Brain Topography (2019) 32:418–434
https://doi.org/10.1007/s10548-019-00698-9

ORIGINAL PAPER

Cortical Inhibition of Face and Jaw Muscle Activity and Discomfort Induced by Repetitive and Paired-Pulse TMS During an Overt Object Naming Task

Carolin Weiss Lucas[1] · Elisa Kallioniemi[2,3] · Volker Neuschmelting[1] · Charlotte Nettekoven[1] · Julia Pieczewski[1] · Kristina Jonas[5] · Roland Goldbrunner[1] · Jari Karhu[4] · Christian Grefkes[6,7] · Petro Julkunen[2,8]

Received: 11 July 2018 / Accepted: 16 January 2019 / Published online: 23 January 2019
© Springer Science+Business Media, LLC, part of Springer Nature 2019

Abstract

Modulatory effects of transcranial magnetic stimulation (TMS) strongly depend on the stimulation parameters. Here, we compared the immediate, task-locked inhibitory effects on speech-related muscles and the tolerability of different TMS protocols during a language production task. Repetitive TMS (rTMS) and paired-pulse TMS (PP) were applied in 13 healthy subjects over the primary motor cortex (M1) during a finger-tapping/tongue-twisting tasks. The lowest subject-specific TMS intensity leading to movement disruptions was used for TMS over left-sided speech-related areas during picture naming. Here, time-locked PP and rTMS (10/30/50 Hz; randomized sequence) were applied. Cortical silent periods (cSPs) were analyzed from electromyography obtained from various face muscles. 30 Hz- and 50 Hz-rTMS reliably evoked tongue movement disruption (ICC = 0.65) at lower rTMS intensities compared to 10 Hz-rTMS or PP. CSPs were elicited from the left hemisphere by all TMS protocols, most reliably by PP ($p < 0.001$). Also, cSPs with longest durations were induced by PP. Exploratory analyses of PP suggest that the trials with strongest motor inhibitory effects (presence of cSP) were associated with more articulatory naming errors, hence hinting at the utility of TMS-elicited, facial cSP for mapping of language production areas. Higher-frequency rTMS and PP evoked stronger inhibitory effects as compared to 10 Hz-rTMS during a language task, thus enabling a probably more efficient and tolerable routine for language mapping. The spatial distribution of cranial muscle cSPs implies that TMS might affect not only M1, but also distant parts of the language network.

Keywords rTMS · cSP · Tolerability · Tongue · Language · Inhibition

Abbreviations

APB	Abductor pollicis brevis muscle
aILT	Inferior longitudinal tongue muscle; anterior third
cSP	Cortical silent period
FDR	False discovery rate
E-field	Electric field

Carolin Weiss Lucas and Elisa Kallioniemi contributed equally (shared first-authorship)

Handling Editor: Christoph M. Michel.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10548-019-00698-9) contains supplementary material, which is available to authorized users.

✉ Carolin Weiss Lucas
carolin.weiss@uk-koeln.de

[1] Faculty of Medicine and University Hospital Cologne, Center of Neurosurgery, University of Cologne, Cologne, Germany

[2] Department of Clinical Neurophysiology, Kuopio University Hospital, Kuopio, Finland

[3] Department of Psychiatry, UT Southwestern Medical Center, Dallas, TX, USA

[4] Nexstim Plc, Helsinki, Finland

[5] Department of Special Education and Rehabilitation, Faculty of Human Sciences, University of Cologne, Cologne, Germany

[6] Institute of Neuroscience and Medicine (INM-3), Research Centre Jülich, Juelich, Germany

[7] Faculty of Medicine and University Hospital Cologne, Department of Neurology, University of Cologne, Cologne, Germany

[8] Department of Applied Physics, University of Eastern Finland, Kuopio, Finland

EMG	Electromyography
ICC	Intraclass correlation coefficient
ISI	Interstimulus interval
M1	Primary motor cortex
MEP	Motor-evoked potential
MIT	Motor inhibition threshold
MSO	Maximum stimulator output
NRS	Numeric rating scale (0–10; for pain assessment)
nTMS	Neuronavigated transcranial magnetic stimulation
PP	Paired-pulse TMS
RMT	Resting motor threshold
rTMS	Repetitive transcranial magnetic stimulation
SEM	Standard error of the mean
TMS	Transcranial magnetic stimulation

Introduction

Over the last decades, transcranial magnetic stimulation (TMS) has become an important tool for the localization of functional representations of the motor cortex (Di Lazzaro and Rothwell 2014) and the language system (Devlin and Watkins 2007). Moreover, repetitive TMS (rTMS) has been used for therapy and rehabilitation (Lefaucheur et al. 2014), e.g., for treatment of stroke (Grefkes and Fink 2016), tinnitus (Theodoroff and Folmer 2013), depression (Downar and Daskalakis 2013), pain (Lefaucheur et al. 2008; O'Connell et al. 2014) and movement disorders (Kamble et al. 2014). Recently, immediate rTMS effects have attracted increasing interest due to the option to map cortical sites reflecting functionally important foci of the language network, not only in healthy subjects, but also in patients with brain tumours (Lioumis et al. 2012; Tarapore et al. 2013).

Usually, 5–10 Hz rTMS has been used to interfere with neural tissue underneath the stimulation coil, causing a transient behavioral deficit ("jamming" technique). Although long-lasting effects of high-frequency rTMS as used in the context of therapy are generally considered excitatory (e.g., Wassermann et al. 2001 *for review*), short rTMS trains can transiently disrupt cortical function within the addressed cortical area which has been referred to as temporary "virtual lesion" in the past (e.g., Pascual-Leone et al. 2000 *for review*). However, the measured rTMS effects on language function seem to be rather unspecific and may partially reflect effects on the facial motor system rather than on the associated language network. Moreover, discomfort evoked by 5–10 Hz stimulation is usually high (Tarapore et al. 2016b). In particular, repeated stimulations of the cortical representations of the face or the tongue area are often associated with considerable unpleasantness, limiting their use in clinical practice such as the preoperative work-up before tumour surgery. Thus, further investigation of the cortical inhibitory effects and testing of alternative, potentially more tolerable rTMS protocols are necessary.

The facial motor system is particularly well suited, yet surprisingly little studied, for gaining further insights into the effects of TMS on the balance between cortical excitation and inhibition. In contrast to the limbs, here, inhibitory effects are not relevantly influenced by reciprocal or recurrent inhibition mediated by proprioceptors (Patton and Amassian 1954; Terao and Ugawa 2002; Cruccu et al. 1997; Jaberzadeh et al. 2008). It has been suggested that inhibition elicited by focal TMS applied to the facial motor system is predominantly caused by cortical GABAergic interneurons (Rösler et al. 1989; Cruccu et al. 1996). A frequently used index of cortical GABAergic inhibition is the interruption of muscle activity following a TMS pulse, referred to as the cortical silent period (cSP) (Säisänen et al. 2008; Kallioniemi et al. 2014). However, while this parameter is well established for the stimulation of the hand motor area, reliable cSPs are more difficult to evoke in cranial muscles, potentially due to bilateral representations and less presynaptic projections (i.e., input by excitatory afferent interneurons) to pyramidal cells (Guggisberg et al. 2001).

Several studies have investigated the impact of TMS coil positioning on the characteristics and cortical topography of the elicited motor-evoked potentials (MEPs) in facial muscles (McMillian et al. 1998; Rödel et al. 1998; Paradiso et al. 2005; Säisänen et al. 2015). Moreover, both MEPs and cSPs are known to reflect task-dependent mechanisms (Watson et al. 2000; Butler et al. 2001; McMillian et al. 2001; Suppa et al. 2015). Voluntary biting, for example, has been shown to reduce the excitability of the corticobulbar neurons within the primary motor cortex (M1) which supply the contralateral masseter muscle (Butler et al. 2001; Nordstrom 2007). However, the influence of other tasks on corticobulbar excitability has been poorly investigated to date. Apart from simple reflex responses, it has been hypothesized that corticobulbar projections have an important influence on jaw muscle control during speech (Nordstom 2007). Consequently, the effects evoked by rTMS in speech and language studies may strongly depend on the corticobulbar excitability and the cortical excitation-inhibition balance. Vice-versa, behavioural changes (like errors in word pronunciation/articulation) due to online rTMS, which represent the most usual primary outcome measure in TMS language mapping (Krieg et al. 2017), might originate from interference not solely with language processing but also with motor processing (articulation). Such language-related motor inhibition could be indirectly measured by cSPs recorded from the muscles typically involved in speech. We also hypothesized that, mediated by remote network connections, such inhibitory effects on the motor network (as measured by cSPs) could even be elicited over distinct/connected regions outside M1.

In order to improve our understanding of inhibitory rTMS effects on speech production, we thus set out to investigated the effects of different (r)TMS protocols on the excitability of the corticobulbar system during an active speech task by measuring the induced cSPs in different facial muscles. In particular, not only the amount of the cSPs induced by the distinct TMS protocols but also durations, latencies and cortical sites corresponding to the cSPs were assessed. Since tolerability is a common and intensity-dependent problem of rTMS, especially when stimulating the frontolateral and temporal region, we also studied the levels of pain and discomfort. We hypothesized that higher rTMS frequencies (i.e., 30 Hz and 50 Hz) as well as paired-pulse TMS (PP) may allow for inducing similar inhibitory effects as compared to 10 Hz rTMS at lower stimulation intensities and may thus cause less discomfort.

Methods

Subjects and Study Design

Fifteen healthy, right-handed volunteers without previous medical history of seizures or migraine were recruited. The absence of epileptiform potentials was confirmed by a standard 21-channel electroencephalography. Handedness was verified according to the Edinburgh Handedness Inventory (Oldfield 1971). Two subjects did not accomplish all stimulation sessions due to prolonged headache occurring after the first stimulation. The remaining thirteen subjects (7 males, mean age 30 years, range 25–41 years) were studied with TMS in three sessions: (i) session 1, (ii) session 2 (2–5 days after session 1), and (iii) session 3 (2–5 weeks after session 2). During each session, short trains of rTMS were applied over the facial motor representation and functionally associated, speech-relevant areas using three different protocols (10, 30 and 50 Hz). In addition, PP was applied over the same cortical areas once per subject in session 3. At each session, (a) topographic motor cortex mapping of the facial representation was performed using single-pulse TMS followed by (b) the above-mentioned rTMS mappings during a visual object naming task in a randomized order. At the end of each rTMS sequence, the average and the maximum level of discomfort/pain (one rating category) was assessed on a subjective 0–10 numeric rating scale (NRS). EMG recordings were analyzed with respect to amount, duration and latency of cSPs which are regarded a valuable instrument to measure alterations in motor cortical excitability and inhibitory circuits (Abbruzzese and Trompetto 2002). Moreover, stimulation locations, i.e., estimated electric field (E-Field) maxima, were assessed for each cSP. The study was conducted according to the declaration of Helsinki (1969, last revision 2013), and approved by the ethics committee of the University of Cologne. Written informed consent was obtained from all subjects.

