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Short Communication

Functional relevance of ipsilateral motor activation in congenital hemiparesis as tested by fMRI-navigated TMS

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ABSTRACT

Many, but not all patients with congenital hemiparesis (i.e., hemiparesis due to a pre-, peri- or neonatally acquired brain lesion) control their paretic hands via ipsilateral cortico-spinal projections from the contra-lesional hemisphere (CON-H). Patients who still control their paretic hands via preserved crossed cortico-spinal projections from the damaged hemisphere nevertheless show increased fMRI activation during paretic hand movements in the CON-H. We used fMRI-navigated rTMS induced functional lesions over the primary motor cortex (M1) hand area, the dorsal premotor cortex (dPMC) and the superior parietal lobe (SPL) of the CON-H in four of these patients to investigate whether this increased ipsilateral activation during finger movements of the paretic hand contributes to movement performance. Functional lesions of the dPMC and M1 but not SPL of the CON-H induced decreased temporal preciseness of finger sequences. The present results argue for a possible role of dPMC and M1 of the CON-H on complex motor behavior even in those patients with congenital hemiparesis who control their paretic hands via crossed cortico-spinal projections from the damaged hemisphere.

Introduction

A large proportion of patients with congenital hemiparesis show unilateral defects in the periventricular white matter, which occur either as complications of premature birth or as prenatally acquired lesions during the early third trimester of pregnancy (Krageloh-Mann et al., 1995). Since the immature nervous system has superior compensatory capabilities as compared with those of the adult brain (Kennard, 1936), patients with specific lesions location and/or larger lesion size show abnormal motor projections projecting from the hemisphere contralateral to the lesion (CON-H) to the body (Benecke et al., 1991; Staudt et al., 2002). When such lesions are small, crossed cortico-spinal motor tracts from the lesioned hemisphere remain at least partially intact, the functional deficit is only mild and no such abnormal projections can be detected. Nevertheless, these patients typically show increased motor activation in the contra-lesional hemisphere when moving the paretic hand (Staudt et al., 2002). We were now interested whether this increased ipsilateral activation (observed during simple opening/closing of the paretic hand) contributes to movement performance of complex movements in a group of patients suffering form congenital hemiparesis due to unilateral defects in the periventricular white matter. Therefore, these patients were highly homologous in respect to the lesion location, lesion size and the maturational stage of the brain at the time of the insult. Additionally, they did not show any motor potentials in the affected hand evocable from single pulse TMS over the primary motor cortex of the CON-H. By using a highly sensitive method of functional lesions induced by rTMS triple pulses (Lotze et al., 2006) we were interested which regions of the CON-H might functionally show a relevant contribution to complex motor behavior of the paretic hand.

We investigated 4 patients (3 male, average age 21 years; + (standard deviation) 2.45; two strongly right handed (average 88 points) and two strongly left handed (average − 80) as tested according to Oldfield, 1971) with congenital hemiparesis due to unilateral periventricular brain lesions (acquired during the early third trimester of pregnancy; three left hemispheric lesions). The lesions of patients, and demographic data are given in Table 1. A standardized video-documented neurological examination was performed in all patients. The degree of paresis was measured after the MRC-scale (Medical Research Council; Daniels and Worthingham, 1972); all patients showed a paresis of 1. Hand function additionally was graded with the sequential finger opposition task as 1 = normal; 2 = slow and/or incomplete performance; 3 = inability to perform a finger opposition task (Staudt et al., 2000). All patients showed a function of 1. Patients gave their written informed consent to the experiment approved by the University of Tübingen ethics committee.

