Oscillatory entrainment of the motor cortical network during motor imagery is modulated by the feedback modality

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A B S T R A C T

Neurofeedback of self-regulated brain activity in circumscribed cortical regions is used as a novel strategy to facilitate functional restoration following stroke. Basic knowledge about its impact on motor system oscillations and functional connectivity is however scarce. Specifically, a direct comparison between different feedback modalities and their neural signatures is missing.

We assessed a neurofeedback training intervention of modulating β-activity in circumscribed sensorimotor regions by kinesthetic motor imagery (MI). Right-handed healthy participants received two different feedback modalities contingent to their MI-associated brain activity in a cross-over design: (I) visual feedback with a brain–computer interface (BCI) and (II) proprioceptive feedback with a brain–robot interface (BRI) orthosis attached to the right hand. High-density electroencephalography was used to examine the reactivity of the cortical motor system during the training session of each task by studying both local oscillatory power entrainment and distributed functional connectivity.

Both feedback modalities activated a distributed functional connectivity network of coherent oscillations. A significantly higher skill and lower variability of self-controlled sensorimotor β-band modulation could, however, be achieved in the BRI condition. This gain in controlling regional motor oscillations was accompanied by functional coupling of remote β-band and θ-band activity in bilateral fronto-central regions and left parieto-occipital regions, respectively. The functional coupling of coherent θ-band oscillations correlated moreover with the skill of regional β-modulation thus revealing a motor learning related network.

Our findings indicate that proprioceptive feedback is more suitable than visual feedback to entrain the motor network architecture during the interplay between motor imagery and feedback processing thus resulting in better volitional control of regional brain activity.

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Introduction

The acquisition and learning of motor skills are associated with practice (Doyon and Benali, 2005; Halsband and Lange, 2006). When physical practice is not possible, e.g. in patients with lost motor function following brain damage, motor imagery (MI) might be an effective surrogate for physical practice (Boe et al., 2014; Halsband and Lange, 2006) by activating the sensorimotor system without any overt behavior (Gao et al., 2011; Szameitat et al., 2012). This self-regulation of brain activity during MI can be supported by providing visual or proprioceptive feedback about the current user’s brain state (Boe et al., 2014; Dobkin, 2004; Gomez-Rodriguez et al., 2011) using brain–computer interfaces (BCIs) or brain–robot interfaces (BRIs), respectively (Birbaumer and Cohen, 2007; Fetz, 2007; Wolpaw, 2007). First studies applying these approaches in stroke rehabilitation are promising (Ang et al., 2011, 2014; Buch et al., 2008, 2012; Gomez-Rodriguez et al., 2011; Prasad et al., 2010; Ramos-Murguialday et al., 2013; Shindo et al., 2011).

For the purpose of restoring lost motor functions, both BCI and BRI approaches aim at the modification of neural activity via operant conditioning, e.g. challenging the patient to attain specific brain states that guide activity-dependent neural plasticity and thus might facilitate motor recovery (Bauer and Gharabaghi, 2015a,b; Daly and Wolpaw, 2008). Oscillations in the β-band (15–30 Hz) over the sensorimotor cortex are particularly suited for this approach (Gharabaghi et al., 2014a,b,c) as they are linked to the natural communication between cortex and peripheral muscular activity (Davis et al., 2012; Kilavik et al., 2013; Riddle and Baker, 2005; Witham et al., 2011), and reflect sensorimotor control (Brittain et al., 2014), motor learning (Herrojo-Ruiz et al., 2014; Pollok et al., 2014), corticospinal excitability (Takemi et al., 2013a,b), and the extent of functional impairment after stroke (Rossiter et al., 2014).

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Recent studies showed that providing visual feedback of MI-associated β-oscillations with a BCI increased the laterality at targeted brain regions (Boe et al., 2014) and the movement-associated desynchronization of the targeted β-frequency band (Bai et al., 2014). Proproceptive feedback of MI-associated β-oscillations with a BRI facilitated decoding of MI induced brain states (Gomez-Rodriguez et al., 2011), activated a distributed cortical network (Vukelić et al., 2014), and bridged the gap between the abilities and cortical networks of motor imagery and motor execution (Bauer et al., 2015). A direct comparison of these two feedback modalities and their neural oscillatory signatures, particularly with regard to the skill for regional self-regulation of β-oscillations and the engagement of distributed functional cortical networks, is however still missing.

We therefore assessed sensorimotor β-activity modulation in participants who received two different feedback modalities in a cross-over design: (I) visual feedback with a BCI and (II) proproceptive feedback with a BRI. During each session we examined the MI-related cortical patterns with high-density electroencephalography (EEG) and functional connectivity analysis. We hypothesized that closing the sensorimotor loop with a BRI would be superior to BCI with visual feedback in supporting self-regulation of β-activity and that this improvement would be mediated by a distinct cortical network resembling the natural activation during overt movement.

Material and methods

Subjects

Eleven right-handed healthy volunteers (mean age = 25.83 ± 3.1 years, 4 female), assessed by the Edinburgh Handedness Inventory (Oldfield, 1971), were recruited for this experiment. Participants gave their written informed consent before participation and received monetary compensation. The study protocol was approved by the local ethics committee.

