

The differential roles of contralesional frontoparietal areas in cortical reorganization after stroke



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ARTICLE INFO

Article history:

Received 25 May 2019

Received in revised form

10 January 2020

Accepted 28 January 2020

Available online 1 February 2020

Keywords:

Premotor cortex

Parietal cortex

Plasticity

Rehabilitation

Recovery of function

ABSTRACT

Background: Studies examining the contribution of contralesional brain regions to motor recovery after stroke have revealed conflicting results comprising both supporting and disturbing influences. Especially the relevance of contralesional brain regions beyond primary motor cortex (M1) has rarely been studied, particularly concerning the temporal dynamics post-stroke.

Methods: We, therefore, used online transcranial magnetic stimulation (TMS) interference to longitudinally assess the role of contralesional (right) frontoparietal areas for recovery of hand motor function after left hemispheric stroke: contralesional M1, contralesional dorsal premotor cortex (dPMC), and contralesional anterior intraparietal sulcus (IPS). Fourteen stroke patients and sixteen age-matched healthy subjects performed motor tasks of varying complexity with their (paretic) right hand. Motor performance was quantified using three-dimensional kinematic data. All patients were assessed twice, (i) in the first week, and (ii) after more than three months post-stroke.

Results: While we did not observe a significant effect of TMS interference on movement kinematics following the stimulation of contralesional M1 and dPMC in the first week post-stroke, we found improvements of motor performance upon interference with contralesional IPS across motor tasks early after stroke, an effect that persisted into the later phase. By contrast, for dPMC, TMS-induced deterioration of motor performance was only evident three months post-stroke, suggesting that a supportive role of contralesional premotor cortex might evolve with reorganization.

Conclusion: We here highlight time-sensitive and region-specific effects of contralesional frontoparietal areas after left hemisphere stroke, which may influence on neuromodulation regimes aiming at supporting recovery of motor function post-stroke.

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Introduction

Focal brain lesions as induced by stroke trigger a cascade of cellular and biochemical processes [1]. Animal studies have demonstrated that such changes are not limited to perilesional tissue but extend to remote areas including the contralesional hemisphere [2]. Using neuroimaging in stroke patients, similar observations have been reported: Altered neural activation in ipsilesional as well as contralesional brain regions typically accompanies impaired motor function after stroke [3–5]. In healthy

subjects, upper limb muscles are innervated by projections from both the contralateral and ipsilateral motor cortex [6], and ipsilateral brain regions also contribute to the coordination of upper limb movements [7,8]. For post-stroke recovery, however, the contralesional hemisphere is assumed to play a particular role. Yet, the specific functional implications of altered neural activity still remain controversial [9–11]. On the one hand, the vicariation hypothesis suggests functional compensation by intact contralesional brain regions. Likewise, neural activity gradually increases in both hemispheres concurrent to early motor recovery [3,12,13]. On the other hand, at the chronic post-stroke phase, persistent activity increases in the contralesional hemisphere have been linked to a less favorable motor outcome [9]. Additional information has been derived from electrophysiological data obtained with transcranial magnetic stimulation (TMS), which also challenge the assumption

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of contralesional compensation by unmasking maladaptive inter-hemispheric competition. Here, particularly contralesional primary motor cortex (M1) has been suggested to exert abnormally high inhibitory influences upon ipsilesional M1, thereby hindering motor performance and recovery [14–16]. However, recent results have suggested that these changes might also constitute a representation of the underlying recovery processes rather than a cause of poor motor recovery, given that abnormal interhemispheric inhibition emerges over time parallel to motor recovery [17]. Inconsistent results concerning the functional role of the contralesional hemisphere have been attributed to differences between subacute and chronic stroke, differences of mild, moderate, and severe motor impairment, lesion size and location, or the functional integrity of corticomotor pathways [1,9,10,18]. Likewise, patients with more severe impairments and worse damage of ipsilesional white matter tracts might rely more on contralesional activity than mildly affected patients with functionally intact pathways [18].

Importantly, movements of the paretic hand have not only been associated with enhanced activity of contralesional primary motor cortex (M1), but likewise with activity changes of contralesional premotor and superior parietal cortex [19–21], which can be detected already in the first weeks post-stroke [12]. However, little is known about the behavioral relevance of these areas in the early post-stroke phase. At least in the chronic phase, a few TMS studies provide the notion that contralesional frontoparietal regions support motor performance of the stroke-affected hand [22,23].

Therefore, probing the relevance of the contralesional hemisphere should involve an extended motor network comprising also frontoparietal brain regions. Yet, it remains elusive whether these areas also contribute to early motor recovery in the first few weeks after stroke where patients usually achieve the most considerable amount of functional recovery [24,25]. Furthermore, understanding the functional contribution of the contralesional hemisphere early after a stroke may have a direct impact on potential therapeutic neuromodulation approaches as this period might be especially critical for supporting cortical reorganization and functional recovery [26,27].

Therefore, to elucidate the differential contribution of contralesional frontoparietal areas to motor recovery, we applied neuronavigated, online TMS interference both in the first week, and after more than three months post-stroke to interfere with the activity of contralesional (i) primary motor cortex (M1), (ii) dorsal premotor cortex (dPMC), and (iii) anterior intraparietal cortex (IPS). As TMS interference effects might also depend on the motor task under investigation, we assessed three motor tasks of different complexity and visuomotor demands: (i) maximum finger-tapping, (ii) maximum hand-tapping, and (iii) rapid alternating pointing.

We hypothesized that direct TMS interference with contralesional frontoparietal cortex modulates task performance already in the first week after stroke, given that for this period enhanced activity has frequently been reported for all three cortical sites [12]. In case of a supportive role of the respective area, TMS interference with activity of the stimulated region should deteriorate motor performance. In contrast, an improvement of motor performance during TMS-induced disturbance of neural activity indicates a maladaptive influence. Moreover, given the time-dependency of contralesional over-activity, we expected a longitudinal change of TMS-induced effects during motor recovery with a supportive influence of frontoparietal areas at the later stage post-stroke [22,23].

Materials and methods

Subjects

Fourteen hospitalized stroke patients with first-ever ischemic stroke in the left hemisphere were recruited from the Department

of Neurology, University Hospital of Cologne (Table 1). Patients had to be able to perform the motor tasks at least in parts, limiting the accessible cohort to patients with mild to moderate motor deficits. Inclusion criteria were: (i) age: 40–90 years, (ii) left-hemispheric ischemic stroke as verified by diffusion-weighted MRI (DWI), (iii) within the first week post-stroke (≤ 7 days from symptom onset) (iv) unilateral hand motor deficit at admission and examination. Exclusion criteria were: (i) any contraindication to TMS [28], (ii) bihemispheric infarcts, (iii) cerebral hemorrhage, (iv) presence of other neurological deficits at examination, i.e. aphasia, apraxia, neglect, visual field deficits, somatosensory deficits.

Nine of the fourteen patients could be re-assessed after more than three months post-stroke (average: 108.9 ± 17.5 SD (range: 91–138) days post-stroke). All patients had experienced substantial recovery as indexed by a decrease in the NIHSS over time (Table 1; $p = 0.02$, Mann-Whitney-U-Test). The same effect was evident when considering the motor score of the NIHSS only (NIHSS first session: 3.2 ± 1.4 SD (2–6); NIHSS second session: 1.4 ± 1.3 SD (0–4); $p = 0.01$).

Sixteen age-matched healthy participants without any history of neurological or psychiatric disease (3 females, all right-handed, mean age 65.1 ± 9.1 SD (56–89) years) served as controls. Although age did not significantly differ between groups ($p = 0.14$, independent two-sided t -test), we included age as a covariate of no interest in further analyses to account for residual differences in age between groups.

All participants gave informed written consent before entering the study, which was approved by the local ethics committee at the University of Cologne and carried out following the Declaration of Helsinki.

Experimental design

We used a single-blinded, sham-controlled mixed design to test for the effects of TMS interference with three different contralesional brain regions in the task of interest for which increased neural activity during movements of the stroke-affected hand have been repeatedly demonstrated after stroke [3,12,14]: (i) contralesional M1, (ii) contralesional dPMC, and (iii) contralesional IPS (Fig. 1). The criteria used for the anatomical identification of the three TMS interference sites are described in the Supplementary material. In all participants, a sham stimulation with the same intensity served as a control condition to account for unspecific stimulation effects like tactile and auditory sensation. Accordingly, the coil was tilted over the parieto-occipital vertex in a posterior-anterior direction paralleling the interhemispheric fissure, and angled at 45° , touching the skull only with the rim opposite the handle [16,29].

