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# Learned Control of Inter-Hemispheric Connectivity: Effects on Bimanual Motor Performance

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**Abstract:** Bimanual movements involve the interactions between both primary motor cortices. These interactions are assumed to involve phase-locked oscillatory brain activity referred to as inter-hemispheric functional coupling. So far, inter-hemispheric functional coupling has been investigated as a function of motor performance. These studies report mostly a negative correlation between the performance in motor tasks and the strength of functional coupling. However, correlation might not reflect a causal relationship. To overcome this limitation, we opted for an alternative approach by manipulating the strength of inter-hemispheric functional coupling and assessing bimanual motor performance as a dependent variable. We hypothesize that an increase/decrease of functional coupling deteriorates/facilitates motor performance in an out-of-phase bimanual finger-tapping task. Healthy individuals were trained to volitionally regulate functional coupling in an operant conditioning paradigm using real-time magnetoencephalography neurofeedback. During operant conditioning, two discriminative stimuli were associated with upregulation and downregulation of functional coupling. Effects of training were assessed by comparing motor performance prior to (pre-test) and after the training (post-test). Participants receiving contingent feedback learned to upregulate and downregulate functional coupling. Comparing motor performance, as indexed by the ratio of tapping speed for upregulation versus downregulation trials, no change was found in the control group between pre- and post-test. In contrast, the group receiving contingent feedback evidenced a significant decrease of the ratio implicating lower tapping speed with stronger functional coupling. Results point toward a causal role of inter-hemispheric functional coupling for the performance in bimanual tasks. *Hum Brain Mapp 38:4353–4369, 2017*. © 2017 Wiley Periodicals, Inc.

**Key words:** neurofeedback; coherence; behavior; magnetoencephalography; braincomputer interface; motor

## INTRODUCTION

Humans can produce complex bimanual movements, such as typing an article on a computer keyboard or playing piano with both hands executing different tunes. In these tasks, fingers of both hands are either moved simultaneously or rather independently, yet in a coordinated fashion. Such bimanual movements require precise coordination of the timing of muscular activation in both sides of the body and close interactions between cortical areas of motor control [Cardoso de Oliveira et al., 2001].

Studies investigating the neurophysiological and neuroanatomical basis of bimanual coordination have identified various cortical and subcortical regions [Rouiller et al., 1994; Wiesendanger et al., 1994, 1996]: starting with neocortical regions, bilateral supplementary motor area (SMA: crucial role in bimanual coordination), primary motor areas (M1: motor coding), and dorsal pre-motor areas posterior parietal cortex, cingulate cortex (spatial and temporal coordination) and subcortical structures like basal ganglia and cerebellum have also been found to play a role in bimanual coordination in both, healthy individuals and patients with motor disorders such as Parkinson's and Huntington disease. The interaction between these areas for bimanual coordination is mainly indexed by functional coupling, that is, phase-locked oscillatory activity, collaborating at different frequencies [Banerjee and Jirsa, 2007; Gerloff and Andres, 2002]. As a metric of functional coupling, correlations of amplitudes, as well as parameters measuring the extent of phase-locked activity have been introduced [Akam and Kullmann, 2012; Bastos et al., 2015; Fries, 2005, 2015].

Although functional coupling occurs on various levels of the motor control system, its role in bimanual coordination might be best studied in primary motor cortices [Donchin et al., 1998, 2002] as they control the muscular activity via cortical output and thus constitutes a major easy-to-study hub for motor networks.

From behavioral as well as neurophysiological studies, two different biological models that attempt to explain the neural mechanisms involved in bimanual motor coordination have been put forward: the model of general motor programs (GMP) [Schmidt, 1975; Schmidt et al., 1979] and the model of inter-manual cross talk [Marteniuk et al., 1984; Marteniuk and MacKenzie, 1980]. The model of GMP is derived from the observation of strong spatiotemporal similarities of bimanual coordination suggesting that there is a common motor plan for both limbs. In contrast, the model of inter-manual crosstalk suggests that there are independent motor plans for each hand and that these plans interact via crosstalk between motor control signals at various levels of the motor system.

Strong support for the inter-manual crosstalk model comes from studies by Cardoso de Oliveira et al. [2001]. Using single unit recordings [Cardoso de Oliveira et al., 2001] they found that inter-hemispheric but not intra-hemispheric coupling was consistently related to the degree of bimanual coordination: symmetric bimanual movements were accompanied by significantly stronger increases of correlation than out-of-

phase, asymmetric bimanual movements. However, in contrast to this study, also a decrease of inter-hemispheric functional coupling between bilateral M1 regions for symmetric bimanual movements as compared to out-of-phase bimanual tasks has been reported [Rueda-Delgado et al., 2014]. The contradicting results point to the fact that the role of functional coupling for bimanual motor control is still a matter of debate and calls for more elaborated studies.

Previous studies investigating the role of inter-hemispheric functional coupling in bimanual coordination have often varied the motor tasks as an independent variable and studied the concurrent changes of functional coupling as dependent variable. These studies deduced the role of functional coupling for bimanual movements from the correlative relation between the type of task and the degree of coupling. In our study, we follow an alternative approach that overcomes the limitations of not implying causation in correlative studies: we manipulate the degree of inter-hemispheric functional coupling between left and right primary motor cortex using a neurofeedback training and explore its effects on motor performance. In our neurofeedback approach, the dependent variable is recorded down-stream from the site of modulation and thus allows for a more causal interpretation of the relation between functional coupling and behavior.

To investigate the effects of modulating inter-hemispheric functional coupling on motor performance, the neurofeedback training should enable participants to reliably upregulate and downregulate functional coupling on request and in a motor performance task scheduled after the neurofeedback training. Given these requirements we opted for an operant conditioning paradigm for the neurofeedback training. The sole motivation for this approach comes from the dual process theory by Groves and Thompson, [Groves and Thompson, 1970] which posits that there is a fast, unconscious implicit and effortless cognitive control system for actions (System I) and a slow, conscious, explicit, effortful one, that involves deliberate reasoning and critical thinking (System II). They both activate brain areas and neuronal networks in a task-related fashion and thus eventually evoke behavior. According to Grooves and Thompson, System II is shaped by insight and observational learning and System I is modulated by classical and operant conditioning associating a reaction to a stimulus [Birbaumer et al., 2013; Chaudhary et al., 2016, 2017; Daly et al., 2012].

In our study, we trained healthy individuals using real-time magnetoencephalography neurofeedback (rt-MEG) [Kajal et al., 2015; Sacchet et al., 2012] to modulate inter-hemispheric functional coupling and to observe its effects on an asymmetric out-of-phase, bimanual finger-tapping task (AOBFT). The conditioning associated upregulation and downregulation to a discriminative stimulus $S^D$, with $S^+$ cueing the upregulation and the $S^-$ the downregulation functional coupling. Presenting $S^+/S^-$ in the motor performance task was supposed to elicit increased/reduced inter-hemispheric functional coupling and alter motor performance. This operant conditioning approach has been widely used to modulate brain states in neurofeedback studies [Fetz, 1969; Nowlis and Kamiya, 1970; Ramos-Murguialday and Birbaumer, 2015]. To account for unspecific effects, we trained upregulation and downregulation of functional coupling to individuals who received sham feedback (SF).

Training-induced changes in motor performance were assessed prior to (pre-test) and after (post-test) the neurofeedback training. We hypothesize that learned upregulation of inter-hemispheric functional coupling will deteriorate motor performance in the AOBFT in the presence of the $S^+$-stimulus. Presenting the $S^-$-stimulus we expect an improvement of performance from pre-test to post-test sessions. Results would provide insight into the role of inter-hemispheric functional coupling for bimanual motor tasks.

## MATERIAL AND METHODS

### Participants

rt-MEG-neurofeedback was performed on 30 healthy participants ($M \pm SD = 26.0 \pm 3.1$ years; 20 males) with no history of neurological or psychiatric illness or head trauma. None of the participants were taking any medication. Participants were evenly and randomly assigned to one of two groups: the contingent feedback (CF) group or the SF group ($n = 15$ each). The ethics committee of the Faculty of Medicine at the University of Tubingen, Germany approved the experimental protocol. Written informed consent was acquired from all participants. Participants received financial compensation of Euro 10/hour for their participation in the study.

### Experimental Procedure

The experimental protocol includes four main experimental parts that were presented across five days: (1) pre-test: execution AOBFT (day one); (2) functional localizer: participant-specific identification of the MEG sensors from which the feedback signal was computed (day two), the frequency bands of the MEG oscillatory activity from which the feedback signal was computed (day three); (3) neurofeedback training (day four); and (4) post-test: AOBFT identical to pre-test on day1 to assess the impact of the training on performance (day five).

In the following, the different sessions of the experiments are explained in the same order as they appear in the above list. Only the post-test session is explained together with the pre-test session because both setups are essentially the same.

