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Plasticity of premotor cortico-muscular coherence in severely impaired stroke patients with hand paralysis

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ABSTRACT

Motor recovery in severely impaired stroke patients is often very limited. To refine therapeutic interventions for regaining motor control in this patient group, the functionally relevant mechanisms of neuronal plasticity need to be detected. Cortico-muscular coherence (CMC) may provide physiological and topographic insights to achieve this goal. Synchronizing limb movements to motor-related brain activation is hypothesized to reestablish cortico-motor control indexed by CMC.

In the present study, right-handed, chronic stroke patients with right-hemispheric lesions and left hand paralysis participated in a four-week training for their left upper extremity. A brain-robot interface turned event-related beta-band desynchronization of the lesioned sensorimotor cortex during kinesthetic motor-imagery into the opening of the paralyzed hand by a robotic orthosis. Simultaneous MEG/EMG recordings and individual models from MRIs were used for CMC detection and source reconstruction of cortico-muscular connectivity to the affected finger extensors before and after the training program. The upper extremity-FMA of the patients improved significantly from 16.23 ± 6.79 to 19.52 ± 7.91 ($p = 0.0015$). All patients showed significantly increased CMC in the beta frequency-band, with a distributed, bi-hemispheric pattern and considerable inter-individual variability. The location of CMC changes was not correlated to the severity of the motor impairment, the motor improvement or the lesion volume. Group analysis of the cortical overlap revealed a common feature in all patients following the intervention: a significantly increased level of ipsilesional premotor CMC that extended from the superior to the middle and inferior frontal gyrus, along with a confined area of increased CMC in the contralesional premotor cortex.

In conclusion, functionally relevant modulations of CMC can be detected in patients with long-term, severe motor deficits after a brain-robot assisted rehabilitation training. Premotor beta-band CMC may serve as a biomarker and therapeutic target for novel treatment approaches in this patient group.

1. Introduction

Despite dedicated rehabilitation programs (Dobkin, 2004; Feigin et al., 2008; Jørgensen et al., 1999), motor recovery in severely impaired stroke patients with a long-lasting hand paralysis is limited. In this patient group, functionally relevant biomarkers of neuronal plasticity need to be detected to refine therapeutic targets and generate novel treatment approaches for regaining motor control (Ward, 2015). However, not all post-stroke neuronal reorganization relates to functional restoration (von Carlowitz-Ghori et al., 2014). Cortico-muscular coherence (CMC) may serve as a measure to detect functionally relevant neuronal plasticity and to provide physiological and topographic insight related to the mechanisms of motor recovery. As summarized by Carlowitz-Ghori and colleagues (von Carlowitz-Ghori et al., 2014), CMC indicates the amount of synchronization between cortical and spinal cord activity during the execution of a movement (Brown et al., 1998; Mima and Hallett, 1999; Salenius and Hari, 2003); it appears predominantly during periods of isometric contraction (Kilner et al., 2000; Riddle and Baker, 2006) and reaches its peak in the beta frequency range over the primary sensorimotor cortices contralateral to the innervated limb (Salenius et al., 1997; Tsujimoto et al., 2009; Witham et al., 2010).

A longitudinal study from the acute to the chronic stage of stroke in patients with very good motor restoration revealed dynamical changes of CMC (von Carlowitz-Ghori et al., 2014). The fact that these changes were primarily localized in the contralateral sensorimotor cortices might reflect the underlying process of recovery. No inter-hemispheric

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or group differences between the CMC of these patients during the chronic stage and that of a group of healthy controls were ultimately found. For detecting candidate biomarkers and cortical areas for novel interventions, it would, therefore, be necessary to study patients whose motor impairment in the chronic stage persists after stroke, and to longitudinally explore their physiological response during a therapeutic intervention. Previous CMC studies performed at the chronic post-stroke stage (Braun et al., 2007; Fang et al., 2009; Graziadio et al., 2012; Mima et al., 2001; Rossiter et al., 2013) were, however, cross-sectional, included patients with various degrees of recovery, i.e., a broad range of impairment levels from mild to severe, and did not examine intervention-related changes.

To better distinguish between the compensatory processes that already took place (Rijntjes, 2006) and factors necessary for recovery, patients would, however, need to be selected with regard to their severity of impairment. This would ensure that the detected physiological changes in the course of the intervention reflected the recovery mechanism (Ward, 2015). Severely impaired chronic stroke patients with a persistent hand paralysis would be particularly suitable for revealing a direct brain-behavior interaction, since motor improvements in this patient group would undoubtedly be related to the respective interventions rather than to the *natural* course of recovery. Source reconstructed cortical CMC distribution would, furthermore, improve its topographic specificity, particularly for detecting connectivity peaks beyond the contralateral motor cortex (Rossiter et al., 2013).

