Time-dependent functional role of the contralesional motor cortex after stroke

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ABSTRACT

After stroke, movements of the paretic hand rely on altered motor network dynamics typically including additional activation of the contralesional primary motor cortex (M1). The functional implications of contralesional M1 recruitment to date remain a matter of debate.

We here assessed the role of contralesional M1 in 12 patients recovering from a first-ever stroke using *online* transcranial magnetic stimulation (TMS): Short bursts of TMS were administered over contralesional M1 or a control site (occipital vertex) while patients performed different motor tasks with their stroke-affected hand.

In the early subacute phase (1–2 weeks post-stroke), we observed significant improvements in maximum finger tapping frequency when interfering with contralesional M1, while maximum grip strength and speeded movement initiation remained unaffected. After > 3 months of motor recovery, disruption of contralesional M1 activity did not interfere with performance in any of the three tasks, similar to what we observed in healthy controls.

In patients with mild to moderate motor deficits, contralesional M1 has a task- and time-specific negative influence on motor performance of the stroke-affected hand. Our results help to explain previous contradicting findings on the role of contralesional M1 in recovery of function.

1. Introduction

Impaired motor function after stroke is typically accompanied by altered motor network activation and interaction patterns (Grefkes and Fink, 2014). During movement of the paretic hand, changes in neural activity are not limited to the affected hemisphere, but also occur in the contralesional, i.e., "healthy" hemisphere (Chollet et al., 1991; Ward et al., 2003; Weiller et al., 1992). Yet to date, the functional implications of altered contralesional neural activation remain controversial: on the one hand, data from both animal models and humans suggest a supportive role of the contralesional hemisphere on motor function (Biernaskie et al., 2005; Johansen-Berg et al., 2002; Lotze et al., 2006; Rehme et al., 2011). By contrast, this view is challenged by results from multiple studies emphasizing a potentially maladaptive influence of the contralesional hemisphere, and specifically the contralesional M1 which may exert a functionally relevant inhibition upon the ipsilesional M1 and thereby deteriorate motor function of the paretic hand (Grefkes

et al., 2010; Murase et al., 2004; Takeuchi et al., 2012). These contradictory results have been attributed to different levels of motor impairment and varying time points post-stroke, which may affect the neural activation levels in contralesional M1 and their functional implications (please see Grefkes and Ward, 2014 for detailed discussion). For example, the functional role of contralesional M1 may critically depend on the extent of damage to ipsilesional M1 and its descending pathways (Di Pino et al., 2014).

Taken together, these findings highlight the question whether the functional role of the contralesional hemisphere may primarily depend on (i) the stage of cortical reorganization, i.e., time point following stroke, and (ii) which motor task has to be executed by the affected hand.

One way to assess the causal role of a cortical region in a given task lies in applying transcranial magnetic stimulation (TMS) to this region during task performance (i.e., creating a *virtual lesion* by *online TMS*) (Gerloff et al., 1998a, 1998b; Lotze et al., 2006; Pascual-Leone et al.,

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1991). Alternatively, repetitive TMS (rTMS) can be applied *offline* i.e., prior to task performance, making use of aftereffects induced by rTMS. However, these aftereffects have been shown to be inconsistent and sometimes even opposite between subjects (Hamada et al., 2013). Conversely, online TMS directly depolarizes neural tissue, thereby transiently deteriorating the task-induced fine-tuned neural activation, which in turn results in altered task performance during the time of stimulation (Walsh and Cowey, 2000) and represents a well-established and safe experimental approach (e.g., Gerloff et al., 1998a, 1998b; Lotze et al., 2006; Rossi et al., 2009; Schluter et al., 1998). As behavioral and neural effects are time-locked to the stimulation period without relevant carry-over effects, online TMS allows testing several tasks and areas within the same experimental session, yielding a better balancing of verum and control stimulation, which is hardly possible when using offline rTMS designs with repeated application of protocols on the same day (for further details see Rossi et al., 2009). Such a setup is especially useful in time-sensitive and dynamic conditions which may change over days, e.g., (sub-) acute stroke.

Therefore, in order to further our insights into the task- and time-dependent functional role of the contralesional M1 after stroke, we here applied online TMS to the contralesional M1 of recovering stroke patients during the execution of three motor tasks of varying motor demands. In a cross-over, sham-stimulation controlled, longitudinal design, 12 first-ever stroke patients were tested for (i) maximum grip strength, (ii) maximum index finger tapping frequency, and (iii) speeded movement initiation in a simple reaction time task. In order to probe time-dependent effects, patients were tested twice, i.e., in the early subacute phase (1–2 weeks post-stroke) and in the early chronic phase (3–6 months post-stroke). In addition, a group of 14 healthy age-matched controls served as physiological reference for motor performance and TMS intervention effects. Since simple motor tasks typically rely on activation within M1 contralateral to the moving hand, we hypothesized that interfering with M1 activity ipsilateral to the moving hand would not affect motor performance in healthy participants. In contrast, we expected that interfering with the contralesional "healthy" M1 modulates task performance in stroke patients, especially in the early subacute phase when contralesional activity is typically upregulated (Rehme et al., 2011; Ward et al., 2003). Moreover, we hypothesized that TMS interference with contralesional M1 may have task-dependent effects, since the level of bilateral neural activity (extending to contralesional M1), has been shown to strongly depend on the utilized motor task (Rehme et al., 2012).

2. Materials and methods

2.1. Subjects

Twelve patients (mean age: 69.3 years ± 11.4 years (SD); 4 female; 1 left-handed) suffering from a first-ever ischemic stroke that caused a mild to moderate unilateral hand motor deficit (NIHSS score: 4.1 ± 1.9, range: 1–7) were recruited from the Department of Neurology, University Hospital of Cologne. Eight of twelve originally included patients could be re-assessed at a chronic stage > 3 months after stroke (158.5 days ± 67.3 days post-stroke).

Inclusion criteria were: (i) age 40–90 years; (ii) ischemic stroke as verified by diffusion-weighted magnetic resonance imaging (DWI); (iii) time elapsed from symptom onset < 14 days (average: 5.0d ± 3.2d, range: 1–10 d); (iv) unilateral hand motor deficit; (v) absence of severe aphasia, apraxia, and neglect; (vi) no visual field deficit; and (vii) no other neurological disorders. Exclusion criteria were: (i) any contra-indication to TMS (e.g., epilepsy); (ii) infarcts in multiple territories; (iii) hemorrhagic stroke, and (vi) inability to perform the motor tasks because of severe hand weakness. Patient details are given in Table 1.

14 healthy controls (61.8 years ± 6.6 years; 9 female; 1 left-handed) were enrolled in the study. 5 out of 11 right-handed patients suffered from paresis of the non-dominant (left) hand. Accordingly, 5

out of 13 right-handed controls were tested with their non-dominant (left) hand. Furthermore, as the left-handed patient presented with a paretic dominant (left) hand, the left-handed control also performed the tasks with the dominant (left) hand. No significant age differences were evident when comparing patients and controls tested with the right hand (patients: 68.7 ± 11.8 years; controls: 61.9 ± 6.7 years; $p = 0.195$, independent t-test) nor for subjects performing the tasks with the left hand (patients: 69.8 ± 12.1 years; controls: 61.7 ± 7.0 years; $p = 0.183$, independent t-test).

All participants provided informed written consent before inclusion. The study was approved by the local ethics committee at the University of Cologne and it was performed in accordance to the Declaration of Helsinki.

2.2. Experimental design

TMS effects on motor performance were assessed using a within-subject cross-over design, i.e., all patients performed all motor tasks during both M1 and control stimulation during the same session. Recording both stimulation conditions in the same session has the advantage that a comparable behavioral readout is obtained, in contrast to offline rTMS where control and M1-stimulation have to be performed on different days or across different subjects due to the lasting influence on cortical excitability. This seems particularly important since sub-acute stroke patients may show improvements in motor function at a day-to-day rate. Of note, the order of stimulation, i.e., M1 and control stimulation, was counterbalanced across subjects.