### Pre-Test and Post-Test (Day One and Five)

Examination of behavioral data from the pre-test and the post-test sessions allowed us to study how upregulation and

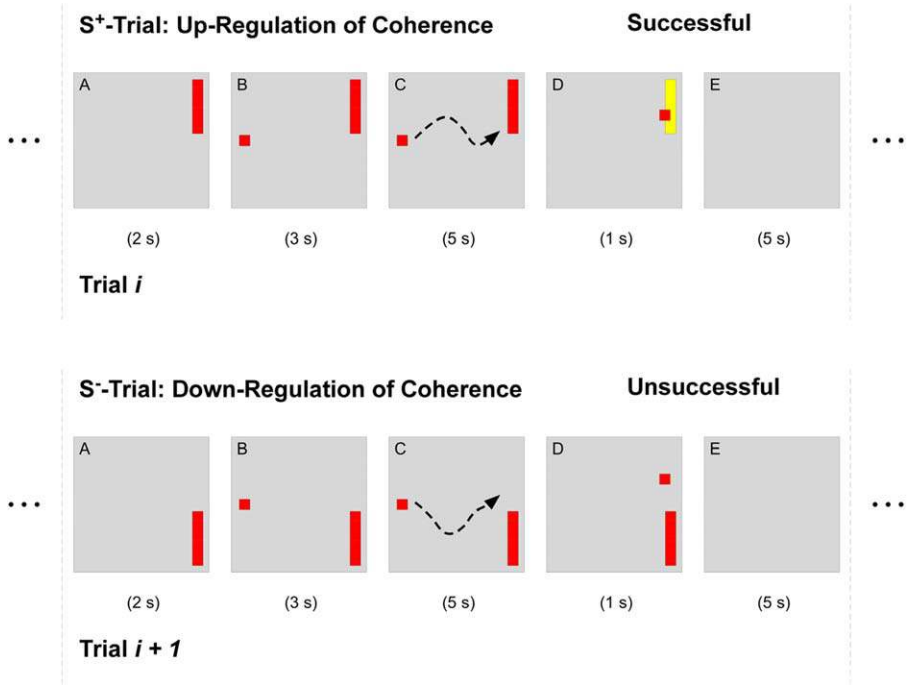


**Figure 1.**

Schematic of a real-time functional coupling neurofeedback trial. (A) Cue phase: the discriminative stimulus $S^D$ appears for 2 s, indicating whether the current trial is either an $S^+$ or $S^-$ trial; (B) initiation phase: cursor appears and remains stationary for 3 s while the initial real-time functional coupling is calculated and the participant begins self-regulation of functional coupling (C) active feedback phase: for 5 s the cursor moves in the *x*-direction at a constant velocity and in the *y*-direction with an amplitude relative to the functional coupling calculated from the immediately preceding 3 s interval; (D) feedback phase: a successful trial is indicated by the target changing to yellow for 1 s, and the target remains red for an unsuccessful trial; (E) intertrial interval of 5 s. dots) indicate continuation of the next trial. [Color figure can be viewed at wileyonlinelibrary.com]

downregulation of inter-hemispheric functional coupling affects behavioral performance, and whether effects of neurofeedback training generalize to a "no feedback" condition.

Specifically, pre-test and post-test sessions used the AOBFT involving left and right hand index and middle fingers. Participants pressed four optical buttons in a self-paced, predefined sequence involving both hands (AOBFT) as follows: right hand index finger, left hand index finger, right hand middle finger and left hand middle finger. This sequence was to be completed as quickly and as accurately as possible. The AOBFT was chosen as task instead of a task that involves only one finger and its contralateral homologue, to provide sufficient room for the potential variations in tapping performance.

In both, the pre-test and post-test sessions, the two experimental conditions were indicated by the discriminative stimulus $S^D$s (either $S^+$ or $S^-$) that were presented on the screen in front of the participants. In the pre-test, the $S^D$ were meaningless since the association between the discriminative stimuli and the modulation of functional coupling had not yet been established. Only after the neurofeedback training, $S^D$s were assumed to have acquired relevance such that $S^+$ was associated with upregulation and $S^-$ with downregulation of functional coupling. As in the neurofeedback session, $S^+$ was a red bar on the right upper part, and $S^-$ a red bar on the lower part of the screen (see Fig. 1).

Each trial started with the presentation of the $S^D$, which was supposed to modulate subject's functional coupling and at the same time instructed participants to start the AOBFT. All participants were requested to continue AOBFT as long as the $S^D$ remained on the screen. Both pre-test and post-test sessions comprised 100 trials. Across trials, $S^+$ or $S^-$ were presented in a pseudo-randomized manner with 50 trials per condition. Each trial lasted for 10 s. During pre-test and post-test sessions, neuro-magnetic brain activity was recorded with MEG.

## Functional Localizer: Parameter Identification for Neurofeedback (Day Two and Three)

In this part of the experiment, we sought to identify participant-specific parameters of MEG signatures to be trained in the neurofeedback training. To determine the MEG channels that captured activity generated in primary motor cortex, we explored the modulation of sensorimotor rhythm

(SMR) by activity of each hemisphere (2 sensors per hemisphere). Furthermore, the individual dominant SMR frequency band in two distinct motor tasks, that produce high and low inter-hemispheric functional coupling, was determined.

For the identification of the four participant-specific MEG channels representing activity generated in primary motor cortex, participants performed self-paced hand movements, that is, hand-opening and -closing versus rest (day two). Two sensors were chosen on each hemisphere. To capture the dipolar character of motor cortex activity the two sensors showing strongest SMR activity with opposite polarity were chosen. Each session consisted of 200 trials, 100 trials each for left and right hand movements. Left and right hand movements and rest were performed in pseudo-random order. Visual cues were used to indicate which hand to move. Sequences of hand movements of 5 s were interspersed with 2 s of rest. Hand opening and closing as well as rest were different from the movement tasks in pre- and post-test sessions to avoid any interfering training effects.

To identify the frequency for which functional coupling feedback was provided (day three), participants performed the following five self-paced, continuous finger-tapping tasks: (a) tapping of the right index finger; (b) tapping of the left index finger; (c) bimanual tapping of the index fingers in a symmetric manner; (d) bimanual tapping of the index fingers in an asymmetric manner; and (e) rest. For each task, a spectrum of inter-hemispheric coupling was obtained. The pair of tasks showing the maximum difference in functional coupling was selected and the corresponding frequency was chosen to be used in the coupling feedback. Each participant completed 200 trials, that is, 40 trials for each movement type. Tasks were requested in pseudo-randomized order and participants were visually cued regarding the type of task to perform. The interval between start and stop of each trial was 5 s. The inter-trial interval, during which participants relaxed, was 2 s.

## Neurofeedback Training (Day Four)

Neurofeedback training was realized in an operant conditioning setup and involved differential upregulation and downregulation of inter-hemispheric functional coupling of SMR. Coherence was estimated from the time-series of MEG signals in the four selected sensors and the frequency band identified during the functional localizer session. A real-time measure of functional coupling between the four MEG sensors over the motor cortex was used as a representation of inter-hemispheric functional coupling. Participants received real-time visual feedback of functional coupling during each trial. Indication to upregulate or downregulate inter-hemispheric functional coupling was provided by two $S^D$s already introduced in the pre-test session: (a) a red bar appearing either at the right upper half of the screen ($S^+$) to indicate the upregulation, or (b) at the right lower half of the screen ($S^-$) to indicate downregulation of functional coupling. In each trial of the neurofeedback session, the goal was to direct an on-screen red cursor (Fig. 1) toward a red rectangular target (the $S^D$). Participants were not informed that S+ required upregulation and S- required downregulation of the coupling but only that two different brain states should be "produced" during the two $S^D$'s.

Neurofeedback training was given in an identical manner to both groups of 15 participants each, namely: CF group which received CF and the SF group receiving SF serving as a control group. The participants in both groups and experimenters were blind regarding the type of feedback they received. Post experimental questioning indicated that the SF group did not realize the lack of contingency in the feedback, but believed that the feedback was veridical feedback as in the CF group. For the SF group, the experimental instructions provided to the participants were identical to that of the participants in the CF group. The number of blocks, trial number, and trial structure were the same as in the CF sessions.

The neurofeedback training comprised 200 trials. During half of the trials, participants performed upregulation, and in the remaining trials, participants performed downregulation of the neuro-magnetic signals. Trials of upregulation and downregulation of coupling were pseudo-randomized across trials.

A single trial started with a 2 s preparation interval during which the $S^D$ prompted the participant to be prepared for either upregulation or downregulation (Fig. 1). At the same time, a cursor appeared on the screen remaining stationary on the screen for 3 s. During this period, the baseline for the neurofeedback was acquired. Thereafter the active feedback phase begun, lasting for 5 s. In the feedback phase, the cursor moved horizontally with a constant velocity. While for the CF group the vertical cursor movement velocity was proportional to the real-time measure of inter-hemispheric functional coupling, it was random for the SF group. The random values were modeled with a Rayleigh distribution by fitting to the histograms of the functional coupling values obtained during CF. The amount of positive and negative feedback in the SF group was identical to the CF group. The period of active feedback was followed by a 1 s interval in which the performance in the feedback task for that trial was indicated: the target either changed to yellow, indicating a successful trial, or remained red indicating an unsuccessful trial. After the feedback of the trial outcome, the $S^D$ disappeared. Inter-trial intervals consisted of the presentation of a blank screen for 5 s. Participants were encouraged to produce as many successful trials as possible. At the end of each block they were informed about the number of generated hits.

