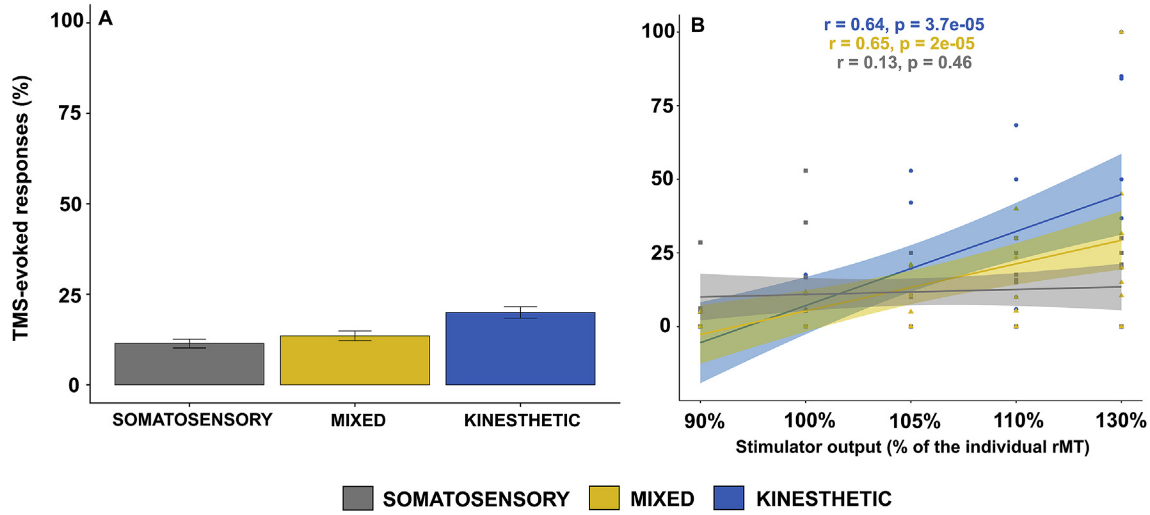

Fig. 1. *Qualitative report of TMS-evoked hand perceptions.* TMS-evoked hand perceptions respectively referred as kinesthetic (blue), somatosensory (grey) or mixed (yellow) sensations are here expressed as percentage of total administered pulses (A) or as a function of the intensities of stimulation (B). See Supplementary Materials for a detailed description of the procedure and the results. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

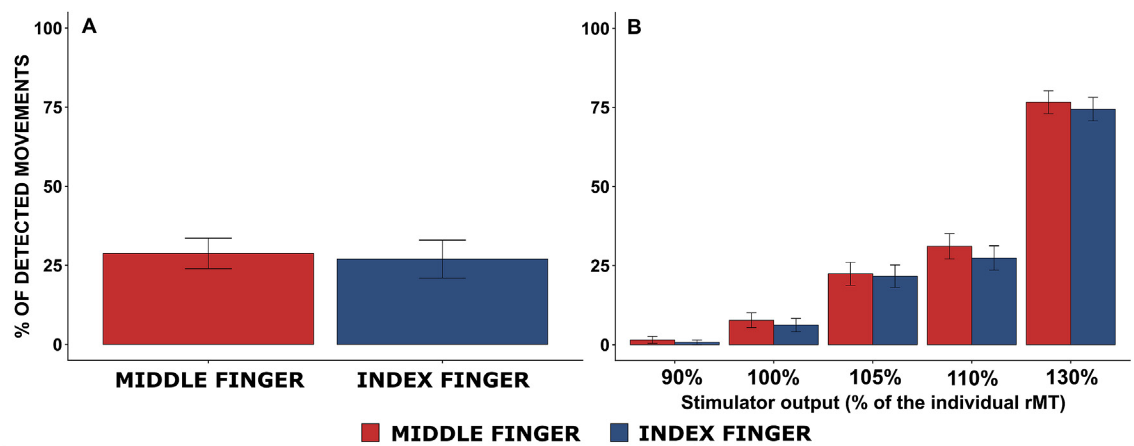

Fig. 2. *TMS-evoked movements as a function of the placement of the accelerometer.* TMS-evoked movements recorded from the accelerometer placed over the middle finger knuckle (red) and from the accelerometer placed on the metacarpal bone of the index finger (blue) expressed as percentage of total administered pulses (A) or divided for each stimulation intensity (B). See Supplementary Materials for a detailed description of the procedure and the results. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

analysis in order to avoid possible biases ascribable to uncontrolled MEPs facilitation [23,45,46].

In addition to the EMG data, we also recorded movements evoked by the TMS pulse (TMS-evoked movements) through a 3-dimensional accelerometer (Noraxon Sensors DTS 3D Accelerometer) fixed over the middle finger knuckle (but see the comparison with a second accelerometer placed on the index finger, Fig. 2, Supplementary results 2). Data were acquired for the 3 separate axes (x, y, z) at the same sampling frequency of the EMG, were filtered (0.4 Hz–100 Hz) and analyzed by a custom-made software written in MATLAB (MATLAB R2016b), following methods already proposed in previous works [10,16,42]. The acceleration modulus was first computed for a 200 ms window starting from TMS delivery. We then calculated the acceleration onset as the time when 5% of the peak acceleration was detected. Trials were included in the analysis if peak acceleration appeared between 20 and 55 ms after the TMS pulse [47] and its amplitude was equal to or higher than 0.09 m/s^2 in one axis [10].

Experimental design

Participants were instructed to keep their right hand still and as relaxed as possible, palm down on table. A bandage around the wrist assured the contact between subjects' arm and the table. The position of the hand was visually checked by the co-experimenter for the entire duration of the stimulation. To standardize what participants observed during the stimulation, subjects wore a head-mounted display (Oculus rift DK1) and observed a virtual scene that consisted of a table in an otherwise empty room.