During the maximum finger tapping task and the simple reaction time task, the performing hand was fixed to the table using two Velcro straps placed at the wrist and metacarpophalangeal joints. Hence, movements were constrained to the fingers in order to reduce the variability of task execution, which seems particularly important regarding potential changes in movement patterns compensating for loss of function after stroke (Buma et al., 2013). During the assessment of maximum grip strength, the Velcro strap placed over the metacarpophalangeal joints was removed so that subjects could hold the grip force sensor in a physiological and comfortable position.

Visual cues for all motor tasks were presented using Presentation® software (Version 0.70, www.neurobs.com), which also recorded keyboard motor responses for the simple reaction time and maximum finger tapping task. Maximum grip force was recorded using LabChart version 6.0 (ADInstruments Ltd., Dunedin, New Zealand) and analyzed via in-house MATLAB software.

All participants performed three different motor tasks probing different aspects of motor abilities in a highly standardized fashion time-locked to the brief TMS pulse trains. Each motor task was tested in several blocks of trials, and blocks were randomized across and between conditions (control-/M1-stimulation) to control for learning effects and fatigue.

2.3. Maximum finger tapping frequency task

This task was used to test fastrepetitive movements. Subjects performed vertical index finger tapping movements (approximately 2 cm in height, limited by a metacarpophalangeal Velcro strap) at maximum speed on a computer keyboard button upon a visual cue (trial duration: 3 s). A total of 10 assessments were recorded in 2 blocks with 5 trials for each condition (control stimulation, M1-stimulation).

2.4. Maximum grip strength task

This task was used to test maximum grip force generation. Maximum grip strength was assessed with a digital dynamometer (ADInstruments Ltd., Dunedin, New Zealand, connected to LabChart), upon a visual cue (trial duration: 3 s). A total of 9 assessments were performed in 3 blocks with 3 trials for each condition (i.e., 9

Table 1

Subject information. Abbreviations: f: female, m: male, r: right, l: left, NIHSS: National Institutes of Health Stroke Scale. Days since stroke refer to how many days after symptom onset patients were included into the study. NIHSS values reflect the neurological impairment of patients at inclusion (session 1). FT: maximum finger tapping frequency; RT: reaction times. FT, RT and grip strength values were assessed during sham stimulation (session 1).

|	Subject	Age	Gender	Handedness	Affected hand	Days post stroke	NIHSS	FT [Hz]	RT [ms]	Grip strength
Patients	1	55	m	r	r	8	6	5.10	294	367
	2	76	m	r	r	2	5	5.13	395	140
	3	78	f	r	l	10	5	2.46	381	170
	4	77	m	l	l	2	1	4.11	304	580
	5	46	m	r	l	8	5	1.99	395	124
	6	76	m	r	l	3	2	4.85	355	273
	7	72	f	r	l	4	4	3.48	347	105
	8	80	f	r	r	1	1	6.25	306	305
	9	54	m	r	r	3	3	5.18	275	457
	10	70	f	r	l	5	7	2.78	403	61
	11	79	m	r	r	10	5	5.10	306	435
	12	68	m	r	r	4	5	4.13	324	306
Controls	1	63	f	r	l			4.99	279	117
	2	66	f	r	l			5.33	302	232
	3	60	f	r	r			6.14	279	201
	4	67	f	r	l			5.55	285	250
	5	55	f	l	l			5.04	238	289
	6	68	m	r	l			6.25	259	746
	7	61	m	r	r			5.97	304	247
	8	61	m	r	r			6.34	273	353
	9	63	m	r	r			6.17	265	379
	10	62	m	r	r			5.90	274	659
	11	77	m	r	r			6.45	309	125
	12	51	f	r	l			5.29	259	447
	13	56	m	r	r			5.99	265	295
	14	55	m	r	r			6.99	230	637

assessments during control stimulation, and 9 assessments during M1-stimulation).

2.5. Speeded movement initiation: Simple reaction time task

This task was used to test speeded reaction time performance, which not only relies on basic motor abilities but also on movement selection and visuospatial attention. Hence, this task also tested more "cognitive-executive" aspects of motor performance. Patients performed a button press with the index finger of their stroke-affected hand as fast as possible upon appearance of a visual cue (Fig. 1, red circle centered on a black screen; cue duration: 500 ms). A total of 24 trials were recorded in 2 blocks with 12 consecutive reaction time assessments for each condition (control stimulation, M1-stimulation). Since time-constraints were less prominent in healthy controls, additional trials (total of 60 trials) were recorded to assess the robustness of performance measures. The first 12 trials of each block were considered for further analysis in order to ensure comparable task structure, i.e., comparing the same amount of trials between patients and healthy participants.

Task design
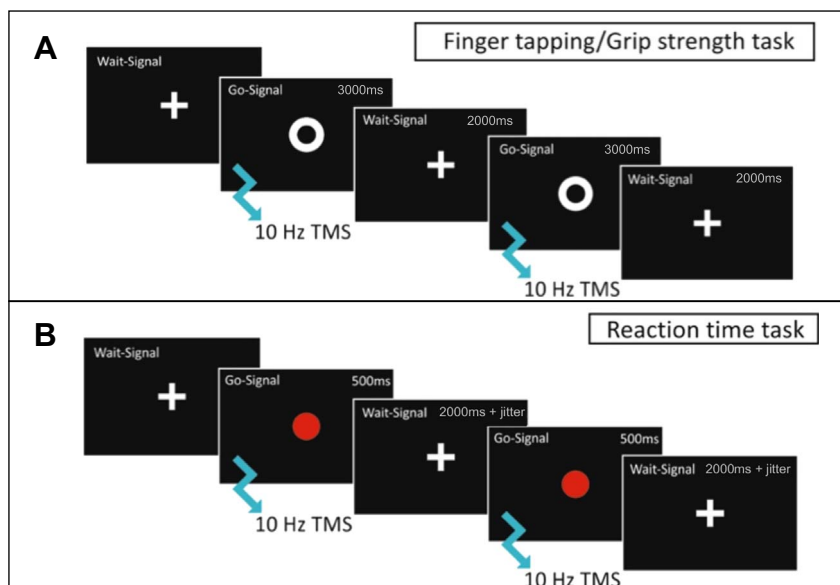
Fig. 1. *Online TMS* task design: (A) During the finger tapping and grip strength task, 10 Hz TMS was applied synchronously to the go-signal for 3 s, i.e., covering the entire performance period. (B) For the reaction time task, 500 ms (5 pulses) of 10 Hz TMS were applied 100 ms, 125 ms, or 150 ms after the go-signal. Accurate timing of the stimulation relative to the task performance was ensured by in-house Presentation® software controlling the TMS device.

2.6. TMS: cortical excitability and threshold determination

Cortical excitability was assessed via motor evoked potentials (MEPs). EMG activity was recorded from the abductor pollicis brevis muscle of the non-paretic hand, using Ag/AgCl surface electrodes in a belly-to-tendon montage. The EMG signal was sampled at 5 kHz, amplified, filtered (0.5 Hz high-pass and 30–300 Hz band-pass) and digitized using a Power-Lab 26 T device and the LabChart software package (ADInstruments Ltd., Dunedin, New Zealand). TMS was performed using a Magstim SuperRapid2 stimulator (The Magstim Co. Ltd., Whitland, UK) equipped with a 70 mm figure-of-eight air-cooled coil. The coil was oriented postero-laterally at an angle of ~ 45° to midline, to induce posterior-anterior (PA) directed electrical current at stimulation onset. Coil positions were recorded and maintained with a Brainsight2 computerized frameless stereotaxic system (Rogue Research Inc., Montreal, Canada). The resting motor threshold (RMT) was defined using an algorithm provided by the TMS Motor Threshold Assessment Tool 2.0 (http://www.clinicalresearcher.org/software.htm; Awiszus, 2003), which performs parameter estimation by sequential testing.