One hour before the MEG-neurofeedback training, participants were informed and familiarized with the experimental paradigm and the tasks to be performed. During the experiment, participants sat upright in the MEG chair facing a 40 cm $\times$ 30 cm screen displaying instructions and feedback

information to the participants. Participants of both the groups, CF and SF, were informed about the experiment and instructed not to perform any overt movement during the neurofeedback training session. We monitored the participants using a video camera. None of the participants performed any visible overt hand movement, although it cannot be fully excluded that subjects might have used some muscle activation escaping the observation of the experimenter. Head movements were tracked using the MEG head localization system. Participants were informed that they were free to try any cognitive strategy and to apply what worked best for them in terms of positive feedback to modulate inter-hemispheric coupling.

### MEG Data Acquisition

During the experiment, participants were seated in a magnetically shielded dimly lit room (VacuumSchmelze, Hanau, Germany) at the MEG Center of the University of Tübingen with their head placed in the helmet of a whole-head MEG System (VSM Omega system MISL, Vancouver, Canada).

The MEG system comprises 275 first-order axial gradiometers with a gradiometer baseline of 5 cm. Data were sampled at a rate of 1,172 Hz, with an anti-aliasing low-pass filter set at 416 Hz. Head position was continuously monitored using localization coils affixed to the participant's head at predefined fiducial locations (nasion, and left and right preauricular points). The coils were driven using sinusoidal currents at frequencies (156.25 Hz, 125.00 Hz, and 104.16 Hz) distant from the range of brain signals of interest (< 45 Hz). The three fiducial points defined the head-centered coordinate system used in all data analyses. Using the head localization information, it was ensured that the participant's head was repositioned to the pre-test session.

### Real-Time Signal Processing

The magnitude squared coherence between the two neural signals were computed as the measure of functional coupling which can be defined as follows:

$$Cxy(f) = \frac{[Sxy(f)]^2}{[Sxx(f)]x[Syy(f)]} \quad (1)$$

where $S_{xy}$ is the cross spectral density between signal $x$ and $y$ and $S_{xx}$ and $S_{yy}$ are the auto spectral densities of $x$ and $y$, respectively, at frequency $f$ Hz. We used squared magnitude coherence for the online calculation of the feedback signal as well as during off-line data analysis. We used 19 segments of 0.208 s duration overlapping by 50% to compute a 2 s baseline coherence for each trial. As the trial proceeded, functional coupling was continuously updated using the most recent 3 s intervals for the computation.

The weighted overlapping-segment averaging (WOSA) estimator was used as a coherence estimator. This method was chosen for its advantage of minimum bias and variance in the coherence estimation [Zaveri et al., 1999]. In this method, two signals of Qs duration are divided into $n$ segments which might overlap up to a certain percentage $p$ and for which Fourier sample spectra are calculated. Based on the spectra, squared magnitude coherence is derived. In our experiment, functional coupling was quantified in the most recent 3 s intervals of the constantly updated input data. The interval was divided into 28 segments of 0.208 ms duration and 50% overlap.

To reduce computational cost, the WOSA neural coherence was not calculated for all frequencies. Instead, a FIR filter was used to extract signals at the participant-specific frequency of interest identified in the functional localizer session. The digital signal-processing module of the BCI2000 software performed spatial filtering and spectral analysis of the signals, which were then transformed into cursor movements.

BCI2000 software was used to provide real-time, visually presented neurofeedback of MEG functional coupling [Mellinger et al., 2007; Schalk et al., 2004]. The computer running BCI2000 was connected to the standard MEG data acquisition hardware via Ethernet interface using TCP/IP. Real-time data was accessed immediately after the CTF Acquire program had stored the raw digitized MEG data in memory. The BCI2000 computer accessed the raw data in shared memory in a constant block size of 44 samples (after digitization). The data blocks were transmitted from the MEG computer to BCI2000 software in intervals of 70.4 ms. On the computer running BCI2000, a second program acted as a relay to BCI2000 via a TCP/IP-based socket interface.

During the neurofeedback trials, the horizontal movement of the cursor ($v_x$) was kept constant, whereas the vertical amplitude of the cursor ($v_y$) changed in relation to the amount of neural coherence (NC) computed using the last 3 s of the MEG signal:

$$v_y = b^*(\mathrm{NC} - a) \quad (2)$$

where intercept "$a$" and gain "$b$" were adapted dynamically to optimize the control over cursor movement. Specifically, the intercept "$a$" was dynamically adapted to facilitate the accessibility of both $S^+$ and $S^-$. At the end of each trial, "$a$" was recalculated as:

$$a = \frac{1}{2}(S^+ - S^-) \quad (3)$$

where $S^+$ and $S^-$. are the adaptive online estimates of the mean of neural coherence (S) computed separately over the three preceding trials for $S^+$ and $S^-$, respectively. The gain parameter determined the rate at which the cursor moved vertically on the screen and was adjusted such that the rate of the cursor movement was neither too fast nor too slow. This was desirable as small gains require high visual sensitivity and do not utilize the whole screen, and large gains result in erratic cursor movement. The gain of the feedback procedure was adjusted after each trial as:

$$b \propto \frac{1}{(S^{+} - S^{-})} \quad (4)$$

## Off-Line Data Analysis

Offline data analysis was conducted in MATLAB (The Mathworks, Natick, USA) using the FieldTrip toolbox [Oostenveld et al., 2011] and in-house Matlab scripts. To study the neural generators of the activity recorded at sensor level and to localize cortical sources that showed coherent activity to the sensor level motor activity (SLMA), we used the Beamformer method "Dynamic Imaging of Coherent Sources (DICS)" [Gross et al., 2001]. Potential source positions were defined using a regular 3D grid with 8 mm resolution covering the whole brain. For each potential source position, the leadfield matrix that depends on the electrical properties of the head tissues and on the geometrical relation between the sources and the sensors and describes the contribution of a preassumed source to the MEG sensors was calculated. In the second step, filter coefficients were estimated that define the contribution of the activity at each sensor to the source activity at that target location. Filter coefficients depend on the cross-spectral density matrix that characterizes the correlation between the activities at different sensors for a given frequency band. In general, the Beamformer is a source estimation procedure that projects and optimally focuses sensor level activity to source space.

## Analysis of the Functional Localizer Data

Offline analysis of functional localizer session data included the creation of topographical maps of SMR-power changes for left and right hand movements versus rest. From each hemisphere, two MEG sensors were identified showing the highest determination coefficients ($R^2$-values signifying the amplitude variance of SMR for hand opening and closing versus rest) over contralateral primary motor cortex (Fig. 2). Since the two MEG channels of one hemisphere were selected such that they capture the out- and ingoing magnetic fields of the activity generated by primary motor cortex, an estimate of the time course of motor cortical activity was obtained by subtracting the activity recorded at these two channels. Using the identified SMR-MEG sensors, data from the functional localizer session were further analyzed to identify two tasks (from five total tasks) for which the difference in functional coupling was highest. The frequency at which the highest functional coupling difference occurred was chosen as frequency of coupling for which feedback was given in the training.

For the spectral analysis, continuously recorded data were segmented into 40 epochs of 5 s duration each representing the activity of an individual trial. For each epoch, the first and the last 0.5 s of data were discarded to exclude potential artifacts resulting from the initiation or termination of movements. Next, pre-processing was conducted, including demeaning, trend removal, and filtering of 50 Hz power line noise. Trials containing eyeblinks, muscular artifacts, and in which the magnetic activity exceed ± 1 pT were removed. Then, Fast Fourier Transform with multi-Hanning taper [Percival and Walden, 1993] was applied to consecutive 0.208 s intervals of the previously epoched data to estimate spectral information. Finally, magnitude squared coherence was computed.

## Analysis of the Real-Time Neurofeedback Data

Neurofeedback data were segregated into upregulation ($S^{+}$) and downregulation ($S^{-}$) trials. Depending on participants' performance in controlling inter-hemispheric functional coupling in the individual trials, trials were further classified into successful (the desired increase/decrease in functional coupling was achieved) or unsuccessful trials (the desired increase/decrease of functional coupling was not achieved). The first and the last 0.5 s of each trial were discarded. Datasets were pre-processed and analyzed as for the task identification session. Trials containing eyeblinks, muscular artifacts, and in which the magnetic activity exceed ± 1 pT were removed. For all participants, a minimum of 160 artifact-free trials was obtained. To assess the time-course of training-induced changes of functional coupling, the first 160 artifact-free trials were subdivided into 8 blocks of 20 trials for each participant and the percentage of successful trials was computed. Statistical significance of changes was tested by a two-way ANOVA with the within-subject factor BLOCK (8 levels) and the between subject factor GROUP (levels: CF and SF). Post hoc tests were done by *t*-tests. To study the possible changes in the inter-hemispheric functional coupling due to differential head movements, we performed a statistical analysis of the three fiducial positions for upregulation and downregulation using a paired *t*-test for the neurofeedback session (Left, Right preauricular points and nasion).

