

Rewiring Cortico-Muscular Control in the Healthy and Poststroke Human Brain with Proprioceptive β -Band Neurofeedback

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In severely affected stroke survivors, cortico-muscular control is disturbed and volitional upper limb movements often absent. Mental rehearsal of the impaired movement in conjunction with sensory feedback provision are suggested as promising rehabilitation exercises. Knowledge about the underlying neural processes, however, remains vague. In male and female chronic stroke patients with hand paralysis, a brain-computer interface controlled a robotic orthosis and turned sensorimotor β -band desynchronization during motor imagery (MI) of finger extension into contingent hand opening. Healthy control subjects performed the same task and received the same proprioceptive feedback with a robotic orthosis or visual feedback only. Only when proprioceptive feedback was provided, cortico-muscular coherence (CMC) increased with a predominant information flow from the sensorimotor cortex to the finger extensors. This effect (1) was specific to the β frequency band, (2) transferred to a motor task (MT), (3) was proportional to subsequent corticospinal excitability (CSE) and correlated with behavioral changes in the (4) healthy and (5) poststroke condition; notably, MI-related enhancement of β -band CMC in the ipsilesional premotor cortex correlated with motor improvements after the intervention. In the healthy and injured human nervous system, synchronized activation of motor-related cortical and spinal neural pools facilitates, in accordance with the communication-through-coherence hypothesis, cortico-spinal communication and may, thereby, be therapeutically relevant for functional restoration after stroke, when voluntary movements are no longer possible.

Key words: β -oscillations; cortico-muscular coherence; cortico-spinal excitability; motor recovery; neurofeedback; stroke

Significance Statement

This study provides insights into the neural processes that transfer effects of brain-computer interface neurofeedback to subsequent motor behavior. Specifically, volitional control of cortical oscillations and proprioceptive feedback enhances both cortical activity and behaviorally relevant connectivity to the periphery in a topographically circumscribed and frequency-specific way. This enhanced cortico-muscular control can be induced in the healthy and poststroke brain. Thereby, activating the motor cortex with mental rehearsal of the impaired movement and closing the loop by robot-assisted feedback synchronizes ipsilesional premotor cortex and spinal neural pools in the β frequency band. This facilitates, in accordance with the communication-through-coherence hypothesis, cortico-spinal communication and may, thereby, be therapeutically relevant for functional restoration after stroke, when voluntary movements are no longer possible.

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Introduction

After stroke, active movements are particularly relevant for motor rehabilitation to be effective in improving outcome beyond spontaneous neurobiological processes (Murphy and Corbett, 2009; Langhorne et al., 2011). When active physical practice, e.g., of the upper extremities is no longer possible, the re-learning of movements remains restricted (Doyon and Benali, 2005; Halsband and Lange, 2006). Motor recovery in severely impaired stroke patients with a long-lasting hand paralysis is therefore limited (Dobkin et al., 2004; Feigin et al., 2008; Jørgensen et al., 1999).

In these patients, motor imagery (MI) might be an alternative to physical practice (Boe et al., 2014; Halsband and Lange, 2006) since it activates the sensorimotor system without any overt

movement, particularly when reinforced by feedback (Gao et al., 2011; Szameitat et al., 2012; Vukelić and Gharabaghi, 2015a; Bauer et al., 2015; Naros et al., 2016). Neurofeedback of motor intention or MI-related brain states with brain-computer/brain-machine interfaces (BCI/BMI) or peripheral electrical stimulation is therefore being explored as an experimental training to improve the motor outcome of stroke rehabilitation (Biasucci et al., 2018). Controlled trials demonstrated that MI with contingent feedback resulted in greater improvement than interventions that provided no or only random feedback (Cervera et al., 2018). However, these studies revealed also considerable heterogeneity of the intervention effects (Cervera et al., 2018). Moreover, these BCI interventions have often not achieved clinical benefits beyond those of dose-matched robot-assisted therapy (Ang et al., 2010, 2014), which has, in turn, provided only little additional benefit over dose-matched classical physiotherapy up to now (Kwakkel et al., 2008; Lo et al., 2010; Klamroth-Marganska et al., 2014). In this context, current BCI interventions resemble (if applied contingently to MI) other priming interventions such as transcranial electrical (Allman et al., 2016) or magnetic brain stimulation techniques (Volz et al., 2016). These approaches increase, unlike sham stimulation, the general responsiveness of the brain for subsequent active practice.

However, to provide the rationale for translating BCI interventions into clinical settings for severely impaired stroke patients, who lack upper limb function and are unable to engage their hand in useful physical training, more specific effects beyond the practice of primed physiotherapy are required (Naros and Gharabaghi, 2015; Brauchle et al., 2015). Such a specificity requires the demonstrating of brain-behavior relationships (Gharabaghi, 2016): we need to demonstrate (1) an evolution of the oscillatory dynamics trained by the neurofeedback task, (2) correlated modulations of functionally relevant networks related to the therapeutic goal, and (3) a correlation between the modulated neural dynamics and the task-specific behavioral changes.

Previous findings serve as building blocks toward this goal: movement-related β -oscillations were shown to be compromised in stroke patients and correlated with the impairment level (Rossiter et al., 2013; Shiner et al., 2015). In the early poststroke period, these oscillations may reflect impairment only and not recovery (Bönstrup et al., 2019). Less is known about the role of β -oscillations in chronic stroke patients. In healthy subjects, however, volitional modulation of these sensorimotor β -oscillations could be learned via BCI feedback and correlated with corticospinal excitability (CSE) increases (Kraus et al., 2016a) and improved motor performance (Naros et al., 2016); β -oscillations in the healthy brain predicted, moreover, a power-dependent and phase-dependent intrinsic response modulation of corticospinal signal propagation at rest (Khademi et al., 2018, 2019) and in the active motor system (Naros et al., 2020).

More specific knowledge about the underlying neural processes that transfer effects of the BCI intervention to the following behavioral motor task (MT), particularly in the poststroke condition, remains, however, vague. In this context, we conjectured in accordance with the communication-through-coherence hypothesis (Fries, 2005), synchronized activation of motor-related cortical and spinal neural pools, e.g., captured by cortico-muscular coherence (CMC), as the functionally relevant substrate to mediate the above-mentioned effects. We, furthermore, hypothesized a frequency-specificity to the β -band and the relevance of proprioceptive feedback to volitional modulation of sensorimotor oscillations for this coherence to ensue. We also expected β -CMC as the functionally relevant substrate to mediate BCI

training-related network dynamics to subsequent motor improvements in the poststroke condition, thereby, being potentially relevant for functional restoration when voluntary hand opening is no longer possible.

Materials and Methods

Subjects

The research was approved by the ethics committee of the University of Tübingen Faculty of Medicine and conformed to the standards set by the latest version of the Declaration of Helsinki. All participants gave their written informed consent before participation.

In study 1, we recruited twenty-seven, right-handed healthy human subjects (mean age, 27.30 ± 4.38 years, range 19–37 years, 22 male) with no history of psychiatric or neurologic disorders. Fifteen subjects participated in one session with proprioceptive feedback, and twelve subjects participated in one session with visual feedback. The Edinburgh handedness inventory (Oldfield, 1971) was used to confirm right-handedness. In this healthy subject population, we have already reported (Kraus et al., 2016a) an increase of CSE, indexed by motor-evoked potential (MEP) changes in electromyographic (EMG) recordings in response to transcranial magnetic stimulation (TMS). This MEP increase occurred in the steep part of the stimulus-response curve (SRC). In this previous work (Kraus et al., 2016a), we investigated CSE of the stimulated sensorimotor cortex (indexed by MEPs) at rest, after the BCI intervention.

In the present study, we analyzed the electroencephalographic (EEG) data acquired during the intervention, and afterward in the course of a MT that was performed before and after the intervention (Fig. 1). This allowed capturing on a moment-to-moment basis corticocortical (ciCOH) and cortico-muscular oscillatory phase coherence (CMC) of both hemispheres (beyond the right sensorimotor cortex that was previously studied with MEPs) in the course of the BCI intervention and the behavioral MT (Schnitzler and Gross, 2005; Mehrkanoun et al., 2014).

The data acquired during the intervention and the MT were analyzed separately. Thereby, the task-related network-level connectivity, a potential generalization to the MT, and the underlying neurophysiological mechanisms could be analyzed and compared with each other, and to the reported MEP changes and behavioral effects.

In study 2, eight right-handed human stroke subjects (mean age, 57 ± 11 years, range 34–68 years, seven male) participated in the same BCI intervention with proprioceptive feedback like the healthy subjects. As part of a larger study on the underlying neurophysiological mechanisms of BCI feedback in the lesioned brain, these severely affected chronic stroke subjects performed 20 sessions of this intervention within a four-week training period, i.e., one session per day. Clinical details of this group of stroke subjects (Table 1; P8 of the present study is P9 of Belardinelli et al., 2017; where the original P8 was excluded from further analysis because of left-handedness) have already been reported (Belardinelli et al., 2017; Grimm et al., 2016) and are cited here accordingly. Here, we included right-handed subjects only, since recent work of our group suggests that right and left handers show different oscillatory entrainment of cortical alpha band networks during β -band neurofeedback (interhemispheric vs intrahemispheric interactions), when using the very same approach applied in this study (Vukelić et al., 2019). The stroke subjects were in the chronic phase after stroke (70 ± 34 months) and presented with a severe and persistent hemiparesis of the left side because of a right hemispheric lesion with an upper extremity Fugl-Meyer Assessment (UE-FMA) score of 16.23 ± 6.79 [range 6.80–28.60] (Belardinelli et al., 2017). They had a left-hand paralysis and were unable to extend their fingers. After the four-week intervention, the UE-FMA score of the stroke subjects showed a small but significant improvement by 3.15 ± 2.06 ($p = 0.003$; paired t test; Cohen's $d = 0.42$), with a distributed improvement pattern across arm (UE-FMA part A) by 1.63 ± 0.80 ($p < 0.001$; Cohen's $d = 0.37$), wrist (UE FMA part B) by 0.80 ± 0.77 ($p = 0.022$ Cohen's $d = 0.33$), and hand (UE-FMA part C) by 0.71 ± 1 ($p = 0.083$, Cohen's $d = 0.47$).