2.7. Online TMS

Brief trains of TMS pulses were applied at a frequency of 10 Hz and 90% RMT during task performance. A sub-threshold stimulation intensity was chosen to prevent the induction of muscle twitches in the hand contralateral to the stimulated M1, which may irritate participants and impact upon task performance.

During grip strength and finger tapping trials, the stimulation was administered throughout the trial for 3 s (= 30 pulses at 10 Hz). The stimulator was controlled and triggered by an in-house Presentation® script. While every TMS burst was triggered to ensure reliable timing of TMS application (see Fig. 1 A), the burst frequency of 10 Hz was defined as part of protocol within the stimulator. Importantly, potential temporal irregularities or inaccuracies of trigger pulses in the realm of a few milliseconds might have resulted in a very short delay of stimulation onset (which seems negligible given the stimulation duration of 500 ms or 3 s), but not a shift of stimulation frequency.

During the reaction time trials, stimulation lasted 500 ms (5 pulses) and was applied in a jittered fashion, i.e., 100, 125, or 150 ms after the visual go cue. The jitter prevented that subjects could anticipate the visual cue and hence ensured that the movement was triggered by the visual cue rather than the sound of the TMS pulse (see Fig. 1 B). Due to technical difficulties, some stimuli were applied without a jitter (i.e., simultaneous to visual-cue presentation) and were excluded from further analysis. The considerably shorter stimulation period (500 ms vs. 3 s) was chosen for the reaction time trials since motor responses were expected to be completed 500 ms after the movement cue (which indeed was the case for all participants, cf. Fig. 2). Extending the stimulation duration to be identical in all tasks, would have therefore led to most of the TMS pulses being applied after the motor response in the reaction time task had already been completed. Hence, a longer stimulation duration (like in the other two task) would not have resulted in any further interference with task performance but would have increased the total number of TMS pulses which was not desirable for the reason of safety and comfort.

For all trials, a between-trial interval of 2 s was inserted to clearly separate trials (thereby avoiding carry-over effects) and prevent muscular fatigue. M1-stimulation was applied over the hotspot of the contralesional hemisphere with the coil handle pointing outwards and backwards (enabling a posterior-anterior flow of current perpendicular to the central sulcus). Control stimulation was delivered at the same stimulation intensity utilized for M1-stimulation over the parieto-occipital vertex (Pz) in posterior-anterior direction in parallel to the inter-hemispheric fissure. To reduce possible cortical stimulation effects in

the control condition, the coil was angled at 45°, touching the skull not with the center but with the rim opposite the handle. In this position, the coil–cortex distance is increased such that the electromagnetic field, if at all reaching the cortex, is substantially weaker and far outside the target range (Herwig et al., 2010), to reduce potential current spread (Koch et al., 2007) or projection of stimulation induced activity to remote but inter-connected brain region (Nettekoven et al., 2014), ultimately resulting in modulation of neural activity in task-relevant regions. Importantly, this procedure has been shown to result in skin sensations that are indistinguishable from stimulation with the center of the coil touching the skull and therefore represents a valid control stimulation (Herwig et al., 2010).

Order of stimulation blocks was randomized across subjects. While the investigator applying the stimulation (M.V.) could not be blinded with regard to the nature of the stimulation (i.e., whether M1-stimulation or control stimulation was applied), automated data recording ensured interleaved M1-stimulation and control stimulation in a randomized order, and data analysis was performed by a separate author (L.J.V.) to minimize the risk of any investigator-bias introduced by the knowledge about the nature of the stimulation.

2.8. Voxel lesion symptom mapping

Magnetic resonance images were acquired in a clinical routine setting within the first 2 days after stroke for all patients on a 1.5 T MRI scanner using standard sequences (Philips, Guildford, UK). Individual lesion maps were created based on diffusion-weighted images (DWI), using ITK-SNAP (www.itksnap.org). After determination of individual lesion volumes, DWI images and lesion maps were first co-registered to individual T2-weighted images and subsequently normalized to the T2-weighted MNI template implemented in Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/). Lesions located in the right hemisphere (n = 5) were flipped along the mid-sagittal plane, so all lesions are shown in the left hemisphere.

To assess whether stimulation effects were associated with lesion location, voxel lesion symptom mapping (VLSM) was performed using the non-parametric mapping (NPM) software package (Rorden et al., 2007) with correction for multiple comparisons by the non-parametric permutation tests, as recommended for medium-sized samples (Kimberg et al., 2007; Medina et al., 2010).

2.9. Statistical analysis

Statistical analyses were performed using SPSS version 23 (Statistical Package for the Social Sciences, IBM). Median values were calculated across trials and utilized for further analysis to account for the considerable amount of within-subject variance in motor behavior observed in our patient cohort.

Motor performance for each paradigm was compared using a two-factorial ANOVA with the within-subject factor STIMULATION (M1, control) and the between-subject factor GROUP (patients, healthy controls). Data assessed in the subacute stage (session 1) and follow-up (session 2) were compared to healthy controls in separate ANOVAs, because control subjects were only assessed once and not at two different time-points. This simplification of the experimental design was chosen due to the systematic difference in anticipated variance. While stroke patients were expected to show substantial recovery (i.e., changes in variance of motor performance), variance in performance was expected to be considerably lower and adequately reflected by a single session in healthy controls.

To assess whether stimulation effects observed in patients early after stroke (session 1) were also evident after patients had recovered for > 3 months, a second ANOVA was computed including the within-subject factors STIMULATION (M1, control) and SESSION (session 1, session 2). Of note, only the 8 out of 12 patients that could be re-assessed > 3 months after stroke were included in this ANOVA due to

within-subject nature of the comparison. Post-hoc two-sided *t*-tests Bonferroni corrected for multiple comparisons were used to identify significant effects ($p < 0.05$).

In order to exclude a substantial bias of differences in stimulation intensities on stimulation effects (e.g., high intensity stimulation may have startled participants and thereby additionally disrupted task-performance) and the residual age difference between the control and patient cohort, additional ANOVAs including the RMT and age as covariates of no interest were computed.

3. Results

3.1. Cortical excitability

The RMT of the contralesional hemisphere did not differ between baseline (51.0% maximum stimulator output (MSO) ± 11.0%) and follow-up session in patients (53.6% MSO ± 10.8%; paired *t*-test: $t = 0.919$, $p = 0.389$) or between patients and healthy controls (56.43% MSO ± 12.6%; independent *t*-test session 1: $t = 1.172$, $p = 0.253$; independent *t*-test session 2: $t = 0.551$, $p = 0.589$), which is in line with a recent meta-analyses on cortical excitability changes after stroke (Mcdonnell and Stinear, 2017).

3.2. Motor performance in the subacute stage

The comparison of patients in the subacute stage and healthy controls (see Fig. 2) revealed a significant main effect of GROUP for finger tapping ($F_{(1,24)} = 15.825$, $p = 0.001$) and reaction times ($F_{(1,24)} = 15.105$, $p = 0.001$), but not maximum grip strength ($p = 0.2$). Hence, stroke patients featured significantly reduced finger tapping frequency and slower reaction times compared to healthy controls whereas grip strength

did not significantly differ between groups.

Moreover, there was no significant main effect or interaction involving the factor STIMULATION for maximum grip strength or simple reaction times (all $p > 0.2$). However, a significant main effect of STIMULATION ($F_{(1,24)} = 10.568$, $p = 0.003$) and a significant STIMULATION x GROUP interaction effect ($F_{(1,24)} = 6.541$, $p = 0.017$) were evident for finger tapping frequency.

Post-hoc *t*-tests revealed that patients featured faster maximum finger tapping frequencies during M1 stimulation compared to control stimulation ($t = 3.844$, $p = 0.005$, Bonferroni-corrected for multiple comparisons), while no effect was observed in healthy controls ($t = 0.524$, $p > 0.5$). When plotting the individual effects (displayed as z-scores after Fisher transformation in order to account for between-subject differences in absolute motor performance), it becomes evident that compared to both control stimulation and control subjects, stroke patients featured a clearly differential response upon TMS interference with contralesional M1 (Fig. 3). Directly comparing the effect of M1-stimulation and control stimulation revealed that maximum finger tapping frequency increased in patients by 7.3% ± 6.8% during M1-stimulation compared to control stimulation, while it remained almost constant in controls 0.6% ± 4.2% (independent *t*-test: $t = 3.049$, $p = 0.006$). This nicely demonstrates the specificity of the stimulation effect, which was exclusively observed in patients.