To verify that the inter-hemispheric sensor-level coherence used in the neurofeedback trainings was a good estimate of the source level functional coupling between left and right primary motor cortices, DICS [Gross et al., 2001] was used to localize cortical sources that showed coherent activity to the SLMA of both hemispheres. Due to volume conduction, we expected strong coupling between the activity of *ipsilateral* motor cortex and the SLMA recorded from the corresponding hemisphere independently of whether individuals managed to modulate inter-hemispheric coupling. Unilateral motor cortex activity and the corresponding ipsilateral SLMA are expected to reflect identical activities either on the source or sensor level respectively. However, functional coupling between unilateral motor cortex activity on one hemisphere and *contralateral* SLMA should reflect inter-hemispheric functional coupling. Thus, we expect increased functional coupling between motor cortex activity and contralateral SLMA for trials in which $S^{+}$ was requested and which were classified as hit $C^{S^{+}}_{\text{successful}}$. Vice versa, we expected lower inter-hemispheric functional coupling for trials in which $S^{+}$ was

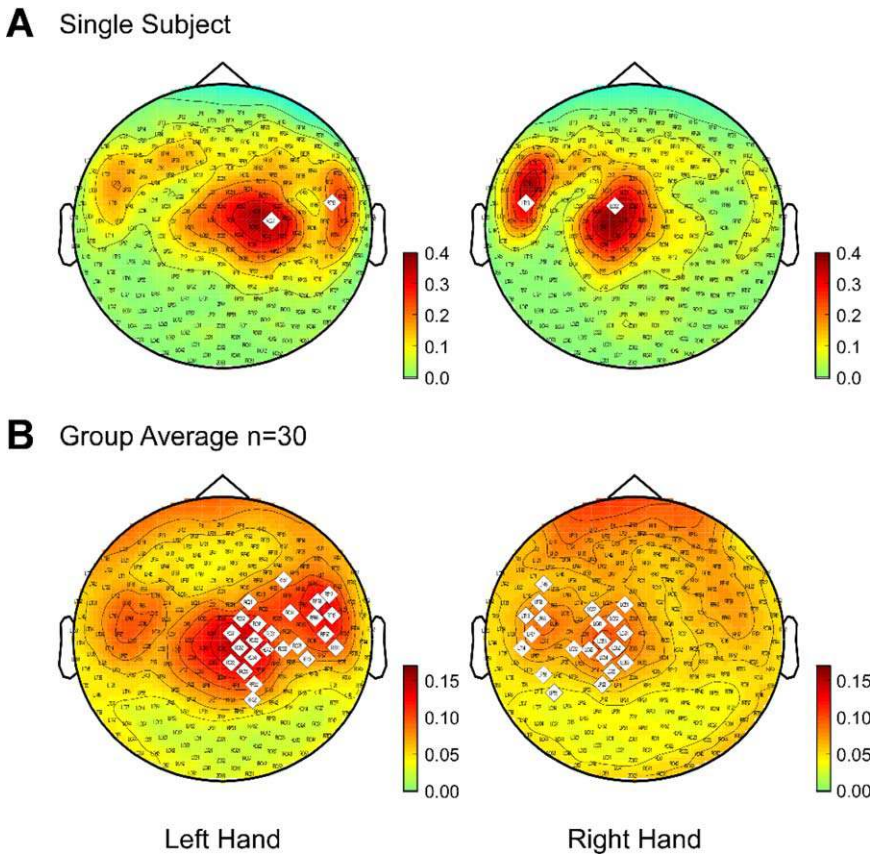


**Figure 2.**

Functional localizer for the identification of MEG channels to be used in the neurofeedback training. (**A**) Data from a representative participant; $R^2$-plots of SMR computed on data between hand closing and opening vs. rest (left panel presents results for the left hand; right panel presents results from the right hand). Patches of increased $R^2$-values represent maximal desynchronization and correspond to a dipolar source pattern. These sources are located approximately in the center of the hemisphere contralateral to the side of hand movement. Two channels were selected from each hemisphere from which functional coupling between left and right motor-related sensors was computed (see text). (**B**) Grand average $R^2$-plots of SMR for all participants of the CF group and for the SF group combined.

requested, yet not achieved according to the online feedback algorithm. Thus, subtracting the functional coupling obtained for miss (unsuccessful) trials in the $S^+$ condition from the corresponding hit trials $C^{S^+}_{\text{successful}} - C^{S^+}_{\text{unsuccessful}}$ should cancel the coherent activity due to volume conduction and the local spread of activity on the hemisphere ipsilateral to SLMA and reveal source level inter-hemispheric functional coupling between SLMA and the motor cortex activity contralateral to it. Similarly, subtracting functional coupling between SLMA and the source activity for trials classified as misses in the $S^-$ condition from hit trials $C^{S^-}_{\text{successful}} - C^{S^-}_{\text{unsuccessful}}$ should yield lowest coupling values for the motor cortex contralateral to SLMA. As can be seen in the example presented in Figure 6: the double difference $(C^{S^+}_{\text{successful}} - C^{S^+}_{\text{unsuccessful}}) - (C^{S^-}_{\text{successful}} - C^{S^-}_{\text{unsuccessful}})$ of the functional coupling values reveals a pronounced patch of functional coupling between SLMA and source level activity in contralateral primary motor cortex. These results support the notion that left and right SLMA capture functional coupling to the right and left motor cortices, respectively.

### Analysis of Pre-Test and Post-Test Data

To infer behavioral effects of the neurofeedback training on the AOBFT task, we compared the tapping frequency between the $S^+$ and $S^-$ trials, corresponding to upregulation and downregulation trials for pre- and post-test. Tapping frequency $v$ was defined as the inverse of the average time interval between any two-subsequent finger-taps. In case of an error in the tapping sequence, taps with erroneous sequence were discarded from the analysis until the correct sequence was reproduced again. Tapping intervals

smaller than 0.1 s and longer than 2.0 s were removed prior to averaging. To reduce the inter-subject variability of finger-tapping frequency values in the AOBFT, absolute ratios $r_{pre}$ and $r_{post}$ of finger-tapping frequency for $S^+$ to $S^-$ trials were computed for pre- and post-test: $r_{pre}=\frac{v^{S^+}_{pre}}{v^{S^-}_{pre}}$ and $r_{post}=\frac{v^{S^+}_{post}}{v^{S^-}_{post}}$, respectively. Since, $S^+$ and $S^-$ do not have any functional relevance in the pre-test session, tapping frequencies are supposed to be similar for both conditions and thus $r_{pre}$ should approximate 1. In the post-test session, however, $r_{post}$ will only approach to 1 if the training has not affected the $S^+$ and the $S^-$ conditions differentially. $r_{post}>1$ reflects a differential effect of the training on tapping speed, with higher speed for $S^+$ than for $S^-$. In contrast, $r_{post}<1$ reflects higher tapping speed in $S^-$ than in $S^+$. To summarize the training effects on motor performance, the Motor Performance Index (MPI) was calculated as the ratio between $r_{post}$ and $r_{pre}$:MPI$=\frac{r_{post}}{r_{pre}}$. If MPI does not deviate significantly from 1, motor performance is assumed not to be affected by the feedback training. MPI $>1$ suggests a differential effect of the training on $S^+$ and $S^-$ trials with higher tapping speed for $S^+$ than for $S^-$ trials. In contrast, MPI $<1$ reflects a higher tapping speed for $S^-$ than for $S^+$ trials.

To quantify training-induced changes in inter-hemispheric functional coupling in the post-test session as compared to the pre-test session, a functional connectivity index (FCI) was defined in analogy to MPI. First, the mean functional couplings $\gamma^{S^+}_{left}$, $\gamma^{S^+}_{right}$, $\gamma^{S^-}_{left}$, and $\gamma^{S^-}_{right}$ were calculated for left and right reference sensors across $S^+$ and $S^-$ trials. Then, ratios for left and right reference sensors were averaged yielding $c_{pre}=\frac{1}{2}\left(\frac{\gamma^{S^+}_{left,pre}}{\gamma^{S^-}_{left,pre}}+\frac{\gamma^{S^+}_{right,pre}}{\gamma^{S^-}_{right,pre}}\right)$ and $c_{post}=\frac{1}{2}\left(\frac{\gamma^{S^+}_{left,post}}{\gamma^{S^-}_{left,post}}+\frac{\gamma^{S^+}_{right,post}}{\gamma^{S^-}_{right,post}}\right)$. In a final step, FCI was calculated as FCI$=\frac{c_{post}}{c_{pre}}$.

A two-way ANOVA with the within factor session (levels: pre-test and post-test) and the between factor group (levels: CF and SF) was computed to test the group-specific effects of the neurofeedback training on behavior. Unpaired *t*-tests tested whether MPI and FCI differed significantly between the CF and SF group. To determine whether MPI and FCI differed significantly from one in the CF or the SF group or in both groups, one-sample *t*-tests were performed. To investigate the relation between changes in inter-hemispheric functional coupling and changes in motor performance, MPI and FCI were correlated across all 30 participants.