The clinically important difference (CID) for the UE-FMA score in chronic stroke (i.e., 5.25) Page et al. (2012) has been estimated for stroke subjects with minimal to moderate impairment (UE-FMA score of ≥ 28 to ≤ 50 and active extension in the affected wrist of at least 5°; 109), and not

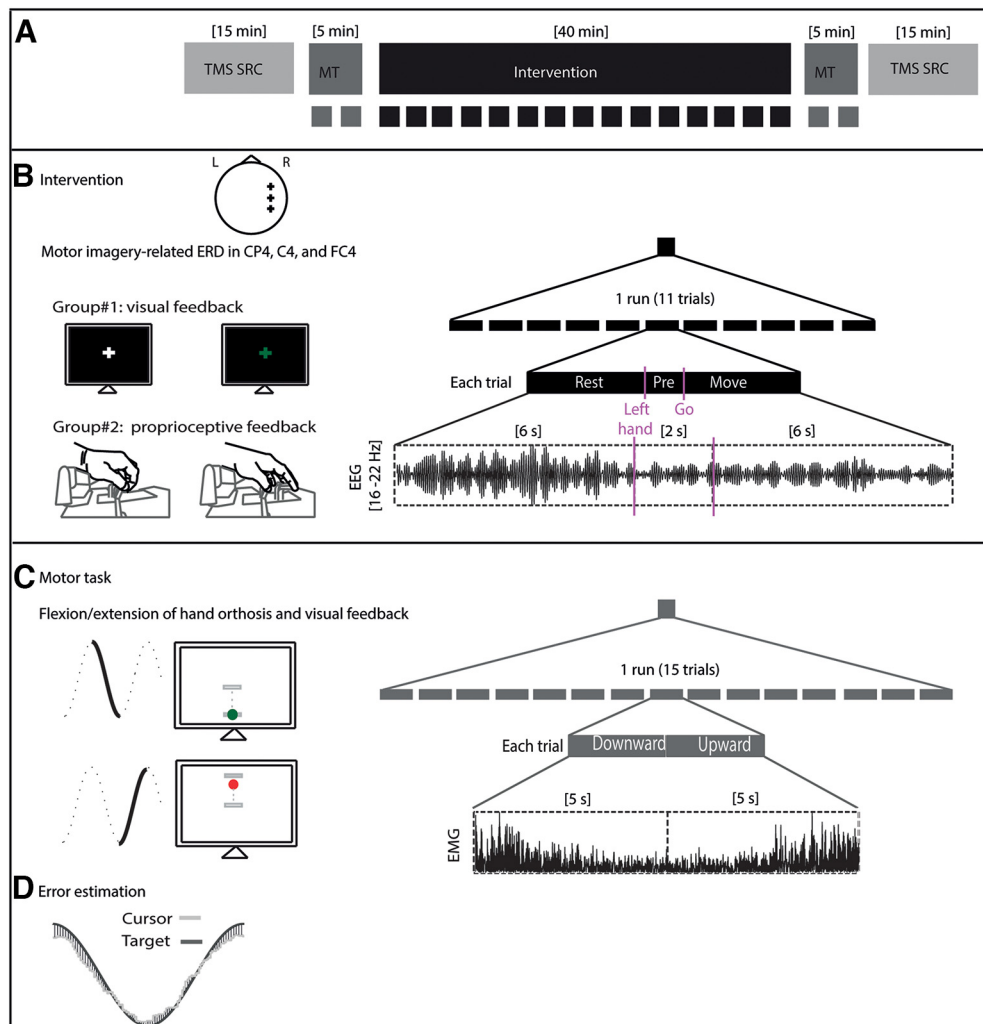


Figure 1. Experimental design and example data (healthy subjects). **A**, Schematic illustration of the experimental design and timeline. **B**, Healthy subjects underwent a neurofeedback intervention of modulating β activity (16–22 Hz) in circumscribed premotor and sensorimotor regions (marked by + on the topography; L and R stand for the left and right cortical hemispheres) of the right hemisphere by kinesthetic MI. Healthy subjects participated in an intervention session (~40 min), during which they received feedback which was contingent to their MI-associated brain activity in a parallel-group design with one of two different modalities: (1) visual feedback with a brain–computer interface ($n = 12$) or (2) proprioceptive feedback with a brain–computer interface ($n = 15$) orthosis attached to the left hand. **C**, Healthy subjects (both visual and proprioceptive groups) performed a MT (~5 min) before (pre-MT) and after (post-MT) the intervention. An oscillating target (0.1 Hz) was presented to the subjects on a screen. The subjects were instructed to follow the target using a cursor. This was controlled by isometric flexion and extension of the left hand that was attached to a hand orthosis. **D**, Motor performance was defined as the difference between the targeted and the actual force applied to the hand orthosis which was paralleled by a deviation between the target and the actual oscillation on the screen, i.e., the closer the target and the actual oscillation, the better the performance.

Table 1. Clinical characteristics of the stroke subjects (modified from Belardinelli et al., 2017)

Pat.nr.	Age (year)	FMA pre	FMA post	FMA Change	Sex	Hand dominance	Lesion hemisphere	Lesion type	Lesion volume (voxel)	Disease duration (months)
P1	56	28.60	35.25	6.65	Male	Right	Right	Hemorrhage	79,013	78
P2	63	16.10	18.35	2.25	Female	Right	Right	Ischemic	95,476	78
P3	52	22.40	26.45	4.05	Male	Right	Right	Ischemic	80,144	156
P4	67	6.80	10.85	4.05	Male	Right	Right	Hemorrhage	87,923	75
P5	68	16.40	20.20	3.80	Male	Right	Right	Hemorrhage	2879	34
P6	34	13.40	13.40	0.00	Male	Right	Right	Hemorrhage	44,957	45
P7	63	15.80	16.80	1.00	Male	Right	Right	Ischemic	111,162	58
P8	55	10.35	13.73	3.38	Male	Right	Right	Hemorrhage	39,073	80

for severely impaired stroke subjects with a hand paralysis such as those of this study. Therefore, UE-FM changes of ~3 might be still clinically important in the severely affected stroke subject population studied here; however, a formal CID estimation in this patient population needs to be done in the future.

However, the underlying neural processes during the BCI intervention with proprioceptive feedback and their impact on actual motor improvements remained unclear and necessitated a secondary analysis on the brain–behavior relationship. The present study therefore evaluated the motor-network changes in the course of the intervention in

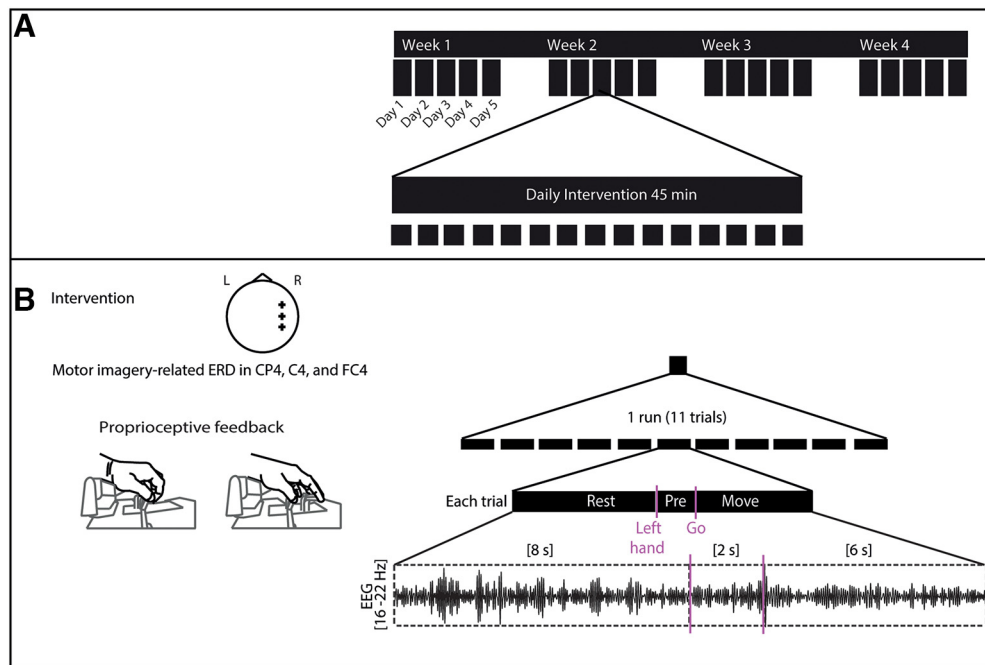


Figure 2. Experimental design and example data (stroke subjects). **A**, Schematic illustration of the experimental design and timeline. Proprioceptive BCI feedback was applied to the paralyzed left hand in 20 sessions in the course of four weeks. Each session consisted of 15 runs. **B**, Stroke subjects underwent a neurofeedback intervention of modulating β activity (16–22 Hz) in circumscribed premotor and sensorimotor regions (marked by + on the topography; L and R stand for the left and right cortical hemispheres) of the right, ipsilesional hemisphere by kinesthetic MI.

relation to subsequent behavioral changes. Importantly, the same data analysis pipeline was applied for both studies to allow for comparisons between healthy and stroke subjects. It should be noted that the current study design cannot disentangle the impact of simple tactile as compared with the proprioceptive feedback.

Data acquisition

The data acquisition methods applied in this study have been described in detail in our previous work (Kraus et al., 2016a) and are cited here where appropriate: EMG/EEG data were recorded at a sampling rate of 5 kHz using an antialiasing bandpass filter with cutoff frequencies at 0.16 Hz and 1 kHz. In a next step, data were downsampled to 1 kHz by the BrainAmp Amplifier (Kraus et al., 2016a). Since the estimation of CMC might be particularly sensitive to aliasing effects, the preprocessing needs to be done cautiously. Specifically, the low-pass filter needs to apply a cutoff frequency (LPF = 1 kHz) based on the ratio between sampling rate (SR = 5 kHz) and down-sampling factor ($d = 5$), before down-sampling by this factor d . Furthermore, the data needs to be analyzed with adapted filter boundaries by using finite impulse response (FIR) filters that do not lead to phase or delay distortion.

We used Ag/AgCl AmbuNeuroline 720 wet gel surface electrodes (Ambu GmbH) to record EMG activity from the left extensor digitorum communis (EDC) muscle (Kraus et al., 2016a). Two electrodes were placed 2 cm apart from each other on the muscle belly. To record EEG signals, we used Ag/AgCl electrodes (BrainCap for TMS, Brain Products GmbH) and BrainVision software with DC amplifiers and an antialiasing filter (BrainAmp, Brainproducts GmbH). A 32-channel EEG setup, which complied with the international 10–20 system, was used (FP1, FP2, F3, Fz, F4, FT7, FC5, FC3, FC1, FC2, FC4, FC6, FT8, C5, C3, C1, Cz, C2, C4, C6, TP7, CP5, CP3, CP1, CPz, CP2, CP4, CP6, TP9, P3, P4, and POz with FCz as reference). We kept the impedances at all electrodes below 10 k Ω . The EEG signals were later transferred to the BCI2000 software (Schalk et al., 2004) for online analysis and offline storage (Kraus et al., 2016a).