In the present study, severely impaired chronic stroke patients with hand paralysis participated in a four-week training for their affected upper extremity. This training included motor imagery-related self-regulation of the oscillatory beta-band in the lesioned sensorimotor cortex that was reinforced by contingent proprioceptive feedback (Darvishi et al., 2017), i.e., the opening of the paralyzed hand by a robotic orthosis (Naros and Gharabaghi, 2015, 2017; Gharabaghi, 2016); our brain-robot interface (BRI)–based intervention has already been shown to induce distributed increases of corticospinal connectivity (Kraus et al., 2016b) and subsequent gains in an isometric motor task in healthy subjects (Naros et al., 2016). We also performed simultaneous MEG/EMG recordings during a motor task of trying to open and close the paralyzed hand (without BRI support) before and after the four-week training period to address the hypothesis that the intervention induces CMC increases in patients with severe and persistent impairments. While expecting a distributed connectivity pattern that embraces the contralesional hemisphere (Rossiter et al., 2013), we were particularly interested in identifying a specific cortical area showing increased CMC for the affected muscles in all patients, thereby serving as a common neuronal substrate for experience-dependent plasticity.

2. Materials and methods

2.1. Patients

We recruited eight right-handed patients (7 males, mean age: 57 ± 11 [34 68] years) who were in the chronic phase after stroke (70 ± 34 [34156] months) and who presented with a severe and persistent hemiparesis of the left side due to a right hemispheric lesion (volume in mm^3: 67,578 ± 35,638 [2879 111162]). Seven of these patients (P1–P7) are also reported elsewhere (Kern et al., 2016) with regard to *cortico-cortical* oscillatory networks *during* the four-week intervention; here, they are studied with regard to changes of *cortico-muscular* coherence *following* the intervention. Patient P8 in the other study was left-handed and was therefore not included in this study; we instead introduced an additional right-handed patient, P9. The inclusion criteria, intervention and clinical evaluation were identical in both studies and are cited here:

All patients had a hand paralysis and were unable to extend their fingers. The patients were evaluated with the upper extremity Fugl-Meyer-Assessment (UE-FMA) before and after the intervention, respectively; these assessments were videotaped. Five independent raters evaluated these video tapes and were blinded with regard to the time point of assessment (pre- vs post-training). For further analysis, a modified score without coordination, speed and reflexes was applied to increase the sensitivity of the measurement in our severely affected patients (Grimm et al., 2016a). Capturing reflexes introduced unreliability in this patient group, and coordination and speed could not be measured properly since the patients could not touch their noses with the index finger fully extended due to a lack of finger extension. This resulted in a modified UE-FMA score of 16.23 ± 6.79 [6.80 28.60] for our group of patients. The patients' characteristics are summarized in Table 1.

The study was conducted in accordance with the guidelines of the ethic committee of the local medical faculty. The patients participated in a 20-session training program over a period of four weeks. Each session consisted of beta-band brain self-regulation and proprioceptive feedback with a hand robot (approximately 150 trials per day; Naros and Gharabaghi, 2015) prior to a physiotherapy training (Grimm et al., 2016a).

2.2. Brain-robot interface training

A detailed description of the neurofeedback environment applied in this study has already been provided in previous work of our group with healthy subjects and stroke patients and is cited here accordingly: The effector of the device applied in this study is a commercially available electromechanical hand orthosis (Amadeo, Tyromotion GmbH, Graz, Austria) which enables mass finger extension and flexion, while the wrist remains fixed without any movement (Bauer et al., 2016a; Bauer et al., 2016b). This robotic orthosis is regularly used in standard rehabilitation exercises independent of brain-interfacing. When applied in conjunction with brain-computer interface (BCI)/brain-machine interface (BMI) technology, it is also referred to as a brain-robot interface (BRI) (Bauer and Gharabaghi, 2015, 2017; Vukelić and Gharabaghi, 2015a, 2015b). This BCI/BMI/BRI opens and closes the paralyzed hand when triggered by ipsilesional oscillatory brain activity during cued kinesthetic motor imagery which is classified with a linear classifier (Gharabaghi et al., 2014; Walter et al., 2013).

Every session contained 15 runs, each lasting 2–3 min. Every run consisted of 11 trials, each of which began with a 2 s rest period and a preparation period of 2 s, followed by a 6 s movement imagination period and a 6 s rest period. The onset of the preparation, imagination and rest periods were indicated by the commands 'left hand', 'go' and 'rest', respectively. The BRI environment was designed to passively open the patient's paralyzed left hand during the movement imagination period as soon as motor imagery-related event-related desynchronization (ERD) in the beta-band was detected in the ipsilesional, i.e., right, hemisphere (Gharabaghi et al., 2014; Naros and Gharabaghi, 2015; Walter et al., 2013). The BRI algorithm was based on the spectral power values between 17 and 23 Hz for three selected electroencephalography (EEG) channels (FC4, C4 and CP4). EEG was recorded with BrainAmp DC amplifiers and an antialiasing filter (Brain Products, Munich, Germany) from 32 Ag/AgCl scalp electrodes (sampling rate: 1000 Hz) in accordance with the international 10–20 system (FP1, FP2, F3, Fz, F4, FC5, FC3, FC1, FCz, FC2, FC4, FC6, C5, C3, C1, Cz, C2, C4, C6, CP5, CP3, CP1, CPz, CP2, CP4, CP6, P3, POz, P4, POz, O1, O2; reference: FCz, ground: AFz). Electrode impedances were maintained below 10 kΩ. We selected these three electrodes to cover premotor, primary motor, and somatosensory areas (Bauer et al., 2016b; Brauchle et al., 2015; Gharabaghi et al., 2014; Kraus et al., 2016a; Kraus et al., 2016b; Vukelić et al., 2014; Vukelić and Gharabaghi, 2015a, 2015b), all of which are known to be involved in functional restoration following stroke. However, the limited anatomical specificity of the sensor-based electroencephalography (EEG) used during the intervention (unlike the higher spatial resolution and source reconstruction of the pre/post CMC recordings with magnetencephalography, MEG) must be taken into consideration. The