As all patients suffered from a left hemispheric stroke, all participants performed the tasks with their right (dominant) hand. The order of stimulation sites was pseudo-randomized per subject before the experiment and balanced within subjects.

Protocol of TMS interference

TMS was performed using a Magstim Super Rapid² stimulator (The Magstim Co. Ltd, Whitland, United Kingdom) equipped with an Air Film Coil. The position of the coil was tracked and recorded using a neuronavigation system throughout the whole TMS sessions (BrainSight V.2.0.7; Rogue Research Ltd; Montreal, Canada). TMS was applied at 90% of resting motor threshold (RMT) time-locked to task execution [16]. A sub-threshold stimulation intensity was chosen to prevent the induction of muscle twitches in the contralateral hand, which may distract participants and impact their performance.

Table 1
Demographic and clinical parameters of stroke patients.

Patient	Age	Sex	Handed-ness	Lesion side	Lesion location	Lesion volume [mm3]	Days post-stroke	NIHSS		
								Admission	TMS session I	TMS session II
1	74	F	R	L	Internal capsule	1164.4	2	9	2	0
2	58	M	R	L	Striatocapsular	2750.6	2	3	2	1
3	68	F	R	L	Pons	556.9	7	4	2	
4	59	M	R	L	Thalamus, cortical (parietooccipital)	661776.0	2	6	5	1
5	77	M	R	L	Thalamus	482.6	4	6	4	1
6	77	M	R	L	Internal capsule	1113.8	3	3	3	0
7	56	F	R	L	Basal ganglia	13007.3	6	14	5	
8	79	F	R	L	Thalamus	2490.8	6	8	6	3
9	75	F	R	L	Basal ganglia	1650.4	5	9	7	4
10	72	M	R	L	Cortical (postcentral gyrus)	16233.8	3	4	2	1
11	56	F	R	L	Cortical (parietal, temporoparietal)	45410.7	3	2	2	1
12	82	M	R	L	Cortical (precentral gyrus)	1508.6	2	3	2	
13	79	M	R	L	Cortical (frontal and temporal operculum, precentral gyrus)	5811.8	3	3	1	
14	52	M	R	L	Cortical (precentral gyrus)	1613.3	3	2	1	
Mean	70.3						3.6	5.4	3.1	1.4
SD	9.3						1.7	3.5	1.9	1.3

For all stroke patients age, sex (F: female, M: male), handedness (R: right, L: left), lesion side (R: right, L: left), lesion location and lesion volume, days post-stroke, and the NIHSS score at the time of admission to the hospital, at the first examination and at the second examination are listed (NIHSS: National Institutes of Health Stroke Scale, F: female, M: male, R: right, L: left, SD: standard deviation).

Brief trains of 10 Hz repetitive TMS (rTMS), which started with the onset of a visual “go” signal presented on a computer monitor, were used to interfere with brain activity concurrent to task execution and lasted throughout the entire trial for about 2.0–2.5s depending on the respective motor task (see below) [16,30,31]. The software Presentation® (Version 9.9, Neurobehavioral Systems, USA, <http://www.neurobs.com>) was used for both stimulus presentation and time-locked triggering of the TMS machine [16]. In contrast to the more widely used approach of offline rTMS which

makes use of the after-effects following the application of several hundreds of TMS pulses, online TMS interference uses the immediate effects of rTMS on neuronal processing underneath the stimulation coil, and thereby alters task performance concurrent with the stimulation [16,22,23,31]. This technique is considered to have no relevant carry-over effects, and hence, compared to offline TMS, it is more flexible with respect to randomization of different stimulation sites within a single session [16]. Importantly, online rTMS interference is considered to invariably interfere with the

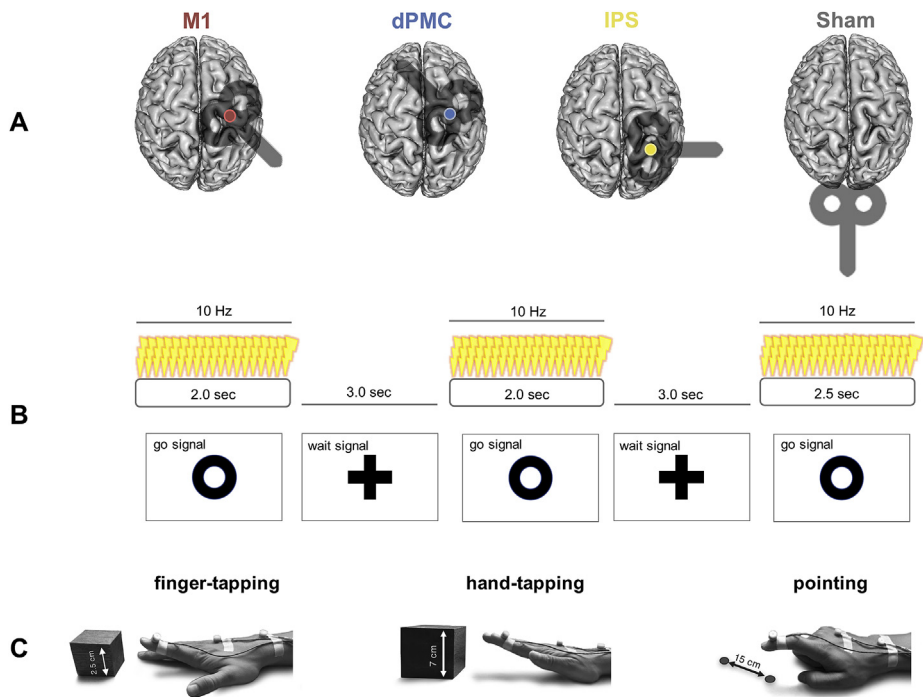


Fig. 1. Online TMS task design. A: Contralesional stimulation sites (i) right contralesional primary motor cortex (M1), (ii) right contralesional dorsal premotor cortex (dPMC), (iii) right contralesional anterior intraparietal sulcus (IPS) and (iv) sham stimulation tilted over the parieto-occipital vertex. Each subject performed the tasks (C) under all four TMS conditions in a single TMS session. B: By synchronously applying 10 Hz rTMS to the go-signal and covering the entire performance period, online TMS directly disturbs neural activity during task performance without relevant carry-over effects. C: Employed motor tasks during online TMS: (i) index finger-tapping, (ii) hand-tapping, and (iii) rapid alternating pointing movements between two targets.

neural processing and thereby disturb task performance, in contrast to offline rTMS protocols which can have both effects, i.e. disturbing or enhancing neural activity [32–34]. Please see the Supplementary material for further details on TMS parameters and TMS interference.

Motor tasks

All participants performed three different motor tasks probing different aspects of motor proficiency in a highly standardized fashion, time-locked to the TMS trains (Fig. 1):

Index finger-tapping

This task tested fast isolated finger movements. Participants performed repetitive vertical index finger-tapping movements as fast as possible upon the appearance of a visual cue. A dice with a height of 2.5 cm indicated the required tapping amplitude. Each tapping trial lasted 2 s with a pause interval of 3 s to prevent fatigue and rTMS carry-over effects.

Hand-tapping

The hand-tapping task was supposed to involve similar motor components as the finger-tapping task mentioned above but included more proximal muscle groups. Hence, this task was considered to be easier to conduct particularly for stroke patients as stroke-induced motor deficits are typically more pronounced for more distal movements [35,36]. A cube of 7 cm height indicated the target movement amplitude. Similarly to (i), one tapping trial lasted 2 s with a pause interval of 3 s.

Pointing task

The rapid pointing task strongly relied on visuomotor-coordinated transformation processes and visuospatial attention [37,38]. Subjects performed repetitive sagittal pointing movements with their index finger between two targets. The distance between the pointing targets was 15 cm in the sagittal plane and 3 cm in the vertical plane. Each trial lasted 2.5 s followed by a pause interval of 3 s. To avoid interference with the visual target, movement onsets were indicated by a brief acoustic tone.

The testing battery for each stimulation site consisted of nine blocks, three blocks per task. One block was composed of five repetitions of each motor task. Written instructions were displayed for 3 s on a computer monitor centered in front of the subjects, indicating the upcoming block of the motor task. The order of blocks was pseudo-randomized. The entire experiment lasted about 60 min (15 min per site). Before the TMS sessions, subjects were trained in all tasks until they reached a steady performance level as indexed by stable kinematic parameters in at least three consecutive trials of each tasks.