## RESULTS

### Functional Localizer: Selection of Channels

The functional localizer session identified the MEG sensors over bilateral primary motor cortices induced by event-related desynchronization (ERD) in SMR by hand opening and closing compared to rest in each participant (Figs. 2 and 3). For each participant, two channels (one for each pole of the bipolar pattern) were selected from each hemisphere for subsequent use in the neurofeedback training. Since the two poles of one hemisphere have opposite polarity, their difference was taken as a proxy for the activity of the underlying motor cortex activity of the corresponding hemisphere (SLMA). $R^2$-values (signifying the amplitude variance of SMR for hand opening and closing versus rest) for the selected sensors reached significance in all participants ($R^2>0.0487$, $t$ (98) $=2.24$, $P=0.027$ after Bonferroni-Holm's correction for multiple comparisons [Holm, 1979]), indicating that SMLA differentiates significantly between hand movements and rest.

### Parameter Selection for Neurofeedback Training

To determine the individual frequencies for training of coherence, out of the five motor tasks, functional coupling differences were computed for all pairs of tasks for each participant (Fig. 4). Frequency was selected for the range of 0 to 30 Hz. Coherence was computed at the previously identified sensors. Across participants, the frequencies exhibiting the largest functional coupling differences ranged from 5 to 23 Hz [Andres et al., 1999; Daly et al., 2012; Pfurtscheller, 1992; Pfurtscheller and Aranibar, 1979; Pfurtscheller and Da Silva, 1999; Stančák et al., 2002; Zito et al., 2014] (CF group: $M \pm SE$: 13.5 ± 6.8 Hz; SF group: $M \pm SE$: 17.1 ± 9.4 Hz).

#### *Neurofeedback training*

In this analysis, the hit rate was assessed as a measure of successful training. Analysis of block-by-block performance involving the factors GROUP (levels: CF and SF) BLOCKS (levels: block 1 to 8) revealed a significant difference in the number of hits for both $S^+$ and $S^-$ between the CF and the SF groups ($F$ (1, 28) $=17.56$, $P=0.0003$) (Fig. 5). A significant main effect of BLOCKS ($F$ (7, 196) $=3.44$, $P=0.0017$) and a significant interaction between factors GROUP × BLOCKS were also found ($F$ (7, 196) $=8.56$, $P<0.001$). Separate posthoc analysis within groups revealed a significant effect of BLOCKS for the CF group: $F$ (7, 98) $=13.36$, $P<0.0001$), but not for the SF group ($F$ (7, 98) $=1.41$, $P>0.2$). The significant effect of BLOCKS in the CF group became evident as a significant positive correlation between block number and hit rate ($r=0.96$, significance for the correlation being larger than zero: $t(6)=8.17$, unidirectional $P<0.0001$). As revealed by pairwise posthoc *t*-tests the success-rate significantly differed from chance level (50%) from the third block onwards in the CF group, ($P$-values $=P_i$, where $i=$ block number from one to eight: $P_1=0.46$, $P_2=0.12$, $P_3=0.01$, $P_4=0.02$, $P_5=0.003$, $P_{6–8}<0.001$). Success rate peaked in the eighth with a hit rate of 74.7 ± 2.4% (M ± SE). No significant correlation between block numbers and the number of successful trials was obtained for SF ($r=-0.55$, $t$ (6) $=1.62$, $P<0.078$)

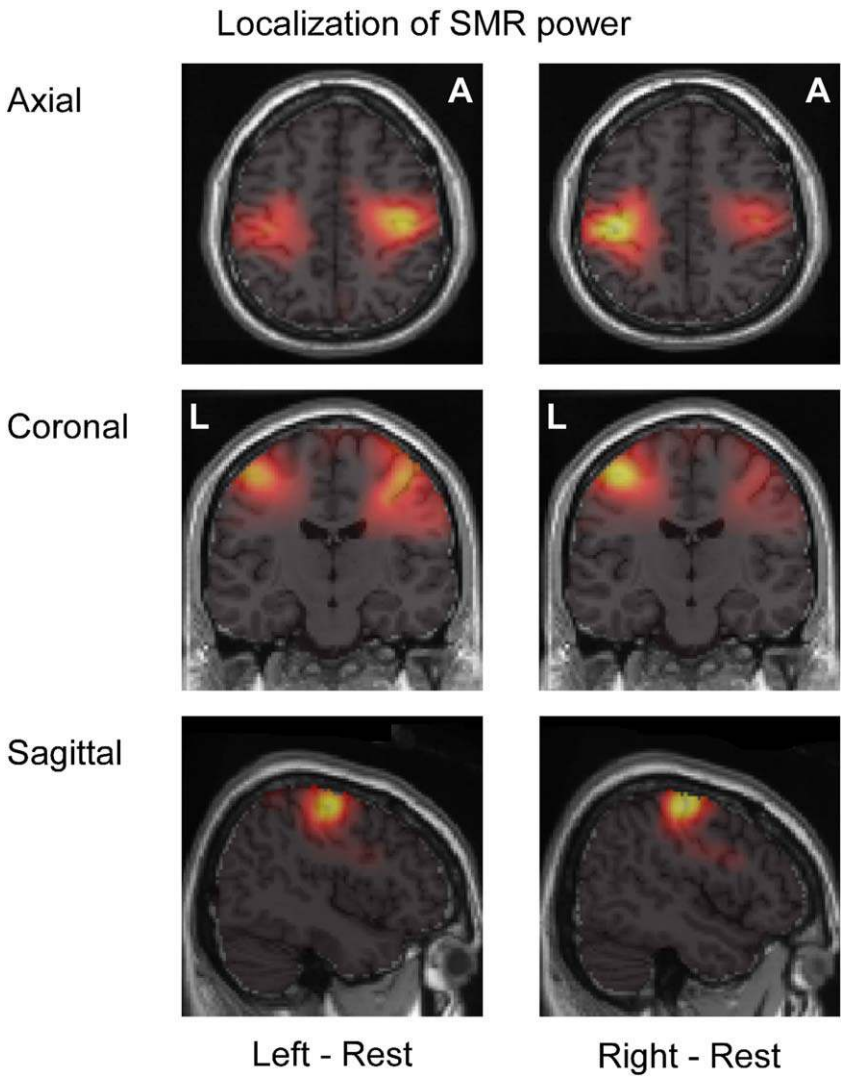


**Figure 3.**

Source localization of the MEG signals acquired during the functional localizer session. Source localization results are depicted for a representative participant. The left column presents source localization of Event-Related Desynchronization (ERD) of SMR, that is, the power difference between hand movement (opening and closing) versus rest and right hand was at relaxing. In general, ERD for overt, voluntary movements or motor imagery result in a decrease of SMR power over pre-motor, motor and supplementary motor cortices. ERD is more pronounced contralateral to the involved hand [Pfurtscheller and Aranibar, 1979; Pfurtscheller et al., 1979]. The right column presents sources of ERD results for the right hand. Non-overlapping windows of 0.208 s duration were used for sensor and source level analysis. Highest ERD were found for point (MNI-coordinates: −33, −19, 52) for left M1 and point (MNI-coordinates: 36, −18, 52) for right M1.

indicating that across all blocks the success rate did not deviate from the chance level in the SF group.

Since coherence values are limited between 0 and 1 and might have a skewed frequency distribution, a Kolmogorov-Smirnov test for testing normality of the sample was performed prior to the ANOVA of the coherence values. For all cells of the ANOVA, the error probability for significantly deviating from a normal distribution did not become significant ($F(1,28)$, CF ($P < 0.15$) and SF ($P < 0.55$)) and thus a parametrical analysis using ANOVA is justified.