Controlling for the difference in stimulation intensity and age across subjects by including the RMT and age as covariates still resulted in a significant STIMULATION x GROUP interaction ($F_{(1,22)} = 5.841$, $p = 0.024$). Moreover, no significant correlation was evident between time-post stroke at recruitment and TMS effect on maximum finger tapping frequency ($r = 0.211$, $p = 0.510$), hence rendering a substantial bias of the recruitment time on our findings highly unlikely.

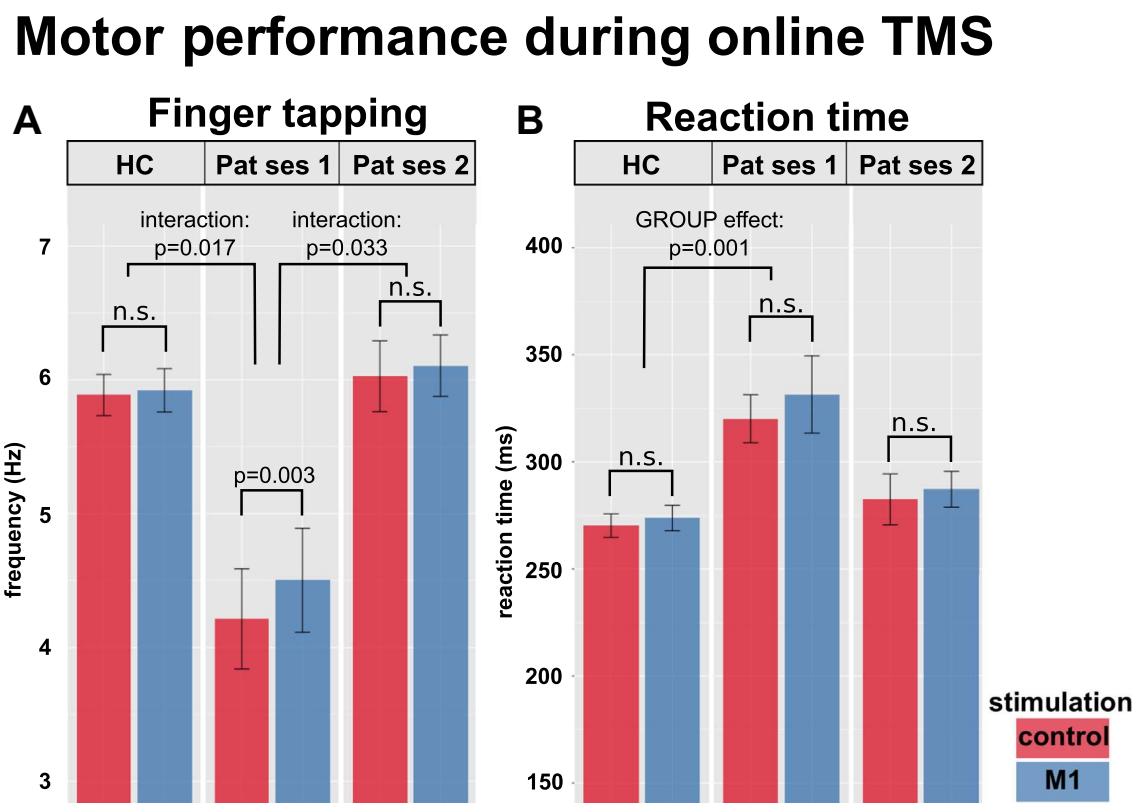Since 6 out of 12 patients, but 8 out of 14 controls performed the

Fig. 2. Motor performance during online TMS: Stimulation of the contralesional M1 led to significantly higher maximum finger tapping frequency in subacute patients (Pat ses 1, *post-hoc *t*-test: $p = 0.003$; error bars depict SEM) but not chronic stroke patients (Pat ses 2) or healthy controls (HC) compared to sham stimulation (A). In contrast, no significant stimulation effects were observed for the reaction times task (B) or maximum grip strength (not shown due to lack of significant effects).

TMS effect on finger tapping
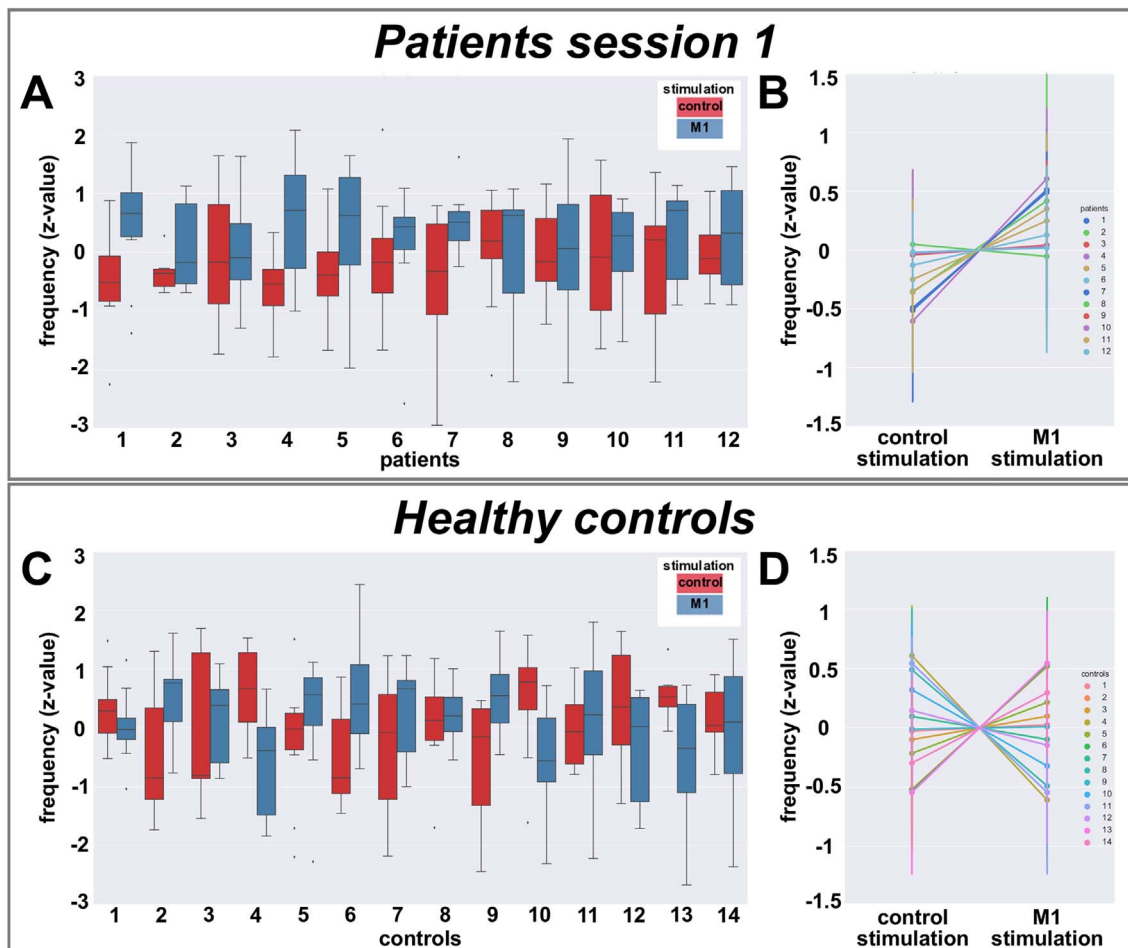
Fig. 3. Effect of online TMS on finger tapping: Subject specific changes in maximum finger tapping frequency for subacute patients in session 1 (A) and healthy controls (B). Maximum finger tapping frequencies are depicted as z-scores after Fisher transformation performed for each subject. While stimulation of contralesional M1 led to improved performance in (almost) all patients (A), healthy controls showed highly variable effects of M1-stimulation compared to control stimulation (B). Hence, the observed significant effect of M1-stimulation in subacute stroke patients was reliably observed across all patients and not driven by outliers, corroborating this finding despite the moderate sample size.