The four blocks of stimulation were separated by a 1-min break. In each block, single pulses were delivered over the left M1 hand area at 5 different intensities of stimulation in a pseudorandom sequence (20 pulses each intensity, a total of 100 pulses split into 4 blocks, each including 5 pulses per intensity) to avoid as much as possible hysteresis effects [48]. Five intensities of stimulation were used: 90%, 100%, 105%, 110% and 130% of the individual rMT (in % of maximum stimulator output). By definition, the absolute threshold for MEPs (MEPs present in half of the trials) thus corresponds to the intensity of 100% of rMT. The interval between two consecutive pulses was of a minimum of 10 s (range 10–12 s), to ensure no changes in motor cortex excitability [49,50]. To quantify the TMS-evoked hand perceptions elicited at the right hand, after each pulse, subjects were instructed to report if they had perceived "any kinesthetic or somatosensory perception including (but not limited to) contractions, movements, changes in hand position, tingling sensation, or any other perceptions at the right hand" with a yes/no answer. We chose to include any type of sensation because we wanted to avoid an underestimation of the phenomenon by just focusing on one specific sensation or to introduce any bias due to possible different perceptions evoked at different intensities of stimulation (see Supplementary results 1).

Data analysis

We separately calculated the percentage of trials in which a TMS pulse evoked (i) MEPs (peak-to-peak amplitude higher than 0.05 mV, e.g. [7]; [8]); (ii) a TMS-evoked movement (peak acceleration between 20 and 55 ms after the TMS pulse, e.g. [16,42]) with an amplitude equal to or higher than 0.09 m/s^2 [10] (iii) a TMS-evoked hand perception (i.e. "yes" response); reported by the subject regarding a kinesthetic or somatosensory perception evoked by the TMS on the hand when a MEP was present.

The occurrence of the TMS-evoked responses (MEPs, movements or hand perceptions) was calculated as a percentage of valid trials, i.e. all administered pulses (i.e. 100) after the rejection of trials with EMG background activity higher than 0.05 mV (3.1% considering the all administered stimuli among all participants). We did not include in the calculation of the TMS-evoked perceptions those trials in which participants answered "yes" but no MEPs were present (i.e. false positives, 3.4% of the total stimuli, less than 1.5% in each intensity of stimulation).

First, we compared the number of responses evoked at the different intensities of stimulation for MEPs, movements or hand perceptions expressed as a percentage of the total valid trials through a generalized linear mixed model with a logit link function on the occurrence of the evoked responses with "intensity of stimulation" (5 levels) and "type of responses" (3 levels) as within-in subject factors. This approach has been already demonstrated to be effective to treat proportional data, by overcoming the limitations of the ANOVA (e.g. [51]). To correct for multiple comparisons, we used Tukey post hoc test. Then, we determined an "absolute threshold", that is the intensity of stimulation (in % of maximum stimulator output with respect to the individual resting motor threshold) necessary to evoke each response in half of the trials (50%, chance level) by comparing the percentage of MEPs, TMS-evoked movements, and TMS-evoked hand perceptions averaged among all subjects at each stimulation intensity with respect to the chance level (one sample Wilcoxon test, Bonferroni corrected, the α value was set at 0.05 divided by the 5, i.e. five intensities of stimulation, the response was considered not different from the chance level if $p > 0.01$). See Fig. 3 for further explanation.

Second, to further analyze these aspects and compare the absolute threshold among the three TMS-evoked responses, we investigated the relation between MEPs, TMS-evoked movements, and TMS-evoked hand perceptions, by fitting logistic curves (maximum likelihood method) to each TMS-evoked response as a function of the used stimulation intensities (expressed as percentage of individual rMT). For each curve, we computed the central point defined as the point where the function crossed 50% (half of the trials, chance level); in other words, it represents the point (that is the intensity of stimulation with respect to individual rMT) where the presence or absence of the specific TMS-evoked responses was equally likely. Furthermore, we computed the "semi-

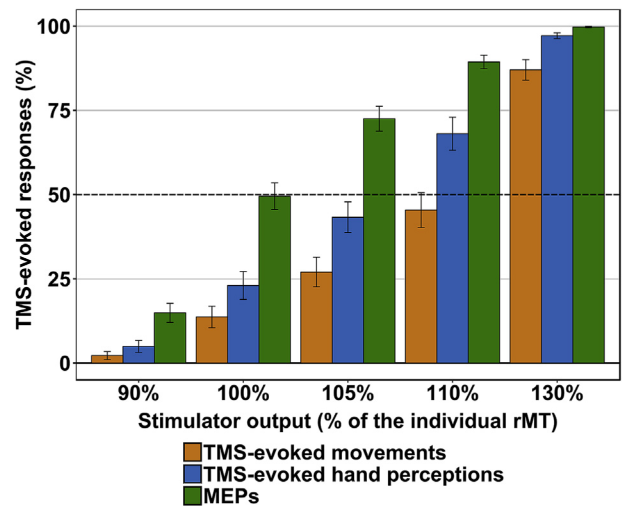

Fig. 3. *MEPs, TMS-evoked movements and hand perceptions at different intensities of stimulation.* The figure illustrates on the ordinate the percentage of evoked MEPs (green), TMS-evoked hand perceptions (blue) and TMS-evoked movements (orange) with respect to the total of valid trials (all administered trials excluded the trials with EMG background activity > 0.05). On the abscissa, the stimulus intensities are shown in term of percentage of MSO with respect to the individual rMT. The error bars indicate the standard error. The comparison against the chance level (black broken line) revealed that different intensities of stimulation are necessary to evoke MEPs, TMS-evoked movements and TMS-evoked hand perceptions at threshold. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

interquartile range" (as one half the difference between the 75th percentile and the 25th percentile) that can be interpreted as the minimum increase of the stimulation intensity (expressed as percentage of individual rMT) that makes a response detectable in half of the trials, i.e. a stimulation intensity sufficient to leap from responses rarely evoked (25% of the total administered pulses) to responses evoked at chance level (50%). Specifically, it can also be interpreted as an index of "detectability" of the three TMS-evoked responses. The present "central point" and "semi-interquartile range" correspond respectively to the point of subjective equality (PSE) and just noticeable difference (JND) of a putative psychometric function (a term not applicable here for MEPs and TMS-evoked movement because these are neurophysiological and not subjective responses). According to the results of the Shapiro-Wilk test used to check for normality, individual central point and "semi-interquartile range" were compared by means of a one-way ANOVA (main factor: TMS-evoked responses, 3 levels) or by applying the equivalent non-parametric test (Friedman test). Post hoc test was corrected for multiple comparisons (Tukey correction or Wilcoxon test Bonferroni corrected).