MRI Acquisition

Structural MR images were obtained from each subject prior to session 1 on a 3T MR scanner (Trio, Siemens, Erlangen, Germany) equipped with gradients of maximum strength of 40 mT/m per axis. High resolution T1-weighted volumes were acquired using a Modified Driven-Equilibrium Fourier Transformation sequence (parameters: TR = 2250 ms, TE = 3.93 ms, FOV = 256 mm, 176 sagittal slices, voxel size = $1.0 \times 1.0 \times 1.0$ mm^3) and were used for navigation of the TMS system.

EMG

MEPs were recorded using surface electrodes (Ambu Neuroline, Bad Nauheim, Germany) mounted above the contralateral (right) abductor pollicis brevis (APB), orbicularis oculi, nasalis, masseter and mentalis muscles as well as the orbicularis oris muscle on both sides. For the topographic mapping of the face representation, an additional electrode was placed on the anterior (subapical) underside of tongue, i.e., the inferior longitudinal tongue muscle (aILT) (Weiss et al. 2013). The 6-channel EMG unit used was part of the nTMS system.

TMS

TMS was conducted using a navigated figure-of-eight shaped stimulation coil and biphasic stimulation waveform (system version 4.3, Nexstim Plc., Helsinki, Finland). Subjects were seated comfortably in an adjustable armchair with headrest. The tracking unit was fixed to the subject's forehead using an elastic band and additional tapes. The head of the subject was co-registered with the corresponding high-resolution anatomical MR image before beginning the TMS.

Hand and Face Motor Mapping by Single-Pulse TMS

To obtain an intra-individual, functional reference, first the "hotspot", i.e., the stimulation site yielding the largest peak-to-peak MEP amplitude, and the respective resting motor threshold (RMT; unit: % of maximum stimulator output) were determined separately for both the hand (APB) and the tongue area (aILT) according to the "five out of ten"-rule (Rothwell et al. 1999). Next, for the topographic mapping at rest, the stimulation intensity was adjusted to 110% of the RMT of the tongue (Weiss et al. 2013, 2015; Säisänen et al. 2015). The coil was oriented perpendicular to the central sulcus for the hand mapping and strictly posterior-anteriorly (p.-a.) for the face mapping, i.e., parallel to the midline

between the hemispheres. This orientation elicits responses of cortical origin (Dubach et al. 2004) and avoids direct stimulation of trigeminal and facial nerve branches which can evoke MEPs of short latencies (Sowman et al. 2008). Potentials with latencies lower than 6 ms were discarded in order to exclude MEPs elicited by peripheral cranial nerve stimulation (Weiss et al. 2012).

Normalization of the Stimulation Intensity for Language Mapping

The stimulation intensity was kept constant during each session and rTMS protocol. Since we hypothesized that the individual threshold of cortical inhibition at different rTMS frequencies may not be linear to the RMT (as evaluated by single-pulse TMS), the stimulation intensity was adjusted to the "motor inhibition threshold" (MIT). The MIT was defined as the minimum stimulation intensity which led to a visible interference with the voluntary movement of interest, i.e., stopping or discoordination of either thumb abduction or tongue twisting, as observed online in at least 3 out of 5 stimulations of the respective motor hotspots by both of two independent raters. During the thumb abduction task, subjects performed an additional speech production task (counting from one to ten, repeatedly) to control for alertness and speech-related effects similar to those evoked by the language task. In the tongue twisting task, subjects were asked to perform simultaneous alternating finger tapping, in analogy to counting in the other task. The MIT was separately determined with each TMS protocol, i.e. PP, 10 Hz, 30 Hz and 50 Hz, for both the tongue twisting task (which served to determine the protocol-specific stimulation intensity for the language mapping experiment) and for the thumb abduction task (Table 1). Generally, the MIT and thus the stimulation intensity during the rTMS session was limited to a maximum of 130% of the tongue RMT for safety reasons (Rossi et al. 2009).

Language Mapping Parameters

Stimulation was performed at the individual MIT, dependent on the TMS protocol. The stimulation parameters for rTMS were chosen in order to optimize the read-out while assuring the compliance with the latest risk and safety guidelines (Chen et al. 1997; Wassermann 1998; Rossi et al. 2009): train durations were intended to cover the period of language execution (on average, 1.5 s according to our own pilot data, not shown) as far as uncritical regarding safety. Moreover, the total intensity applied during train stimulations was within a comparable range, given the device-specific decay in stimulation intensity over time during continuous trains of 30 Hz and 50 Hz rTMS (40–60% per min.). Accordingly, the TMS parameters were (i) PP, spaced by 7 ms inter-stimulus-interval (ISI) with the stimulator output amplitude of the second pulse reaching 80% of that of the first pulse, (ii) 10 Hz, 1.5 s train duration, (iii) 30 Hz, 1 s train duration, and (iv) 50 Hz, 0.5 s train duration. Of note, comparable pulse numbers were chosen for 30 Hz and 50 Hz rTMS (i.e., 25 vs. 30 pulses). The inter-train interval was 5 s. The inter-train-interval as well as the different lengths and durations of the trains were chosen in order to maximize the stimulation effect while considering the risk and safety guidelines for rTMS. The order of the rTMS protocols was pseudo-randomized between subjects.

Table 1 Motor thresholds compared for different (r)TMS protocols

Motor threshold	10 Hz	30 Hz	50 Hz	Paired-pulse
RMT in V/m (%-MSO), mean ± SD				
Thumb (ICC [Conf. interval])	57 ± 13 (34 ± 5) *(ICC = 0.77 [0.52–0.91])*			
Tongue (ICC [Conf. interval])	71 ± 15 (38 ± 4) *(ICC = 0.65 [0.35–0.86])*			
MIT				
Thumb MIT in V/m (%-MSO), mean ± SD	60 ± 13 (35 ± 5)	54 ± 11 (31 ± 4)	52 ± 11 (30 ± 5)	70 ± 16 (43 ± 5)*
ICC [Conf. interval]	*0.51 [0.17–0.79]*	*0.73 [0.45–0.90]*	*0.68 [0.39–0.88]*	*n.d.*
Tongue MIT in V/m (%-MSO), mean ± SD	77 ± 19 (41 ± 6)	63 ± 15 (33 ± 5)	61 ± 13 (33 ± 4)	88 ± 20 (48 ± 5)*
ICC [Conf. interval]	*0.36 [0.01–0.70]*	*0.66 [0.36–0.87]*	*0.64 [0.33–0.86]*	*n.d.*
Thumb MIT, normalized to hand RMT	104 ± 12 %	94 ± 9 %	90 ± 9 %	> 125 %
Tongue MIT, normalized to tongue RMT	108 ± 16 %	89 ± 15 %	87 ± 14 %	> 125 %

Resting motor thresholds (RMT) and motor-inhibition thresholds (MIT) were assessed for each TMS protocol. RMTs are reported in V/m as well as %-MSO. MITs are provided in absolute values (V/m, %-MSO) as well as normalized to the RMT of the body part corresponding to the task. Of note, normalized MIT values based on the electric field strength (V/m) as reported in the table (lowest two rows) did not differ significantly from the respective %-MSO-values (thus, the latter are not displayed to avoid redundancy). Test-retest-reliability, as assessed by the intraclass correlation coefficient (ICC) are displayed in italics. MIT values (tongue motor task) determined the stimulation intensity for TMS language mapping

*Estimate of lower end of MIT range (maximum tested stimulation intensity = 130% of RMT)

The stimulation was performed during an active language task, i.e. a naming task of black-and-white drawings of 50 daily-life objects. The pictures were taken from the Snodgrass–Vanderwart standardized picture set (Snodgrass and Vanderwart 1988). All subjects were trained on the data set until stable naming performance was reached before the stimulation. Naming of the pictures was always introduced by the German phrase "Das ist ein(e)" ["this is a(n)"] during the task. The rTMS trains were given upon the onset of the respective picture (Krieg et al. 2017). The picture presentation duration was 500 ms. Hence, all TMS protocols were active during the entire presentation period of the picture, except for PP.

TMS Language Experiment

Stimulation was performed over the left (dominant) hemisphere. The stimulated cortical area included (i) the inferior frontal gyrus, (ii) dorsal parts of the medial frontal gyrus, (iii) lateral parts of the precentral gyrus (according to the tongue / face representation), (iv) the inferior parietal lobule as well as (v) the superior and medial temporal gyrus (Fig. 1). In case of significant pain or discomfort (NRS > 5/10, as indicated by squeezing a squeak ball) evoked by TMS, supposedly due to direct stimulation of trigeminal and facial nerve branches, the stimulation was interrupted at the respective stimulation site so that not all of the mentioned areas could always be tested. The mean number of trains applied per session was 175 ± 31 (no significant difference between protocols). According to the topographic face mapping, the orientation of the TMS-induced electric field was strictly posterior-anterior over the frontoparietal region. However, over the temporal lobe, the orientation was perpendicular to the Sylvian fissure. In order to achieve a systematic mapping of the above-mentioned stimulation sites (i–v), a grid was projected onto the respective anatomical position to guide the stimulation with a density of utmost 5 mm (Fig. 1). The stimulation order of the grid squares was pseudo-sequential. In order to increase the resting time of distinct cortical areas, the space between two consecutive TMS trains was kept to a minimum of 15 mm. The experiments were video-taped.

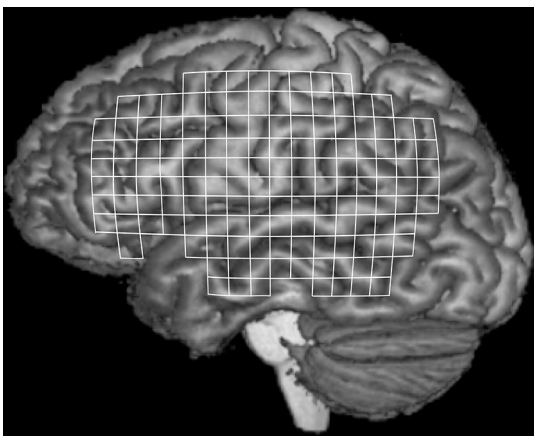

Fig. 1 Stimulation area. The figure exemplifies the total stimulated area as outlined by the margins of the grid. In order to control the distribution of TMS sites, a grid (5 mm side length) was plotted onto the 3D-rendered brain surface throughout the TMS session. With each TMS protocol, grid squares were addressed in a pseudo-sequential order (p.-a. direction of stimulation)

Data Analysis

Running EMG recordings were analysed in Matlab (version 2013b, The Mathworks, Inc. Natick, MA, USA). The amount, latency and duration of cSPs were assessed in time-windows of 50 ms before the last pulse to 400 ms after the last pulse of each rTMS burst / the second pulse of the PP. Of note, silence in the EMG was only considered a cSP when occurring after the last TMS pulse and following at least one MEP. The time-window of 50 ms before, however, served to evaluate the baseline level of EMG activity. For each detected cSP, the beginning of the cSP was defined by the time point where the EMG crossed the baseline after the MEP. The duration of the cSPs was set to the total length of the period of the EMG signal silencing (Fig. 2). Only cSPs with a duration of at least 10 ms were accepted (Kallioniemi et al. 2014). The rater (same rater for all EMG analyses) was blind to the rTMS frequency and to the cortical location at which the cSPs were evoked (Indefrey 2011).