Data acquisition

All participants were comfortably seated upright in a chair. High resolution scalp EEG potentials were recorded (BrainAmp, Brainproducts GmbH, Germany) from 128 positions according to the extended international 10-05 system, with Ag/AgCl electrodes (actiCAP, Brainproducts GmbH, Germany). The left mastoid was used as common reference and EEG was grounded to AFz. All impedances were kept below 20 kΩ.

EEG was recorded using the BrainAmp hardware (BrainAmp, Brainproducts GmbH, Germany). The left mastoid was used as common reference and EEG was grounded to AFz. All impedances were kept below 20 kΩ. The EEG was digitized at 1 kHz, high-pass filtered with a time constant of 10 s, and transmitted to the BCI2000 software (Schalk et al., 2004) for online processing and stored for offline analysis.

Experimental paradigm and classification procedure

Fig. 1 indicates an overview of the time course of the experimental paradigm. Each participant was exposed to two MI-associated neurofeedback training sessions in a cross-over design. The sessions were randomized across participants. Each session consisted of three runs lasting 4 min with each run consisting of sixteen trials. Every trial consisted of a cued task design with different task epochs. Each trial was initiated by a preparatory epoch, lasting for 2 s, followed by a MI epoch, lasting for 6 s, and completed by a rest period lasting for 6 s. During each trial, the regional oscillatory activity of the preceding 500 ms was estimated every 40 ms using an autoregressive model based on the Burg Algorithm with a model order of 32 (McFarland and Wolpaw, 2008). Participants were instructed to perform kinesthetic MI (Neuper et al., 2005) of right-hand opening, thus resulting in event-related desynchronization of β-oscillations (β-ERD) over contralateral sensorimotor electrodes (FC3, C3, and CP3) which were used for online classification. We applied an adaptive linear classifier to decode the β-ERD during the MI epoch relative to the average power of the rest and preparation phases of the last 15 s (Charabaghi et al., 2014a; Vukelić et al., 2014). Hence, during each session we used 9 features for our linear classification consisting of 2-Hz frequency bins (16–22 Hz) and three electrodes overlying sensorimotor areas contralateral to the movement imagination (FC3, C3, and CP3). When a sufficient predefined (see below) level of positively classified β-ERD (five consecutive 40 ms epochs) was reached participants were rewarded with contingent feedback which was either visual via a BCI (one session, lasting 12 min) or proproceptive via a BRI (one session, lasting 12 min).

To account for different abilities of β-band modulation, prior to the experiment one calibration run was performed, i.e. detecting the strongest individual β-ERD of each participant. This calibration run was done separately for MI + proproceptive feedback and MI + visual feedback. From each calibration run three threshold values were defined representing different difficulty levels, i.e. the 50% (low difficulty), 30% (moderate difficulty), or 10% (high difficulty) of the strongest, subject-specific β-ERD level, respectively. In the following experimental runs, feedback was only provided when subjects reached either 50% (first run), 30% (second run), or 10% (third run) of their strongest β-ERD. Thereby, the difficulty level increased subsequently throughout the session keeping the participants in the deliberate phase of skill acquisition with high demands for volitional brain modulation. Thus, this study addressed the cortical physiology rather during the task than a classical pre/post comparison. During both sessions the participants were instructed to perform no movements to minimize the influence of muscular activity. This was ensured by online monitoring of bilateral forearm muscle activity of the Flexor Carpi Radialis (FCR) and Extensor Carpi Radialis (ECR) muscles, which was further visually inspected offline. Hence, all activities larger than 50 μV were discarded. This was necessary in less than 1% of all trials.

Control of a brain–robot interface (MI + proproceptive feedback)

During the BRI feedback session the finger tips of the subject were attached to a hand orthosis (Amadeo® system, Tyromotion GmbH, Austria). This orthosis provided closed-loop feedback by opening the hand contingent to volitional modulation of regional sensorimotor β-oscillations as described previously (Charabaghi et al., 2014a; Vukelić et al., 2014). Subjects were instructed to watch the robotic hand.
opening. This congruent incorporation of feedback from visual, haptic and proprioceptive modalities has recently been shown to enhance cortically controlled brain–machine applications in non-human primates (Suminski et al., 2010). For simplicity we refer here to this condition as MI + proprioceptive feedback as we consider this as the prominent component. When participants reached a sufficient level of β-ERD (i.e. 200 ms of consistent β-ERD), the robotic hand orthosis extended the fingers of the participants. When the predefined level of β-ERD was not met, the orthosis movement stopped. At the end of the trial, the orthosis returned to the starting position.

Control of a brain–computer interface (MI + visual feedback)

During the MI + visual feedback session the successful classification of MI-associated β-ERD was translated to contingent control of a cursor ball towards a target on a computer screen positioned in front of the participant. Here, the initiation (2 s preparation phase) of the trial started by the presentation of the target (yellow rectangle on the bottom-right edge of the screen). Subsequently, a yellow screen cursor ball appeared at the left edge of the screen (indicating the start of the 6 s MI phase). A sufficient level of MI-associated β-ERD resulted in left-to-right downward movement of the cursor ball towards the target, whereas an insufficient level of β-ERD resulted in upward movement of the cursor ball at a fixed rate. When the cursor ball successfully contacted the target the cursor ball changed colors from yellow to green. The completion of the MI phase was indicated by disappearance of both the target and the cursor ball indicating the rest period (lasting for 6 s).