Finally, to explore the relationship between TMS-evoked hand perceptions and the MEP amplitude, we conducted a further analysis by fitting a psychometric curve (maximum likelihood method) for the percentage of TMS-evoked hand perceptions with respect to the MEP amplitude. This procedure enables us to estimate the MEPs amplitude necessary to reach a 50% detection rate for the hand perceptions (point of subjective equality, PSE). The same procedure was adopted to assess the relationship between TMS-evoked hand perceptions and the amplitude of the TMS-evoked movement (accelerometric data). Considering that the peak of movement acceleration was acquired in three spatial axes (x, y, z), the Euclidean norm was computed to obtain a single value representing the global hand acceleration (movement norm).

Statistical analysis, pictures and curve fitting were performed by using R Studio (R Core Team, 2017. R: a language and environment or statistical computing. R Foundation for statistical computing, Vienna, Austria. URL http://www.R-project.org/) and custom-made scripts written in MATLAB (MATLAB R2016b).

Results

Preliminary results

All participants easily completed the experiment, without any adverse effects to TMS.

All participants reported kinesthetic (e.g. muscles contractions, movements, changes in hand position or posture), somatosensory (e.g. tingling, touch sensations, pins and needles sensations) or mixed (kinesthetic + somatosensory) hand perceptions due to stimulation. No participant reported unpleasant perceptions.

In the subgroup of subjects specifically asked to specify if the reported sensation corresponds to one of the above mentioned three categories, it emerged that the judgement was influenced by the intensity of stimulation, with the percentage of kinesthetic and mixed sensations augmenting at higher intensities (see Fig. 1, Supplementary results 1). Rarely (3.4% of the total amount of trials), participants reported some TMS-evoked hand perceptions, even when no MEPs and movements were evoked ("paresthesia-like perceptions").

Moreover, in the same subgroup of subjects, the percentage of movements recorded by the accelerometer placed on the middle finger was comparable to that of movements recorded by a second additional accelerometer placed on the index finger (see Fig. 2, Supplementary results 2).

TMS-evoked responses at different intensities of stimulation

The model (generalized linear mixed model) on the percentage of evoked responses revealed an interaction between the type of response (MEPs, movements, hand perceptions) and the intensity of stimulation ($\chi2\ (15) = 3547.9$, $p < 0.001$). Post hoc (Tukey correction) showed that MEPs, TMS-evoked hand perceptions and movements increased with increasing intensities (all p values < 0.001). At the maximum intensity of stimulation (130%), the percentage of responses was equally high for MEPs and hand perceptions (all p values $= 0.14$), while these were higher than the percentage of TMS-evoked movements (both p-values $p < 0.001$). For all other intensities, the percentage of MEP was higher than that of hand perceptions and movements (all $p < 0.001$). The percentage of MEP at 100% was comparable to that of perceptions at the intensity of 105% ($p = 0.54$) and of movements at 110% ($p = 1$) (please see below the comparisons against the chance level). The percentage of hand perceptions was similar to that of evoked movements at the lowest intensity (i.e. 90% $p = 0.54$), while it was higher than the percentage of the movements at the intensity of 100%, 105% and 110% (all p values < 0.01) (Fig. 3).

The analysis of the percentage of the evoked responses with respect to chance level (absolute threshold, Wilcoxon test against the chance level, Bonferroni corrected alpha set at 0.05/5 stimulation intensities) revealed that hand perceptions were evoked in half of the trial at 105% ($Z = 81.5$, $p = 0.148$). This differed for evoked movements, which were evoked in 50% of trials at 110% of the subjective rMT ($Z = 102$, $p = 0.435$). As defined, MEPs were evoked in half of the trials (50%, chance level) when the intensity of the TMS pulse corresponded to the rMT (100%, $Z = 125$, $p = 0.974$) (Fig. 3, Table A for a summary).

Finally, we note that these results did not change if we included in the analysis the "false positives" (3.4% of the total amount of trials). The main interaction between the type of response (MEPs, movements, hand perceptions) and the intensity of stimulation remained significant ($\chi2\ (15) = 3407$, $p < 0.001$), with similar post hoc comparisons except for the percentage of hand perceptions that turned out as significant higher than that of evoked movements at the lowest intensity (i.e. 90% $p = 0.004$). Importantly, even when the false positives were included, the analysis of the percentage of the evoked responses with respect to chance level (Wilcoxon test, Bonferroni corrected) showed that hand perceptions were evoked in half of the trial at 105% ($Z = 121$, $p = 0.615$, all the other p values < 0.002).

Logistic curve fitting between TMS-evoked responses (MEPs, movements and hand perception) and TMS intensity

To investigate if the three TMS-evoked responses have different absolute thresholds, i.e. they require different intensities of stimulation to be elicited, we compared the central point for the MEPs, hand perceptions, and movements obtained by the fitting of the percentage of the evoked responses as a function of the stimulation intensities. Shapiro-Wilk test showed that all the data were normally distributed (MEPs: $p = 0.274$, TMS-evoked perceptions: $p = 0.948$, TMS-evoked movements: $p = 0.900$). One-way ANOVA revealed a significant difference among the three obtained central point values ($F\ (2,66) = 31.38$, $p < 0.001$). Post hoc comparisons (Tukey correction) showed that the mean intensity to evoke the MEPs at chance level ($M = 99.62$, $SD = 3.83$) was significantly lower than the intensity to elicit hand perceptions ($M = 106.52$, $SD = 5.66$, $p < 0.001$) and hand movements ($M = 113.80$, $SD = 8$, $p < 0.001$). Furthermore, the intensity to elicit TMS-evoked hand perceptions at chance level was lower than that used to induce movements ($p = 0.001$, Fig. 4 and see Fig. 5).