For the cSP analysis, first, the effect of the TMS measurement repetition on the variables cSP amount, cSP duration and cSP latency was tested using repeated-measures ANOVA to investigate the test-retest-reliability of rTMS-evoked cSPs at three different time points (data set A, Fig. 3). Levels of significance and F-values resulting from tests of within-subject effects are referred to as p and F throughout the manuscript. The variable "muscle" was included as a between-subjects factor in the model. Moreover, the TMS protocol was included as a fixed effect into the analysis. Mauchly's test was used to assess violations of sphericity in repeated-measures ANOVA; if the Greenhouse–Geisser estimate of sphericity (ε) was > 0.75, then Huynh-Feldt correction was applied, otherwise (if ε < 0.75) the Greenhouse-Geisser correction was used (Greenhouse and Geisser 1959; Huynh and Feldt 1976; Girden 1992).

Secondly, for evaluating the influence of the different factors (fixed effects), i.e. all TMS protocols (including PP) and muscle, on the variables cSP amount, cSP duration and cSP latency, a within-subject ANOVA was performed on data set B (Fig. 3). Pairwise comparisons of cSP amounts between different TMS protocols as well as

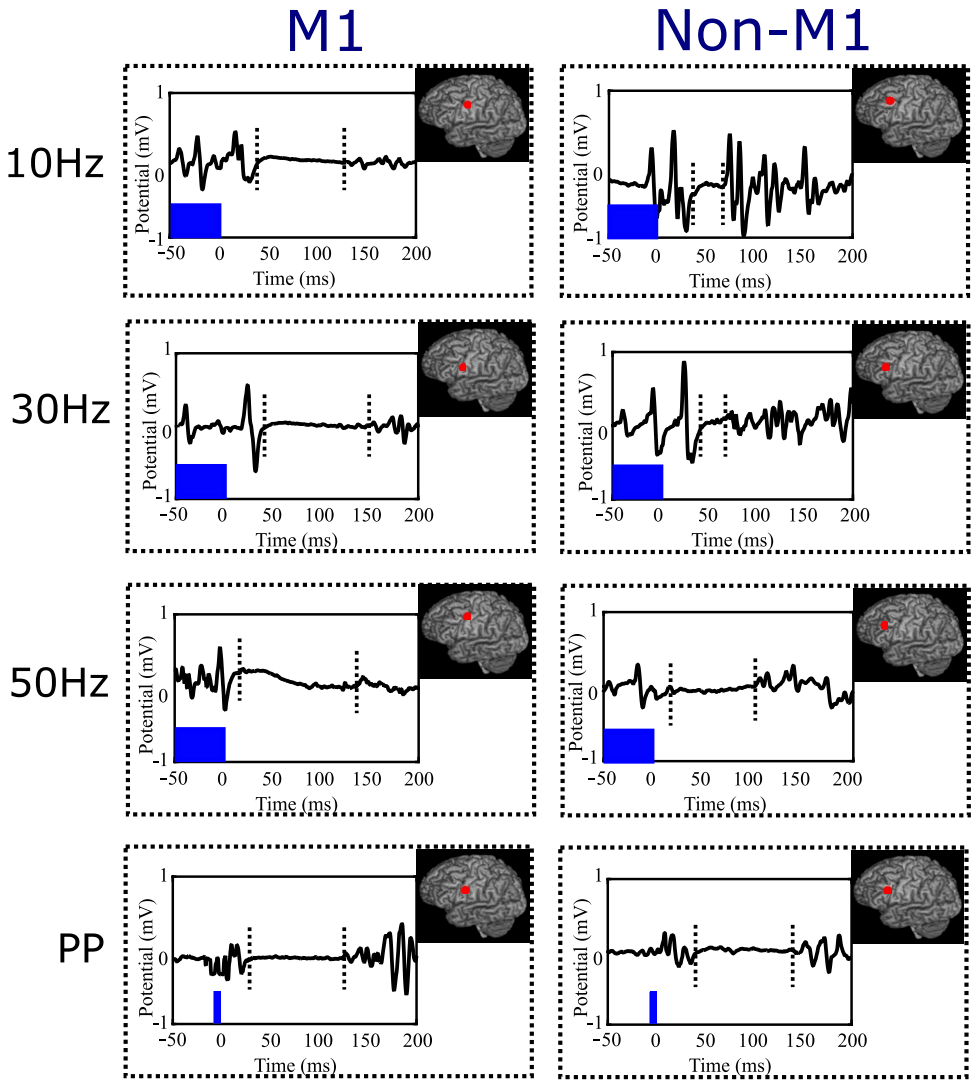

Fig. 2 An example of a facial cSP from mentalis muscle for each TMS protocol. The train duration of the paired-pulse (PP) as well as the last 50 ms of the respective rTMS train (10 Hz, 30 Hz, 50 Hz) are indicated in blue. Examples are given for stimulations of the primary motor cortex (M1) as well as elsewhere in the frontal lobe (non-M1). The beginning of the cSP was marked from the point where the EMG curve crossed the baseline after the ending of the MEP. Latency and duration of the cSP were measured according to (i) the stimulus onset at time = 0, (ii) the onset and (iii) the end of the cSP (indicated by dashed lines in the figure)

Session	TMS condition			
	10 Hz	**30 Hz**	**50 Hz**	**PP**
1	X	X	X	
2	X	X	X	
3	X	X	X	X

A
B

Fig. 3 General study design. Repeated measures were obtained for all three rTMS protocols (session 1–3) whilst PP was only applied additionally in one session. Repeated measures analysis was applied to data set A (light red) including 10 Hz, 30 Hz and 50 Hz rTMS whereas comparisons between all four TMS protocols were based on data set B (light yellow)

between different muscles were based on the estimated marginal means (referred to as p_{EMM} in the manuscript).

Third, to investigate the influence of TMS protocols and muscles on cSP durations and latencies, however, paired means were compared in order to overcome the problem of missing values (due to a high number of stimulation sites at which no cSPs were evoked). Here, cases were excluded pairwise where data were missing.

Fourth, as an exploratory analysis, the occurrence rates of articulation-related speech errors were compared between (1) all data regardless of the occurrence of a cSP and (2) only stimulations with observed cSPs for the PP condition.

This analysis was added to test the link between speech performance and cSPs evoked in the time-window of the first 400 ms after picture presentation, which is critical for language processing (see, e.g., Indefrey 2011 for review). Speech errors clearly related to articulation (i.e., speech-motor-disturbances, dysarthria, speech arrest) were identified via offline video-analysis by two independent raters which were blinded to the cSP results and were controlled by a clinical linguist.

The reliability of RMT and MIT values over the three sessions was assessed by a two-way intraclass correlation coefficient (*ICC)* for absolute agreement. Spearman's Rho was calculated to check for correlations between stimulation intensities and pain levels (NRS). Whenever appropriate, non-parametric partial correlations were calculated using the {ppcor} library implemented in R (R Studio, Version 0.98.507, Boston, MA, USA).

For comparisons of means regarding normally distributed data according to the Saphiro-Wilk Test ($p > 0.1$), the paired T-Test was used, otherwise Wilcoxon's Signed Rank Test. Please note that for any comparisons between all TMS protocols (thus, including PP) or muscles, only one (the last) session was included into the data set (data set B; Fig. 3) in order to allow for pairwise comparisons. The significance threshold for all analyses was set to $p = 0.05$ (except for the test of normality, $p = 0.1$). All p-values were corrected for multiple comparisons using the false-discovery rate (FDR) approach (Benjamini and Hochberg 1995) whenever comparing more than one pair of data. The statistical analyses were performed using SPSS (Version 21.0; IBM Corporation, Somers, NY, USA) and R.

Results

RMT and MIT

The RMT of the hand and the tongue were repeatable between the sessions (*ICC* hand = 0.77, *ICC* tongue = 0.65; Table 1). For the APB, the average RMT was 57 ± 13 V/m, corresponding to 34 ± 5% of the maximum stimulator output (MSO). Compared to the hand, the RMT of the tongue was significantly higher, i.e., 71 ± 15 V/m (38 ± 4%-MSO; $p < 0.001$). Amongst rTMS frequencies, the MIT values differed significantly and lowered along with the increasing rTMS frequency ($p < 0.001$ for all pairwise comparisons, FDR-corrected), ranging from average values of 52 V/m (50 Hz) to 60 V/m (10 Hz) in the thumb abduction task and from 61 V/m (50 Hz) to 77 V/m (10 Hz) in the tongue twisting task (Table 1). In PP, the MIT was always higher than in rTMS protocols and could usually not be determined precisely (11/13 cases) due the absence of evident movement disturbances in the motor tasks (thumb abduction, tongue twisting) when stimulating at the maximum tested intensity (i.e., 130% RMT). Normalized to the RMT of either the thumb or the tongue, the mean MIT of the 10 Hz, 30 Hz and 50 Hz rTMS ranged between 90% (50 Hz) and 104% (10 Hz) of the RMT for thumb movements, and between 87% (50 Hz) and 108% (10 Hz) as assessed by the tongue twisting task (Table 1). In PP, normalized MITs were at least 113% of the RMT (mean: 127 ± 9%).

The reliability of the MIT between the three sessions was good for the rapid-frequency rTMS protocols, i.e. 30 Hz and 50 Hz, for the thumb abduction task (*ICC* = 0.72 [30 Hz]/0.68 [50 Hz]) as well as for the tongue twisting task (*ICC* = 0.66 [30 Hz]/0.64 [50 Hz]) and fair to moderate for 10 Hz rTMS (thumb: *ICC* = 0.51 [thumb]/0.36 [tongue]; Table 1).

Tolerability and Side Effects

In general, all stimulation protocols were rather well tolerated. Nevertheless, especially when stimulating over the temporal and frontolateral region, immediate stimulation effects on the facial/trigeminal nerves resulted in intermittent, short-lasting neuralgiform sensations and jaw muscle contractions in most sessions. Asking the participants more in detail, those effects were described as the major reason for relevant pain sensations as rated by the NRS (reported below). No seizures occurred during the stimulations. However, mild headache was reported by participants after 34% of the rTMS sessions. Moreover, one subject complained of transient neck pain after the sessions. There was a statistical trend towards better tolerability of the 50 Hz rTMS as compared to 10 Hz rTMS (max. NRS 10 Hz vs. 50 Hz: $p < 0.1$, FDR-corrected). By contrast, no significant difference was observed between the other rTMS protocols with respect to the maximum and mean NRS (max. NRS values: range 5.4/10 [50 Hz]–6/10 [10 Hz]; mean NRS values: range 3.2/10 [30/50 Hz]–3.6 [10 Hz]; Table 2). Lowest levels of pain and discomfort were reported for the PP protocol (mean NRS: 2.4/10 ± 1.6; max. NRS: 4.6/10 ± 2.2; $p < 0.05$ compared to any rTMS condition, FDR-corrected; Table 2). Of note, there was no significant correlation between rTMS stimulation intensities (%-SO) during language mapping and mean pain/discomfort levels (rho = − .03; $p = 0.80$). However, we observed a trend towards a weak correlation between stimulation intensities and the maximum pain levels (rho = .16; $p = 0.09$). Between sessions, maximum pain levels showed good to excellent test–retest reliability (*ICC* range 0.60 [30 Hz]–0.82 [50 Hz], Table 2).