motor task with the right (dominant) hand, one might argue that this imbalance between control group and patient cohort may bias the STIMULATION x GROUP interaction. Therefore, the ANOVA was re-calculated for different sub-cohorts of 12 controls featuring 6 participants who performed the task with the right (dominant) hand, perfectly matching the patient cohort. Of note, a significant STIMULATION x GROUP interaction was observed for all of these sub-cohorts, rendering a considerable influence of the composition of the control group on our findings highly unlikely (STIMULATON x GROUP interaction for sub-cohort 1 (excluding controls 10 & 11, see Table 1): $F_{(1,22)} = 5.693$, $p = 0.026$; sub-cohort 2 (excluding controls 3 & 7): $F_{(1,22)} = 4.619$, $p = 0.043$; sub-cohort 3 (excluding controls 8 & 9): $F_{(1,22)} = 7.629$, $p = 0.011$).

To rule out that either learning or fatigue effects biased the stimulation effect observed on maximum finger tapping frequency in patients, measurements in the first block were compared to measurement in the last (out of 10) blocks of finger tapping. No significant difference was observed, neither for M1 stimulation ($t = 0.888$, $p = 0.394$, paired t-test), nor for control stimulation ($t = -0.8334$, $p = 0.422$, paired t-test), rendering a systematic change in performance alongside repetitions unlikely.

While maximum finger tapping frequency of the left-handed patient was similar to our cohort of right-handed subjects (session 1: left-handed patient: 4.11 Hz; right-handed patients: average: 4.22 Hz ± 1.36 Hz;

session 2: left-handed patient: 5.99 Hz; right-handed patients: average: 6.03 Hz ± 0.81 Hz), significantly lower maximum finger tapping frequency was evident in patients with right hemispheric lesions compared to patients suffering from lesions to the left hemisphere (lesion in right hemisphere: 3.28 Hz ± 1.08 Hz; lesion in left hemisphere: 5.14 ± 0.67 Hz; independent t-test: $t = 3.605$, $p = 0.005$). However, no statistical difference was evident for reaction times ($t = 1.556$, $p = 0.151$), maximum grip strength ($t = 1.274$, $p = 0.231$) or NIHSS ($t = 0.143$, $p = 0.889$). Of note, the side of the lesion was confounded with dominance (while 5 out of 6 patients with left hemispheric lesions performed the tasks with their dominant (right) hand, only 5 out of 6 patients with right hemispheric lesions performed the tasks with their non-dominant (left) hand), complicating the interpretation of this finding. Importantly, the TMS effect on maximum finger tapping frequency (reflected by the ratio of M1-stimulation/control stimulation) was not statistically different between groups ($t = 1.619$, $p = 0.136$), rendering a considerable impact of lesion location on our findings rather unlikely.

3.3. Effects of time post-stroke

Significant improvement of motor function over time was also observed for the finger tapping task. Accordingly, when comparing patient data between sessions (subacute phase, chronic phase), we observed a significant main effect of SESSION for maximum finger tapping

frequency (F$_{(1,7)}$ = 109.744, p < 0.001). Hence, patients showed an increase of maximum finger tapping frequency across sessions independent of the stimulation, likely reflecting functional recovery between the subacute and chronic stage post-stroke. Importantly, for finger-tapping frequency, we observed a significant SESSION x STIMULATION interaction (F$_{(1,7)}$ = 7.011, p = 0.033). Thus, the effect of TMS between sessions differed for finger tapping: Post hoc t-tests confirmed that TMS applied to contralesional M1 increased maximum tapping frequency in session 1 compared to control stimulation (t = 3.844, p = 0.005) but not in the chronic phase after stroke (session 2: t = 0.823, p > 0.5). In contrast, we did not find significant differences over time for reaction times or grip strengths (p > 0.2). Moreover, when comparing motor performance > 3 months after stroke to healthy controls, we did not observe a statistical difference between patients and healthy controls as indicated by the lack of a main effect of GROUP or STIMULATION x GROUP interaction (all p > 0.1). Hence, patients that could be re-assessed did not show significant impairment of motor hand function compared to healthy controls > 3 months after stroke.

3.4. VLSM

The highest overlap of individual lesions was located in subcortical white matter at the level of the internal capsule (Fig. 4). VLSM for the TMS effect on maximum finger-tapping frequency did not result in any significant result (t-test: p > 0.1, corrected for multiple comparisons), i.e., a relationship between stimulation induced performance improvement and lesion location could not be detected. Of note, given the moderate sample size and lesion heterogeneity of our cohort, these results do not support the notion that lesion location and size are not impacting on TMS effects, but merely illustrate the lack of a prominent effect that we could have detected in this study.

4. Discussion

We here found that the functional role of contralesional M1 in motor performance of the affected hand in patients recovering from a first-ever stroke is time-dependent. While maximum finger tapping frequency increased in subacute patients when TMS was applied over M1 (as compared to control stimulation), no such effect was observed in chronic patients or healthy controls. Furthermore, TMS neither affected speeded movement initiation nor maximum grip strength of the paretic hand, suggesting a task-specificity of the effect observed. In summary, contralesional M1 seems to exert a detrimental influence on specific aspects of paretic hand motor function early after stroke, implicating differential network dynamics underlying distinct movement patterns.
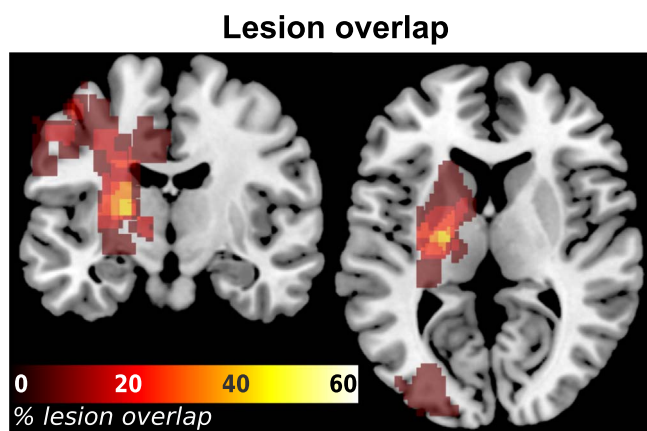
Lesion overlap

Fig. 4. Lesion overlap: Stroke patients showed maximum overlap of the ischemic lesion in the internal capsule as evaluated by diffusion MRI. No significant relationship was evident between lesion location and TMS-induced changes in motor performance.

4.1. The model of hemispheric competition

The role of contralesional M1 for motor function and recovery thereof after stroke has been addressed by numerous studies with heterogeneous conclusions ranging from beneficial influences to a maladaptive impact upon motor recovery in both animal models and human patients (for recent reviews see Buetefisch, 2015; Caleo, 2015). While some factors such as lesion extent and localization have been discussed to determine whether the contralesional M1 may promote or impair motor function of the paretic hand (Di Pino et al., 2014), longitudinal data and tasks-specific influences have rarely been addressed. In the following paragraphs, we will discuss how pathological dysregulation of interhemispheric inhibition from contralesional onto ipsilesional M1 may have slowed down repetitive high frequency movements of the paretic hand. The alleviation of increased interhemispheric inhibition by TMS applied to contralesional M1 may help to explain our current findings.