Data pre-processing

All runs were concatenated, resulting in a data stream of 12 min of EEG data per session and participant. We focused on two temporal windows for the analysis of the functional connectivity networks: rest epoch (6 s, attaining a stable rest phase) and MI epoch (6 s, attaining and maintaining β-ERD). Epochs were rejected when they contained a maximum deviation above 100 μV in any of the EEG channels (Sanei, 2007). The EEG signals were detrended, zero-padded and band-pass filtered between 1 and 42 Hz, for calculation of functional connectivity networks. For calculation of event-related spectral perturbation (ERSP, see below), signals were band-pass filtered between 14 and 24 Hz. The filtering procedures were performed with a first order zero-phase lag FIR filter. We performed an independent component analysis (ICA), using the logistic infomax ICA algorithm as implemented in the EEGLab toolbox (Delorme and Makeig, 2004), and removed further cardiac and eye movement artifacts. This was done by visual inspection of the topography and time course of the ICA components. Finally, the artifact-free EEG data was re-referenced to mathematically linked mastoids (Nunez, 2006).

Estimation of the ability for sensorimotor β-modulation

We analyzed the effect of both feedback modalities during brain self-regulation by calculating two performance measures for different aspects of the ability of sensorimotor β-modulation:

A) Time of true positive β-ERD (i.e. sensitivity) during the motor imagery period: This measure reflected the maximum time each participant was successful with regard to modulating β-power and maintaining the decrease of β-power up to the required β-ERD level of each trial. Hence, this measure indicated how often the classifier detected sufficient self-regulation, when the participant was expected to perform self-regulation of oscillatory brain activity.

B) Individual maximum range of β-modulation: This previously introduced measure (Vukelić et al., 2014) was more neurophysiologically based indicating the potential of each subject to maximally desynchronize/synchronize during the task and thereby reflecting the individual skill to maximally exploit the capacity to modulate sensorimotor brain oscillations during the task. Furthermore, this approach accounted for the inter-individual variability of different spectral β-peaks in the time course of the different task epochs which could affect the dynamics of β-modulation and therefore the estimation of ERSP as discussed in detail elsewhere (Lemm et al., 2009).

The estimation of the β-modulation range entailed an off-line calculation of the ERSP between 16 and 22 Hz with a frequency resolution of 0.24 Hz for each electrode, as implemented in the EEGLab toolbox (Delorme and Makeig, 2004). Since, the online classification consisted of the detection of β-ERD during the MI epoch relative to the average of the rest and preparation epochs we estimated the individual β-modulation range accordingly. Hence, in a next step we averaged over the contralateral sensorimotor electrodes (FC3/C3/CP3) for each frequency bin. Then, the individual frequency bin of the ERSP with the largest difference between the minimum in the MI epoch (describing the maximum desynchronization potential) and the maximum in the rest or preparatory epoch (describing the maximum synchronization potential) was selected. The ERSP was calculated trial-wise (normalized with respect to the rest baseline) for MI + proprioceptive feedback and MI + visual feedback sessions, respectively. In cases where no trials had to be removed due to artifacts, we excluded the first trial in each run to adjust the number of trials in each subject. This resulted in trials 1–15, 16–30, 31–45 for the first, second and third run, respectively. Furthermore, we averaged the ERSP across trials on an individual basis and across the subject’s individual maximum β-modulation range on a group level, resulting in ERSP at individual β-frequency peak differences for MI + proprioceptive feedback and MI + visual feedback sessions (see Fig. 2D).

Estimation of functional motor cortical networks

To calculate functional connectivity we utilized the imaginary part of coherence (iCOH) (Nolte et al., 2004). iCOH is a robust connectivity measure ignoring relations at zero phase lag and is therefore insensitive to volume conduction properties, thus indicating the relative coupling of phases, i.e. the time-lag between two brain processes. Since the original proposed iCOH might exhibit a spatial bias towards long-range synchronizations, we used the corrected version of the iCOH function (ciCOH) as suggested by Ewald et al. (2012). This version shares the same properties as the original iCOH function but includes additional features of compensating for preference for remote interactions. The ciCOH generally results in an increase of SNR, which potentially leads to observations of interactions which are otherwise hidden in the noise when studying connectivity between sensors. Since the ciCOH is based on an estimation of the complex coherency function, each valid epoch was subdivided into segments of 1 s length with 50% overlap, corresponding to a frequency resolution of Δf = 1 Hz (Nolte et al., 2004). Each segment was multiplied with a Hanning window. A Fourier transformation of the data resulted in an estimation of the cross-spectra between two time-series (Nolte et al., 2004). The complex coherency function was defined as the normalized cross-spectrum for channels i and j, respectively:

\[ C_{ij}(f) = \frac{S_{ij}(f)}{\sqrt{S_{ii}(f)S_{jj}(f)}} \]

where \( S_{ij}(\cdot) \) was the cross-spectrum between channels i and j, and \( S_{ii}(\cdot), S_{jj}(\cdot) \) represented the auto-spectra for channels i and j.
respectively. Next, the ciCOH function was calculated from the complex coherency function (Ewald et al., 2012)

\[
\text{ciCOH}_{ij}(f) = \frac{\text{Im}(C_{ij}(f))}{\sqrt{1 - \text{Re}(C_{ij}(f))^2}}
\]

where \(\text{Im}(\cdot)\) and \(\text{Re}(\cdot)\) denote the imaginary and real parts, respectively. The ciCOH was further fisher z-transformed to fit a Gaussian distribution (Nolte et al., 2004; Rosenberg et al., 1989). We evaluated the functional connectivity within predefined frequency bands of interest (FOI): \(\theta\)-band (3–7 Hz), \(\alpha\)-band (8–14 Hz), low \(\beta\)-band (15–25 Hz), and high \(\beta\)-band (26–40 Hz).