3-D ultrasound movement kinematics

Motor performance was assessed via kinematic recordings using the Zebris CMS20 motion analyser system (Zebris Medical Company, Isny, Germany) [38,39]. The 3D-tracking markers were fixed onto the dorsal side of the distal interphalangeal joint of the right index finger (marker I), the dorsal side of the third metacarpophalangeal joint (marker II), and between the styloid processes of ulna and radius (marker III). The x-, y-, and z-directions of the position marker coordinates referred to the medio-lateral, antero-posterior, and vertical directions. Kinematic data were

continuously recorded throughout the entire experiment and analyzed offline (offline data analyses: Supplementary Material).

Voxel lesion symptom mapping

To assess whether stimulation effects were associated with lesion locations, we conducted voxel lesion symptom mapping (VLSM) using the non-parametric mapping (NPM) software [40] (see Supplementary material for further details).

Statistical analysis

Statistical analyses were performed using the software SPSS (Statistical Package for the Social Science, version 23, IBM). In order to compare baseline motor performance of patients in the first week post-stroke and healthy subjects, we first computed repeated measures analyses of variance (rm-ANOVA) on the performance in the control condition for each of the three tasks with the factor PARAMETER (two levels: velocity, amplitude/target deviation) and GROUP (two levels: patients, healthy control).

To assess region-specific stimulation effects and in order to control for unspecific TMS effects, we computed the difference between the real (M1, dPMC, IPS) and the control (sham) condition (REAL-SHAM). For each task, these values were then entered into rm-ANOVA comparing the within-subject factor STIMULATION SITE (three levels: M1, dPMC, IPS) and the between-subject factor GROUP (two levels: patients, healthy controls). As mentioned above, we included age as a covariate of no interest in all analyses to account for residual differences in age between groups. Post-hoc two-sided t-tests were used to elucidate significant effects ($p < 0.05$). Results were Bonferroni-corrected.

Importantly, control subjects were assessed once only given that both the tapping task and pointing task were reported to have stable between session performance in healthy subjects [41,42].

Moreover, to assess whether effects observed in the first week after stroke were still present after more than three months, we computed additional rm-ANOVA comparing the within-subject factor STIMULATION SITE (three levels: M1, dPMC, aIPS) and the between-subject factor TIME (two levels: first week, three months) including only the patients that could be re-assessed after three months. To account for residual differences in RMT between sessions, we included RMT as a covariate of no interest to this analysis. Due to the reduced statistical power, data of the second assessment were not Bonferroni-corrected. To account for a relationship between TMS effects and stroke severity as well as functional recovery, TMS effects on movement kinematics were tested for correlations with the NIHSS and subsequently with improvements of the NIHSS score ($d(x,y)=(x-y)/x$). Of note, given that recovery after stroke is known to be substantially influenced by the degree of initial impairment [25,42,43], we have computed correlation analyses for recovery as partial correlations considering the initial impairment.

Results

Behavioral group differences

First, we compared the motor performance of left hemispheric stroke patients in the first week post-stroke (3.6 ± 1.7 SD days post-stroke) and healthy participants in the control condition (sham) as an index of motor performance in the absence of a specific neural perturbation. For all tasks we found a significant interaction effect involving the factors PARAMETER x GROUP (finger-tapping: $F_{(1,27)} = 6.07$, $p = 0.02$; hand-tapping: $F_{(1,27)} = 23.03$, $p < 0.001$; pointing: $F_{(1,27)} = 9.99$, $p = 0.004$). Post-hoc tests indicated that

patients compared to healthy controls featured reduced velocities (finger-tapping: $p = 0.04$; hand-tapping: $p < 0.001$; pointing: 0.008) while tapping amplitudes or pointing deviation from target did not differ significantly ($p > 0.2$), indicating sufficient accuracy when performing the tasks.

TMS effects in the first week after stroke

Finger-tapping

Comparing the sham-normalized TMS data, the analysis of the finger-tapping task did not reveal a significant main or interaction effect for tapping velocity ($p > 0.2$). Hence, neither patients compared to healthy controls nor patients compared to control stimulation featured significantly different finger-tapping velocities due to TMS interference with any of the three contralesional/ipsilateral stimulation sites (Fig. 2).

Hand-tapping

For the hand-tapping task, we found a significant interaction effect for STIMULATION SITE \times GROUP for hand-tapping velocity ($F_{(2,52)} = 3.75$, $p = 0.03$) (main effect STIMULATION SITE: $F_{(2,52)} = 0.58$, $p = 0.56$), indicating a group-dependent TMS effect for the three stimulation sites. Post-hoc tests disclosed a between-group difference for interference with contralesional IPS ($p = 0.003$), but not for M1 or dPMC ($p > 0.4$). For healthy subjects, we found a decrease in hand-tapping velocity, whereas stroke patients showed an increase in tapping velocity upon interference with contralesional IPS (patients: $p = 0.048$; healthy controls: $p = 0.024$) (Fig. 2). Plotting the individual

effects revealed that compared to control stimulation and healthy subjects, the majority of patients featured an increase of tapping velocity upon contralesional IPS-interference (Fig. 2).

Pointing task

For the pointing task, we did not find a significant TMS effect concerning pointing velocity ($p > 0.7$). By contrast, for the absolute deviation from the target, as an index for movement accuracy, we found a significant main effect involving the factor STIMULATION SITE ($F_{(2,52)} = 3.60$, $p = 0.034$) and a significant interaction for STIMULATION SITE \times GROUP ($F_{(2,52)} = 5.51$, $p = 0.007$). Post-hoc tests revealed a between-group difference for interference with contralesional IPS ($p = 0.04$). While disruption of contralesional IPS improved the pointing accuracy of patients in the first week post-stroke as indicated by a decrease in target deviation, controls increased their deviation from the target upon ipsilateral IPS-interference (Fig. 2).

TMS effects three months post-stroke

In the follow-up measurement after three months, we again did not find a significant main or interaction effect concerning finger-tapping velocity, similar to the first week post-stroke.

However, for the hand-tapping task after three months, a significant main effect for tapping velocity involving the factor STIMULATION SITE ($F_{(2,44)} = 3.37$, $p = 0.04$) and a significant interaction effect for STIMULATION SITE \times GROUP ($F_{(2,44)} = 7.08$, $p = 0.002$) was evident. Post-hoc t-tests showed that IPS-interference again caused