Table 1
Clinical characteristics of the patients.

Pat. nr.	Age (years)	Sex	Hand dominance	Lesion hemisphere	Lesion type	Lesion volume (voxels)	Disease duration (months)
P1	56	Male	Right	Right	Hemorrhage	79,013	78
P2	63	Female	Right	Right	Ischemic	95,476	78
P3	52	Male	Right	Right	Ischemic	80,144	156
P4	67	Male	Right	Right	Hemorrhage	87,923	75
P5	68	Male	Right	Right	Hemorrhage	2879	34
P6	34	Male	Right	Right	Hemorrhage	44,957	45
P7	63	Male	Right	Right	Ischemic	111,162	58
P9	55	Male	Right	Right	Hemorrhage	39,073	80

spectral power range for feedback was chosen on the basis of our previous findings. These had indicated that the effective corticospinal connectivity is mediated in this frequency band (Kraus et al., 2016b; Royter and Gharabaghi, 2016, Raco et al., 2016), which also correlated with subsequent motor gains (Naros et al., 2016). Moreover, movement-related desynchronization in the ipsilesional sensorimotor cortex is compromised in stroke patients compared to healthy controls, i.e., the more severe the patient's motor impairment, the less beta-band desynchronization (Rossiter et al., 2014). Accordingly, a restorative training approach would need to increase this oscillatory modulation range again. We therefore applied the same frequency-range and setup as in our previous BRI studies with healthy subjects and stroke patients (Bauer et al., 2016a; Bauer et al., 2016b; Brauchle et al., 2015; Gharabaghi et al., 2014; Kraus et al., 2016b; Vukelić et al., 2014). Following each BRI training session, goal-oriented physiotherapy with a gravity-compensating multi-joint exoskeleton (Armeo Spring, Hocoma, Volketswil, Switzerland), described in detail elsewhere (Grimm and Gharabaghi, 2016; Grimm et al., 2016a; Grimm et al., 2016b; Naros et al., 2016), was applied to facilitate reach-to-grasp exercises and to consolidate the previously trained movements.

2.3. Experimental paradigm during CMC recording

The CMC measurements were conducted before and after the four-week intervention period, respectively. MEG (instead of EEG) recordings and source reconstruction were applied to achieve a higher spatial resolution. In each pre/post session, patients were placed on the MEG chair 1 m away from a screen. Auditory and visual cues were presented simultaneously; these corresponded to two consecutive and seamless hand movements: one hand extension and one hand flexion movement of 1 s duration each, initiated by the “open” and “close” instruction, respectively. Both auditory instructions were accompanied by a visual cue on the screen (open/closed circle). The patients had to try to perform these movements with their paretic (left) hand. Compensatory movements were discouraged. Due to the severity of the impairment, the task often resulted in small and non-articulated and/or no visible movements (but muscle contractions). Patients were instructed to move as focally as possible, i.e., to avoid co-activation of proximal and/or contralateral muscles. EMG-electrodes were placed on both forearms to control for command execution and for co-activation. EMG data were acquired for the 1) Extensor Carpi Ulnaris (ECU), 2) Extensor Digitorum Communis (EDC), and 3) Flexor Carpi Radialis (FCR) muscles. The EDC muscle showed the clearest activity in both open and close phases, and was therefore used for further analysis. Blocks of 2 s, i.e., comprising both open and close phases, were considered for CMC analysis between brain source activity and the EDC of the paretic side. The mean inter-trial period was 10 s. Pre- and post-training sessions each consisted of 5 runs; one run consisted of 16 s (8 trials), thus resulting in a total of 40 trials before and after the training, respectively.

2.4. Electromyographic recordings

During the pre- and post-training MEG assessment, ipsilateral and contralateral EMG recordings from three muscles (EDC, ECU and FDR) in each arm were collected using 6 bipolar surface Ag/AgCl electrodes from Myotronics-Noromed (Tukwila, WA, USA). The EMG signals were recorded as part of the MEG dataset and had the same preprocessing parameters. Data were demeaned, zero-phase band-pass filtered (20–500 Hz) with a Butterworth filter of 3rd order. Moreover, a 3rd order zero-phase Butterworth notch filter (49–51 Hz) was applied to reduce power line noise.