In a next step, the functional connectivity measure was obtained by calculating the event-related ciCOH (ER-ciCOH) as the contrast between the MI and rest epoch (Andrew and Pfurtscheller, 1996; Nolte et al., 2004; Notturno et al., 2014):

\[
\text{ER-ciCOH}_{\text{Seed}}(f) = 100 \times \frac{\text{abs}(\text{ciCOH}_{\text{Seed}}(f))_{\text{MI}} - \text{abs}(\text{ciCOH}_{\text{Seed}}(f))_{\text{Rest}}}{\text{abs}(\text{ciCOH}_{\text{Seed}}(f))_{\text{Rest}}}
\]

where \(\text{Seed}\) denotes the seed electrode, \(f\) indicates the FOI, and \(\text{abs}\) indicates the absolute value of ciCOH. The ER-ciCOH provides a measure for functional connectivity between electrode sites, where positive and negative values indicated increased functional connectivity during the MI epoch and the rest epoch, respectively. We thus obtained ER-ciCOH values for each MI + proprioceptive feedback (Proprioceptive) and MI + visual feedback (Visual) session, respectively. All data analysis was performed offline with custom written scripts in MATLAB®.
To analyze the impact of feedback modality on functional connectivity networks the ER-ciCOH was compared between the MI + proprioceptive feedback and MI + visual feedback sessions. Possible spatial differences of oscillatory power of the targeted \( \beta \)-band (ERSP) during the respective task epochs were further compared between the MI + proprioceptive feedback and MI + visual feedback sessions. Furthermore, we compared possible functional connectivity differences (absolute value of ciCOH) between the MI and rest epochs for both the proprioceptive and visual feedback conditions, separately (see Supplementary Fig. S2). We applied a multiple dependent sample t-test (Proprioceptive versus Visual feedback session) on the level of individual electrodes for ER-ciCOH, ERSP during the rest and motor imagery epoch (see below the time intervals of interest), and a multiple dependent sample t-test (MI versus rest period) on the level of individual electrodes for functional connectivity differences. For this purpose, we utilized a cluster-based non-parametric randomization approach which included correction for multiple comparisons as implemented in FieldTrip (Maris et al., 2007; Oostenveld et al., 2011). Here, a dependent sample t-statistic was conducted to establish the topography of functional motor cortical networks in which the ER-ciCOH (for each FOI), and ERSP (\( \beta \)-band) showed significant differences between the Proprioceptive versus Visual feedback session. Furthermore, a dependent sample t-statistic was conducted to establish the topography of functional motor cortical differences between the MI and rest periods for the proprioceptive and visual feedback conditions, separately. Hence, t-values exceeding a priori threshold of \( p < 0.05 \) were spatially clustered based on neighboring electrodes. The cluster level statistics were defined as the sum of t-values within every cluster. The correction of multiple comparisons was realized by calculating the 95th percentile (two tailed) of the maximum values of summed t-values estimated from an empirical reference distribution. t-Values exceeding this threshold were thus considered as significant at \( p < 0.05 \) (corrected). The reference distribution of maximum values was obtained by means of a permutation test (randomly permuting the ER-ciCOH and ERSP across the Proprioceptive and Visual feedback conditions or across MI and rest periods for 1000 times). Thereby we could evaluate the statistics of the actual data.

Furthermore, we analyzed the results with a two by two ANOVA to test the factors “feedback modality” (Proprioceptive versus Visual) and regions of interest (ROI) with regard to their impact on the distribution of the ER-ciCOH values. Accordingly we averaged across EEG electrodes by defining ROIs in the left (L) and right (R) hemispheres, and in medial (M) regions based on different cortical regions (Noturno et al., 2014): fronto-polar cortex (FP, three electrodes nearest to Fp1 and Fp2), fronto-central cortex (FRC, four electrodes nearest to F3–FC3, F4–FC4, and Fz–FCz), central regions (C, two electrodes nearest to C3 and C4), superior parietal cortex (SPC, seven electrodes nearest to P3–P1, P4–P2, and four electrodes nearest to Pz–POz), inferior parietal cortex (IPC, two electrodes nearest to P7 and P8), and occipital regions (five electrodes nearest to O1 and O2).