Experimental conditions

Figures 1 and 2 represent the schematic illustration of the experimental design for the healthy (Fig. 1) and stroke subjects (Fig. 2), respectively.

In healthy subjects, the experiment commenced with an isometric MT (5 min), which was followed by the intervention (40 min) and a further isometric MT (5 min). The intervention consisted of a visual or proprioceptive feedback task. The proprioceptive feedback task (intervention) and the pre/post MT differed, entailing dynamic movement and isometric movement, respectively.

The proprioceptive feedback task was identical for healthy and stroke subjects. A brain-computer interface controlled a robotic orthosis and turned sensorimotor β -band desynchronization (ERD) during MI of finger extension into contingent hand opening. A full and continuous opening of the hand orthosis was achieved when an individual desynchronization threshold was reached and when ERD was maintained for the MI period. Movement stopped as soon as ERD was absent, but could be reinitiated in the same trial if the threshold was met again.

More specifically, the intervention consisted of 15 runs. Each run lasted ~2.5 min and included 11 trials. Each trial began with a 6-s rest phase which was followed by a 2-s preparation phase and a 6-s move phase, i.e., kinesthetic MI (Fig. 1B). The audio taped cues of a female voice: “relax,” “left hand,” and “go” were used to initiate the rest, preparation, and move phases, respectively. All subjects were instructed to keep their muscles relaxed throughout the intervention. During the move phase, the subjects were instructed to perform kinesthetic MI, i.e., to imagine the feeling of opening their left hand, i.e., finger extension, from a first-person perspective. During the move phase, the passive opening of the left hand (proprioceptive group) and changing the color of the cross on a screen (visual group) was initiated by the BCI2000 software after detection of MI-related event-related desynchronization (ERD) in the β -band (16–22 Hz; Gharabaghi et al., 2014). In future, a richer visual feedback (i.e., visualized hand opening) may be considered to explore the full potential of this feedback modality. Details with regard to the online ERD evaluation are specified below. This feedback was contingent, i.e., the participants were rewarded with robotic opening of the hand (proprioceptive group) or color change on a screen (visual group), when the predefined brain state (i.e., β -ERD) was achieved and sustained (Bauer et al., 2016a,b; Bauer and Gharabaghi, 2017). Before the experiment, a desynchronization task, consisting of three MI training runs, was performed for offline calibration to account for each subject’s ability for desynchronization. Following this calibration session, an individual desynchronization threshold, described in detail elsewhere (Bauer

and Gharabaghi, 2015a,b; Gharabaghi, 2016; Naros and Gharabaghi, 2015, 2017), was implemented for the intervention. Whenever the respective ERD was insufficient during the intervention, the robotic movement ceased but could be restarted and continued when the ERD threshold was reached again. Importantly, the robotic hand opening was synchronized to the respective MI-related brain activation, whereas the robotic hand closing occurred after the relax command automatically and independent of the respective brain state (Kraus et al., 2016a). The frequency band, i.e., 16–22 Hz, to extract the ERD feature was the same for healthy and stroke subjects, and was selected on the basis of previous work by our group in healthy subjects indicating that volitional modulation of these sensorimotor β -oscillations could be learned via BCI and proprioceptive feedback and correlated with CSE increases (Kraus et al., 2016a) and improved motor performance (Naros et al., 2016).

ERD was analyzed over the right surface EEG channels FC4, C4, and CP4 (Fig. 1B) during the move phase (McFarland et al., 2000). ERD detection was performed with an adaptive linear classifier (Gharabaghi et al., 2014; Kraus et al., 2016a). The spectral power was computed with an autoregressive model of order 16 (McFarland and Wolpaw, 2008), fitted to the last 500 ms of the signal and updated every 40 ms. To rule out a noisy control signal for the orthosis, five consecutive 40-ms time periods (i.e., 200 ms) had to be classified as ERD positive (negative) to start (stop) feedback (Bauer and Gharabaghi, 2015a, 2017; Vukelić and Gharabaghi, 2015a,b).

The MT was an isometric one; the fingers of the healthy subject were connected to the robotic orthosis via small magnets which were attached to the finger tips. This ensured that the fingers could not be moved and so the applied forces were instead translated into cursor movements on a screen. Before and after the intervention, the isometric MT was performed (only by healthy subjects). This task has been described in detail elsewhere (Naros et al., 2016) and is cited here accordingly. During the isometric MT, the fingers of the healthy subject were connected to the robotic orthosis via small magnets which were attached to the finger tips. The orthosis was blocked in the middle position between maximum extension and flexion. This ensured that the fingers could not be moved and so the applied forces were instead translated into cursor movements on a screen, where a horizontal target bar, which oscillated vertically with a frequency of 0.1 Hz, was presented ~150 cm in front of the subject. The healthy subjects were asked to control the vertical position of a simultaneously presented cursor via the force of the fingers (Digits II–V) to follow a vertically oscillating target (Fig. 1C). This task consisted of 15 trials (10 s each) per run (two runs). Each trial had one flexion (5 s) and extension (5 s) phase, i.e., downward and upward direction of the cursor, respectively (Fig. 1C).

Online data analysis

To estimate the task-related brain activity, ERD of the right sensorimotor area (i.e., at the electrodes FC4, C4, and CP4) was analyzed during the MI phase (McFarland et al., 2000). Our approach has been described in detail elsewhere (Kraus et al., 2016a) and is cited here accordingly. A full opening of the hand orthosis was achieved when ERD was maintained for the MI period. Movement stopped as soon as ERD was absent. The power was estimated by an autoregressive model with a model order of 16 based on the Burg Algorithm (McFarland and Wolpaw, 2008). A linear classifier with nine features consisting of three channels (FC4, C4, and CP4) and three independent 2-Hz frequency bins for estimation of spectral power from 16 to 22 Hz were used to detect decreases in sensorimotor rhythm power in the β -band. To ensure robotic movements only during sufficiently long periods of ERD, five consecutive 40-ms time periods had to be classified as ERD to initiate hand opening by the orthosis. Three calibration runs were performed before the experiment to implement an individual desynchronization threshold and to consider each subject's ability for desynchronization. This assured that each subject was facing the same task-related demand. During the intervention feedback was given only when subjects reached 20% of their strongest β -ERD modulation in the motor-imagery epoch (Gharabaghi et al., 2014). Whenever the threshold was not met because of insufficient ERD either no robotic opening of the hand occurred or ongoing robotic opening stopped, but could be reinitiated in the same trial if the threshold

was met again. The orthosis moved back to the “hand closed” position after the “relax” command within the first 1.5 s of the rest phase (Kraus et al., 2016a).

Offline data analysis

Apart from the online analysis indicated above, all other data were analyzed offline using MATLAB (The MathWorks) and the FieldTrip open-source MATLAB toolbox (<http://fieldtrip.fcdonders.nl/>; The MathWorks). This included bandpass filtering (FIR) between 2 and 46 Hz (for both EEG and EMG signals), linear detrending, and visual inspection for ocular/muscular artifact rejection.

Assessing intervention-related cortical and cortico-muscular modulation

We analyzed EEG spectral modulation and EEG-EMG CMC during the BCI interventions with proprioceptive and visual feedback. We studied time periods (with 1000-ms length) of the move phase before feedback onset (in comparison to the rest phase) with at least 500-ms continuous MI-related ERD below the predefined threshold which resulted on average in 93 ± 27 time periods per subject. To capture the evolution of EEG oscillations in the course of the intervention, time periods were divided into 10 subgroups, yielding an average of 9 ± 3 time periods per subgroup. A Hann window was applied on each time period to attenuate edge effects (Nuttall, 1981). The power spectral density (PSD) of each epoch was calculated frequency-wise from 2 to 46 Hz in steps of 1 Hz using fast Fourier transform (FFT). Later, the average of estimated PSD for each subgroup was estimated. For coherence estimation, we applied the FIR filter, and not the infinite impulse responses (IIRs) filter, to avoid interference with the phase of the signal.

Assessing MT-related cortico-muscular modulation

We studied the synchronous oscillatory activity between EEG and rectified EMG of the EDC muscle by analyzing CMC (Myers et al., 2003). To estimate CMC, each trial of the MT (10 s) was divided into ten nonoverlapping time-windows (1-s intervals) denoted by F1–F5 and E1–E5 during flexion and extension, respectively. Data from each interval were visually inspected for ocular/muscular artifacts, yielding an average of 26 ± 4 time periods (each 1000-ms length) per interval and subject.

CMC was estimated as the cross-spectral density matrix frequency between EEG and EMG channels (Schulz et al., 2014). This was calculated frequency-wise using the multi-taper method (nine tapers) over the frequency range from 2 to 46 Hz in steps of 1 Hz. We then obtained the magnitude of the coherence values by normalizing the magnitudes of the summed cross-spectral density matrix for each frequency to the corresponding power values at that frequency (Schulz et al., 2014). Furthermore, we found no changes in EEG or EMG spectral power between conditions (BCI with proprioceptive vs visual feedback), nor did we detect a correlation between EEG or EMG spectral power with the difference in CMC strength values in the course of the intervention in healthy and stroke subjects. This indicates that CMC modulation was not confounded by amplitude changes of neuronal oscillations (von Carlowitz-Ghori et al., 2015), which were shown to affect the estimation of CMC (Bayraktaroglu et al., 2013), since they relate to the signal-to-noise ratio (Nikulin et al., 2011).

Assessing MEP modulation and the corresponding relation with the MT-related cortico-muscular modulation

To estimate the modulation of MEP amplitude we followed the procedure described previously (Kraus et al., 2016a). After peak-to-peak MEP amplitude estimation, we fitted a three parameter Boltzman sigmoidal function per healthy subject resulting in a SRC. We have previously reported that the proprioceptive condition resulted in an increase of CSE in the steep part of SRC (Kraus et al., 2016a). Hence, MEPs of the steep part of the SRC were chosen for further analysis (i.e., 120% resting motor threshold). Then, Spearman's rank correlation was used to evaluate the relationships between the CMC magnitude during the MT (CMC [motor task]) and the corresponding MEP amplitudes in the subsequent CSE evaluation. Because of technical reasons, the SRCs from two of the 15 subjects could not be included in this analysis.

