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Reading and modulating cortical beta bursts from motor unit spiking activity

Abbreviated title: Cortical and peripheral beta bursts

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Declaration of interests

DF and DYB are inventors in a patent (Neural 690 Interface. UK Patent application no. GB1813762.0. August 23, 2018) and DF, DYB, JI, and MB are inventors in a patent application (Neural interface. UK Patent application no. GB2014671.8. September 17, 2020) related to the methods and applications of this work.

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Author Contribution

MB, JI, DYB, and DF conceived the study. MB, JI, and ADV carried out the experiments. MB conducted the analysis. MB, JI, and DF interpreted the data, MB wrote and DYB, ADV, JI, and DF edited the manuscript.

Abstract

Beta oscillations (13-30Hz) are ubiquitous in the human motor nervous system. Yet, their origins and roles are unknown. Traditionally, beta activity has been treated as a stationary signal. However, recent studies observed that cortical beta occurs in 'bursting events', which are transmitted to muscles. This short-lived nature of beta events makes it possible to study the main mechanism of beta activity found in the muscles in relation to cortical beta. Here, we assessed if muscle beta activity mainly results from cortical projections. We ran two experiments in healthy humans of both sexes (N=15 and N=13, respectively) to characterize beta activity at the cortical and motor unit (MU) levels during isometric contractions of the tibialis anterior muscle. We found that beta rhythms observed at the cortical and MU levels are indeed in bursts. These bursts appeared to be time-locked and had comparable average durations (40-80ms) and rates (~3-4 bursts/second). To further confirm that cortical and MU beta have the same source, we used a novel operant conditioning framework to allow subjects to volitionally modulate MU beta. We showed that volitional modulation of beta activity at the MU level was possible with minimal subject learning and was paralleled by similar changes in cortical beta activity. These results support the hypothesis that MU beta mainly results from cortical projections. Moreover, they demonstrate the possibility to decode cortical beta activity from MU recordings, with a potential translation to future neural interfaces that use peripheral information to identify and modulate activity in the central nervous system.

Significance statement

We show for the first time that beta activity in motor unit populations occurs in bursting events. These bursts observed in the output of the spinal cord appear to be time-locked and share similar characteristics of beta activity at the cortical level, such as the duration and rate at which they occur. Moreover, when subjects were exposed to a novel operant conditioning paradigm and modulated motor unit beta activity, cortical beta activity changed in a similar way as peripheral beta. These results provide evidence for a strong correspondence between cortical and peripheral beta activity, demonstrating the cortical origin of peripheral beta and opening the pathway for a new generation of neural interfaces.

1. Introduction

Neural oscillations of brain activity in the beta range (13-30Hz) are ubiquitous in the motor nervous system (Kilavik et al., 2013). Alongside their pervasive appearance in the brain, beta oscillations with cortical origin are transmitted linearly and at fast and stable speeds to tonically active muscles (Ibáñez et al., 2021; Witham et al., 2011). Beta activity can indeed represent an important portion of the neural inputs received by spinal motor neurons and their innervated muscle fibres, i.e. motor units (MUs) (Dideriksen et al., 2018; Farina et al., 2014; Grosse et al., 2002). However, the prominence of beta activity at the MU level contrasts with the fact that, so far, it has been difficult to find a direct link between these oscillations and motor function (Baker, 2007; Davis et al., 2012; Engel and Fries, 2010; Jenkinson and Brown, 2011; Little et al., 2019). One aspect of beta inputs to MU that makes them hard to study is not knowing which main sources are contributing to these inputs. Are the characteristics of beta activity in MUs similar to the non-stationary features of beta oscillations at the cortical level? Is the motor cortex the main structure projecting common beta inputs to muscles? Or are there other relevant sources elsewhere in the central nervous system?

An interesting recent observation is that cortical beta activity is not a continuous signal, but it appears in short-lived bursts (Bonaiuto et al., 2021; Feingold et al., 2015; Little et al., 2019; Pfurtscheller et al., 2005; Shin et al., 2017). Such temporal non-stationary characteristics of beta activity require new approaches, based on joint time and frequency analysis, to study these oscillations (van Ede et al., 2018; Jones, 2016; Tal et al., 2020) and their possible links to motor function (Bonaiuto et al., 2021; Little et al., 2019; Shin et al., 2017; Wessel, 2020). The tracking of the non-stationary, burst-like behavior of cortical beta allows for directly following its propagation to the peripheral nervous system by identifying its main characteristics, such as burst duration and frequency, at the cortical and peripheral level. The analysis of the transmission of beta from the central to the peripheral nervous system would provide new insights into the role of beta oscillations on motor control. Moreover, understanding beta transmission would enable the development of neural interfaces to monitor and extract cortical activity non-invasively from the periphery to supplement and overcome current limitations of traditional brain monitoring interfaces.