**Results**

**Ability of modulating sensorimotor \( \beta \)-oscillations**

We analyzed the results with a two by two ANOVA to test the factors (runs and feedback modality) with regard to their impact on the distribution of true positive \( \beta \)-ERS classification time. The two-way ANOVA revealed a main effect for “runs” \( F_{(2,84)} = 907.23, p = 0.0001 \) (Figs. 2A and B) and “feedback modality” \( F_{(1,84)} = 12.14, p < 0.001 \) but not for the interaction between these factors \( F_{(2,84)} = 1.89, p = 0.16 \). Fig. 2C shows the average of the true positive \( \beta \)-ERS classification over trials separately for MI + proprioceptive and MI + visual feedback. The combination of MI with proprioceptive feedback significantly reduced inter-subject variability and resulted in higher true positive \( \beta \)-ERS classification time as compared to visual feedback condition.

A two-way ANOVA for the \( \beta \)-modulation range across runs revealed no main effects for “runs” \( F_{(2,84)} = 0.6, p = 0.54 \) or “feedback modality” \( F_{(1,84)} = 0.56, p = 0.45 \) nor for the interaction between these factors \( F_{(2,84)} = 2.0, p = 0.14 \). The temporal dynamics of individual \( \beta \)-frequency peak differences showed a striking difference of \( \beta \)-power modulations in the rest phase (from \(-5.5\) s to \(-2.5\) s) and in the MI phase (from \(4.5\) s to \(6\) s) between the two conditions (Fig. 2D). We tested whether the difference between the two conditions in the rest phase were significantly deviating from chance level, and found significant difference (t-test, \( p < 0.0001 \)). Furthermore, we tested whether the difference between the two conditions in the MI phase was significantly deviating from chance level, and found also significant differences (t-test, \( p < 0.05 \)).

**Effect of feedback modality on \( \beta \)-oscillations**

In a next step, we calculated for the identified time windows the area under the curve (AUC) along the time axis, i.e. from \(-5.5\) s to \(-2.5\) s (rest epoch) and from \(4.5\) s to \(6\) s (MI epoch). The AUC was calculated from the estimated ERSP at the individual \( \beta \)-frequency peak differences from the modulated contralateral sensorimotor electrodes (FC3, C3, and CP3). This measure quantified the individual maximum regional oscillatory changes of \( \beta \)-activity, and referred to regional \( \beta \)-ERS/ERD. The combination of MI with proprioceptive feedback resulted in higher \( \beta \)-ERS during the respective time window in the rest epoch (Fig. 3A, two-sided t-test, \( p = 0.02 \)) and in higher \( \beta \)-ERD during the respective time window in the MI epoch (Fig. 3B, two-sided t-test, \( p = 0.04 \)).

The plots in Figs. 3C and D show the topographical distribution of individual \( \beta \)-frequency peak differences (Proprioceptive versus Visual feedback) during the respective time windows. The non-parametric randomization test revealed significant changes of ERSP beyond contralateral sensorimotor electrodes, which were used for neurofeedback, during the respective rest and motor imagery epochs. More specifically, we observed stronger event-related synchronization of \( \beta \)-power (\( \beta \)-ERS) during the time window from \(-5.5\) s to \(-2.5\) s in electrodes over midline fronto-central regions when MI was combined with proprioceptive feedback (Fig. 3C). We found furthermore stronger event-related desynchronization of \( \beta \)-power (\( \beta \)-ERD) in electrodes over bilateral fronto-central regions during the time window from \(4.5\) s to \(6\) s when MI was combined with proprioceptive feedback (Fig. 3D).

**Relation between regional and remote sensorimotor \( \beta \)-oscillations**

Next, we calculated AUC along the time axis from \(-5.5\) s to \(-2.5\) s (rest epoch) and from \(4.5\) s to \(6\) s (MI epoch) for the significant electrode clusters found in Figs. 3C (midline fronto-central regions from the estimated ERSP at individual \( \beta \)-frequency peak differences) and D (bilateral fronto-central regions from the estimated ERSP at individual \( \beta \)-frequency peak differences), referred to as remote \( \beta \)-ERS/ERD changes. We correlated this remote activity with the regional changes of \( \beta \)-ERS/\( \beta \)-ERD in the contralateral sensorimotor electrodes used for self-regulation and neurofeedback. We found that higher states of \( \beta \)-ERS in electrodes over midline fronto-central regions showed a significant positive correlation with regional \( \beta \)-ERS when MI was combined with proprioceptive feedback (Fig. 4A, Pearson’s correlation coefficient \( r_{p} = 0.89, p\text{-value} < 0.0001 \), linear regression analysis, \( R^{2} = 0.79 \)). Furthermore, a higher state of \( \beta \)-ERD in electrodes over bilateral fronto-central regions showed a significant positive correlation with regional \( \beta \)-ERD when MI was combined with proprioceptive feedback (Fig. 4B, Pearson’s correlation coefficient \( r_{p} = 0.95, p\text{-value} < 0.0001 \), linear regression analysis, \( R^{2} = 0.9 \)). Both the regional and the remote AUC of \( \beta \)-ERD showed furthermore a significant positive correlation with...
Fig. 3. Effect of feedback modality on β-oscillations. Area under the curve (AUC) of regional ERSP during the rest epoch (from $-5.5$ s to $-2.5$ s) (A), and motor imagery epoch (from $4.5$ s to $6$ s) (B). (A) The barplot shows the normalized area under the curve (AUC) of regional β-ERS estimated from contralateral sensorimotor electrodes (FC3, C3, and CP3) during the rest epoch (from $-5.5$ s to $-2.5$ s). The combination of MI with proprioceptive feedback revealed significantly higher regional β-ERS as compared to visual feedback (two-sided t-test, $p = 0.02$). (B) The barplot shows the normalized AUC of regional β-ERD estimated from contralateral sensorimotor electrodes (FC3, C3, and CP3) during the MI epoch (from $4.5$ s to $6$ s). The combination of MI with proprioceptive feedback showed significantly higher and prolonged regional β-ERD as compared to visual feedback (two-sided t-test, $p = 0.04$). Topographical differences of ERSP during the rest epoch (from $-5.5$ s to $-2.5$ s) (C), and motor imagery epoch (from $4.5$ s to $6$ s) (D). The plots represent t-value topography differences of ERSP by comparing the proprioceptive feedback session with the visual feedback session. Electrode clusters, showing significant differences in the non-parametric randomization test, are indicated by filled white circles. Colors indicate event-related synchronization (ERS, red) and event-related desynchronization (ERD, blue).