Assessing behavioral changes

The difference between the cursor movements on a screen controlled by the healthy subject and the oscillating horizontal target bar resulted in the error rate during the MT, i.e., area under the curve (AUC; summing all the differences). Reduction of this error rate was defined as a changed behavior in motor performance (Fig. 1D).

$$\text{Performance} = \frac{\text{Error}_{\text{post}} - \text{Error}_{\text{pre}}}{\text{Error}_{\text{pre}}} * 100$$

Assessing the relationships between intervention-related and MT-related cortico-muscular modulation and behavioral changes

Assessing the relationships between these different measures will reveal brain-behavior relationships even for single-session interventions (as in the healthy subject study) that are not intended to reveal behavioral group or condition effects. We used Spearman's rank correlation to evaluate the relationship between CMC magnitude during the intervention (CMC [intervention]) and the MT (CMC [motor task]), as well as between CMC [motor task] and behavioral change across subjects. For each subject, we had a set of channels that showed significant modulation of the CMC magnitude. To provide a correlation analysis between the measures (i.e., CMC [intervention], CMC [motor task], behavioral changes) we needed to decrease the number of channels to one per subject. The statistically significant clusters of the previous analyses were chosen for this estimation. However, neither the average of all channels in this cluster nor the channel with maximum change could be used for this purpose. The former approach would miss the strongest change, the latter would not be applicable as well, since the channel with maximum change was not the same for all the subjects, e.g., C4 in one and C2 in another participant. We, therefore, implemented an approach that considered both the maximum CMC value and the individual variability of the spatial distribution. Specifically, the maximum CMC value from each cluster was subtracted from the median value of the respective cluster for each subject. Then, one pair of CMC [intervention]/CMC [motor task] per healthy subject was used for further analysis.

Assessing the phase-frequency relationships of cortico-muscular modulation

The phase-frequency relationships of CMC were estimated frequency-wise (every 1 Hz). This estimation allows to determine the dominant directionality between cortex and periphery. Specifically, the phase was estimated by taking the argument from the estimated EEG-EMG cross-spectrum (Witham et al., 2011; see below, Statistical analysis).

Assessing directed CMC

The directed CMC was estimated frequency-wise (every 1 Hz) for the descending (from EEG to EMG) and ascending pathways (from EMG to EEG), separately, using the partial directed coherence (PDC) implemented in Fieldtrip (Oostenveld et al., 2011). PDC estimates the direction of connectivity through two time series and decomposes the partial coherence using a multivariate autoregressive model (Witham et al., 2011).

Stroke subject data

Data analysis for the group of stroke subjects was identical to the approaches described above for the group of healthy subjects. Since the stroke subject group performed 20 intervention sessions (compared with the one session performed by each healthy subject), the sessions were evaluated individually, yielding 20 different datasets for ERD and CMC modulation per stroke subject. For each session (i.e., training day), the ERD and CMC averages across subjects are reported in the results (section: ERD and CMC changes in stroke subjects). The findings indicate an evolution of these measures from the start until the third week, while showing a large session-by-session variability. This ERD and CMC variability in the course of the whole four-week period would not be sufficiently captured by comparing the last to the first session only. However, to allow for comparisons between the ERD and CMC changes in the course of the training period on the one side, and the pre/post behavioral

changes on the other side, we needed to operationalize the training-related ERD and CMC changes. For this purpose, we defined the average of the first two sessions as baseline and the rest of the sessions as training related changes, since the first relevant change of both ERD and CMC ensued from the third session on (see Fig. 8H,I). The resulting physiological changes were then compared with the motor improvement assessed by the UE-FMA score, i.e., before and after the four-week intervention.

$$\text{Improvement} = \frac{\text{UEFMA}_{\text{post}} - \text{UEFMA}_{\text{pre}}}{\text{UEFMA}_{\text{pre}}} * 100.$$

Localization of CMC using dynamic imaging of coherent sources (DICS)

We used the DICS method (Gross et al., 2001) to illustrate the cortical map of CMC magnitude at source level. DICS uses the beamformer (Van Veen et al., 1997) to leverage the linear projection of the sensor level activity through a spatial filter. The spatial filter was estimated from the lead field of the source of interest and the estimated cross-spectral density (frequency domain). We employed DICS to estimate the similarity between EEG and EMG oscillatory activities and their linear dependencies (Belardinelli et al., 2017). DICS was applied for each of the sessions of every stroke subject following cross-spectral estimation. As for the sensor level analysis, data of sessions 3–20 of each stroke subject were averaged and compared with baseline (sessions 1 and 2).

Statistical analysis

Testing significance of ERD and CMC modulation

We used a nonparametric randomization test with 1000 repetitions to test the modulation of ERD/CMC magnitude and directed coherence. The null hypothesis was that observed increases in ERD/CMC magnitude were not related to the intervention and were therefore exchangeable within the intervention and for the premotor and post-MT values.

Since the artifact rejection led to an unequal degree of freedom (df; a maximum of 540 for healthy subjects) for each group of time periods (with 1000-ms length), we converted the coherence differences (Fig. 3A, B) to Z-statistic (Fig. 3C,D) before the nonparametric statistical test (Maris et al., 2007). The distribution of the nonconverted coherence is estimated using the bootstrapping method (Fig. 3E,F). Following the same procedure, we converted the coherence difference of study 2 (df, a maximum of 900 for stroke subjects) to Z-statistic. We performed the cluster-based randomization test for each frequency band of interest. The frequency bands were selected to cover the feedback frequency band of the intervention (16–22 Hz) and the neighboring frequency bands with the same bandwidth (9–15, 23–29, and 30–36 Hz) for balanced statistical comparisons. When the maximum of t-statistic (paired *t* test; ERD) or Z-statistic (CMC) exceeded the threshold α level of 5%, adjacent EEG channels were clustered in the same set (Maris et al., 2007). Cluster-level statistics were then conducted by taking an average of the *t*-statistics. In cases where multiple clusters were observed, the maximum of the cluster-level statistics was used for later comparisons. The *p*-value to reject the null hypothesis was the proportion of cluster-based randomizations that resulted in larger test statistics than were observed here (without randomization).

To address the multiple comparison issue, we applied nonparametric cluster-based test statistics that controlled for the family-wise error rate across EEG channels (Maris and Oostenveld, 2007). This cluster-based approach uses one test for the spatio-spectral grid instead of multiple tests.

For the stroke subjects, the null hypothesis was that the observed cortical and corticospinal modulations were not caused by the intervention so that the baseline sessions could be exchanged with the following sessions.

Testing significance of the relationships between intervention-related and MT-related cortico-muscular modulation and behavioral changes

We tested the significance of the relationship between intervention-related and MT-related CMCs as well as between the MT-related CMCs and motor behavioral changes across subjects. Additionally, we tested

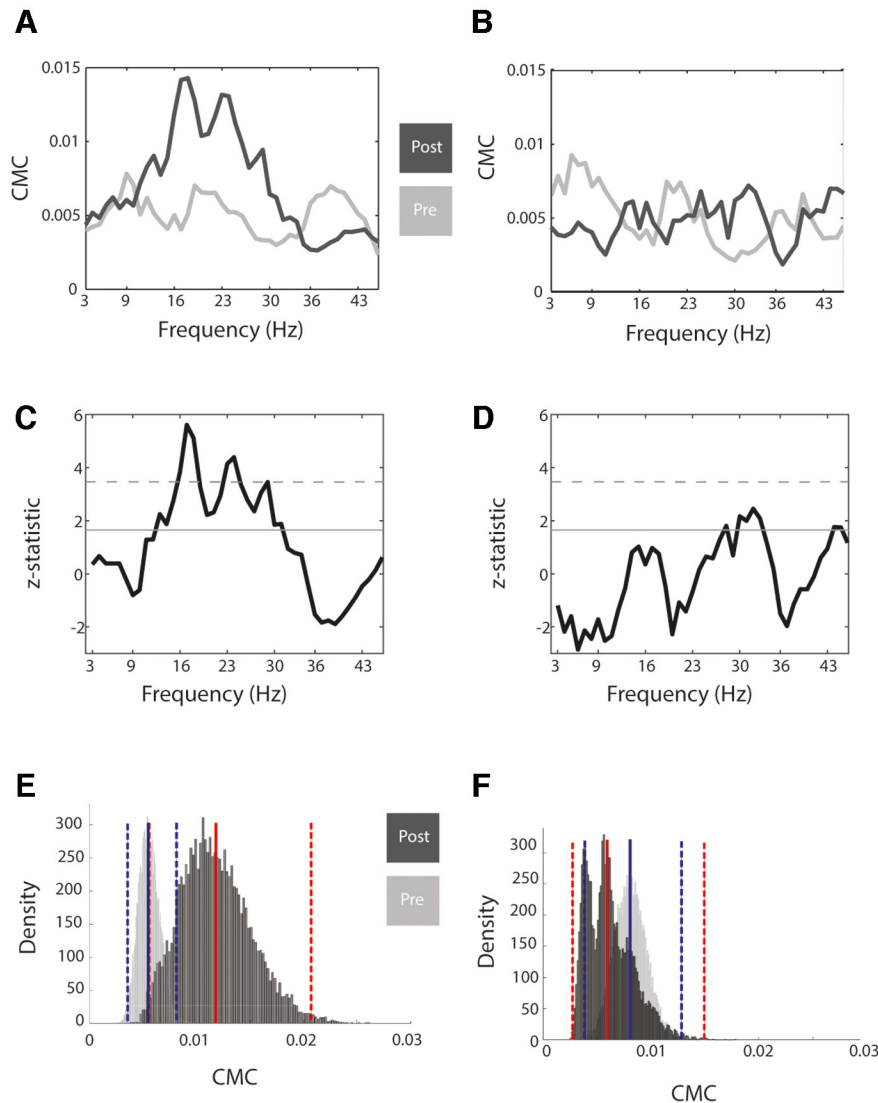


Figure 3. Changes of CMC. **A**, Preintervention (light-gray) versus postintervention (dark-gray) CMC magnitude during the MT (channel C4; group analysis for the transition from flexion to extension, i.e., E1 in Fig. 4) for the proprioceptive feedback group. **B**, Same as **A** but for visual group. **C**, The CMC magnitude differences (post vs pre) converted from coherence values to z-values. The solid and dashed line represents the α level of 5%, uncorrected and corrected for the number of frequency bins, respectively. **D**, Same as **C** but for visual group. **E**, The distribution of the unconverted CMC magnitudes (coherence; 16–22 Hz) after bootstrapping (10,000 times) for the proprioceptive group, postintervention (dark-gray) versus preintervention (light-gray). The vertical red and blue lines represent the mean and 95% of the confidence intervals for the corresponding groups. **F**, Same as **E** but for visual group.

the significance of the relationship between MT-related CMCs and MEP changes. Our null hypothesis was that they were not correlated and that independent/dependent variables were exchangeable, i.e., intervention-related CMC/MT-related CMC/behavioral change/MEPs. We began by shuffling the independent versus dependent variables with 1000 repetitions. At each repetition, we calculated Spearman's rank correlation. The p -value to reject the null hypothesis was the proportion of randomizations that resulted in larger test statistics than we observed (without randomization).