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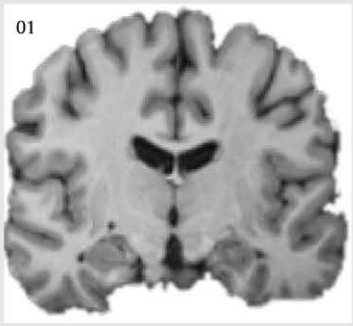
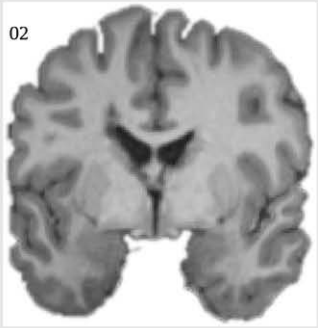
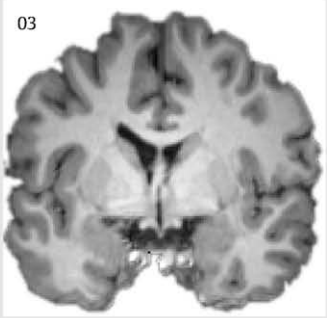
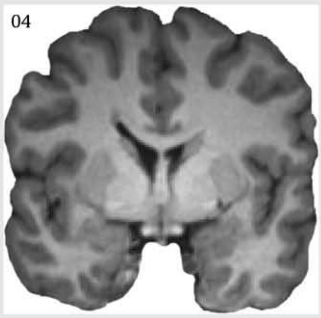
Table 1

01	02	03	04
			
Remaining degree of paresis[a]: 1 age: 25 years BOLD M1i [*t*-value][b]: 8.18 Temporal errors by rTMS[c]: 2.67*	Remaining degree of paresis:1 age: 19 years BOLD M1i [*t*-value]: 17.31 Temporal errors by rTMS: 2.00	Remaining degree of paresis:1 age: 18 years BOLD M1i [*t*-value]: 13.31 Temporal errors by rTMS: 2.33	Remaining degree of paresis: 1 age: 22 years BOLD M1i [*t*-value]: 12.89 Temporal errors by rTMS: 3.00

[1]Degree of paresis after the differentiation of the Medical Research Council (MRC).
[2]BOLD-signal magnitude as expressed as highest *t*-value in the primary motor cortex in the CON-H during finger sequence performance with the affected hand.
[3]Temporal errors induced by rTMS jamming over the highest activated voxels in the precentral gyrus; tapping rate after TMS minus baseline.

Patients performed a sequential finger-tapping task of 10 visually presented numbers indicating button presses with digits 2, 3, 4, and 5 (corresponding to index, middle, ring and small finger). Tapping was trained with a 1 Hz (paced by an auditory presented metronome beat) and a maximum tapping velocity (without making mistakes in sequence order) for 10 min for each hand prior to fMRI measurement. During scanning tapping was performed with their paretic hand (both maximal frequency: 1.9 + 0.3 Hz and with auditory paced 1 Hz frequency). Conditions were performed in a block design alternating rest and performance four times on specially constructed MR suitable keyboards with physiologically ordered buttons of 1.5 cm in diameter connected via optic fiber cable to a recording computer outside the scanner room and recorded with Labview (Version 5.6; National Instruments, USA).

Subjects underwent MRI scanning at 3 T (Siemens Trio, 12 HF-head-coil) with 30 oblique transverse slices (3 mm thickness, 1 mm gap) covering the whole head using a T2*-weighted echo-planar imaging sequence (EPI; TR 2 s, matrix size 64*64, TE 30 ms, flip angle 90°). The subjects were in supine position on the padded scanner couch and wore hearing protection. Additionally a T1 weighted 3D image (MPrage; TR 2.3 sec; TE 3.93 ms; 160 sagittal slices 1 + 0.5 mm) was acquired.

Spatial preprocessing and data analysis were performed with SPM2 (Wellcome Department of Imaging Neuroscience, London). Each time-series was realigned and resliced after unwarping in phase encoding direction (anterior/posterior) to account for movement and susceptibility artifacts. EPIs were coregistered and resliced to the T1-weighted structural dataset and smoothed with a Gaussian filter of 4 mm (full width at half maximum; FWHM), in order to achieve a high precision of navigation within functional maps. Data were high-pass filtered (128 s) and statistically evaluated for each individual. Conditions were modeled with a canonical hemodynamic response function using standard SPM2 settings. For navigation, significance thresholds of $p<0.05$, corrected for multiple comparisons (FWE) were used, which enabled to detect activated voxels within the regions of interest in the CON-H. Functional images were saved and underwent further superposition with the T1-anatomy and segmentation by using Brainsight frameless (Rogue Research, Montreal, Canada).