2.5. Structural MRI recordings

The anatomical, T1-weighted MR images of the patients were acquired with a SIEMENS MAGNETOM Prisma 3 T (Voxel size = 1.0 × 1.0 × 1.0 mm; FoV read = 250, FoV phase 93.8%, TR 2300.0 ms, TE = 4.18 ms, FA = 9.0°). The anatomical images were initially preprocessed with SPM (www.fil.ion.ucl.ac.uk/spm/). The coordinate system of the MR image was realigned to the Montreal Neurological Institute coordinate system (RAS) and a correction for magnetic field inhomogeneities was applied. Coregistration between MRI and MEG coordinate systems was obtained using three fiducial points: nasion, left and right ear.

2.6. MEG recordings

MEG signals were measured continuously at 600 Hz during the task using a whole-head CTF Omega 275 MEG system (CTF, Vancouver, Canada). Head localization was monitored continuously during the recordings to determine any excessive movement. The coils were energized shortly before measurement, and their locations were determined with respect to anatomical landmarks, identified with a 3D digitizer (Isotrak 3S1002, Polhemus Navigation Science).

2.7. MEG preprocessing

The data were pre-processed offline using Fieldtrip (www.fieldtriptoolbox.org) (Oostenveld et al., 2011). The signals were filtered 5–100 Hz and segmented from the onset of the auditory cue for opening the hand until the next auditory stimulus. The segments did not overlap in coherence estimation. Visual inspection of independent Component Analysis (ICA) components was performed and ICs with eye blinks, heart artifacts and/or muscle artifacts were excluded from further analysis.

2.8. Data processing and analysis

Leadfields were calculated according to a realistic single-shell head model which corrects the leadfield for a spherical volume by superimposing basis functions with coefficients that fit the inner skull mesh of the patient's MR image (Nolte, 2003). Coherence levels between MEG and EMG signals from the forearm extensor muscles (EDC) were statistically estimated at sensor level (Rosenberg et al., 1989). The selection of the frequency band for coherent source analysis was determined from the CMC spectrum, taking the average spectrum of the channels over the motor and premotor areas into account (Belardinelli et al., 2007; Rossiter et al., 2013). The coherence spectra

were thresholded at the 95% confidence interval. Since all the participants revealed a significant peak in the high beta frequency range, further source CMC analysis was performed in the 18–30 Hz range.

In a second step, the cortical areas showing significant coherent activity with the forearm movement of the patient during the motor task were identified using Dynamic Imaging of Coherent Sources (DICS) (Gross et al., 2001). DICS employs a beamforming approach in the frequency domain to obtain the activity mapping at source level. The beamformer (Van Veen et al., 1997) leverages the linear projection of sensor data through a spatial filter computed from the lead field of the source of interest and the covariance (time domain) or the cross-spectral density matrix (frequency domain). DICS for CMC estimates the similar oscillatory components of MEG and EMG signals and their linear dependencies. These are represented by means of the Cross Spectrum Density (CSD) between the MEG signals and the EMG.

In the present analysis, CSDs across all MEG gradiometer signals and the high-pass-filtered, unrectified EMG signal were calculated for each frequency across all the epochs. These calculations used Welch's averaged periodogram method (Hanning window 2048-point window; 0.3 Hz, 50% overlap). The source coherence values were computed on a 3D grid in Montreal Neurological Institute space with a step of 5 mm bounded by the volume conduction tessellated surface and a regularization factor of 5%.

2.9. Source statistical analysis

After localizing the coherent source activities pre and post training, we tested the significance of changes by a statistical cluster test implemented in Fieldtrip (Oostenveld et al., 2011).

This statistical test consisted of two steps:

(i) The effect of interest (i.e. relevant change between the functional sets of source-coherence values pre and post training calculated for each patient and each trial with the DICS common spatial filter) was evaluated for each voxel by means of a *t*-test. *t*-values exceeding a threshold of 0.05 were considered for the subsequent clustering analysis.

(ii) To deal with the potential violation of normality assumption of the data we used a nonparametric test statistic based on clusters of nearby voxels that exhibit the same effect. The multiple comparison problem was solved by calculating a cluster-based test statistic and its relative significance probability.

In the clustering step, the nearby voxels which crossed the previous threshold, were grouped into clusters. A statistical evaluation was then assigned to each cluster (i.e., the sum of the single voxel statistics for all the voxels belonging to the cluster) (Maris et al., 2007). After this, a Monte-Carlo approximation of the randomization distribution of the cluster statistics was performed. Shuffling the data-samples of the pre and post training conditions allowed to create new surrogate datasets with non-normal distribution of statistics. Clusters were considered to be significant at an alpha level of 5%.

3. Results

The UE-FMA of the patients in this study improved significantly from 16.23 ± 6.79 [6.80 28.60] to 19.52 ± 7.91 [10.85 35.25] ($p = 0.0015$, paired *t*-test). UE-FMA improvements for single subjects and group data are specified in Fig. 1.