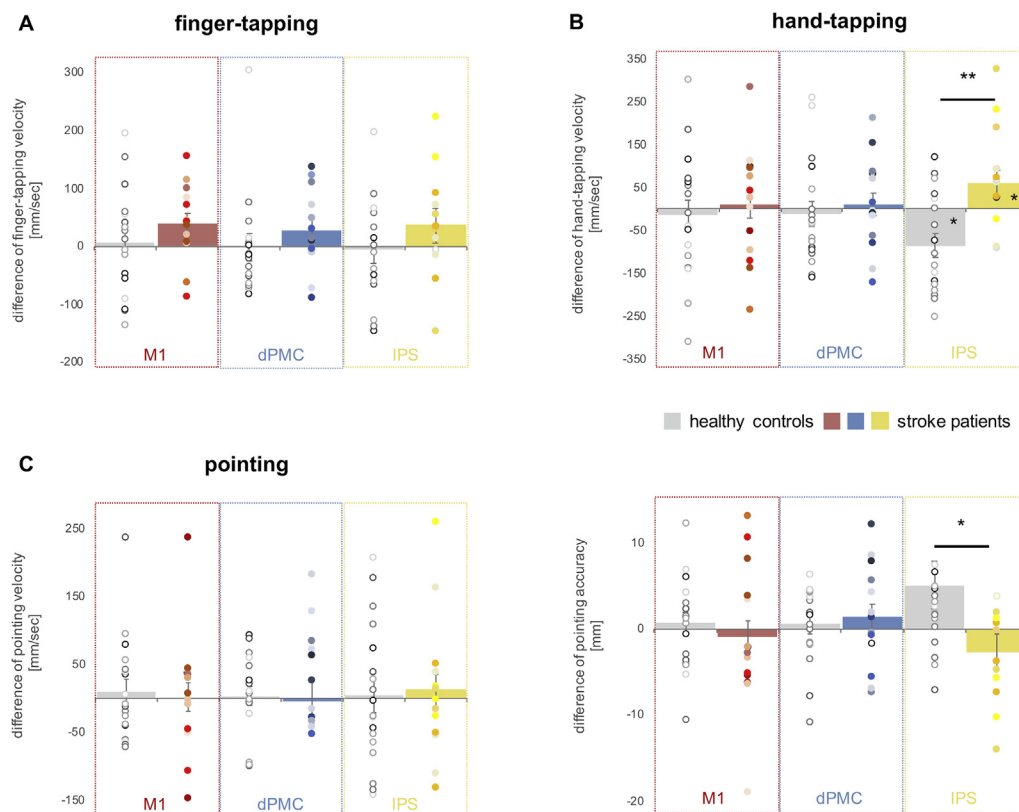


Fig. 2. TMS effects in the first week after stroke. Effects of online TMS on the finger-tapping (A), hand-tapping (B), and pointing tasks (C) superimposed with the distribution of individual data points. B: While we found a decrease in hand-tapping velocity for healthy subjects (grey columns), stroke patients (colored columns) showed an increase in tapping velocity upon interference with contralesional IPS. C: Furthermore, for the pointing task, disruption of IPS improved the accuracy of patients as indicated by a decrease of target deviation, whereas controls increased their deviation from target upon ipsilateral IPS-interference. In contrast, no significant stimulation effects were observed for the finger-tapping task (A) or for pointing velocity (C). Note that sham-normalized TMS effects are presented in the figure; (* <0.05 , ** <0.01 , two-sided t-test, error bars indicate standard error of the mean, asterisks between columns indicate between-group differences, asterisks within columns indicate differences to sham).

an increase in tapping velocity ($p = 0.031$) in stroke patients (Fig. 3). Additionally, and in contrast to the first week post-stroke, disruption of contralesional dPMC led to a slowing of hand-tapping velocity ($p = 0.030$). Consistent with these results, comparing hand-tapping velocity of patients between the two sessions revealed a significant interaction effect for STIMULATION SITE \times TIME ($F_{(2,30)} = 4.58$, $p = 0.018$). Post-hoc tests featured a between-group difference for dPMC ($p = 0.031$) with a slowing of hand-tapping velocity after more than three months post-stroke, underlining the supportive influence of contralesional dPMC in later stages but not early after stroke (Fig. 3).

For the pointing task, we found similar effects as for the first week post-stroke. Accordingly, while pointing velocity was not influenced by TMS interference with any of the three stimulation sites, we again found a significant interaction effect involving the factor STIMULATION SITE \times GROUP ($F_{(2,42)} = 3.50$, $p = 0.04$), and a significant post-hoc t -test for contralesional IPS ($p = 0.033$) (M1: $p = 0.70$; dPMC: $p = 0.63$). While, as mentioned above, controls increased their deviation from target upon ipsilateral IPS-disruption, contralesional IPS-interference still decreased target deviation of stroke patients (Fig. 3).

Relationship of TMS effects and impairment and functional recovery

To account for a relationship between TMS effects and patients' impairment, significant TMS-induced effects on movement kinematics were tested for correlations with both the NIHSS and the NIHSS motor subscore. Accordingly, impairment was not related to the effects of TMS interference in early phase after stroke (all p -values > 0.2). However, after more than three months post-stroke, the decrease of pointing target deviation upon IPS-disruption correlated with the NIHSS obtained in the early post-stroke phase (Spearman correlation: $r = -0.86$, $p = 0.003$) (Fig. 4). Consequently, patients with greater initial impairment showed greater

improvement with higher decreases of target deviation upon contralesional IPS-interference in the later phase more than three months post-stroke. Importantly, the same association was found when considering only the motor subscore of the NIHSS ($r = -0.84$, $p = 0.005$).

We subsequently aimed at relating the observed TMS-evoked performance changes to functional recovery after three months post-stroke. Here, improvements of the NIHSS score were identified to be linked with the change of pointing accuracy upon IPS-disruption early after stroke ($r = 0.75$, $p = 0.019$) (Fig. 4). A similar effect was identified when considering the NIHSS motor subscore only ($r = 0.76$, $p = 0.018$), indicating that a TMS-evoked decrease of target deviation in the early phase post-stroke, i.e., a negative influence of contralesional IPS, was associated with less favorable recovery. Furthermore, we found that the TMS effect of contralesional dPMC on hand-tapping velocity after more than three months was also related to functional recovery as indexed by both the NIHSS difference score ($r = -0.86$, $p = 0.003$) and the NIHSS motor subscore difference ($r = -0.71$, $p = 0.031$) (Fig. 4). Hence, greater TMS-induced decreases of hand-tapping velocity, i.e., a potentially supportive influence of contralesional dPMC in the later post-stroke phase, were linked to greater neurological recovery.

Voxel-based lesion symptom mapping

The highest overlaps of individual lesions were located in the left superior parietal lobe (SPL) and left basal ganglia at the level of the crus posterius of the internal capsule (Fig. 5).

For the first week after stroke, we did not find a significant relationship between the TMS effect and lesion location. In contrast, after more than three months post-stroke, VLSM analysis revealed that the enhancement of hand-tapping velocity upon contralesional IPS-disturbance was associated with lesions

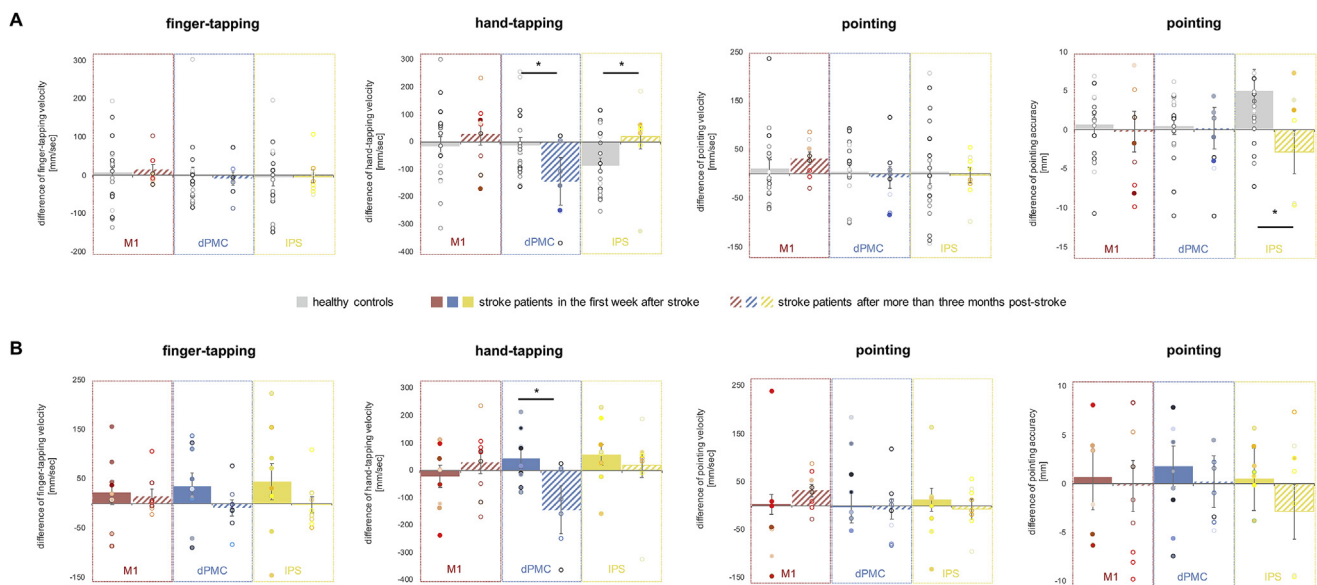


Fig. 3. TMS effects after more than three months post-stroke. Sham-normalized effects of online TMS on the finger-tapping, hand-tapping, and pointing tasks compared to (A) healthy controls, and to (B) the TMS effects early after stroke: Similar to the early phase after stroke (colored columns), IPS-interference again caused an increase of hand-tapping velocity in the second assessment after three months (striped columns). However, disruption of contralesional dPMC led to a slowing of hand-tapping velocity exclusively after more than three months post-stroke. For the pointing task, contralesional IPS-interference still decreased target deviation of stroke patients (striped columns) compared to healthy controls (grey columns). No significant stimulation effects were observed for the finger-tapping task and for pointing velocity; (* < 0.05 , two-sided t -test, error bars indicate standard error of the mean). Please note that group averages early after stroke differ from the data depict in Fig. 2, since these analyses include only patients participating at the follow-up session.