Fig. 4. Relation between regional and remote sensorimotor β-oscillations. Relation between regional and remote ERSP during the rest epoch (from $-5.5$ s to $-2.5$ s) (A), and motor imagery epoch (from $4.5$ s to $6$ s) (B). The scatter plots represent the area under the curve (AUC) of regional β-ERS (A) and β-ERD (B) on the ordinate while the abscissa indicates the AUC of remote β-ERS and β-ERD, respectively. The gray lines are the result of a robust regression analysis of the AUC of regional β-ERS/ERD onto AUC of remote β-ERS/ERD using iteratively reweighted least squares with a bisquare weighting function [(A) Pearson’s correlation coefficient $r_{ps} = 0.89$, p-value < 0.0001, $R^2 = 0.79$, (B) Pearson’s correlation coefficient $r_{ps} = 0.95$, p-value < 0.0001, $R^2 = 0.9$].
the true positive β-ERD classification time when motor imagery was combined with proprioceptive feedback (see Supplemental Fig. S1).

**Motor cortical network modulations**

We observed that in the θ-band higher functional coupling was present during the MI epoch as compared to the rest epoch. While for the sensorimotor rhythms, namely the α-band and β-band, the opposite was the case, i.e. stronger functional coupling was present during the rest epoch as compared to the MI epoch. These different couplings during the rest and MI epochs were captured by calculating the event-related ciCOH (ER-ciCOH) and comparing this value between the proprioceptive and visual feedback conditions (non-parametric randomization test), separately for each frequency band of interest (FOI). We calculated furthermore the functional connectivity differences (ciCOH) by taking the contrast between the MI and rest periods for each FOI and visualized this topographically on a t-value scale (non-parametric randomization test) over all subjects for the motor cortical network (see Supplemental Fig. S2) for both the proprioceptive feedback and visual feedback conditions, separately.

The non-parametric randomization test revealed significant changes of ER-ciCOH for the θ-band and low β-band (Fig. 5), but not for the α-band and high β-band. More specifically, we observed that the C3 seed electrode overlying the left M1 cortex showed stronger functional connectivity with electrodes overlying the left parietal and occipital regions in the θ-band when MI was combined with proprioceptive feedback (Fig. 5, left side, upper plot). Furthermore, the ANOVA results confirmed the main effect for “feedback modality” $F_{(1,280)} = 5.21, p = 0.02$, while showing no effect for “ROI” $F_{(1,280)} = 0.78, p = 0.68$, nor for the interaction between these factors $F_{(1,280)} = 1.05, p = 0.41$. The post-hoc analysis consisted of a two-sided t-test and showed that the significant differences between the two feedback modalities were present for the connection between the C3 electrode overlying the left M1 cortex with electrodes overlying the left superior parietal cortex and occipital cortex (Fig. 5, right side, upper plot).

For the low β-band the C3 seed electrode overlying the left M1 cortex showed stronger functional connectivity with electrodes overlying the left and right premotor and prefrontal regions, while this network showed higher functional connectivity with electrodes overlying the right temporo-parietal regions when MI was rewarded with proprioceptive feedback (Fig. 5, left side, lower plot). The ANOVA results confirmed the main effect for “feedback modality” $F_{(1,280)} = 8.47, p = 0.004$, while showing no effect for “ROI” $F_{(1,280)} = 0.7, p = 0.77$, nor for the interaction between these factors $F_{(1,280)} = 1.4, p = 0.16$. The post-hoc analysis consisted of a two-sided t-test while showing that the significant differences between the two feedback modalities were present for the connection between the C3 electrode overlying the left M1 cortex with electrodes overlying the left and right fronto-polar cortex, right central regions, and right inferior parietal cortex (Fig. 5, right side, lower plot).