Early evidence for a potentially maladaptive role of the contralesional M1 was reported by Murase and colleagues who observed a persisting interhemispheric inhibition of the ipsilesional hemisphere during single paretic hand movements in a reaction time task in chronic stroke patients suffering from chronic motor deficits (Murase et al., 2004). From a mechanistic perspective, any pathophysiological influence of the contralesional hemisphere may be even stronger for movements that rely on the frequent modulation of interhemispheric interactions (Hinder, 2012; Liuzzi et al., 2011). In line with this notion, we here observed a significant improvement in finger tapping frequency, but not speeded reaction time or grip strength during TMS applied to contralesional M1 (Fig. 2). Hence, the stroke-induced performance decline of high-frequency movements might result from a disturbance of the fine-tuned modulation of interhemispheric inhibition. Support for this hypothesis stems from a recent animal study where electric inhibition of the contralesional M1 reduced interhemispheric inhibition onto the ipsilesional M1 alongside improved forelimb function (Barry et al., 2014). The modulation of interhemispheric inhibition might primarily impact on the timing of muscle recruitment, as suggested by a recent study that found TMS applied to ipsilateral M1 to delay muscle recruitment timing in healthy subjects during a grip-lift task (Davare et al., 2006). Furthermore, interhemispehric inhibition between bilateral M1 is constantly modulated during unimanual movements in healthy subjects. To prepare a unimanual movement, interhemispheric inhibition from the "inactive" M1 (ipsilateral to the moving hand) to the "active" M1 is reduced (disinhibited) in order to release the planned action whereas inhibition of the "inactive" M1 is increased to prevent unwanted mirror activity (Duque et al., 2007; Hinder, 2012; Hinder et al., 2010). Thus, the performance of repetitive finger movements with the paretic hand may rely on the constant modulation of interhemispheric inhibition. This may well explain our current findings, with a decreased accuracy in muscle recruitment timing being most critical for finger tapping. Since no direct assessment of interhemispheric inhibition was performed here, this interpretation remains speculative and should be addressed by future research.

One might argue that more complex tasks, such as motor sequence production may be more sensitive to uncover altered muscle recruitment timing (Lotze et al., 2006). Indeed, we did not observe a stimulation effect in healthy subjects, suggesting that interference with the physiological interhemispheric influence on muscle recruitment timing may not be sufficient to significantly deteriorate basic motor tasks in healthy participants, whereas inhibition of the pathophysiological influence of contralesional M1 in subacute stroke is beneficial for fast repetitive movements. Apart from impacting upon interhemispheric interactions between M1 homologues, TMS over contralesional M1 may also impact on hand function via activation of uncrossed M1-fibers projecting to the ipsilateral hand. However, primate studies found direct ipsilateral corticospinal fibers to be absent for hand and finger muscles (Soteropoulos et al., 2011). Furthermore, electrophysiological

recordings after lesions to the corticospinal tract do not support the idea of a functionally meaningful input from the ipsilateral corticospinal tract onto neurons projecting to forearm muscles (Zaaimi et al., 2012). This renders a functionally relevant influence of M1 neurons projecting directly to the ipsilateral, affected hand after TMS over contralesional M1 rather unlikely.

Of note, the beneficial influence of interfering with contralesional M1 activation via online TMS was exclusively observed in the early subacute but not chronic phase post-stroke (Fig. 2). In line with these findings, connectivity analyses of neuroimaging data revealed a detrimental inhibitory influence from the contralesional M1 onto the ipsilesional M1 during paretic hand movements in subacute stroke patients (Grefkes et al., 2008), which decreased to lower levels of interhemispheric inhibition in chronic patients (Volz et al., 2015). Assuming a similar time course of pathophysiological interhemispheric interactions in the current patient cohort may well explain our findings: While interfering with contralesional M1 activity via TMS may have reduced pathologically increased inhibition exerted upon ipsilesional M1 and hence might have partially corrected pathophysiological motor network dynamics at the early stage, we did not observe a TMS effect on motor performance in the chronic phase.

In light of the cumulative evidence supporting the functional role of interhemispheric M1-interaction for motor performance after stroke, our data strongly suggest that further research is warranted into the mechanistic underpinnings of the observed behavioral stimulation effects to allow deeper insights into how interhemispheric interactions are modulated during different tasks after stroke. Moreover, it remains to be investigated whether a similar functional role of contralesional M1 can also be observed in patients with considerably poorer recovery compared to our patient cohort. As the neural activation in contralesional M1 during movements of the paretic hand has been shown to strongly depend on the nature of the task and the severity of motor impairment (Rehme et al., 2012), contralesional M1 may have a distinct impact on motor function of the paretic hand in severely impaired patients, which should be addressed in future studies.

4.2. Movement-specific role of the contralesional hemisphere

Similar to our findings, Johansen-Berg et al. (2002) reported that inhibiting the contralesional M1 does not affect reaction times in chronic stroke patients or healthy controls. Rather, interference with the contralesional dorsal premotor cortex led to a deterioration of reaction times in chronic stroke, a finding compatible with a role of premotor cortex in movement initiation (Johansen-Berg et al., 2002). Of note, in both studies TMS interference was applied at different time points relative to the movement cue. As reaction times showed a considerable amount of variance in patients (Fig. 2), future studies should address whether applying TMS relative to the individual reaction times rather than the movement cue may affect movement initiation in stroke patients.

Investigating more complex finger movement sequences of the paretic hand in chronic patients, Lotze and colleagues observed impaired performance during online TMS applied to several regions of the contralesional hemisphere, including M1 (Lotze et al., 2006). Hence, contralesional M1 seems to contribute to the performance of movement sequences with the paretic hand in chronic stroke patients. In contrast, our data do not support the notion of a beneficial influence of the contralesional M1 on motor performance in the chronic phase, but rather highlight a detrimental role in the early phase after a stroke. The most parsimonious explanation for this apparent discrepancy is that the generation of complex movement sequences relies on different neural mechanisms than the generation of repetitive index finger movements. Consistent with this, several neuroimaging studies revealed that increased motor task complexity results in enhanced functional recruitment of motor areas not only in the hemisphere contralateral to the moving hand but also within the ipsilateral hemisphere (Buetefisch

et al., 2014; Hummel et al., 2003; Verstynen and Ivry, 2011). Thus, a higher level of task complexity results in the recruitment of bihemispheric motor resources. In particular, movement sequence production elicits highly differential activation in M1 ipsilateral to the moving hand, which allows to decode which finger is moved at a given time (Diedrichsen et al., 2013). Thus, disrupting such highly effector-specific activation patterns in contralesional M1 may disturb multi-finger sequences (Lotze et al., 2006) but not necessarily reduce the frequency at which a finger can be moved.

4.3. Limitations

One might argue that stimulation during task-performance may induce effects unspecific to the stimulated cortical area. For example, improvements in task performance may stem from unspecific facilitation effects due to the audio-tactile input associated with TMS (Duecker and Sack, 2013) or the inhibition of a brain region that is task-irrelevant but competing for (e.g., attentional) resources (Walsh and Cowey, 1998). However, we did not observe any improvements in task performance in healthy subjects, hence rendering the notion that improvements observed in patients derived from unspecific effects induced by our stimulation protocol unlikely.

As healthy controls did not show any TMS intervention effects, there was no reason to assume that a second stimulation session 3 months later would have led to different results.

Finally, the question remains how findings in the experimental settings translate into clinical practice. It is important to note that for the present study the choice of tasks was based on testing different motor aspects in a highly standardized fashion with a low degree of freedom in order to reduce variability. This experimental design enabled us to demonstrate a task- and time-dependent role of contralesional M1 in cortical reorganization of function. Therefore, our data highlights the importance of carefully selecting the primary outcome measures of therapeutic interventions aiming at correcting pathological network configurations by means of non-invasive brain stimulation.