Silent Periods

CSPs (Fig. 2) were detected in all muscles (i.e., right/contralateral: masseter, mentalis, orbicularis oris, nasalis,

Table 2 Pain levels compared for different TMS protocols

Subjective pain level	10 Hz	30 Hz	50 Hz	Paired-pulse
Mean of mapping (NSR [0–10])	3.6/10 ± 1.8	3.2/10 ± 1.6	3.2/10 ± 1.6	2.4/10 ± 1.6
Peak of mapping (NSR [0–10])	6/10 ± 2.3	5.6/10 ± 2.2	5.4/10 ± 2.4	4.6/10 ± 2.2
ICC [Conf. interval]	*0.79 [0.55–0.93]*	*0.60 [0.28–0.85]*	*0.82 [0.59–0.94]*	*n.d*

Mean and maximum levels of pain and discomfort were rated by the subjects on a 0–10 numeric rating scale (NRS) at the end of each TMS sequence. Best tolerability was reported for PP as compared to all rTMS frequencies ($p < 0.05$, FDR-corrected). Amongst the rTMS protocols, 50 Hz rTMS was tolerated best. Moreover, retest-reliability of the maximum pain ratings was determined using the intraclass correlation coefficient (ICC) are displayed in italics

Table 3 Retest–reliability of rTMS-induced cSPs

CSP	ICC (sessions 1–3)		
	10 Hz	30 Hz	50 Hz
Amount	0.500	0.493	0.733
Duration	0.587	0.667	0.649
Latency	0.715	0.693	0.757

Intraclass correlation coefficients (ICC) are reported including sessions 1–3. The amounts of rTMS-evoked cSP showed moderate (ICC 0.5–0.75) consistency for 10 and 50 Hz and low reliability (ICC < 0.5) for the 30 Hz rTMS over the three sessions. Regarding cSP durations and latencies, however, moderate to good (ICC > 0.75) reproducibility was observed in all the rTMS frequencies

orbicularis oris; left/ipsilateral: orbicularis oris) and in all (r)TMS protocols.

Reliability of (r)TMS-Induced cSPs

Measurement repetition had no significant effect on amount, latency or duration of the rTMS-induced cSPs. However, the retest-reliability of the cSP characteristics, i.e., amount, duration and latency, was mostly moderate, particularly regarding the amount of cSPs induced by 10 Hz and 30 Hz rTMS (Table 3). This finding, potentially mirroring alertness and brain-state effects on cortical excitability, suggests that direct comparison between TMS protocols obtained at different time points may be considerably biased. Therefore, the further statistical analyses, whenever taking also PP into account (only assessed in one session), include data from session 3 alone (data set B, Fig. 3) in order to allow for direct comparison of paired data.

Amounts of cSPs

The number of cSPs differed between muscles as well as between different TMS protocols (muscle: $F_{2.9,34.9} = 6.1$; TMS protocol: $F_{1.4,10}1.3 = 14.6$, both Greenhouse–Geisser-corrected; $p < 0.01$). Of note, for both within-subject factors (i.e., muscle and condition), the assumption of sphericity was violated as indicated by Mauchly's test ($p < 0.05$). As compared to rTMS, PP elicited more cSPs (mean 7.5 ± 11.8 [0–50]; $p_{EMM} < 0.01$). Amongst rTMS protocols, most cSPs were observed following 50 Hz rTMS (mean 3.0 ± 5.3 [0–28]; $p < 0.1$; significant when considering data set A $p < 0.05$; supplementary Figure S1) whereas 10 Hz and 30 Hz rTMS had a similar effect on eliciting cSPs (10 Hz: mean 1.4 ± 3.0 [0–15], 30 Hz: mean 2.0 ± 3.9 [0–20]; Fig. 4a). Accordingly, the cSP amounts in distinct muscles were strongly influenced by the TMS protocol ($p < 0.001$). The distribution of cSP amounts amongst the distinct recorded muscles was comparable in the different rTMS frequencies but differed from PP. Due to the data distribution, pairwise comparison between cSP amounts in different muscles was conducted for (i) all rTMS frequencies pooled and (ii) PP, separately. Despite differences in data distribution, all TMS protocols had in common that most cSPs were elicited in the lower face muscle of facial nerve supply, particularly in the mentalis muscle (rTMS: $p_{EMM} < 0.1$ compared to right lower face muscles, $p_{EMM} < 0.01$ compared to any other muscle; PP: $p_{EMM} < 0.05$ compared to all other muscle, FDR-corrected; Fig. 4b). By contrast, cSPs were only very rarely observed in the upper face muscles. Accordingly, less cSPs were elicited in the orbicularis oculi muscle than in any of the (crossed) lower face muscles (rTMS: $p_{EMM} < 0.001$; PP: $p_{EMM} < 0.05$). Amongst upper face muscles (i.e., orbicularis oculi and nasalis muscle), no difference in cSP amounts was observed in the rTMS protocols whereas there was a statistical trend towards more cSP elicited in the nasalis muscle in PP ($p_{EMM} < 0.1$). Due to the very low number of cSPs elicited in the upper face muscles, which are not primarily involved in speech production and thus rather inactive during the object naming task, those cSPs were not taken into account for between-muscle comparisons of cSP latencies and durations. The stimulated cortical locations from which the cSPs were induced (total of all muscle recordings) showed a large inter-subject variability, with a tendency towards accumulation in the frontolateral, the inferior-parietal and the superior-temporal region (Fig. 5).

Latency of cSPs

The mean cSP latencies were within a range of 11–63 ms (PP: 35 ± 10 [21–63] ms, 10 Hz: 39 ± 9 [16–52] ms, 30 Hz:

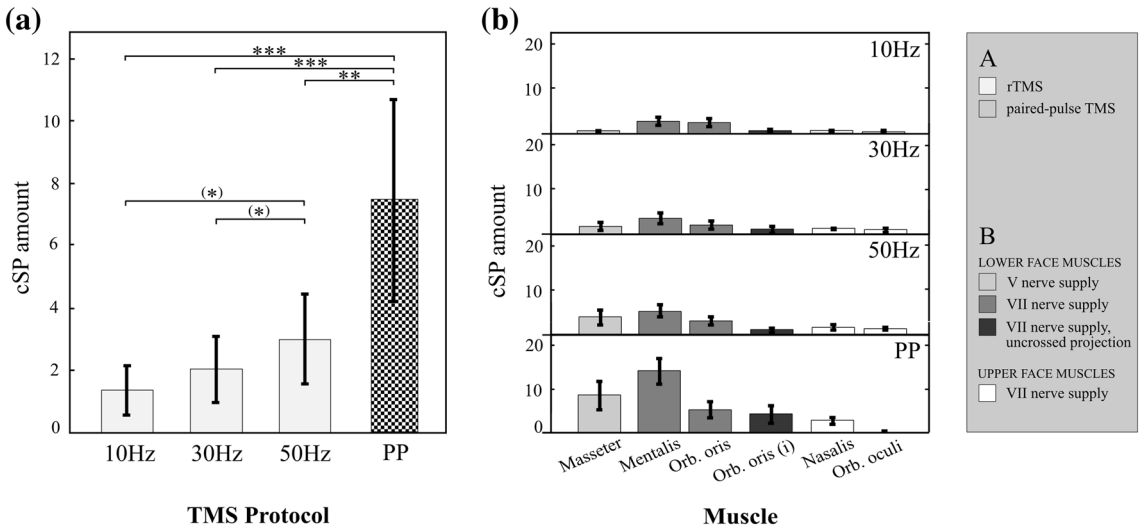

Fig. 4 Amounts of cSPs induced by different TMS paradigms (A) and in different muscles (B). Mean absolute amounts of cSP elicited in the third session by different TMS protocols (A) and in distinct face muscles (B) are displayed (data set B; number of incidents of cSP events per, on average, 169 ± 35 trials, n.s. difference between protocols). Mean and inter-individual variability are expressed as standard error of the mean (SEM). Significant differences between frequencies are indicated with an asterisk ($^{(*)}p_{EMM}<0.1$, $^{**}p_{EMM}<0.01$, $^{***}p_{EMM}<0.001$, FDR-corrected). **a** On average, PP induced more cSPs than rTMS ($p<0.01$). The increasing amount of cSPs with higher rTMS frequency did only meet statistical significance when considering all sessions (supplementary Figure S1). **b** Most cSPs occurred in the lower face muscles with facial nerve supply (in particular, mentalis muscle)

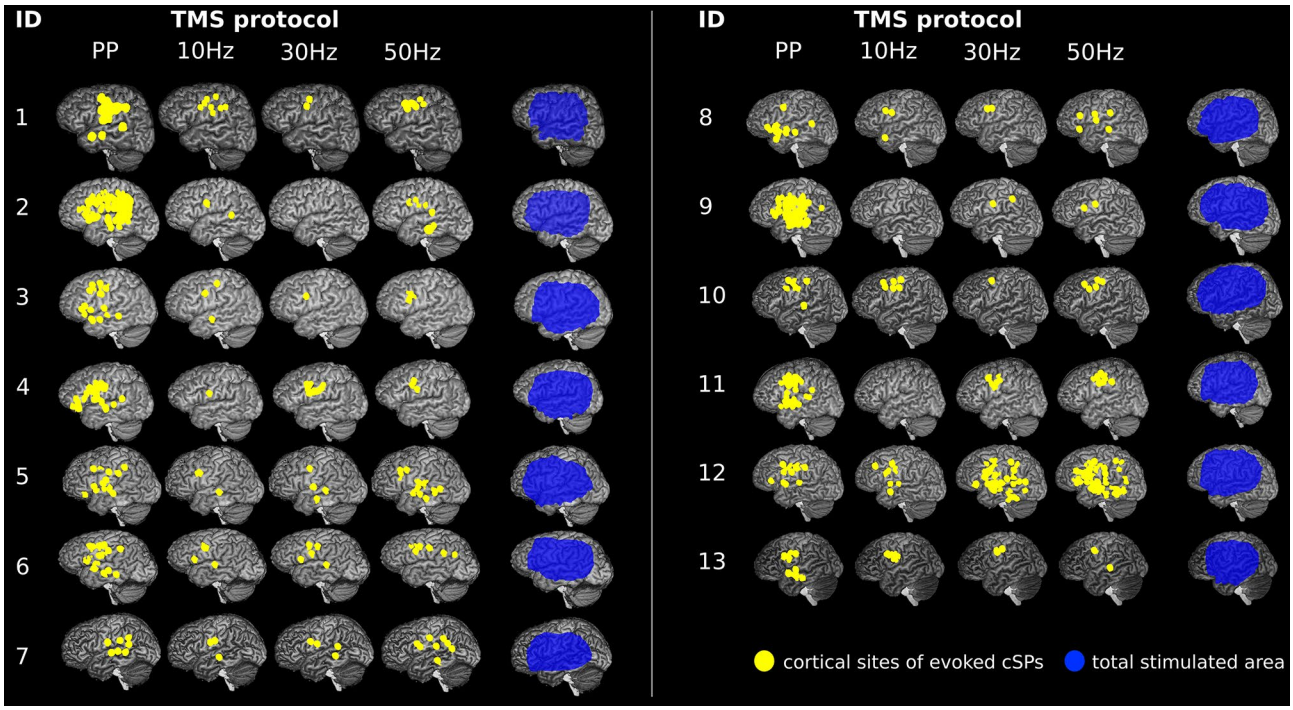

Fig. 5 Individual cortical representations of cSPs. The locations where cSPs were evoked by PP as well as by 10 Hz, 30 Hz, and 50 Hz rTMS in the same session (data set B) are plotted onto the brain surface (outlined in yellow). Of note, TMS protocols were applied in a pseudo-randomized order. The extents of the total stimulated areas are provided for each subject (blue) since they slightly varied between subjects, mostly due to stimulation-related discomfort