3.1. Sensor level analysis

In Fig. 2 the pre/post-training coherence spectra between the average of 20 channels covering both sensorimotor cortices and SMA are shown (upper row). The significance threshold was calculated according to Rosenberg et al. (1989). The significant range of beta was then considered for further source analysis. Three patients (P1, P7, P9) showed significant gamma activity at sensor level as well. However, no significant changes in this frequency band were detected at source level.

Topoplots in the range of individual significant beta coherence are shown in the middle row of the figures for each patient. In the lower row, the EMG signals of the left arm are shown during the task (40 trials and 80s) pre and post training are shown.

To access possible effects of training on the EMG signals alone, we compared RMS of the EMG pre and post intervention. We calculated RMS of the EMG signals for each trial. Then, a Wilcoxon Signed Rank test was applied to the pre and post RMS datasets. For five patients (P1, P3, P5, P6, P9) the amplitude of muscle activity was found to be significantly increased ($p < 0.001$). For two patients (P4, P7) it was significantly decreased ($p < 0.001$). For one patient (P2) no significant changes ($p = 0.08$) were recorded.

3.2. Source level analysis

All patients showed significantly increased CMC in the beta frequency band after the intervention by presenting a distributed, bihemispheric pattern with considerable interindividual variability (Fig. 3). All patients had relevantly increased CMC beyond primary motor areas. The CMC cluster distance of the positive peak from the right M1 hand knob MNI coordinates was not correlated to the severity of the motor impairment ($r^2 = 0.06$, $p = 0.51$) the motor improvement ($r^2 = 0.02$, $p = 0.60$), time since stroke ($r^2 = 0.15$, $p = 0.44$) or the

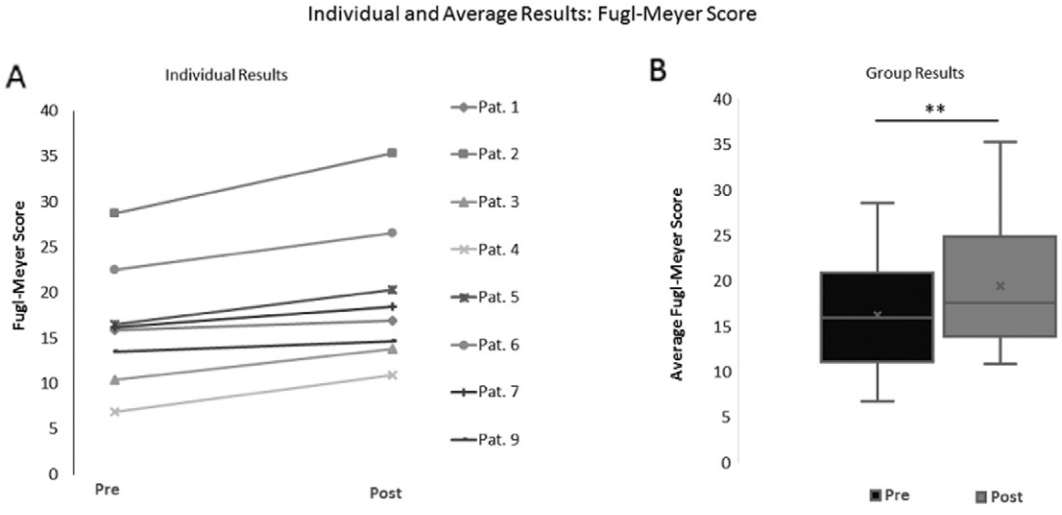

Fig. 1. Histograms of individual (A) and mean (B) Fugl-Meyer Score values pre- and post-training.