At least 3 h after fMRI-measurement subjects were investigated with TMS using a Magstim rapid stimulator (Magstim, Whitland, UK) with a maximum output of 2.2 T equipped with a figure-of-8 coil, each wing with a diameter of 7 cm.

TMS was delivered with the coil held tangentially to the scalp, 45° from the mid-sagittal line, with the handle pointing backwards. The current induced in the brain was therefore directed approximately perpendicular to the line of the central sulcus (Werhahn et al., 1994). For sham stimulation the coil was turned 90° so that only one wing touched the scalp at the Cz position (10/20 system) but the pulses were not applied to the head surface.

Resting motor threshold (rMT), measured for the hand flexors of the non-performing intact hand was defined as the minimum stimulus intensity that produced motor evoked potentials (MEPs) of at least 50 μV peak-to-peak amplitude in at least 3 out of 5 trials (Rossini et al., 1994).

All patients were additionally investigated in respect to inducible MEPs of the paretic hand by stimulation over the motor cortex of the CON-H and the damaged hemisphere (DAM-H). MEPs were recorded with the relaxed target muscles of the hand contralateral but also ipsilateral to the hemisphere (Maegaki et al., 1997; Staudt et al., 2002). The absence of ipsilateral responses was documented by stimulation with 200% rMT or 100% stimulator output (whatever was reached first) at the optimal point for the contralateral response and at positions 1 cm and 2 cm anteriorly, posteriorly, laterally and medially. None of the patients selected showed any elicitable MEPs in the affected hand extensors by stimulating the CON-H.

For navigation of target regions we used a frameless, fMRI-guided stereotaxic system with a Polaris IR tracker camera (Northern Digital, Waterloo, ON, Canada) and Brainsight frameless software (Rogue, Montreal, Canada). FMRI-maps were overlaid on the T1-weighted anatomy, and the brain was manually segmented and visualized for the three-dimensional 3–6 mm surface rendering (see Fig. 1A). ROIs have been selected prior to the beginning of the study. We tested three different verum-locations: dPMC (located as the fMRI-activation maximum anterior to the precentral sulcus, inferior to the superior frontal sulcus at the posterior part of the medial frontal sulcus; (Fridman et al., 2004)), M1 (posterior half of precentral gyrus; location of activation maxima nearest to the anatomical hand knob) and SPL (superior parietal lobe; posterior to the postcentral sulcus and superior to the parietal sulcus). The TMS coil was navigated over the individual fMRI-activation maxima within the preselected ROIs but not further adjusted for instance to elicit maximal excitation of the contralateral healthy hand during stimulation of CON-H M1. Additionally, we tested three different placebo-stimulations: with a 90° flipped coil (SHAM), prefrontal (FRO) and peripheral (PERI) stimulation. The later two were expected to control for two types of aversiveness: the stimulation of the scalp and adjacent face muscles and the peripheral movement of the hand. The prefrontal stimulation