Here we ran two experiments to characterize beta oscillations present at the level of MUs in the tibialis anterior muscle and their association with cortical beta rhythms in the context of mild isometric contractions. In the first experiment, we asked subjects to hold a constant force level while concurrently recording cortical activity via electroencephalography (EEG) and muscle activity via high-density electromyography (EMG). The EMG was decomposed into the underlying MU activity associated with force generation. Then, in the second experiment, we used a decomposition algorithm to extract MU activity from the EMG in real-time (Barsakcioglu et al., 2021) and a novel

neural feedback paradigm to operantly conditioning beta in the MUs (Bräcklein et al., 2020). By doing this, we were able to assess how the relationship between cortical and peripheral beta rhythms is influenced by volitional modulation of MU beta power. Overall, our results demonstrate that beta activity in the MUs is short-lived, mainly driven by cortical bursts, and can be volitionally modulated, imposing parallel modulation at the cortical level.

2. Materials and methods

2.1. Subjects

In this study, 28 healthy subjects (3 females, all subjects between 24 and 35 years old) participated, of whom 15 (2 females) in Experiment 1 and 13 (1 female) in Experiment 2. All subjects were naïve to the experimental paradigms. None of the subjects reported any history of sever neuronal or lower limb injuries. Experiment 1 was approved by the University College London Ethics Committee (Ethics Application 10037/001) and Experiment 2 by the ethics committee at Imperial College London (reference number: 18IC4685).

2.2. Data acquisition

High-density surface EMG (HDsEMG) from the tibialis anterior muscle of the dominant leg (self-reported) was acquired via a 64-electrode grid (5 columns and 13 rows; gold-coated; 1 mm diameter; 8 mm interelectrode distance; OT Bioelettronica, Torino, Italy). The electrode grid was placed over the muscle belly aligned to the muscle's fiber direction. In addition, single-channel EMG of the medial and lateral head of the gastrocnemius muscle was recorded via wet electrodes (Ambu Ltd, St Ives, United Kingdom) placed above the muscle belly throughout Experiment 2. The EMG signals were monopolar recorded, amplified via a Quattrocento Amplifier system (OT Bioelettronica, Torino, Italy), sampled at 2048Hz, A/D converted to 16 bits, and digitally band-pass filtered (10-500Hz). Subjects were seated throughout the experiments while the foot of the dominant leg was locked into position to allow dorsiflexion of the ankle only. The force due to ankle dorsiflexion was recorded via a CCT TF-022 force transducer, amplified (OT Bioelettronica, Torino, Italy), and low-pass filtered at 33Hz. The communication between the amplifier and the computer was conducted via data packages of 256 samples (one buffer corresponds to a signal length of 125ms). All incoming EMG signals were band-pass filtered between 20-500 Hz using a 4^{th} order Butterworth filter.

Furthermore, EEG signals were acquired from 31 positions according to the International 10-20 system via active Ag/AgCl electrodes (actiCAP, Brain Products GmbH, Munich, Germany). FCz was used as a reference. The signal was amplified (BrainVision actiCHamp Plus, Brain Products GmbH, Munich, Germany) and sampled at 1000 Hz. The EEG was offline band-pass filtered between 0.5 and 45 Hz (4^{th} order Butterworth filter). A surface Laplacian filter covering the central part of the brain by taking the neighboring positions of Cz into account was applied (Kayser and Tenke, 2015). Both EMG and EEG signals were offline resampled at 512 Hz and synchronized with a common digital trigger signal.

For one subject, no EMG of the lateral nor medial head of the gastrocnemius muscle was recorded due to a material failure.

2.3. Experimental paradigm

The experimental paradigm for both experiments is visualized in Figure 1A.

2.3.1. Pre-experimental processing

Before the start of the experiments, subjects were asked to perform a single maximum dorsiflexion of the ankle to estimate the maximum voluntary contraction level (MVC). The obtained MVC was set as a reference for the following experiment to ensure that stable forces were produced by the tibialis anterior muscle.

In addition to force feedback, Experiment 2 also informed the subjects about the amount of beta activity in the MU innervating the tibialis anterior muscle. For this, an online decomposition algorithm was used to decode MU activity in real-time (Barsakcioglu et al., 2021). In order to estimate the separation matrix used to decode MU activity from the HDsEMG recordings, subjects were instructed to perform an additional ramp and hold task. This involved a 4s period of linear increase in the contraction level departing from a relaxed position and reaching a contraction level of 10% of the MVC (ramp phase) and steady contraction at 10% of the MVC level held for 40s (hold phase). The decomposed MU discharge behavior was visually inspected following established guidelines (Del Vecchio et al., 2020) while subjects were instructed to gradually increase the force due to dorsiflexion tup to 10% MVC to recruit MUs.

2.3.2. Experiment 1 – force task

Experiment 1 aimed to assess the characteristics of cortical and MU beta activity during constant isometric contraction at a mild force level. This experiment consisted of two blocks. In each block, subjects were provided with visually guided feedback on the exerted force and asked to follow a ramp and hold trajectory for 40s at 10% MVC presented on a screen while EEG was recorded concurrently. Between blocks, subjects were instructed to rest to avoid muscle fatigue.

2.3.3. Experiment 2 – beta modulation

In Experiment 2, the relationship between cortical and MU beta was assessed while subjects were allowed control over MU beta. For this, subjects were instructed to move a cursor inside a target rectangle by exerting a force due to ankle dorsiflexion at 10% MVC. While holding the cursor inside the rectangle, i.e. exerting a constant force at 10% MVC, subjects were asked to change the color of the cursor to match a presented target by modulating the MU beta power at ~20Hz. Similar to Experiment 1, EEG was recorded throughout Experiment 2.