To examine how the CF training group differed from the SF group, a three-way ANOVA of functional coupling between left and right SLMA at the training frequency with between factors GROUP (levels: CF and SF) and the within factors CONDITION (levels: $S^+$ and $S^-$) and PERFORMANCE (levels: hit and miss) was performed. No

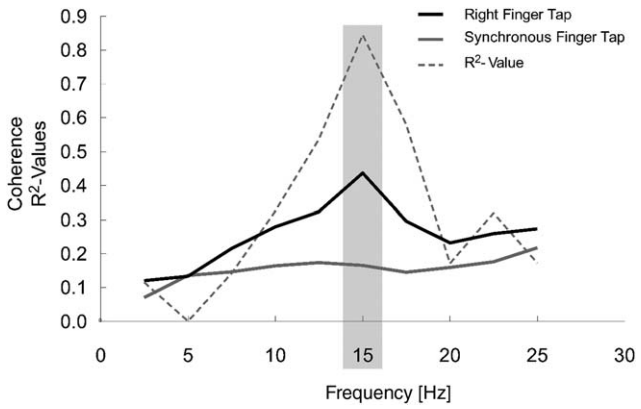


**Figure 4.**

Identification of participant-specific feedback frequency. Depicted is the functional coupling for right finger-tapping (black line) and symmetric finger-tapping (gray solid line) which yielded the strongest coupling differences for this participant in the functional localizer session. Right finger-tapping and symmetric finger-tapping were two out of five motor tasks for which the maximum functional coupling difference was searched for. Frequency-specific $R^2$–values of functional coupling are plotted. The selection of the frequency bin to be used in both, the neurofeedback training and the pre- and post-test was based on such individual plots. In this participant 15 Hz (shaded gray area) was selected as neurofeedback training frequency.

main effect for GROUP was found $F(1,28)=2{,}534$, $P = 0.1227$. Results revealed a main effect CONDITION ($F(1, 28) = 17.05$, $P = 0.0003$). Functional coupling was significantly higher for $S^+$ (M ± SE: 0.195 ± 0.016) than for $S^-$ (0.168 ± 0.014). In addition, there was a significant interaction between GROUP x CONDITION x PERFORMANCE, $F(1, 28) = 11.814$, $P = 0.0019$). A post hoc pairwise *t*-test revealed that functional coupling differed significantly between $S^+$ and $S^-$ for hit trials in the CF group ($t(14) = 7.7$, $P < 0.001$; M ± SE for $S^+$: 0.265 ± 0.037, and $S^-$: 0.178 ± 0.033), but not for the SF group ($t(14) = 1.13$, $P > 0.10$; M ± SE for $S^+$: 0.158 ± 0.021, and $S^-$: 0.145 ± 0.018). The results further indicate that the main effect of CONDITION was due to the large difference of functional coupling between $S^+$ and $S^-$ found in the CF group. For missed trials, no significant difference in functional coupling between $S^+$ and $S^-$ was found, neither for the CF group ($t(14) = 0.11$, $P = 0.91$) nor for the SF group ($t(14) = 0.56$, $P > 0.10$) (Fig. 7). Additionally, as revealed by a post hoc ANOVA involving the factors GROUP (levels: CF and SF) and CONDITION (levels: $S^+$ and $S^-$) for missed trials, there was neither a significant group difference ($F(1,28)=1.92$, $P = 0.1768$) nor a significant effect of CONDITION ($F(1, 28) = 0.22$, $P = 0.644$), nor any interaction GROUP x CONDITION ($F(1, 28) = 0.094$, $P = 0.761$). A post hoc test between Successful $S^-$ and the mean between Unsuccessful $S^-$ and $S^+$ for the CF group yielded a significant difference $F(1,14)=7.821$, $P = 0.0143$ (Successful $S^-$: (M ± SE 0.178 ± 0.033); Unsuccessful $S^+$ and $S^-$: (M ± SE: 0.205 ± 0.034).

To verify that the modulation of inter-hemispheric functional coupling is not due to the condition-specific head movements, head positions of all three fiducials were compared between upregulation and downregulation conditions. However, none of the three fiducial positions revealed a significant change in position during the neurofeedback session for upregulation and downregulation as revealed by paired *t*-tests (left, right preauricular points and nasion) (Left: $P = 0.17$, $t(8) = 1.47$, Right: $P = 0.35$, $t(8) = -0.97$, Nasion: $P = 0.38$, $t(8) = -0.92$).

To rule out, that the volitional modulation of the inter-hemispheric functional coupling can simply be explained by changes in the signal power, we correlated the power difference between upregulation ($S^+$) and downregulation ($S^-$) for successful and unsuccessful trials with changes of functional coupling. Spearman rank correlation was calculated across the CF and SF groups of participants. No significant correlation was found ($r = 0.22$; $t(28) = 1.19$, $P = 0.243$) suggesting no significant contribution of changes in power to the modulation of functional coupling.

## Pre- and Post-Feedback Training Behavioral Tests

To infer the effects of functional coupling neurofeedback training on behavioral performance, changes of tapping frequency between the pre-test and the post-test session were studied. As evidenced by a significant interaction between the factors GROUP and SESSION for the ratio of tapping speed $r = \frac{v^{S^+}}{v^{S^-}}$ during $S^+$- and $S^-$ -condition ($F(1,28) = 9.14$, $P = 0.005$), tapping speed differed between pre- and post-test only for the CF ($t(14)=3.41$, $P = 0.0042$; M ± SE: $r_{pre} = 100.4 \pm 0.4\%$, $r_{post} = 91.4 \pm 2.3\%$), but not for the SF (M ± SE: $r_{pre} = 99.8 \pm 0.5\%$, M ± SE: $r_{post} = 98.9 \pm 0.4\%$) group. Significant main effects GROUP ($F(1,28) = 9.58$, $P = 0.0044$) and SESSION ($F(1,28) = 13.33$, $P = 0.0011$) were not further interpreted because they were driven by the significant interaction as could be shown by posthoc tests. The

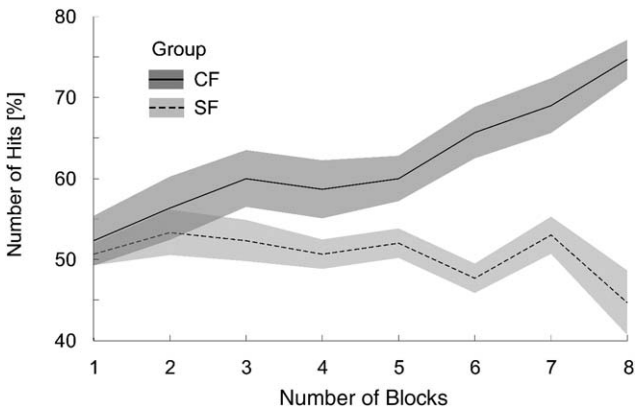


**Figure 5.**

Neurofeedback performance across blocks of the training for CF and SF groups. The gray shaded areas indicate standard errors of the mean.

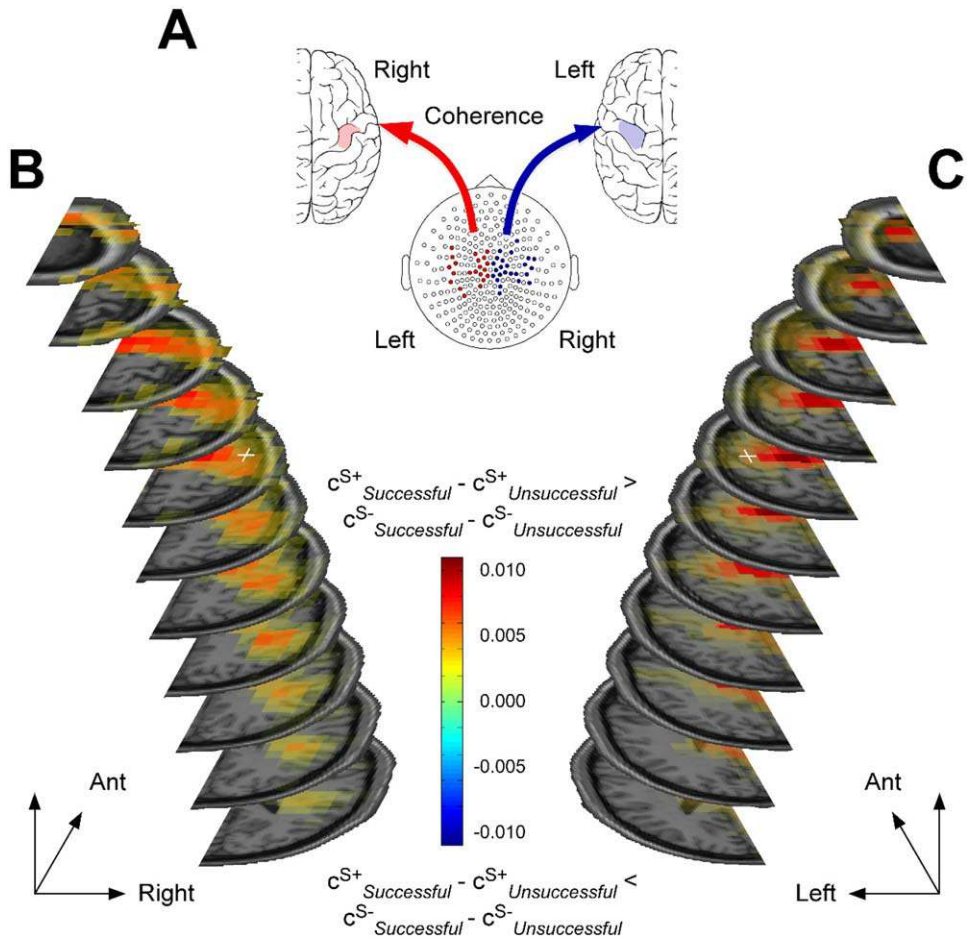


**Figure 6.**

(**A**) SLMA exhibits increased functional coupling between reference channels of the left (red) or right side (blue) of the head and the contralateral motor-related cortices (indicated in red and blue respectively on the sketch) during $S^+$ and reduced functional coupling during $S^-$. A template MNI brain with a resolution of 8 mm was used for source analysis. (**B** and **C**) The highest functional coupling values were found for point (–33, −19, 52) for left M1 and point (36, −18, 52) for right M1. The double difference $(c^{S^+}_{successful} - c^{S^+}_{unsuccessful}) - (c^{S^-}_{successful} - c^{S^-}_{unsuccessful})$ for the functional coupling between SLMA and the cortical source activity for $S^+$ and $S^-$ and for hit and miss trials are presented here for a single participant (functional coupling differences are color coded). For this participant, functional coupling was calculated at the individual training frequency of 13.5 Hz. (B) Specifically, showing the functional coupling pattern in right hemisphere with the reference channel in the left hemisphere and (C) showing the functional coupling pattern in the left hemisphere with the reference channel in the right hemisphere.

tapping speed ratio neither differed significantly for the pretest session between groups ($t_{unpaired}(28)=0.973$, $P = 0.339$) nor for the SF group between sessions ($t_{paired}(14)=1.488$, $P = 0.159$) (Fig. 8A). Results indicate that the CF induced a slowing down of tapping speed for the $S^+$ conditions with respect to the $S^-$ condition. MPI varied accordingly with a significantly lower MPI was found for CF (M ± SE: 91.2 ± 2.6%) than for SF (M ± SE: 99.2 ± 0.6; $t(28) = -3.024$, $P = 0.0053$) (Fig. 8B).