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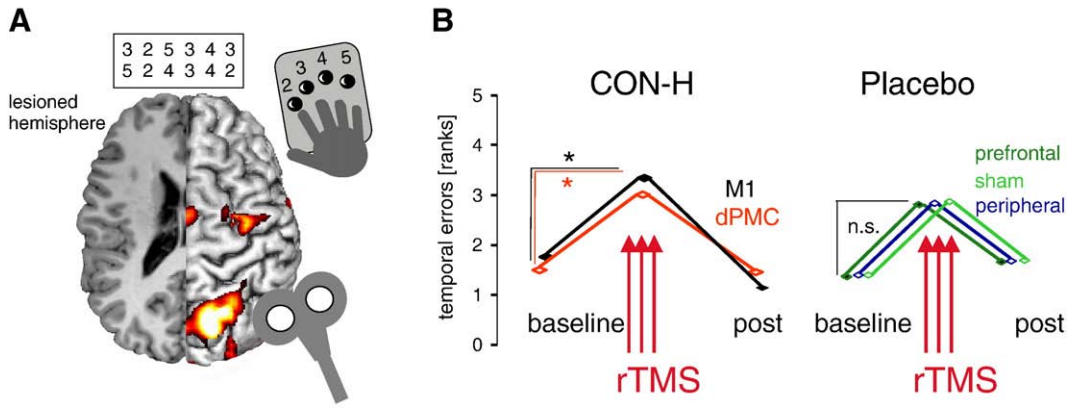

Fig. 1. (A) Graph for the illustration of the method used: rTMS was applied over the intact hemisphere and navigated by fMRI-activation maxima in preselected regions of interest, known to be activated during the task performance. The subject performed a finger sequence coded by numbers with their affected hand. A triple rTMS pulse was randomly applied during finger performance ipsilateral to movement execution and delay in finger press served as the dependent variable. (B) Left: Temporal errors shown for the primary motor cortex (M1) and the dorsal premotor cortex (dPMC) of the hemisphere ipsilateral to movement (contralateral to the lesion; CON-H) plotted for three time units: baseline, during rTMS and post-stimulation. Only the differences between the pre and the rTMS-condition for the locations plotted here were significant (marked with a star). Right: Temporal errors plotted for the placebo conditions (sham, peripheral and prefrontal) revealed no significant effect on the number of temporal errors.

was structurally navigated over the interhemispheric sulcus in a maximal anterior area which elicited tolerable aversive feelings during rTMS. Peripheral stimulation above the forearm contralateral to the movement was administered with an intensity, which elicited about the same motor response as stimulation over M1 (average intensity of stimulator output: 57% + 5.00).

Psychological rating was obtained with visual analogue scales (VAS; length of 10 cm; 0: no effect to 10: maximally aversive) for both aversiveness and amount of subjective TMS induced disturbance during the finger sequence. Ratings between sham and the three verum-conditions were statistically compared using Wilcoxon tests.

Before TMS measurement patients trained the same sequence (presented visually) as during the fMRI-session. Before we started the TMS-investigation subjects had to be able to play the sequence ten times in succession without a mistake in order to avoid learning effects during TMS-interference of performance testing. To be able to detect timing errors with high sensitivity, during TMS subjects were instructed to tap precisely at a movement rate of 1 Hz, paced with beep-tones. Data were recorded with Presentation (Version 0.52, Neurobehavioral Systems, Albany, CA USA).

Each of the TMS locations was stimulated in a balanced order with 10 runs of a finger sequence for each position before moving on to the next stimulation site. During each finger sequence a triple pulse with an intensity of 120% rMT and an interpulse interval of 50 ms (high frequency jamming with 20 Hz) was administered for each stimulus location. Additionally, during each of the 10 trials, pulses were administered at a randomized time point between the third and the eighth finger tap. The first two sequences were not used for further evaluation in order to exclude contamination by novelty of stimulation due to the new location.

The dependent variable of this study was the temporal preciseness of button presses and the number of accuracy errors performed between baseline (three taps before the stimulus was applied), right after TMS pulses (one tap) as well as 3 responses after TMS (post). Temporal preciseness was estimated as follows: In each subject for each stimulation condition latencies between acoustically paced tones and responses from 128 trials (16 responses for each of the 8 available sequences) were used to estimate mean and standard deviation. Then for each of the 16 sequence positions the number of latencies with more than 2 standard deviations above or below the mean was determined. These temporal errors could range between 0 and 8, as 8 full 16-response sequences were used for each condition. Statistical evaluation of the performance data was performed with Friedman tests for each location site. Therefore, number of temporal errors was compared between baseline, the response exactly after rTMS was delivered and three responses after rTMS (post). Temporal errors for the placebo stimuli were averaged for further comparisons. All statistical comparisons were performed with the Statistical Package for the Social Sciences (SPSS 14).