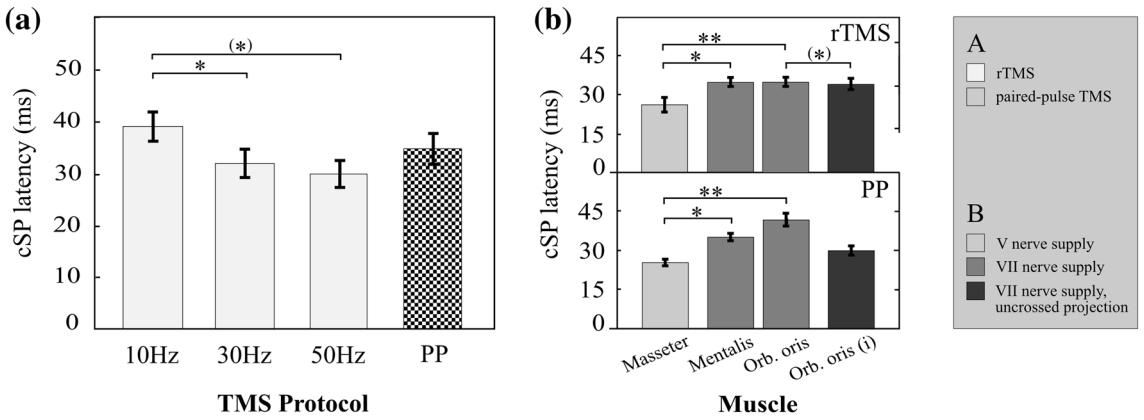

Fig. 6 Latencies of cSPs. Mean latencies of cSP elicited in the third session (data set B) by different rTMS protocols (grey) vs. PP (dark grey) (**a**) and in distinct lower face muscles (**b**) are displayed. Mean and inter-individual variability are expressed as standard error of the mean (SEM). Missing values (stimulation which did not result in any cSP at all) were not included. Significant differences between rTMS frequencies are indicated with an asterisk ($^{(*)}p<0.1$, $^{**}p<0.01$, $^{***}p<0.001$, FDR-corrected). For separate comparison of different rTMS protocols and for the upper face muscles see supplementary Figure S2. (*i* ipsilateral)

32 ± 8 [16–46] ms, 50 Hz: 30 ± 8 [11–48] ms; Fig. 6). On average, latencies were longest in the 10 Hz-rTMS condition (10 Hz vs. 30 Hz: $p<0.05$; 10 Hz vs. 50 Hz: $p<0.1$, FDR-corrected) and shortest following 50 Hz-rTMS (Fig. 4a). Besides being significantly influenced by the TMS protocol ($p=0.001$; $F_{2.8,203.7}=5.9$, Huynh-Feldt-corrected), cSP latencies were also dependent on the muscle ($p<0.001$; $F_{5,60}=14.5$). Pairwise comparison of latencies in different muscles revealed a similar distribution amongst different rTMS frequencies (supplementary Figure S2) but differed in PP. Thus, rTMS data were pooled for paired between-muscle comparisons of means (Fig. 6b). Shortest cSP latencies were found in mentalis muscle which is the only recorded muscle with trigeminal nerve supply. Unlike expected, the differences in cSP latencies from crossed vs. uncrossed corticobulbar projections (i.e., right vs. left orbicularis oris muscle) did not meet the level of statistical significance in pairwise comparison of means. Overall, latencies in the different facial muscles seemed to be more homogeneous in rTMS as compared to PP (Fig. 6b).

Duration of cSPs

Overall, the cSP durations were not longer than 170 ms (PP: mean 76 ± 29 [35–170] ms, 10 Hz: mean 61 ± 24 [20–125] ms, 30 Hz: mean 69 ± 25 [27–125] ms, 50 Hz: mean 62 ± 23 [27–121] ms). Both muscle ($p<0.001$; $F_{5,60}=9.5$) and TMS protocol ($p<0.001$; $F_{2.5,12.7}=11.1$, Huynh-Feldt-corrected) had a significant effect on the cSP duration. PP elicited longer cSPs as compared to rTMS ($p=0.01$; *Wilcoxon test, unpaired*). In pairwise comparison with distinct rTMS protocols, however, a significant difference was found only for 50 Hz ($p<0.05$, FDR-corrected). Amongst rTMS protocols, longest cSP durations were observed using 30 Hz (30–50 Hz: $p<0.05$, FDR-corrected) (Fig. 7a).

Similar to the latencies, the data distribution of the cSP durations by muscle did not differ significantly between rTMS protocols (supplementary Figure S3) and were, therefore, pooled (Fig. 7b). In general, cSPs elicited by rTMS showed very little variability between muscles. Interestingly, cSP durations of the masseter muscle were longest in the rTMS protocols but shortest in PP, showing a statistical trend in comparison to the lower face muscles of facial nerve supply ($p<0.1$, FDR-corrected) (Fig. 7b).

Exploratory Analysis in Relation to Articulation Errors

In the PP condition, articulation-related speech errors accounted for 25.1% of all language errors. As a tendency, compared to all trials (2.8 ± 2.6%; range 0–38.1%), mean articulation-related speech error rates were higher in the data subset which only included trials with evoked cSPs (6.8 ± 10.7%; range 0–9.3%; n.s.).

Discussion

Brief Summary of Key Findings

The design of this study, i.e., repeated testing of TMS jamming protocols during both motor and language tasks enabled us to further the understanding of the motor-language interaction during TMS-locked picture naming performance and to address a series of specific research questions: First, since discomfort is a major issue for language mapping particularly when stimulating the temporal lobe, the tolerability

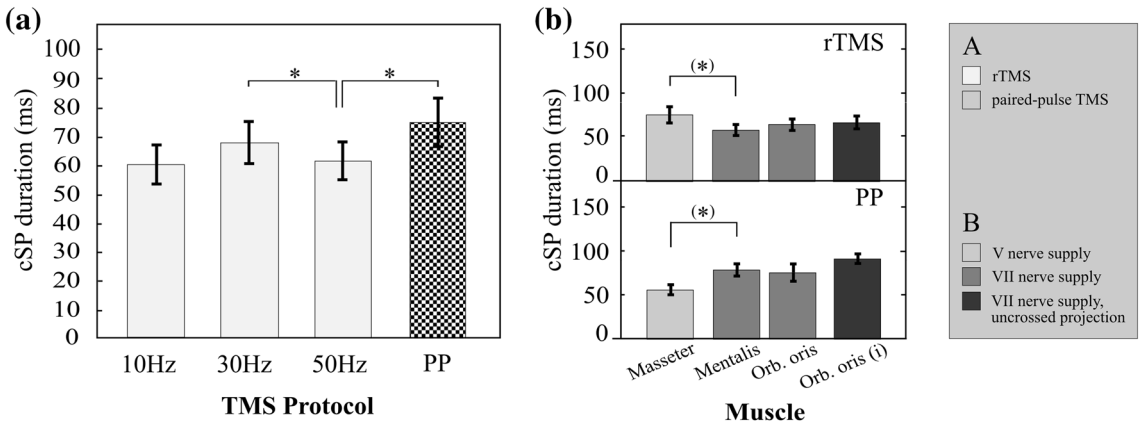

Fig. 7 Durations of cSPs. Mean durations of cSPs elicited in the third session (data set B) by different TMS protocols (**a**) and in distinct lower face muscles (**b**) are displayed. Mean and inter-individual variability are expressed as standard error of the mean (SEM). Missing values were not included. Significant differences between frequencies are indicated with an asterisk ($^{(*)}p < 0.1$, $^{*}p < 0.05$, FDR-corrected). (*i* ipsilateral)

of the distinct TMS protocols was assessed. Second, based on the hypothesis that TMS-induced language errors might be partly related to direct or remote inhibition of motor network components, we investigated the time-locked cortical inhibition in face muscles during both tasks by assessing cSPs.

The key results showed that discomfort was a major issue during TMS jamming over the frontotemporal junction. However, discomfort levels could be reduced significantly by using PP, followed by applying 50 Hz-rTMS.

As a proof-of-principle, we could show that cSPs occurred during language task performance, mostly in the more speech-related face muscles like mentalis muscle, and after PP TMS. The spatial distribution of cSPs, exceeding M1, supports our hypothesis of remote effects of task-locked TMS on the facial motor system. Although further research is required to investigate the link between language and motor-speech functions, between behavioural effects (on language performance) and cSPs in more detail, this novel approach to consider face-muscle cSPs as an objectively measurable counterpart of motor-speech inhibition opens new vistas for the field of rTMS language mapping.

RMT

The intra-subject reliability of the RMT was good for the hand and the tongue. Some variability, however, must be attributed to non-avoidable differences in the setting, e.g. different levels of sleepiness / alertness at the different time points (De Gennaro et al. 2007). Such small variations of the RMT between different time points can significantly alter the result of M1 mapping, especially regarding the extent of the map (van de Ruit and Grey 2016). An individual "default" RMT, once determined for each body part representation, should, therefore, only be regarded as an approximate but can be helpful to serve as a starting stimulation intensity in order to accelerate the RMT determination. Moreover, the RMT of the tongue/ face muscle representation can be roughly estimated by (on average) 125% of the hand RMT (in terms of induced E-field in the individual brain, which accounts for varying distance and angulation between the stimulation coil to the reacting cortex; V/m). Using this intensity as an initial setting may speed-up the precise determination of the face RMT (in case the hand RMT is known).