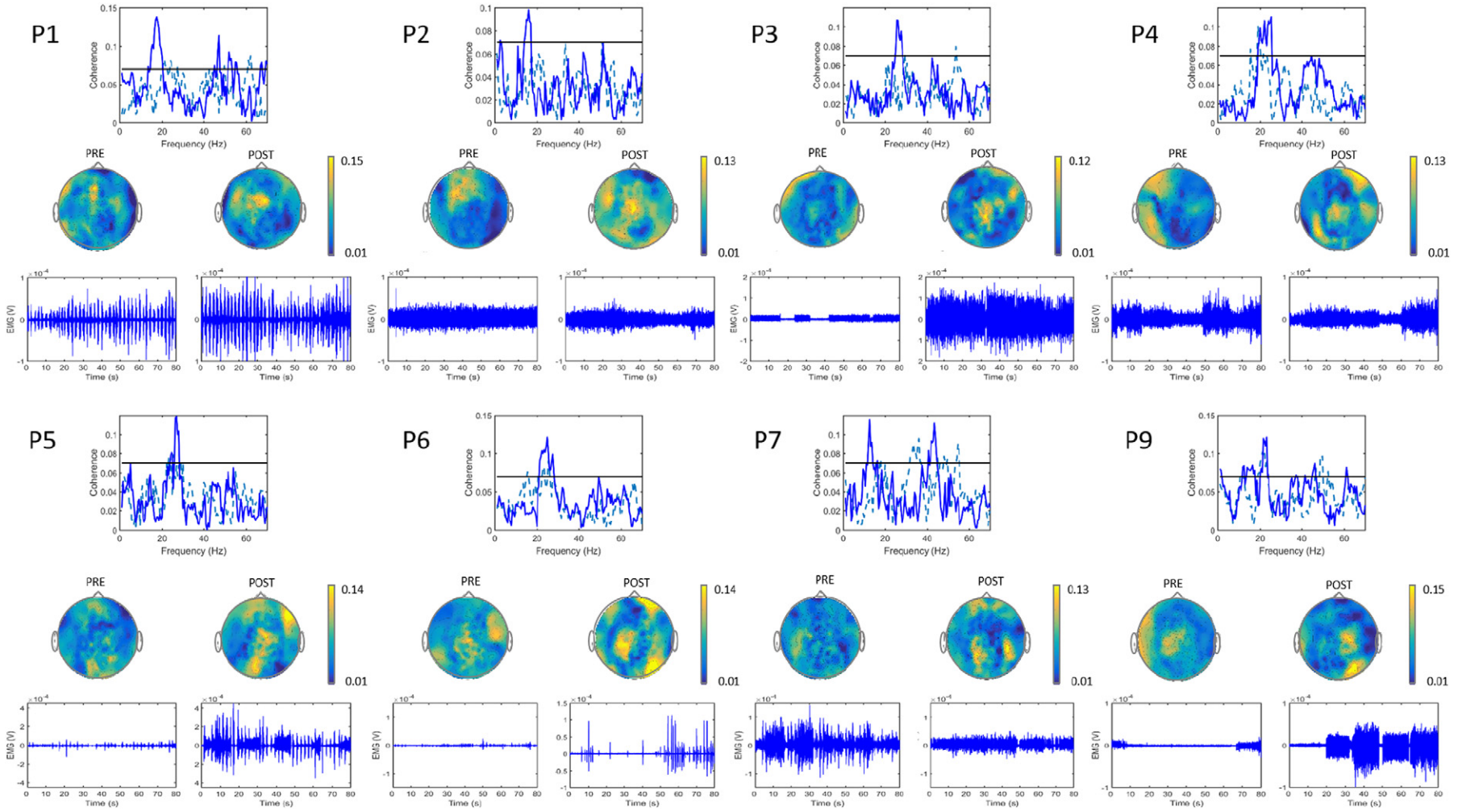

Fig. 2. Sensor level plots for each single patient. In the upper row of each panel, CMC spectra for pre (light blue, dashed curve) and post-training (deep blue solid curve) are shown. The spectra result from the average of coherence between channel signals covering the bi-hemispheric sensorimotor system and the EMG signal. In the middle row, topoplots of significant beta coherence in the pre and post condition are shown. In the lower panel EMG signals are plotted in the time domain for the entire duration of the motor task.