Higher modulations of θ-band ER-ciCOH between the C3 seed electrode overlying the left motor cortex and electrodes overlying the parieto-occipital regions (significant electrode clusters found in Fig. 5) showed a significant inverse correlation with true positive β-ERD
classification time when MI was combined with proprioceptive feedback (Fig. 6A, Pearson’s correlation coefficient $r_{\beta} = -0.8$, $p$-value = 0.003). This accounted for 64% of the variance in this skill (linear regression analysis, $R^2 = 0.64$). Furthermore, $\beta$-band motor-parieto-occipital network modulation showed a significant inverse correlation with higher states of regional $\beta$-ERD (Fig. 6B, Pearson’s correlation coefficient $r_{\beta} = -0.66$, $p$-value < 0.02, linear regression analysis, $R^2 = 0.44$) and remote $\beta$-ERD (Fig. 6C, Pearson’s correlation coefficient $r_{\beta} = -0.67$, $p$-value < 0.02, linear regression analysis, $R^2 = 0.45$) during the time window from 4.5 s to 6 s when MI was combined with proprioceptive feedback. This indicated that stronger regional and remote $\beta$-ERD during the MI epoch was associated with less functional coupling of the C3 seed electrode over left M1 regions with electrodes over left parieto-occipital regions in the $\theta$-band. No correlations were found between $\beta$-modulation and $\theta$-band during the visual feedback session.

Differences in sensorimotor $\beta$-modulations

Spectral perturbations of $\beta$-band activity display different neurophysiological properties within pre- and postcentral regions during different phases of MI-associated brain activity (Kilavik et al., 2013), which are commonly summarized as event-related synchronization/desynchronization (ERS/ERD) (Pfurtscheller and Lopes da Silva, 1999). The combination of MI with proprioceptive feedback resulted in increased and prolonged states of regional sensorimotor and remote ERS during the rest epoch and ERD during the MI epoch of the targeted $\beta$-frequency band.

Synchronization of $\beta$-power during the rest period following MI is related to the same physiological mechanism as the $\beta$-rebound after actual movements (Pfurtscheller and Solis-Escalante, 2009; Solis-Escalante et al., 2012). This represents an active inhibition of sensorimotor areas following termination of a mentally processed motor program, i.e. MI of hand movements, thus indicating efficient cortico-muscular communication (Schulz et al., 2013; Takeini et al., 2013b).

Discussion

This study investigated the reactivity of the motor cortical system during the interplay between MI and feedback processing. We used a neurofeedback training intervention in which participants had to voluntarily modulate $\beta$-band activity in circumscribed sensorimotor regions via kinesthetic MI (Gharabaghi et al., 2014a; Vukelić et al., 2014), and compared the impact of two different feedback modalities, i.e. visual feedback and proprioceptive feedback. We detected a higher skill and lower variability of self-controlled sensorimotor $\beta$-band modulations when MI was combined with proprioceptive feedback (Figs. 2 and 3). We also observed increased functional coupling of distributed cortical regions with the self-regulated left motor cortex in the $\beta$-band and $\theta$-band when proprioceptive feedback was provided (Fig. 5). Functional connectivity of this $\theta$-band network was furthermore inversely correlated with the skill of regional $\beta$-band self-regulation (Fig. 6).

By contrast, synchronization of oscillatory $\beta$-power during the preparatory epoch reflects an efficient preparation or anticipatory up-regulation of attention in the sensorimotor system of regional neuronal

**Fig. 6.** Relation between $\theta$-band connectivity and modulation of sensorimotor $\beta$-band oscillations. (A) The scatter plot represents time of true positive $\beta$-ERD classification on the ordinate where the abscissa indicates the ER-ciOCH of the left M1 (seed electrode C3) functionally connected with electrodes over left superior parietal and occipital regions in the $\theta$-band during motor imagery combined with proprioceptive feedback. The gray line is the result of a robust regression analysis of time of true positive $\beta$-ERD classification onto ER-ciOCH using iteratively reweighted least squares with a bisquare weighting function [Pearson’s correlation coefficient $r_{\beta} = -0.8$, $p$-value = 0.003, $R^2 = 0.64$]. (B) The scatter plot represents the area under the curve (AUC) of regional $\beta$-ERD estimated from contralateral sensorimotor electrodes (FC3, C3, CP3) during the MI epoch (from 4.5 s to 6 s) on the ordinate where the abscissa indicates the ER-ciOCH of the left M1 (seed electrode C3) functionally connected with electrodes over left superior parietal and occipital regions in the $\theta$-band during motor imagery combined with proprioceptive feedback. The gray line is the result of a robust regression analysis of AUC of $\beta$-ERD onto ER-ciOCH using iteratively reweighted least squares with a bisquare weighting function [Pearson’s correlation coefficient $r_{\beta} = -0.66$, $p$-value = 0.02, $R^2 = 0.44$]. (C) The scatter plot represents AUC of remote $\beta$-ERD during the MI epoch (from 4.5 s to 6 s) on the ordinate where the abscissa indicates the ER-ciOCH of the left M1 (seed electrode C3) functionally connected with electrodes over left superior parietal and occipital regions in the $\theta$-band during motor imagery combined with proprioceptive feedback. The gray line is the result of a robust regression analysis of AUC of $\beta$-ERD onto ER-ciOCH using iteratively reweighted least squares with a bisquare weighting function [Pearson’s correlation coefficient $r_{\beta} = -0.67$, $p$-value = 0.02, $R^2 = 0.45$].
communication (Kilavik et al., 2013), which was present in both conditions and thus independent of the feedback modality.