Experiment 2 consisted of three parts: i) an *initialization phase* to determine all parameters necessary for real-time neurofeedback on the MU beta activity, ii) *familiarization phase* to allow subjects to get familiar with the experimental neurofeedback environment and task, and iii) the

neurofeedback task in which subjects were exposed to real-time feedback on the exerted force and MU beta activity.

Initialization phase

The initialization phase mimicked the paradigm previously performed in (Bräcklein et al., 2020). Subjects were asked to exert a force at 10% MVC for 40s guided visually by a force trajectory. During this period, the underlying MU activity was used to identify the most prominent peak inside the beta band of the intramuscular coherence (IMC). The IMC was used in this case as it allowed us to estimate the common input to the MU pool at a given frequency (Castronovo et al., 2015; Dideriksen et al., 2018). The power inside a 5Hz band of the cumulative MU spike train (CST) centered around the IMC peak in the beta band was extracted online using a 3rd-order Butterworth filter. The mean of this beta feature in the initial training block was used for normalization during the neurofeedback part in Experiment 2. The logarithm of this normalized beta feature was then fitted to a Gaussian distribution to provide feedback on the beta activity using a color code. Specifically, a blue-to-white-to-red colormap was mapped to the logarithmical beta feature ranging from two standard deviations below the mean (blue) to two standard deviations above the mean (red), while the mean was coded via the color white (see Figure 1B). If the beta feature value was outside the range of the colormap, i.e. more than two standard deviations off the mean, the displayed color was set to the closest extrema (either blue or red).

Familiarization phase

The familiarization phase provided subjects with the same feedback environment as they experienced later in the neurofeedback task. Subjects were instructed to move a cursor up into a target rectangle by modulating the force exerted during dorsiflexion of the ankle. This target rectangle was centered at 10% MVC with a lower and upper bound at 9.5% and 10.5% MVC, respectively. The cursor's color changed accordingly to the underlying beta feature and its corresponding value in the blue-white-red colourmap. If the cursor was outside the target rectangle, its color was changed to black. Hence, subjects only received feedback on the underlying beta feature when the cursor was inside the target. By doing this, subjects were encouraged to exert stable forces. Cursor position and color were updated every 125ms. The beta feature amplitude was averaged across the amplitudes observed in the seven most recent 125ms buffers analyzed as previously performed by (Bräcklein et al., 2020). Subjects had approximately 10min to get themselves familiar with this neurofeedback environment.

Neurofeedback task

The neurofeedback task was divided into multiple blocks. Subjects were asked to perform a minimum of three and a maximum of six blocks of training before three last consecutive blocks were used for further analysis. Each block consisted of three trials. Each trial started with subjects contracting their tibialis anterior muscle to produce ankle dorsiflexion forces that moved the cursor inside the target rectangle at 10% of the MVC. Once the cursor was within the target rectangle, the force produced had to be kept constant for 30s while beta activity had to be modulated. Specifically, subjects were asked to either keep the cursor blue for as long as possible (beta down-modulation condition), or red (up-modulation condition). In a third condition, no feedback on the underlying beta activity was given (the cursor stayed white when held inside the target; see Figure 1B). The color target indicating the modulation condition of each trial, was provided verbally by the experimental instructor and as visual clues by the color of the cursor edge. Hence, the cursor edge was blue when subjects were asked to keep the cursor blue (down-modulating MU beta), red (up-modulating beta), or black if no neurofeedback on MU beta was provided. Per block, each modulation condition was presented once in a randomized order. Between each trial, subjects rested for at least 1 min to minimize muscle fatigue.

2.4. Analysis

2.4.1. Spectral analysis

The time-frequency representation of the CST and the surface Laplacian EEG was obtained using the continuous wavelet transform implemented via the `cwt` function in MATLAB (Version 2018b, MathWorks Inc., MA, USA). The cortico-muscular coherence (CMC) was estimated using magnitude-squared wavelet coherence implemented via the MATLAB function `wcoherence`. A similar approach was chosen to estimate the temporal evolution of the IMC via a custom MATLAB script built upon the `wcoherence` function. To estimate the IMC, the MU pool was split into two randomly selected sub-pools of equal size. The magnitude-squared wavelet coherence between the CSTs of both MU sub-pools was calculated. This step was repeated over 100 iterations, always choosing a different configuration of MU sub-pools. The IMC was obtained by averaging the coherence estimates obtained during the 100 iterations.