The RMT of the face (71 ± 15 V/m/38 ± 4%-MSO) was slightly lower than previously reported values which were in the range of 40–65%-MSO (Watson et al. 2000; Paradiso et al. 2005; Jaberzadeh et al. 2008; Pilurzi et al. 2013). This finding could mirror a higher cortical excitability of the tongue representation as compared to other face muscles like mentalis or masseter. However, different study settings regarding the stimulator pulse characteristics, coil orientation and tilt do not allow for direct comparison (Danner et al. 2008) and minor variations amongst the reported RMTs should, therefore, not be over-interpreted.

MIT

One of the novel aspects of the present study was the use of an individual MIT to determine the stimulation intensity for "jamming" during task performance for each TMS protocol. In contrast to 10 Hz rTMS, the individual MITs of 30 Hz and 50 Hz rTMS were usually sub-threshold, i.e., 75–100% of the respective RMT. Those lower MIT values may reflect an overall elevated susceptibility of motor cortex neurons for higher-frequency rTMS-induced inhibition during task performance. Moreover, the lower MIT values and, thus, the lower stimulation intensities seemed likely to explain the

slightly better tolerability of 30 Hz and 50 Hz rTMS (see "Tolerability and Side Effects" section).

Tolerability and Side Effects

Apart from short-lasting discomfort during the TMS trains, headache was the only relevant side effect (34%) and usually started at the end of the session or within several hours afterwards. This percentage was within the previously reported ranges of 10% and 60% which depend on the stimulation protocol, the subjects and the stimulation site (Machii et al. 2006). In line with our findings, headache has been reported as the most frequent side effect of (r)TMS (Rossi et al. 2009) but usually lasts no longer than a few days (Janicak et al. 2008; Anderson et al. 2009). Of note, one of the two subjects, which were excluded due to headache, reported afterwards to suffer from frequent cephalalgia which is a known risk factor for non-tolerance of rTMS (Teo et al. 2014). In line with our results from comparing the pain levels using different rTMS protocols, Machii et al. (2006) also observed a trend towards better tolerability of higher-frequency rTMS when stimulating over the dorsolateral prefrontal cortex as compared to lower frequencies. However, our study design of consecutive application of different rTMS protocols in a randomized order does not readily attribute prolonged headache to a single rTMS frequency.

The mean reported levels of pain and discomfort evoked by TMS jamming ranged from 2.4/10 to 3.6/10 NRS. The maximum levels were between 4.6/10 and 6.0/10 NRS and were mostly reported when stimulating the frontolateral, temporopolar or perisylvian region. These findings agree with the results of Bockardt et al. (2006) who reported pain levels of 5–6/10 (stimulation intensity 100% RMT) vs. 7–8/10 (stimulation intensity 120% RMT) when applying 10 Hz rTMS over the dorsolateral prefrontal cortex and are in line with recent multicentre data on language mapping side effects (Tarapore et al. 2016a). Moreover, muscle-related discomfort during stimulations over the inferior frontal and the superior temporal gyrus has previously been observed (Lioumis et al. 2012). When comparing rTMS protocols, we observed a statistical trend towards better tolerability of the 50 Hz rTMS as compared to 10 Hz rTMS. We hypothesized that the discomfort of rTMS language mapping was mainly a result of unavoidable stimulation of trigeminal and facial nerve branches in the magnetic field area and, therefore, might be at least partially linked to the applied stimulation intensity which was roughly 10% lower in the 30/50 Hz condition as compared to 10 Hz (due to the MIT results). We assumed that, if our hypothesis was correct, the stimulation intensities of the respective sessions and TMS protocols should show a positive correlation with the discomfort levels, which did not prove right in this data set where we only found a statistical trend towards a weak non-parametric correlation with the maximum NRS scores ($rho = .16$; $p < 0.1$) but no significant correlation with the average NRS pain levels. High stimulation intensity alone, therefore, should be regarded a minor reason for discomfort during language mapping and seems to be out-run by other influences, mainly related to the stimulation frequency and possibly train duration. In line with this rather unexpected result, PP was best tolerated although stimulated with highest intensities as compared to all rTMS protocols ($p < 0.05$). Here, the much shorter train duration in PP (7 ms vs. 500–1500 ms for rTMS) might be responsible for the significant difference in tolerability. Thus, our findings agree only partly with those of previous studies which have shown a significant correlation between stimulation intensity and discomfort (Bockardt et al. 2006).

The stimulation-related discomfort might, however, explain the low specificity of task-locked rTMS language mapping strategies (Kuipers et al. 2013; Picht et al. 2013) to some extent and emphasize the necessity to optimize rTMS protocols, at least when aiming at the frontolateral and anterior temporal region. Previous attempts to overcome this problem by local injection of anaesthetics (lidocaine) in the targeted scalp area prior to rTMS, as suggested by Bockardt et al. (2006), have not yet proven effective since the encouraging results from the pilot study could only partially be repeated afterwards (Trevino et al. 2011).

Silent Periods

CSPs were compared between the different TMS protocols and face muscles regarding the frequency of occurrence (amount), latency and duration.

Amounts

Most cSPs were evoked in the PP protocol with the given ISI of 7 ms, thus corresponding to a frequency of ~ 140 Hz, and in the rTMS conditions of highest frequencies (i.e., 30 and 50 Hz). We, therefore, suggest that higher-frequency stimulation may be more powerful to elicit cSPs—both when applied at low stimulation intensities (e.g., 50 Hz rTMS) or using less stimuli per train (PP). TMS-induced excitatory effects on both cortical inhibitory interneurons (Cruccu et al. 1997) and descending corticobulbar pathways, affecting inhibitory interneurons on the brainstem level (Sowman et al. 2008), have been discussed as potential mechanisms. Although a significant correlation between the ISI and the amount of cSPs was observed ($rho = -.51$, $p = 0.0004$; data not shown), pulse repetition rate (frequency) might not fully explain the differences in outcome between protocols: e.g., jamming effects related to the number of pulses per train might have influenced the cortical excitation-inhibition-balance unequally. Another important factor is the train length

which interferes with the timing of language processing. In particular, the significantly different train durations ranging from 7 to 1500 ms, given the time-window of cSP analysis of up to 400 ms after the last train pulse, might have been a major reason why most cSPs were found following PP since language processing for picture naming occurs mainly between 150 and 500 ms after stimulus presentation (Salmelin 2007; Indefrey 2011; Strijkers et al. 2017) and hence only the TMS-elicited cSPs of the PP protocol fell into this 150–500 ms window. The increased rate of articulation-related speech errors in the data subset only including trials with evoked cSPs as compared to all trials (PP condition; n.s.) further support this hypothesis.

As expected due to the stronger involvement in speech, most cSPs in this study were elicited in the contralateral lower face muscles as compared to upper face muscles, i.e., orbicularis oculi and nasalis muscle. This finding may mirror the higher activation level and wider cortical distribution of lower face muscle representations during a speech task. Since voluntary, goal-directed muscle activity modulates cortical excitability significantly (Ortu et al. 2008), lower face muscles may be most prone to various intensity- and frequency-dependent rTMS and PP effects and polysynaptic inhibition during speech. Our results should, therefore, be interpreted with caution when compared with studies conducted at rest (Paradiso et al. 2005). The bilateral detection of cSPs in the orbicularis oris muscles supports the hypothesis of Muellbacher et al. (2001) who suggested a common cortical network for ipsi- and contralateral face muscles, showing highly similar intracortical inhibition and facilitation on both face sides by PP. The bilaterality of the mouth and tongue somatosensory system further supports this notion (Karhu et al. 1991).

Latencies

The latencies of cSPs were influenced by both recorded muscles and TMS protocols. Amongst rTMS protocols, there was a trend towards shorter cSP latencies at higher rTMS frequencies. In all TMS conditions, shortest latencies were observed in the masseter muscle. The data distribution amongst the other muscles, however, differed significantly between rTMS and PP conditions. A tendency towards shorter latencies of cSPs from the ipsilateral (left) vs. the contralateral orbicularis oris muscle was observed. Although not statistically significant-probably as a result of insufficient statistical power-this tendency may be explained by shorter conduction times of the uncrossed corticobulbar projections. In contrast, short latencies in the masseter muscle may be due to faster poly-synaptic conduction in the trigeminal system (Cruccu et al. 1997). The cortical locations of the TMS-evoked cSPs showed high inter-individual variability in all of the TMS protocols which reflects the overall heterogeneity of rTMS and PP effects on the human brain. Interestingly, the cSPs were not only evoked when stimulating over the M1 representation of the face (i.e. frontolateral), but also, e.g., in the inferior-parietal and superior-temporal region. Thus, the data suggest that rTMS and PP of associated, yet distinct cortical areas involved in speech production/language processing can evoke cSPs in face muscles. This finding may contribute to the understanding of the underlying neurophysiological mechanisms which lead to non-response errors or speech errors such as dysarthria in language mapping studies and, therefore, deserves being specifically addressed in future studies, including a limited bunch of anatomical locations and tasks (rest, tonic contraction, speech task).

Duration

In line with previous findings of high inter-individual variability of cSP durations, ranging from 22 ± 7 ms (masseter muscle) over 32 ± 12 ms (orbicularis oris muscle) (Desiato et al. 2002) to 134 ± 32 ms for mentalis muscle as investigated by supra-threshold single-pulse TMS (stimulation intensity 150% RMT) (Werhahn et al. 1995), we observed a wide range of cSP durations and a significant influence of both muscle and rTMS protocol on this parameter. At least for PP, our data (statistical trend) tend to support previous findings of slightly shorter cSP durations in masseter muscle as compared to orbicularis oris muscle in healthy subjects (Desiato et al. 2002). However, other studies did not find any differences in cSP duration between facial muscles with trigeminal and facial nerve supply (Cruccu et al. 1997). Longest cSPs were evoked by PP, but a significant difference was found only in comparison to 50 Hz rTMS. In part, higher stimulation intensities applied in the PP protocol may explain the slightly prolonged cSP durations (Lang et al. 2006). Moreover, the data distribution differed clearly between rTMS and PP, in particular regarding the relationship between cSP durations in the trigeminal- vs. facial-nerve-supplied muscles. This supports not only the finding of a significant muscle-protocol-interaction in general but also highlights the differences in neurophysiological mechanisms underlying rTMS vs. PP effects.

Depending on the inter-stimulus interval, PP seems to act mainly via short-interval intracortical inhibition (mainly if ISI < 5 ms) or facilitation (mainly if ISI > 10 ms) of peripheral (Kujirai et al. 1993) as well as on corticobulbar (Ortu et al. 2008) motor responses, primarily based on GABA-mediated effects on cortical interneurons and the I-wave-periodicity (Ilic et al. 2002). PP, applied with an ISI of 7 ms in active conditions like in this study, can have both facilitating and inhibitory effects (Pilurzi et al 2013) which may partially explain the rather low rate of induced cSPs. In contrast, high-frequency rTMS applied at (sub-)threshold intensities,

presumably best investigated with a stimulation frequency of 5 Hz, seems to act via short-lasting reduction of GABAergic intracortical inhibition (Di Lazzaro et al. 2002).