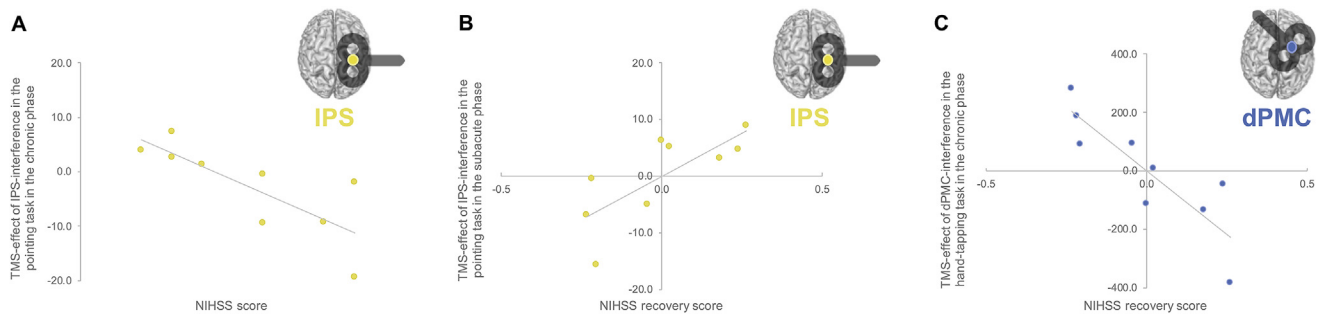


Fig. 4. Correlation analyses. A: Stroke patients with greater initial impairment featured greater improvements of pointing accuracy upon contralesional IPS-interference after more than three months post-stroke. B: Greater increases of pointing accuracy upon contralesional IPS-interference in the first week after stroke were associated to less favorable recovery. C: The effect of dPMC-disruption on hand-tapping velocity after three months post-stroke was also linked to functional recovery. Please note, that correlation analyses for recovery are computed as partial correlations and thereby the axes depict residual values.

in the postcentral gyrus and SPL ($p < 0.05$, FDR-corrected). The decrease of hand-tapping velocity upon dPMC-interference was related to lesions in the anterior intraparietal sulcus ($p < 0.05$, FDR-corrected) (Fig. 6). Furthermore, the improvement in pointing target deviation due to TMS applied over IPS was linked to lesions of the crus posterius of the internal capsule ($p < 0.05$, FDR-corrected) (Fig. 6).

Discussion

Interfering with contralesional neural activity during task performance resulted in differential effects depending on time post-stroke and stimulation site. A novel finding of our study is a potentially disturbing impact of contralesional IPS on motor performance, across different motor tasks and time points. In particular, while in acute left hemispheric stroke patients interference with contralesional IPS increased velocity in the tapping task as well as accuracy in the visuomotor task, both effects were still present after more than three months after stroke. By contrast, the data suggest that contralesional premotor cortex exerts a supportive influence only in later stages after stroke and only on the velocity in the tapping task. These differential effects concerning region specificity and time points after stroke might reflect various mechanisms occurring with post-stroke recovery such as responses to structural damage or reorganization processes.

Contralesional primary motor cortex in the first week post-stroke

After stroke, neuroimaging studies have typically revealed increased brain activity in the contralesional hemisphere during movements of the affected hand which can be detected already within the first days after stroke onset [3,21]. As the amount of activity increase correlated with the degree of early functional recovery within the first two weeks post-stroke [12], contralesional BOLD activity has been argued to be beneficial. Importantly, a shift towards a more unilateral activation pattern, as observed in healthy controls, has been associated with good recovery in the chronic phase post-stroke, while bilateral activation is frequently observed in patients with poor recovery [3,12]. However, functional neuroimaging studies face an inherent limitation as they cannot directly assess the functional relevance of a region for motor performance and recovery.

By contrast, online TMS interference allows a more direct assessment of the functional significance of cortical brain regions for behavior. Both online and offline TMS studies have challenged theories that early after stroke contralesional areas hold a supportive role for motor performance by emphasizing potentially maladaptive influences from contralesional primary motor cortex [16,45,46]. These findings are typically explained in the framework of the interhemispheric competition model, in which contralesional M1 is assumed to exert an inhibitory influence upon

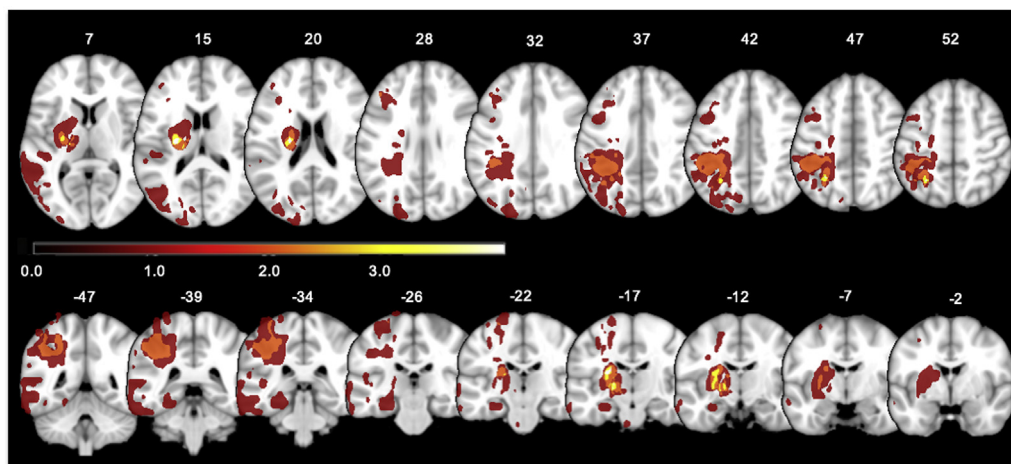


Fig. 5. Lesion overlap. Stroke patients showed the maximum overlap in the left superior parietal lobe (SPL), the left crus posterius of the internal capsule, and the putamen.

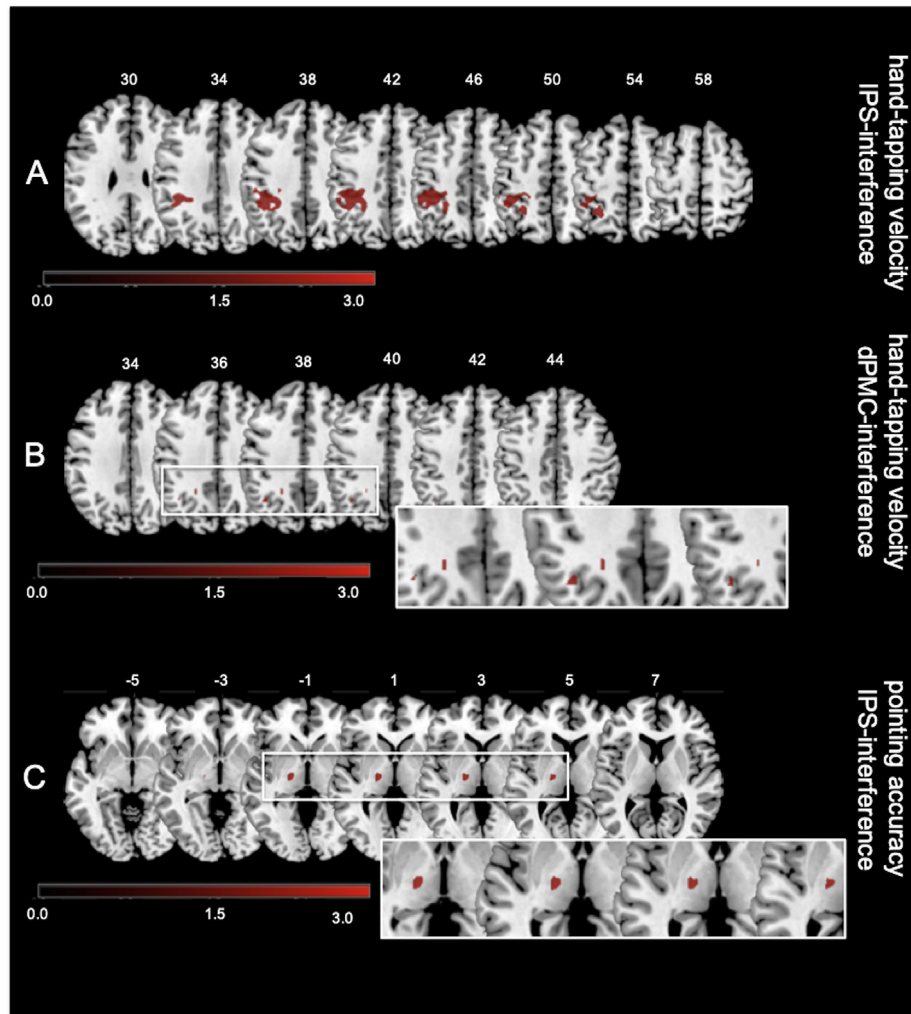


Fig. 6. Voxel Lesion Symptom Mapping. Lesions associated with TMS effects as revealed by VLSM. (A) Lesions associated with the enhancement of hand-tapping velocity upon IPS-disturbance after more than three months post-stroke. (B) Lesions related with a decrease of hand-tapping velocity upon dPMC-interference after more than three months post-stroke. (C) The lower panel represents lesions associated with an improvement in pointing target deviation of TMS applied over IPS. The color bars represent the corresponding t-values of the VLSM analysis. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

ipsilesional M1, thereby deteriorating motor function of the paretic hand [14,15].