The beta bursting activity present in the CST and EEG signals was extracted using a band-pass filter (13-30Hz, 4^{th}-order Butterworth). The envelopes of the band-pass-filtered signals were used to determine when beta bursts occurred. The threshold above which the envelope was classified as a bursting event was empirically determined similar to the methods used in (Little et al., 2019; Shin et al., 2017). For Experiment 1, the envelopes from EEG and CST in each block were split into 1s windows. In each window, the correlation between the power of the signal and the percentage of

signal above the threshold was determined using the Pearson correlation coefficient and averaged across blocks. Hereby, the threshold was increased from 0 to 6 times the median in .25 steps. The threshold that resulted in the maximum correlation between power and percentage of signal above threshold was used to identify beta events. This procedure was repeated for Experiment 2 on block-level for the non-beta power feedback trials. The results are visualized in Figure 2. For Experiment 1, the empirically determined threshold was 2.50 and 2.75 times the median for CST and EEG, respectively. For Experiment 2, it was 2.25 and 2.75 times the median for CST and EEG. Consecutive periods where the envelopes were above the threshold were marked as ON periods (beta bursting events), similarly as previously performed in (Echeverria-Altuna et al., 2021). Hence, the length of ON periods was used to estimate the duration of beta events. The beta event power was calculated as sum of all ON events divided by the recording time. The remaining periods, i.e. when the envelope was below the threshold, were identified as OFF periods. The time points of ON and OFF events were set to the center of the respective periods. To analyze neural activity around ON and OFF periods, the wavelet transposed spectra of CST and EEG, the wavelet CMC and IMC were averaged in 500ms windows centered at the times of ON and OFF events. Furthermore, the percental mismatch between ON and OFF events was calculated as: ((ON - OFF) / OFF) * 100.

2.4.2. Experiment 1 – force task

The HDsEMG recorded during 40s of isometric ankle dorsiflexion at 10% MVC was offline decomposed into the underlying MU activity using the algorithm proposed in (Negro et al., 2016). The decomposition results were manually inspected as detailed in (Del Vecchio et al., 2020). To control if the identified bursts in the EEG and the MU pool result from underlying amplitude modulations or in contrast from isolated bursting events, the lagged coherence method was employed (Fransen et al., 2015) using the NeuroDSP Python toolbox (Cole et al., 2019). This spectral measure examines coherence between the signal and a delayed version of the same signal at each frequency. If the lagged coherence is large, it provides evidence that the observed bursting events occur in periodically and thus may be due to an underlying modulation. However, when the examined signal occurs in de-coupled events, detached from any ongoing modulations, the lagged coherence is smaller. The power spectral density was calculated using Welch's method (2s window, 50% overlap) and normalized between 1 and 40Hz.

2.4.3. Experiment 2 – beta modulation

The online decomposed MU activity was post-hoc cleaned from artefacts. Action potentials that were fired with an instantaneous discharge rate above 30 spikes-per-second (sps) were neglected. Only the 30s-time interval during which subjects were instructed to modulate the beta activity while keeping the force constant were analyzed. In addition, the beta activity and discharge rate were

recalculated by neglecting MUs that had an average discharge rate below 5sps or above 30sps or a discharge rate coefficient of variation (CoV) above 0.5 in any of the recorded blocks. The resulting cleaned pools of MUs were used in the subsequent analysis, also for example, to recalculate the beta feature and wavelet transformed CST activity, CMC, and IMC.

Functional values obtained during up- and down-modulation of MU beta activity, such as the mean force, beta amplitude, average rectified EMG, i.e. global EMG, bipolar EMG, and the corresponding CoVs to all values mentioned before, and the mean MU discharge rates were normalized by the averaged values obtained during the control condition (when no neurofeedback on the MU beta activity was provided). The wavelet transformed CST and EEG, CMC, and IMC were interpolated to transform the logarithmical frequency scale into a linear one for further analysis to ensure an equally weighted representation of all frequencies. The results were averaged inside the entire beta band (13-30Hz) and within in 500ms window centered around the ON-triggered averaged. The values obtained during neurofeedback were normalized by the corresponding values obtained during the control condition.

The custom scripts used for analysis are available upon reasonable request from the corresponding author.

2.5. Statistics

Statistical analysis was performed via SPSS (IBM, Armonk, NY, USA) and custom MATLAB routines. Results were reported as mean ± standard deviation. Significant clusters of beta activity in the difference in the time-frequency representation of beta ON and OFF events were determined using the cluster-level analysis proposed by (Maris and Oostenveld, 2007). In brief, this approach assessed clusters of adjacent samples in both frequency and time dimensions under a single permutation distribution (we used 10 000 permutations and an univariant clustering threshold of .05). This approach allows to bypass multi-comparison issues present in multi-dimensional data. The characteristics of beta bursting events in the MUs and the EEG were compared by using two-sided paired t-tests. The effect of volitional beta modulation on multiple motor behavioral properties of the innervated leg were tested by a repeated measures MANOVA. Hereby, the independent variables were the different modulation conditions, i.e. beta down- and up-modulation. Dependent variables were the mean force, mean rectified EMGs of agonist and antagonist muscles, the CoV of these values and the mean discharge rates of the decomposed MUs across subjects. Differences in the mean beta feature amplitude were assessed by two-sided paired t-tests. To assess whether the temporal evolution of the modulated beta feature correlated with muscle activation, the correlation coefficient between the exerted force, the rectified EMG of the agonist muscle or the discharge rate of the identified MU pool, and the beta feature were estimated using the Pearson correlation

296 coefficient. To do this, force, rectified EMG and discharge rate were post-processed in a similar
297 fashion as the beta feature, i.e. corresponding values were averaged per each recording buffer.