General Considerations Regarding Comparative Statistics and Limitations

Overall, cSPs were rare events, ranging from 0 to 10% of stimulation sites, and depended on various factors, i.e., muscle, TMS protocol and neurobiological conditions (as reflected by the factor 'subject'). Moreover, (i) spontaneous fluctuations of cortical excitability as a result of non-constant brain-state in general as well as (ii) different neurobiological effects depending on the stimulation site must be considered but are extremely hard to control (Silvanto et al. 2007; Ridding and Ziemann 2010). In addition, using an overt speech task instead of a rather steady, tonic muscle contraction as usual for the investigation of cSPs introduces an unevitable fluctuation in the EMG signal, thus leading to reduced reliability and sensitivity with regard to the detection of cSP's. For the analysis of the frequency of cSP occurrence, this statistical problem was addressed using an ANOVA. The analysis of the durations and latencies, however, was a major concern. Here, it did not seem appropriate to include the data points corresponding to TMS trains which did not evoke a cSP ('missing values') as numerical values (i.e., 0) when aiming at comparison of means. Therefore, the analysis was performed in two steps: (i) analysis of effects using ANOVA with 'missing values' included as zeros (Girden 1992), followed by (ii) comparison of paired means ('missing values' excluded). The relative rareness of cSP events in general and, particularly, the comparison of means from partially paired data (as a result of rare events) has been controversially discussed (Guo and Yuan 2017) and certainly represents a limitation regarding the interpretation of the results regarding cSP durations and latencies. However, we are convinced that we provided a coherent and rather conservative interpretation of the data obtained in this study.

Apart from methodological challenges related to the rareness of cSP events, the heterogeneous characteristics of the tested TMS protocols (i.e., stimulation intensity as adjusted to MIT, train duration and number of pulses) must be considered as potential contributors in addition to the pulse repetition rate/ rTMS frequency, as already discussed above (see Amounts). However, probably due to the study design which aimed at normalizing the stimulation intensity for the naming task to the individual susceptibility for neuromodulatory TMS effects on the cortex (as expressed by the MIT), no significant influence of the stimulation intensity on the cSP amounts was observed for rTMS (rho = .09, $p = 0.64$; data not shown). When including PP, an intensity effect was evident but likely represented an epi-phenomenon of the influence of the factor ISI, as revealed by partial correlations with the amount of cSPs (ISI: rho = − 0.32, $p = 0.05$; stimulation intensity: rho = .026, $p = 0.12$).

Also in the literature, important factors, especially the TMS protocols but also tasks, vary between studies which turns the discussion of the data, particularly MIT and cSP results, extremely difficult. Moreover, the electrical field distribution and strength are not comparable between different coil types and, indeed, not considered in the majority of studies (e.g., Desiato et al. 2002). However, these facts also confirm the need to investigate cortical excitability under conditions that correspond as exactly as possible to those of a potential clinical setting, *e.g.*, rTMS language mapping for presurgical diagnostics. Further studies are required to deepen the understanding for the correlation between TMS effects on motor language execution and behaviour, e.g. using short train stimulations ending in the time-window corresponding best to cortical processing during performance of the investigated task.

Conclusions

MIT determination seems to be a reliable and feasible approach to determine the task-dependent inhibitory effects of rTMS on motor cortex excitability. As compared to 10 Hz rTMS, the motor cortex seems more susceptible to inhibition induced by higher-frequent rTMS protocols. Those were more powerful in eliciting a visible movement disruption at sub-threshold stimulus intensities (in comparison with the RMT assessed by single-pulse TMS) which, given the dependency of discomfort on stimulation intensity, might partly explain the better tolerability. Moreover, a statistical trend towards more elicited cSPs was observed for rTMS at higher frequencies compared to 10 Hz-rTMS. PP, however, induced more cSPs than any rTMS frequency, presumably reflecting a stronger intracortical inhibition for short inter-stimulus intervals (corresponding to a frequency of > 100 Hz) and due to the short train duration which allowed for analyzing cSPs the time-window of important language processing steps (i.e., up to 407 ms after picture presentation).

In all rTMS frequencies, cSPs were evoked not only over the M1 representation of the face, but also in language-associated and anatomically connected cortical areas such as the inferior-parietal and superior-temporal region. This may mirror the potential of rTMS and, particularly, PP to evoke polysynaptic inhibition in the language network from distant cortical sites during speech and should be explored more in detail in future studies.

Taken together, this study does not only contribute to the understanding of the neurophysiological mechanisms leading to inhibition of the motor and speech network but may also help to improve the design and the interpretation of

future TMS language experiments by considering (i) the use of better tolerated and probably more efficient train stimulation with short ISI, (ii) the potential of using cSPs induced in lower face muscles as a marker for TMS jamming effects and (iii) the motor-speech component of behavioural (r)TMS effects on language execution, e.g., dysarthria or stuttering.

Acknowledgements The navigated TMS system used in the study was funded by the German Research Foundation (DFG, INST 1850/50-1). Author CWL received funding from the University of Cologne, Faculty of Medicine (Grant: Gerok 8/2016). The study received funding from the State Research Funding granted for the Kuopio University Hospital Catchment Area (project 5041730, Kuopio, Finland). In addition, author EK was funded by the Kaute Foundation, Helsinki, Finland, The Paulo Foundation, Helsinki, Finland, and The Finnish Concordia Fund, Helsinki, Finland.

Compliance with Ethical Standards

Disclosure of Potential Conflicts of interest Petro Julkunen has received unrelated consulting pay from Nexstim Plc., manufacturer of the nTMS device. Jari Karhu is employed part-time by Nexstim Plc., manufacturer of the nTMS device and holds shares of the company but was not involved in data acquisition, processing or analysis.

Research Involving Human Participants and/or Animals The research involved voluntary human participants who received a minor financial compensation for participating in the study. The study was approved by the local Ethics Committee. All procedures were performed in accordance with the ethical standards of the institutional committee and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed Consent Written informed consent was obtained from all individual participants included in the study.

References

Abbruzzese G, Trompetto C (2002) Clinical and research methods for evaluating cortical excitability. J Clin Neurophysiol 19(4):307–321

Anderson BS, Kavanagh K, Borckardt JJ, Nahas ZH, Kose S, Lisanby SH, McDonald WM, Avery D, Sackeim HA, George MS (2009) Decreasing procedural pain over time of left prefrontal rTMS for depression: initial results from the open-label phase of a multi-site trial (OPT-TMS). Brain Stimulation 2:88–92

Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc B 57(1):289–300

Bockardt JJ, Smith AR, Hutcheson K, Johnson K, Nahas Z, Anderson B, Schneider MB, Reeves ST, George MS (2006) Reducing pain and unpleasantness during repetitive transcranial magnetic stimulation. J ECT 22(4):259–264

Butler SL, Miles TS, Thompson PD, Nordstrom MA (2001) Task-dependent control of human masseter muscles from ipsilateral and contralateral motor cortex. Exp Brain Res 137:65–70

Chen R, Gerloff C, Classen J, Wassermann EM, Hallett M, Cohen LG (1997) Safety of different inter-train intervals for repetitive transcranial magnetic stimulation and recommendations for safe ranges of stimulation parameters. Electroencephalogr Clin Neurophysiol 105(6):415–421

Cruccu G, Inghilleri M, Berardelli A, Romaniello A, Manfredi M (1997) Cortical mechanisms mediating the inhibitory period after the magnetic stimulation of the facial motor area. Muscle Nerve 20:418–424

Danner N, Julkunen P, Könönen M, Säisänen L, Nurkkala J, Karhu J (2008) Navigated transcranial magnetic stimulation and computed electric field strength reduce stimulator-dependent differences in the motor threshold. J Neurosci Methods 174(1):116–122

De Gennaro L, Marzano C, Veniero D, Moroni F, Fratello F, Curcio G, Ferrara M, Ferlazzo F, Novelli L, Pellicciari MC, Bertini M, Rossini PM (2007) Neurophysiological correlates of sleepiness: a combined TMS and EEG study. NeuroImage 33:1277–1287

Desiato MT, Bernardi G, Hagi HA, Boffa L, Caramia MD (2002) Transcranial magnetic stimulation of motor pathways directed to muscles supplied by cranial nerves in amyotrophic lateral sclerosis. Clin Neurophysiol 113:132–140

Devlin JT, Watkins KE (2007) Stimulating language: insights from TMS. Brain 130(3):610–622

Di Lazzaro V, Rothwell JC (2014) Corticospinal activity evoked and modulated by non-invasive stimulation of the intact human motor cortex. J Physiol 592(19):4115–4128

Di Lazzaro V, Oliviero A, Mazzone P, Pilato F, Saturno E, Dileone M, Insola A, Tonali PA, Rothwell JC (2002) Short-term reduction of intracortical inhibition in the human motor cortex induced by repetitive transcranial magnetic stimulation. Exp Brain Res 147:108–113

Downar J, Daskalakis ZJ (2013) New targets for rTMS in depression: a review of convergent evidence. Brain Stimulation 6:231–240

Dubach P, Guggisberg AG, Rösler KM, Hess CW, Mathis J (2004) Significance of coil orientation for motor evoked potentials from nasalis muscle elicited by transcranial magnetic stimulation. Clin Neurophysiol 115(4):862–870

Girden E (1992) ANOVA: Repeated measures. Sage university paper series on quantitative applications in the social sciences. Sage, Newbury Park, 07–084

Greenhouse SW, Geisser S (1959) On methods in the analysis of profile data. Psychometrika 24:95–112

Grefkes C, Fink GR (2016) Noninvasive brain stimulation after stroke: it is time for large randomized controlled trials! Curr Opin Neurol 29(6):714–720

Guggisberg AG, Dubach P, Hess CW, Wüthrich C, Mathis J (2001) Motor evoked potentials from masseter muscle induced by transcranial magnetic stimulation of the pyramidal tract: the importance of coil orientation. Clin Neurophysiol 112:2312–2319

Guo B, Yuan Y (2017) A comparative review of methods for comparing means using partially paired data. Stat Methods Med Res 26(3):1323–1340

Huynh H, Feldt LS (1976) Estimation of the Box correction degrees of freedom from sample data in randomised block and split-plot designs. J Educ Stat 1(1):69–82

Ilić TV, Meintzschel F, Cleff U, Ruge D, Kessler KR, Ziemann U (2002) Short-interval paired-pulse inhibition and facilitation of human motor cortex: the dimension of stimulus intensity. J Physiol 545(1):153–167

Indefrey P (2011) The spatial and temporal signatures of word production components. Front Neuropsychol 2:255

Jaberzadeh S, Sakuma S, Zoghi M, Miles TS, Nordstrom MA (2008) Focal transcranial magnetic stimulation of the motor cortex evokes bilateral and symmetrical silent periods in human masseter muscles. Clin Neurophysiol 119:693–703

Janicak PG, O'Reardon JP, Sampson SM, Husain MM, Lisanby SH, Rado JT, Heart KL, Demitrack MA (2008) Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. J Clin Psychiatry 69:222–232

Kallioniemi E, Säisänen L, Könönen M, Awiszus F, Julkunen P (2014) On the estimation of silent period thresholds in transcranial magnetic stimulation. Clin Neurophysiol 125(11):2247–2252