4.4. Significance for understanding post-stroke reorganization

The small size of our patient cohort may limit the interpretability of our findings, with the non-significant effects observed for the grip strength and reaction time task potentially resulting from insufficient statistical power. Likewise, a larger sample might have revealed a significant relationship between lesion characteristics (location and extent) and TMS effects. This leads to the question how the presented findings further our mechanistic understanding of cerebral reorganization after stroke. Importantly, the differential effect found for the finger tapping task despite the small sample size highlights the robustness and size of this effect. Of note, selecting different sub-cohorts of controls to more closely match the patient group (testing dominant/non-dominant hand) replicated this effect, corroborating its validity. Moreover, the fact that M1-stimulation resulted in increased finger tapping frequencies in the majority of patients, while showing highly mixed results compared to control stimulation in healthy controls (as expected for random performance fluctuations in the absence of a systematic stimulation effect), further supports our finding (Fig. 3). This is of particular interest given that TMS effects generally show a considerable degree of inter-individual variability in healthy subjects (for example see Hamada et al., 2013), as observed in our control group. This relative robustness presumably stems from the relative homogeneity of our patient cohort with regard to the mild deficit in motor function featured by all patients. For example, while patients showed a significant slowing of reaction times and maximum finger tapping frequencies compared to healthy controls, grip strength did not significantly differ between patients and controls, underlining the mild impairment of our patient cohort. On the other hand, this homogeneity precludes potentially interesting sub-group analyses that may address

whether the TMS effect on maximum finger tapping frequency may hold predictive information regarding the individual outcome of motor recovery. While it seems conceivable that more successful cerebral re-organization after stroke may rely on a different set of mechanisms compared to less successful recovery, which may be differentially affected by regional interference via TMS, the current sample cannot address this question due to a lack in outcome variability. Hence, this question could be addressed by future studies. The relative homogeneity of our sample also has to be considered in the interpretation of our finding. To our knowledge, we, here investigated for the first time how online TMS interferes with motor performance early after stroke, and how this effect evolves alongside functional recovery. Of note, early stroke patients constitute a particular sample of participants who can only be studied in specialized facilities and with a number of limitations not present in other cohorts, aiming at minimizing the efforts, risk and inconvenience for patients shortly after stroke.

5. Conclusion

We observed that interfering with contralesional M1 by online-TMS increases maximum finger tapping performance in subacute but not chronic stroke patients, highlighting a detrimental influence of contralesional M1 for specific aspects of motor performance early after stroke. The time- and task-dependency of our observation strongly suggests that this effect is specific and opens new vistas for therapeutic approaches targeting contralesional M1 activation via non-invasive brain-stimulation.

Conflict of interest statement

None of the authors have potential conflicts of interest to be disclosed.

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References

Awiszus, F., 2003. TMS and threshold hunting. Suppl. Clin. Neurophysiol. 56, 13–23.

Barry, M.D., Boddington, L.J., Igelstrom, K.M., Gray, J.P., Shemmell, J., Tseng, K.Y., Oorschot, D.E., Reynolds, J.N.J., 2014. Utility of intracerebral theta burst electrical stimulation to attenuate interhemispheric inhibition and to promote motor recovery after cortical injury in an animal model. Exp. Neurol. 261, 258–266. http://dx.doi.org/10.1016/j.expneurol.2014.05.023.

Biernaskie, J., Szymanska, A., Windle, V., Corbett, D., 2005. Bi-hemispheric contribution to functional motor recovery of the affected forelimb following focal ischemic brain injury in rats. Eur. J. Neurosci. 21, 989–999. http://dx.doi.org/10.1111/j.1460-9568.2005.03899.x.

Buetefisch, C.M., 2015. Role of the contralesional hemisphere in post-stroke recovery of upper extremity motor function. Front. Neurol. 6, 1–10. http://dx.doi.org/10.3389/fneur.2015.00214.

Buetefisch, C.M., Revill, K.P., Shuster, L., Hines, B., Parsons, M., 2014. Motor demand-dependent activation of ipsilateral motor cortex. J. Neurophysiol. 112, 999–1009. http://dx.doi.org/10.1152/jn.00110.2014.

Buma, F., Kwakkel, G., Ramsey, N., 2013. Understanding upper limb recovery after stroke. Restor. Neurol. Neurosci. 31, 707–722. http://dx.doi.org/10.3233/RNN-130332.

Caleo, M., 2015. Rehabilitation and plasticity following stroke: insights from rodent models. Neuroscience. http://dx.doi.org/10.1016/j.neuroscience.2015.10.029.

Chollet, F., DiPiero, V., Wise, R.J., Brooks, D.J., Dolan, R.J., Frackowiak, R.S., 1991. The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. Ann. Neurol. 29, 63–71. http://dx.doi.org/10.1002/ana.410290112.

Davare, M., Duque, J., Vandermeeren, Y., Thonnard, J.-L., Olivier, E., 2006. Role of the ipsilateral primary motor cortex in controlling the timing of hand muscle recruitment. Cereb. Cortex 17, 353–362. http://dx.doi.org/10.1093/cercor/bhj152.

Di Pino, G., Pellegrino, G., Assenza, G., Capone, F., Ferreri, F., Formica, D., Ranieri, F., Tombini, M., Ziemann, U., Rothwell, J.C., Di Lazzaro, V., 2014. Modulation of brain plasticity in stroke: a novel model for neurorehabilitation. Nat. Rev. Neurol. 10, 597–608. http://dx.doi.org/10.1038/nrneurol.2014.162.

Diedrichsen, J., Wiestler, T., Krakauer, J.W., 2013. Two distinct ipsilateral cortical representations for individuated finger movements. Cereb. Cortex 23, 1362–1377. http://dx.doi.org/10.1093/cercor/bhs120.

Duecker, F., Sack, A.T., 2013. Pre-stimulus sham TMS facilitates target detection. PLoS One 8, 4–9. http://dx.doi.org/10.1371/journal.pone.0057765.

Duque, J., Murase, N., Celnik, P., Hummel, F., Harris-Love, M., Mazzocchio, R., Olivier, E., Cohen, L.G., 2007. Intermanual Differences in movement-related interhemispheric inhibition. J. Cogn. Neurosci. 19, 204–213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17280510.

Gerloff, C., Richard, J., Hadley, J., Schulman, A.E., Honda, M., Hallett, M., 1998a. Functional coupling and regional activation of human cortical motor areas during simple, internally paced and externally paced finger movements. Brain 121, 1513–1531. http://dx.doi.org/10.1093/brain/121.8.1513.

Gerloff, C., Corwell, B., Hallett, M., Cohen, L.G., 1998b. The role of the human motor cortex in the control of complex and simple finger movement sequences. Brain 121, 1695–1709. http://dx.doi.org/10.1093/brain/121.9.1695.

Grefkes, C., Fink, G.R., 2014. Connectivity-based approaches in stroke and recovery of function. Lancet Neurol. 13, 206–216. http://dx.doi.org/10.1016/S1474-4422(13)70264-3.

Grefkes, C., Ward, N.S., 2014. Cortical Reorganization After Stroke. Neuroscientist 20, 56–70. Available at: http://journals.sagepub.com/doi/10.1177/1073858413491147%5C, http://www.ncbi.nlm.nih.gov/pubmed/23774218.

Grefkes, C., Nowak, D.A., Eickhoff, S.B., Dafotakis, M., Kust, J., Karbe, H., Fink, G.R., 2008. Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. Ann. Neurol. 63, 236–246. http://dx.doi.org/10.1002/ana.21228.

Grefkes, C., Nowak, D.A., Wang, L.E., Dafotakis, M., Eickhoff, S.B., Fink, G.R., 2010. Modulating cortical connectivity in stroke patients by rTMS assessed with fMRI and dynamic causal modeling. NeuroImage 50, 233–242. Doi: S1053-8119(09)01317-2 [pii];http://dx.doi.org/10.1016/j.neuroimage.2009.12.029 [doi].

Hamada, M., Murase, N., Hasan, A., Balaratnam, M., Rothwell, J.C., 2013. The role of interneuron networks in driving human motor cortical plasticity. Cereb. Cortex 23, 1593–1605. http://dx.doi.org/10.1093/cercor/bhs147.