Testing significance of phase-frequency relationships

We calculated the mean of the estimated CMC phase for each frequency across subjects, yielding one phase-frequency spectrum. We then fitted a line to the phase-frequency plot using a linear regression of phase at the healthy subject level and subsequently averaging estimates of time delay (i.e., over a range of frequencies with significant CMC). The regression slope differed significantly from zero when $p < 0.05$.

Testing significance of cortico-muscular connectivity using DICS

To test the significance of the changes, the randomization test was employed. For this, the estimated coherent preintervention and postintervention sources were randomly shuffled among subjects. Similar to the sensor level analysis, the threshold of $Z > 1.65$ (α level of 5%; Maris et al., 2007) was used at each stage of randomization. As we assumed that the observed increase of the coherent source was not because of the intervention, the p -value to reject the null hypothesis was the proportion of cluster-based randomizations that resulted in a larger test statistic than the one observed (with no randomization). The p -value to reject the null hypothesis was the proportion of randomizations that resulted in larger test statistics than the observed one (without randomization).

Results

ERD and CMC modulation

Healthy subjects learned to modulate MI-related sensorimotor ERD in the feedback frequency range (16–22 Hz) independent of the feedback modality; however, significant CMC changes ensued only when proprioceptive feedback was provided; since CMC changes are tiny by nature, their robustness was verified by applying the respective statistical tests (Fig. 3). The ERD and CMC changes in the course of the intervention, i.e., the changes during each training session, were frequency-specific, and were restricted to the right hemisphere, i.e., contralateral to the left hand that was moved by the robotic orthosis, and overlapped in the primary sensorimotor and premotor cortex (Fig. 4). Specifically, a cluster-based randomization test (1000 repetitions) revealed significant ERD modulation in the frequency range of 16–22 Hz for the proprioceptive (EEG channels FC2, C2, C4, Cp2, and CP4; $p = 0.017$, cluster-based randomization test, 1000 repetitions; Cohen's $d = 1.6528$; Fig. 4A) and visual (EEG channels C2, C4, C6, CPz, CP2, CP4, CP6, and P4; $p = 0.004$, cluster-based randomization test, 1000 repetitions; Cohen's $d = 1.2044$; Fig. 4B) groups. The CMC changes were frequency-specific (16–22 Hz) as well, but occurred in the proprioceptive group only (EEG channels: FC2, FC6, C2, C4, C6, CP2, CP4, CP6, and P4; $p = 0.014$, cluster-based randomization test, 1000 repetitions; Cohen's $d = 0.9474$; Fig. 4A).

CMC, MEP, and behavioral changes

This increase in CMC magnitude (16–22 Hz) in the course of the MI intervention was also observed in the MT after the intervention (cluster-based randomization test, 1000 repetitions; Fig. 5). The topography of the MT-related CMC modulation was restricted to the right hemisphere, i.e., contralateral to the left hand that was moved by the robotic orthosis, and projected to the primary sensorimotor and premotor cortex. In the proprioceptive group, the MT-related increase in CMC magnitude occurred at

movement intervals reflecting transitions between finger flexion (16–22 Hz, $p = 0.002$; and 23–29 Hz, $p = 0.002$, cluster-based randomization test, 1000 repetitions; respective Cohen's $d = 0.3373$ and 0.3956) and extension (16–22 Hz, $p = 0.007$; and 23–29 Hz, $p = 0.006$, cluster-based randomization test, 1000 repetitions; respective Cohen's $d = 0.5567$ and 0.5370). In the visual group, this increase occurred during finger extension independent of the transition intervals (23–29 Hz, $p = 0.007$; and 30–36 Hz, $p < 0.001$, cluster-based randomization test, 1000 repetitions; respective Cohen's $d = 0.9492$ and 1.5004).

In the proprioceptive group, the increase of CMC magnitude correlated significantly ($r = 0.56$, $p = 0.015$; Spearman's rank correlation, randomization test, 1000 repetitions; Fig. 6A) between the MI-related finger extension (Fig. 4A, 16–22 Hz) and the MT-related finger extension (Fig. 5A, 16–22 Hz). Additionally, there was a positive correlation between the CMC magnitude during MT-related finger extension and the subsequent increase of the MEP amplitude ($r = 0.70$, $p = 0.004$; Spearman's rank correlation, randomization test, 1000 repetitions; Fig. 6B). The increase in CMC magnitude during the transitions between finger flexion and extension in the proprioceptive group correlated (Fig. 6C) with the decrease in error rate in the same movement interval (E1) for 16–22 Hz ($r = 0.74$, $p < 0.01$, Spearman's rank correlation, randomization test, 1000 repetitions), but not 23–29 Hz ($r = 0.11$, $p = 0.70$, Spearman's rank correlation).

Cortico-muscular control

The directionality of CMC coupling following the intervention was captured with two complementary measures, i.e., estimation of phase-frequency relationships and of directed transfer functions. Specifically, the intervention led to a significant change in the phase-frequency relationships (in the EEG channels used to estimate the cortical power during the feedback task) in the course of the intervention (Fig. 7A, middle column), which persisted in the MT after the intervention (Fig. 7A, right column). This phase-frequency relationship showed a consistently negative slope that differed significantly from zero, indicating an enhanced direction of interaction from cortex to muscle. The respective cortical topography included extended sensorimotor and premotor areas of the right hemisphere, i.e., contralateral to the left hand that was moved by the robotic orthosis (EEG channels: F4, FC2, FC4, FC6, Cz, C2, C4, C6, CPz, CP2, CP4, and CP6; Fig. 7B), which persisted during the postintervention MT (EEG channels: FC2, FC4, Cz, C2, C4, C6, CPz, CP2, CP4, CP6, P4, CP1, P3, and POz; Fig. 7B). The average phase delays of the phase-frequency relationships were 33.5 ± 10.12 and 25.16 ± 7.45 ms for the MI-intervention and post-MT, respectively. Moreover, the directed CMC revealed a significant modulation for the descending but not the ascending pathways, which was frequency-specific (i.e., 16–22 Hz). The topography of this information flow from cortex to periphery overlapped with the estimated phase-frequency relationships (EEG channels: FC2, FC4, C1, Cz, C2, C4, C6, CPz, CP2, CP4, and P4;

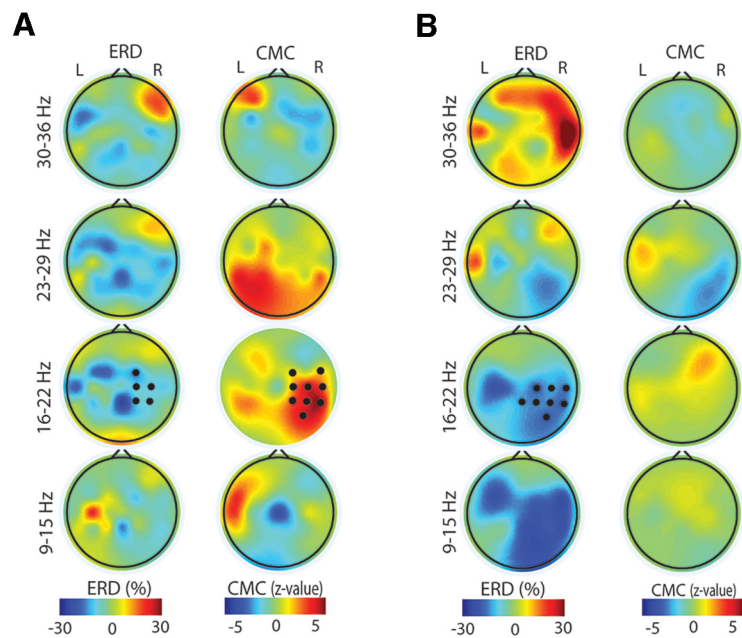


Figure 4. Cortical topography of MI-related ERD and CMC. **A**, Group data of the proprioceptive group in healthy subjects. Black circles indicate clusters with statistically significant modulation (nonparametric randomization test) in the course of the intervention (the contrast between end and start, see methods). Cortical topographies are presented for the feedback frequency band (16–22 Hz) and the neighboring bands (9–15, 23–29, and 30–36 Hz). L and R stand for the left and right cortical hemispheres. **B**, Same as **A** except for the visual group.

$p < 0.01$; cluster-based randomization test, 1000 repetitions; Fig. 7C).

ERD and CMC changes in stroke subjects

Stroke subjects [respective axial magnetic resonance images (MRIs) shown in Fig. 8A] learned modulating MI-related sensorimotor ERD over the feedback frequency range (16–22 Hz) and channels (FC4, C4, and CP4; $p < 0.01$, randomization test, 1000 repetitions; Cohen's $d = 1.1074$; Fig. 8B, left column). An increase in ERD magnitude was also observed over the frequency range of 9–15 Hz ($p < 0.01$ randomization test, 1000 repetitions; Cohen's $d = 0.8409$). These ERD changes were restricted to the ipsilesional right hemisphere, i.e., contralateral to the paralyzed left hand that was moved by the robotic orthosis. The changes in CMC magnitude, however, were bilateral (Fig. 8B, right column). Specifically, ipsilesional premotor CMC increased in the β -band (16–22 Hz), whereas contralesional CMC of extended sensorimotor, premotor and parietal areas increased in the α -band and β -band (9–15 and 16–22 Hz; $p < 0.01$ randomization test, 1000 repetitions with the respective Cohen's $d = 2.5938$ and 2.7518). The average phase delays of the phase-frequency relationships during the intervention were 23.75 ± 12.32 and 26.55 ± 7.09 ms for the ipsilesional and contralesional hemisphere, respectively. The statistical analysis of CMC changes (Fig. 8C–E) is performed in the same way as for the healthy subjects (Fig. 3). The session-wise, average ERD ($\beta = -10.26$, $p = 0.047$ randomization test, 1000 repetitions; Fig. 8H) and CMC ($\beta = 6.64$, $p = 0.001$ randomization test, 1000 repetitions; Fig. 8I) measures showed significant changes until the third training week.