298 The difference in beta event features at the cortical and MU level was assessed using linear mixed
299 models. Linear mixed models were also used to evaluate the effect of volitional beta modulation at
300 MU level on the beta bursting characteristics and spectral values, such as wavelet-transformed CST
301 and EEG, CMC, and IMC, on single blocks, in which the difference between beta down- and up-
302 modulation was the dependent variable and the subject-wise grouping a random effect. Values
303 during up- and down-modulation were normalized using data from the non-feedback condition as
304 described in 2.4.3. The partial eta-squared (η_p^2) was used to assess the effect size of the changes
305 between beta modulations. Values greater than 0.14 indicate that a “large” effect can be observed
306 in the particular comparison (Cohen, 1988). The threshold for statistical significance was set to $p <$
307 .05.

308

3. Results

3.1. Experiment 1 – force task

In total, 22.73 ± 7.95 MUs per block were identified in Experiment 1. Figure 3 visualizes the time-frequency spectra inside the beta band of cortical (EEG signals) and muscle (the CST generated with the decomposed MUs) signals during a period of isometric ankle dorsiflexion at 10% MVC. Both spectra indicated that beta activity at the cortical and muscle levels occurred in short intervals, i.e. bursts of activity, while subjects held constant forces. The zoomed-in plot (Figure 3, bottom) suggested that some bursts observed in the muscle overlapped with bursts observed in the EEG.

While the observed beta burst might occur as infrequent uncoupled bursting events, they could also result from an underlying amplitude-modulated oscillation. Hence, we conducted a control analysis to assess whether beta bursts in MUs and EEG result from a sustained amplitude modulation. In this case, the phase inside the beta band should predict the phase in upcoming cycles. In contrast, if these bursts do not originate from an underlying sustained modulation, the current phase inside beta should correlate less with future cycles (Fransen et al., 2015). Figure 4 illustrates that although both cortical and MU show prominent beta activity in their spectra, the lagged coherence decreases inside this range compared to other spectral components. Further, this effect seems prolonged across multiple cycles. This indicates that in both EEG and MU activity, beta bursting events seem to be isolated, thus not resulting from underlying modulation.

To understand activity around the short-lived beta bursts found in the EEG and CST signals, the wavelet-transformed data were averaged at the center of ON and OFF periods found in the EEG across blocks. Figure 5 visualizes these triggered averages for the wavelet-transformed EEG, CST, the CST-EEG coherence (CMC), the intramuscular coherence (IMC), and the force profile at respective time intervals. While the exerted force did not significantly change between ON and OFF periods (no significant clusters, always $p > .05$), beta activity present in the EEG was significantly pronounced during ON relative to OFF periods in a cluster at the center of EEG beta events ($p = .024$). Also, beta activity in the CST was pronounced during ON periods compared to OFF, despite the time points of ON and OFF being determined by the EEG activity ($p = .042$). It is worth noting that the maximum difference between ON and OFF in the EEG was around time lag 0 (-.49ms), while the maximum difference in the CST was delayed by 24.41ms. Furthermore, a significantly pronounced bursting activity in the CMC was observed ($p = .001$). Similarly, the results suggested that the IMC was also of transient behavior inside the beta band (IMC, $p = .026$).

The previous results indicated that beta activity observed in cortical and muscle recordings occurred in bursts. Moreover, the significant beta activity in the CST identified during EEG beta bursting

342 events suggested that beta bursts in the MU overlapped with those present at the cortical level. This
343 confirms previous observations made using surface EMG signals (Echeverria-Altuna et al., 2021). In
344 addition, we observed that the common input inside the beta range to the MU pool was of bursting
345 behavior and appeared to be time-locked to cortical beta bursts. To further assess how beta bursts
346 observed in the MU pool matched with the beta bursts in the EEG we compared the rate and
347 duration of the beta bursts extracted from the CST and EEG (Figure 6). Beta events observed at the
348 MU level appeared at a rate of 3.56 ± .41 events per second while beta events in EEG at a slightly but
349 significantly lower rate of 3.23 ± .30 ($p = .003$, $\eta_p^2 = .469$). There was no significant difference
350 detected between the average duration of the beta bursts observed on the MU level (55.61 ±
351 11.27ms) and the bursts in the EEG (53.10 ± 9.23; $p = .398$, $\eta_p^2 = .052$).

352 ### 3.2. Experiment 2 – beta modulation

353 Results from Experiment 1 showed that beta activity occurs in bursts both at the cortical and muscle
354 levels. Moreover, the bursts observed at both levels are similar in features such as duration and rate
355 of events and appear to be temporarily aligned with a small offset. These results therefore support
356 the notion that beta activity in the EEG and CST have a shared underlying source. If this is the case, it
357 is expected that modulation of beta activity at the MU level should correspond to a similar
358 modulation of cortical beta observed in the EEG. To test this, Experiment 2 used a novel neural
359 interface based on real-time decomposition of MU activity from the interference EMG.