All patients selected showed a paresis of 1 on the MRC-scale and an impairment of 1 during sequential finger tapping with the affected hand. Cortico-spinal motor pathways in the patients were – at least partially – intact; we observed no relevant delay of MEP over the affected hemisphere (DAM-H) in contrast to the unaffected (CON-H). During fMRI all patients showed significant activation in the ROIs above the selected statistical threshold; therefore all patients showed significant ipsilateral activation during the finger sequence performance in M1, dPMC and SPL of the CON-H. Ratings of aversiveness and destruction of motor performance between sham (average aversiveness: 1.87; disruption: 0.97) and the three verum-conditions (average aversiveness: 2.74; disruption: 1.45) were statistically comparable (aversiveness: Wilcoxon $z(3) = 1.46$; n.s.; disruption: Wilcoxon $z(3) = 1.83$; n.s.). TMS-jamming delayed movements of the impaired hand over M1 (Friedman Test: chi-square $(2) = 7.60$; $p = 0.022$) and dPMC (chi-square $(2) = 6.00$; $p = 0.050$) of the CON-H (see Fig. 1). In contrast, placebo TMS (chi-square $(2) < 6$; n.s.) and jamming over SPL of the CON-H showed no significant effect. The averaged delay induced by the jamming over the ROIs of the CON-H and those detected in a group of seven healthy controls ipsilateral to movement execution of the right hand described in a previous investigation (Lotze et al., 2006) were plotted in Table 2.

There were no significant effects with (special) accuracy as dependent measure.

Table 2
Delay effect for the patients investigated and healthy control subjects described previously using the same method (Lotze et al., 2006).

Region stimulated	Delay effect in patients	Delay effect in healthy controls
M1[a]	81.48 ms (±27.86)	34.24 ms (±14.66)
dPMC[b]	64.16 ms (±22.73)	43.24 ms (±13.05)
SPL[c]	44.13 ms (±15.74)	43.69 ms (±36.96)
Sham[d]	41.50 ms (±34.72)	52.12 ms (±34.72)

[a] Primary motor cortex of the CON-H or the hemisphere ipsilateral to the moving left hand in healthy control subjects, respectively.
[b] Dorsal premotor cortex of the CON-H or the hemisphere ipsilateral to the moving left hand in healthy control subjects, respectively.
[c] Superior parietal lobe of the CON-H or the hemisphere ipsilateral to the moving left hand in healthy control subjects, respectively.
[d] Placebo TMS-stimulation.

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Both in adulthood stroke and in congenital hemiparesis, the recruitment of brain areas in the contra-lesional hemisphere (CON-H; i.e., ipsilateral to the paretic hand) has been demonstrated as an important principle of post-lesional reorganization of hand functions. This mechanism has first been discovered using activation studies (Weiller et al., 1992; Seitz et al., 1998), showing that, during paretic hand movements, brain activation was increased in a network of multiple primary and non-primary sensorimotor areas of the CON-H. These studies, however, could not demonstrate that this increased ipsilateral co-activation was functionally relevant. This question could only be addressed after the advent of techniques inducing "functional lesions", such as rTMS. Using rTMS, we have recently demonstrated that functional lesions to such co-activated brain regions in the CON-H in patient who recovered motor function after a unilateral infarct in the internal capsule during late adulthood, does indeed lead to a deterioration in the dexterity of paretic hand movements (Lotze et al., 2006). Therefore in adult patients who recovered from unilateral capsular stroke, the CON-H has gained functional relevance for the performance of complex finger sequences.