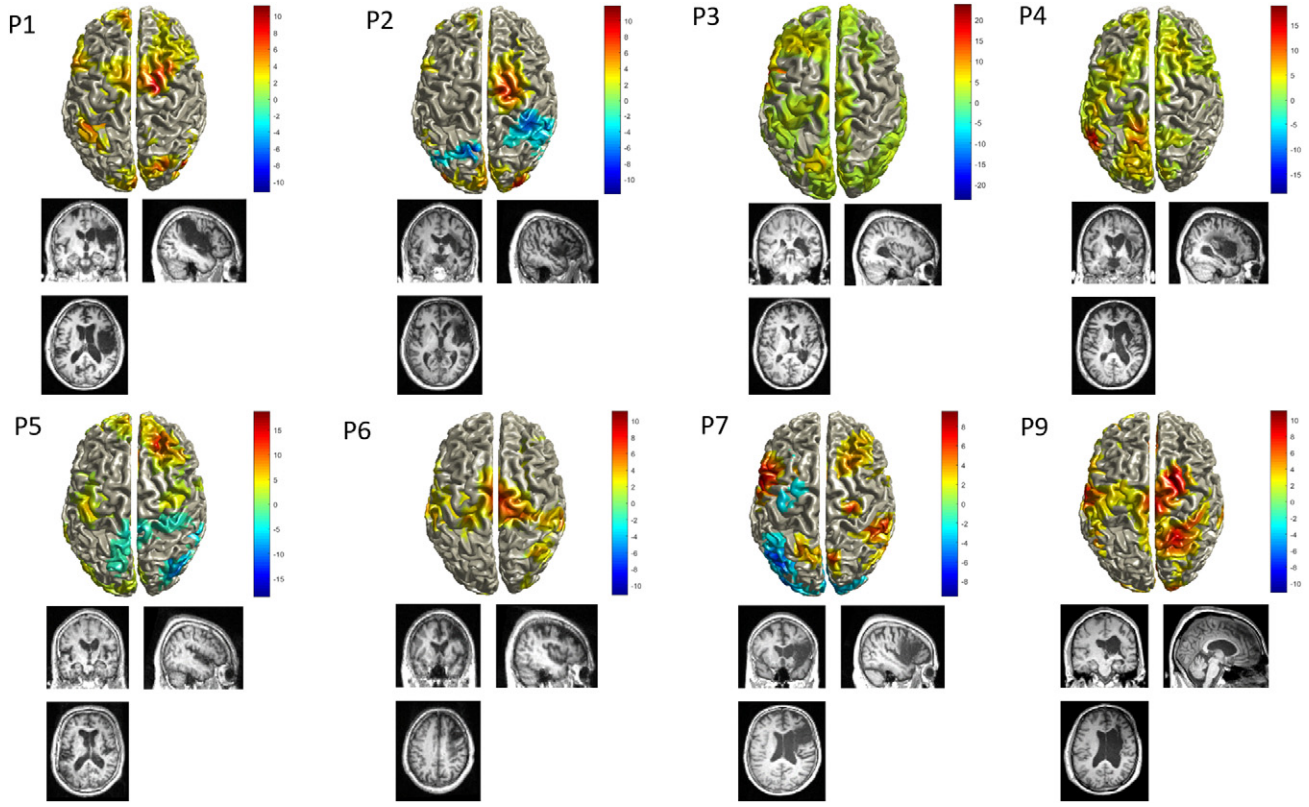

Fig. 3. Single patient's positive (increase) and negative (decrease) clusters after the training (Pat. 1–9, upper panel) and respective brain structural damage (lower panel, MR images). *t*-Statistic maps of the CMC post-training vs pre-training differences. Colored areas show significant changes post vs pre. Red and blue represent increase and decrease in connectivity, respectively. For further details, see Material and methods.

lesion volume ($r^2 = 0.08$, $p = 0.71$). Furthermore, the CMC variability was not related to the lesion side (all lesions were in the right hemisphere) or to the handedness (all patients were right-handed). A physiological comparisons across subjects was therefore possible without having to introduce an artificial flip at the sagittal plane to superimpose functional images (Oswal et al., 2016; Rossiter et al., 2013). Notably, three patients (Pat. 1, Pat. 2, Pat. 5) also showed a significant decrease of CMC, which occurred bihemispherically along with significant CMC increases in other cortical areas. No significant changes were detected in the gamma band for the three patients with relevant gamma activity (P1, P7, P9).

Group analysis of the cortical overlap showed that all patients had significantly increased ipsilesional premotor CMC after the intervention. This extended from the superior to the middle and inferior frontal gyrus, together with a confined area of increased CMC in the contralesional premotor cortex (Fig. 4). Decreased CMC occurred in bilateral parietal areas and in the contralesional motor/premotor cortex.

4. Discussion

We studied cortico-muscular coherence following a four-week rehabilitative intervention in severely impaired stroke patients. All patients achieved motor gains in their affected upper limb, resulting in a significant group effect with regard to the upper-extremity Fugl-Meyer score. A pure order effect of this finding appears quite unlikely in this patient group of severely affected patients in the chronic phase after stroke. More specifically, all patients had a hand paralysis and were unable to extend their fingers for at least 34 months before the intervention. The specificity of the treatment effects regarding the applied therapy, however, cannot be demonstrated in this study due to a missing control

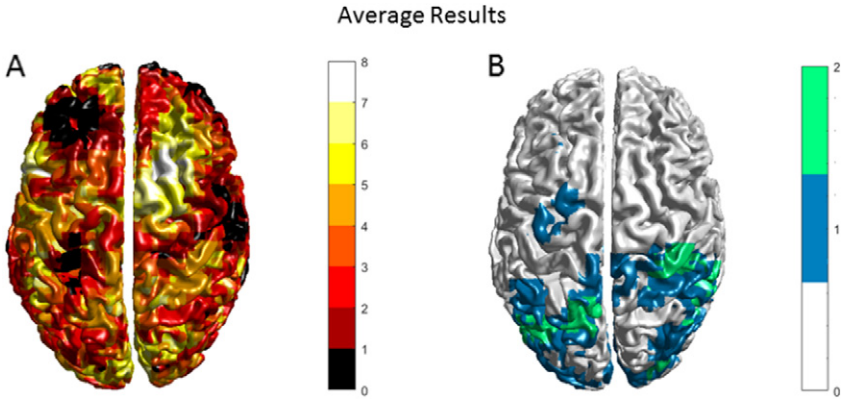

Fig. 4. Union of statistical cluster maps on a standard brain surface. Overlaid positive clusters are shown in (A). The negative clusters were detected in 3 patients only, in 2 of whom overlapping was also observed (B).

group/intervention. Future controlled studies are necessary to undoubtedly attribute the reported findings to the applied intervention.

The behavioral improvements were paralleled by a significant CMC increase in the beta frequency-band, which had previously been found to reflect efferent drive of the cortex to the muscle (Braun et al., 2007; Gerloff et al., 2006a; Gerloff et al., 2006b; Rossiter et al., 2013). Each patient revealed a distributed, bi-hemispheric pattern with considerable inter-individual variability, which could not be explained by any of the captured parameters. These findings are in line with previous evidence that a wide range of cortical regions can influence muscle activity and that these are involved in supporting recovered hand function after stroke (Rossiter et al., 2013).