Concerning the semi-interquartile range, obtained by the same fitting of the percentage of the evoked responses as a function of the stimulation intensities, data were not normally distributed for the TMS-evoked hand perceptions (TMS-evoked perceptions $p < 0.001$). Significant differences emerged among the three responses at the Friedman test ($\chi2\ (2) = 11.217$, $p = 0.004$). Post hoc comparisons (Wilcoxon test Bonferroni corrected, alpha set at 0.05/3 comparisons) revealed lower values for the TMS-evoked hand perceptions ($p = 0.0156$) and MEPs ($p = 0.006$) with respect to TMS-evoked hand movements, while we found similar values of

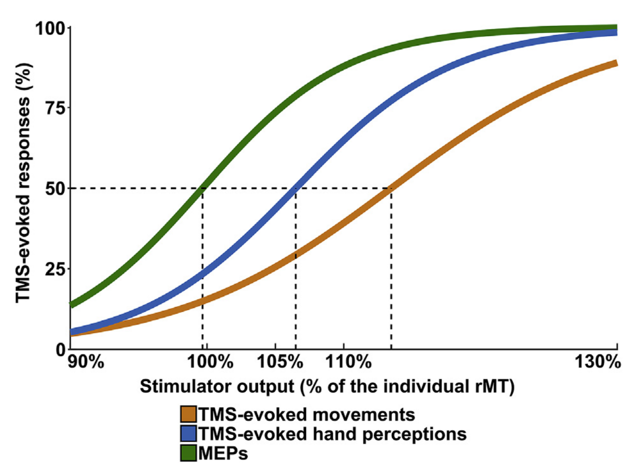

Fig. 4. *Comparison among TMS-evoked responses (MEPs, movements and hand perceptions).* The figure shows the results of the logistic curve fitting between (on the ordinate) the percentage of the evoked responses in terms of MEPs (green), TMS-evoked hand perceptions (blue) and TMS-evoked movements (orange) and (on the abscissa) the intensity of stimulation (percentage of MSO with respect to the individual rMT). TMS-evoked hand perceptions required an intensity of stimulation higher than MEPs, but lower than TMS-evoked movements to be elicited at the 50% (ANOVA on central point values). TMS-evoked movements require a bigger increase of stimulation intensity to be detected at threshold compared to the other two TMS-evoked effects (Friedman test on the semi-interquartile range). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

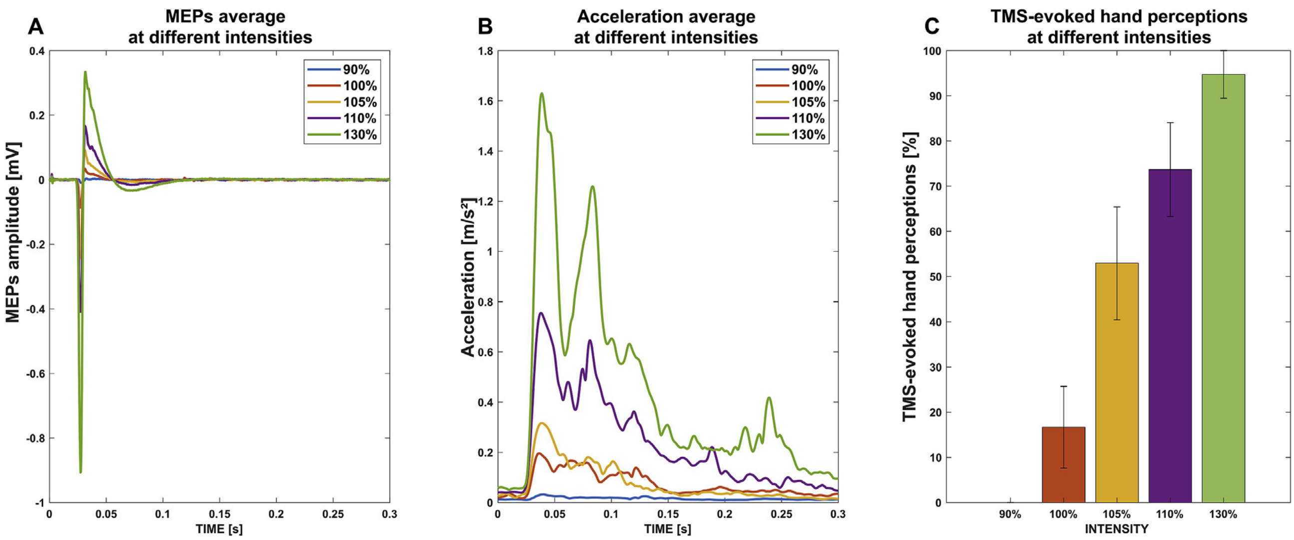

Fig. 5. *TMS-evoked responses in a representative subject*. The average MEPs amplitude (mV), acceleration profile (movement norm of the acceleration on the 3 axes, m/s^2) and percentage of reported TMS-evoked hand perceptions (%) for each intensity of stimulation (represented in different colors) in one representative subject are respectively shown in panel A, B and C. The x axis in panel A and B represents the time (s) and the zero refers to the TMS pulse. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

the semi-interquartile range between TMS-evoked hand perceptions and MEPs ($p = 1$, see Fig. 4).