Cortico-muscular control and behavioral changes in stroke subjects

In the stroke subject group, the ipsilesional increase (F4, FC2, and FC4) in CMC magnitude (16–22 Hz) in the right

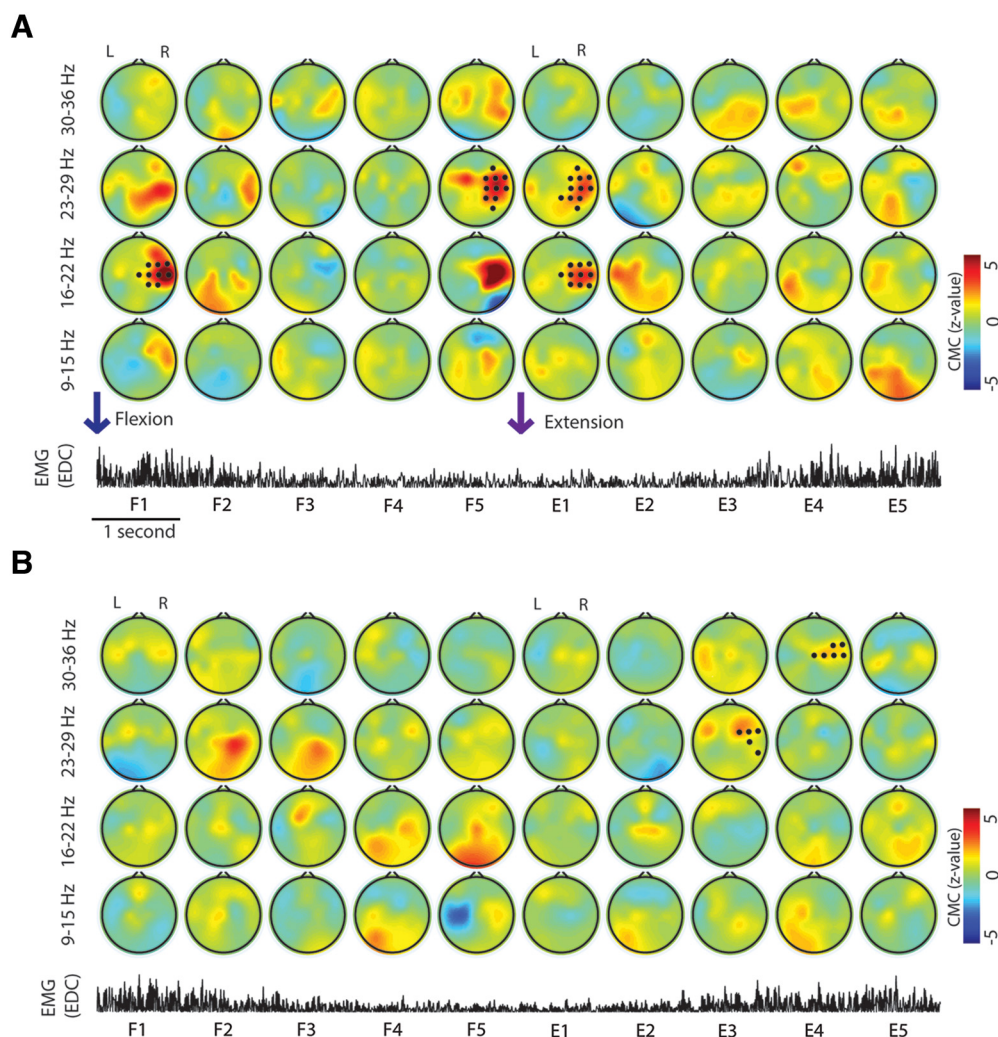


Figure 5. Modulation of MT-related CMC. **A**, Group data of the proprioceptive group in healthy subjects. Black circles indicate clusters with statistically significant modulation (nonparametric cluster-based randomization test) in the course of the experiment (the contrast between post-MT vs pre-MT). Cortical topographies are presented across the MT in 1-s intervals, i.e., during flexion (F1–F5) and extension (E1–E5), for the feedback frequency band (16–22 Hz) and the neighboring bands (9–15, 23–29, and 30–36 Hz). L and R stand for the left and right cortical hemispheres. Transitions of the MT are marked with arrows (blue: flexion to extension; purple: extension to flexion). The grand-average of the EMG of the EDC muscle across all subjects is plotted below the topographies. **B**, Same as **A** except for the visual group.

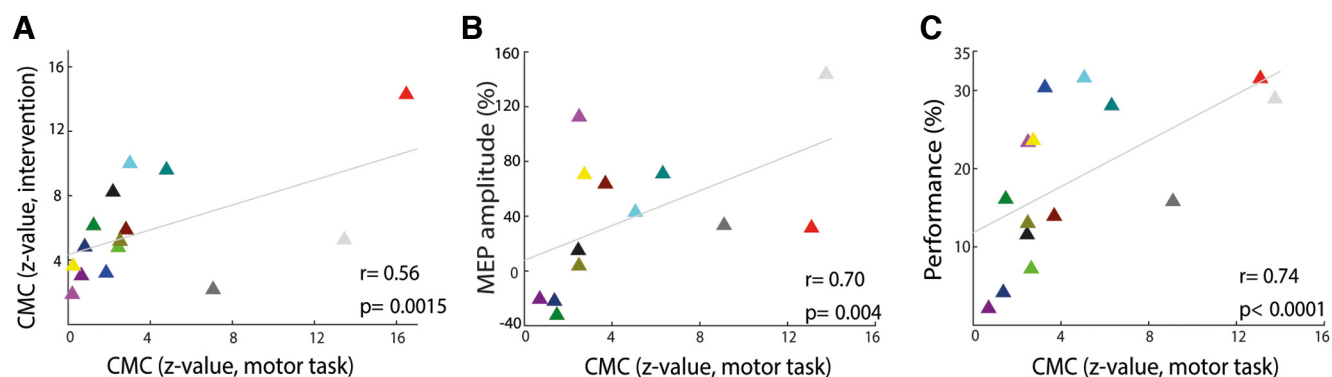


Figure 6. Modulation of CMC correlates with behavioral changes. **A**, Group data of the proprioceptive group of healthy subjects. The increase of intervention-related CMC (16–22 Hz) from baseline correlates with the (postintervention vs preintervention) increase of the motor-task-related CMC (16–22 Hz) during the flexion to extension transition of the MT ($r = 0.56$, $p = 0.015$, Spearman's rank correlation, randomization test, 1000 repetitions); each triangle represents one subject. The regression line is represented in gray. **B**, The increase of CMC (16–22 Hz) during the flexion to extension transition of the MT correlates with the postchanges versus prechanges in of the MEP amplitude ($r = 0.70$, $p = 0.004$, Spearman's rank correlation, randomization test, 1000 repetitions); each triangle represents one subject. The regression line is represented in gray. **C**, The behavioral change correlated significantly with the increase in CMC magnitude of the MT (16–22 Hz; $r = 0.74$, $p < 0.001$, Spearman's rank correlation, randomization test, 1000 repetitions). Each triangle represents one subject. The regression line is represented in gray.

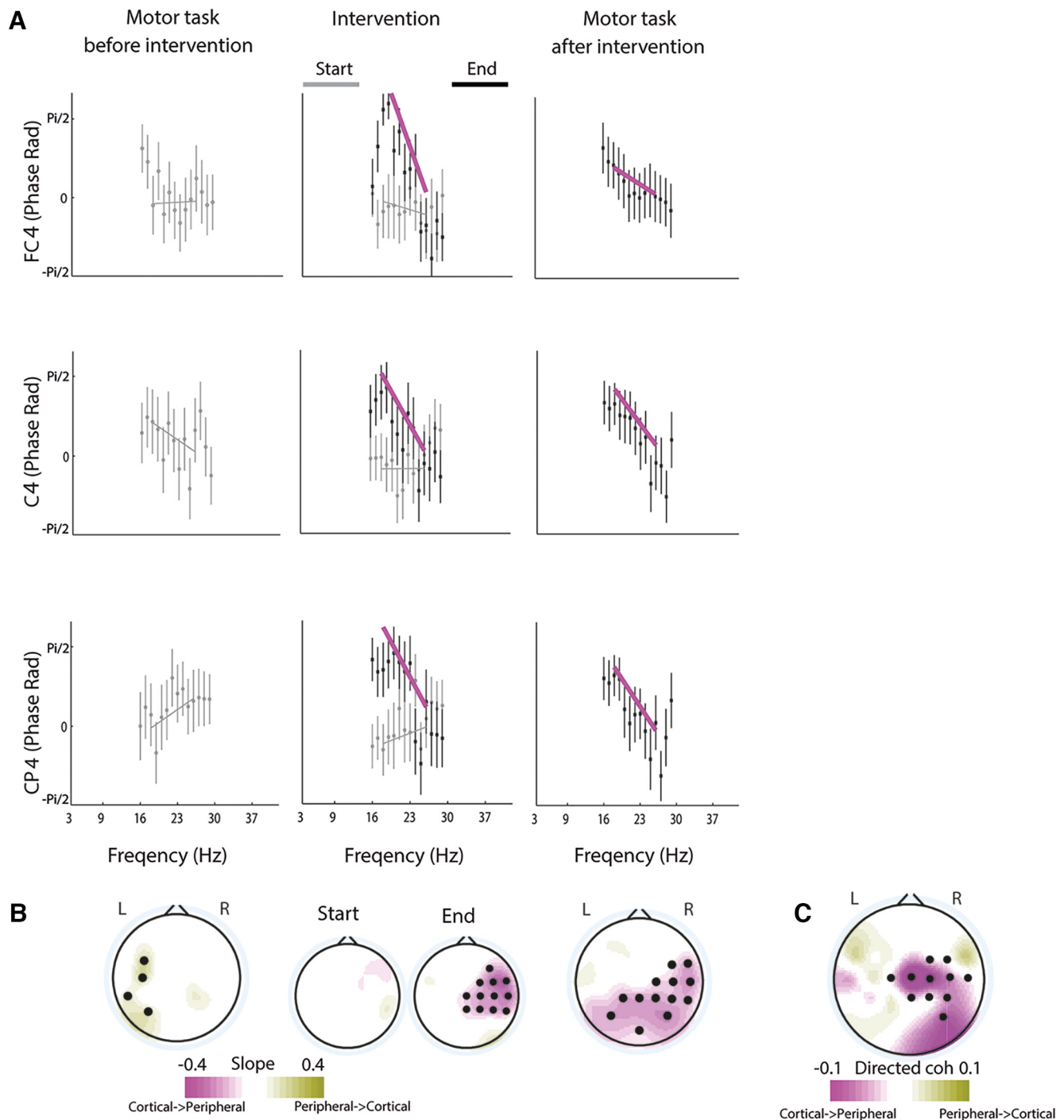


Figure 7. Directionality of CMC. **A**, Phase-frequency plots of healthy subjects in the proprioceptive group (mean and SE) for the EEG channels that were used to calculate the cortical power for providing feedback (FC4, C4, and CP4), and the frequencies with significant CMC modulation. Left and right columns represent the MT-related findings before (gray) and after (black) the intervention, respectively. The middle column represents the intervention-related findings at the onset (gray) and end (black) of the intervention, respectively. The regression slopes for the β frequency band are represented by lines and indicated by magenta when significantly different from zero. **B**, Topographies of the respective regression slopes. Magenta and yellow colors indicate the directionality of information flow from the cortex to the periphery and from the periphery to the cortex, respectively. Black circles represent the EEG channels, the regression slopes of which differ significantly from zero. **C**, The topography of the modulated directional coherence (postintervention vs preintervention MT; 16–22 Hz) indicates an information flow from cortex to periphery.