360 In this online experiment 11.92 ± 2.48 MUs per subject were identified and tracked in real time.
361 Subjects could significantly reduce the normalized mean beta amplitude during down-modulation to
362 0.91 ± 0.20, compared to up-modulation at 1.07 ± 0.26 (two-sided paired t-test, $t(12) = -2.454$, $p =$
363 .030; see Figure 7A). In the context of volitional MU beta modulation, neither the mean exerted
364 force nor other functional measures of the innervated leg changed significantly (repeated measures
365 MANOVA Wilks' Lambda corrected, $p = .424$, $\eta_p^2 = .811$). Furthermore, across all subjects, no
366 temporal correlation between the beta feature and the force, rectified EMG of the tibialis anterior
367 muscle, and discharge rate of MUs were detected (Figure 7B; all medians are below the significance
368 level). Taken together, these results suggested that subjects were able to modulate the beta band
369 activity present in a MU pool without critically altering the motor output.

370 To study the impact that modulation of beta activity in the MU pool has on cortical beta activity, we
371 compared the burst power and the three burst features that contribute to the power estimate, i.e.
372 peak amplitudes of the beta bursts, the bursts durations, and the number of bursts, between beta
373 down- and up-modulation conditions normalized by the corresponding values obtained when no
374 beta feedback was provided (Figure 8). The power of the beta bursts in both CST and EEG increased

during up-modulation compared to down modulation from 0.89 ± .27 to 1.09 ± .37 ($p = .003$, $\eta_p^2 = .540$) in the CST, and from 0.75 ± .25 to .83 ± .26 ($p = .013$, $\eta_p^2 = .415$) in the EEG. The amplitudes of beta bursts in the CST and in the EEG were significantly higher in the up-regulation condition than in the down-modulation condition (CST: from 0.96 ± .09 to 1.02 ± .12, $p = .002$, $\eta_p^2 = .581$; EEG: from 0.94 ± .09 to 0.96 ± .09, $p = .038$, $\eta_p^2 = .311$). The duration of the beta events did also change between conditions at the MU level from 0.93 ± .12 to 1.00 ± .11 during down- and up-modulation, respectively ($p < .001$, $\eta_p^2 = .652$) but was not significant at the cortical level with longer durations of beta events during up-modulation (from .92 ± 0.10 to 0.96 ± 0.11, $p = .079$, $\eta_p^2 = .235$). The rate of observed beta events at the MU level increased significantly from 0.98 ± .15 to 1.05 ± .18 ($p = .023$, $\eta_p^2 = .363$). On average, the rate of beta events did also increase at the cortical from .85 ± .14 to 0.89 ± .14, but this effect was marginally not significant ($p = .058$, $\eta_p^2 = .268$).

The appearance of beta bursts in the EEG and MU activity changed during volitional beta feature modulation. Figure 9 shows the impact of volitional beta modulation on the MU and EEG beta activity during beta ON events. The spectral power in the beta band during ON events increased significantly in the CST from .99 ± .20 to 1.09 ± .23 ($p = .019$, $\eta_p^2 = .378$) and in the EEG from .90 ± .11 to .94 ± .11 ($p = .026$, $\eta_p^2 = .351$) during down- and up-modulation conditions, respectively. Similarly, the IMC increased significantly during up-modulation from 0.97 ± .06 to 0.98 ± .05 ($p = .034$, $\eta_p^2 = .321$) suggesting a stronger common input in the beta band during the up-regulation condition. Interestingly, the CMC did not change significantly from 1.00 ± .06 to 1.00 ± .06 between conditions ($p = .994$, $\eta_p^2 = .000$), which implies that while the common input to the MU inside the beta range increased during beta up-modulation relative to down-modulation, the spectral connectivity between cortical beta and MU beta remained unaffected. These results indicated that cortical beta power mirrored the changes in the MU. Finally, it should be noted that the same overall effects were observed when using beta bursting events in the CST to define the timing of ON periods (see Figure 9).

4. Discussion

We studied the correspondence of cortical beta activity with beta oscillations found in the output of spinal motor neurons. To do this, we assessed how cortical and peripheral beta bursting events relate to each other during muscle contractions. We then used a MU-driven neurofeedback approach to modulate the beta inputs to muscles to test if cortical beta activity followed the modulation of peripheral beta activity. Our results demonstrate, for the first time, that beta activity present in a MU pool appears in isolated bursts that closely correspond to the beta activity observed at the cortical level. In addition, when modulated at the periphery, cortical beta showed the same modulation pattern. We conclude that beta activity in the periphery is mainly determined by cortical projections.

The common beta activity present in the MU population strongly corresponded to the cortical beta projections. We showed that beta activity present in a MU pool is short-lived and shares the characteristics of the cortical beta rhythms, i.e. rate and duration of beta events. Moreover, the common input to the MU pool inside the beta range and the resulting MU beta activity were time-locked and followed cortical beta rhythms by tens of milliseconds. Although determining the transmission delay by only analyzing the beta power is not robust against noise that may mask the underlying shape of beta bursts, our observation is in strong agreement with previous investigations using the averaged CMC (Ibáñez et al., 2021; Mima et al., 2000). When we asked subjects to perform volitional modulations of the beta activity present in the MUs via a novel neurofeedback paradigm (Bräcklein et al., 2020), changes in the cortical beta power were shown to be coherent with those induced in the periphery. These findings suggest a strong and stable correspondence between peripheral and cortical beta oscillations during steady force contractions.