Herwig, U., Cardenas-Morales, L., Connemann, B.J., Kammer, T., Schonfeldt-Lecuona, C., 2010. Sham or real–post hoc estimation of stimulation condition in a randomized transcranial magnetic stimulation trial. Neurosci. Lett. 471, 30–33. Doi:S0304-3940(10)00007-8 [pii];http://dx.doi.org/10.1016/j.neulet.2010.01.003 [doi].

Hinder, M.R., 2012. Interhemispheric connectivity between distinct motor regions as a window into bimanual coordination. J. Neurophysiol. 107, 1791–1794. http://dx.doi.org/10.1152/jn.00822.2011.

Hinder, M.R., Schmidt, M.W., Garry, M.I., Summers, J.J., 2010. Unilateral contractions modulate interhemispheric inhibition most strongly and most adaptively in the homologous muscle of the contralateral limb. Exp. Brain Res. 205, 423–433. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20686888.

Hummel, F., Kirsammer, R., Gerloff, C., 2003. Ipsilateral cortical activation during finger sequences of increasing complexity: representation of movement difficulty or memory load? Clin. Neurophysiol. 114, 605–613.

Johansen-Berg, H., Rushworth, M.F.S., Bogdanovic, M.D., Kischka, U., Wimalaratna, S., Matthews, P.M., 2002. The role of ipsilateral premotor cortex in hand movement after stroke. Proc. Natl. Acad. Sci. U. S. A. 99, 14518–14523. http://dx.doi.org/10.1073/pnas.222536799.

Kimberg, D.Y., Coslett, H.B., Schwartz, M.F., 2007. Power in voxel-based lesion-symptom mapping. J. Cogn. Neurosci. 19, 1067–1080. http://dx.doi.org/10.1162/jocn.2007.19.7.1067.

Koch, G., Fernandez, M., Olmo, D., Cheeran, B., Ruge, D., Schippling, S., Caltagirone, C., Rothwell, J.C., Kingdom, U., Clinica, N., Lucia, F.S., Neurologica, C., Neuroscienze, D., 2007. Focal Stimulation of the Posterior Parietal Cortex Increases the Excitability of the Ipsilateral Motor Cortex. 27. pp. 6815–6822. http://dx.doi.org/10.1523/JNEUROSCI.0598-07.2007.

Liuzzi, G., Horniss, V., Zimerman, M., Gerloff, C., Hummel, F.C., 2011. Coordination of uncoupled bimanual movements by strictly timed interhemispheric connectivity. J. Neurosci. 31, 9111–9117. http://dx.doi.org/10.1523/JNEUROSCI.0046-11.2011.

Lotze, M., Markert, J., Sauseng, P., Hoppe, J., Plewnia, C., Gerloff, C., 2006. The role of multiple contralesional motor areas for complex hand movements after internal capsular lesion. J. Neurosci. 26, 6096–6102. http://dx.doi.org/10.1523/JNEUROSCI.4564-05.2006.

Mcdonnell, M.N., Stinear, C.M., 2017. Brain stimulation TMS measures of motor cortex function after stroke: a meta-analysis. Brain Stimul. 10, 721–734. http://dx.doi.org/10.1016/j.brs.2017.03.008.

Medina, J., Kimberg, D.Y., Chatterjee, A., Coslett, H.B., 2010. Neuropsychologia Inappropriate Usage of the Brunner – Munzel Test in Recent Voxel-Based Lesion-Symptom Mapping Studies. 48. pp. 341–343. http://dx.doi.org/10.1016/j.neuropsychologia.2009.09.016.

Murase, N., Duque, J., Mazzocchio, R., Cohen, L.G., 2004. Influence of interhemispheric interactions on motor function in chronic stroke. Ann. Neurol. 55, 400–409. http://dx.doi.org/10.1002/ana.10848.

Nettekoven, C., Volz, L.J., Kutscha, M., Pool, E.-M., Rehme, A.K., Eickhoff, S.B., Fink, G.R., Grefkes, C., 2014. Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system. J. Neurosci. 34,

6849–6859. http://dx.doi.org/10.1523/JNEUROSCI.4993-13.2014.

Pascual-Leone, A., Gates, J.R., Dhuna, A., 1991. Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. Neurology 41, 697–702. http://dx.doi.org/10.1212/WNL.41.5.697.

Rehme, A.K., Fink, G.R., von Cramon, D.Y., Grefkes, C., 2011. The role of the contralesional motor cortex for motor recovery in the early days after stroke assessed with longitudinal FMRI. Cereb. Cortex 21, 756–768. http://dx.doi.org/10.1093/cercor/bhq140.

Rehme, A.K., Eickhoff, S.B., Rottschy, C., Fink, G.R., Grefkes, C., 2012. Activation likelihood estimation meta-analysis of motor-related neural activity after stroke. NeuroImage 59, 2771–2782. http://dx.doi.org/10.1016/j.neuroimage.2011.10.023.

Rorden, C., Karnath, H.-O., Bonilha, L., 2007. Improving lesion-symptom mapping. J. Cogn. Neurosci. 19, 1081–1088. http://dx.doi.org/10.1162/jocn.2007.19.7.1081.

Rossi, S., Hallett, M., Rossini, P.M., Pascual-Leone, A., Safety of, T.M.S.C.G, 2009. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin. Neurophysiol. 120, 2008–2039. http://dx.doi.org/10.1016/j.clinph.2009.08.016.

Schluter, N.D., Rushworth, M.F.S., Passingham, R.E., Mills, K.R., 1998. Temporary interference in human lateral premotor cortex suggests dominance for the selection of movements. A study using transcranial magnetic stimulation. Brain 121, 785–799. http://dx.doi.org/10.1093/brain/121.5.785.

Soteropoulos, D.S., Edgley, S.A., Baker, S.N., 2011. Lack of evidence for direct corticospinal contributions to control of the ipsilateral forelimb in monkey. J. Neurosci. 31, 11208–11219. http://dx.doi.org/10.1523/JNEUROSCI.0257-11.2011.

Takeuchi, N., Oouchida, Y., Izumi, S., 2012. Motor control and neural plasticity through interhemispheric interactions. Neural Plast. 2012, 823285. http://dx.doi.org/10.1155/2012/823285.

Verstynen, T., Ivry, R.B., 2011. Network dynamics mediating ipsilateral motor cortex activity during unimanual actions. J. Cogn. Neurosci. 23, 2468–2480. http://dx.doi.org/10.1162/jocn.2011.21612.

Volz, L.J., Sarfeld, A.S., Diekhoff, S., Rehme, A.K., Pool, E.M., Eickhoff, S.B., Fink, G.R., Grefkes, C., 2015. Motor cortex excitability and connectivity in chronic stroke: a multimodal model of functional reorganization. Brain Struct. Funct. 220, 1093–1107. http://dx.doi.org/10.1007/s00429-013-0702-8.

Walsh, V., Cowey, A., 1998. Magnetic stimulation studies of visual cognition. Trends Cogn. Sci. 2, 103–110. http://dx.doi.org/10.1016/S1364-6613(98)01134-6.

Walsh, V., Cowey, A., 2000. Transcranial magnetic stimulation and cognitive neuroscience. Nat. Rev. Neurosci. 1, 73–79. http://dx.doi.org/10.1038/35036239.

Ward, N.S., Brown, M.M., Thompson, A.J., Frackowiak, R.S., 2003. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. Brain 126, 2476–2496. Doi: http://dx.doi.org/10.1093/brain/awg245 [doi];awg245 [pii].

Weiller, C., Chollet, F., Friston, K.J., Wise, R.J., Frackowiak, R.S., 1992. Functional reorganization of the brain in recovery from striatocapsular infarction in man. Ann. Neurol. 31, 463–472. http://dx.doi.org/10.1002/ana.410310502.

Zaaimi, B., Edgley, S.A., Soteropoulos, D.S., Baker, S.N., 2012. Changes in descending motor pathway connectivity after corticospinal tract lesion in macaque monkey. Brain 135, 2277–2289. http://dx.doi.org/10.1093/brain/aws115.