In patients with congenital hemiparesis and preserved crossed cortico-spinal projections, we did also observe the phenomenon of increased co-activation in the CON-H by using fMRI of paretic hand movements (Staudt et al., 2002). However, evidence for the functional relevance of this ipsilateral co-activation could not be provided by fMRI alone. Using triple TMS pulses, which induced functional lesions of individually localized areas of ipsilateral co-activation in M1 and dPMC of the CON-H, we decreased the temporal preciseness of finger sequences of the paretic hand in a group of four patients with congenital hemiparesis and intact cortico-spinal motor pathways. No such changes were observed for the three placebo conditions and for SPL stimulation. This demonstrates that, in such patients with congenital hemiparesis, the increased activation in the contra-lesional hemisphere indeed possesses functional relevance.

Admittedly, this study has the limitation of a small sample size, which is due to the low number of patients who fulfill our rather strict inclusion criteria (congenital unilateral lesions in the periventricular white matter, preserved contralateral MEPs in the paretic hand after TMS of the affected hemisphere, no ipsilateral MEPs in the paretic hand after TMS of the contra-lesional hemisphere). On the other hand, we are convinced that this homogeneity of our sample is necessary for the conclusions we wanted to draw, even if this meant a decrease in statistical power.

Another critical point is that we did not investigate a control group. However, in our previous study (Lotze et al., 2006), we described already data for control subjects, who were investigated with the same experimental design. In these healthy subjects, the delay effect over M1 and dPMC was on average 34.24 ms (+14.66) over M1 and of 43.24 ms (+13.05) over dPMC, an effect comparable to the sham condition (52.12 ms; +34.72; see Table 2). In contrast, the delay effect in the patient group reported here in absolute values was 81.48 ms (+27.86) over M1 and 64.16 ms (+22.73) over dPMC, whereas the sham stimulation showed an effect of 41.50 ms (+34.72). Therefore, our data suggest a considerably higher effect of the functional involvement of the CON-H in patients with congenital paresis than observed for the ipsilateral hemisphere for the performance of unilateral hand movements in a healthy subject group. But again, due to the low number of subjects investigated here, this could not be tested formally.

In conclusion, combining and comparing the findings of fMRI and rTMS studies in adulthood stroke and congenital hemiparesis (with preserved cortico-spinal projections), we detected similar mechanisms of post-lesional reorganization: In both situations, M1 and dPMC in the CON-H apparently possess a specific functional relevance for complex motor performance of the paretic hand. Despite the well-known superiority of post-lesional reorganization in the developing brain (Kennard 1936), the mechanisms of reorganization in these two situations might be partially comparable. Despite the apparent similarity of the mechanisms involved in interhemispheric reorganization in adult hemiparetic stroke and in congenital hemiparesis, some important difference have to be acknowledged: One is, that a retrieval of motor associated programs of the healthy hemisphere is not possible in patients with congenital hemiparesis, since most of the knowledge necessary to perform voluntary movements is gained for both hemispheres, simultaneously after having already experienced a lesion. Therefore, contributions of the non-affected hemisphere during performance of the affected hand cannot be attributed to a transfer of knowledge of the non-affected to the affected hemisphere. Another is, that – with only few exceptions – adult hemiparetic stroke patients *realize* the sensorimotor deficit they developed as a consequence of their stroke, resulting in motivation for therapy, which might drive or facilitate reorganization. Voluntary motivation based on awareness of the deficit does certainly not occur in fetuses and infants with congenital hemiparesis — especially not when it is only mild as in the patients in our sample. This means that this type of interhemispheric take-over of sensorimotor functions we observed can also take place in the absence of voluntary motivation, but rather uses "intrinsic" mechanisms of the brain to compensate for focal lesions.

Additionally, there are no comparable mechanisms in reorganization with adult patients for those patients with congenital hemiparesis who suffered a disruption of the normal crossed cortico-spinal pathways: As a general rule, these patients develop (or better: maintain from previous stages of brain development) fast-conducting ipsilateral cortico-spinal projections, thus allowing the contra-lesional hemisphere to exert motor control over the paretic hand. This phenomenon has indeed only been reported after early brain lesions (up to two years of age), and is therefore specific for the superior reorganizational capability of the developing human brain.

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