β-ERD is known to be present during both actual movements and MI (McFarland et al., 2000), thus indicating the release from active inhibition of the sensorimotor system in association with an increase in cortical and peripheral communication (Miller et al., 2012; Schulz et al., 2013; Takemi et al., 2013a,b). The activation of a more distributed β-network in electrodes over bilateral fronto-central regions (Figs. 3D and 4B), functionally coupled to the seed electrode C3 over the left motor cortex (Figs. 5 and S2) most probably reveals top-down control, as caused by attentive, deliberative motor processing and the mental effort of conscious processing (Hipp et al., 2011; Miller et al., 2010, 2012). The presented findings therefore suggest that proprioceptive feedback allows for mimicking actual movements more naturally during neurofeedback training and may therefore promote prolonged states of β-ERD during MI.

Motor related θ-networks

Oscillations in the θ-band are linked to working memory processes (Brookes et al., 2011; Ospova et al., 2006), long-term memory formation and retrieval of motor schemata (Perfetti et al., 2011). The inter-regional functional coupling of brain structures in the θ-band is also necessary for the emergence of visuospatial working memory during motor planning, motor skill learning and target selection during movements (Kaplan et al., 2012; Rawle et al., 2012; Sauseng et al., 2010). The functional coupling of left parietal regions with the left motor cortex gives supportive evidence for the retrieval of stored motor schemata, and bottom-up integration of sensory and motor information during MI combined with proprioceptive feedback (Caplan et al., 2003; Cruikshank et al., 2011), a pattern not present during the visual feedback condition. A similar link between state and frequency dependency of the motor system has recently been demonstrated by Feurra et al. (2013), showing that transcranial alternating current stimulation (tACS) in the θ-range enhanced endogenously generated oscillations during MI thus resulting in increased cortico-spinal excitability.

We found a relation between the skill of modulating oscillatory β-ERD and large-scale functional connectivity in the θ-band during proprioceptive feedback processing (Fig. 6). The cortical regions underlying the electrodes, which were coupled to the seed electrode C3 over the left motor cortex, i.e. frontal and parieto-occipital regions (Fig. S2A), are also known to represent a “scaffolding role” (Kelly and Garavan, 2005). These attentional- and learning-related regions are susceptible to redistribution, with decreased activity when task-specific performance becomes reliant and automatized. The functional coupling with electrodes over fronto-occipital regions was present during both feedback conditions (Figs. S2A and B), while the functional coupling with electrodes over parieto-occipital regions was only present when MI was combined with proprioceptive feedback (Fig. 5). The functional involvement of occipital regions might be linked to visuo-motor transformation reflecting greater capacity for integration of multiple sensory modalities (Beuter and Modolo, 2009; Suminski et al., 2010; Wu et al., 2014). This is further supported by the interconnection with electrodes from left parietal regions which are essential for the incorporation of multisensory signals as well, i.e. integrating visual, somatosensory and proprioceptive information important for the planning and control of voluntary movements (Desmurget and Sirigu, 2009; Lloyd et al., 2006). Along these lines, intact fibers of the superior longitudinal fasciculus, connecting frontal motor related regions with parietal and occipital regions, have been shown to play a key role for skill acquisition of MI related brain-self regulation after stroke (Buch et al., 2012). Accordingly, during proprioceptive input of the endogenously modulated neuronal state, θ-coupling might represent the physiological marker of the re-integration of this feedback thereby establishing a functional link between the involved regions. Moreover, this sensorimotor mechanism may reflect the interaction of internal movement models (Andersen et al., 1997) with the current state of the hand. In this context, proprioceptive feedback may comprise feed-forward information important for motor skill learning (Gandolla et al., 2014; Hardwick et al., 2013). We intentionally increased the task difficulty in our study to keep participants in the deliberative phase of skill acquisition with high demands for activating distributed motor learning related cortical networks (Miller et al., 2010; Wander et al., 2013), thereby disentangling the underlying neural mechanisms. Those participants with a lower ability to maintain prolonged states of β-ERD during MI were recruiting to a higher degree the learning related “scaffolding” β-network (Fig. 6), thus indicating that different skill levels for brain-self-regulation applied specific neural computations.

This information might serve in future studies as the neurophysiological basis for interventions which intend to improve the skill of brain self-regulation. In this context, enhancing θ-coupling between motor and parieto-occipital regions via non-invasive brain stimulation techniques, i.e. θ-tACS (Polania et al., 2012), might be a reasonable approach. Future work will need to study furthermore whether the improved skill of brain self-regulation (with and without adjunct brain stimulation) would translate into behavioral gains in motor tasks resembling the MI training as well.

Conclusion

We investigated the impact of the feedback modality during MI on oscillatory β-power entrainment and functional connectivity of the cortical motor network. Our findings provide conclusive evidence that proprioceptive feedback is resulting in lower variability and higher ability to maintain and reproduce stable states of self-controlled β-activity as compared to visual feedback. This gain in controlling regional motor oscillations was accompanied by functional coupling of remote β-band and θ-band activity in electrodes over bilateral fronto-central regions and left parieto-occipital regions, respectively. The functional coupling of coherent θ-band oscillations correlated moreover with the skill of regional β-modulation thus revealing a motor learning related network which might in the future be targeted by adjacent interventions.

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Conflict of Interest

The authors declare that they have no competing interests.

References