To detect common factors relevant for functional restoration, the selected patients were unified as far as possible. This ensured that the detected CMC changes were attributable to the recovery mechanism; as previously suggested by Carlowitz-Ghori and colleagues, the patients were selected on the basis of their clinical symptoms and not on the basis of their lesion location. The impaired transmission along the efferent pathway in the corticospinal tract was the common factor in all patients. This is due to the fact that the recruitment of cortical areas during motor performance (Ward et al., 2007; Ward et al., 2006) and motor function (Stinear et al., 2012; Stinear et al., 2007) depends on corticospinal integrity post-stroke (von Carlowitz-Ghori et al., 2014). Our patients therefore had a similar severity level of motor impairment, i.e., a persistent hand paralysis in the chronic stage after stroke. They were, moreover, all right-handers and had their lesion in the right, non-dominant hemisphere. Although other factors such as lesion type, volume and location, age or time since stroke differed between the patients, none of these properties influenced the motor gains or CMC changes. Moreover, the motor gains and the pattern of CMC changes were not correlated in this study, thereby, preventing us from making any specific conclusions about direct brain-behavior interactions. Rossiter and colleagues did not detect any correlations between the impairment level and the CMC pattern either, e.g., the involvement of the contralesional hemisphere, even when exploring patients with a wider range of motor impairments, less severely affected patients and patients at shorter (subacute) time periods after stroke. Nonetheless, our findings support their theory that the contralesional hemisphere can act as a source of coherent descending cortical drive to functionally relevant muscles after stroke (Rossiter et al., 2013). Moreover, the significant CMC increase cannot be attributed to increased EMG activity alone, since the RMS of EMG signals increased in 5 patients but decreased in two and remained unchanged in one.

To the best of our knowledge, we present the first evidence that non-primary motor cortex and contralesional sources of CMC are dynamically modulated by therapeutic interventions despite severe and persistent motor impairments in the chronic stage after stroke. Notably, the same BRI intervention as used in the present stroke study also led to distributed increases of corticospinal connectivity (captured with transcranial magnetic stimulation, TMS) in premotor and somatosensory cortical areas of healthy subjects (Kraus et al., 2016b). Importantly, these changes of corticospinal connectivity correlated with the self-regulated beta-band modulation during the intervention, thus signifying that there is a physiological link between these two biomarkers (Kraus et al., 2016b). Moreover, recent refinements of TMS motor maps revealed that the non-dominant hemisphere (which was the ipsilesional in the present study) showed a larger fluctuation of the premotor corticospinal connectivity than the dominant hemisphere in healthy subjects, thereby, suggesting that this pathway may serve as a dormant reserve for compensatory activation, for example, when lesions of the motor cortex-spinal connections necessitate alternative pathways (Kraus and Gharabaghi, 2016, Mathew et al., 2016). Furthermore, in an isometric hand task in another group of healthy subjects who trained with the very same neurofeedback set-up as applied here, the acquired skill for sustained sensorimotor beta-desynchronization correlated significantly and frequency-band specifically with subsequent motor improvements (Naros et al., 2016). These complementary findings imply relevant interactions between the volitional control of sensorimotor beta-oscillations, cortico-spinal connectivity, and subsequent behavioral gains. However, it should be borne in mind that cortical beta-oscillations and beta-band CMC are functionally dissociated (Baker and Baker, 2003; Riddle and Baker, 2006; von Carlowitz-Ghori et al., 2014), even when both may be modulated by the same BRI intervention.

Group analysis of the cortical overlap in the present study revealed a common topographic CMC feature following the intervention; more specifically, all patients presented with an extended premotor area of significantly increased ipsilesional CMC covering the superior, middle and inferior frontal gyrus, together with a confined area of increased CMC in the contralesional premotor cortex. A CMC shift anteriorly and medially from the ipsilesional primary motor cortex has already been described in chronic stroke patients, albeit at the sensor level and with EEG (Mima et al., 2001).

This observation of increased influence of non-primary motor areas over muscles in the affected limb, as demonstrated in the present study, complements earlier reports of widespread changes of brain activity, particularly in patients with more severe impairment (Cramer, 2008; Gerloff et al., 2006b; Serrien et al., 2004; Ward et al., 2003). Moreover, TMS studies targeting the dorsal premotor cortices in either hemisphere disrupted motor performance in chronic stroke patients but not in control subjects (Fridman et al., 2004; Johansen-Berg et al., 2002; Lotze et al., 2006), thereby suggesting that these regions also contribute to post-stroke motor recovery.

In conclusion, the present study underlines the variability of cortical plasticity across patients and provides evidence that functionally relevant CMC to affected muscles can be detected and modulated by rehabilitation despite severe motor deficits in the chronic phase after stroke. More specifically, premotor beta-band CMC may serve as a biomarker and therapeutic target for supporting recovered function with novel treatment approaches in severely impaired stroke patients.

Competing interests

The authors declare that they have no competing interests.

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