Interestingly, while so far contralesional M1 has predominantly been in the focus of research, we here did not observe a significant involvement of contralesional M1 for movement kinematics early after stroke. Besides differences in the study designs and motor tasks, another explanation is that disturbing effects of contralesional M1 might evolve at later stages. Support for this hypothesis stems from fMRI studies, which have shown that enhanced activity of contralesional M1, as well as inhibitory influences from contralesional M1, did not occur in the first days after stroke, but rather at later subacute and chronic stages [12,14,47].

Contralesional intraparietal sulcus and the model of interhemispheric competition

While numerous studies have addressed the relevance of the contralesional hemisphere [3,12,14,16], data exceeding contralesional primary motor cortex are scarce [22,23]. We here found that particularly TMS-induced disturbance of contralesional IPS-activity led to higher tapping velocity and higher target accuracy in the

pointing task in patients, compatible with a non-beneficial influence of this area for motor performance after stroke, irrespective of time post-stroke. Importantly, for pointing movements, we even found evidence that a more negative influence of contralesional IPS for pointing movements in the early post-stroke phase is associated with a less favorable recovery.

In healthy subjects, IPS is critically engaged in visuospatial aspects of visually guided or coordinated hand movements [48–50]. Accordingly, and in line with previous results [49,51], we found that in healthy subjects interference with ipsilateral IPS impaired the accuracy of reaching movements relying on visuomotor integration, and additionally decreased the velocity in a coordinated hand-tapping task.

In left hemisphere stroke patients, we observed opposite effects, which may result from disturbances in interhemispheric inhibition at the level of parietal cortex: Similar to the primary motor cortex, areas within the parietal lobes are strongly interconnected by transcallosal pathways [52,53]. Compatible with the theory of interhemispheric competition between bilateral M1 after stroke [14,15], there is also evidence of interhemispheric imbalances between bilateral parietal regions [54,55]. A symptom that has

frequently been associated with parietal cortex dysfunction and over-activity of the contralesional hemisphere due to imbalanced inhibitory interactions is neglect, which affects the awareness of the side of space and body opposite the site of injury [56]. Thus, inhibitory rTMS [57] or tDCS [58] exerted upon the contralesional posterior parietal cortex have been shown to ameliorate neglect symptoms after stroke, thereby paralleling findings obtained from motor cortex inhibition for hand motor function [59]. Importantly, none of our patients featured clinical symptoms of neglect at both time points of examination. This is even less to expect as all patients featured a left-hemispheric lesion. However, the restriction to the left hemisphere simultaneously imposes a limitation of our study as our conclusion might not necessarily apply to right-hemispheric stroke.

Further evidence for the role of parietal regions in motor recovery stems from structural imaging. For example, Schulz and colleagues have found that the parietal areas contribute to hand motor function via corticocortical connections with premotor regions, i.e. anterior IPS-premotor cortex connections of the superior longitudinal fascicle [60]. This relationship could already be observed for basic hand and arm motor functions [60]. Of note, the VLSM analysis revealed a significant relationship between TMS-induced improvements in hand-tapping and lesion location in the superior parietal cortex, supporting the interpretation of disturbed parietal interactions contributing to motor deficits.

Besides, fMRI studies have equally shown that in patients suffering from motor stroke, functional connectivity between ipsilesional M1 and contralesional parietal regions is diminished [61,62], lending further support to the notion of a relevant contribution of contralesional IPS.

Contralesional premotor cortex and its time-dependent relevance

Some studies have provided evidence for a time-dependent functional contribution of the contralesional hemisphere after stroke [12]. In line with neuroimaging studies revealing persistent over-activity in the chronic phases post-stroke to be associated with poor motor recovery [3,12], the notion of maladaptive influences is supported by TMS studies using inhibitory rTMS protocols upon contralesional M1 and revealing an improvement of motor performance in chronic stroke patients [59].

However, for well-recovered chronic stroke patients, Lotze and colleagues observed that interference with the contralesional hemisphere, precisely M1, dPMC, and SPL, deteriorated patients' performance during a complex finger sequence task [23]. We here did not observe a supporting effect of contralesional M1 or IPS. In fact, in the present study, TMS-induced improvements upon contralesional IPS in the first week post-stroke were still detectable after more than three months post-stroke, indicating a persisting maladaptive role of contralesional IPS resulting in impaired motor performance over time. There are several systematic differences between studies that might explain conflicting findings: While Lotze and colleagues investigated a selected sample of seven patients with lesions confined to the internal capsule, which were all severely affected up to hemiplegia in the acute phase post-stroke, we had a sample of mild and moderate affected patients with more widespread and heterogeneous lesions. Besides, the finger sequence task employed by Lotze and colleagues substantially differs to our more basic motor tasks, which most likely impacts on the susceptibility to TMS interference.

The disruption of contralesional dPMC-activity deteriorated hand-tapping velocity only in the later stage post-stroke, indicating a time-dependent beneficial role during motor recovery. As a stronger supporting influence of contralesional dPMC was linked to greater recovery, this region seems to hold a crucial role in

functional reorganization after stroke. Findings from previous studies have equally suggested an essential role of premotor areas in post-stroke recovery [3,12,22]. Thus, as dPMC is engaged in movement preparation and motor control [63], the observed contribution of contralesional dPMC to motor performance after more than three months post-stroke may reflect neural reorganization processes promoting motor recovery in accordance with the vicariation theory [64].

Limitations

The small and homogenous cohort bears some constraints that may limit the interpretability and generalizability of the data: Although a clinically homogeneous sample may reduce variance and hence strengthen the robustness of the data, the recruitment restriction to left hemisphere lesions raises concerns that right-hemispheric strokes would behave similar upon rTMS interference. As one main purpose of the present work has lain in assessing the functional role of contralesional parietal cortex, i.e., IPS, we reduced the probability that attention deficits like visuospatial neglect, a condition typically observed in patients with right-hemispheric lesions, interfered with performance.

Furthermore, the experimental design with a spectrum of different motor tasks required a certain level of residual motor function limiting the accessible cohort to mildly and moderately impaired patients. While the correlations indicated an association of TMS effects with impairment and functional recovery, mechanisms in more severely affected patients may profoundly differ. In addition, research with larger samples is needed to confirm the findings of our study. Although the assessment of acute stroke patients requires specialized facilities and has to face a relevant number of limitations constantly aiming at minimizing the efforts and risks for patients, it forms the foundation to a profound understanding of cerebral reorganization which will further enable therapeutic approaches aspiring to promote recovery of function.

Conclusion

In conclusion, we here provide evidence for a differential relevance of contralesional frontoparietal areas for motor recovery after left hemisphere stroke. Although the small sample size bears limitations, our results extend existing theories regarding functional implications of contralesional neural over-activity by suggesting that it is primarily contralesional IPS rather than contralesional M1 that exerts detrimental influences on a patient's motor performance both early after stroke and after more than three months post-stroke. At the same time, we observed evidence supporting the notion that contralesional dPMC has a beneficial role in motor recovery. Thus, our data strongly suggest that recovery of motor function post-stroke is accompanied by regionally distinct and functionally specific neural processes within the contralesional hemisphere. Finally, these findings may have important implications with respect to future neuromodulatory approaches aiming at promoting recovery of function. Given that we found evidence for a maladaptive influence of contralesional IPS early after stroke that was related to less favorable recovery, our data might inspire to envisage IPS as a potential aim.

Author contributions section

Caroline Tscherpel: Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing.

Lukas Hensel: Data curation, Validation, Visualization, Writing – review & editing.