hemisphere (Fig. 8B) correlated significantly with the improvement of the UE-FMA score after the intervention period ($r = 0.88$, $p = 0.007$; Spearman's rank correlation; randomization test, 1000 repetitions; Fig. 8F). The source level analysis confirmed the topography of increased CMC demonstrated in the sensor level analysis (Fig. 8G). Furthermore, the

intervention also led to a significant change in the phase-frequency relationships in the stroke subject group (Fig. 8J). The phase-frequency relationships at the end of the intervention showed a negative slope that differed significantly from zero, indicating an enhanced direction of interaction from cortex to muscle. The respective cortical

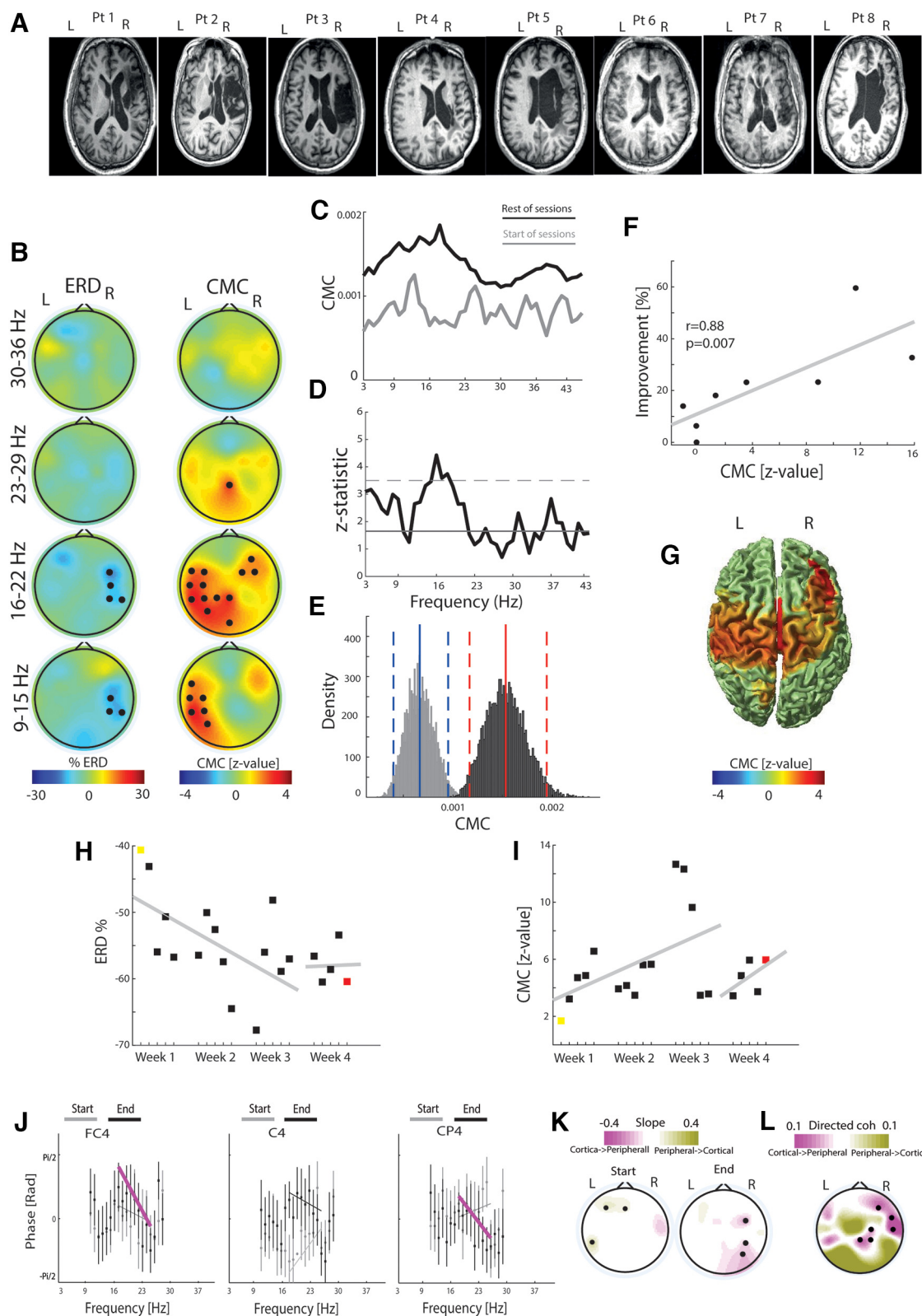


Figure 8. Modulation of CMC correlates with motor improvement in stroke subjects. **A**, Axial MRI for each stroke subject. **B**, Modulation of MI-related ERD and CMC. Group data of stroke subjects with proprioceptive BCI feedback. Black circles indicate clusters with statistically significant modulation (randomization test) during the training in comparison to baseline. Cortical topographies are presented for the feedback frequency band (16–22 Hz) and the neighboring bands (9–15, 23–29, and 30–36 Hz). **C**, Changes of CMC magnitude (group analysis; channel F4) for the start (light-gray) versus rest (dark-gray) of training sessions. **D**, The CMC magnitude differences (start vs rest of training sessions) converted from coherence values to z-values. The solid and dashed lines represent the α level of 5%, uncorrected and corrected for the number of frequency bins, respectively. **E**, The distribution of the unconverted CMC magnitudes (coherence; 16–22 Hz) after bootstrapping (10,000 times) for the start (dark-gray) versus rest (light-gray) of training sessions. The vertical red and blue lines represent the mean and 95% of the confidence intervals for the corresponding groups. **F**, The relationship between improvement in the FMA score and the CMC modulation (16–22 Hz; F4, FC2, and FC4 channels). Each circle represents one stroke subject. The regression line is represented in gray ($r=0.88$ $p=0.007$ Spearman's rank correlation, randomization test, 1000 repetitions). **G**, Source level analysis of CMC magnitude (16–

topography included premotor (FC4), somatosensory (CP4), and parietal (P4) channels in the ipsilesional right hemisphere, i.e., contralateral to the paralyzed left hand that was moved by the robotic orthosis (Fig. 8K). Finally, the directed CMC revealed a significant modulation for the descending (but not the ascending) pathways in the ipsilesional hemisphere (EEG channels: F2, FC6, C2, C6, CPz, CP2, $p < 0.01$; randomization test, 1000 repetitions; Fig. 8L) in the β -band (16–22 Hz) only.

Discussion

This work shows that MI and sensory feedback may lead to reorganization of cortico-spinal pathways in the healthy and post-stroke brain with an associated improvement in motor function. We provide novel findings about potential neural processes involved in the transfer of effects related to the BCI intervention to the following motor behavior:

1. Synchronizing MI of hand opening with proprioceptive feedback (and not visual feedback only) to sensorimotor β -band desynchronization increased CMC in healthy subjects and chronic stroke subjects with hand paralysis.
2. This effect (1) was specific to the β frequency band, (2) transferred to a MT, (3) was proportional to subsequent CSE and correlated with behavioral changes in the (4) healthy, and (5) poststroke condition; specifically, MI-related enhancement of β -band CMC in the ipsilesional premotor cortex correlated with motor improvements after the intervention.

Neural processes related to brain-computer interface feedback

Healthy subjects learned to enhance ERD in the targeted sensorimotor area in a frequency-specific way, i.e., in the feedback frequency band (16–22 Hz), regardless of the feedback modality provided (proprioceptive or visual). This was not surprising, given that sensorimotor oscillations are modulated by thalamo-cortical and corticocortical interactions (Thut and Miniussi, 2009; Jensen and Mazaheri, 2010) and do not necessarily depend on proprioceptive input. However, only when proprioceptive feedback was provided, was this specific activation pattern paralleled by CMC increases as well. These occurred in the same cortical area and frequency band as the ERD modulation, thereby suggesting that interacting processes are at work (Fig. 4A). Since MI-related ERD has been shown to reduce intracortical inhibition (Takemi et al., 2013), it may serve as the presynaptic input for an excitatory drive via proprioceptive input (Kraus et al.,

2016a). This is in accordance with previous studies which concluded that pairing specific brain states with peripheral (Mrachacz-Kersting et al., 2012, 2016), cortical (Kraus et al., 2016a,b), or combined stimulation (Gharabaghi et al., 2014; Royter and Gharabaghi, 2016; Kraus et al., 2018) increase CSE. We speculate that the kinesthetic MI applied in this study modulated the susceptibility of an extended cortical motor network to the proprioceptive input provided and thus fulfilled the requirements of associative stimulation (Hebb, 1949; Harel and Carmel, 2016).

The same BCI intervention with proprioceptive feedback was recently studied with TMS and MEPs by applying refined TMS protocols (Kraus and Gharabaghi, 2015, 2016; Mathew et al., 2016). This evaluation provided a link between the ERD modulation and the changed connectivity to the periphery (Kraus et al., 2016a). Specifically, the largest MEP gains were found in those cortical areas that were most strongly modulated by the intervention (Kraus et al., 2016a). Furthermore, this topographic specificity was paralleled by a correlation between the ERD changes and the increased connectivity to the periphery, i.e., the largest MEP gains were observed in the subjects with the strongest ERD modulation range (Kraus et al., 2016a).

β -Band CMC and behavioral changes

The present study complements and augments these earlier findings; it proposes, consistent with the communication through coherence hypothesis (Fries, 2005), that synchronized neural activity at cortical and spinal level in the feedback frequency range may contribute to the effects induced by BCI with proprioceptive feedback, since the control intervention (with visual feedback only) did not lead to such connectivity changes (Fig. 4B). However, since behavioral changes occurred in the BCI condition with visual feedback as well, other factors than changes in CMC, e.g., the cognitive demands of the feedback task, have likely contributed to the behavioral changes.