Although the effective beta activity at the MU level could potentially result from other neural centers (Thompson et al., 2019), as it was suggested to be the case for MU activity in the alpha range (8-12Hz) during tremor (Christakos et al., 2006), it seems that these non-cortical contributions may be minimized or suppressed in the context of cortical inputs during isometric contractions. If their contribution would have superseded the presence of cortical projections at the MU level, the resulting beta activity in the periphery would be expected to differ from beta patterns observed at the cortical level. Moreover, the common input to the MUs inside the beta band was increased during volitional up-modulation of the MU beta power while the connectivity between cortical and peripheral sites remained unaffected (Figure 9). Hence, the coherence between the cortical regions and the MU pool inside the beta band (CMC) did not change, but the strength of the common input received by the MU pool (IMC) did. This provides additional evidence for MU beta signals mainly emerging from the cortical sites: if successful beta modulation resulted from additional modulation

of non-cortical sources, the CMC would have been affected by the volitional beta feature modulation (Negro and Farina, 2011).

The dominance of cortical beta inputs to muscles contrasts with the observed lack of direct influence on the produced force. No significant relationship between the force output of the tibialis anterior muscle and the presence of beta rhythms in the innervating MU pool was detected. Still, despite the absence of any evidence for a direct link between beta bursts and the motor output, beta oscillations at the MU level could determine a non-linear effect on the neural drive to the innervated muscle and therefore on the force output (Watanabe and Kohn, 2015). Our results show, however, that these beta events at the MU level are infrequent, i.e. approximately four events per second (Figure 6). While a stationary beta that changes amplitude continuously, as simulated in (Watanabe and Kohn, 2015), may influence force control, a bursting beta is very unlikely to do so since the corrections in force would be far too slow to improve steadiness. Alternatively, the motor system could utilize the observed beta events as a sonar signal integrating sensory information from the muscle (Baker et al., 2006), yet this hypothesis requires further experimental validation. During Experiment 2, when subjects were instructed to modulate MU beta power, and cortical beta changed coherently, the exerted force remained unchanged. This provides further evidence that apart from the timing of beta bursting events, also the modulation of the beta event amplitude does lie inside a motor null-space relative to force production. Hence, the strong link between cortical and spinal neurons via beta activity observed in this study did not seem to have any direct influence on motor output.

When subjects were exposed to neurofeedback on the MU beta activity, beta modulations at the cortical and MU levels were mainly driven by altering the amplitude. Also rate and duration of beta events increased during beta-up modulation, however, this effect was only significant at MU level. It yet remains unknown what underlying mechanism led to a volitional increase in beta power via increase in the amplitude of beta bursts. One possible explanation would be that subjects were able to recruit larger cortical networks involved in the projection of beta activity to the muscle. It was previously shown that the duration of beta bursts was not affected by the performed motor task in normal conditions (Echeverria-Altuna et al., 2021). Here, we observed, although not always significant, slightly longer periods of beta events during beta up-modulation compared to down-modulation of MU beta. Subjects did not receive feedback on the instantaneous amplitude of beta events, nor about their duration or rate. Instead, the feedback provided on the beta feature amplitude during Experiment 2 was smoothed with a moving average and aimed to motivate subjects to modulate the beta activity across the entire duration of the trial, i.e. suppressing or promoting beta activity as long and as often as possible. Further experiments with different

468 neurofeedback approaches (e.g., using the instantaneous behavior of beta events) are necessary to
469 investigate whether subjects could learn to modulate other characteristics of beta activity in the
470 brain and the muscles. This would be highly useful to advance our understanding of the possible
471 roles of beta oscillations in movement.

472 Finally, the strong presence of cortical projections at the MU level opens up new means of studying
473 cortical beta: peripheral neural interfaces, such as presented in (Barsakcioglu et al., 2021), would
474 allow an indirect yet reliable window into cortical activity and may contribute to an advanced
475 understanding of the functional role of beta oscillations in the human motor nervous system by
476 complementing traditional interfaces, such as based on EEG or magnetoencephalography. We
477 showed that by closing the loop with a peripheral neural interface based on MU activity, subjects
478 could volitionally modulate the power of cortical beta bursts. This could provide new possibilities to
479 exploit cortical beta, for example, as a control signal for virtual or robotic effectors (Dominijanni et
480 al., 2021; Eden et al., 2021).

481 In conclusion, we have shown for the first time that the final neural drive to muscles contains
482 bursting beta activity. Moreover, these beta bursts in the MU behavior shared the appearance and
483 were time-locked to those observed on the cortical level. Volitional modulation of MU beta activity
484 was accompanied by coherent changes in cortical beta manifesting the strong correspondence
485 between cortical and MU beta. The observed bursting activity inside the beta band appeared in
486 infrequent events at low rate and thus may, at most, influence force generation as a disturbing
487 factor rather than supporting accurate force control. Cortical beta oscillations seem to be the main
488 contribution to MU beta activity and the strong correspondence between cortical and peripheral
489 beta suggests the potential use of peripheral neural interfaces to track and modulate cortical
490 activity.