Psychometric curve on the relationship between TMS-evoked subjective response (hand perception) and neurophysiological responses (MEPS and movements amplitude)

The fitting between TMS-evoked hand perceptions and MEPs amplitude revealed a PSE of 0.62 mV ($R^2 = 0.68$, JND = 0.37). This indicates that only MEPs with amplitude higher than 0.62 mV, approximately 10 times higher than the amplitude used to define a discernible MEPs (0.05 mV), induces reliable hand perceptions (Table B.1 for a summary). The same approach on the movement norm revealed a PSE of 0.42 m/s^2 ($R^2 = 0.64$, JND = 0.25). This suggests that the acceleration of a TMS-evoked movement has to be higher than 0.42 m/s^2 to elicit hand perceptions at threshold (Table B.2 for a summary).

Discussion

Main features of TMS-induced hand perception

This is the first study that systematically investigates hand perceptions elicited by TMS over M1 at different intensities of stimulation. Interestingly, a recent work quantified the number of hand movement perceptions in healthy participants after single pulse TMS over M1 at threshold [52] and used this measurement as an index of participants' ability in monitoring involuntary actions. They showed that participants' detection ability of TMS stimuli was altered by concomitant tDCS over posterior parietal cortex, suggesting that this area is involved in movement awareness during involuntary actions. Differently, here we compared subjective hand perceptions with the well-known and widely used neurophysiological TMS parameters of MEPs and TMS-evoked movements and found that different stimulation intensities are necessary to evoke TMS-evoked hand perceptions as compared to MEPs and movements. Specifically, the stimulation necessary to induce hand perceptions was ($\approx$105% of the individual rMT) between the threshold for MEPs (corresponding to the individual rMT 100% according to MEPs' definition) and TMS-evoked movements ($\approx$110%). Then, a second analysis based on logistic curve fitting on each TMS-evoked response further confirms that MEPs, hand movements and hand perceptions are associated with different stimulation intensities.

These results show that healthy participants are able to report hand perceptions after a single pulse of TMS over M1 if the stimulation is applied above the MEP threshold. It also shows that TMS-evoked hand perceptions can be dissociated from the presence of MEPs: considering only MEPs to estimate hand perceptions is not valid and would lead to an overestimation of the amount of TMS-evoked hand perceptions, given that not all the MEPs correspond to a TMS-evoked perception. Our results also differentiate TMS-evoked hand perceptions from the presence of significant TMS-evoked movements. Dependence on the latter would result in an underestimation of such subjective responses, given that hand perceptions occurred even without any recorded movements. Accordingly, we claim that TMS-evoked hand perceptions should be considered as a separate TMS-evoked response, modulated by stimulation intensity that does not correspond to the presence of MEPs or TMS-evoked movements. This suggests that hand perceptions reported by the participants were not directly linked to the amplitude of the muscular contractions or the acceleration of movements, respectively recorded by the EMG and accelerometer. We instead hypothesize that TMS-evoked hand perceptions could be mainly driven by somatosensory and kinesthetic sensations related to skin and muscle stretch, these latter likely captured by muscle spindles. In support to this, it has been recently demonstrated that differences in the firing of muscle spindle could be independent from differences in kinematics or EMG activity and could have a role in sensory forward models [53,54].

Moreover, the result that hand perceptions may arise in the absence of peripheral movements or muscle contractions is in line with previous studies using TMS [55,56] as well as direct brain stimulation in epileptic patients [57]. For instance, movement perceptions evoked by TMS have been reported in subjects undergoing ischemic block and even in the absence of MEPs [55]. In the case of invasive brain stimulation, stimulation of parietal areas elicited an illusory sense of motion, even in the absence of EMG activity, while it was reported that stimulation of premotor areas induces involuntary movements [58,59].

Finally, our data revealed another important feature of TMS-evoked hand perceptions, indicated by the semi-interquartile range, a measure of detectability obtained from the fitting between the three TMS-evoked responses and the intensities of stimulation (expressed as a percentage of individual rMT, see Fig. 4). Namely, similar semi-interquartile ranges were found between MEPs (semi-interquartile range = 5.7%) and TMS-evoked hand perceptions (semi-interquartile = 6.3%), thus suggesting that for both types of responses a small increase of intensity is sufficient to leap from responses rarely evoked (25%) to responses evoked at chance level (50%). This proposes a similar detectability between the two responses, and more precisely indicates that TMS-evoked hand perceptions are sensitive to even small changes of stimulation intensity ($\approx$6% of rMT), similarly to what we observed for MEPs. This result points out that the precision of the present verbal reports about TMS-induced hand perceptions could be comparable to well-established objective TMS measures, like MEP detection through EMG activity. This further supports the use of hand perceptions as reliable TMS-evoked responses.

The neurophysiological responses evoked by TMS: MEPS and TMS-evoked movements

We observed that even the two well-known neurophysiological responses evoked by TMS, MEPs and movements, did not fully overlap. Indeed, the intensity of stimulation to elicit TMS-evoked movements was higher than the intensity needed to induce MEPs. This is in line with previous studies reporting higher threshold for TMS-evoked movements than MEPs, both when the movements were evaluated with the accelerometer [10], as in this present study, and by means of the visual observation. In particular, previous authors [60] found that an 11.3% increase of the stimulation (expressed in % of maximum stimulator output) was necessary to determine the movement threshold, if the judgment was based on visual observation of movements instead than MEPs, a result very close to the present findings (113.47%). Moreover, a new result concerns the detectability of the TMS-evoked movements. We found that the change in stimulation intensity was higher for evoked movements (at chance level) than those found for MEPs and TMS-evoked hand perceptions, suggesting that evoked movements are less sensitive to changes in intensity. This could be considered as a methodological constraint in the design of protocols aiming at recording MEPs or TMS-evoked movements.