Kamble N, Netravathi M, Pal PK (2014) Therapeutic applications of repetitive transcranial magnetic stimulation (rTMS) in movement disorders: a review. Parkinsonism Relat Disord 20:695–707

Karhu J, Hari R, Lu ST, Paetau R, Rif J (1991) Cerebral magnetic fields to lingual stimulation. Electroencephalogr Clin Neurophysiol 80(6):459–468

Krieg SM, Lioumis P, Mäkelä JP, Wilenius J, Karhu J, Hannula H, Salvolainen P, Lucas CW, Seidel K, Laakso A, Islam M, Vaalto S, Lehtinen H, Vitikainen AM, Tarapore PE, Picht T (2017) Protocol for motor and language mapping by navigated TMS in patients and healthy volunteers; workshop report. Acta Neurochir 159(7):1187–1195

Kuipers JR, van Koningsbruggen M, Thierry G (2013) Semantic priming in the motor cortex: evidence from combined repetitive transcranial magnetic stimulation and event-related potential. Neuroreport 24(12):646–651

Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P, Marsden CD (1993) Corticocortical inhibition in human motor cortex. J Physiol 471:501–519

Lang N, Harms J, Weyh T, Lemon RN, Paulus W, Rothwell JC, Siebner H (2006) Stimulus intensity and coil characteristics influence the efficacy of rTMS to suppress cortical excitability. Clin Neurophysiol 117:2292–2301

Lefaucheur JP, Antal A, Ahdab R, Ciampi de Andrade D, Fregni F, Khedr EM, Nitsche M, Paulus W (2008) The use of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) to relieve pain. Brain Stimulation 1:337–344

Lefaucheur JP, Adré-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, Cantello RM, Cincotta M, de Carvalho M, De Ridder D, Kimiskidis VK, Koch G, Langguth B, Nyffeler T, Oliviero A, Padberg F, Poulet E, Rossi S, Rossini PM, Rothwell JC, Schönfeldt-Lecuona C, Siebner HR, Slotema CW, Stagg CJ, Valls-Sole J, Ziemann U, Paulus W, Garcia-Larrea L (2014) Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol 125(11):2150–2206

Lioumis P, Zhdanov A, Mäkelä N, Lehtinen H, Wilenius J, Neuvonen T, Hannula H, Deletis V, Picht T, Mäkelä JP (2012) A novel approach for documenting naming errors induced by navigated transcranial magnetic stimulation. J Neurosci Meth 204:349–354

Machii K, Cohen D, Ramos-Estebanez C, Pascual-Leone A (2006) Safety of rTMS to non-motor cortical areas in healthy participants and patients. Clin Neurophysiol 117:455–471

McMillian AS, Watson C, Walshaw D (1998) Transcranial magnetic-stimulation mapping of the cortical topography of the human masseter muscle. Arch Oral Biol 43:925–931

McMillian AS, Graven-Nielsen T, Romaniello A, Svensson P (2001) Motor potentials evoked by transcranial magnetic stimulation during isometric and dynamic masseter muscle contraction in humans. Arch Oral Biol 46:381–386

Muellbacher W, Boroojerdi B, Ziemann U, Hallett M (2001) Analogous corticocortical inhibition and facilitation in ipsilateral and contralateral human motor cortex representations of the tongue. J Clin Neurophysiol 18(6):550–558

Nordstrom MA (2007) Insights into the bilateral cortical control of human masticatory muscles revealed by transcranial magnetic stimulation. Arch Oral Biol 52:338–342

O'Connel NE, Wand BM, Marston L, Spencer S, Desouza LH (2014) Non-invasive brain stimulation techniques for chronic pain. Cochrane Database Syst Rev 11(4):CD008208

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9(1):97–113

Ortu E, Deriu F, Suppa A, Giaconi E, Tolu E, Rothwell JC (2008) Intracortical modulation of cortico-bulbar responses for the masseter muscle. J Physiol 586(14):3385–3404

Paradiso GO, Cunic DI, Gunraj CA, Chen R (2005) Representation of facial muscles in human motor cortex. J Physiol 567(1):323–336

Pascual-Leone A, Walsh V, Rothwell J (2000) Transcranial magnetic stimulation in cognitive neuroscience—virtual lesion, chronometry, and functional connectivity. Curr Opin Neurobiol 10(2):232–237

Patton HD, Amassian VE (1954) Single- and multiple-unit analysis of cortical stage of pyramidal tract activation. J Neurophysiol 17:345–363

Picht T, Krieg SM, Sollmann N, Rösler J, Niraula B, Neuvonen T, Savolainen P, Lioumis P, Mäkelä JP, Deletis V, Meyer B, Vajkoczy P, Ringel F (2013) A comparison of language mapping by preoperative navigated transcranial magnetic stimulation and direct cortical stimulation during awake surgery. Neurosurgery 72(5):808–819

Pilurzi G, Hasan A, Saifee TA, Tolu E, Rothwell JC, Deriu F (2013) Intracortical circuits, sensorimotor integration and plasticity in human motor cortical projections to muscles of the lower face. J Physiol 591(7):1889–1906

Ridding MC, Ziemann U (2010) Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. J Physiol 588(13):2291–2304

Rödel R, Laskawi R, Markus H (1998) Transcranial cortical magnetic stimulation of lower-lip mimetic muscles: effect of coil position on motor evoked potentials. ORL J Otorhinolaryngol Relat Spec 61:119–125

Rösler KM, Hess CW, Schmid UD (1989) Investigation of facial motor pathways by electrical and magnetic stimulation: sites and mechanisms of excitation. JNNP J Neurol Neurosurg Psychiatry 52:1149–1156

Rossi S, Hallett M, Rossini PM, Pascual-Leone A, The Safety of TMS Consensus Group (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 120: 2008–2039

Rothwell JC, Hallett M, Berardelli A, Eisen A, Rossini P, Paulus W (1999) Magnetic stimulation: motor evoked potentials. The international federation of clinical neurophysiology. Electroenceph Clin Neurophysiol Suppl 52:97–103

Säisänen L, Pirinen E, Teitti S, Könönen M, Julkunen P, Määtä S, Karhu J (2008) Factors influencing cortical silent period: Optimized stimulus location, intensity and muscle contraction. J Neurosci Meth 169:231–238

Säisänen L, Julkunen P, Kemppainen S, Danner N, Immonen A, Mervaala E, Määttä S, Muraja-Murro A, Könönen M (2015) Locating and outlining the cortical representation areas of facial muscles with navigated TMS. Neurosurgery 77(3):394–405

Salmelin R (2007) Clinical neurophysiology of language: The MEG approach. Clin Neurophysiol 118:237–254

Silvanto J, Muggleton NG, Cowey A, Walsh V (2007) Neural adaptation reveals state-dependent effects of transcranial magnetic stimulation. Eur J Neurosci 25:1874–1881

Snodgrass JG, Vanderwart M (1988) A standardized set of 260 Pictures: norms for name agreement, image agreement, familiarity and visual complexity. J Exp Psychol 6(2):174–215

Sowman PF, Flavel SC, McShane CL, Miles TS, Nordstrom MA (2008) Transcranial magnetic stimulation reduces masseter motoneuron pool excitability throughout the cortical silent period. Clin Neurophysiol 199:1119–1129

Strijkers K, Costa A, Pulvermüller F (2017) The cortical dynamics of speaking: lexical and phonological knowledge simultaneously recruit the frontal and temporal cortex within 200 ms. Neuroimage 163:206–219

Suppa A, Marsili L, Giovannelli F, Di Stasio F, Rocchi L, Upadhyay N, Ruoppolo G, Cincotta M, Berardelli A (2015) Abnormal motor cortex excitability during linguistic tasks in adductor-type spasmodic dysphonia. J Eur Neurosci 42:2051–2060

Tarapore PE, Findlay AM, Honma SM, Mizuiri D, Houde JF, Berger MS, Nagarajan SS (2013) Language mapping with navigated repetitive TMS: proof of technique and validation. NeuroImage 82:260–272

Tarapore PE, Picht T, Bulubas L, Shin Y, Kulchytska N, Meyer B, Nagarajan SS, Krieg SM (2016a) Safety and tolerability of navigated TMS in healthy volunteers. Clin Neurophysiol 127(3):1916–1918

Tarapore PE, Picht T, Bulubas L, Shin Y, Kulchytska N, Meyer B, Berger MS, Nagarajan SS, Krieg SM (2016b) Safety and tolerability of navigated TMS for preoperative mapping in neurosurgical patients. Clin Neurophysiol 127(3):1895–1900

Teo WP, Kannan A, Loh PK, Chew E, Sharma VK, Chan YC (2014) Poor tolerance of motor cortex rTMS in chronic migraine. J Clin Diagn Res 8(9):MM01–M2

Terao Y, Ugawa Y (2002) Basic mechanisms of TMS. J Clin Neurophysiol 19(4):322–343

Theodoroff SM, Folmer RL (2013) Repetitive transcranial magnetic stimulation as a treatment for chronic tinnitus: a critical review. Otology Neurotology 34:199–208

Trevino K, McClintock SM, Husain MM (2011) the use of topical lidocaine to reduce pain during repetitive transcranial magnetic stimulation for the treatment of depression. J ECT 27(1):44–47

van de Ruit M, Grey MJ (2016) The TMS Map Scales with Increased Stimulation Intensity and Muscle Activation. Brain Topogr 29:56–66

Wassermann EM (1998) Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop of the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalogr Clin Neurophysiol 108, 1–16

Wassermann EM, Lisanby SH (2001) Therapeutic application of repetitive transcranial magnetic stimulation: a review. Clin Neurophysiol 112:1367–1377

Watson C, Walshaw D, McMillian AS (2000) Effect of motor tasks on the cortical topography of the human masseter muscle. Arch Oral Biol 45:767–773

Weiss C, Nettekoven CM, Rehme A, Neuschmelting V, Eisenbeis A, Goldbrunner R, Grefkes C (2012) The importance of latency correction for navigated TMS mapping, especially of the face and the tongue area: a Technical Note. Klin Neurophysiol 43:P137

Weiss C, Nettekoven C, Rehme AK, Neuschmelting V, Eisenbeis A, Goldbrunner R, Grefkes C (2013) Mapping the hand, foot and face representations in the primary motor cortex–retest reliability of neuronavigated TMS versus functional MRI. NeuroImage 66:531–542

Weiss C, Tursunova I, Neuschmelting V, Lockau H, Nettekoven C, Oros-Peusquens AM, Stoffels G, Rehme AK, Faymonville AM, Shah NJ, Langen KJ, Goldbrunner R, Grefkes C (2015) Improved nTMS- and DTI-derived CST tractography through anatomical ROI seeding on anterior pontine level compared to internal capsule. NeuroImage: Clin 7:424–437

Werhahn KJ, Classen J, Benecke R (1995) The silent period induced by transcranial magnetic stimulation in muscles supplied by cranial nerves: normal data and changes in patients. JNNP J Neurol Neurosurg Psychiatry 59:586–596

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.