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Figure legends

Figure 1: Schematic overview of the experimental paradigms used in both experiments. *A: Experimental flow-chart for Experiment 1 and 2. Both experiments start with estimating the maximum voluntary contraction level (MVC). In Experiment 1, subjects are asked to repeat two blocks of ramp-and-hold force task at 10% MVC separated by a rest period. Experiment 2 continues with two initialization steps in which the online decomposition ("Initialization online decomposition") and the neurofeedback parameters ("Initialization phase") are initialized. In "Familiarization phase" subjects are exposed to the neurofeedback paradigm used during the "Neurofeedback task". A single block of the "Neurofeedback task" consisted of three trails: beta down, beta up, and control. The trials were presented in randomized order and separated by a rest period. A minimum of six and a maximum of nine blocks were presented to each subject separated by a rest period while only the last three blocks were used for the analysis. B: Schematic overview of Experiment 2. HDsEMG of the tibialis anterior muscle was decomposed into the underlying neural activity while, concurrently, the force due to ankle dorsiflexion and the EEG were recorded. Subjects were asked to navigate a cursor inside a target rectangle by performing ankle dorsiflexion at 10% ± .5% MVC. Color of the cursor changed based on the beta power in the MU pool. Subjects were asked to keep the cursor inside the force target and change the cursor color to either blue (down-modulation of the beta activity) or red (up-modulation of the beta activity). In a control condition, no feedback on the beta feature was provided and, instead, the cursor turned white when placed inside the target.*

***Figure 2**: **Beta burst threshold estimation.** Correlation between beta band power and number of samples above threshold for Experiment 1 (top) and Experiment 2 (bottom) for the MU (left) and EEG (right) data. Grey lines indicate single blocks while solid black line indicate mean across blocks. For Experiment 2, only the control condition was used. Dashed black lines indicate maximum correlation value and corresponding threshold.*

Figure 3: Beta power present in the EEG and MU pool shown in a representative subject. *TOP: Force due to dorsiflexion of the ankle, interpolated time-frequency spectrum inside the beta band for surface Laplacian EEG and CST via continuous wavelet transform. BOTTOM: Zoom-into force, interpolated time-frequency-spectra of surface Laplacian EEG and CST, and beta band power (blue) and maxima envelope (red) extracted from the band-pass filtered CST. The Black dashed line indicates the threshold used to identify beta bursts (ON, grey shaded areas) and valleys in between bursts (OFF).*

Figure 4: Lagged coherence analysis for EEG (left) and MU activity (right). *Top: Mean power spectral density normalized between 1 and 40Hz across all blocks. Shaded areas indicate standard error of the mean. Middle: Mean lagged coherence at three cycles across all blocks. Shaded areas indicate standard error of the mean. Bottom: Mean lagged coherence for cycles 3 to 7 across blocks.*

Figure 5: Neural activity during beta bursting events present in the EEG. *ON and OFF periods were aligned and averaged across blocks. From top row to bottom: force (shading indicates 95% percentile), interpolated wavelet-transformed EEG, wavelet-transformed-MU activity, CMC, and IMC, at the center time points of ON periods (left), OFF periods (center), and percental mismatch (right). Black boundaries indicate significant clusters ($p < .05$).*

Figure 6: Relationship between beta bursts observed at the cortical and muscle levels. *The rate at which beta events occurred (left) and their mean duration (right) are shown for cortical (EEG) and peripheral (CST) signals across blocks by their median and quantiles. Values for individual blocks are marked in grey and connected observation sides of beta events (i.e. CST and EEG). **$p < .01$*

Figure 7: Functional values during beta power modulation. *A: Mean force and beta feature amplitude (normalized by mean amplitude during non-feedback condition) during down- and up-modulation conditions (blue and red, respectively) shown by their median and quantiles all subjects. Grey points indicate the mean value per subject, while grey lines combine data of the same subject. * p < .05. B: Temporal correlation between the beta power feature and the force, global EMG of the tibialis anterior and the mean discharge rate (DR) shown across subjects with their median and quantiles. Black bar indicates significance level of correlation.*

Figure 8: Normalized beta events features during modulation. *Mean power, amplitude, duration and rates of beta events are shown across blocks. Corresponding values for beta down-modulation (blue), and up-modulation (red) are normalized by the control condition (no neurofeedback on beta activity). The top row shows values observed on the MU level (CST) and the bottom one for EEG level. Grey dots indicate values for single blocks. Grey lines combine values corresponding to the same block. *p < .05*

Figure 9: Impact of volitional beta feature modulation on spectral measures*. From left to right: beta band power extracted from the MU activity and EEG, beta-band coherence in the CMC and IMC across subjects during beta feature down- (blue) and up-modulation (red). Mean values were extracted from a 500ms window centered around the ON periods identified in the EEG (top) and MU activity (CST, bottom) and were normalized by the corresponding values obtained during the control condition (no beta neurofeedback). Grey dots indicate values for single block, while grey lines combine values corresponding to the same block. *p < .05*