The unpaired *t*-test comparing FCI between CF and SF yielded a significant group difference ($t(1,28) = 2.1280$, $P < 0.0422$)). Post hoc analysis one-sample *t*-test comparing FCI for the CF and SF group to a value of one showed a significant effect only for the CF group ($t(1,14) = 2.155$, $P < 0.0491$, M ± SE 115.2 ± 7.00), but not for the SF group ($t(1,14) = -0.447$, $P = 0.6619$, M ± SE 98.4 ± 3.5))(Fig. 8C). Results indicate that the ratio of inter-hemispheric coupling between $S^+$ and $S^-$ trials increased due to the neurofeedback training.

To study relate effects of neurofeedback training to motor performance, we correlated the percentage change in functional coupling and tapping frequency from pre-

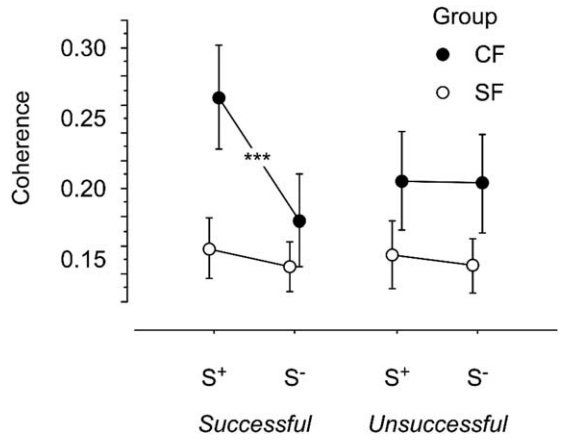


**Figure 7.**

Mean inter-hemispheric magnitude squared coherence across feedback sessions. The coherence is calculated between left and right SLMA for both, the CF and the SF group and successful and unsuccessful trials (*** indicates $P < 0.001$). Error bars represent the standard error of the mean.

test to post-test for both groups (Fig. 9). The presence of a significant negative Spearman rank correlation ($r = -0.389$, $t(28) = 2{,}234$, $P = 0.033$) indicated that an increase in the inter-hemispheric functional coupling was associated with a decrease in finger-tapping frequency.

## DISCUSSION

In the present study, we demonstrate that the acquired modulation of inter-hemispheric functional coupling is associated with significant modifications in motor performance. Our results show that effects are stable, outlast the neurofeedback training and generalize to motor tasks. Modulating the strength of inter-hemispheric functional coupling as the independent variable and assessing its effects on motor performance complements previous approaches in which the inter-hemispheric functional coupling was studied as a function of different motor tasks. The relative decrease in tapping speed as a consequence of the learned increase of functional coupling points toward a causal role of functional coupling for the control of bimanual coordination.

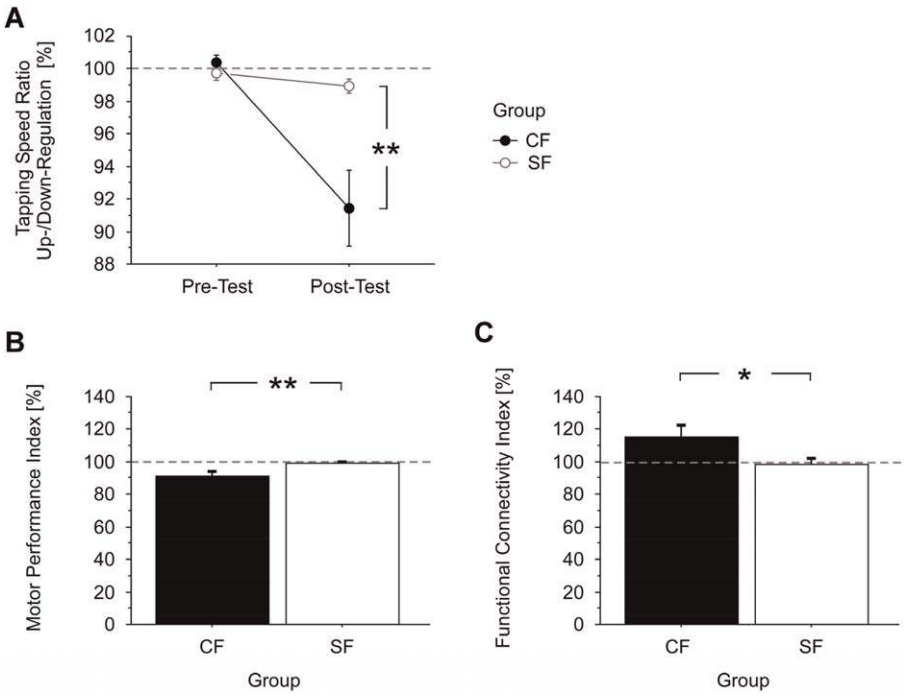


**Figure 8.**

(**A**) Relative tapping speed in pre- and post-test for both, the CF and the SF group. To remove interindividual variations the ration of tapping speed $r = \frac{v_{S^+}}{v_{S^-}}$ is depicted. (**B**) The MPI represents the ratio of finger-tapping speed for $S^+$ and $S^-$ trials in the post session as referenced to the pre-test session for both, the CF (black filled bar) and the SF group (white filled bar). The MPIs differs significantly between the CF and the SF group (double black asterisks, $P < 0.01$). Error bars indicate the standard error of the mean across participants. (**C**) The FCI represents the ratio of coherence for $S^+$ and $S^-$ trials in the post session relatively to the ratio in the pre-test session. A significant difference was found for trials for the CF (black filled bar) and SF group (white filled bar). The FCIs for the post sessions differ significantly between the CF and the SF group (black asterisk, $P < 0.05$). Error bars indicate the standard error of the mean across participants.

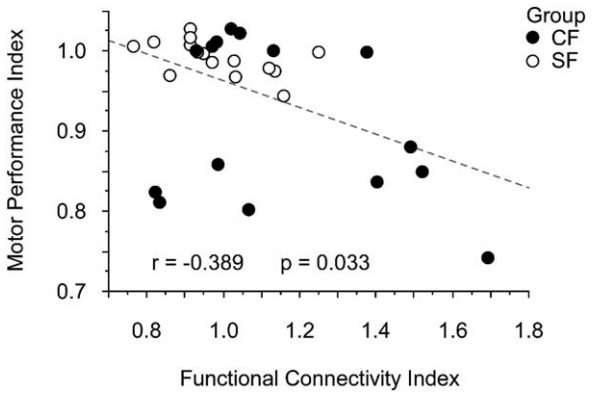


**Figure 9.**
Correlation between the MPI and functional coupling index at the individually trained tapping frequencies. Black dots represent CF participants, white dots SF participants. The regression line is plotted as dashed line.

Prior to speculating about the implications of our results on the organization of bimanual motor control, we will discuss possible confounding variables that might affect the interpretation of our results. The interpretation of our results with respect to bimanual motor control will consider previous research in humans and animals. The discussion will finish with an outlook suggesting future research strategies and potential applications.

## Potential Confounding Variables

### *Effects of signal power on coherence*

Squared magnitude coherence is a measure of functional coupling that depends on both, phase synchronization and amplitude correlation across time. It has been suggested that functional coupling not only reflects phase synchronization but also signal amplitude [Pikovsky et al., 1997]. Thus, it might be objected that the acquired control of inter-hemispheric functional coupling presumably reflects changes in signal amplitude rather than phase synchronization. However, in our study, the analysis of power changes for $S^+$ and $S^-$ confirmed that the modulation of functional coupling cannot be explained by changes of SMR power and therefore the interpretation about the modulation of inter-hemispheric coupling as alterations of functional coupling appear to be justified.