Katharina Lemberg: Data curation, Writing – review & editing.
 Mattias Vollmer: Methodology, Writing – review & editing.

Lukas J. Volz: Conceptualization, Methodology, Writing – review & editing.

Gereon R. Fink: Conceptualization, Validation, Supervision, Writing – review & editing.

Christian Grefkes: Conceptualization, Validation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Funding

C.G. and G.R.F. are supported by the University of Cologne Emerging Groups Initiative (CONNECT group) implemented into the Institutional Strategy of the University of Cologne and the German Excellence Initiative. G.R.F. gratefully acknowledges additional support from the Marga and Walter Boll Stiftung.

Declaration of competing interest

The authors confirm that there are no conflicts of interest associated with this publication. Furthermore, there has been no significant financial support for this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2020.01.016>.

References

- [1] Cramer SC. Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. *Ann Neurol* 2008;63:272–87. <https://doi.org/10.1002/ana.21393>.
- [2] Jones TA, Kleim JA, Greenough WT. Synaptogenesis and dendritic growth in the cortex opposite unilateral sensorimotor cortex damage in adult rats: a quantitative electron microscopic examination. *Brain Res* 1996;733:142–8.
- [3] Ward NS, Brown MM, Thompson AJ, Frackowiak RSJ. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. *Brain* 2003;126:2476–96. <https://doi.org/10.1093/brain/awg245>.
- [4] Chollet F, DiPiero V, Wise RJ, Brooks DJ, Dolan RJ, Frackowiak RS. The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. *Ann Neurol* 1991;29:63–71. <https://doi.org/10.1002/ana.410290112>.
- [5] Weiller C, Chollet FO, Friston KJ, Wise RJS, Frackowiak RSJ. Functional reorganization of the brain in recovery from striatocapsular infarction in man. *Ann Neurol* 1992;31:463–72. <https://doi.org/10.1002/ana.410310502>.
- [6] Lemon RN. Descending pathways in motor control. *Annu Rev Neurosci* 2008;31:195–218. <https://doi.org/10.1146/annurev.neuro.31.060407.125547>.
- [7] Cramer SC, Finkelshtein SP, Schaechter JD, Bush G, Rosen BR. Activation of distinct motor cortex regions during ipsilateral and contralateral finger movements. *J Neurophysiol* 1999;81:383–7. <https://doi.org/10.1152/jn.1999.81.1.383>.
- [8] Tinazzi M, Zanette G. Modulation of ipsilateral motor cortex in man during unimanual finger movements of different complexities. *Neurosci Lett* 1998;244:121–4.
- [9] Grefkes C, Ward NS. Cortical reorganization after stroke: how much and how functional? *Neuroscientist* 2014;20:56–70. <https://doi.org/10.1177/1073858413491147>.
- [10] Di Pino G, Pellegrino G, Assenza G, Capone F, Ferreri F, Formica D, et al. Modulation of brain plasticity in stroke: a novel model for neuro-rehabilitation. *Nat Rev Neurol* 2014;10:597–608. <https://doi.org/10.1038/nrneurol.2014.162>.
- [11] Grefkes C, Fink GR. Connectivity-based approaches in stroke and recovery of function. *Lancet Neurol* 2014;13:206–16. [https://doi.org/10.1016/S1474-4422\(13\)70264-3](https://doi.org/10.1016/S1474-4422(13)70264-3).
- [12] Rehme AK, Fink GR, Cramon von DY, Grefkes C. The role of the contralesional motor cortex for motor recovery in the early days after stroke assessed with longitudinal fMRI. *Cerebr Cortex* 2011;21:756–68. <https://doi.org/10.1093/cercor/bhq140>.
- [13] Marshall RS, Perera GM, Lazar RM, Krakauer JW, Constantine RC, DeLaPaz RL. Evolution of cortical activation during recovery from corticospinal tract infarction. *Stroke* 2000;31:656–61.
- [14] Grefkes C, Nowak DA, Eickhoff SB, Dafotakis M, Küst J, Karbe H, et al. Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. *Ann Neurol* 2008;63:236–46. <https://doi.org/10.1002/ana.21228>.
- [15] Murase N, Duque J, Mazzocchio R, Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol* 2004;55:400–9. <https://doi.org/10.1017/S031716710000196>.
- [16] Volz LJ, Vollmer M, Michely J, Fink GR, Rothwell JC, Grefkes C. Time-dependent functional role of the contralesional motor cortex after stroke. *Neuroimage: Clinical* 2017;16:165–74. <https://doi.org/10.1016/j.nicl.2017.07.024>.
- [17] Xu J, Branscheidt M, Schambra B, Steiner L, Widmer M, Diedrichsen J, et al. Rethinking interhemispheric imbalance as a target for stroke neuro-rehabilitation. *Ann Neurol* 2019;1–36. <https://doi.org/10.1002/ana.25452>.
- [18] Bradnam LV, Stinear CM, Barber PA, Byblow WD. Contralesional hemisphere control of the proximal paretic upper limb following stroke. *Cerebr Cortex* 2012;22:2662–71. <https://doi.org/10.1093/cercor/bhr344>.
- [19] Buetefisch CM. Role of the contralesional hemisphere in post-stroke recovery of upper extremity motor function. *Front Neurol* 2015;6:214. <https://doi.org/10.1002/14651858.CD008862.pub2>.
- [20] Gerloff C. Multimodal imaging of brain reorganization in motor areas of the contralesional hemisphere of well recovered patients after stroke. *Brain* 2006;129:791–808. <https://doi.org/10.1093/brain/awh713>.
- [21] Rehme AK, Eickhoff SB, Rottschy C, Fink GR, Grefkes C. Activation likelihood estimation meta-analysis of motor-related neural activity after stroke. *Neuroimage* 2012;59:2771–82. <https://doi.org/10.1016/j.neuroimage.2011.10.023>.
- [22] Johansen-Berg H, Rushworth MFS, Bogdanovic MD, Kischka U, Wimalaratna S, Matthews PM. The role of ipsilateral premotor cortex in hand movement after stroke. *Proc Natl Acad Sci U.S.A* 2002;99:14518–23. <https://doi.org/10.1073/pnas.222536799>.
- [23] Lotze M, Markert J, Sauseng P, Hoppe J, Plewnia C, Gerloff C. The role of multiple contralesional motor areas for complex hand movements after internal capsular lesion. *J Neurosci* 2006;26:6096–102. <https://doi.org/10.1523/JNEUROSCI.4564-05.2006>.
- [24] Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. *Lancet* 2011;377:1693–702. [https://doi.org/10.1016/S0140-6736\(11\)60325-5](https://doi.org/10.1016/S0140-6736(11)60325-5).
- [25] Stinear CM, Barber PA, Petoe M, Anwar S, Byblow WD. The PREP algorithm predicts potential for upper limb recovery after stroke. *Brain* 2012;135:2527–35. <https://doi.org/10.1093/brain/awh146>.
- [26] Grefkes C, Fink GR. Noninvasive brain stimulation after stroke: it is time for large randomized controlled trials! *Curr Opin Neurol* 2016;29:714–20. <https://doi.org/10.1097/WCO.0000000000000395>.
- [27] Hummel FC, Celnik P, Pascual-Leone A, Fregni F, Byblow WD, Buetefisch CM, et al. Controversy: noninvasive and invasive cortical stimulation show efficacy in treating stroke patients. *Brain Stimul* 2008;1:370–82. <https://doi.org/10.1016/j.brs.2008.09.003>.
- [28] Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009;120:2008–39. <https://doi.org/10.1016/j.clinph.2009.08.016>.
- [29] Nettekoven C, Volz LJ, Kutscha M, Pool EM, Rehme AK, Eickhoff SB, et al. Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system. *J Neurosci* 2014;34:6849–59. <https://doi.org/10.1523/JNEUROSCI.4993-13.2014>.
- [30] Davare M, Duque J, Vandermereen Y, Thonnard J-L, Olivier E. Role of the ipsilateral primary motor cortex in controlling the timing of hand muscle recruitment. *Cerebr Cortex* 2006;17:353–62. <https://doi.org/10.1093/cercor/bhj152>.
- [31] Gerloff C, Cohen LG, Floeter MK, Chen R, Corwell B, Hallett M. Inhibitory influence of the ipsilateral motor cortex on responses to stimulation of the human cortex and pyramidal tract. *J Physiol (Lond)* 1998;510:249–59. <https://doi.org/10.1111/j.1469-7793.1998.249b.x>.
- [32] Walsh V, Cowey A. Transcranial magnetic stimulation and cognitive neuroscience. *Nat Rev Neurosci* 2000;1:73–9. <https://doi.org/10.1038/35036239>.
- [33] Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol* 2015;126:1071–107. <https://doi.org/10.1016/j.clinph.2015.02.001>.
- [34] Rossi S. Age-related functional changes of prefrontal cortex in long-term memory: a repetitive transcranial magnetic stimulation study. *J Neurosci* 2004;24:7939–44. <https://doi.org/10.1523/JNEUROSCI.0703-04.2004>.
- [35] Beebe JA, Lang CE. Absence of a proximal to distal gradient of motor deficits in the upper extremity early after stroke. *Clin Neurophysiol* 2008;119:2074–85. <https://doi.org/10.1016/j.clinph.2008.04.293>.
- [36] Twitchell TE. The restoration of motor function following hemiplegia in man. *Brain* 1951;74:443–80.
- [37] Grefkes C, Fink GR. The functional organization of the intraparietal sulcus in humans and monkeys. *J Anat* 2005;207:3–17. <https://doi.org/10.1111/j.1469-7580.2005.00426.x>.
- [38] Wang LE, Fink GR, Dafotakis M, Grefkes C. Noradrenergic stimulation and motor performance: differential effects of reboxetine on movement kinematics and visuo-motor abilities in healthy human subjects. *Neuropsychologia* 2009;47:1302–12. <https://doi.org/10.1016/j.neuropsychologia.2009.01.024>.
- [39] Nowak DA, Grefkes C, Dafotakis M, Küst J, Karbe H, Fink GR. Dexterity is impaired at both hands following unilateral subcortical middle cerebral artery