Finally, in a further analysis, we have evaluated the amplitude of MEPs and TMS-evoked movements necessary to induce a liminal hand perception (chance level). Surprisingly, our findings reveal that the MEP amplitude necessary to perceive a discernible TMS-evoked hand perception at threshold is $\approx$ 10 times higher than the EMG activity used to define liminal MEP detection (0.05 mV). In addition, we found that the acceleration profile of a TMS-evoked movement corresponding to hand perception is $\approx$ 5 times higher than the movement threshold differentiating movements from signal noise. These data provide new reference values linking TMS-evoked hand perceptions to the neurophysiological parameters of MEPs and TMS-evoked movements (at least in healthy young participants under similar experimental conditions). These values could have implications in single pulse TMS protocols measuring MEPs or TMS-evoked movements, in which TMS-evoked hand perception could play an important role (e.g. studies in which an unwanted difference among conditions could emerge because of different TMS-evoked hand perceptions could be elicited).

Limitations

One possible limitation of our study is that we recorded MEPs only from the FDI muscle. Thus, we cannot exclude that the presence of MEPs in more or other hand muscles would alter the estimated relationship between TMS-evoked hand perceptions and MEPs. Indeed, in our study, the presence of MEPs in any other hand muscle could lead to an underestimation of participants' abilities to report TMS-evoked hand perception with respect to MEPs, by excluding such "false positives" (reported hand perception when no MEPs at the FDI, but MEPs at other muscles were present). However, this hypothesis seems unlikely given that false positives occurred in a very low percentage of trials (3.4% of the total amount of trials) and that the results did not change if those trials were integrated in the analysis. Moreover, this aspect does not affect the results related to the TMS-evoked movements, which absolute threshold is in any case higher than the one related to hand perception. In addition, the presence of TMS-induced sensations in the absence of MEPs, is not new, being already reported by previous studies [30]. Furthermore, since the present results refer to the dominant hand, in a precise posture (e.g. palm down on the table, thus preventing closing movements against the table surface) our claims should be mainly limited to these conditions. Indeed, one could hypothesize that TMS-evoked hand perception could be affected by handedness, use, motor skills or different postures leading to other evoked movements (e.g. closing movements) or to different sensory feedback.

Conclusions

Our results showed that neurophysiological (MEPs), kinematics (TMS-evoked movements) and subjective (TMS-evoked hand perceptions) responses to TMS stimulation are three discernible components of single pulse TMS over M1. We argue that the evoked hand perceptions reported by the subjects could be based on somatosensory and kinesthetic perceptions elicited by TMS. In addition, we provide reference values in terms of stimulation intensities to elicit the three TMS-evoked responses and in terms of minimal MEPs amplitude and acceleration of TMS-evoked movements required to elicit TMS-evoked hand perceptions in young healthy participants under similar experimental conditions. The protocol described in the present work could be adopted as a simple task to study hand movement perception, but also more cognitive aspects such as body awareness or sense of agency in different experimental conditions that could specifically alter MEPs, TMS-evoked movements or perceptions. Thanks to its simplicity, the present protocol could also be theoretically applied in neurological patients with the aim of assessing sensorimotor and bodily functions.

Funding

Support for this study was provided by the Swiss National Science Foundation (SNSF), Ambizione grant to MB (PZ00P1_161210) and the Bertarelli Foundation.

Acknowledgements

We thank Javier Bello Ruiz for the development of the original version of the VR software used in this experiment.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2018.12.972.

Conflicts of interest

The authors report no commercial or competing interests.

References

[1] Siebner HR, Rothwell J. Transcranial magnetic stimulation: new insights into representational cortical plasticity. Exp Brain Res 2003;148:1–16. https://doi.org/10.1007/s00221-002-1234-2.

[2] Rothwell J, Thompson P, Day B, Boyd S, Marsden C. Stimulation of the human motor cortex through the scalp. Exp Physiol 1991;76:159–200. https://doi.org/10.1113/expphysiol.1991.sp003485.

[3] Rothwell JC. Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. J Neurosci Methods 1997;74:113–22. https://doi.org/10.1016/S0165-0270(97)02242-5.

[4] Hallett M. Transcranial magnetic stimulation and the human brain. Nature 2000;406:147–50. https://doi.org/10.1038/35018000.

[5] Terao Y, Ugawa Y. Basic mechanisms of TMS. J Clin Neurophysiol 2002;19:322–43. https://doi.org/10.1097/00004691-200208000-00006.

[6] Bestmann S, Krakauer JW. The uses and interpretations of the motor-evoked potential for understanding behaviour. Exp Brain Res 2015;233:679–89. https://doi.org/10.1007/s00221-014-4183-7.

[7] 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.

[8] Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application: an updated report from an I.F.C.N. Committee. Clin Neurophysiol 2015;126:1071–107. https://doi.org/10.1016/j.clinph.2015.02.001.

[9] Muellbacher W, Ziemann U, Wissel J, Dang N, Kofler M, Facchini S, et al. Early consolidation in human primary motor cortex. Nature 2002. https://doi.org/10.1038/nature712.

[10] Classen J, Liepert J, Wise SP, Hallett M, Cohen LG, Baranyi A, et al. Rapid plasticity of human cortical movement representation induced by practice. J Neurophysiol 1998;79:1117–23. https://doi.org/10.1038/290413a0.

[11] Bütefisch CM, Davis BC, Wise SP, Sawaki L, Kopylev L, Classen J, et al. Mechanisms of use-dependent plasticity in the human motor cortex. Proc Natl Acad Sci U S A 2000;97:3661–5. https://doi.org/10.1073/pnas.050350297.

[12] Fadiga L, Fogassi L, Pavesi G, Rizzolatti G. Motor facilitation during action observation: a magnetic simulation study. J Neurophysiol 1995:2608–11. 10.1.1.299.4524.

[13] Kasai T, Kawai S, Kawanishi M, Yahagi S. Evidence for facilitation of motor evoked potentials (MEPs) induced by motor imagery. Brain Res 1997;744:147–50. https://doi.org/10.1016/S0006-8993(96)01101-8.

[14] Serino A, Annella L, Avenanti A. Motor properties of peripersonal space in humans. PLoS One 2009;4. https://doi.org/10.1371/journal.pone.0006582.