Importantly however, the enhanced β -band CMC during the BCI task with proprioceptive, i.e., dynamic movement, feedback transferred to the subsequent isometric MT. It occurred during the transition intervals between flexion and extension and in a broader β frequency band (16–22, 23–29 Hz), which may be related to increased attentional demands (Murthy and Fetz, 1992; Kristeva-Feige et al., 2002). The magnitude of β -band CMC during the BCI and the MTs correlated with each other (Fig. 6A) and with the behavioral changes (Fig. 6E). The task-related correlation between β -band CMC and motor behavior is a known phenomenon and reflects its proposed role in effective corticospinal interactions (Baker et al., 1999; Kristeva et al., 2007). Moreover, motor learning has been shown to both increase preexisting (Houweling et al., 2010) and develop new β -band CMC (Mendez-Balbuena et al., 2012).

In this study, the brain-behavior relationship in the proprioceptive group revealed task-specificity by occurring during the initiation of finger extension only, i.e., the very movement that was reinforced during the preceding BCI task (E1 interval; Fig. 5A). Moreover, this brain-behavior relationship was specific for the feedback frequency (16–22 Hz) but not for the higher β -band (23–29 Hz) which changed as well. Together, these observations suggest a link between sensorimotor processing during the BCI task and the following motor-task related β -band CMC; this relationship implies the generation of the later dependent on memory traces induced by the former (Omlor et al., 2011).

←

22 Hz) using the DICS method. **H**, ERD modulation during the training. Each square represents the average of one session (group analysis). The yellow and red squares represent the first and the last sessions of the training. **I**, CMC modulation during the training. Each square represents the average of one session (group analysis). The yellow and red squares represent the first and the last session of the training. **J**, Phase-frequency plots (mean and SE) for the EEG channels that were used to calculate the cortical power for providing feedback (FC4, C4, and CP4), and the frequencies with significant CMC modulation at the onset (gray) and end (black) of the intervention, respectively. The regression slopes for the β frequency band are represented by lines and indicated by magenta when significantly different from zero. **K**, Topographies of the respective regression slopes. Magenta and yellow colors indicate the directionality of information flow from the cortex to the periphery and from the periphery to the cortex, respectively. Black circles represent the EEG channels which have a regression slope that is significantly different from zero. **L**, The topography of the modulated directional coherence (postintervention vs preintervention MT; 16–22 Hz) indicates an information flow from cortex to periphery.

A similar mechanism has already been described for the primary motor cortex in association with the preceding motor experience (Chouinard et al., 2005; Nowak et al., 2005; Berner et al., 2007; Loh et al., 2010) and for β -band CMC during steady force following a dynamic force task (Omlor et al., 2011). Along these lines, β -band CMC has been proposed to serve as the major functional corticospinal gateway for efficient integration and transmission of sensorimotor information (Omlor et al., 2011; Aumann and Prut, 2015). In our study, the magnitude of β -band CMC during the initiation of finger extension (E1 interval; Fig. 5D) correlated also with the MEP increase after the intervention (Fig. 6B). Since this MEP increase was captured at rest (Kraus et al., 2016a), this observation indicates the memory traces to persist in different brain states. The present findings suggest that BCI with proprioceptive feedback is a means of enhancing this process.

Shaping directionality of CMC

The estimation of the phase–frequency relationships and directional coherence indicated, moreover, an enhancement of the predominant information flow from the cortex to the finger extensors (Halliday et al., 1998; Mima et al., 2000; Witham et al., 2011) in the course of the intervention and thereafter (Fig. 6A). To the best of our knowledge, this is the first observation of CMC directionality being shaped by an intervention. Importantly, this phenomenon occurred in an extended sensorimotor area beyond the primary motor cortex (Fig. 6B). This indicates the functionally relevant engagement of an extended motor network for the behavioral task, thus providing the rationale for the application of this technique in subjects with a lesioned primary corticospinal tract. These observations are in line with earlier studies (He et al., 1993; Kombos et al., 1999; Teitti et al., 2008; Schmidt et al., 2013; Kraus and Gharabaghi, 2016), which had indicated that corticospinal connections are not limited to the primary motor cortex but may originate from different regions of the sensorimotor system. The phase delays estimated in this study are consistent with a range of conduction times and may thereby reflect the involvement of both direct and indirect (e.g., cortico-rubro-spinal, cortico-reticulospinal) pathways.

Poststroke reorganization related to brain-computer interface feedback

The BCI intervention with proprioceptive feedback resembled in stroke subjects the neurophysiological processes observed in healthy subjects: enhancement of ERD in the cortical area targeted by the feedback; increase of the CMC magnitude in the course of the intervention; enhancement of the predominant information flow from the cortex to the finger extensors.

However, stroke subjects differ from healthy subjects with regard to their cortical topography and frequency spectrum of the cortico-motor connectivity pattern. Both ERD and CMC changes were not restricted to the feedback frequency in the β -band, but also included the α frequency band. Based on the topographic overlap of these to frequencies it remains an open question whether the observed α and β changes are truly independent. Consistent with this observation, cortical networks in the oscillatory α and β -band have been related to both BCI control (Buch et al., 2012; Vukelić et al., 2014; Bauer et al., 2015; Vukelić and Gharabaghi, 2015a,b) and poststroke recovery (Dubovik et al., 2012; Westlake et al., 2012; Nicolo et al., 2015). One might speculate that the stroke subjects in our study relied

on a different mode of sensorimotor processing than healthy subjects during integration of sensory reafference into the motor command to ensure maintenance of a stable output (Witham et al., 2011). This observation complements earlier work on the relevance of lower frequency bands for motor restoration (Hall et al., 2014; Ramanathan et al., 2018; Bönstrup et al., 2019; Khanna et al., 2021). Specifically, invasive recordings of units and field potentials suggest that movement execution and restoration after stroke may be linked to low frequency oscillations and correlated local spiking. We may, therefore, assume that activity in different frequencies may have complementary roles for movement control and proprioceptive feedback during post-stroke motor recovery. Furthermore, different frequencies may play a role during early and late phases of recovery (Bönstrup et al., 2019).

Nonprimary motor areas and cortical reorganization after stroke

The cortical CMC topography of the stroke subjects group was, moreover, characterized by the extended bi-hemispheric involvement during the intervention (Fig. 8B,G). Bearing in mind that not all poststroke neuronal reorganization relates to functional restoration, CMC may nonetheless serve as a measure to detect functionally relevant efferent drive (Gerloff et al., 2006a,b; Braun et al., 2007; Rossiter et al., 2013) and neural plasticity (von Carlowitz-Ghori et al., 2014; Belardinelli et al., 2017). Therefore, our observation of increased influence of nonprimary motor areas over the finger extensors in the course of the intervention complements earlier reports of widespread changes of brain activity in stroke subjects with more severe impairment (Serrien et al., 2004; Gerloff et al., 2006b; Ward et al., 2006; J.A. Brown, 2008; Volz et al., 2015; Belardinelli et al., 2017; Diekhoff-Krebs et al., 2017).

Furthermore, experimental work indicates that the motor control system maintains a variability of representations so that it can adapt to unpredictable changes (Peters et al., 2017); similarly, the descending corticospinal connectivity is known to be malleable (Brus-Ramer et al., 2007; Mosberger et al., 2017). In this context, our findings indicate that the amount of synchronization between cortical and spinal cord activity (P Brown et al., 1998; Mima and Hallett, 1999; Salenius and Hari, 2003) during the execution of a (robot-assisted) movement will represent the task-relevant recruitment of the available corticospinal output after stroke and the corresponding motor network representation. This view is supported by cross-sectional and longitudinal structural (Koch et al., 2015) and functional MRI (Grefkes and Fink, 2011, 2014) studies in stroke patients. Specifically, in chronic stroke damage to the descending output fibers from one region of the cortical motor system was compensated by activity in areas that retain corticofugal outputs, e.g., from secondary motor areas such as the dorsal premotor cortex (Newton et al., 2006; Riley et al., 2011; Schulz et al., 2012, 2015a,b; Potter-Baker et al., 2016).

Our findings support the observation that the contralesional hemisphere can act as a source of cortical coherence with functionally relevant muscles after stroke (Rossiter et al., 2013). Moreover, we provide empirical support that BCI with proprioceptive feedback serves as a technique to enhance this connectivity. The predominant information flow from cortex to periphery increased, however, in a restricted perilesional area of the affected hemisphere only. Specifically, training-related enhancement of β -band CMC in the ipsilesional premotor cortex correlated with clinical improvements after the intervention. Future approaches may directly address this

biomarker by applying CMC feedback (von Carlowitz-Ghori et al., 2015) between this specific area and the targeted muscles. A shift of CMC anteriorly and medially from the ipsilesional primary motor cortex has already been described in chronic stroke patients (Mima et al., 2001). This has led to the development of interventions that specifically target premotor areas with brain stimulation (Cunningham et al., 2015; Sankarasubramanian et al., 2017). Furthermore, inhibition of the dorsal premotor cortices in either hemisphere with magnetic stimulation disrupted motor performance in chronic stroke patients, but not in control subjects (Johansen-Berg et al., 2002; Fridman et al., 2004; Lotze et al., 2006), thereby implicating that these regions contribute to poststroke motor recovery (Belardinelli et al., 2017).

Limitations and future perspectives

Direct comparisons between the healthy subject and stroke subject groups have to be drawn with caution because of apparent differences with regard to age, extent of intervention and motor evaluation. Future work may apply a dose-matched intervention in age-matched healthy subjects to better delineate physiological patterns related specifically to poststroke reorganization. Direct comparisons with MRI metrics may, furthermore, enable us to gain a better understanding as to how structural determinants of connections interrelate with task-related functional connectivity measures (Koch et al., 2015).

The present study aimed to elucidate neurophysiological mechanisms related to BCI feedback and not its impact on motor outcome improvement after stroke. This would have necessitated a controlled study design. The observed correlation of ipsilesional premotor β -band CMC with clinical improvement might have been influenced by nonspecific factors in the course of the training program. This intervention requires therefore replication in controlled studies with larger cohorts and longer follow-up periods.

In conclusion, volitional control of cortical oscillations with proprioceptive feedback enhances both cortical activity and behaviorally relevant connectivity to the periphery. This enhanced cortico-muscular control can be induced in the healthy and poststroke brain. Thereby, activating the motor cortex with MI and closing the loop by robot-assisted feedback may facilitate neurorehabilitation in the absence of volitional muscle control.

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