### *Sensor level spreading of magnetic brain activity*

The analysis of sensor level functional coupling in neuromagnetic imaging suffers from the problem of local brain activity spreading to surrounding sensors and thus generating coherent activity among them which might be erroneously interpreted as interregional functional coupling. To tackle this confounding variable, it is often suggested to use imaginary coherence that suppresses those proportion of both signals that are in phase or phase shifted by multiples of pi [Nolte et al., 2004]. However, in reciprocal symmetric connections as between left and right motor cortices, a phase difference with multiples of pi is very probable [Fries, 2005, 2015]. Using imaginary coherence, existing functional coupling might be missed and appears therefore not to be a suitable approach. Considering the difference of functional coupling between unsuccessful and successful trials and between upregulation and downregulation suppressed at least effects of apparent functional coupling due to spreading of neuromagnetic activity that is unrelated to upregulation and downregulation of functional connectivity.

### *Motor activity*

Although we demonstrate the effects of the modulating inter-hemispheric functional coupling on motor performance, it might be objected that the modulation of inter-hemispheric functional coupling between left and right motor cortices is mediated by covert movements and differential muscle activations rather than by brain control. For example, it could be argued that participants might have learned to systematically move their heads with respect to the spatially fixed magnetic field sensors to modulate the measured neuro-magnetic coupling depending on the $S^D$. However, analyzing the absolute individual head positions and its variation over time, tracked with millimeter precision during the MEG recording, no differentially significant head movements for $S^+$ and $S^-$ could be detected. Furthermore, video supervision of participants did not reveal any systematic gross body movements. Thus, we can exclude any direct effects of small head and gross body movements as a mediator for the modulation of inter-hemispheric functional coupling. However, task-related changes in muscle tension at any part of the body and even the execution of small movements with any limb can still be a source of modulation of the inter-hemispheric functional coupling. To control this type of confounding variable, measuring myoelectric activity is often suggested. However, even with careful recordings of many EMG electrode positions, differential myoelectric activity at different body parts, muscles and at different levels of the spinal and peripheral motor system during $S^+$ and $S^-$ cannot be excluded. Only curarization or complete paralysis allows the control of subtle differential myoelectric modulations. This problem of "motor mediation" was extensively investigated in biofeedback experiments with curarized animals [Dworkin and Miller, 1977] and in paralyzed humans' neurofeedback studies [Birbaumer et al., 2013; Chaudhary et al., 2016, 2017] without conclusive results.

Even if in the present experiment differential movement-mediated modulation of inter-hemispheric functional coupling cannot be fully excluded, our results documenting a causal relationship between changes in inter-hemispheric functional coupling and motor performance are intriguing and provide strong insight into the cortical control of bimanual coordination.

## Coherence in the Motor System and Bimanual Movements

The negative correlation between the strength of inter-hemispheric functional coupling and tapping speed in an AOBFT that has been found in our study complements previous work in which motor tasks have been varied and functional coupling was studied as a dependent variable. In the study by Gross et al. (2005), decreased inter-hemispheric functional coupling between primary motor cortices was shown for anti-phase bimanual movements against in-phase bimanual movements. While van Wijk et al. [2012] reported stable inter-hemispheric alpha- and beta-band coupling for iso-frequency bimanual finger-tapping, [Houweling et al., 2010a] demonstrated a reduction of functional coupling for polyrhythmic bimanual finger-tapping, that requires a more independent control of the fingers of both hands. Cardoso de Oliveira et al. [2001] measured inter-hemispheric functional coupling using single-unit recordings in awake monkey. They found that coupling is significantly decreased for out-of-phase asymmetric bimanual movements as compared to symmetric movements of both hands. In other words, as in our study, decreased inter-hemispheric functional coupling seems to be the generally preferred mode of operation in bimanual movements, in which movements of both hands are independent. On the contrary, increased functional coupling proved to be detrimental to motor performance in AOBFT, but seemed to be the preferred mode for symmetric movements in the cited studies. In conclusion, results of the different studies suggest that decreased inter-hemispheric functional coupling is beneficial for AOBFTs, while increased coupling is advantageous in symmetric finger-tapping tasks. Given the ample evidence that our motor system facilitates symmetric bimanual movements [Houweling et al., 2010a; Swinnen, 2002; van Wijk et al., 2012], one may conclude that higher inter-hemispheric functional coupling is the "default mode," and its downregulation is required for unimanual movements, and movements requiring independent control of both hands. In the framework of the GMP and the inter-manual crosstalk model, one might conclude that in AOBFT primary motor cortex of each hemisphere controls the contralateral hand independently, yet according to a general motor plan. In contrast, in symmetric in-phase finger-tapping both primary motor regions are closely linked to coordinate movement execution via oscillatory activity. According to this view both models of bimanual coordination are not exclusive, and motor control might be best explained by a task-dependent activation of either processing mode.

Studies investigating the inter-hemispheric functional coupling highlight the importance of corpus callosum, which is the most dominant inter-hemispheric connection of the brain, for the coordination of activities of bimanual upper limb movements [Gerloff and Andres, 2002]. The involvement of corpus callosum in bimanual coordination has been corroborated by various studies of split-brain patients whose direct inter-hemispheric connections had been cut for medical reasons and thus abolishing inter-hemispheric functional coupling completely. Cutting the corpus callosum can be regarded as a quasi-elimination of inter-hemispheric coupling. Studies investigating split brain patients in an out-of-phase bimanual finger-tapping task revealed that patients performed better than healthy individuals [Eliassen et al., 1999], yet exhibit problems in producing symmetric bimanual movements [Geffen et al., 1994; Preilowski, 1975; Swinnen and Wenderoth, 2004]. These findings in patients suggest that functional coupling is less important in out-of-phase bilateral movements [Eliassen et al., 1999; Franz et al., 2000; Preilowski, 1972, 1975; Stephan et al., 1999].

Work in non-human primates has documented widespread functional coupling associated with periodic oscillatory activity in sensorimotor cortex [Baker et al., 1999a, 1999b; Donoghue et al., 1998; Engelhard et al., 2013; Murthy and Fetz, 1996b], including inter-hemispheric functional coupling [Murthy and Fetz, 1996a]. In the context of motor control, synchronization and crosstalk at different sites along the neural axis constitutes an important signatures for the execution of macroscopic movement [Baker et al., 1999b; Houweling et al., 2010b]. With regard to bimanual coordination, left and right motor cortices showed stronger functional coupling in the beta frequency range depending on whether monkeys performed bimanual or unimanual manipulations [Murthy and Fetz, 1996b]. Although the synchrony appeared under different experimental circumstances in these studies, a common explanation is that the modulation of the inter-hemispheric functional coupling can be modulated in a top-down fashion via operant conditioning [Fetz, 2013]. Human studies also reported stable inter-hemispheric alpha- and beta-band coupling for iso-frequency bimanual finger-tapping

With the current study, using modulation of inter-hemispheric functional coupling in conjunction with an asynchronous out-of-phase finger-tapping task for pre- and post-tests, we provided the basis for future studies investigating the role of inter-hemispheric functional coupling on bimanual motor performance. Further experiments investigating the impact of the modulation of inter-hemispheric functional coupling on different types of motor tasks in the pre- and post-test sessions will verify our interpretations of the role of inter-hemispheric coupling for bimanual coordination. In particular, studies investigating effects of upregulation and downregulation of functional coupling on in-phase, out-of-phase bimanual movements, as well as on synchronous and asynchronous finger-tapping are suggested.

## Perspectives of Neurofeedback of Functional Coupling

Our results demonstrate that the learned modulation of functional coupling by means of rt-MEG neurofeedback is feasible, and is the first step toward the development tools for the better understanding of the role of functional coupling in sensory and motor processes. Further research

might consider volitional modulation of inter-hemispheric functional coupling as an approach to investigate the reorganization of the brain [Fetz, 2013]. We also see a strong potential of the presented method for the treatment of diseased brains with impaired neuronal communication. However, even though volitional modulation of functional coupling was achieved in our study after a very short training of less than an hour, follow-up studies are needed that document the long-term persistence of the trained effects that is essentially needed in clinical applications.

The observed behavioral changes following the neurofeedback training of coherence suggest that functional coupling-based neurofeedback [Birbaumer et al., 2013] offers a unique opportunity to train coherent or randomly synchronized neural activities that might subsequently impact related cognitive, emotional, and behavioral processing. Despite current theories emphasizing the role of abnormal functional coupling (including long-range functional coupling/synchrony and abnormal BOLD correlations in fMRI) as the neural substrate of a variety of neurological and psychiatric disorders, such as, schizophrenia [Ruiz et al., 2013a, 2013b], epilepsy [Elshahabi et al., 2015], and Alzheimer's dementia [D'Amelio and Rossini, 2012; De Lacoste and White, 1993], only few studies have attempted to train individuals to directly modulate neural functional coupling using neurofeedback [Daly et al., 2012; Kajal et al., 2015; Koush et al., 2013; Ruiz et al., 2013b; Shibata et al., 2011]. Concluding, future studies on the modulation of functional coupling by neurofeedback should address the impact of functional coupling on different brain functions for the development of innovative non-invasive strategies, both to study normal brain function, and to examine and modify neurological and psychiatric disorders.

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