[15] Makin TR, Holmes NP, Brozzoli C, Rossetti Y, Farne A. Coding of visual space during motor preparation: approaching objects rapidly modulate corticospinal excitability in hand-centered coordinates. J Neurosci 2009;29:11841–51. https://doi.org/10.1523/JNEUROSCI.2955-09.2009.

[16] Finisguerra A, Canzoneri E, Serino A, Pozzo T, Bassolino M. Moving sounds within the peripersonal space modulate the motor system. Neuropsychologia 2015;70:421–8. https://doi.org/10.1016/j.neuropsychologia.2014.09.043.

[17] Avanzino L, Bassolino M, Pozzo T, Bove M. Use-Dependent hemispheric balance. J Neurosci 2011;31:3423–8. https://doi.org/10.1523/JNEUROSCI.4893-10.2011.

[18] Bassolino M, Campanella M, Bove M, Pozzo T, Fadiga L. Training the motor cortex by observing the actions of others during immobilization. Cerebr Cortex 2014;24:3268–76. https://doi.org/10.1093/cercor/bht190.

[19] Werhahn KJ, Mortensen J, Kaelin-Lang A, Boroojerdi B, Cohen LG. Cortical excitability changes induced by deafferentation of the contralateral hemisphere. Brain 2002;125:1402–13. https://doi.org/10.1093/brain/awf140.

[20] Wassermann EM, McShane LM, Hallett M, Cohen LG. Noninvasive mapping of muscle representations in human motor cortex. Electroencephalogr Clin Neurophysiol Evoked Potentials 1992;85:1–8. https://doi.org/10.1016/0168-5597(92)90094-R.

[21] Pascual-Leone A, Dang N, Cohen LG, Brasil-Neto JP, Cammarota A, Hallett M. Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. Journal of neurophysiology 1995:74. print i n USA.

[22] Hummel F, Celnik P, Giraux P, Floel A, Wu W-H, Gerloff C, et al. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. Brain 2005;128:490–9. https://doi.org/10.1093/brain/awh369.

[23] Rossini PM, Rossi S. Clinical applications of motor evoked potentials. Electroencephalogr Clin Neurophysiol 1998;106:180–94. https://doi.org/10.1016/S0013-4694(97)00097-7.

[24] Chen R, Cros D, Curra A, Lazzaro V Di, Lefaucheur J-P, Magistris MR, et al. The clinical diagnostic utility of transcranial magnetic stimulation: report of an IFCN committee. Clin Neurophysiol 2008;119:504–32. https://doi.org/10.1016/j.clinph.2007.10.014.

[25] Gentner R, Classen J. Modular organization of finger movements by the human central nervous system. Neuron 2006;52:731–42. https://doi.org/10.1016/j.neuron.2006.09.038.

[26] Gentner R, Gorges S, Weise D, Aufm Kampe K, Buttmann M, Classen J. Encoding of motor skill in the corticomuscular system of musicians. Curr Biol 2010;20:1869–74. https://doi.org/10.1016/j.cub.2010.09.045.

[27] Stefan K, Classen J, Celnik P, Cohen LG. Concurrent action observation modulates practice-induced motor memory formation. Eur J Neurosci 2008;27:730–8. https://doi.org/10.1111/j.1460-9568.2008.06035.x.

[28] Karabanov AN, Raffin E, Siebner HR. The resting motor threshold - restless or resting? A repeated threshold hunting technique to track dynamic changes in resting motor threshold. Brain Stimul 2015;8:1191–4. https://doi.org/10.1016/j.brs.2015.07.001.

[29] Amassian VE, Cracco RQ, Maccabee PJ. A sense of movement elicited in paralyzed distal arm by focal magnetic coil stimulation of human motor cortex. Brain Research, vol. 479; 1989.

[30] Amassian VE, Som Asundaram M, Rothwell JC, Britton T, Cracco JB, Cracco RQ, et al. Paraesthesias are elicited by single pulse. Magnetic Coil Stimulation Of Motor Cortex In Susceptible Humans, vol. 114; 1991 [Brain].

[31] Luscher C, Rosler KM, Mathis J, Beer S, Hess CW. The perception of movements elicited by magnetic cortex stimulation depends on the site of stimulation. Exp Brain Res 1996;109:154–7. https://doi.org/10.1007/BF00228637.

[32] Brugger P, Kollias SS, Muri RM, Crelier G, Hepp-Reymond M-C, Regard M. Beyond re-membering: phantom sensations of congenitally absent limbs. Proc Natl Acad Sci United States Am 2000;97:6167–72. https://doi.org/10.1073/pnas.100510697.

[33] Bestmann S, Oliviero A, Voss M, Dechent P, Lopez-Dolado E, Driver J, et al. Cortical correlates of TMS-induced phantom hand movements revealed with concurrent TMS-fMRI. Neuropsychologia 2006;44:2959–71. https://doi.org/10.1016/j.neuropsychologia.2006.06.023.

[34] Mercier C, Reilly KT, Vargas CD, Aballea A, Sirigu A. Mapping phantom movement representations in the motor cortex of amputees. Brain 2006;129:2202–10. https://doi.org/10.1093/brain/awl180.

[35] Ellaway PH, Prochazka A, Chan M, Gauthier MJ. The sense of movement elicited by transcranial magnetic stimulation in humans is due to sensory feedback. J Physiol 2004;556:651–60. https://doi.org/10.1113/jphysiol.2003.060483.

[36] Bruno V, Fossataro C, Bolognini N, Zigiotto L, Vallar G, Berti A, et al. The role of premotor and parietal cortex during monitoring of involuntary movement: a combined TMS and tDCS study. Cortex 2017;96:83–94. https://doi.org/10.1016/j.cortex.2017.09.001.

[37] Christensen MS, Lundbye-Jensen J, Grey MJ, Vejlby AD, Belhage B, Nielsen JB. Illusory sensation of movement induced by repetitive transcranial magnetic stimulation. PLoS One 2010;5:13301. https://doi.org/10.1371/journal.pone.0013301.