- stroke. *Eur J Neurosci* 2007;25:3173–84. <https://doi.org/10.1111/j.1460-9568.2007.05551.x>.
- [40] Rorden C, Bonilha L, Nichols TE. Rank-order versus mean based statistics for neuroimaging. *Neuroimage* 2007;35:1531–7. <https://doi.org/10.1016/j.neuroimage.2006.12.043>.
- [41] Gill DM, Reddon JR, Stefanyk WO, Hans HS. Finger tapping: effects of trials and sessions. *Percept Mot Skills* 1986;62:675–8. <https://doi.org/10.2466/pms.1986.62.2.675>.
- [42] Platz T, Prass K, Denzler P, Bock S, Mauritz KH. Testing a motor performance series and a kinematic motion analysis as measures of performance in high-functioning stroke patients: reliability, validity, and responsiveness to therapeutic intervention. *Arch Phys Med Rehabil* 1999;80:270–7. [https://doi.org/10.1016/s0003-9993\(99\)90137-5](https://doi.org/10.1016/s0003-9993(99)90137-5).
- [43] Veerbeek JM, Kwakkel G, van Wegen EEH, Ket JCF, Heymans MW. Early prediction of outcome of activities of daily living after stroke. *Stroke* 2011;42:1482–8. <https://doi.org/10.1161/strokeaha.110.604090>.
- [45] Du J, Tian L, Liu W, Hu J, Xu G, Ma M, et al. Effects of repetitive transcranial magnetic stimulation on motor recovery and motor cortex excitability in patients with stroke: a randomized controlled trial. *Eur J Neurol* 2016;23:1666–72. <https://doi.org/10.1111/ene.13105>.
- [46] Lüdemann-Podubecká J, Bösl K, Nowak DA. Inhibition of the contralesional dorsal premotor cortex improves motor function of the affected hand following stroke. *Eur J Neurol* 2016;23:823–30. <https://doi.org/10.1111/ene.12949>.
- [47] Rehme AK, Eickhoff SB, Wang LE, Fink GR, Grefkes C. Dynamic causal modeling of cortical activity from the acute to the chronic stage after stroke. *Neuroimage* 2011;55:1147–58. <https://doi.org/10.1016/j.neuroimage.2011.01.014>.
- [48] Binkofski F, Dohle C, Posse S, Stephan KM, Heftner H, Seitz RJ, et al. Human anterior intraparietal area subserves prehension – a combined lesion and functional MRI activation study. *Neurology* 1998;50:1253–9.
- [49] Davare M, Zénon A, Desmurget M, Olivier E. Dissociable contribution of the parietal and frontal cortex to coding movement direction and amplitude. *Front Hum Neurosci* 2015;9:241. <https://doi.org/10.3389/fnhum.2015.00241>.
- [50] Grefkes C, Ritzl A, Zilles K, Fink GR. Human medial intraparietal cortex subserves visuomotor coordinate transformation. *Neuroimage* 2004;23:1494–506. <https://doi.org/10.1016/j.neuroimage.2004.08.031>.
- [51] Davare M, Zénon A, Pourtois G, Desmurget M, Olivier E. Role of the medial part of the intraparietal sulcus in implementing movement direction. *Cerebr Cortex* 2012;22:1382–94. <https://doi.org/10.1093/cercor/bhr210>.
- [52] Hofer S, Frahm J. Topography of the human corpus callosum revisited—comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. *Neuroimage* 2006;32:989–94. <https://doi.org/10.1016/j.neuroimage.2006.05.044>.
- [53] Zarei M, Johansen-Berg H, Smith S, Ciccarelli O, Thompson AJ, Matthews PM. Two phases of interhemispheric inhibition between motor related cortical areas and the primary motor cortex in human. *J Anat* 2006;209:1654–65. <https://doi.org/10.1111/j.1469-7580.2006.00615.x>.
- [54] Corbetta M, Kincade MJ, Lewis C, Snyder AZ, Sapir A. Neural basis and recovery of spatial attention deficits in spatial neglect. *Nat Neurosci* 2005;8:1603–10. <https://doi.org/10.1038/nn1574>.
- [55] Kinsbourne M. Hemi-neglect and hemisphere rivalry. *Adv Neurol* 1977;18:41–9.
- [56] Halligan PW, Fink GR, Marshall JC, Vallar G. Spatial cognition: evidence from visual neglect. *Trends Cognit Sci* 2003;7:125–33. [https://doi.org/10.1016/S1364-6613\(03\)00032-9](https://doi.org/10.1016/S1364-6613(03)00032-9).
- [57] Oliveri M, Bisiach E, Brighina F, Piazza A, La Bua V, Buffa D, et al. rTMS of the unaffected hemisphere transiently reduces contralesional visuospatial hemi-neglect. *Neurology* 2001;57:1338–40.
- [58] Sparing R, Thimm M, Hesse MD, Küst J, Karbe H, Fink GR. Bidirectional alterations of interhemispheric parietal balance by non-invasive cortical stimulation. *Brain* 2009;132:3011–20. <https://doi.org/10.1093/brain/awp154>.
- [59] Nowak DA, Grefkes C, Dafotakis M, Eickhoff S, Küst J, Karbe H, et al. Effects of low-frequency repetitive transcranial magnetic stimulation of the contralesional primary motor cortex on movement kinematics and neural activity in subcortical stroke. *Arch Neurol* 2008;65:741–7. <https://doi.org/10.1001/archneur.65.6.741>.
- [60] Schulz R, Koch P, Zimmerman M, Wessel M, Boenstrup M, Thomalla G, et al. Parietofrontal motor pathways and their association with motor function after stroke. *Brain* 2015;138:1949–60. <https://doi.org/10.1093/brain/awv100>.
- [61] Park C-H, Chang WH, Ohn SH, Kim ST, Bang OY, Pascual-Leone A, et al. Longitudinal changes of resting-state functional connectivity during motor recovery after stroke. *Stroke* 2011;42:1357–62. <https://doi.org/10.1161/STROKEAHA.110.596155>.
- [62] Rehme AK, Volz LJ, Feis DL, Bomilcar-Focke I, Liebig T, Eickhoff SB, et al. Identifying neuroimaging markers of motor disability in acute stroke by machine learning techniques. *Cerebr Cortex* 2015;25:3046–56. <https://doi.org/10.1093/cercor/bhu100>.
- [63] Genon S, Li H, Fan L, Müller VI, Cieslik EC, Hoffstaedter F, et al. The right dorsal premotor mosaic: organization, functions, and connectivity. *Cerebr Cortex* 2016. <https://doi.org/10.1093/cercor/bhw065>.
- [64] Wiesendanger M. Constantin von Monakow (1853–1930): a pioneer in interdisciplinary brain research and a humanist. *Comptes Rendus Biol* 2006;329:406–18. <https://doi.org/10.1016/j.crv.2006.03.011>.