[38] Pascual-Leone A, Cohen LG, Brasil-Neto JP, Valls-Solé J, Hallett M. Differentiation of sensorimotor neuronal structures responsible for induction of motor evoked potentials, attenuation in detection of somatosensory stimuli, and induction of sensation of movement by mapping of optimal current directions. Electroencephalogr Clin Neurophysiol Evoked Potentials 1994;93:230–6. https://doi.org/10.1016/0168-5597(94)90045-0.

[39] Nicholls MER, Thomas NA, Loetscher T, Grimshaw GM. The flinders handedness survey (FLANDERS): a brief measure of skilled hand preference. Cortex 2013;49:2914–26. https://doi.org/10.1016/j.cortex.2013.02.002.

[40] Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Avanzini G, Bestmann S, et al. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120:2008–39. https://doi.org/10.1016/j.clinph.2009.08.016.

[41] Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Screening questionnaire before TMS: an update. Clin Neurophysiol 2011;122:1686. https://doi.org/10.1016/j.clinph.2010.12.037.

[42] Bassolino M, Franza M, Bello Ruiz J, Pinardi M, Schmidlin T, Stephan MA, et al. Non-invasive brain stimulation of motor cortex induces embodiment when integrated with virtual reality feedback. 2018. https://doi.org/10.1111/ejn.13871. 0–3.

[43] Pascual-Leone A, Cohen LG, Brasil-Neto JP, Hallett M. Non-invasive differentiation of motor cortical representation of hand muscles by mapping of optimal current directions. Electroencephalogr Clin Neurophysiol Evoked Potentials 1994;93:42–8. https://doi.org/10.1016/0168-5597(94)90090-6.

[44] Werhahn KJ, Fong JKY, Meyer BU, Priori A, Rothwell JC, Day BL, et al. The effect of magnetic coil orientation on the latency of surface EMG and single motor unit responses in the first dorsal interosseous muscle. Electroencephalogr Clin Neurophysiol Evoked Potentials 1994;93:138–46. https://doi.org/10.1016/0168-5597(94)90077-9.

[45] Hess CW, Mills KR, Murray NMF. Magnetic stimulation of the human brain: facilitation of motor responses by voluntary contraction of ipsilateral and contralateral muscles with additional observations on an amputee. Neurosci Lett 1986;71:235–40. https://doi.org/10.1016/0304-3940(86)90565-3.

[46] Stedman A, Davey NJ, Ellaway PH. Facilitation of human first dorsal interosseous muscle responses to transcranial magnetic stimulation during voluntary contraction of the contralateral homonymous muscle. Muscle Nerve 1998;21:1033–9. https://doi.org/10.1002/(SICI)1097-4598(199808)21. 8<1033::AID-MUS7>3.0.CO;2-9.

[47] Finisguerra A, Maffongelli L, Bassolino M, Jacono M, Pozzo T, D'Ausilio A. Generalization of motor resonance during the observation of hand, mouth, and eye movements. J Neurophysiol 2015. https://doi.org/10.1152/jn.00433.2015.

[48] Möller C, Arai N, Lücke J, Ziemann U. Hysteresis effects on the input-output curve of motor evoked potentials. Clin Neurophysiol 2009;120:1003–8. https://doi.org/10.1016/j.clinph.2009.03.001.

[49] Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997;48:1398–403. https://doi.org/10.1212/WNL.48.5.1398.

[50] Borgomaneri S, Gazzola V, Avenanti A. Temporal dynamics of motor cortex excitability during perception of natural emotional scenes. Soc Cognit Affect Neurosci 2014;9:1451–7. https://doi.org/10.1093/scan/nst139.

[51] Jaeger TF. NIH public access. J Mem Lang 2008;59:434–46. https://doi.org/10.1016/j.jml.2007.11.007.Categorical.

[52] Bruno V, Fossataro C, Bolognini N, Zigiotto L, Vallar G, Berti A, et al. The role of premotor and parietal cortex during monitoring of involuntary movement: a combined TMS and tDCS study. Cortex 2017;96:83–94. https://doi.org/10.1016/j.cortex.2017.09.001.

[53] Dimitriou M, Edin BB. Human muscle spindles act as forward sensory models. Curr Biol 2010;20:1763–7. https://doi.org/10.1016/j.cub.2010.08.049.

[54] Dimitriou M. Enhanced muscle afferent signals during motor learning in humans. Curr Biol 2016;26:1062–8. https://doi.org/10.1016/j.cub.2016.02.030.

[55] Brasil-Neto JP, Valls-Sole J, Pascual-Leone A, Cammarota A, Amassian VE, Cracco R, et al. Rapid modulation of human cortical motor outputs following ischaemic nerve block. Brain 1993;116:511–25.

[56] Christensen MS, Lundbye-Jensen J, Grey MJ, Vejlby AD, Belhage B, Nielsen JB. Illusory sensation of movement induced by repetitive transcranial magnetic stimulation. PLoS One 2010;5. https://doi.org/10.1371/journal.pone.0013301.

[57] Lesser RP, Luders HO, Klem G, Dinner DS, Morris HH, Hahn JF, et al. Extraoperative cortical functional localisation patients with epilepsy. J Clin Neurophysiol 1987;4:27–53.

[58] Haggard P. Conscious intention and motor cognition. Trends Cognit Sci 2005;9:290–5. https://doi.org/10.1016/j.tics.2005.04.012.

[59] Desmurget M, Reilly KT, Richard N, Szathmari A, Mottolese C, Sirigu A. Movement intention after parietal cortex stimulation in humans. Science 2009;324:811–3. https://doi.org/10.1126/science.1169896.

[60] Westin GG, Bassi BD, Lisanby SH, Luber B. Determination of motor threshold using visual observation overestimates transcranial magnetic stimulation dosage: safety implications. Clin Neurophysiol 2014;125:142–7. https://doi.org/10.1016/j.clinph.2013.06.187.